

## No Rebound of Morbidity following Intermittent Preventive Sulfadoxine-Pyrimethamine Treatment of Malaria in Infants in Gabon

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In the context of a trial studying intermittent preventive sulfadoxine-pyrimethamine treatment of malaria in infants in Lambaréné, Gabon, children aged 18–30 months were followed up after having received their last dose at an age of 15 months. In the intention-to-treat population, the protective efficacy against all malaria episodes was  $-18.0$  (95% confidence interval,  $-97.4$  to  $29.5$ ;  $P = .529$ ). The protective efficacy against first or only anemia episode was  $-45.3$  (95% confidence interval,  $-234.5$  to  $36.3$ ;  $P = .375$ ). The protective efficacies were negative and were not statistically significant. These results do not appear to support the concept of a rebound effect after intermittent preventive sulfadoxine-pyrimethamine treatment of malaria in infants.

**Clinical trials registration.** NCT00167843.

Intermittent preventive sulfadoxine-pyrimethamine treatment of malaria in infants (IPTi-SP) is a novel tool to control malaria

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[1]. In a series of clinical trials performed in recent years, this concept was tested across sub-Saharan Africa [2].

In Lambaréné, Gabon, 1189 infants received either SP (250 mg and 12.5 mg, respectively) or placebo at 3, 9, and 15 months of age in a randomized, placebo-controlled, double-blind trial. The drug was safe and well tolerated. At the end of the intervention period at month 18, the intervention was efficacious but did not reach statistical significance, with a reduction in risk of anemia of 22% (95% confidence interval [CI],  $-1\%$  to  $40\%$ ;  $P = .06$ ) and a reduction in risk of malaria of 17% (95% CI,  $-24\%$  to  $45\%$ ;  $P = .36$ ) [3].

IPTi aims to maximize the protective effects of malaria chemoprophylaxis while minimizing deleterious effects [1]. Continuous chemoprophylaxis has been shown to result in a rebound effect of malaria morbidity and/or mortality and/or an excess of malaria-related anemia after cessation of the intervention and is understood to be a result of a loss or delay in the acquisition of naturally acquired immunity attributable to a lack of exposure to parasites, independent from the drug used [1, 4–7]. We report here on a 12-month follow-up period from 18 through 30 months of age, to assess for a possible rebound in morbidity after the cessation of IPTi-SP in the Lambaréné, Gabon study cohort.

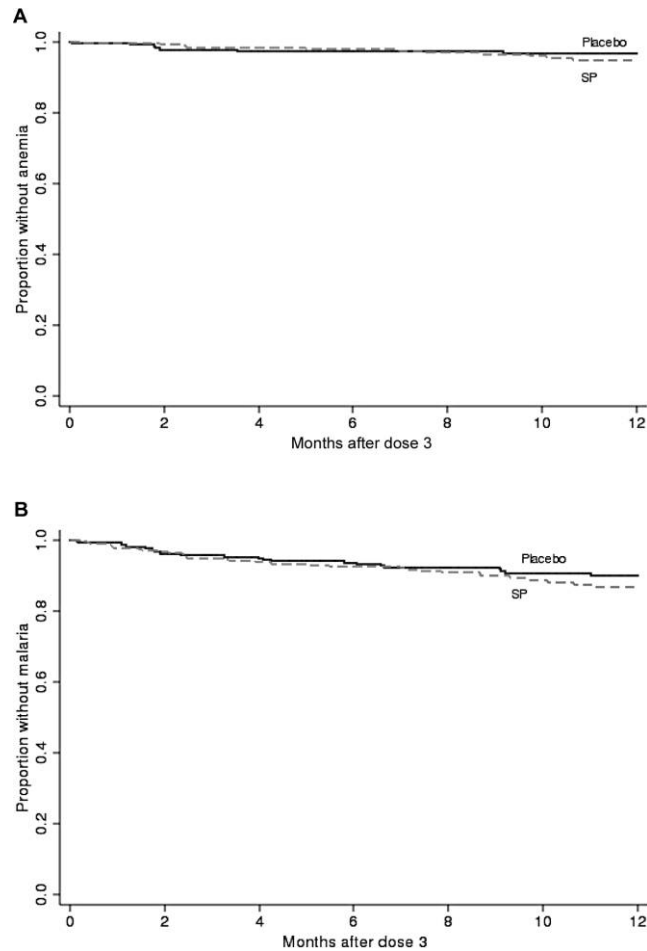
**Patients and methods.** The study took place in Lambaréné, Gabon. The local malaria epidemiology, the study subjects, the trial methodology, and the results up to 18 months of age for this randomized, placebo-controlled, double-blind trial have been described in detail elsewhere [3]. The study was 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 independent of site and funding with a local safety monitor was constituted and was informed weekly about the study proceedings and possible adverse events. A safety panel convened by the IPTi Consortium collected and analyzed safety data from the individual study sites and their data and safety monitoring boards. The ethics committee of the International Foundation of the HAS approved the study. The trial was registered at clinicaltrials.gov (registration NCT00167843).

This study reported here covers a 12-month follow-up period encompassing months 18–30 of life of the study subjects, to assess a possible rebound effect of morbidity. Primary end points for rebound were (1) the proportion of children with at least 1 episode of anemia (defined as a hemoglobin level  $< 8.0$  g/dL) during months 18–30 of life and (2) the proportion

**Table 1. Clinical Malaria and Anemia during Extended Follow-up of Children in a Clinical Trial of Intermittent Preventive Sulfadoxine-Pyrimethamine Treatment of Malaria in Infants in Lambaréné, Gabon**

Cohort or outcome definition	Control group					Sulfadoxine-pyrimethamine group					PE (95% CI), %	P
	No of malaria cases	PYAR	Incidence, cases per PYAR	No of patients	Patients with malaria, %	No of malaria cases	PYAR	Incidence, cases per PYAR	No of patients	Patients with malaria, %		
ITT cohort 18–24 months												
All malaria episodes	21	128.9	0.16	...	...	20	139.7	0.14	...	...	14.8 (–72.1 to 57.9)	.654
First or only malaria episode	19	...	...	340	5.59	18	...	...	364	4.95	11.5 (–65.8 to 52.8)	.703
First or only anemia episode	7	...	...	340	2.06	6	...	...	364	1.65	19.9 (–136.0 to 72.8)	.687
ATP cohort 18–24 months												
All malaria episodes	17	108.1	0.16	...	...	18	119.2	0.15	...	...	5.2 (–105.1 to 56.2)	.892
First or only malaria episode	15	...	...	283	5.30	16	...	...	310	5.16	2.6 (–93.4 to 51.0)	.939
First or only anemia episode	6	...	...	283	2.12	5	...	...	310	1.61	23.9 (–146.8 to 76.5)	.649
ITT cohort 24–30 months												
All malaria episodes	12	105.1	0.11	...	...	23	112.5	0.20	...	...	–80.3 (–288.0 to 16.2)	.132
First or only malaria episode	11	...	...	283	4.03	20	...	...	295	6.78	–68.3 (–244.9 to 17.9)	.155
First or only anemia episode	2	...	...	283	0.73	9	...	...	295	3.05	–316.4 (–1812.9 to 9.3)	.067
ATP cohort 24–30 months												
All malaria episodes	9	89.8	0.10	...	...	15	93.1	0.16	...	...	–57.2 (–316.3 to 40.6)	.363
First or only malaria episode	8	...	...	230	3.48	12	...	...	248	4.84	–39.1 (–234.5 to 42.1)	.461
First or only anemia episode	1	...	...	230	0.43	7	...	...	248	2.82	–549.2 (–5147.5 to 19.7)	.079
ITT cohort 18–30 months												
All malaria episodes	33	233.2	0.14	...	...	43	251.4	0.17	...	...	–18.0 (–97.4 to 29.5)	.529
First or only malaria episode	29	...	...	340	8.53	37	...	...	364	10.16	–19.2 (–89.4 to 25.0)	.458
First or only anemia episode	9	...	...	340	2.65	14	...	...	364	3.85	–45.3 (–231.5 to 36.3)	.375
ATP cohort 18–30 months												
All malaria episodes	26	197.3	0.13	...	...	33	211.7	0.16	...	...	–15.6 (–114.7 to 37.7)	.646
First or only malaria episode	22	...	...	283	7.77	27	...	...	310	8.71	–12.0 (–92.2 to 34.7)	.680
First or only anemia episode	7	...	...	283	2.47	11	...	...	340	3.55	–43.5 (–265.3 to 43.7)	.449

**NOTE.** ATP according-to-protocol analysis; CI, confidence interval; ITT, intention-to-treat analysis; PE, protective efficacy; PYAR, person-years at risk.



**Figure 1.** A, Kaplan-Meier plot for time to first episode of anemia. B, Kaplan-Meier plot for time to first episode of malaria. Both plots represent months 18–30 of life; month 0 after dose represents month 18 of life. SP, sulfadoxine-pyrimethamine.

of children with at least 1 episode of malaria (defined as presence of any asexual *Plasmodium falciparum* parasitemia and either a rectal temperature of  $\geq 38.5^{\circ}\text{C}$  or a history of fever during the last 48 h reported by the mother) during months 18–30 of life. Field workers conducted monthly home visits for health status assessment. In cases of acute febrile disease, a finger-prick blood sample was obtained, and a thick blood film was examined. The active follow-up continued until 30 months of age.

Analysis was based on a modified intention-to-treat population (ie, all infants that received at least 1 dose of IPTi). The according-to-protocol population included all subjects who had previously received all 3 drug administrations within the specified time limits. Time at risk started at 18 months and ended at 30 months of age. Children who were not actively seen for 6 consecutive months were not included in the according-to-protocol analysis. Rate ratios (episodes per person-year at risk) were calculated using negative binomial regression without covariates and was 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.** Of 1189 study subjects (594 in the SP group and 595 in the placebo group) included in the study at birth, 602 (315 in the SP group and 287 in the placebo group) entered the follow-up phase at month 18 [3]. At month 30, 287 children in the SP group completed the 12-month follow-up period (28 children were lost to follow-up; 24 were lost to migration, 3 withdrew consent, and 1 died [death unrelated to study drug]), and 262 children in the placebo group completed the 12-month follow-up period (25 children were lost to follow-up because of migration). The loss to follow-up primarily attributable to migration observed here is in line with previously reported figures of the intervention phase. In the intention-to-treat analysis, protective efficacy against all malaria episodes was  $-18.0\%$  (95% CI,  $-97.4$  to  $29.5$ ;  $P = .529$ ). The protective efficacy

against the first or only anemia episode was  $-43.5\%$  (95% CI,  $-265.3$  to  $43.7$ ;  $P = .449$ ). Full results are given in Table 1 and Figure 1.

**Discussion.** In line with data published elsewhere [8], our data confirm that IPTi-SP is not associated with a rebound effect of significance in an area of perennial malaria transmission and low insecticide-treated bed net coverage. Five trials with IPTi-SP have been reported so far apart from ours in Gabon [3], 1 each from Tanzania [9, 10] and Mozambique [8] and 3 from Ghana [11–13]. One was performed in an area of highly seasonal transmission [11], whereas all others were performed in areas of stable malaria transmission.

There was no significant rebound in the pooled analysis of all 6 trials looking at the 5-month period after the IPTi schedule was finished [2]. In the initial Tanzanian study, a 36% protective efficacy against malaria (parasitemia and fever) was sustained during the follow-up period from 10 through 24 months of age [10]. In the study in Mozambique, no rebound effect was reported during follow-up through the age of 24 months [8]. The IPTi trial in Navrongo [11] reported a 19% increase in malaria with high-density parasitemia ( $\geq 5000$  parasites/ $\mu\text{L}$ ) 4–12 months after the last dose of IPTi (ie, during 16–24 months of age) but did not find any evidence of a rebound using other measures, including malaria (with a parasite density of  $< 5000$  parasites/ $\mu\text{L}$ ), malaria hospitalizations, and anemia. In the Tamale and Kumasi trials [12, 13] in Ghana, a rebound in anemia was observed in the second year of life in subgroup analyses, but there was no rebound in other morbidity outcomes.

In the current study, we found negative protective efficacies that could be consistent with a rebound effect for malaria and anemia, although neither measure was statistically significant. This could be attributable to a lack of power because of the relatively low malaria incidence in our study population. However, a pooled analysis of data published elsewhere [2] did not find evidence that IPTi-SP is associated with a significant rebound effect. On the balance, we think that the present results are in line with those published in the other studies and do not support the concept of a rebound effect after the intervention.

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## References

1. Grobusch MP, Egan A, Gosling RD, Newman RD. Intermittent preventive therapy for malaria: progress and future directions. *Curr Opin Infect Dis* 2007; 20:613–20.
2. Aponte JJ, Schellenberg D, Egan A, et al. Efficacy and safety of intermittent preventive treatment with sulfadoxine-pyrimethamine for malaria in African infants: a pooled analysis of six randomised, placebo-controlled trials. *Lancet* 2009 [Epub ahead of print].
3. Grobusch MP, Lell B, Schwarz N, et al. Intermittent preventive treatment in infants of malaria in Gabon: a randomized, double-blind, placebo-controlled trial. *J Infect Dis* 2007; 196:1595–602.
4. Greenwood BW, Greenwood AM, Smith AW, et al. A comparative study of lapudrine (chlorproguanil) and maloprim (pyrimethamine and dapsone) as chemoprophylaxis against malaria in Gambian children. *Trans R Soc Trop Med Hyg* 1989; 83:182–8.
5. Greenwood BW, David PH, Otoo-Forbes LN, et al. Mortality and morbidity from malaria after stopping malaria chemoprophylaxis. *Trans R Soc Trop Med Hyg* 1995; 89:629–33.
6. Menendez C, Kahigwa E, Hirt R, et al. Randomised placebo-controlled trial of iron supplementation and malaria chemoprophylaxis for prevention of severe anaemia and malaria in Tanzanian infants. *Lancet* 1997; 350:844–50.
7. Aponte JJ, Menendez C, Schellenberg D, et al. Age interactions in the development of naturally acquired immunity to *Plasmodium falciparum* and its clinical presentation. *PLoS Med* 2007; 4:e242.
8. Macete E, Aide P, Aponte JJ, et al. Intermittent preventive treatment for malaria control administered at the time of routine vaccinations in Mozambiquan infants: a randomized, placebo-controlled trial. *J Infect Dis* 2006; 194:276–85.
9. Schellenberg D, Menendez C, Kahigwa E, et al. Intermittent treatment for malaria and anemia control at time of routine vaccinations in Tanzanian infants: a randomized, placebo-controlled trial. *Lancet* 2001; 357:1471–7.
10. Schellenberg D, Menendez C, Aponte JJ, et al. Intermittent preventive antimalarial treatment for Tanzanian infants: follow-up to age 2 years of a randomized, placebo-controlled trial. *Lancet* 2005; 365:1481–3.
11. Chandramohan D, Owusu-Agyei S, Carneiro I, et al. Cluster randomised trial of intermittent preventive treatment for malaria in infants in an area of high, seasonal transmission in Ghana. *Brit Med J* 2005; 331: 727–33.
12. Mockenhaupt FP, Reither K, Zanger P, et al. Intermittent preventive treatment in infants as a means of malaria control: a randomized, double-blind, placebo-controlled trial in Northern Ghana. *Antimicrob Agents Chemother* 2007; 51:3273–81.
13. Kobbe R, Kreuzberg C, Adjei S, et al. A randomized controlled trial of extended intermittent preventive antimalarial treatment in infants. *Clin Infect Dis* 2007; 45:16–25.