

Intermittent Preventive Treatment for Malaria Control Administered at the Time of Routine Vaccinations in Mozambican Infants: A Randomized, Placebo-Controlled Trial

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(See the editorial commentary by ter Kuile and Steketee, on pages 269–72.)

Background. There is an urgent need to deploy and develop new control tools that will reduce the intolerable burden of malaria. Intermittent preventive treatment in infants (IPTi) has the potential to become an effective tool for malaria control.

Methods. We performed a randomized, double-blind, placebo-controlled trial of sulfadoxine-pyrimethamine (SP) treatment in 1503 Mozambican children. Doses of SP or placebo were given at 3, 4, and 9 months of age. The intervention was administered alongside routine vaccinations delivered through the Expanded Program on Immunization (EPI). Hematological and biochemical tests were done when infants were 5 months old. Morbidity monitoring through a hospital-based passive case-detection system was complemented by cross-sectional surveys when infants were 12 and 24 months old.

Results. IPTi was well tolerated, and no adverse events associated with SP were documented. During the first year of life, intermittent SP treatment reduced the incidence of clinical malaria by 22.2% (95% confidence interval [CI], 3.7%–37.0%; $P = .020$) and the rate of hospital admissions by 19% (95% CI, 4.0%–31.0%; $P = .014$). Although the incidence of severe anemia (packed cell volume of <25%) did not differ significantly between the 2 groups (protective effect, 12.7% [95% CI, –17.3% to 35.1%]; $P = .36$), there was a significant reduction in hospital admissions for anemia during the month after dosing for both the first and second dose. The serological responses to EPI vaccines were not modified by the intervention.

Conclusions. IPTi with SP has been shown to moderately reduce the incidence of clinical malaria in Mozambican infants without evidence of rebound after stopping the intervention or of interactions with EPI vaccines. Its recommendation as a malaria control strategy in Mozambique needs to be balanced against the scarcity of affordable control tools and the burden of malaria in children.

Malaria caused by *Plasmodium falciparum* continues to be one of the main killers of children in sub-Saharan Africa. Conservative figures estimate that between 25% and 30% of deaths in children <5 years old can be attributed to malaria [1].

Although it is associated with protection from ma-

laria episodes and death [2], malaria chemoprophylaxis in children may also result in the loss [3] or delay the acquisition [4, 5] of immunity. This may lead to a period of increased episodes of clinical malaria after the cessation of the intervention [2]. The relevance of this rebound still needs to be established, although a recent

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Registry's URL, <http://clinicaltrials.gov>; trial registration number, NCT00209795.

analysis of a long term follow-up of a chemoprophylaxis trial in Tanzania in which infants received weekly Deltaprim suggested that the net effect of the intervention was a reduction in episodes of severe malaria and anemia (J.J.A., C.M, D. Schellenberg, E. Kahigwa, H. Mshinda, P. Vounatsou, M. Tanner, P.L.A., unpublished data). However, despite this reassuring effect, fears of promoting the spread of resistance and the costs and low feasibility of the long-term administration of chemoprophylaxis to large populations makes it an unattractive option for widespread malaria control.

With the aim of retaining some of the protective effects of chemoprophylaxis without compromising the development of immunity to malaria, the use of malaria drugs during the first year of life was explored in Tanzania [6]. This approach, which is commonly referred to as “intermittent preventive treatment” (IPT), consists of the provision of treatment doses of antimalarials, irrespective of the presence of parasites or symptoms. IPT in infants (IPTi), delivered through the Expanded Program on Immunization (EPI), has the potential to become a major tool for malaria control in Africa, because IPTi would be administered at the time of routine childhood vaccination.

The intermittent administration of sulfadoxine-pyrimethamine (SP) to Tanzanian infants during the first year of life through the EPI scheme was shown to halve the risk of both malaria and anemia in this target group [6]. On the basis of the first Tanzanian findings, a consortium of independent research groups, together with UNICEF and the World Health Organization (WHO), was established to further evaluate IPTi

[7]. The present trial was conducted within the auspices of the IPTi Consortium. We describe a randomized, placebo-controlled, double-blind study in Mozambican infants of IPTi with SP, delivered alongside routine EPI vaccinations at the ages of 3, 4, and 9 months, in a setting with moderate perennial malaria transmission.

SUBJECTS AND METHODS

Study area and population. The trial was conducted at the Centro de Investigação em Saude da Manhiça (CISM), Manhiça District (Maputo Province), in southern Mozambique. Adjacent to CISM is the Manhiça Health Center, a 110-bed referral health-care facility that provides curative and preventive services. The characteristics of the area have been described in detail elsewhere [8]. The climate is subtropical, with a warm rainy season from November to April and a cool dry season during the rest of the year. Perennial malaria transmission is mostly due to *Plasmodium falciparum*. *Anopheles funestus* is the main vector, and the estimated average number of infective mosquito bites per person per year is 38. During the course of the study, first-line treatment for uncomplicated malaria changed from chloroquine to combination therapy with amodiaquine and SP. The most recent data on the efficacy of SP in children in this area showed a combined (early and late) therapeutic efficacy rate of 83%, with an in vivo parasitological sensitivity of 83.6% at day 14 [9].

Study design. This double-blind, individually randomized,

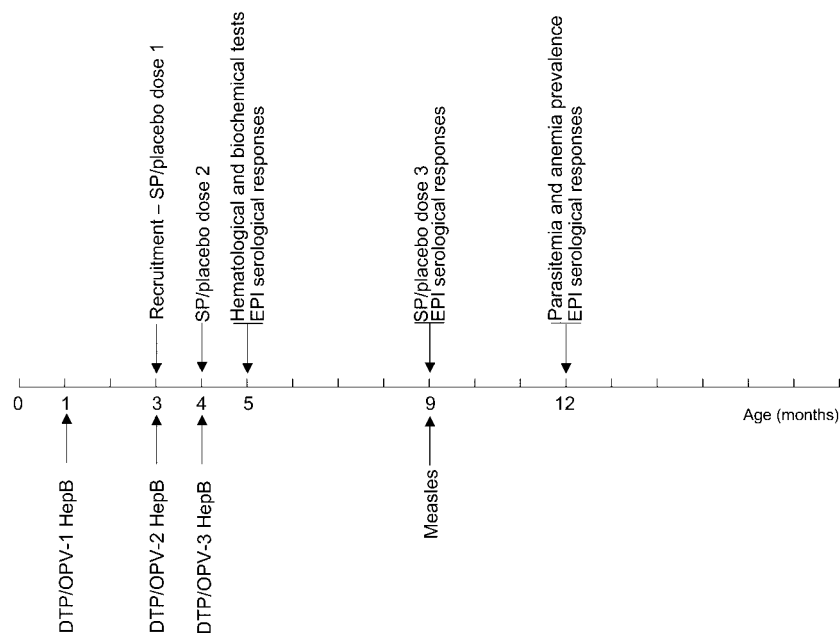


Figure 1. Individual time line. DTP, diphtheria-tetanus toxoid–pertussis vaccine; EPI, Expanded Program on Immunization; HepB, hepatitis B vaccine; OPV, oral polio vaccine; SP, sulfadoxine-pyrimethamine.

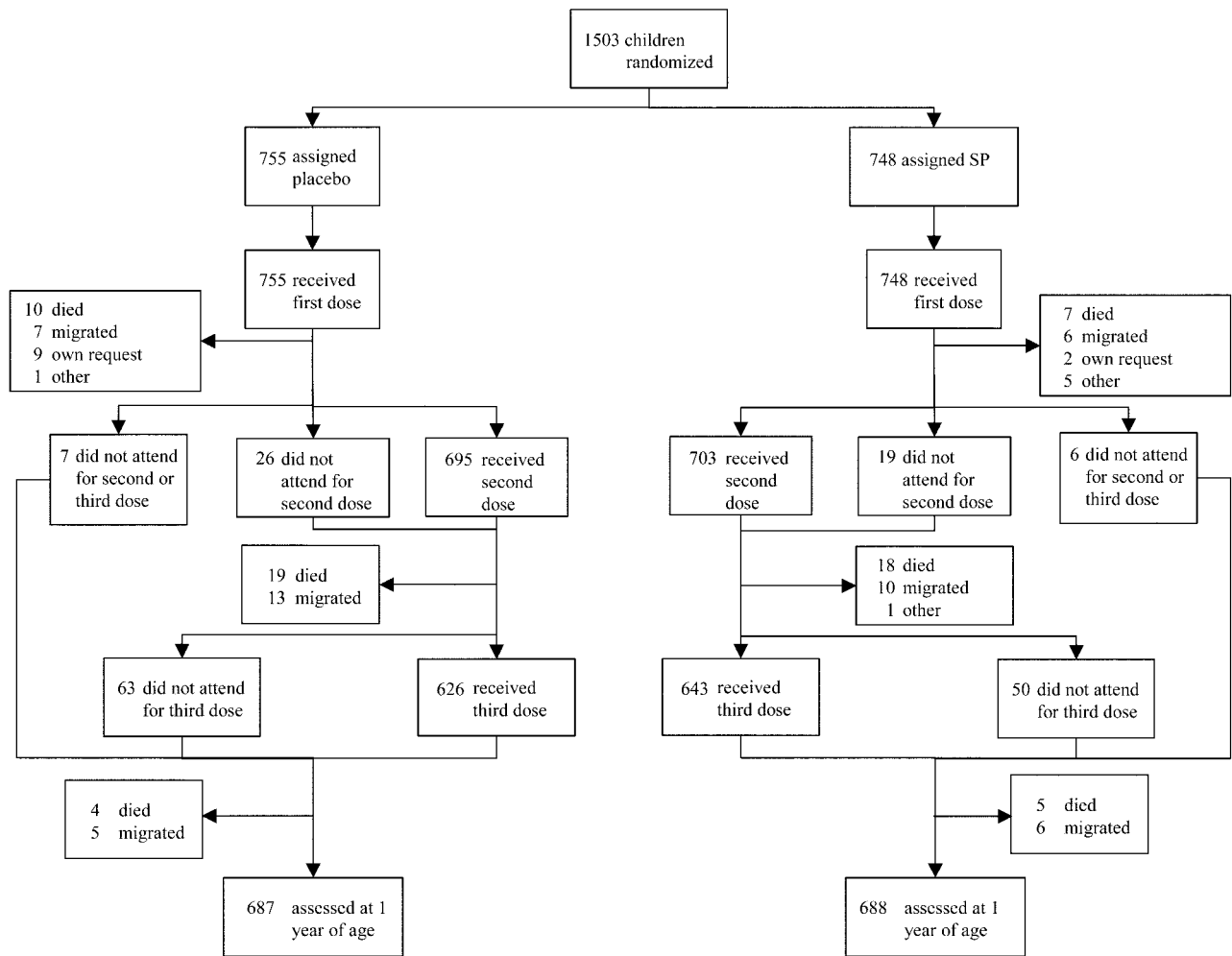


Figure 2. Trial profile. SP, sulfadoxine-pyrimethamine.

placebo-controlled trial had the primary objective of estimating the effect of IPTi—given at 3, 4, and 9 months of age alongside routine EPI vaccinations—on the incidence of clinical malaria during the first year of life. On the basis of available malaria-rate estimates of 0.33 cases/year, a sample size of 1498 was estimated to provide 80% power to detect a 30% reduction in the incidence of clinical malaria in the treatment group, from 0.33 to 0.23 cases/year. The study protocol was approved by the ethics review committees of Mozambique and the Hospital Clinic, Barcelona, Spain.

Enrollment and administration of IPTi. Infants were recruited at the EPI clinics of the Manhiça Health Center and the Maragra Health Post immediately after they received dose 2 of diphtheria-tetanus toxoid–pertussis (DTP)/oral polio (OPV) vaccine between September 2002 and February 2004. Permanent residents of the CISM study area who did not report allergies to sulfa drugs and did not require admission to the hospital were eligible for inclusion. The study was explained to parents/guardians; when they gave written, informed con-

sent, the lowest available study identification number was assigned. A computer-generated sequential list contained the study numbers linked to treatment identification letters, randomly ordered in blocks of 10. Tablets of SP and placebo were identical in shape and color and were stored in 10 bottles labeled only with a single treatment identification letter. Doses of SP or placebo were administered according to body weight (<5 kg, one-quarter tablet; 5–10 kg, one-half tablet; >10 kg, 1 tablet), crushed and mixed with water on a tablespoon. Infants were observed for 30 min, and a repeat dose was administered if vomiting occurred. A computer-generated treatment-allocation list was used by the health assistant to ensure that subsequent doses were administered from the bottle with the same treatment identification letter as the first dose. The dosing regimen was such that the second dose of SP or placebo was administered immediately after dose 3 of DTP/OPV vaccination and the third dose at the time of measles vaccination (figure 1).

Follow-up. Plastic photo cards were produced to facilitate identification at every contact. Parents were encouraged to at-

Table 1. Comparison of study groups.

Parameter	Placebo (n = 755)	SP (n = 748)
Sex, no. (%)		
Male	361 (48)	368 (49)
Female	394 (52)	380 (51)
Used bed net, ^a no. (%)		
Yes	78 (14)	84 (15)
No	465 (85)	463 (84)
No data	3 (1)	1 (0)
Age at first dose, mean ± SD, months	3.3 ± 0.6	3.3 ± 0.6
Age at second dose, mean ± SD, months	4.5 ± 0.7	4.4 ± 0.7
Age at third dose, mean ± SD, months	9.5 ± 0.7	9.4 ± 0.7
Weight-for-age z score at first dose, mean ± SD, months	-0.0 ± 1.2	0.0 ± 1.2
Length-for-age z score at first dose, mean ± SD, months	-0.3 ± 1.1	-0.3 ± 1.2
Weight-for-length z score at first dose, mean ± SD, months	0.0 ± 1.3	0.1 ± 1.4

NOTE. SP, sulfadoxine-pyrimethamine.

^a Non-insecticide-treated nets. Data are for children attending the visit at 12 months of age (557 received placebo and 560 received SP).

tend the outpatient clinic at the Manhiça Health Center and the Maragra Health Post whenever the child became ill. An around-the-clock hospital-based clinical surveillance system has been operating in the area since 1997 and has been described in detail elsewhere [10]. In brief, at each consultation, a detailed standardized questionnaire was completed that doc-

umented signs and symptoms. Blood films were prepared for malaria-parasite examination, and the packed cell volume (PCV) was measured if there was a history of fever during the preceding 24 h or if the infant's axillary temperature was $\geq 37.5^{\circ}\text{C}$. Episodes of uncomplicated malaria in study infants were treated with 7 days of oral quinine if the IPTi intervention had been administered within the preceding 2 weeks. Besides the passive case-detection surveillance, the assessment of safety was conducted through home visits to assess morbidity 1 week after each dose, through specific registration of dermatological complaints of children attending the hospital and through blood tests performed 1 month after receipt of the second IPTi dose.

Blood samples were collected 1 month after the second dose of SP or placebo for the assessment of potential hematological and liver toxicity [11]. Total and differential white-blood-cell, platelet, and red-blood-cell counts and indices and alanine aminotransferase, bilirubin, and creatinine levels were measured in 1 mL of capillary blood collected by fingerprick. PCV and *P. falciparum* parasitemia were measured in capillary samples collected when infants were 12 months old.

Serological responses to EPI vaccines were assessed in a subsample of study infants consecutively selected as they were coming to the clinic until the estimated sample size of 600 children was completed. Antibodies to DTP, OPV, and hepatitis B were assessed when infants were 5 months old, and antibodies to measles were assessed when infants were 9 and 12 months old.

Laboratory methods. Thick and thin blood films were stained and read according to standard quality-control procedures [12]. PCV was measured in a microcapillary tube after centrifugation for 5 min at 9000 g. Biochemical parameters

Table 2. Hematological and biochemical parameters 1 month after dose 2.

Parameter	Placebo		SP		P
	No. of subjects	Mean ± SD	No. of subjects	Mean ± SD	
Bilirubin, $\mu\text{mol/L}$	341	8.8 ± 6.9	355	8.1 ± 4.0	.412
ALT, U/L	574	23.1 ± 14.1	602	24.0 ± 17.8	.155
Creatinine, mmol/L	341	30.8 ± 4.2	358	30.9 ± 4.6	.373
WBCs, no. $\times 10^9/\text{L}$	564	11.0 ± 3.4	582	10.7 ± 3.2	.119
RBCs, no. $\times 10^9/\text{L}$	564	4.47 ± 0.57	582	4.52 ± 0.51	.037
Hemoglobin, g/L	564	99.2 ± 11.9	582	100.4 ± 11.7	.258
PCV, %	564	31.9 ± 3.5	582	32.2 ± 3.2	.350
MCV, fl	564	73.1 ± 29.3	582	72.6 ± 26.6	.246
MCH, pg	564	22.4 ± 2.5	582	22.3 ± 2.6	.801
MCHC, g/L	564	310.8 ± 21.2	582	312.1 ± 22.9	.178
Platelets, no./L	564	445.4 ± 190.4	582	436.0 ± 161.9	.656
Lymphocytes, no. $\times 10^9/\text{L}$	562	6.7 ± 2.1	580	6.7 ± 2.5	.308
Neutrophils, no. $\times 10^9/\text{L}$	293	3.5 ± 1.9	281	3.4 ± 2.0	.248
RDW, fl	563	40.3 ± 9.3	581	39.1 ± 9.1	.010

NOTE. ALT, alanine aminotransferase; fl, femtomoles; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration; MCV, mean corpuscular volume; PCV, packed cell volume; RBC, red blood cells; RDW, red-blood-cell distribution width; SP, sulfadoxine-pyrimethamine; WBC, white blood cells.

Table 3. Serological responses to Expanded Program on Immunization vaccines.

Vaccine	Placebo, % (no. protected/total no.)	SP, % (no. protected/total no.)	Equivalence, % (95% CI)	P ^a
Tetanus	98.8 (244/247)	99.2 (261/263)	-0.45 (-2.8 to 1.6)	<.001
Diphtheria	98.8 (327/331)	97.3 (320/329)	1.5 (-0.0 to 4.0)	<.001
Polio 1	92.0 (230/250)	91.2 (227/249)	0.8 (-4.2 to 5.9)	<.001
Polio 3	89.6 (224/250)	86.7 (216/249)	2.9 (-2.9 to 8.7)	.008
Hepatitis B	96.4 (241/250)	96.7 (237/245)	-0.3 (-3.8 to 3.1)	<.001
Measles	94.6 (261/276)	92.9 (261/281)	1.7 (-2.5 to 5.9)	.059

NOTE. Protective antibody levels were defined as 0.1 IU/mL for diphtheria and tetanus toxoids, 10 mIU/mL for hepatitis B, 1 and 8 IU/mL for polio 1 and 3, and 120 mIU/mL for measles. CI, confidence interval; SP, sulfadoxine-pyrimethamine.

^a Test of noninferiority (*P* values mean the probability of not being truly different), for 5% difference for measles and 10% for all other antigens.

were measured in a dry biochemistry photometer (VITROS DT II; Orto Clinical Diagnostics). Hematological tests were performed using a Sysmex KX-21N cell counter (Sysmex).

Antibodies to diphtheria toxoid, tetanus toxoid, and pertussis antigens (toxoid and filamentous hemagglutinin) were measured using in-house ELISAs calibrated against international standard sera. Antibodies to hepatitis B surface antigen were measured using a commercial quantitative ELISA (Enzygnost Ant-HBs II; Dade-Behring). Antibodies to polio were measured by microneutralization test and to measles by plaque-reduction neutralization (PRN) assays. Serological analysis was done at the Health Protection Agency, London, United Kingdom.

Data management, definitions, and statistical methods.

Data were double-entered with weekly range and internal consistency checks performed. The analysis proceeded according to an analytical plan drawn up before data were unblinded.

An episode of clinical malaria was defined as an axillary temperature of $\geq 37.5^{\circ}\text{C}$ together with asexual *P. falciparum* parasitemia of any density. The sensitivity and specificity of this definition are $\sim 100\%$ and 84% , respectively, in infants and 100% and 79.4% in children 1–4 years old [13]. Severe anemia was defined as a PCV of $<25\%$, and severe malaria was defined according to WHO guidelines [14].

The primary efficacy analysis was based on intent-to-treat protocols and included all randomized children. Cox regression models were used to estimate the risk of the first or only episode of clinical malaria during the period starting from recruitment and ending at 1 year of age or censoring because of withdrawal or death. The protective effect (PE) was estimated from the hazard ratio (HR) as $\text{PE} = 100(1 - \text{HR})\%$. The effect of time on efficacy since dose 1 was estimated using a time-versus-treatment interaction in a Cox time-dependent model. The function of time was selected from a predefined set of 1-degree fractional polynomial functions of the time (-2 , -1 , -0.5 , \ln , 0.5 , 1 , 2 , and 3), using Akaike's criterion. Secondary analyses included assessments of multiple episodes of malaria and admissions to the hospital, using Poisson regression models with random effects to take into account between-child heterogeneity. Children were not considered to be at risk for 28 days after the start of each episode of clinical malaria. Secondary analyses were performed that included only children who had completed 3 doses of SP or placebo and that considered time at risk with respect to randomization. The objective of these analyses was to evaluate the effect of noncompliance on the efficacy estimates derived from the main primary analysis. Nutritional indices were generated using the growth reference

Table 4. Mean geometric titers (GMTs) for Expanded Program on Immunization vaccines.

Vaccine	Placebo, GMT (95% CI)	SP, GMT (95% CI)	Ratio (95% CI)	P
Tetanus	5.46 (4.64–6.42)	4.89 (4.24–5.63)	0.90 (0.72–1.11)	.312
Diphtheria	1.66 (1.52–1.82)	1.62 (1.44–1.82)	0.98 (0.84–1.13)	.754
Pertussis FHA	30.1 (26.9–33.7)	29.3 (26.5–32.3)	0.97 (0.84–1.00)	.717
Pertussis toxin	184 (157–217)	147 (121–178)	0.80 (0.62–1.02)	.075
Hepatitis B	1068 (820–1391)	1124 (864–1462)	1.05 (0.72–1.51)	.786
Measles	978 (827–1158)	941 (791–1121)	0.96 (0.81–1.33)	.756

NOTE. CI, confidence interval; FHA, filamentous hemagglutinin antibodies; SP, sulfadoxine-pyrimethamine.

Table 5. Incidences of outpatient attendances and hospital admissions for relevant clinical outcomes during the month after the first and second dose.

Outcome	Placebo			SP			RR (95% CI)	P
	Episodes, no.	PYAR	Incidence	Episodes, no.	PYAR	Incidence		
Outpatient attendances during the month after dose 1								
Chest indrawing	42	61.8	0.679	24	62.1	0.387	0.57 (0.34–0.94)	.025
Splenomegaly	16	62.8	0.255	1	63.2	0.016	0.06 (0.01–0.47)	<.001
Admissions								
Cough								
During the month after dose 1	30	62.1	0.483	13	62.5	0.208	0.43 (0.22–0.83)	.008
During the month after dose 2	32	57.5	0.556	9	59.2	0.152	0.27 (0.13–0.57)	<.001
Chest indrawing during the month after dose 1	20	62.5	0.320	9	62.7	0.143	0.45 (0.20–0.99)	.038
Splenomegaly during the month after dose 1	6	63.3	0.095	1	63.1	0.016	0.17 (0.02–1.39)	.047
Anemia								
During the month after dose 1	14	63.0	0.222	4	63.0	0.064	0.29 (0.09–0.87)	.015
During the month after dose 2	19	58.0	0.327	3	59.4	0.051	0.15 (0.05–0.52)	<.001
Diarrhea	11	58.3	0.189	1	59.4	0.017	0.09 (0.01–0.69)	.002

NOTE. CI, confidence interval; PYAR, person-years at risk; RR, relative risk; SP, sulphadoxine-pyrimethamine.

of the US Centers for Disease Control and Prevention [15]. Throughout the present article, the figures in parentheses following rate ratios (RRs) and PEs are 95% confidence intervals (CIs).

A noninferiority test was done to reject the null hypothesis that IPTi reduces the prevalence of serological responses by $\geq 10\%$ for DTP, polio, and hepatitis B and by $\geq 5\%$ for measles antibodies. Noninferiority test and 95% CIs for the equivalence were calculated using StatXact (version 6.2; Cytel). Geometric mean titers (GMTs) and the proportion of children with pro-

tective antibody concentrations for each antigen were calculated by intervention group. The analysis of measles excluded children who attained protective antibody levels before vaccination.

RESULTS

A total of 1503 infants were randomized to receive either SP or placebo at the time of their second DTP/hepatitis B and third OPV vaccinations at 3 months of age. The trial profile (figure 2) shows that 1375 (91%) of recruited children com-

Table 6. Incidences of the main outcomes during the first year of life.

Outcome	Placebo			SP			Protective efficacy, % (95% CI)	P
	Events	PYAR	Rate	Events	PYAR	Rate		
Malaria								
First or only episode of clinical malaria	191	447.4	0.43	157	470.7	0.33	22.2 (3.9–37.0)	.020
All episodes of clinical malaria	276	498.5	0.55	221	505.6	0.44	22.6 (1.6–39.2)	.036
First or only episode with >500 parasites/ μ L	169	457.4	0.37	135	478.9	0.28	24.0 (4.7–39.4)	.017
First or only episode with >2500 parasites/ μ L	161	461.6	0.35	129	481.8	0.27	23.6 (3.7–39.4)	.022
First or only episode with >15,000 parasites/ μ L	136	472.4	0.29	105	491.6	0.21	26.4 (5.1–42.9)	.018
Severe anemia (PCV of <25%)	93	483.8	0.19	83	494.1	0.17	12.7 (–17.3 to 35.1)	.366
Other								
Outpatient visits	2771	518.4	5.34	2767	520.9	5.31	1.0 (–5.0 to 4.0)	.814
Hospital admissions	312	517.5	0.60	255	520.2	0.49	19.0 (4.0–31.0)	.014

NOTE. CI, confidence interval; PCV, packed cell volume; PYAR, person-years at risk; SP, sulfadoxine-pyrimethamine.

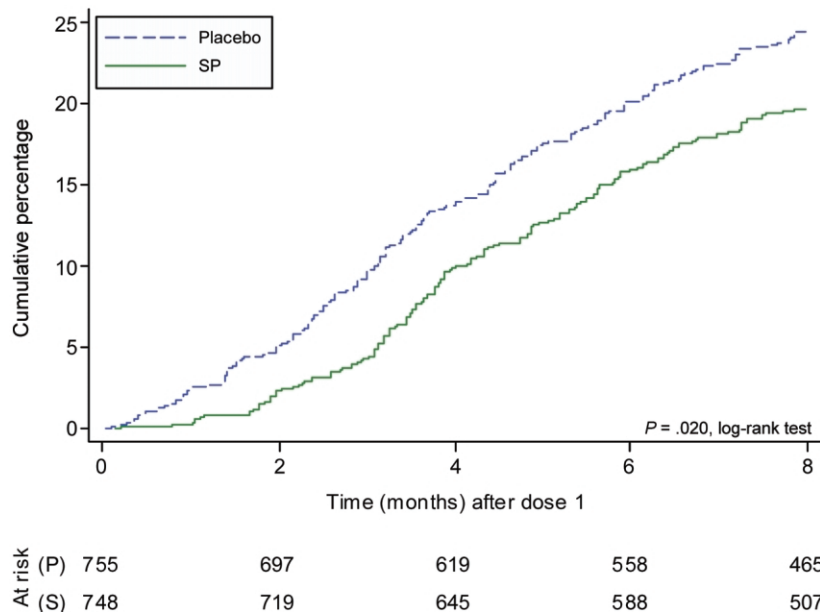


Figure 3. Intent-to-treat cohort—first or only episodes of clinical malaria from first dose until 12 months of age. SP, sulfadoxine-pyrimethamine; (P), placebo group; (S), SP group.

pleted the first year of follow-up. The groups were similar in terms of baseline characteristics and age at the time of each treatment (table 1). Overall, 1224 (81%) of children received all 3 doses of SP or placebo, and an additional 60 (4%) received dose 1 only, 61 (4%) received doses 1 and 2 only, and 45 (3%) received doses 1 and 3 only.

Safety and morbidity. The frequency of vomiting after each dose was low (<2%) and was similar in each group. Other than red-blood-cell counts, which were higher in the SP group than in the placebo group, and the red-blood-cell distribution width, which was lower in the SP group than in the placebo group, there were no statistically significant differences in mean values or in the percentage of abnormal values for any of the hematological and biochemical parameters analyzed 1 month after the second dose of SP or placebo (table 2). No severe skin reactions were reported for any child at any time of the follow-up. Although the numbers of deaths (figure 2) and outpatient attendances (placebo, 5.34/person-years at risk [PYAR]; SP, 5.31/PYAR [RR, 0.99 {95% CI, 0.94–1.05}]; $P = .81$) were similar in the 2 groups, children who received SP had significantly fewer admissions to the hospital than did children who received placebo (RR, 0.81 [95% CI, 0.69–0.96]; $P = .014$). After vaccination, there were no significant differences either in the percentage of children who had serological responses to the EPI vaccines or in antibody GMTs (tables 3 and 4).

Comparisons were made of the rates of presentation to the health-care facility with common signs, symptoms, and diagnoses during the month after each dose and during all time at risk. The only significant differences associated with SP were

concentrated in the month after each of the first 2 doses (table 5). These consisted of a reduction in presentations with cough (during the month after dose 1, RR of 0.43 [95% CI, 0.22–0.83], $P = .008$; during the month after dose 2, RR of 0.27 [95% CI, 0.13–0.57], $P < .001$), chest indrawing (during the month after dose 1, RR of 0.45 [95% CI, 0.20–0.99]; $P = .038$), splenomegaly (during the month after dose 1, RR of 0.17 [95% CI, 0.02–1.39]; $P = .047$), anemia (during the month after dose 1, RR of 0.29 [95% CI, 0.09–0.87], $P = .015$; during the month after dose 2, RR of 0.15 [95% CI, 0.05–0.52], $P < .001$), and diarrhea (during the month after dose 2, RR of 0.09 [95% CI, 0.01–0.69], $P = .002$). With regard to outpatient attendance, there was a reduced risk of children presenting with chest indrawing (RR, 0.57 [95% CI, 0.34–0.94]; $P = .025$) or with splenomegaly (RR, 0.06 [95% CI, 0.01–0.47]; $P < .0001$) during the month after dose 1.

Efficacy of IPTi with SP during the first year of life. Table 6 shows the effect of IPTi SP on various end points. First or only episodes of clinical malaria were reduced by 22.2% (95% CI, 3.7%–37.0%; $P = .020$) in the primary analysis. A malaria case definition that used increased parasite density cutoffs increased this estimate. The effect of SP on clinical malaria declined significantly with time after dosing ($P = .03$). There were 29 episodes of severe malaria in the placebo group and 26 in the SP group (PE, 11.2% [95% CI, –50.8% to 47.7%]; $P = .66$). The incidence of severe anemia up to 1 year of age did not differ significantly between the 2 groups (PE, 12.7% [95% CI, –17.3% to 35.1%]; $P = .36$). There were 8 cases of life-

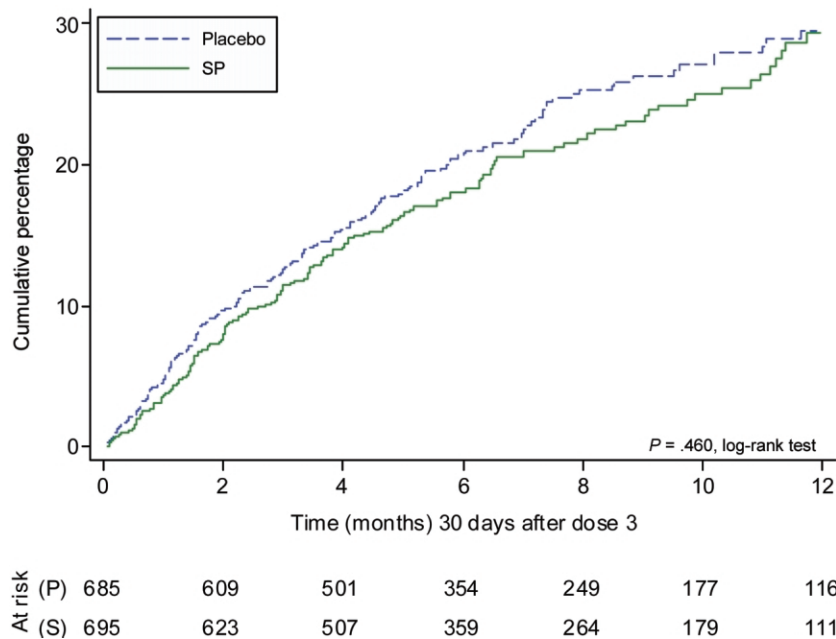


Figure 4. Intent-to-treat cohort—from 30 days after dose 3 until end of follow-up. SP, sulfadoxine-pyrimethamine; (P), placebo group; (S), SP group.

threatening anemia (PCV of <15%): 5 in placebo recipients and 3 in SP recipients ($P = .47$).

Figure 3 shows the Kaplan-Meier survival curves for clinical malaria up to 1 year of age. Figure 4 demonstrates the equivalent survival curve for the period beginning 1 month after dose 3 up to the end of follow-up, and it shows that the incidence of clinical malaria does not increase after the discontinuation of IPTi. Secondary analysis of only children who received all 3 doses of SP or placebo yielded similar estimates of protective efficacy (data not shown).

Except for a lower prevalence of fever in the SP group at 12 months of age (3% vs. 5%; $P = .03$), anthropometric indices, sexual and asexual *P. falciparum* parasitemia, and anemia were similar at the cross-sectional survey conducted when infants were 12 months old (data not shown).

DISCUSSION

IPTi with SP in Mozambican infants administered at 3, 4, and 9 months of age, alongside routine vaccinations, was safe and well tolerated. The incidence of clinical malaria was reduced by 22.2%, and the number of hospital admissions was reduced by 19%. Increasing the specificity of the case definition increased the PE against clinical malaria to 26.4% for parasite densities of >15,000 parasites/ μL . There was a significant reduction in hospital admissions for anemia during the month for both the first and second dose. However, we did not find a significant effect on the incidence of severe anemia (PE, 12.7%; $P = .36$) or on severe malaria (PE, 11.2%; $P = .66$).

There was no evidence of increase in episodes of clinical malaria after the discontinuation of IPTi.

A lack of effect on anemia was also observed in a recent malaria vaccine trial performed in the same area, despite a 30% reduction in episodes of clinical malaria [16]. This lack of impact on anemia of protection against malaria might be explained by malaria being a less important cause of anemia in infants in Manhica. This might have become manifested in the absence of control of probably more important etiologies, such as iron deficiency. The safety assessment at 5 months of age that included the measurement of hematological parameters, and therefore resulted in the treatment of children with a PCV of <25% with hematinics, may have diluted the effect of the intervention.

Safety has been a special concern with regard to the use of SP. Most of the information reported on adverse effects associated with SP has referred to Western travelers who received multiple high doses of SP as prophylaxis [11]. Although all reported adverse drug reactions have been in adults, there is very limited safety information on the use of SP in children and infants. The results of a small series of newborns ($n = 78$) with congenital toxoplasmosis who were treated with SP fortnightly for 2 years suggested that the long-term regimen was well tolerated [17]. Because the rate of adverse reactions to SP would depend on the frequency of doses received, it could be speculated that this should be lower when it is administered as IPTi 3 times, compared with regular prophylaxis. The absence of reported serious adverse reactions associated

with IPT during pregnancy would support this view [18]. We did not find any skin reactions or abnormal analytical parameters that could be related to the administration of SP. These findings are reassuring and in the line with what we have previously reported [6]. Additional safety information from ongoing studies is being compiled by the IPTi Consortium and will help to enrich the limited safety data on SP for African children.

The reduction in all-cause hospital admissions was similar to the observed reduction in episodes of clinical malaria. This may be explained by a reduced incidence of malaria accompanied by a reduction in associated morbidity. An alternative explanation may be that SP has a direct effect on nonmalaria morbidity, mainly by acting as an antibiotic, as is reflected in the reduction of presentations with respiratory or gastrointestinal symptoms [19]. Although it is unclear what the impact of this biologically plausible effect of SP may be on the overall health of children, it needs to be further explored in other studies and should also be considered when making decisions about the use of IPTi.

The main comparative advantage of IPTi over other modes of delivery for malaria control is its integration within the EPI scheme. This requires that any potential interaction with serological responses to EPI vaccines must be ruled out before a policy recommendation can be made. Evidence from the previous Tanzanian trial suggested that SP affected the serological responses to EPI vaccines [6]. We did not find any significant difference in GMTs, in the rates of serological responses to DTP/OPV and hepatitis B, or in seroconversion rates to measles. These results are very reassuring with regard to all EPI antigens. With regard to the serological response to measles, the study had little statistical power to rule out noninferiority at the 5% level. However, further information is being gathered from other IPTi trials, and a pooled analysis of these trials is planned to confirm the safety of the intervention with regard to measles.

A possible policy recommendation on IPTi for sub-Saharan Africa will be based on evidence being gathered by the international IPTi Consortium to evaluate the applicability of the intervention. Until that time, in light of the present results, should IPTi with SP be implemented in Mozambique for malaria control? It might be argued that the level of efficacy is too modest for an intervention to be implemented in the context of limited resources. However, this should be counterbalanced first with the burden of disease, second with the cost of the intervention, and finally with the general situation of limited tools for malaria control. With regard to the first point, data on the malaria burden among children in Mozambique is sufficiently worrying to suggest the need for urgent action, with >50% of hospital admissions and >25% of deaths due to malaria. With regard to the cost of the intervention, this is limited to the cost of the drug itself. In a situation such as that in

Mozambique, where >50% of the population does not have access to standard health care, the EPI system becomes the only functional and accessible health-care structure through which malaria control tools can be delivered.

Presumptive treatment of malaria is needed but is far from reducing the burden of disease and death [20, 21] and has been associated with major increases in drug pressure and cost. Insecticide-treated bed nets (ITNs) are a cost-effective malaria control tool [22], but their wide implementation has been obstructed by political and public debate. Efforts to solve these problems for the wide implementation of ITNs should continue while other strategies—such as IPTi—continue to be evaluated and potentially combined with ITNs.

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