Protective efficacy and safety of three antimalarial regimens for intermittent preventive treatment for malaria in infants: a randomised, double-blind, placebo-controlled trial

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Summary

Background Administration of sulfadoxine-pyrimethamine at times of vaccination—intermittent preventive treatment in infants (IPTi)—is a promising strategy to prevent malaria. However, rising resistance to this combination is a concern. We investigated a shortacting and longacting antimalarial drug as alternative regimens for IPTi.

Methods We undertook a double-blind, placebo-controlled trial of IPTi in an area of high resistance to sulfadoxine-pyrimethamine at sites of moderate (n=1280 infants enrolled) and low (n=1139) intensity of malaria transmission in Tanzania. Infants aged 8–16 weeks were randomly assigned in blocks of 16 to sulfadoxine (250 mg) plus pyrimethamine (12·5 mg; n=319 in moderate-transmission and 283 in low-transmission sites), chlorproguanil (15 mg) plus dapsone (18·75 mg; n=317 and 285), mefloquine (125 mg; n=320 and 284), or placebo (n=320 and 284), given at the second and third immunisations for diphtheria, pertussis, and tetanus, and for measles. Research team and child were masked to treatment. Recruitment was stopped early at the low-transmission site because of low malaria incidence. The primary endpoint was protective efficacy against all episodes of clinical malaria at 2–11 months of age. Analysis was by intention to treat. This study is registered with ClinicalTrials.gov, number NCT00158574.

Findings All randomly assigned infants were analysed. At the moderate-transmission site, mefloquine had a protective efficacy of 38·1% (95% CI 11·8–56·5, p=0·008) against clinical malaria in infants aged 2–11 months, but neither sulfadoxine-pyrimethamine (–6·7%, –45·9 to 22·0) nor chlorproguanil-dapsone (10·8%, –24·6 to 36·1) had a protective effect. No regimen had any protective efficacy against anaemia or hospital admission. Mefloquine caused vomiting in 141 of 1731 (8%) doses given on day 1 (odds ratio *vs* placebo 5·50, 95% CI 3·56–8·46). More infants died in the chlorproguanil-dapsone and mefloquine groups (18 and 15, respectively) than in the sulfadoxine-pyrimethamine or placebo groups (eight deaths per group; p=0·05 for difference between chlorproguanil-dapsone and placebo).

Interpretation IPTi with a longacting, efficacious drug such as mefloquine can reduce episodes of malaria in infants in a moderate-transmission setting. IPTi with sulfadoxine-pyrimethamine has no benefit in areas of very high resistance to this combination. The appropriateness of IPTi should be measured by the expected incidence of malaria and the efficacy, tolerability, and safety of the drug.

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Introduction

Malaria and anaemia are major causes of morbidity and mortality in children in sub-Saharan Africa. Administration of treatment doses of antimalarial drugs at opportunistic times, termed intermittent preventive treatment (IPT), has the potential to reduce this burden. Growing evidence shows the benefits of IPT given to infants (IPTi) at times of vaccination[1] and to children younger than 5 years[2,3] at timepoints that coincide with the peak malaria transmission season. Since 2001, the results of six randomised controlled trials[4–10] of IPTi using sulfadoxine-pyrimethamine have been reported, with protective efficacies against clinical episodes of malaria ranging from 20% to 59% and that against anaemia from 10% to 50% up to 12 months of age. However, whether this treatment will be efficacious in areas with high sulfadoxine-pyrimethamine resistance, which is now detected in eastern[11] and southern Africa,[12] remains unclear. If sulfadoxine-pyrimethamine no longer works for IPTi in these areas and this intervention is implemented, then a replacement drug will be needed. Few drugs have been investigated for this purpose,[13] but the optimum choice of drug to replace sulfadoxine-pyrimethamine depends on the mechanism of IPTi. Evidence suggests that its major action is through prophylaxis.[14,15] If the protective effect of this intervention is mediated mainly through treatment of existing infections, then an effective shortacting antimalarial drug could be used as a replacement. However, if the primary mechanism of action is through prophylaxis, then a longacting drug will be needed.

For these reasons we undertook a study of the protective efficacy of sulfadoxine-pyrimethamine, mefloquine (a longacting antimalarial drug with half-life of between 10 and 40 days[16]), and chlorproguanil-dapsone (a shortacting antimalarial drug with half-life between 1 and 2 days[17]) as

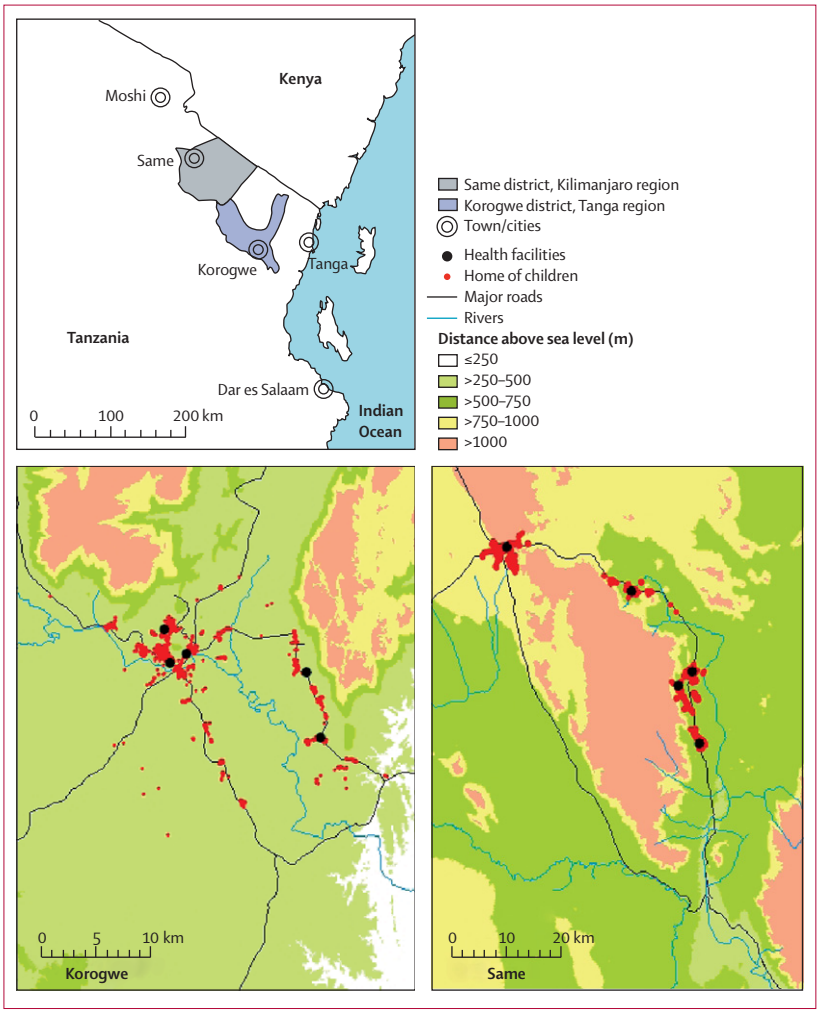

Figure 1: **Map of study sites**
This study was undertaken in two disctricts: Korogwe, a moderate-transmission site; and Same, a low-transmission site.

See Online for webappendix

alternative drugs for IPTi in an area of high sulfadoxine-pyrimethamine resistance in northeast Tanzania.

Methods

Study design, sites, and population

We undertook an individually randomised, double-blind, placebo-controlled trial of three IPTi regimens (sulfadoxine-pyrimethamine, chlorproguanil-dapsone, and mefloquine) between Dec 7, 2004, and May 1, 2008. All drugs were given at the time of routine immunisation with diphtheria, pertussis, and tetanus (DPT) and polio 2 at about 2 months of age; DPT and polio 3 at 3 months of age; and measles vaccines at 9 months of age.

The study was undertaken in two sites: a moderate-transmission site (Korogwe District, Tanga region) and a neighbouring low-transmission site (Same District, Kilimanjaro region) in northeastern Tanzania (figure 1). Korogwe district is situated 32 km north of Muheza Town, where sulfadoxine-pyrimethamine resistance was first detected in Tanzania in 1994[11,18] and where in-vivo efficacy (day 28 adequate clinical and parasitological response) of sulfadoxine-pyrimethamine was recently reported as 18%.[19] The district is situated on the coastal plain (altitude <600 m above sea level) and has a yearly rainfall ranging from 800 to 1400 mm per year. In 2000, the entomological inoculation rate in neighbouring Muheza district was 148 infective bites per person per year.[20] The webappendix p 1 provides a description of Same, the low-transmission site.

All infants aged 8–16 weeks who attended clinics for WHO's Extended Program on Immunization (EPI) at the ten study health facilities (five in each site) for DPT2 and polio vaccination were eligible for inclusion. We excluded infants who had any of the following conditions: history of allergy to study drugs; history of convulsions; clinical features of severe malnutrition or chronic illness, including infants with signs of HIV/AIDS; plans to leave the study area before 12 months of age; weight less than 4·5 kg at enrolment; and no witnessed, written consent from the caretaker.

The protocol was approved by the ethics review board of the National Institute for Medical Research of Tanzania and by the London School of Hygiene and Tropical Medicine ethics committee.

Randomisation and masking

Children who met the inclusion criteria were randomly assigned by the study physician to the next drug group from a pre-assigned list, which was computer generated by an independent statistician. The randomisation list was assigned in blocks of 16 to one of 16 drug groups (four drug codes were used for each of the four study groups to reduce the possibility of unmasking) and kept in a folder under the care of the study physician. Both research team and child were masked to treatment allocation. Study drugs were administered by a designated drug giver in a secluded cubicle. Sulfadoxine-pyrimethamine and chlorproguanil-dapsone had identical placebos, but the drug giver was unmasked to the mefloquine group because these tablets differed in appearance to sulfadoxine-pyrimethamine. However, the drug giver had no other role in the study.

Study drugs were supplied in sealed opaque blisterpacks, identified only by drug group and stored in a plastic envelope. When entering the cubicle for drug administration, the drug giver removed the blisterpack from the envelope and prepared the drugs for day 1 in a standard way. The validity of the masking process was reviewed twice yearly by the independent monitor.

Procedures

The main objective of the trial was determination of the protective efficacy of the three IPTi regimens. The primary outcome measure was incidence of all episodes of clinical malaria in infants aged 2–11 months, which

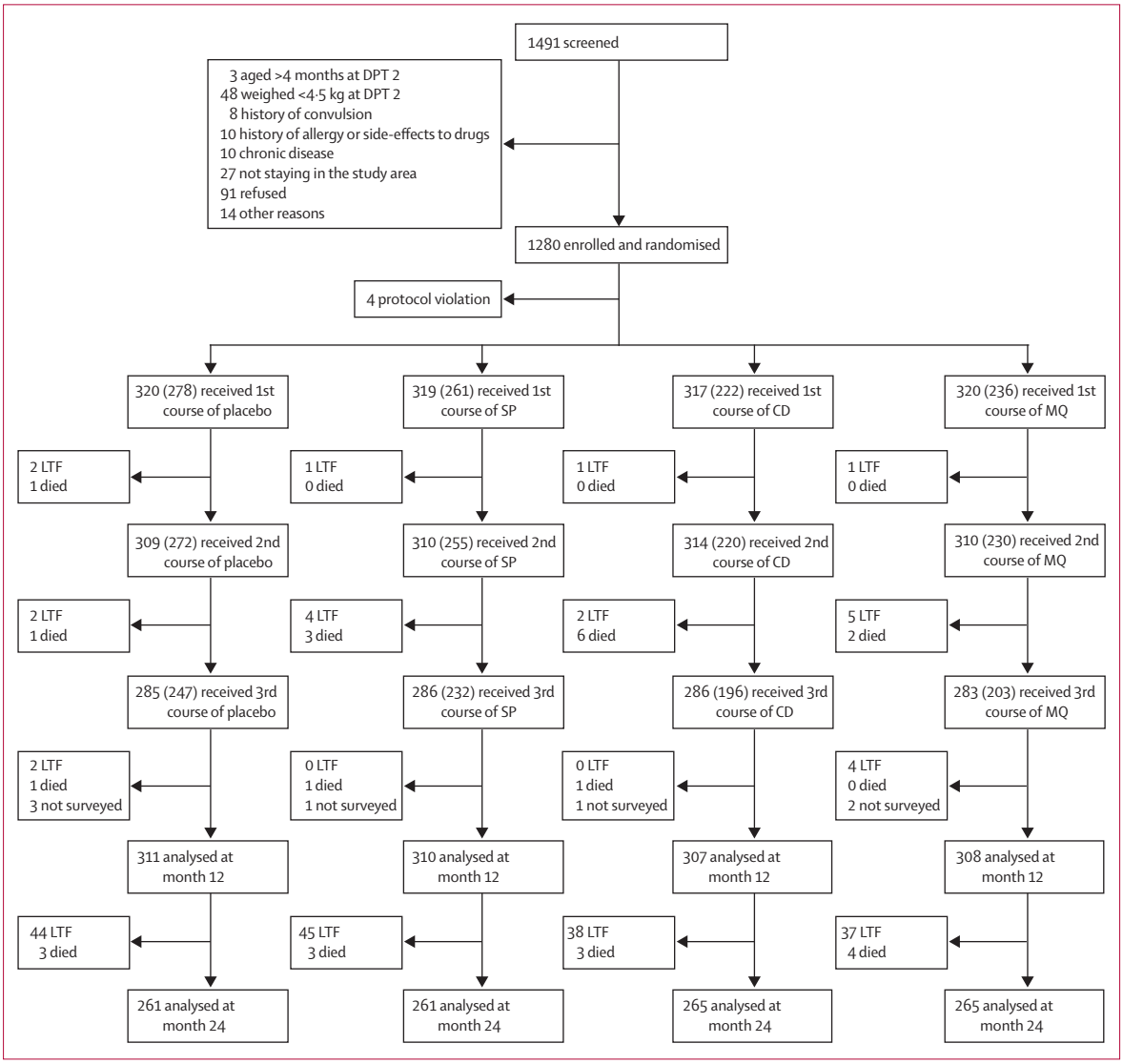

Figure 2: **Trial profile for the intention-to-treat cohort in the moderate-transmission site of Korogwe**
Numbers in parentheses are for the per-protocol analysis. DPT=diphtheria, pertussis, and tetanus. SP=sulfadoxine-pyrimethamine. CD=chlorproguanil-dapsone. MQ=mefloquine. LTF=loss to follow-up.

was defined as either a history of fever during the previous 2 days or an axillary temperature greater than 37·5°C plus parasitaemia of any density. Secondary outcomes were the incidence of one or more episodes of moderate anaemia (haemoglobin <80 g/L), the incidence of hospital admissions associated with malaria parasitaemia, hospital admissions overall, and the safety and tolerability of the drug regimens. The incidences of all these outcomes in children aged 12–23 months (the post-intervention period) were also considered as secondary outcomes to establish whether there was an increased risk (rebound) of malaria or anaemia during the year after treatment had been given.

The first dose of IPTi was either 250 mg sulfadoxine plus 12·5 mg pyrimethamine (Fansidar, F Hoffmann-La Roche, Basel, Switzerland), 15 mg chlorproguanil plus 18·75 mg dapsone (Lapdap, GlaxoSmithKline, London, UK), 125 mg mefloquine (Lariam, F Hoffmann-La Roche, Basel, Switzerland), or placebo. Tablets were crushed, diluted in water, and sweetened with honey. If a child vomited within 30 min, the dose was repeated. If the child vomited a second time, no further drug was given. The mother or caregiver was given a blister pack with doses of the study drug (15 mg chlorproguanil plus 18·75 mg dapsone for the chlorproguanil-dapsone group and placebo for the remaining groups) and instructed in how to administer the tablets at home on the subsequent 2 days. Every child was followed up at home on days 2 and 3 to ensure that the day 2 and 3 doses had been given. At these visits, the field worker assessed the

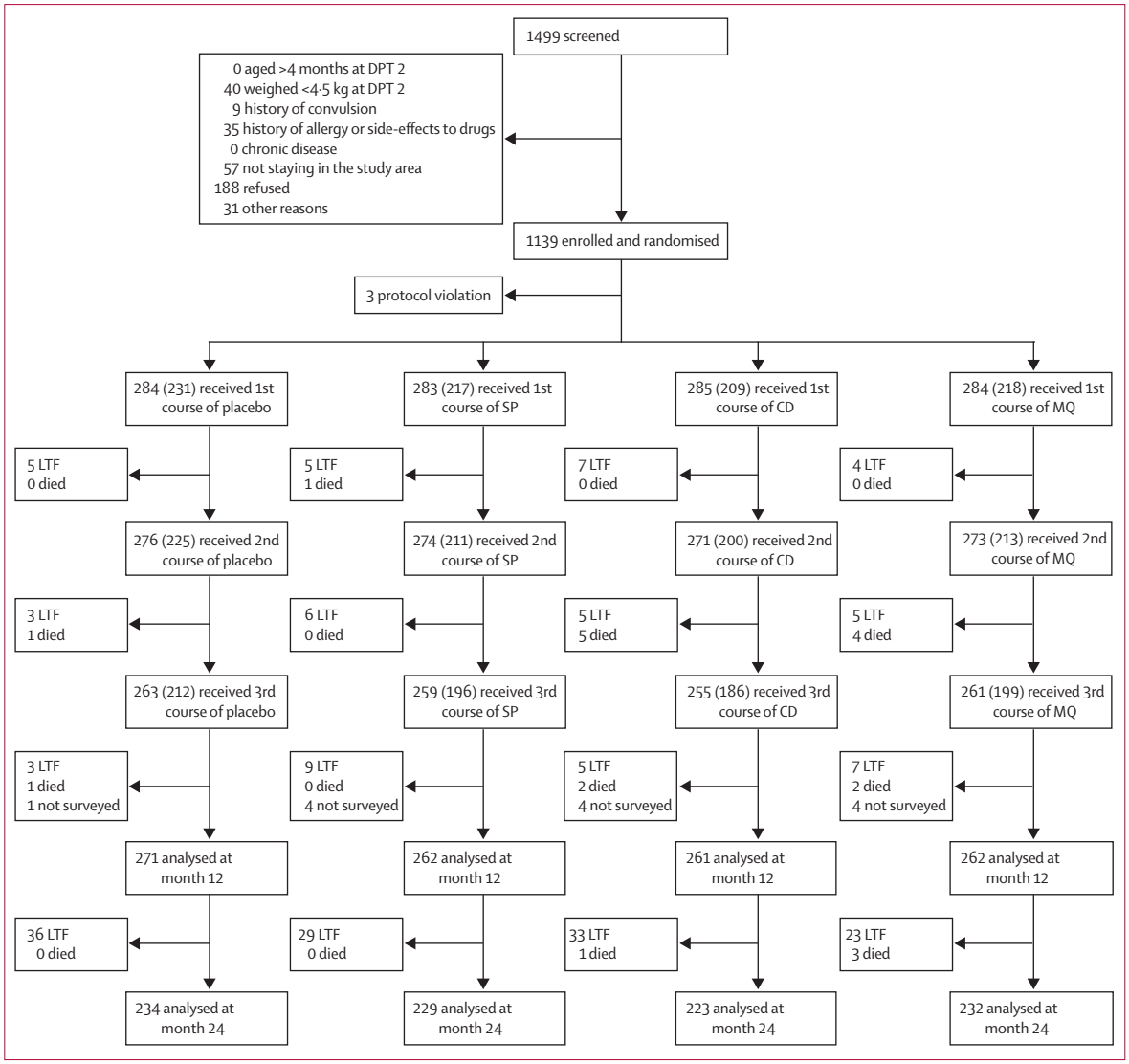

Figure 3: **Trial profile for the intention-to-treat cohort in the low-transmission site of Same**
Numbers in parentheses are for the per-protocol analysis. DPT=diphtheria, pertussis, and tetanus. SP=sulfadoxine-pyrimethamine. CD=chlorproguanil-dapsone. MQ=mefloquine. LTF=loss to follow-up.

child's health, including possible side-effects, observed the bednet if the child was reported to be using one, and checked the blister pack of IPTi drugs. If a dose of drug had not been given, it was given and directly observed by the field worker.

The doses of drugs given for the second course of IPTi, given at the time of the third DPT and polio vaccination, were the same as those used for the first course. Doses were increased for the third course, which was given at the time of measles vaccination. These doses were 500 mg sulfadoxine plus 25 mg pyrimethamine, 22·5 mg chlorproguanil plus 28·125 mg dapsone, 250 mg mefloquine, or placebo on day 1; and 22·5 mg chlorproguanil plus 28·125 mg dapsone or placebo on days 2 and 3.

Any significant side-effects noted by field workers during home visits on days 2 and 3 of each dose of IPTi were reported to the study physician who reviewed the child when necessary. The first 200 infants to receive the first course and the second 200 infants to receive the third course of IPTi at each site (total 800 infants) had their haemoglobin concentration measured on day 7 after drug administration because of concerns about the potential of chlorproguanil-dapsone to cause haemolysis in infants who were deficient in glucose-6-phosphate dehydrogenase (G6PD). G6PD screening was not undertaken before enrolment.

All serious adverse events (defined as any admission to hospital, death, or unusual or unexpected event) occurring within 1 month of IPTi administration, or

	Placebo	SP	CD	MQ
At enrolment				
N	320	319	317	320
Age (months)	2·21 (0·34)	2·25 (0·35)	2·30 (0·40)	2·23 (0·31)
Weight (kg)	5·6 (0·69)	5·5 (0·66)	5·7 (0·75)	5·6 (0·68)
Girls	146 (45·6%)	162 (50·8%)	140 (44·2%)	156 (48·8%)
Haemoglobin (g/L)	106 (12)	104 (13)	104 (12)	105 (12)
Parasite positive	0	4 (1·3%)	2 (0·6%)	1 (0·3%)
Dose of drug received (mg/kg)	..	S: 45·7 (5·2); P: 2·3 (0·3)	C: 2·7 (0·3); D: 3·3 (0·4)	22·6 (2·6)
Witnessed bednet coverage	281 (87·8%)	275 (86·2%)	277 (87·4%)	282 (88·1%)
Reported ITN coverage	177 (55·3%)	163 (51·1%)	173 (54·6%)	163 (50·9%)
Rural residence	174 (54·4%)	171 (53·6%)	155 (48·9%)	187 (58·4%)
Level of maternal education				
None	30/284 (10·6%)	20/270 (7·4%)	30/281 (10·7%)	24/282 (8·5%)
Primary	222/284 (78·2%)	229/270 (84·8%)	226/281 (80·4%)	247/282 (87·6%)
Higher	32/284 (11·3%)	21/270 (7·8%)	25/281 (8·9%)	11/282 (3·9%)
Median distance from health facility (IQR [km])	2·93 (1·48–5·43)	2·68 (1·32–5·12)	2·55 (1·25–4·62)	2·78 (1·35–5·34)
At IPTi 2				
N	309	310	314	310
Age (months)	3·16 (0·35)	3·20 (0·38)	3·25 (0·42)	3·18 (0·33)
Dose of drug received (mg/kg)	..	S: 40·3 (4·9); P: 2·0 (0·5)	C: 2·4 (0·3); D: 3·0 (0·4)	20·1 (2·4)
At IPTi 3				
N	285	286	286	283
Age (months)	9·16 (0·36)	9·14 (0·22)	9·16 (0·25)	9·16 (0·24)
Dose of drug received (mg/kg)	..	S: 60·8 (7·7); P: 3·0 (0·4)	C: 2·7 (0·3); D: 3·3 (0·4)	29·9 (3·7)
At 24 months				
Witnessed bednet coverage	215/251 (85·7%)	207/235 (88·1%)	227/258 (88·0%)	236/258 (91·5%)
Reported ITN coverage	171/246 (69·5%)	164/232 (70·7%)	183/255 (71·8%)	175/253 (69·2%)

Data are mean (SD), n (%), or n/N (%), unless otherwise indicated. SP=sulfadoxine-pyrimethamine. CD=chlorproguanil-dapsone. MQ=mefloquine. ITN=insecticide-treated net.

Table 1: **Characteristics of study participants at baseline, at administration of second and third doses of intermittent preventive treatment for infants (IPTi), and at 24 months of age, for the moderate-transmission site**

deaths and unusual or unexpected events occurring at any time during the study, were reported within 48 h of detection to the Data Safety Monitoring Board (DSMB). All other adverse events and the number of children enrolled were reported to the DSMB every 3 months.

Before the first and third courses of IPTi were given, blood samples were collected for malaria parasite examination and haemoglobin estimation. All children were followed up at 10, 18, and 24 months of age. A 20% random sample was followed up at 11 months and a different 20% random sample at 12 months of age. At these follow-up visits, children were weighed and a blood sample collected for examination for malaria parasitaemia and determination of haemoglobin concentration. If a child was ill at the time of one of these surveys, they were treated as a sick visit.

Project staff supported the clinical management of children at study health facilities to ensure complete assessment and appropriate treatment of any illness. The study team assessed any child reporting sick. If a study child had a temperature of 37·5ºC or higher or a history of fever in the previous 2 days, blood samples for examination for malaria parasitaemia and determination of haemoglobin concentration were obtained. Children with uncomplicated malaria were treated with amodiaquine (December, 2004–October, 2005), artesunate plus amodiaquine (October, 2005–September, 2006), or artesunate plus lumefantrine (September, 2006–study end) because of changes in government recommendations. Children with severe malaria were treated with quinine. Moderate anaemia (haemoglobin <80 g/L) was treated with iron (2 months) and folic acid (1 month) supplementation, and a blood transfusion was given to children with severe anaemia (50 g/L). Other conditions were treated as per guidelines for the Integrated Management of Childhood Illness.[21] Blood slides collected from sick visits were read the day of collection, and those collected as part of routine follow-up within 1 week of collection.

If a child died at home, a verbal autopsy was done. Verbal autopsies were reviewed by two study physicians and the cause of death was reached by consensus. If there was a disagreement, a third physician made an

	2–11 months of age					12–23 months of age					2–23 months of age	
	Number of cases	PYAR	Incidence per PYAR	Adjusted protective efficacy (95% CI)	p value	Number of cases	PYAR	Incidence per PYAR	Adjusted protective efficacy (95% CI)	p value	Adjusted protective efficacy (95% CI)	p value
All SAEs (hospital admissions and/or death)												
Placebo	194	476·5	0·407	..	..	151	542·9	0·278	..	..	..	..
SP	195	471·2	0·414	−1·6% (−24·0 to 16·7)	0·872	161	536·0	0·300	−8·0% (−34·9 to 13·5)	0·497	−4·4% (−21·1 to 9·9)	0·565
CD	209	466·2	0·448	−10·1% (−33·9 to 9·4)	0·334	169	530·8	0·315	−13·9% (−42·0 to 8·7)	0·248	−12·0% (−29·6 to 3·2)	0·127
MQ	204	474·9	0·430	−5·5% (−28·4 to 13·3)	0·594	181	535·4	0·338	−21·6% (−50·9 to 2·1)	0·076	−12·6% (−30·2 to 2·6)	0·109
All-cause hospital admissions												
Placebo	193	476·4	0·405	..	..	150	542·9	0·276	..	..	..	..
SP	190	471·2	0·403	0·5% (−21·6 to 18·5)	0·965	158	536·0	0·295	−6·7% (−33·4 to 14·7)	0·569	−2·7% (−19·2 to 11·5)	0·728
CD	197	466·1	0·423	−4·3% (−27·2 to 14·5)	0·676	167	530·8	0·315	−13·9% (−42·0 to 8·7)	0·248	−8·5% (−25·8 to 6·4)	0·278
MQ	199	474·9	0·419	−3·4% (−26·1 to 15·1)	0·738	179	535·3	0·334	−21·0% (−50·3 to 2·6)	0·085	−11·2% (−28·7 to 3·9)	0·154
All-cause deaths												
Placebo	5	480·1	0·010	..	..	3	545·7	0·005	..		..	..
SP	5	474·8	0·011	−1·1% (−249·3 to 70·7)	0·986	3	539·0	0·006	−1·2% (−401·6 to 79·6)	0·988	−1·2% (−169·6 to 62·0)	0·981
CD	14	469·9	0·030	−186·1% (−694·3 to −3·0)	0·044	4	533·9	0·007	−36·3% (−508·9 to 69·5)	0·685	−129·9% (−428·8 to −0·0)	0·050
MQ	8	478·6	0·017	−60·5% (−390·6 to 47·5)	0·407	7	538·7	0·013	−136·4% (−814·2 to 38·9)	0·213	−89·1% (−346·0 to 19·8)	0·146
Lost to follow-up												
Placebo	17	480·1	0·035	..	..	75	545·7	0·137	..		..	..
SP	25	474·8	0·053	−48·7% (−175·3 to 19·7)	0·207	70	539·0	0·130	5·5% (−30·9 to 31·8)	0·733	−4·5% (−39·2 to 21·6)	0·764
CD	20	469·9	0·043	−20·2% (−129·5 to 37·0)	0·577	64	533·9	0·120	12·8% (−21·7 to 37·5)	0·421	6·7% (−25·4 to 30·6)	0·646
MQ	26	478·6	0·054	−53·4% (−182·7 to 16·8)	0·170	60	538·7	0·111	19·0% (−13·8 to 42·3)	0·225	5·7% (−26·5 to 29·7)	0·694

We adjusted for insecticide-treated net ownership, residence in village or town, and distance to nearest health facility. PYAR=person-years at risk. SAE=serious adverse event. SP=sulfadoxine-pyrimethamine. CD=chlorproguanil-dapsone. MQ=mefloquine.

Table 2: **Serious adverse events and loss to follow-up for infants in each study group (data from both sites combined)**

independent review of the verbal autopsy, and a cause of death reached by the majority of physicians was assigned.

Blood smears were stained with 10% Giemsa for 20 min and read by two independent microscopists for speciation and quantification of parasite density. We estimated parasite density by counting parasites against 200 white blood cells (WBC). A blood smear was considered negative if no asexual forms were seen after observing 500 WBC. Gametocytes were read against 500 WBC. Discordant results (33% difference in quantification or positive or negative results) were read by a third microscopist; agreement between any two microscopists and the average parasite density were deemed to be the correct finding. We calculated parasite density assuming a standard WBC of 8000 cells per µL of blood. Haemoglobin concentration was measured with a Hemocue machine (Hemocue, HemoCue AB, Ängelholm, Sweden).

Statistical analysis

The sample size was calculated to detect a 25% reduction in malaria incidence in children given the IPTi regimen of mefloquine, sulfadoxine-pyrimethamine, or chlorproguanil-dapsone compared with the placebo group. We assumed that the incidence of malaria in the placebo group would be 0·62 episodes per child per year in the moderate-transmission site and thus 320 infants would be needed for each study group to detect a 25% reduction with 80% power at 95% significance level and allowing for 10% loss to follow-up (total of 1280 infants). In the low-transmission site, we assumed a malaria incidence of 0·40 episodes per child per year in the placebo group. Thus we estimated that 610 infants would be needed in each group to detect a 25% reduction and allowing for 10% loss to follow-up (total 2440 infants). Enrolment of children was suspended prematurely in the low-transmission site in August, 2006, when 1139 children had been recruited because an interim analysis by the DSMB showed that the study did not have sufficient power to detect any effect of public health relevance due to a very low incidence of malaria (see webappendix pp 1–3 for more details). Data were double-entered and verified in Microsoft Access 2000. An analytical plan was prepared and approved by the trial's DSMB before the study code was broken.

Analysis was by intention to treat, including all infants recruited at the time of administration of DPT 2 who received the first day's dose of the first course of IPTi. All the data available up to the time of loss, withdrawal, or study completion, irrespective of whether the child received all or only part of the dose, were included. An additional per-protocol analysis was done that included children who had received the first course of IPTi between 8 and 12 weeks of age, the second course of IPTi between 12 and 16 weeks of age and no less than

4 weeks after the first course, and the third course of IPTi between 9 and 10 months of age. Additionally, for the per-protocol analysis, children in the chlorproguanil-dapsone group were required to have received the drug on all 3 days of all three IPTi courses.

Protective efficacies have been calculated for three time periods: the intervention period (2–11 months of age) to assess the expected intervention effect, the post-intervention period (12–23 months of age) to assess any rebound effect resulting from a loss of naturally acquired immunity, and the intervention and post-intervention periods combined (2–23 months of age) to estimate the net public health benefit of IPTi over the first 2 years of life.

We calculated person-time at risk for malaria and anaemia by subtracting the date of administration of the first course of IPTi from the date of exit from the study. The date of exit for infants who completed the whole follow-up was the day before the child reached 12 months of age or the day before the child reached 24 months of age for assessments of efficacy up to 12 and 24 months of age, respectively. The date of exit for children lost to follow-up (migration, refusal, or exclusion) was the date that the event occurred. If the exact date of the event was not known, we used the midpoint between the last date of contact and the date on which the loss was detected. For children who had a clinical episode of malaria or were treated with antimalarial drugs, 21 days were subtracted from the subsequent person-time at risk.

All analyses were undertaken in Stata (version 10.1). We analysed incidence rates of malaria, anaemia, hospital admissions, and death with multivariable Poisson regression models. We analysed the prevalence of anaemia and of malaria at selected timepoints with multivariable logistic regression models. For data with repeated measures on the same individual, such as analysis of safety data at the time of the dose and subsequent follow-up days, data were analysed with random effects models to adjust for non-independence of data from the same individual.

We tested the following covariables for significant association with the primary outcome of malaria incidence in the placebo group: sex, residence in a town or village, distance from the nearest health facility, distance above sea level, bednet ownership, insecticide-treated net (ITN) ownership, level of maternal education, haemoglobin at enrolment, and weight-for-age *Z* score (WAZ) at enrolment. Covariables with a p value less than 0·10 were tested for inclusion in the final model and retained if the significance was less than 0·10. The risk factors included in the final multivariable risk model were included in all subsequent analyses of intervention effect, unless data were missing for more than 10% of observations or otherwise specified.

Since three different interventions were being compared against a placebo group and multiple outcomes were assessed, several statistical comparisons were made. Therefore, spurious associations are likely to have been detected by chance, and a more stringent threshold of statistical significance has been used in interpretation of the final results.

This study is registered with ClinicalTrials.gov, number NCT00158574.

	Placebo	SP	CD	MQ
Day 1				
Number of observations	1737	1731	1728	1731
Anaphylaxis	0	0	0	0
Vomiting once*	30 (1·7%)	23 (1·3%)	50 (2·9%)†	141 (8·2%)‡
Vomiting twice*	3/30 (10·0%)	3/20 (15·0%)	10/49 (20·4%)	73/136 (53·7%)‡
Days 2 and 3 active surveillance				
Number of observations	3330	3350	3347	3350
Vomiting of dose	26 (0·8%)	27 (0·9%)	51 (1·6%)§	29 (0·9%)
Diarrhoea	147 (4·5%)	110 (3·3%)¶	168 (5·1%)	171 (5·1%)
Drowsiness	122 (3·7%)	103 (3·1%)¶	93 (2·8%)¶	96 (2·9%)¶
Irritability	386 (11·7%)	370 (11·1%)	451 (13·6%)¶	482 (14·5%)§
Reduced breastfeeding	53 (1·6%)	34 (1·0%)¶	62 (1·9%)	72 (2·2%)
Convulsion	3 (0·09%)	1 (0·03%)	2 (0·06%)	1 (0·03%)
Puritus	48 (1·5%)	41 (1·2%)	41 (1·2%)	50 (1·5%)
Jaundice	0	2 (0·06%)	1 (0·03%)	1 (0·03%)
Stomatitis	3 (0·09%)	7 (0·21%)	4 (0·12%)	9 (0·27%)
Skin rash	42 (1·3%)	31 (0·9%)	32 (1·0%)	39 (1·2%)
Pale conjunctiva	46 (1·4%)	52 (1·6%)	77 (2·3%)¶	43 (1·3%)
Day 7 active surveillance				
Number of observations	214	211	207	201
Vomiting	6 (2·8%)	12 (5·7%)	16 (7·7%)†	10 (5·0%)
Diarrhoea	21 (9·8%)	12 (5·7%)	24 (11·6%)	17 (8·5%)
Drowsiness	3 (1·4%)	0	4 (1·9%)	1 (0·5%)
Irritability	8 (3·7%)	7 (3·3%)	11 (5·3%)	11 (5·5%)
Reduced breastfeeding	3 (1·4%)	1 (0·5%)	4 (1·9%)	4 (2·0%)
Convulsion	0	0	0	0
Puritus	9 (4·2%)	3 (1·4%)¶	12 (5·8%)	7 (3·5%)
Jaundice	0	0	0	0
Stomatitis	1 (0·5%)	1 (0·5%)	1 (0·5%)	3 (1·5%)
Skin rash	9 (4·2%)	9 (4·3%)	16 (7·7%)	13 (6·5%)
Pale conjunctiva	0	3 (1·4%)	9 (4·4%)§	3 (1·5%)
Haemoglobin				
Mean Hb (g/L) at day 7 (SD)	103 (12)	103 (12)	100 (16)†	103 (12)
Moderate anaemia (Hb <80 g/L at day 1)	30/1132 (2·7%)	41/1126 (3·6%)	30/1129 (2·7%)	37/1127 (3·3%)
Moderate anaemia (Hb <80 g/L at day 7)	2/213 (0·9%)	7/209 (3·4%)	19/207 (9·2%)§	9/199 (4·5%)†
Individual change from non-anaemic (day 1) to moderate anaemia (day 7) (Hb <80 g/L)	0	5 (2·4%)¶	16 (7·7%)‡	4 (2·0%)

Data are n (%), or n/N (%), unless otherwise indicated. Discrepancies between numbers and percentages are due to missing data for some variables for some observations. SP=sulfadoxine-pyrimethamine. CD=chlorproguanil-dapsone. MQ=mefloquine. Hb=haemoglobin. *Vomiting within 1 h observation period immediately after dose of intermittent preventive treatment for infants. Significance of difference between intervention group compared with placebo group: †p<0·05, ‡p≤0·001, §p≤0·01, and ¶p≤0·10.

Table 3: **Reported number of adverse events (%) at days 1, 2, 3, and 7 after intermittent preventive treatment for infants (all treatments combined from both sites)**

	2–11 months of age					12–23 months of age					2–23 months of age	
	Number of cases	PYAR	Incidence per PYAR	Adjusted protective efficacy (95% CI)	p value	Number of cases	PYAR	Incidence per PYAR	Adjusted protective efficacy (95% CI)	p value	Adjusted protective efficacy (95% CI)	p value
All episodes of malaria												
Placebo	76	247·1	0·308	..	..	148	279·3	0·530	..	..	..	..
SP	83	244·8	0·339	−6·7% (−45·9 to 22·0)	0·684	145	274·4	0·528	0·3% (−25·4 to 20·7)	0·981	−2·3% (−23·0 to 15·0)	0·813
CD	63	241·1	0·261	10·8% (−24·6 to 36·1)	0·504	136	276·0	0·493	7·0% (−17·4 to 26·3)	0·542	9·6% (−9·4 to 25·3)	0·300
MQ	52	246·4	0·211	38·1% (11·8 to 56·5)	0·008	146	275·0	0·531	−0·2% (−25·9 to 20·3)	0·986	10·8% (−8·0 to 26·3)	0·242
Malaria (>5000 parasites per μL)												
Placebo	50	247·4	0·202	..	..	116	279·5	0·415	..	..	..	..
SP	62	245·0	0·253	−21·2% (−76·2 to 16·7)	0·314	112	274·8	0·408	1·8% (−27·3 to 24·3)	0·891	−5·6% (−30·7 to 14·6)	0·615
CD	49	241·3	0·203	−5·7% (−56·7 to 28·7)	0·784	114	276·0	0·413	0·5% (−28·9 to 23·1)	0·971	0·0% (−24·1 to 19·5)	0·998
MQ	42	246·6	0·170	23·9% (−14·8 to 49·6)	0·193	114	275·4	0·414	0·3% (−29·2 to 23·0)	0·984	5·2(−18·0 to 23·8)	0·635
Malaria hospital admissions												
Placebo	11	256·2	0·043	..	..	17	292·6	0·058	..	..	..	..
SP	9	254·5	0·035	11·4% (−114·9 to 63·4)	0·789	20	288·9	0·069	−19·2% (−127·5 to 37·6)	0·595	−4·6% (−75·9 to 37·7)	0·864
CD	5	250·3	0·020	51·3% (−40·1 to 83·1)	0·182	17	288·8	0·059	−1·3% (−98·4 to 48·3)	0·970	20·0% (−39·8 to 54·2)	0·433
MQ	9	255·1	0·035	18·0% (−98·3 to 66·1)	0·659	16	289·0	0·055	4·7% (−88·6 to 51·9)	0·890	9·9% (−54·4 to 47·5)	0·703
All-cause hospital admissions												
Placebo	93	254·7	0·365	..	..	71	291·6	0·243	..	..	..	..
SP	105	252·4	0·416	−14·7% (−51·7 to 13·2)	0·335	74	287·9	0·257	−5·6% (−46·2 to 23·8)	0·744	−10·3% (−36·4 to 10·7)	0·362
CD	92	248·7	0·370	−2·1% (−36·2 to 23·5)	0·887	78	287·7	0·271	−11·4% (−53·6 to 19·3)	0·512	−5·6% (−30·8 to 14·8)	0·620
MQ	90	253·6	0·355	2·3% (−30·6 to 26·9)	0·877	96	287·5	0·334	−37·1% (−86·4 to −0·9)	0·044	−14·5% (−41·3 to 7·2)	0·206
All-cause deaths												
Placebo	3	256·4	0·012	..	..	3	292·9	0·010	..	..	..	..
SP	4	254·5	0·016	−26·0% (−464·3 to 71·8)	0·762	3	289·3	0·010	−1·3% (−401·7 to 79·6)	0·988	−17·9% (−250·7 to 60·4)	0·768
CD	7	250·4	0·028	−137·8% (−819·7 to 38·5)	0·210	3	289·1	0·010	−1·3% (−401·9 to 79·6)	0·987	−69·7% (−366·9 to 38·3)	0·306
MQ	2	255·3	0·008	37·2% (−276·7 to 89·5)	0·611	4	289·3	0·014	−35·0% (−503·2 to 69·8)	0·694	−0·9% (−212·8 to 67·5)	0·988
Anaemia (Hb <80 g/L)												
Placebo	80	252·3	0·317	..	..	67	257·2	0·261	..	..	..	..
SP	89	241·2	0·369	−15·9% (−56·9 to 14·3)	0·337	65	249·8	0·260	0·1% (−40·5 to 29·0)	0·993	−3·9% (−35·0 to 20·0)	0·772
CD	86	243·1	0·354	−13·0% (−53·3 to 16·6)	0·431	74	246·1	0·301	−15·4% (−60·6 to 17·1)	0·396	−13·4% (−46·7 to 12·3)	0·338
MQ	84	243·3	0·345	−6·0% (−44·0 to 22·0)	0·711	63	250·2	0·252	3·4% (−36·3 to 31·5)	0·845	3·4% (−26·0 to 25·9)	0·797

We adjusted for insecticide-treated net ownership, residence in village or town, and distance to nearest health facility. PYAR=person-years at risk. SP=sulfadoxine-pyrimethamine. CD=chlorproguanil-dapsone. MQ=mefloquine. Hb=haemoglobin.

Table 4: **Primary and secondary outcomes of intermittent preventive treatment for infants at the moderate-transmission site**

Role of the funding source

The sponsor of the study had no role in study design, data collection, data analysis, data interpretation, or 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

2419 infants were enrolled in the study, 1280 at the moderate-transmission site (figure 2) and 1139 at the low-transmission site (figure 3). 1236 of 1276 (97%) children in the moderate-transmission site and 1056 of 1139 (93%) in the low-transmission site were followed up at 12 months of age, and 1052 of 1276 (82%) and 918 of 1139 (81%) at 24 months of age, respectively. Most loss to follow-up occurred late in the study, thus the observed person-time at risk was more than 88% of the expected time at risk up to 24 months of age. Follow-up rates were much the same between the four intervention groups (figures 2 and 3).

Baseline characteristics of study infants at the two sites were similar across all treatment groups (table 1 and webappendix p 4). At the moderate-transmission site, place of residence (town or village) and its distance above sea level, ownership of an ITN, distance from the nearest health facility, WAZ at enrolment, and level of maternal education were all associated ($p<0·1$) with the incidence of malaria in infants in the placebo group from 2–23 months of age in univariable regression models (data not shown). In the final, multivariable model, all factors apart from distance above sea level and WAZ were retained, and the webappendix pp 1 and 7 shows the results.

Cross-sectional prevalence of parasitaemia and haemoglobin concentration for visits at the first and third

IPTi course, and at ages 10, 18, and 24 months, were similar between groups (webappendix pp 1 and 8–9).

The number of individuals adhering to a 3-day regimen (swallowing tablets on all 3 days) was high (>97%) for all groups at every IPTi visit (data not shown).

For the analysis of the safety and tolerability of the three IPTi regimens, we combined data from moderate-transmission and low-transmission sites. The overall incidence of serious adverse events was similar in the three treatment and placebo groups during and after the intervention (table 2). However, there were more deaths in infants in the chlorproguanil-dapsone and mefloquine groups than in the sulfadoxine-pyrimethamine or placebo groups (p=0·05 for difference between the chlorproguanil-dapsone and placebo groups; table 2). One death of unknown cause occurred in an infant in the chlorproguanil-dapsone group within 1 month of IPTi administration and was reported as possibly linked to drug administration. Time and cause of death did not suggest a causal association with drug administration for the remaining deaths in this group (webappendix p 10). The incidence of all-cause hospital admissions did not differ significantly between treatment groups (table 2).

Table 3 shows the cumulative numbers of adverse events reported at times of active surveillance at days 1, 2, and 3 of IPTi administration, and for a subsample on the 7th day after the first and third doses of IPTi were administered. The formulation of mefloquine used in the study (tablets crushed and mixed with honey) was not well tolerated and caused vomiting in many infants (table 3). The odds ratio (OR) of vomiting once for infants who received mefloquine was 5·50 (95% CI 3·56–8·46) compared with the placebo (p<0·0001). Additionally, infants in the mefloquine group were more likely to be irritable on the second and third days after treatment than were those receiving placebo (OR 1·32, 95% CI 1·07–1·63; p=0·010).

On days 2 and 3 of IPTi there was a suggestion of more infants in the chlorproguanil-dapsone group than in the placebo group having pale conjunctivae (OR 1·82, 95% CI 0·97–3·43; p=0·063), and this difference became significant by day 7 (χ^2 Fisher's exact test p=0·002). At day 7 after IPTi administration, mean haemoglobin concentration had fallen by 5 g/L (95% CI –3·3 to –7·5) more in infants in the chlorproguanil-dapsone group than in the placebo group (p=0·0004). The proportion of children with moderate anaemia (haemoglobin <80 g/L) at day 7 was significantly higher in the chlorproguanil-dapsone group than in the placebo group (OR 10·7, 95% CI 2·2–46·4; p=0·002), and the number of children whose status changed from being non-anaemic at day 1 to anaemic at day 7 was significantly higher in infants who received chlorproguanil-dapsone than in those who received placebo (16 [8%] *vs* 0; p=0·0001).

The webappendix pp 1 and 6 provides the efficacy results for the low-transmission site, none of which were significant. At the moderate-transmission site, IPTi with mefloquine reduced the incidence of malaria substantially (protective efficacy 38·1%, 95% CI 11·8–56·5; p=0·008) but protection was not sustained into the second year of life (–0·2%, –25·9 to 20·3; p=0·99). Mefloquine had no significant protective effect against malaria associated with high-density parasitaemia, moderate anaemia, malaria or all-cause

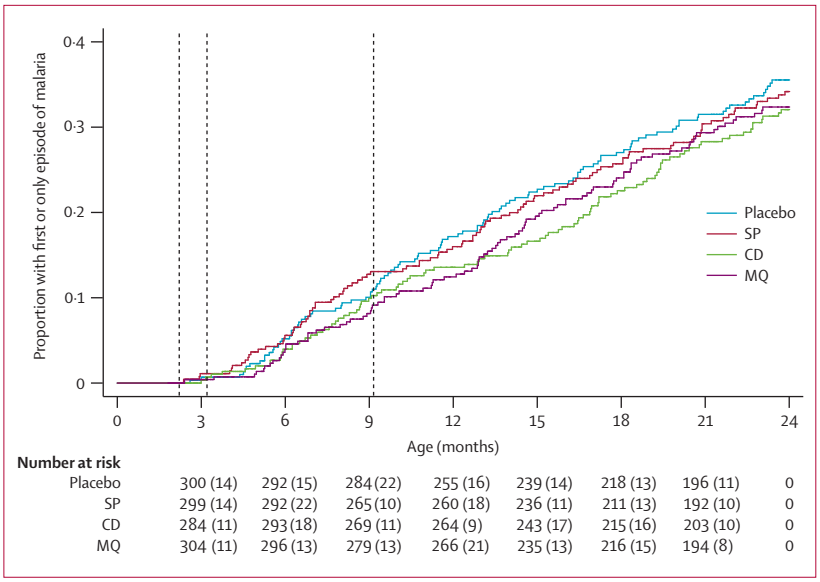

Figure 4: **Survival analysis of time to first or only episode of malaria at the moderate-transmission site of Korogwe**

Dotted lines indicate average timing of intermittent preventive treatment in infants. Numbers at risk are shown at 3-month intervals, and numbers in parentheses are cases of clinical malaria. SP=sulfadoxine-pyrimethamine. CD=chlorproguanil-dapsone. MQ=mefloquine.

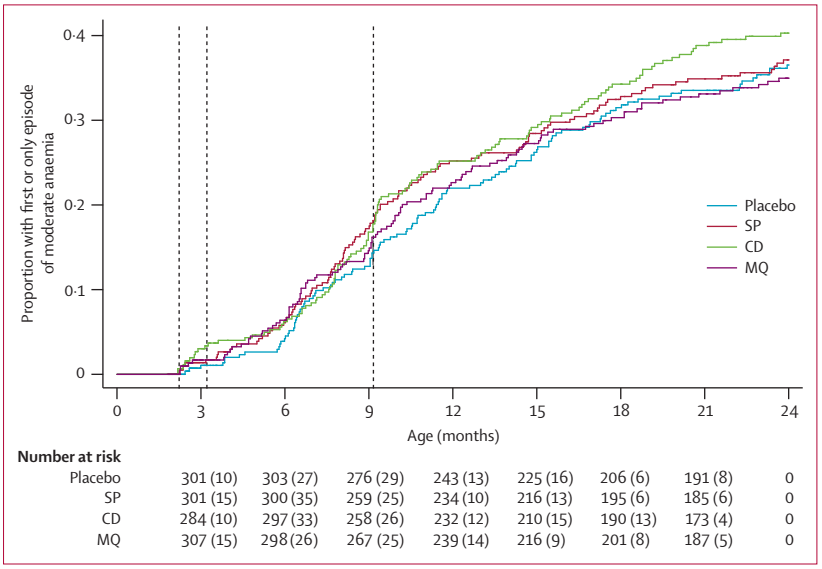

Figure 5: **Survival analysis of time to first or only episode of moderate anaemia (haemoglobin <80 g/L) at the moderate-transmission site of Korogwe**

Dotted lines indicate average timing of intermittent preventive treatment in infants. Numbers at risk are shown at 3-month intervals, and numbers in parentheses are cases of moderate anaemia. SP=sulfadoxine-pyrimethamine. CD=chlorproguanil-dapsone. MQ=mefloquine.

hospital admissions, or death (table 4). Sulfadoxine-pyrimethamine and chlorproguanil-dapsone had no significant effect on the incidence of malaria or moderate anaemia either during or after the intervention (table 4). IPTi with mefloquine seemed to delay the time to first or only episode of clinical malaria in the first year of life, but this effect was not significant (p=0·10) and was gradually lost in the second year (figure 4). Time to first episode of anaemia did not differ between groups (figure 5).

In the per-protocol analysis, 78% of infants met the inclusion criteria, but percentages differed significantly (p<0·0001) between treatment groups: 87% (278/320) for placebo, 82% (261/319) for sulfadoxine-pyrimethamine, 70% (222/317) for chlorproguanil-dapsone, and 74% (236/320) for mefloquine. The major reason for protocol deviation (62% [172/279]) was that the child did not receive all the doses at the specified ages, but this reason did not vary by treatment group (data not shown). A further 30% (83/279) of infants deviating from the protocol did not swallow all three doses, and this finding differed significantly (p<0·0001) between groups: 12% (38/317) in the chlorproguanil-dapsone group and 13% (40/320) in the mefloquine group did not swallow full courses of all three doses, compared with 1·3% (four of 319) in the sulfadoxine-pyrimethamine group and 0·3% (one of 320) in the placebo group.

The protective efficacy against clinical episodes of malaria at the moderate-transmission site during the intervention period was 43·0% (95% CI 14·7–62·0) for mefloquine (p=0·006), 38·5% (5·4–60·0) for chlorproguanil-dapsone (p=0·027), and 5·1% (–34·5 to 33·0) for sulfadoxine-pyrimethamine (p=0·77). In the second year of life, none of the drugs had a significant protective effect: –2·1% (–31·9 to 20·9) for mefloquine (p=0·87), 17·1% (–9·2 to 37·0) for chlorproguanil-dapsone (p=0·18), and 6·3% (–20·8 to 27·3) for sulfadoxine-pyrimethamine (p=0·62). Findings were not significant for any of the secondary outcomes (data not shown).

Discussion

Our study has shown that IPTi with the longacting drug mefloquine reduced the incidence of clinical episodes of malaria substantially in infants, whereas the shortacting drug chlorproguanil-dapsone did not. However, mefloquine did not have any protective effect against moderate anaemia, malaria admissions, or all-cause hospital admissions, as has been recorded with sulfadoxine-pyrimethamine in some previous studies.[4–10] This surprising finding might be partly due to the fairly low incidence of malaria in infants in the study area, the high amount of coverage with ITNs, and the fact that the study children were closely supervised. These findings are similar to the results of another IPT trial undertaken in a low-incidence site in Gabon.[9] Overall, mortality in the study children was roughly 75% lower than was the expected child mortality reported nationally.[22] Postneonatal mortality (death between 1 month and 1 year) in the study children was ten per 1000 compared with an overall figure of 42 per 1000 in northeast Tanzania,[22] probably reflecting the overall effect of the trial. The incidence of malaria in infants in the placebo group was only 0·31 per child per year, and only 12% of all hospital admissions in the first year of life were microscopically confirmed cases of malaria. In the second year of life, the incidence of malaria increased to 0·53 per child and the proportion of hospital admissions associated with malaria to 24%, suggesting a change in the pattern of malaria consistent with a reduction in transmission. If chemoprevention is to be maximally effective in such situations, older children as well as infants need to be protected.

IPTi with sulfadoxine-pyrimethamine did not show any significant reduction in episodes of clinical malaria,[23] which is by contrast with previous trials with this drug, including a trial in Tanzania.[4] This finding is probably due to the high prevalence of sulfadoxine-pyrimethamine resistance that is present in the study area. The adequate clinical and parasitological cure at day 28 was less than 20% for treatment with this combination in children aged 6–59 months with clinical malaria living in a neighbouring area.[19] An increase in the resistance to sulfadoxine-pyrimethamine will probably reduce the duration of prophylaxis and increase late recrudescences. Resistance could become so high that no protective effect is seen, as shown in this study. The shortacting drug chlorproguanil-dapsone was not efficacious in the intention-to-treat analysis but was efficacious in the per-protocol analysis. The reason for this finding seems to be that infants excluded from this analysis were more at risk of malaria than were those included, rather than because of the effect of the drug. This notion was shown by a lower incidence of malaria in the chlorproguanil-dapsone group in children included in the per-protocol analysis than in those who were excluded (rate ratio 0·64, 95% CI 0·48–0·85; p=0·002 compared with other groups).

The strategy of IPTi involves giving antimalarial drugs to healthy children who will be exposed to different levels of malaria risk due to the heterogeneity of malaria transmission[24] in many settings where such an intervention is likely to be implemented. Consequently, risk–benefit differences will vary significantly for individuals in most communities, and consequently any drug used for IPTi must be very safe. That the number of deaths in children who received IPTi with chlorproguanil-dapsone was higher than was expected, on the basis of the mortality rate in the placebo group, is a concern. Although the timing of these deaths and their cause did not suggest direct linkage to the administration of this regimen, a causal association cannot be excluded. Because of concerns about the

potential for chlorproguanil-dapsone to cause haemolysis in people with G6PD deficiency, we used enhanced surveillance for possible haematological side-effects in our trial. We noted that children in the chlorproguanil-dapsone group had a higher risk of moderate anaemia at day 7 after IPTi and a shorter time to first or only episode of anaemia than did those in the placebo or other drug groups. The haematological findings at day 7 were reported to the DSMB during the course of the trial, but the DSMB did not recommend termination of recruitment to this study group. The manufacturer of chlorproguanil-dapsone has recently withdrawn the drug from further clinical development because of the occurrence of severe haemolysis requiring blood transfusion in children treated with this regimen combined with artesunate.[25]

Tolerability is an essential requirement for a drug used for IPTi to ensure compliance and to maintain high levels of attendance at EPI vaccination clinics. We noted that IPTi with sulfadoxine-pyrimethamine, although not efficacious in this setting, was well tolerated with few side-effects. However, this intervention with mefloquine, although efficacious, was not well tolerated in the formulation and dosing strategy used. The formulation of this drug for IPTi is unlikely to be successful in a routine programme because of high rates of immediate vomiting and irritability of children for at least 2 days after the IPT course was administered. Splitting the mefloquine dose into a 2-day[26,27] or 3-day[28] regimen could be considered and might reduce vomiting, but adherence to a two-dose or three-dose regimen is likely to be less than that for a single directly observed dose. A liquid mefloquine formulation could be developed that is more acceptable to infants and young children.

A report by the WHO technical expert group on preventive chemotherapy[29] recommended that IPTi with sulfadoxine-pyrimethamine should be considered for implementation as an additional malaria control intervention in countries in sub-Saharan Africa under the following specific conditions. First, in areas with moderate to high transmission (yearly entomological inoculation rates beyond ten infectious bites per year). Second, when parasite resistance to sulfadoxine-pyrimethamine in the area is not high (no specific cut-off given). Finally, if its implementation does not detract from efforts to scale up access to artemisinin-based combination therapies for early treatment, and to ITNs and indoor residual spraying as preventive measures, all of which have significantly greater efficacy in malaria control. We have shown that in the part of Tanzania in which our study was done, IPT with sulfadoxine-pyrimethamine would be ineffective. However, a substantial reduction in the incidence of malaria in infants can be achieved with an effective, longacting alternative. In our moderate-transmission study area, administration of mefloquine, or an alternative drug with similar efficacy, to 1000 infants would save about 117 episodes of malaria per year. Whether a reduction such as this would justify the additional resources and training needed for including IPTi in the EPI would need to be carefully considered by the national malaria control programme.

IPTi is most likely to benefit infants in high-transmission settings. Since the incidence of malaria is lowered as a result of present enhanced control strategies, as noted in our low-transmission and moderate-transmission areas, the proportion of infants who will benefit from this intervention drops. Any drug used for IPTi in such circumstances must be acceptable, very safe, and efficacious. Furthermore, IPTi should be considered in the context of widespread distributions of ITNs. The results of our study show that chlorproguanil-dapsone is an inappropriate alternative because of safety issues, and that mefloquine, given in the way that was used in this trial, is an inappropriate alternative because it was poorly tolerated. Are there any other registered antimalarial drugs that could be used for IPTi in areas where sulfadoxine-pyrimethamine is no longer effective? A trial undertaken in Kisumu, Kenya, compared chlorproguanil-dapsone, sulfadoxine-pyrimethamine with artesunate, and amodiaquine plus artesunate when used for IPTi (data not yet published). Piperaquine holds promise since it is effective for IPT in older children when given in combination with dihydroartemisinin or sulfadoxine-pyrimethamine;[30] however, this drug has not yet been investigated for use in IPT in infants. If IPT in infants, children, or pregnant women is to remain a key component of malaria control strategies, new longacting and very safe antimalarial drugs are urgently needed.

Contributors

DC and BG designed the study and supervised all aspects of the work. RDG, SG, JFM, and RH did the field work. IC led the analysis with the assistance of DC, RDG, SG, JFM, and RH. ML and FWM supervised the field work. All authors wrote and approved the final version of the paper.

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

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