Intermittent Preventive Treatment against Malaria in Infants in Gabon—A Randomized, Double-Blind, Placebo-Controlled Trial

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Background. Intermittent preventive treatment aims to maximize the protective effects of malaria chemoprophylaxis while minimizing the deleterious effects.

Methods. In Gabon, 1189 infants received either sulfadoxine-pyrimethamine (SP; 250 and 12.5 mg, respectively) or placebo at 3, 9, and 15 months of age. Children were actively followed-up until 18 months of age.

Results. In the intention-to-treat population at 18 months of follow-up, 84 children (17%) in the SP group had ⩾1 episode of anemia, versus 108 (21%) in the placebo group (protective efficacy, 22% [95% confidence interval {CI}, −1% to 40%]; $P = .06$). In the intervention group, there were 66 episodes during 485 person-years at risk, compared with 79 episodes during 497 years in the placebo group (protective efficacy, 17% [95% CI, −24% to 45%; $P = .36$). The effects were similar at 12 months of follow-up. The study drug was safe and well tolerated.

Conclusions. The intervention was efficacious, producing a reduction in risk for anemia but a smaller effect against malaria. It is a valuable additional tool to control malaria in a highly vulnerable age group. Remaining important questions are currently being addressed in further studies.

Trial registration. ClinicalTrials.gov identifier: NCT00167843.

Africa suffers most from malaria in terms of morbidity, mortality, and economic losses [1, 2]; current estimates are 0.5 billion malaria attacks and at least 1 million directly caused deaths per annum. The indirect death toll attributable to malaria is also high. Malaria is a major cause of anemia in pregnant women, infants, and older children, and malaria-associated deaths may account for almost another million lives lost annually [3].

A combination of simple, low-cost preventive tools as a mainstay for successful malaria control—particularly for those most at risk for progressing to severe malaria, pregnant women and young children—is much needed. Intermittent preventive treatment (IPT) consists of the administration of antimalarials at defined time points irrespective of the presence of parasites or symptoms and aims at maximizing the beneficial effects of chemoprophylaxis [4]. IPT of pregnant women (IPTp) with sulfadoxine-pyrimethamine (SP) [5–8] was readily endorsed by the World Health Organization (WHO) as part of the armamentarium against malaria during pregnancy [9].

Schellenberg et al. conducted the first trial of IPT in infants (IPTi) [4]. Administering SP to children receiving routine vaccinations delivered through the WHO's Expanded Programme on Immunization (EPI) at 2, 3, and 9 months of age reduced episodes of malaria and

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anemia by >50%. A strategy of administering fewer drug doses on a large scale than would be used in chemoprophylaxis and piggy-backing IPTi onto EPI routine vaccinations was expected to reduce cost and concerns about logistics, drug toxicity, resistance, and immunologically deleterious effects. By conducting a coordinated series of trials in various epidemiological settings across Africa (ranging from efficacy to effectiveness, acceptability, and implementation trials), the IPTi Consortium aims to generate the scientific evidence required [10, 11].

We report here the results of a double-blind, randomized, placebo-controlled trial to assess the efficacy and safety of SP administered as IPTi at 3, 9, and 15 months of age to Gabonese infants.

PATIENTS, MATERIALS, AND METHODS

Study area. Lambaréné, a town with ~25,000 inhabitants, is located in the Moyen Ogooué province of Gabon near the equator in the Central African rain forest. The entomological inoculation rate is ~50 infective bites/person/year. Malaria transmission is perennial, with little seasonal variation. Bed net use, at least in the peripartal period, appears to be high and was ~80% in our study population. Paradoxically, only a fraction of nets were impregnated, and insecticide-treated bed net (ITN) coverage was ~5% (authors' unpublished data).

Resistance of local *Plasmodium falciparum* strains to SP is intermediate. A recent study found a treatment failure rate of 21% on day 14 in children from Lambaréné [12]. Two recent studies in adjacent regions found failure rates of 14% and 30% on day 28 [13, 14].

Subjects. Study subjects were recruited into a birth cohort. Recruitment took place in the maternity wards of the Albert Schweitzer Hospital (HAS) and the General Hospital (HG) in Lambaréné. Inclusion criteria were (1) provision of parental written informed consent or witnessed oral consent in the case of illiteracy and (2) permanent residentship in the study area. Exclusion criteria were (1) known or suspected allergy to sulfonamides or pyrimethamine and/or signs and symptoms thereof and (2) history of severe hepatic or renal dysfunction. Weight and height at birth were recorded from entries into the child's health care booklet. Bed net usage at the time point of first study drug administration was assessed by interview and, whenever feasible, inspection of the house.

The study was performed according to the International Conference on Harmonization–good clinical practice guidelines and according to the amended Declaration of Helsinki. A trial-specific data and safety monitoring board (DSMB) independent of site and funding with a local safety monitor was constituted and informed weekly about the study proceedings and possible adverse events (AEs). A consortium central safety panel oversaw the activities of the individual study sites and their DSMBs.

The ethics committee of the International Foundation of the HAS approved the study. This study report was prepared in accordance with the CONSORT criteria [15].

Methods. This study was designed as a randomized, placebo-controlled, double-blind trial. Primary end points for efficacy were (1) the proportion of children with at least 1 episode of mild anemia from the first treatment (3 months) to 18 months of life and (2) the proportion of children with at least 1 episode of malaria from first treatment (3 months) to 18 months of life. Primary end points for safety were (1) the proportion of children with at least 1 episode of an AE and (2) the proportion of children with at least 1 episode of a serious AE. A secondary end point for efficacy was the proportion of children with at least 1 episode of severe anemia.

Good manufacturing practice–certified SP (Fansidar) and placebo used in the study were manufactured and donated by Roche. Drugs were provided in sealed aluminum blister packages. Each package contained 2 doses, one for the application and a substitute in case of vomiting.

Randomization was done at the level of individual children in blocks of 10. A treatment allocation list was computer generated by Roche for 1200 subjects. The drug and placebo packages were marked with the patient study number. For emergency decoding, the code was concealed in numbered scratch cards permitting individual decoding. Two copies of the code were stored separately, accessible only to the principal investigator or a delegate.

Mothers were invited to attend treatment visits with their children at 3, 9, and 15 months of age at the HAS research unit, facilitating EPI vaccinations at the same time point on the HAS premises. During these visits, the children were examined clinically by a staff physician, and the recent medical history since the last visit was assessed. The study drug was administered, and blood was drawn as described below.

The children were given half a tablet of SP (total dose of 250 and 12.5 mg of sulfadoxine and pyrimethamine, respectively) or placebo at 3, 9, and 15 months by a member of the study team, orally by spoon after crushing the substance and mixing with water. Children were observed for 30 min, and a repeated dose was given if vomiting occurred within 30 min. Treatment was stopped when the child vomited the second dose.

Safety and tolerability of treatment was assessed on 2 visits on days 7 and 28 after treatment. Field-workers conducted monthly home visits for health status assessment. In the case of an acute febrile disease, a fingerprick blood sample was obtained and a thick blood film examined. The active follow-up continued until 30 months of age was reached.

Parents were encouraged to present at the HAS research unit if the child experienced health problems between the active follow-ups. On days 0 (before) and on days 7 and 28 after each drug administration, clinical chemistry, full blood count, and thick blood smears were performed. Full blood counts were performed on an Abbott Cell-Dyn 3000 device (Abbott Diagnos-

tics) during the initiation phase of the study and later on an ABX Pentra 60 device (ABX Diagnostics). Alanine aminotransferase and creatinine levels were assessed using an ABX Mira Plus device (ABX Diagnostics).

Malaria was diagnosed according to the Lambaréné method, as described elsewhere [16]. A malaria attack was defined as the presence of any asexual *P. falciparum* parasitemia and either a rectal temperature of at least 38.5°C or a history of fever during the last 48 h reported by the mother. Severe malaria was defined by signs and symptoms as specified by [17]. Until mid-August 2004, malaria was treated with artesunate monotherapy [18]. A review of treatment policies then led to a change in treatment regimens; malaria was treated with an oral combination of artesunate (4 mg/kg/day every 24 h over 3 days) and amodiaquine (10 mg/kg/day every 24 h over 3 days) [19] (Arsucam [50 mg of artesunate and 153 mg of amodiaquine]; tablets provided by Sanofi-Synthélabo).

Anemia was defined as a hemoglobin level of $<$8.0 g/dL. Severe anemia was defined as a hemoglobin level of $\leqslant$5.0 g/dL. Anemia was treated following the current HAS safety guidelines and laboratory standard operational procedures (hemoglobin level $>$9 g/dL, no intervention but follow-up as required; hemoglobin level within 9–5 g/dL, oral substitution of iron plus dietary advice to parents and follow-up as required; hemoglobin level $<$5 g/dL, blood transfusion).

AEs occurring within 28 days after study drug administration were categorized according to severity (mild, moderate, and severe), seriousness (serious or not serious), and relationship to study drug (unrelated or unlikely, possibly, probably, or most probably related). To assess all grades of skin and generalized allergic reactions and toxic hepatitis, physical checks, clinical chemistry and a full blood count were performed routinely at these time points, with open additional visits on parents' initiative at any time point of the study. In the case of a possibly or probably drug-related serious AE, the DSMB and the local safety monitor were informed.

Analysis. Sample size calculation was based on data from a previous study in the area [20], and we estimated that 28% of children would have an episode of anemia by the age of 1.5 years. To detect a protective efficacy of 30% with a power of 80%, a significance level of 5%, and 20% loss to follow-up, 531 children were needed in each group. The intention-to-treat (ITT) population included all subjects who correctly received the first study drug administration, regardless of the status of the other administrations. Analysis was based on this "modified ITT" population rather than on all randomized subjects, because, although most children were randomized at birth, no further visits or study procedures were performed until the first treatment. The time at risk started at the first drug administration and ended 3 months after the last dose was given.

The according-to-protocol (ATP) population included all subjects who received all 3 drug administrations within the specified time limits and were followed-up until 18 months of age. Time at risk started at the first administration and ended when the child reached 18 months of age. Children missing treatment for 2 months or not being actively seen for 6 months were not included in the ATP analysis.

Rate ratios (episodes per person-year at risk) were calculated using negative binomial regression without covariates and were expressed as protective efficacy. The 3 weeks after malaria treatment were not included in the time at risk. Survival analysis was based on Kaplan-Meier curves and the log-rank test to compare time to first episode.

Statistical analysis was performed using JMP5 (SAS Institute) and Stata (StataCorp) statistical software.

RESULTS

Study flow and baseline data. During the screening and recruitment phase from December 2002 to February 2005, 1189 infants were recruited (819 at the HAS and 370 at the HG); 1007 (85%) received the first treatment correctly within the time limits (ITT population), and 602 (51%) received 3 doses correctly and were followed up for 18 months (ATP population). Figure 1 depicts the study flow; table 1 provides the baseline data.

Safety and tolerability. Of a total of 2540 treatments, AEs were recorded after 1299 (51%). Of these, 176 AEs were judged to be possibly, probably, or most probably related to study drug intake. No serious cutaneous AEs were recorded in either group. Table 2 summarizes the AEs in both the SP and placebo groups. There was no statistically significant difference in frequency or intensity of drug-related AEs between the study groups (for placebo, 57 mild, 24 moderate, and 4 severe events; for SP, 64 mild, 24 moderate, and 3 severe events; $P = .84$).

Table 3 summarizes laboratory parameters over time. Differences in laboratory parameters between treatment groups over time were analyzed by repeated-measures analysis of variance. There were no statistical differences noted between the placebo and the SP group. Two children experienced a considerable decline in hemoglobin levels after intervention. A 9-month-old girl who presented with severe anemia 1 month after the second study drug administration (10.7 g/dL at treatment 2; 4.7 g/dL on day 27) required a blood transfusion. A 15 month-old girl had a decline in hemoglobin level from 8.2 g/dL at treatment 3 to 5.2 g/dL on day 7 but was asymptomatic. After counseling with our DSMB, the study drug was unblinded for both children, and it was found that both had received SP. Hemoglobin electrophoresis revealed sickle cell anemia (HbSS) in both patients. G6PDH deficiency was excluded in both cases.

Five deaths were recorded in the study cohort between treatment 1 and completion of month 18 of age. Four deaths occurred in the placebo group and were due to AIDS, pneumonia, dehydration, and an unknown reason. One death occurred in the SP group and was due to asphyxia. None of the deaths was

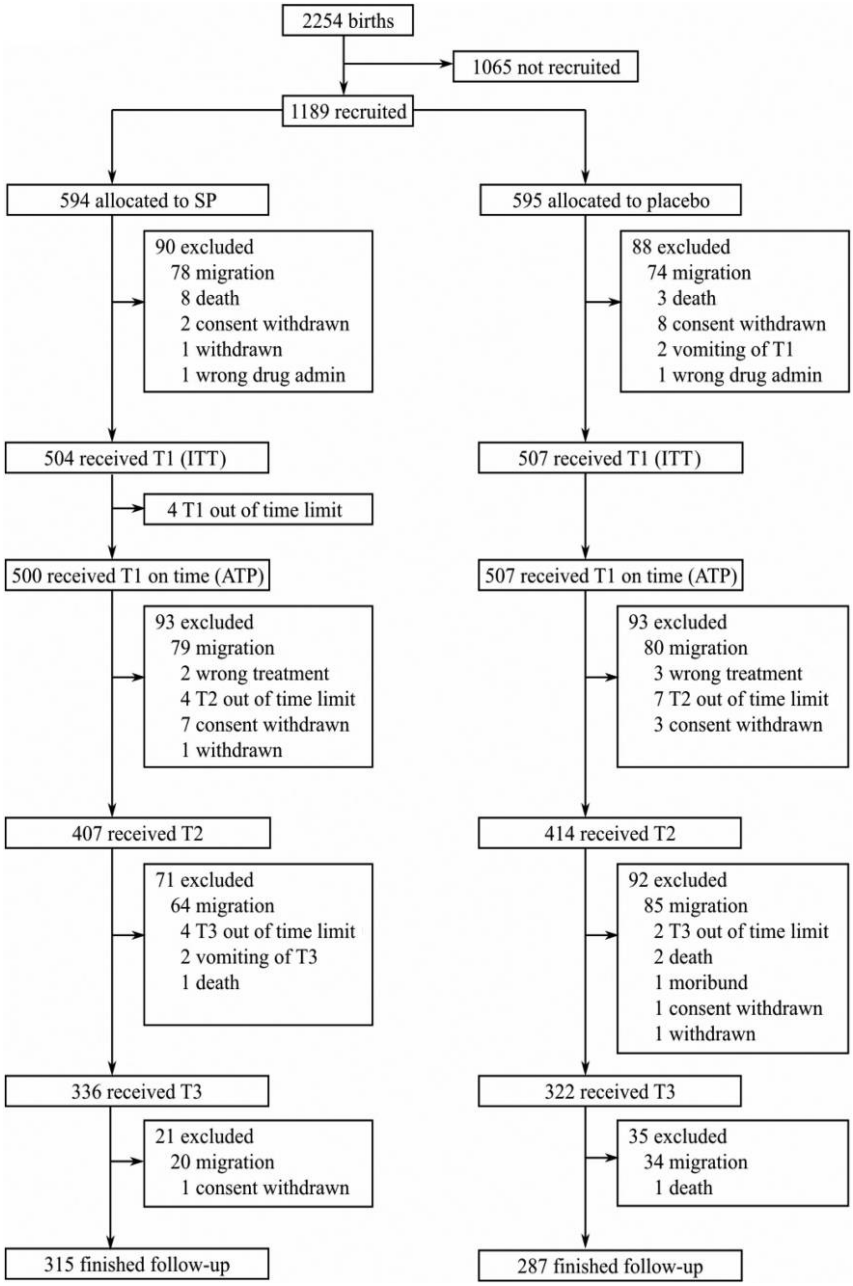

Figure 1. Study flow chart. T1, treatment 1; T2, treatment 2; T3, treatment 3.

considered to be related to treatment. Because of the advanced illness, the third treatment was cancelled for the child with AIDS. He is listed as "moribund" in the study flow chart.

Protective efficacy against malaria and anemia. The intervention had a protective effect against malaria and anemia at both time points and in both analysis populations (table 4). In the ITT population, the effect against anemia was 22% after 18 months, compared with 26% after the first 12 months. The protective effect against the risk and incidence of malaria was less pronounced and did not reach statistical significance in either population.

Survival curves illustrate the effects (figure 2*A* and 2*B*), with the log-rank test confirming the protective effect of the intervention against anemia (figure 2*A*).

DISCUSSION

Three trials using SP for IPTi have been reported to date—1 each from Tanzania [4, 21], Ghana [22], and Mozambique [23]. In the Tanzanian trial, SP was administered along with childhood vaccinations at months 2, 3, and 9; in Ghana, at months 3, 4, 9, and 12 (extra dose outside EPI); and in Mozambique, at months 3, 4, and 9.

Table 1. Basic demographic data.

Characteristic	Total recruited population		ITT population	
	SP (n = 594)	Placebo (n = 595)	SP (n = 500)	Placebo (n = 507)
Male	255 (43)	293 (49)	210 (42)	253 (50)
Weight at birth, mean ± SD, g	3011 ± 485	3017 ± 497	3026 ± 484	3036 ± 500
Height at birth, mean ± SD, cm	49 ± 3	49 ± 3	49 ± 3	49 ± 3
Recruited during first week of life	507 (85)	489 (82)	425 (85)	414 (82)
Children below 2 z scores[a] at T1	NA	NA	3 (0.6)	5 (1.0)
Age, mean ± SD, months				
At T1	NA	NA	3.1 ± 0.4	3.2 ± 0.5
At T2	NA	NA	9.3 ± 0.6	9.3 ± 0.6
At T3	NA	NA	15.4 ± 0.7	15.3 ± 0.6
Bed net use at T1[b]	NA	NA	460 (92)	463 (91)

NOTE. Data are no. (%) of participants, unless otherwise specified. ITT, intention to treat; NA, not available; T1, treatment 1; T2, treatment 2; T3, treatment 3.

[a] Weight for height.

[b] Of which the vast majority were unimpregnated; insecticide-treated bed net coverage was estimated to be 5% (authors' unpublished data).

In the Lambaréné area, malaria is rare in those <3 months old [24]. The incidence then increases rapidly toward the end of the first year of life [20], with the incidence of cerebral malaria episodes peaking during the second and third year of life (P.G.K., unpublished data). This renders an intervention before 3 months of age useless, whereas those at months 9 and 15 (at which a measles booster vaccination is recommended) were spaced into the period of life where malaria incidence and severity of disease episodes start to increase.

In the initial study from Tanzania [4], in an area of perennial malaria transmission and high ITN coverage, IPTi reduced episodes of malaria and anemia by >50%. Similar results—in an area of lower ITN coverage—were yielded with amodiaquine as the drug of choice in another study from Tanzania [25]. In an area of highly seasonal malaria transmission and low ITN coverage in Ghana, Chandramohan et al. [22] found a protective efficacy of IPTi against all episodes of malaria of 25% up to 15 months of age (95% CI, 14% to 34%). Macete et al. [23] reported a reduction in malaria incidence of 22% (95% CI, 4% to 31%) from Mozambique.

In the present study, the effect of IPTi against anemia was comparatively strong. Although lower than the initial results from Tanzania, a protective effect of ~25% is higher than any seen to date in Ghana or Mozambique. On the other hand, we report a similar or slightly lower protective efficacy against malaria than previously found elsewhere. Moderate anemia is common in this study area, and a considerable proportion of the population will experience an episode if observed for long time. A bias toward a null effect will therefore result when the relative risk is measured, and this should be taken into account when comparing the present results with the results of studies using the incidence of anemia as the end point. In addition to unspecific effects [26], site-specific effects may have played a role. It appears from the earlier studies that there is an additional pro-

Table 2. Adverse events (AEs), judged as possibly, probably, or likely being associated with study drug intake.

AE	SP		Placebo		P
	No. of AEs (n = 1276 treatments)	AEs/1000 treatments	No. of AEs (n = 1264 treatments)	AEs/1000 treatments	
Gastrointestinal	38	30	29	23	.28
Respiratory	18	14	18	14	.98
Skin	14	11	17	13	.57
Fever	10	8	12	9	.65
Laboratory abnormalities	9	7	8	6	.96
Loss of appetite	2	2	0	0	.16
Weakness	0	0	1	1	.31

NOTE. The no. of treatments counted for the AE analysis differs from that for the according-to-protocol efficacy analysis, because all treatments are counted here, regardless of whether a treatment time window was missed or the protocol was violated for any reason. SP, sulfadoxine-pyrimethamine.

Table 3. Laboratory parameters throughout study period.

Parameter, treatment	T1		T2		T3		*P*
	d0	d28	d0	d28	d0	d28	
AST level							
Placebo	33 ± 26	33 ± 25	23 ± 17	25 ± 21	26 ± 70	29 ± 120	. . .
SP	32 ± 20	28 ± 16	28 ± 60	25 ± 47	20 ± 18	19 ± 16	.43
Creatinine level							
Placebo	35 ± 9	. . .	31 ± 15	. . .	28 ± 12	. . .	. . .
SP	35 ± 10	. . .	31 ± 16	. . .	28 ± 14	. . .	.13
Hematocrit, %							
Placebo	29 ± 4	30 ± 5	29 ± 3	29 ± 3	29 ± 3	30 ± 3	. . .
SP	30 ± 4	30 ± 4	29 ± 3	30 ± 3	30 ± 3	30 ± 3	.87
Hemoglobin level							
Placebo	9.8 ± 1.3	10 ± 1.4	9.6 ± 1.1	9.6 ± 1.1	9.7 ± 1.1	9.8 ± 1.2	. . .
SP	10 ± 1.2	10 ± 1.3	9.8 ± 1.1	9.9 ± 1.1	9.8 ± 1.2	9.9 ± 1.2	.96
White blood cell count							
Placebo	8.4 ± 2.9	8.7 ± 3	9.4 ± 4	9.2 ± 3.8	8.8 ± 3.5	8.2 ± 3.8	. . .
SP	9 ± 3.1	9 ± 3.5	9.6 ± 3.8	9.7 ± 4.6	9 ± 4	9 ± 5.4	.94

NOTE. Data are mean ± SD values. AST, aspartate aminotransferase; d0, day 0 (before treatment); d28, day 28 after treatment; SP, sulfadoxine-pyrimethamine; T1, treatment 1; T2, treatment 2; T3, treatment 3.

tective effect from a high concomitant use of ITNs. In our study population, bed net use was ~80%. Paradoxically, only a fraction of nets were impregnated, and ITN coverage was ~5% (authors' unpublished data). Although untreated nets do provide a considerable degree of protection unless damaged, their efficacy is clearly below that of ITNs. Whereas malaria incidence appears to be in a steady decline in the Lambaréné area over the past decade (authors' unpublished data), underreporting may have contributed as well. Even though the vast majority of children with a suspected and/or verified diagnosis of malaria were seen and taken care of by our research staff, treatment in health care centers outside the catchment area occurred, resulting from the

Table 4. Primary outcomes.

Time point, parameter	ITT analysis				ATP analysis			
	SP (*n* = 504)	Placebo (*n* = 507)	Protective efficacy, % (95% CI)	*P*	SP (*n* = 315)	Placebo (*n* = 287)	Protective efficacy, % (95% CI)	*P*
18 months								
Malaria								
Children with at least 1 episode	55 (11)	59 (12)	6 (−33 to 34)	.71	38 (12)	40 (14)	13 (−31 to 43)	.50
Total episodes	68	81	. . .	. . .	46	54	. . .	. . .
PYAR	510	495	. . .	. . .	389	353	. . .	. . .
Incidence, episodes/PYAR	0.13	0.16	17 (−24 to 44)	.36	0.12	0.15	23 (−24 to 52)	.28
Moderate anemia, children with at least 1 episode	84 (17)	108 (21)	22 (−1 to 40)	.06	59 (19)	74 (26)	27 (2 to 46)	.04
12 months								
Malaria								
Children with at least 1 episode	37 (7)	43 (8)	13 (−32 to 43)	.50	22 (7)	28 (10)	28 (−22 to 58)	.22
Total episodes	42	54	. . .	. . .	24	34	. . .	. . .
PYAR	332	333	. . .	. . .	232	210	. . .	. . .
Incidence, episodes/PYAR	0.13	0.16	22 (−25 to 52)	.30	0.10	0.16	37 (−14 to 65)	.12
Moderate anemia, children with at least 1 episode	65 (13)	88 (17)	26 (0 to 45)	.05	42 (13)	58 (20)	34 (5 to 54)	.03

NOTE. Data are no. (%) of participants, unless otherwise indicated. ATP, according to protocol; CI, confidence interval; ITT, intention to treat; PYAR, person-years at risk; SP, sulfadoxine-pyrimethamine.

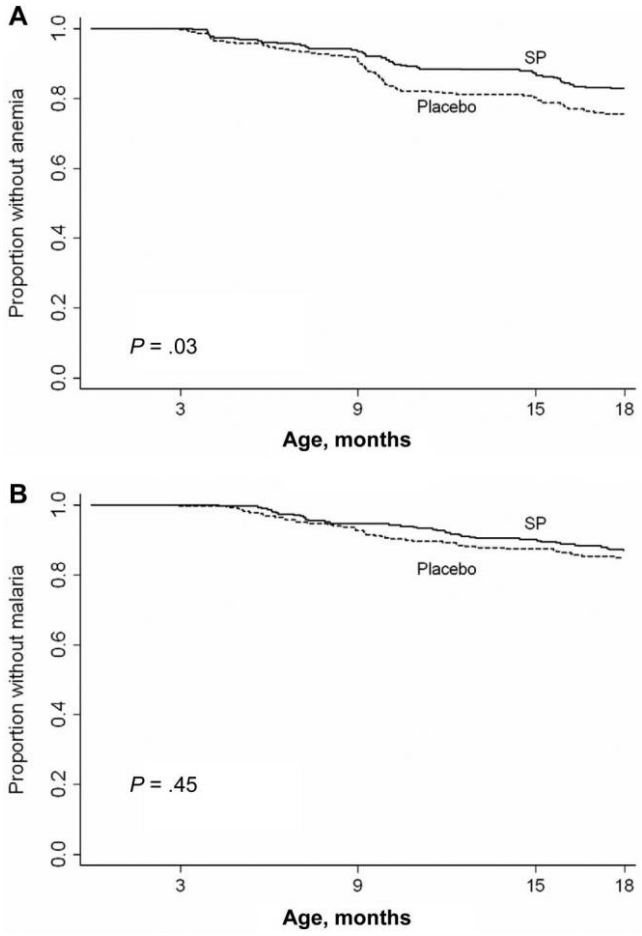

Figure 2. *A,* Kaplan-Meier plot for time to first episode of anemia. *B,* Kaplan-Meier plot for time to first episode of malaria. SP, sulfadoxine-pyrimethamine.

high mobility of the local population, and self-medication is also practiced. Only microscopically confirmed malaria attacks were analyzed in our study.

The mobility of the local population led to a greater-than-anticipated number of subjects lost to follow-up, thus resulting in a loss of power.

Our study design led to the creation of an outstandingly healthy study cohort, which almost represents a Lambaréné birth cohort of more than a year. Only 5 deaths occurred between months 3 and 18 of life in ~1000 infants, attributable to our close-knit passive and active follow-up system, which also included basic health care support for siblings and other family members, thus further indirectly improving the health and living conditions of our study subjects.

In both the ITT and ATP analyses, protective efficacy was higher for the first 12 months of life than for 18 months of age. First, the wide spacing of our intervention may have accounted for marginalizing the intervention effect. Second, the same dose of SP was given at all doses of IPTi, because this was the manufacturer's and WHO's recommendation at the initiation of the trial. Therefore, a lower dose per weight of SP was administered to the older children at 15 months of age. Recent evidence from pharmacokinetic studies suggests that the SP dose should be adapted to body weight [27]. However, on the basis of study results available up to now, the intervention may possibly best be restricted to the first year of life.

The choice of the most appropriate drug for IPTi needs to take into account pharmacokinetic and dosage aspects, safety and tolerability, and possible parasitic drug resistance. On the grounds of its suitable and fairly long half-life [28], its favorable safety profile, vast experience as a therapeutic agent, low cost, and an acceptable resistance level in most settings [29], SP is the drug that has been most intensively investigated in the context of IPTi to date. However, there are other candidate drugs that may be suitable alternatives [25].

The safety profile of sulfa drug combinations, including SP, has been reviewed in detail elsewhere [30]. In our study, the safety and tolerability of SP were high. Although a large proportion of the study subjects experienced an adverse reaction, frequencies were not different between those receiving SP or placebo, and there was no apparent increased likelihood of reporting an AE among those receiving SP.

In 2 children, hemoglobin levels dropped remarkably after SP administration; these children had HbSS. A large number and range of hematological AEs after the administration of SP have been described [31]. However, to the best of our knowledge, individuals with HbSS are not considered to be more prone to developing hemolytic adverse reactions after the administration of SP than healthy individuals.

The mechanism of how IPTi works is not fully understood, but study results, including those described here, suggest that the effect is mainly prophylactic, thus limiting the choice of drugs and combinations to those that are long-acting. By increasing the use of SP, IPTi may trigger the development of drug resistance, but this effect may be counterbalanced by the fact that (1) only very few doses over a considerable time span are used in relatively few individuals of a given population, (2) the drug will be administered under supervision, and (3) fewer infants will require drug treatment. Interestingly, the first IPTi trial to use SP in Tanzania, conducted in 1999/2000, had a protective efficacy against malaria of 62%; the level of drug resistance to SP (percentage of clinical and parasitological treatment failure by day 14 in symptomatic children 6–59 months old) was ~34% [4]. Paradoxically, in the other IPTi trials published to date [22, 23], including ours presented here, both SP IPTi efficacy rates and SP resistance rates (17%–21%) are lower. Therefore, SP resistance probably contributed little to the relatively low protective efficacy seen in the Lambaréné trial reported here.

In conclusion, IPTi appears to be a valuable additional tool to control malarial anemia in an age group most vulnerable to malaria. Important questions for the current process of considering the translation of IPTi into public heath policies remain, com-

prising the issues of the most suitable drugs, resistance development, rebound, interactions with EPI vaccinations, cost-effectiveness, and acceptability. These are being addressed in a range of further studies by the IPTi Consortium that are currently under way across Africa.

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