

Seasonal intermittent preventive treatment with artesunate and sulfadoxine-pyrimethamine for prevention of malaria in Senegalese children: a randomised, placebo-controlled, double-blind trial

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Summary

Background In the Sahel and sub-Saharan regions of Africa, malaria transmission is highly seasonal. During a short period of high malaria transmission, mortality and morbidity are high in children under age 5 years. We assessed the efficacy of seasonal intermittent preventive treatment—a full dose of antimalarial treatment given at defined times without previous testing for malaria infection.

Methods We did a randomised, placebo-controlled, double-blind trial of the effect of intermittent preventive treatment on morbidity from malaria in three health-care centres in Niakhar, a rural area of Senegal. 1136 children aged 2–59 months received either one dose of artesunate plus one dose of sulfadoxine-pyrimethamine or two placebos on three occasions during the malaria transmission season. The primary outcome was a first or single episode of clinical malaria detected through active or passive case detection. Primary analysis was by intention-to-treat. This study is registered with ClinicalTrials.gov, number NCT00132561.

Findings During 13 weeks of follow-up, the intervention led to an 86% (95% CI 80–90) reduction in the occurrence of clinical episodes of malaria. With passive case detection, protective efficacy against malaria was 86% (77–92), and when detected actively was 86% (78–91). The incidence of malaria in children on active drugs was 308 episodes per 1000 person-years at risk, whereas in those on placebo it was 2250 episodes per 1000 person-years at risk. 13 children were not included in the intention-to-treat analysis, which was restricted to children who received a first dose of antimalarial or placebo. There was an increase in vomiting in children who received the active drugs, but generally the intervention was well tolerated.

Interpretation Intermittent preventive treatment could be highly effective for prevention of malaria in children under 5 years of age living in areas of seasonal malaria infection.

Introduction

According to the World Health Organization, 90% of deaths from malaria are in Africa and mostly in children under 5 years of age.¹ Efforts to control this disease in Africa have been hindered by the spread of resistance to chloroquine and, more recently, to sulfadoxine-pyrimethamine.^{2,3} In Senegal, the yearly mortality rate from malaria in children has increased substantially since the beginning of the 1990s.⁴ This rise, associated with the emergence of chloroquine resistance, has been recorded in three regions of the country with different rates of malaria endemicity.⁵ The loss of effective and affordable drugs for the treatment of malaria has focused attention not only on the need for new antimalarial drugs,⁶ but also on the need for new ways to prevent infection, especially in children under 5 years.

Several studies have shown that African children can be protected effectively from the consequences of malaria by chemoprophylaxis, with use of anti-malarial drugs on a regular basis, sometimes in a subtherapeutic dose.^{7–11} In The Gambia, a pyrimethamine-dapsone combination taken fortnightly during the malaria transmission season

reduced overall mortality in children by about 35%.¹¹ However, this approach to malaria control is difficult to sustain and there have been concerns that it would contribute to the spread of drug resistance.¹²

Intermittent preventive treatment differs from chemoprophylaxis because members of an at risk population are given a full therapeutic dose of treatment at set times, whether or not they are known to be infected. By contrast with chemoprophylaxis, drug concentrations might fall below parasite inhibitory concentrations between drug administrations. Such preventive treatment was first shown to be an effective approach for the control of malaria in pregnant women. In Malawi, this treatment method with sulfadoxine pyrimethamine reduced placental malaria by 72%.¹³ Subsequent studies have shown the beneficial effect of such treatment on severe anaemia in pregnant women and on the incidence of low birthweight.^{14,15}

A similar approach has been adapted to the prevention of malaria in infants in two studies in areas of Tanzania where disease transmission is perennial.^{16,17} The frequencies of clinical episodes of malaria and anaemia

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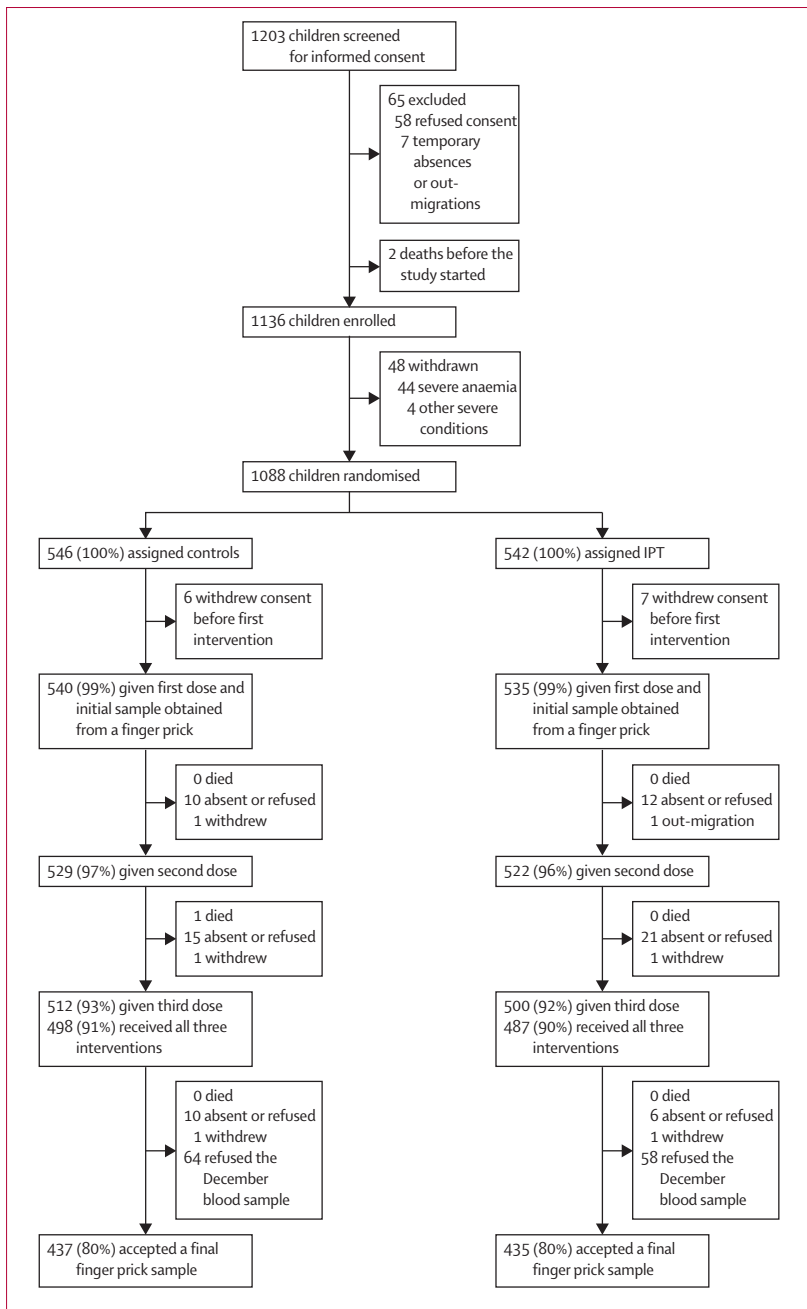


Figure 1: Trial profile

were reduced by about two-thirds. Intermittent treatment has also been investigated in older children, with some success.^{18–20}

In the Sahel and sub-Saharan regions of Africa, which have a population of around 200 million, malaria transmission is highly seasonal and a high proportion of malaria deaths and admissions to hospital with severe malaria are in children older than 1 year.^{21,22} In such situations, a successful programme of intermittent preventive treatment restricted to infants is likely to have

only a modest effect on the overall burden of mortality and morbidity from malaria, and protection of older children is required. We have, therefore, studied the potential role of such treatment for the control of malaria in older children in a rural community.

The study was done in Niakhar, a rural district in central Senegal,²³ where the mortality rate for children under 5 years of age is 40 deaths per 1000 children per year. Malaria accounts for about a quarter of deaths in those aged 1–5 years.^{24,25} Malaria transmission is highly seasonal (from August to October) with an average entomological inoculation rate of ten infective bites per person per year;²⁶ a substantial proportion of children are parasitaemic at the end of the malaria transmission season.²⁷

Methods

Patients and study design

An individually-randomised, double-blind, placebo-controlled trial of seasonal intermittent preventive treatment with one dose of artesunate and one dose of sulfadoxine-pyrimethamine, given on three occasions during the malaria transmission season, was undertaken in 1203 Senegalese children aged 2–59 months. Ethical approval for the study was obtained from the ethics review boards of the Senegalese Ministry of Health and London School of Hygiene & Tropical Medicine. An independent Data Safety Monitoring Board monitored the trial.

The primary outcome measure was a comparison of the occurrence of clinical malaria between children in the two study groups. An episode of clinical malaria was defined as an illness accompanied by: a temperature of 37.5°C or greater, a history of fever or vomiting within the previous 24 hours, or both; no other obvious cause for the fever or vomiting; and the presence of *P. falciparum* asexual stage parasitaemia at a density of 3000 parasites per µL or more. This parasite density was chosen on the basis of previous studies, which have shown that it is the best cutoff value for attributing a fever episode to malaria in the study area.²⁸

Meetings were held with health authorities and community leaders in the proposed study area to explain the trial objective and the role of participants. 11 of 30 villages in the area were selected for participation in the trial on the grounds of accessibility, size, and interest. The selected villages were visited by the principal investigator and project supervisor. The nature of the trial was explained at a village meeting, and village consent was obtained. Since 1983, a demographic surveillance system has been maintained in the study area. This system is updated every 3 months and all deaths are investigated with a standardised verbal-autopsy questionnaire.

From the most recent censuses for the chosen villages, 1203 children aged 2–59 months were selected randomly by an independent information technology consultant for inclusion in the trial. These children represented about 20% of the total eligible population. The family of each of these children was visited, and oral, witnessed, and

documented informed consent for inclusion of their child in the trial was sought. No investigations were done at this time. 2–3 weeks later, children whose families had consented were visited. At this visit, children were examined and finger-prick blood samples were taken. Children who met one or more of the exclusion criteria, which included severe anaemia, were excluded at this point (figure 1).

The remaining children were randomly assigned by an independent information technology consultant to one of eight treatment groups. Eight rather than two groups were used to make it less obvious to staff and participants who was receiving active drugs. Randomisation of each child to one of the groups A to H was undertaken by the information technology manager who played no part in the analysis of the trial results and was not an investigator. Four of the groups were allocated to active drugs and four to placebo by an independent consultant who supervised the package of active drugs and placebo into appropriately labelled containers. A copy of the treatment allocation code was given to the chairman of the Data Safety and Monitoring Board. None of the investigators had access to the code during the trial; the code was provided to the investigators only after a locked copy of the database had been given to the chairman of the Data Safety and Monitoring Board.

Primary analysis was by intention to treat. After randomisation and before the first treatment was given, the families of 13 children withdrew their consent. These 13 children were not included in the intention to treat analysis, which was restricted to children who received a first dose of antimalarial or placebo.

Children in the active drugs groups received one dose of sulfadoxine-pyrimethamine (sulfadoxine [25 mg/kg] + pyrimethamine [1.25 mg/kg]; Cosmos, Nairobi, Kenya) and one dose of artesunate (4 mg/kg) (Sanofi Synthelabo, Paris, France) once a month for 3 months. Dosage was by weight. According to their age, children received half to one and a half tablets of sulfadoxine-pyrimethamine, and half to one and a half tablets of artesunate. The active tablets and placebos were similar in size and shape. Both artesunate and artesunate placebo tablets were bitter to taste, the active tablets being slightly more bitter than the placebo. The manufacturer provided a certificate of analysis for the artesunate tablets. The solubility and drug content of the sulfadoxine-pyrimethamine tablets was confirmed by analysis with high performance liquid chromatography at the London School of Hygiene & Tropical Medicine, which was also used after the trial to confirm that drugs had been allocated to the correct group in accordance with the randomisation code. Drugs were given in health centres by trained nurses under direct observation. To facilitate drug administration in small children, tablets were crushed on a spoon and given with sweetened water. All participants were kept under observation for 15 minutes after drug intake. If vomiting occurred, the drug was re-administered on one further occasion.

Malaria morbidity was monitored through home visits every week and by detection of study children who presented at one of three health centres in the study area. At each assessment, axillary temperature was measured, and if it was 37.5°C or greater, or if there was a history of fever or vomiting during the previous 24 h, a blood film was prepared. Results of the blood film examination were usually available within 2 h. Antimalarial treatment was given when appropriate according to the national guidelines: chloroquine as first-line treatment, quinine or sulfadoxine-pyrimethamine as second-line treatment in cases of failure of treatment with chloroquine, and injectable quinine for cases with persistent vomiting or severe malaria. Study children received iron supplementation if they presented at a health centre with an illness suggestive of anaemia, pale mucosae, or both.

Two surveys of all the available children in the study cohort were done during year 1. The first survey was done in September, 2002, at the start of the intervention period, and the second in December, 2002, 5 weeks after the last intervention. Blood samples were taken for assessment of parasitaemia, packed-cell volume, and for molecular studies at these times. Assessment for a possible rebound in the incidence of malaria was undertaken during the malaria transmission season in the year after the main trial (August–December, 2003). During the follow-on study, malaria was monitored in the same ways as for the main trial.

Adverse events were monitored by the three field-physicians participating in the project. After each round of intermittent preventive treatment, a random sample of about 300 participants were visited at home within 3 days of being given the drug and physically examined, and their parents were interviewed. Particular attention was given to skin reactions, which was the most severe side-effect likely to be related to sulfadoxine-pyrimethamine. The medical team followed-up participants with adverse experiences until the event was cured or had stabilised. Parents were also strongly advised to inform project staff or to go to the nearest health centre if their child became ill after medication.

Laboratory methods

Parasite densities were estimated in thick blood films, assuming an average white blood-cell count of 8000 per μL . All slides related to acute episodes were read by two laboratory technicians. If there was a discrepancy over positivity between the two readers or parasite density estimations varied by more than 30%, a third senior technician was asked to adjudicate. Their observation provided the definitive finding. Packed-cell volume was measured in a microcapillary tube after centrifugation. DNA was extracted from filter papers with the chelex technique.²⁹ Mutations in the *pfdhfr* and the *pfihps* genes, associated with resistance to pyrimethamine and sulfadoxine, respectively, were identified with sequence

	Control	Active treatment
Age (months)		
6–11	103 (19%)	97 (18%)
12–23	111 (20%)	122 (23%)
24–35	102 (19%)	117 (22%)
36–47	111 (20%)	103 (20%)
48–59	119 (22%)	103 (20%)
Sex		
Girl	274 (50%)	288 (53%)
Boy	272 (50%)	254 (47%)
Village of residence		
Village 1	21 (4%)	12 (2%)
Village 2	49 (9%)	50 (9%)
Village 3	28 (5%)	33 (6%)
Village 4	27 (5%)	30 (6%)
Village 5	47 (9%)	46 (8%)
Village 6	67 (12%)	80 (15%)
Village 7	55 (10%)	42 (8%)
Village 8	96 (18%)	78 (14%)
Village 9	60 (11%)	73 (13%)
Village 10	32 (6%)	28 (5%)
Village 11	64 (12%)	70 (13%)
Nutritional status		
Stunted	122/546 (23%)	135/542 (25%)
Wasted (14 missing values)	33/532 (6%)	50/530 (6%)
Underweight (14 missing values)	104/532 (20%)	117/531 (22%)
Anaemia		
Yes (PCV <25%)	87/520 (16%)	108/502 (22%)
Missing values	26	40
Fever		
Febrile	27/546 (5%)	32/542 (6%)
Prevalence of parasitaemia		
No <i>P falciparum</i>	314/512 (61%)	302/516 (59%)
<i>P falciparum</i> asexual only	128/512 (25%)	119/516 (23%)
<i>P falciparum</i> sexual only	14/512 (3%)	24/516 (5%)
<i>P falciparum</i> sexual and asexual	56/512 (11%)	71/516 (14%)
Missing values	34	26

Table 1: Baseline characteristics of the two study groups

specific oligonucleotide probing, after a method adapted from Pearce and colleagues.³⁰

Statistical analysis

Assuming an incidence of 0.4 malaria episodes per child per transmission season, and allowing for 10% loss to follow-up per year, we calculated that if 540 children were randomly assigned to each group, the study would have 80% power at a 5% level of significance to detect an efficacy of intermittent preventive treatment of 30%, and

over 90% to detect an efficacy of 40%. Children were not judged at risk for 28 days after treatment for a malaria attack. The primary result was unadjusted protective efficacy, defined as 1 minus the rate ratio of the incidence in the treatment group compared with that in the placebo group.

The Kaplan Meier method was used to plot the time to the first malaria attack after intervention. A more stringent test (addition of an interaction term) confirmed that the proportionality assumption needed for Cox regression did not hold for the data. Therefore, we split the period of surveillance into three intervals (first to the second dose, second to the third dose, and after the third dose). χ^2 and prevalence-difference analyses were used for comparisons of the prevalences of *pf_{dhfr}51*, *59*, *108*, and *pf_{dhps}437* mutations associated with resistance to pyrimethamine and sulfonamide, respectively, before and after the transmission season according to randomisation group. All analyses were done with STATA software version 8.2.

Role of the funding source

The sponsor had no role in study design, data collection, data analysis, data interpretation, or the writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

1203 children aged between 6 weeks and 59 months were selected from the Niakhar database, 1136 of whom met the entry criteria (figure 1). 1088 were randomly assigned to the control group (546) or to the intermittent preventive treatment group (542). A high rate of compliance was achieved throughout the trial; 1075 children (99%) received the first dose, 1051 (97%) the second dose, and 1012 (93%) the third dose. Compliance was similar in the two treatment groups. The per-protocol population consisted of 985 children (90%), who took three doses of sulfadoxine-pyrimethamine or placebo and who stayed in the study area throughout the surveillance period. Table 1 shows baseline characteristics of both groups.

Use of bednets was limited in the study population. In the control group, 128 children (23%) slept under a bednet, compared with 116 (21%) in the active treatment group. Bednets were usually in a bad condition and had many holes. Only nine nets were impregnated with insecticide.

261 cases of clinical malaria were included in the intention-to-treat analysis; 39 in the treatment group and 222 in the controls. The incidence of malaria in children on active drugs was 308 episodes per 1000 person-years at risk, whereas in controls it was 2250 episodes per 1000 person-years at risk, giving a protective efficacy of 86% (95% CI 80–90; $p < 0.0001$). 17 children had parasitaemia at the time that the first treatment was given, although this was not known until after treatment. If these

	Incidence of malaria per 1000 child years at risk		Protective efficacy (95% CI)
	Active treatment	Placebo	
First year of observation (age, months)			
2–11	130	2049	94% (79 to 98)
12–23	354	2570	86% (73 to 93)
24–35	480	2161	78% (58 to 88)
36–47	370	2805	87% (73 to 93)
48–59	165	1766	91% (74 to 97)
Second year of observation (age, months)			
14–27	2657	3496	24% (-10 to 47)
28–39	3519	3809	8% (-26 to 42)
40–51	3434	3127	-10% (-54 to 22)
52–63	3437	2948	-17% (-62 to 16)
64–75	2676	2322	-15% (-63 to 19)

Table 2: Protective efficacy of intermittent preventive treatment by age group

	Number of episodes		Protective efficacy (95% CI)
	Treatment	Control	
<i>P. falciparum</i> asexual parasites per μL			
40	96	438	79 (73–82)
2000	52	321	80 (77–84)
3000	39	222	86 (80–90)
4000	39	214	86 (80–90)
5000	37	203	86 (80–90)
25 000	24	120	84 (76–90)
100 000	4	28	89 (68–96)

Table 3: Protective efficacy of intermittent preventive treatment according to the parasite threshold used to define a clinical attack of malaria with an intention-to-treat analysis

children are excluded from the intention-to-treat analysis, protective efficacy increases to 88% (83–92).

With passive case detection, protective efficacy against malaria was 86% (77–92), and when detected actively was 86% (78–91). Excluding 12 children who had parasitaemia and vomiting but no fever, protective efficacy was 87% (81–91). Protective efficacy in children who had parasitaemia at the initial survey was 83% (73–89) compared with 89% (82–94) in those who did not. Efficacy in children who slept under a bednet was 86% (68–94) and in children who did not sleep under a net efficacy was also 86% (81–90).

Table 2 shows the effect of age on protective efficacy. A high rate of efficacy was seen across all age groups. Efficacy persisted when a range of parasite densities was used to define clinical malaria (table 3).

Figure 2 shows the distribution of episodes of malaria over time. The Kaplan Meier plot suggested that the effect of intermittent preventive treatment on the incidence of malaria varied over time (figure 3) and the data were not suitable for Cox regression analysis. Therefore, the effect of the intervention was studied over three arbitrarily defined periods; it differed significantly between these

time intervals ($p < 0.0001$). The protective efficacy was 88% (78–93) for the first 4 weeks, 94% (87–97) for the 4 weeks between the second and third doses, and 61% (31–77) for the 5 weeks after the third dose. Efficacy during the first 4 weeks of the last period of observation was 77% (47–90).

36 children had a second episode of malaria 28 days or more after the first, 35 of these episodes were in the controls. Thus, the total number of malaria episodes in the control group was 257 and in children in the treatment group was 40, giving an overall reduction in malaria morbidity of 91% (87–94) over the 13 weeks of follow-up.

At the end of the initial 2002 surveillance period, the prevalence of *P. falciparum* asexual stage infection was significantly lower in children who had received active drugs than in those who had received placebo (14% vs 37%), a prevalence difference of –23% (–27 to –19%). A similar reduction in *P. falciparum* gametocytes was seen from 19% in the control group to 5% in the treatment group, a prevalence difference of –14% (–18 to –10).

At the end of the intervention period, the prevalence of anaemia (packed-cell volume $< 25\%$) was slightly higher in children who had received placebo (11.8%) than in children who had received active drugs (9.5%) but the difference between groups was not significant ($p = 0.26$).

Inquiries were made about possible side-effects in 315 children after the first dose of treatment had been given, in 307 after the second dose, and in 319 after the third, similar proportions of children in each group being seen. Visits were made on day 1 after treatment on 328 occasions, on day 2 on 308, and on day 3 on 280 with an equal distribution of timing between the two study groups. Vomiting, nervousness, and, to a lesser extent, pruritus were reported more frequently in children in the treatment group than in controls

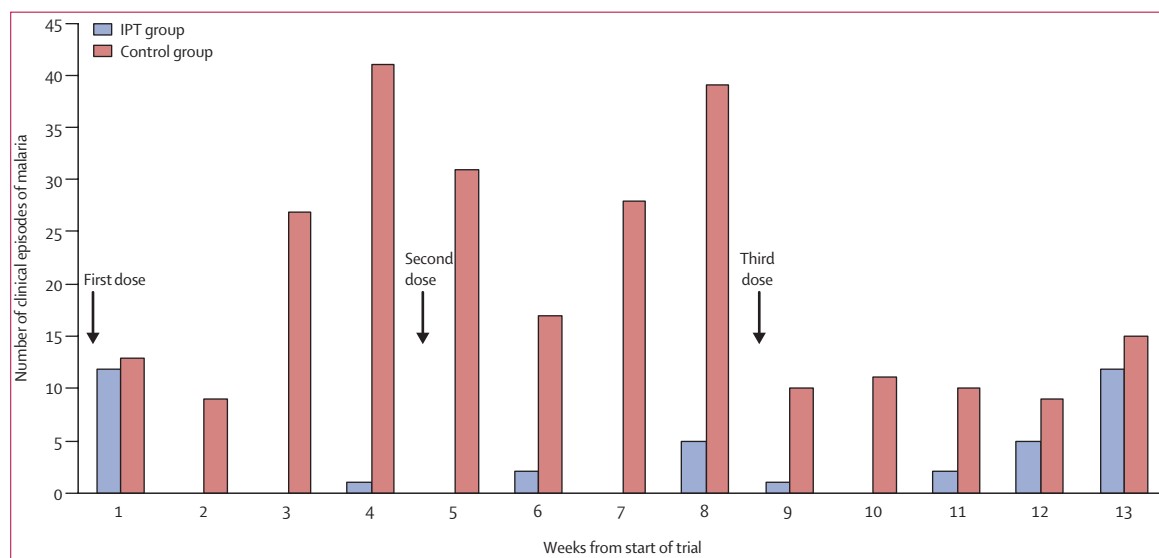


Figure 2: Evolution of clinical episodes of malaria per week by randomisation group

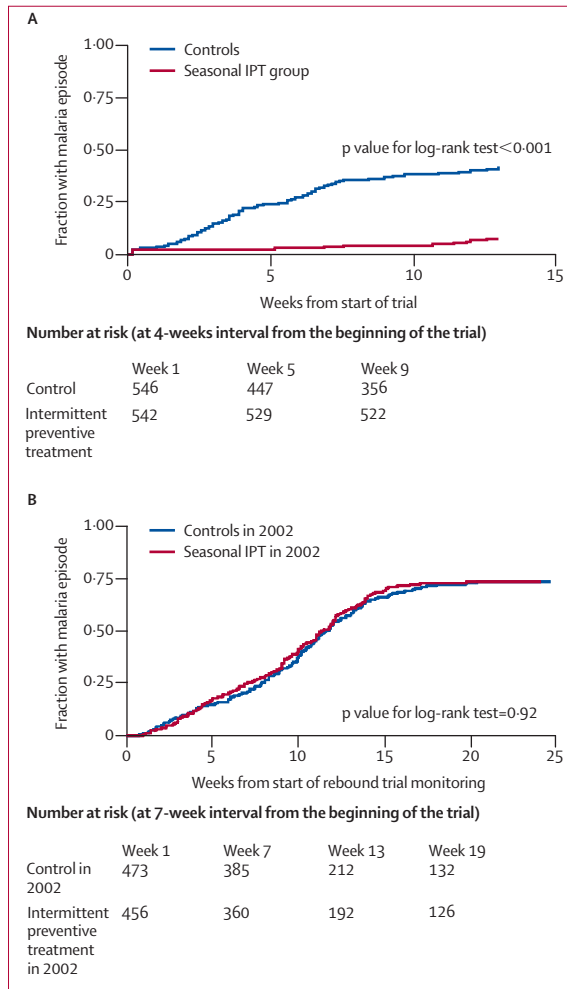


Figure 3: Kaplan Meier curves for time to first clinical episode in the main trial (A) and in the rebound study (B)

(table 4). No severe skin or neurological reactions were reported. One 2-year-old in the control group died from severe malaria.

The prevalences of the triple mutation in the *pfdhfr* gene (codons 51, 59, and 108) and the prevalence of the mutation at codon 437 of the *pfdhps* gene associated with resistance to pyrimethamine and sulphonamides, respectively, were recorded at different points in the study (table 5). The prevalence of each allele in the population was identified pre-intervention with data from children in both placebo and intervention groups and post-intervention with data obtained from children in the placebo group. *Pfdhfr* triple mutant alleles were recorded in 59% (82/140) of parasite-positive children before the intervention, and in 75% (92/122) of parasite positives in the placebo group at the end of the 2002 surveillance period ($p=0.006$). Similarly, *pfdhps*-437G was noted in 29% of parasite-positive children before the intervention, and in 44% (39/89) of parasite positives in the placebo group at the end of 2002 ($p=0.03$).

At the end of the surveillance period the prevalence of parasites with the triple *pfdhfr* mutation was significantly higher in children who had received active drugs (95%) than in those who had received placebo (75%), a prevalence difference of +20% (95% CI 10–30). A similar pattern was seen for the *pfdhps* mutation with a prevalence difference between the two groups at the end of the transmission season of +42% (25–58). However, because the number of parasitaemic children was substantially less in the group who had received active drugs than in those who had received placebo, the total number of children carrying resistant parasites was less in those who had received active drugs than in those who had received placebo (prevalence differences –15% [–25 to –4%] for the *pfdhfr* triple mutation and –4% [–14 to 6%] for the *pfdhps* mutation).

The number of parasites with one or two mutations in the *pfdhfr* gene was much the same in the two study groups before drug treatment. At the end of the intervention there were six single mutations and three double mutations in 122 samples from the placebo group, but no single mutations and two double mutations in 41 samples from the active treatment group (Fisher’s exact test $p=0.33$ for the single mutation in *pfdhfr* and $p=0.66$ for the double mutations).

At the start of the 2003 transmission season, the prevalence of both *pfdhfr* and *pfdhps* resistance markers dropped from those seen at the end of the previous year in children who had previously received active drugs: prevalence difference for *pfdhfr* 19% (95% CI 5–34) and for *pfdhps* 27% (8–46), whereas there was little change in children who had previously received placebo. There was a modest increase in the prevalence of resistance markers during the course of the 2003 surveillance period, which was similar to that seen in children who had received either active drugs or placebo.

929 of the 1008 children initially enrolled (85%) were recruited at the start of the 2003 malaria transmission

	Active treatment n=486	Control n=455	p
Severe skin or neurological reaction	0	0	..
Convulsions	0	1 (0.1%)	0.48*
Nervousness	163 (34%)	110 (24%)	0.002
Pruritus	12 (2%)	3 (0.1%)	0.05*
Minor skin rash	5 (1%)	3 (0.1%)	0.48*
Dizziness	13 (3%)	14 (3%)	0.54
Diarrhoea	33 (7%)	36 (8%)	0.47
Vomiting (after first dose)	8 (0%)	1 (1.6%)	0.14*
Vomiting (after second dose)	31 (6%)	4 (0.9%)	<0.0001*
Vomiting (after third dose)	14 (3%)	1 (0.2%)	0.04*

Adverse events were assessed in a random sample of 315 children seen after the first dose of treatment had been given, in 307 seen after the second dose, and in 319 seen after the third. 328 were seen on the first day after treatment, 308 on the second, and 280 on the third. *Fisher’s exact test.

Table 4: Adverse reactions after 941 random drug administrations in three doses

	Prevalence of parasitaemia* % (n)	Carriage of resistance markers (as % of infections tested)†		Estimated minimum prevalence of resistant parasitaemia ‡	
		dhfr triple mutation % (n)	dhps 437 mutation % (n)	dhfr triple mutation %	dhps 437 mutation %
2002					
Preintervention					
Active drugs	37 (190/516)	51 (36/71)	28 (19/67)	18%	10%
Placebo	36 (184/512)	67 (46/69)	29 (21/72)	24%	10%
Postintervention					
Active drugs	14 (60/440)	95 (39/41)	86 (24/28)	13%	12%
Placebo	37 (165/446)	75 (92/122)	44 (39/89)	28%	16%
2003					
Preintervention					
Previous active drugs	22 (91/412)	76 (34/45)	58 (28/48)	17%	13%
Previous placebo	31 (134/428)	73 (63/86)	43 (36/84)	23%	13%
Postintervention					
Previous active drugs	29 (121/425)	88 (38/43)	64 (41/64)	25%	19%
Previous placebo	30 (130/435)	86 (60/70)	77 (59/77)	26%	23%

*Percentage indicates proportion of children in each treatment group who had asexual stage *P falciparum* parasitaemia at a survey before or after the malaria transmission season.
†Percentages indicate the prevalence of resistance markers among a representative sample of isolates from children positive for *P falciparum* asexual stage parasites by microscopy. Denominators used to calculate the prevalences are the PCR positive samples that yielded a clear genotype. ‡Number obtained by multiplying the prevalence of resistance markers with that of parasitaemia. Indicates the number of children in the population group with resistant parasites.

Table 5: The prevalence of molecular markers of sulphadoxine-pyrimethamine resistance in children who received intermittent preventive treatment with sulphadoxine-pyrimethamine and artesunate or placebo before and after intervention, and at two time points in the year after treatment

season; 891 of these children (96%) were followed-up until the end of the transmission season. No rebound in the incidence of malaria was seen overall in children who had received active drugs the previous year; the incidence ratio was 0.98 (95% CI 0.82–1.17) (figure 3, B). However, a suggestion of an age effect was seen, with children who had received the intervention in the first year of life showing some evidence of persisting protection, whereas this effect was reversed in older children (table 2). There was no increase in the prevalence of anaemia at the start or end of the 2003 malaria transmission season in children who had previously received intermittent treatment.

Discussion

The results of this trial show that seasonal intermittent preventive treatment with sulfadoxine-pyrimethamine plus artesunate confers an impressive amount of protection against malaria in children aged 2–59 months of age in an area of seasonal malaria transmission. The protective effect remained strong even when several definitions of clinical malaria were used and was seen across all age groups. A similar, positive outcome from the use of such treatment has been reported from Kambila, Mali,³¹ where a randomised, controlled trial of sulfadoxine-pyrimethamine given only twice during the transmission season resulted in 40% efficacy (95% CI 25–51) against clinical attacks of malaria. Few children in the study area used bednets and most of these nets were untreated and in a poor condition. No difference in efficacy was seen between net users and non-users, but now that the use of insecticide treated nets is increasing in Africa, an important area of future research will be the degree to which seasonal intermittent preventive treatment provides an added benefit to that provided by treated nets.

Before these trials, the safety and efficacy of sulfadoxine-pyrimethamine combined with a single dose of artesunate had already been shown in phase II and phase III studies in The Gambia, including one in which this drug combination was used for mass administration.^{32–34} Sulfadoxine-pyrimethamine plus one dose of artesunate was chosen for this study on the basis of the Gambian trials, in line with the views of a panel of WHO experts recommending a paediatric formulation of this combination as the first choice for intermittent preventive treatment in infants.³⁵

Assessment of the effect of this treatment on anaemia was influenced by the fact that, throughout the survey, children who presented to the health posts with clinical anaemia were given iron supplementation. The administration of iron, when appropriate, along with a prompt response to incident cases of clinical malaria might account for the similar prevalence of anaemia in the two groups at the end of the transmission season.

The degree to which large-scale and sustained preventive treatment would select for drug resistance is critical, but our study was not designed to address this issue, and the results do not allow firm conclusions. Both the *pf_{dhfr}* triple mutation associated with pyrimethamine resistance and one of the *pf_{dhps}* mutations associated with resistance to sulphonamides were more prevalent at the completion of the 2002 surveillance period in parasite-positive children who had received sulfadoxine-pyrimethamine/artesunate than they were in either children who had received placebo, or in the parasite-positive children identified before the intervention. These alleles also showed an increase in prevalence during the 2002 season in the placebo group (table 5).

Our data suggest that both alleles were increasing in frequency in the parasite population as a whole during the

2002 transmission season, but we cannot establish whether this was an effect of the intervention or an indication of a broader process taking place in the study area. Indeed, this general trend was also apparent for both alleles during the 2003 season when preventive treatment was not applied (table 5). Senegal's treatment policy for uncomplicated falciparum malaria switched from chloroquine monotherapy to a combination of sulfadoxine-pyrimethamine and amodiaquine at the start of the 2003 transmission season, which might have increased selection for resistance to sulfadoxine-pyrimethamine in the parasite population as a whole in the season after the intervention.

Overall, we saw no evidence of a rebound in malaria morbidity during the year after treatment, in keeping with studies of intermittent preventive treatment in infants in Tanzania.^{17,18} However, an interesting age effect was seen; children who received intermittent treatment in the first year of life seemed to have some persisting protection, as reported after treatment in infants in Tanzania,³⁶ whereas the opposite was seen in older children. However, the differences were not significant and so need to be treated with caution. Since delivery of drugs for up to 5 years will be necessary to achieve sustained protection in young children, assessment of rebound morbidity after several years of intervention will be important. Such assessment will require a trial that lasts for several years, and some form of phased intervention study will probably be needed.

Sulfadoxine-pyrimethamine and amodiaquine, the drugs used so far for intermittent treatment in infants, both have long half-lives and they might have achieved their effect by a chemoprophylactic effect, by clearing parasites present at the time that they were given, or by a combination of both mechanisms. Our findings suggest that the chemoprophylaxis effect of sulfadoxine-pyrimethamine is important when it is used for seasonal intermittent preventive treatment. Protection began to wane at the end of each interval between drug administrations, and this effect was especially striking in the last interval when surveillance was followed up for an additional fifth week. An apparent waning of the protective effect with time could also be accounted for by selection of parasites resistant to sulfadoxine-pyrimethamine making it more difficult for the drug to exert a protective effect. However, despite the presence of *pfdhfr* triple mutant alleles and the *pfdhps*-437G allele, unpublished trial data available from Senegal and The Gambia suggest that sulfadoxine-pyrimethamine monotherapy continues to be efficacious in the region, which might be due to the absence of additional mutations in the *pfdhps* gene that occur in other areas of Africa where sulfadoxine-pyrimethamine monotherapy is failing.²⁹ Should such alleles be introduced into Senegal, the protection afforded by intermittent preventive treatment with drug combinations based on sulfadoxine-pyrimethamine might be compromised.

No serious adverse event attributable to study medication was recorded. The intervention was generally well tolerated, although there was a modest increase in vomiting in children who took the active drugs. This finding is important because even minor side-effects could interfere with compliance in a situation in which medication is given to large numbers of healthy children. Drugs used for infants and children have to be very safe and well tolerated. A liquid paediatric formulation could enhance the ease of administration and tolerability of treatment.

Our findings highlight some of the confusion that surrounds the terminology currently being used to describe different forms of chemoprevention in endemic areas. Since a longacting drug was used in this trial the intervention could well be called seasonal chemoprophylaxis rather than intermittent preventive treatment. Even in the case of preventive treatment in infants, much of the effect could be attributable to a period of chemoprophylaxis when longacting drugs such as sulfadoxine-pyrimethamine are used. There is also overlap between mass drug administration and intermittent preventive treatment, since the several rounds of mass drug administration used in some campaigns can be viewed as intermittent preventive treatment. Some of this confusion comes from the fact that how intermittent treatment achieves its effect is not known.^{37,38} Studies of shortacting or longacting drugs in infants should help to clarify this position. Until this effect is known the optimum drug for treatment in infants or older children in areas where sulfadoxine-pyrimethamine is no longer effective is difficult to identify.

The results of this trial are very encouraging and further studies on methods of delivery, choice of drugs and cost effectiveness of intermittent preventive treatment in children are merited. Effectiveness studies are needed to identify ways in which full community participation could be obtained to achieve a high rate of coverage with this highly effective intervention.

Contributors

B Cissé was the principal investigator of this trial. D Boulanger, EH Ba, and C Sokhna assisted him in implementing and coordinating the field activities. Data management was done in collaboration with J Milet, D Boulanger and E H Ba. B Cissé, B M Greenwood, J-F Trape, O Gaye, G Targett, J Lines, N Alexander, R Hallett, C Sutherland, F Simondon, and K Simondon contributed to the trial design. All authors interpreted the analyses that have been processed under an analysis plan developed with N Alexander, B M Greenwood and K Richardson. B Cissé drafted the manuscript, which has been revised and approved by the authors.

Conflict of interest statement

We declare that we have no conflict of interest. The study was funded by the Bill and Melinda Gates Foundation through an award to the Malaria Centre of the London School of Hygiene & Tropical Medicine. The sponsor played no part in the design or implementation of the trial or in the analysis or interpretation of its results.

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