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Efficacy and safety of intermittent preventive treatment with sulfadoxine-pyrimethamine for malaria in African infants: a pooled analysis of six randomised, placebo-controlled trials

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Summary

Background **Intermittent preventive treatment (IPT) is a promising strategy for malaria control in infants. We undertook a pooled analysis of the safety and efficacy of IPT with sulfadoxine-pyrimethamine in African infants.**

Methods **We pooled data from six double-blind, randomised, placebo-controlled trials (undertaken one each in Tanzania, Mozambique, and Gabon, and three in Ghana) that assessed the efficacy of IPT with sulfadoxine-pyrimethamine in children. In all trials, IPT or placebo was given to children at the time of routine vaccinations delivered by WHO's Expanded Program on Immunization. Data from the trials for incidence of clinical malaria, risk of anaemia (packed-cell volume <25% or haemoglobin <80 g/L [A: converted to SI units, ok?]), and incidence of hospital admissions and adverse events in infants up to 12 months of age were reanalysed by use of standard outcome definitions and time periods [A: ok?]. Analysis was by modified intention to treat, including all infants who received at least one dose of IPT or placebo. [A: please check that all edits in this section are correct]**

Findings **The six trials provided data on 7930 infants (IPT, n=3958; placebo, n=3972). IPT had a protective efficacy of 30·3% (95% CI 19·8–39·4, p<0·0001) against clinical malaria, 21·3% (8·2–32·5, p=0·002) against the risk of anaemia, 38·1% (12·5–56·2, p=0·007) against hospital admissions associated with malaria parasitaemia, and 22·9% (10·0–34·0, p=0·001) against all-cause hospital admissions. [A: edit ok?] There were 56 deaths in the ITP group compared with 53 in the placebo group (rate ratio 1·05, 95% CI 0·72–1·54, p=0·79). One death was judged possibly related to study treatment (IPT group). Four of 676 non-fatal hospital admissions in the IPT group were deemed related to study treatment compared with five of 860 in the placebo group. None of three serious dermatological adverse events in the IPT group were judged related to study treatment compared with one of 13 in the placebo group. [A: edits ok?]**

Interpretation **IPT with sulfadoxine-pyrimethamine in infants was safe and efficacious across a range of malaria transmission settings, suggesting that this intervention is a useful contribution to malaria control.**

Funding **Bill & Melinda Gates Foundation.**

Introduction

Plasmodium falciparum malaria is a major cause of disease and death in children in sub-Saharan Africa, and improved control measures are urgently needed. Intermittent preventive treatment (IPT) is the administration of a full course of an antimalarial drug at specified timepoints, whether or not parasites are present. Previous studies have shown that continuous chemoprophylaxis in infants reduces morbidity and mortality caused by malaria. However, this approach has not been implemented in endemic countries because of the major logistical challenges involved and fears that large-scale drug use would hasten the spread of drug resistance and impair the development of naturally acquired antimalarial immunity.[1–5] Since IPT in infants is associated with lower drug exposure than is chemoprophylaxis, the effect of IPT on the spread of resistance and impairment of the development of immunity might also be lower. Furthermore, logistical challenges could be reduced by giving IPT to infants at the time of routine vaccinations delivered through WHO's Expanded Program on Immunization (EPI).

Sulfadoxine-pyrimethamine [A: Our house style is not to abbreviate drug names] could be useful for IPT in infants because this combination is available, affordable, well tolerated, and already recommended for IPT in pregnancy.[6,7] The long half-life of sulfadoxine-pyrimethamine could produce an extended prophylactic effect and enables the combination to be given as a single dose, which can be supervised. From 1999 to 2007, six randomised, placebo-controlled trials of IPT with sulfadoxine-pyrimethamine were completed.[8–13] These trials assessed the effect of three or four doses of IPT on malaria in early childhood. Since the study designs

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differed in terms of dosing schedule, primary endpoints, and duration of follow-up, we were unable to compare the trials using the published results. We therefore reanalysed the data using standardised outcome definitions and time periods to generate a meaningful pooled analysis of the safety and efficacy of IPT given to infants at the time of routine immunisation. We also investigated whether there was a potential increase in morbidity in the period after the intervention.

Methods

[A: please note, subheadings changed to conform with Lancet style]

Search strategy and selection criteria

This analysis was led by the IPTi Consortium, made up of autonomous research institutions, WHO, and UNICEF, and assembled to assess IPT in infants as a potential public health tool.[14–16] [A: URL corrected, ok?]] An independent consortium safety panel and a statistical working group (webappendix) were convened to undertake pooled analyses of safety and efficacy, respectively. In 2005, the IPTi Consortium invited the principal investigator of every completed or continuing trial of IPT with sulfadoxine-pyrimethamine in infants to take part in the pooled analyses. Trials were eligible for inclusion if they had randomly assigned asymptomatic children (younger than 1 year) who were attending routine health contacts to either IPT with sulfadoxine-pyrimethamine or placebo. [A: edit ok? Placebo had not been mentioned] We did not include trials of intermittent treatment that used different drugs, did not deliver IPT alongside EPI vaccinations, used IPT as a treatment for anaemia, or gave IPT at monthly intervals to schoolchildren or children less than 10 years of age in settings with highly seasonal transmission of malaria. These pooled analyses include all six eligible trials of IPT with sulfadoxine-pyrimethamine in infants published up to May, 2009.[8–13] A PubMed search for randomised controlled trials of infants 1–23 months old with the key words "intermittent", "treatment", "malaria", and "infants" did not find any additional studies that met our eligibility criteria.

Patients, study design, and procedures

The six randomised controlled trials, described in detail elsewhere, are summarised in table 1 and figure 1. [A: references have been renumbered so that they appear in order of mention in table 1. Please check throughout carefully] The trials were undertaken in Ifakara in Tanzania, Manhiça in Mozambique, Lambaréné in Gabon, and Navrongo, Kumasi, and Tamale, in Ghana, and assessed the efficacy of IPT with sulfadoxine-pyrimethamine for prevention of clinical malaria and anaemia during the first or second year of life, or both. Block randomisation by individual was done in all trials apart from the one in Navrongo, which was cluster-randomised by community. All trials were double-blind. [A: ok?]

The dosing schedule for IPT and placebo differed between the trials (figure 1). Doses of IPT were given according to bodyweight in the trials in Ifakara and Manhiça, according to dose number in the trial in Navrongo, and as a fixed dose in the trials in Kumasi, Lambaréné, and Tamale. One tablet contained 500 mg sulfadoxine and 25 mg pyrimethamine. All six trials had received ethical approval.

Safety and efficacy were assessed by passive clinical surveillance in all trials. Additionally, active detection of malaria and anaemia was done every month in the trials in Lambaréné and Kumasi, and every 3 months in the trial in Tamale (figure 1); in Lambaréné, a blood sample was taken only if the child was febrile, whereas in Kumasi and Tamale, the sample was taken irrespective of the presence of symptoms. In the trial in Lambaréné, safety was reviewed 1 week after every dose; a blood sample was taken if the child was febrile. In the trial in Manhiça, safety assessment was enhanced by home visits 1 week after every dose, registration of dermatological complaints of children attending a health facility, and blood tests 1 month after the second dose of IPT or placebo [A: ok?]. In the trial in Navrongo, 20% of infants were visited within 4 weeks of IPT or placebo administration so that side-effects could be assessed.

Thick blood films were stained and read by use of standard procedures. Parasite density was calculated on the assumption of a mean [A: ok? Since average can mean medium or mean] of 8000 leucocytes per µL in all trials, apart from the one in Lambaréné, where a volume-based method was used.[17]

The presence of anaemia was determined by packed-cell volume measured in microcapillary tubes in the trials in Ifakara, Navrongo, and Manhiça, and by haemoglobin concentration measured with a HemoCue photometer in the trials in Kumasi (HemoCue, Derbyshire, UK) and Tamale (HemoCue, Angelholm, Sweden). In the trial in Lambaréné, full blood counts were undertaken on an Abbott Cell-Dyn 3000 device (Abbott Diagnostics, Santa Clara, CA, USA). There is no accepted common definition of anaemia in children under 6 months of age; therefore, a cut-off that was common among trials was used (packed-cell volume <25% or haemoglobin <80 g/L).

Statistical analysis

An analytical plan was agreed by all investigators before the reanalysis started. Data were reanalysed at the individual level. To enable a pooled analysis, outcome and follow-up definitions were based on information common to all trials; therefore, results do not necessarily correspond with those in reports published for each study. Analysis was by modified intention to treat, including all children who received at least one dose of IPT or placebo up to the follow-up times defined in table 2. We examined the effect of the IPT intervention during the 35 days after a dose to assess the prophylactic benefit of sulfadoxine-pyrimethamine. We chose this interval because, according

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For more on the **IPTi Consortium** see http://www.ipti-malaria.org/

See Online for webappendix

	Ifakara[8]	Navrongo[9]	Manhiça[10]	Kumasi[11]	Tamale[12]	Lambaréné[13]
Country	Tanzania	Ghana	Mozambique	Ghana	Ghana	Gabon
Recruitment years	1999–2000	2000–02	2002–04	2003–05	2003	2002–04
Pattern of malaria transmission	Perennial	Highly seasonal	Perennial with seasonal peaks	Perennial with seasonal peaks	Perennial with seasonal peaks	Perennial with seasonal peaks
Insecticide-treated bednet use in trial participants (n/N [%]) [A1]	nn/NN (67%)	nn/NN (18%)	nn/NN (0%)	nn/NN (2%)*	nn/NN (3%)†	nn/NN (5%)
Official first-line treatment for uncomplicated malaria	Chloroquine or sulfadoxine-pyrimethamine	Chloroquine	Chloroquine and sulfadoxine-pyrimethamine	Chloroquine	Chloroquine	Chloroquine
Actual drug used in trial [A: ok?] for treatment of uncomplicated malaria	Sulfadoxine-pyrimethamine	Chloroquine	Quinine	Amodiaquine and artesunate	Artesunate	Amodiaquine and artesunate
Sulfadoxine-pyrimethamine in-vivo failure at 14 days in symptomatic 6–59-month old children (% [date assessed] [A: ok?])	31% (1999–2000)	22% (2004)	21% (2001)	Not available	14% (2002)	21% (2004)
Iron supplementation	Unsupervised	Unsupervised	None	None	None	None
HIV prevalence (not measured in trial participants or their mothers, %)	6% in ANCs in Ifakara	About 2% in ANCs	23% in ANCs in Manhiça	2·7% in ANCs	About 2–3% in ANCs	7·5% [A: in which population?]
Randomisation	Individual	Cluster	Individual	Individual	Individual	Individual
Dose of IPT with sulfadoxine-pyrimethamine‡	According to bodyweight (<5 kg, quarter of a tablet; 5–10 kg, half a tablet; >10 kg, one tablet)	According to dose number (half a tablet for first and second doses, one tablet for third and fourth doses)	According to bodyweight (<5 kg, quarter of a tablet; 5–10 kg, half a tablet; >10 kg, one tablet)	Fixed (half a tablet at each dose)	Fixed (half a tablet at each dose)	Fixed (half a tablet at each dose)
Passive case detection	Yes	Yes	Yes	Yes	Yes	Yes
Active case detection	No	No	No	Monthly	Every 3 months	Monthly
Number of children (modified ITT population)§ [A1]						
IPT	350	1221	748	535	600	504
Placebo	351	1225	755	535	599	507
Incidence of clinical malaria (episodes per person-years at risk)¶	0·54	1·10	0·79	1·27	0·95	0·16
Risk of anaemia (of the first or only episode, %)‖	8·6%	6·3%	10·6%	37·6%	31·7%	15·7%

ANC=antenatal clinic. IPT=intermittent preventive treatment. ITT=intention-to-treat. *According to Ghana Demographic and Health Survey, 2003. †Bednet use in 2001 in trial area—not necessarily insecticide-treated nets. ‡Manufacturer of sulfadoxine-pyrimethamine and placebo was La Roche ([A: town, country?]) in all trials apart from the one in Navrongo, where it was Cosmos Pharmaceuticals (A: town?], Nairobi). §Modified ITT population includes all children who received at least one dose of study drug. [A1: is this ok? ie, the ITT population, rather than the total number of children in the trials?] ¶In the placebo group, from first dose until 12 months of age; history of fever or measured fever with any Plasmodium falciparum parasitaemia. History of fever included reported fever during the past 24 h in the trials in Ifakara and Manhiça, and during the past 48 h for the other four trials. Measured fever was defined as an axillary temperature 37·5°C or more for trials in Ifakara, Navrongo, Tamale, and Manhiça; rectal or tympanic temperature 38°C or more for the trial in Kumasi, and 38·5°C or more for the trial in Lambaréné. ‖In the placebo group, from first dose until 12 months of age; packed-cell volume less than 25% in trials in Ifakara, Navrongo, and Manhiça, and a haemoglobin concentration less than 80 g/L in the trials in Kumasi, Lambaréné, and Tamale. [A1: please provide numerators and denominators to accompany %s for ITN use]

Table 1: **Characteristics of six trials of IPT with sulfadoxine-pyrimethamine versus placebo in infants**

to the elimination half-life reported by the manufacturer, residual sulfadoxine plasma concentrations after 5 weeks are less than 5%, which is consistent with negligible inhibitory activity.[18] [A: please mention that the potential rebound effect was examined, and why]

Negative binomial regression, which allows for potential clustering of episodes within individuals, was used to investigate the effect of IPT on the incidence of all episodes of clinical malaria, clinical malaria with a locally sensitive case definition,[19] all-cause hospital admissions, and hospital admissions associated with microscopically confirmed [A: correct?] malaria parasitaemia. To allow for clustering across individuals within the trial in Navrongo, robust SEs were used. Incidence was calculated as the number of episodes divided by the time at risk (for definitions see table 2). [A:is this ok to add here?] Infants were not deemed at risk for 21 days after a clinical malaria episode, hospital admission, or receipt of an antimalarial treatment. This 21-day period was selected to avoid overlap with the 28-day period for active detection visits in the trials in Kumasi and Lambaréné. The effect of IPT on the relative risk of at least one episode of anaemia, with as the denominator the number of children at risk from the first dose until 12 months of age, was analysed by use of a Poisson regression model, with log-link and a robust error variance.[20]

The efficacy of IPT was defined as (1–RR)×100, where RR is the relative rate or relative risk [A: since relative risk can mean rate ratio or risk ratio, please define which is used]. Combined estimates were obtained by meta-

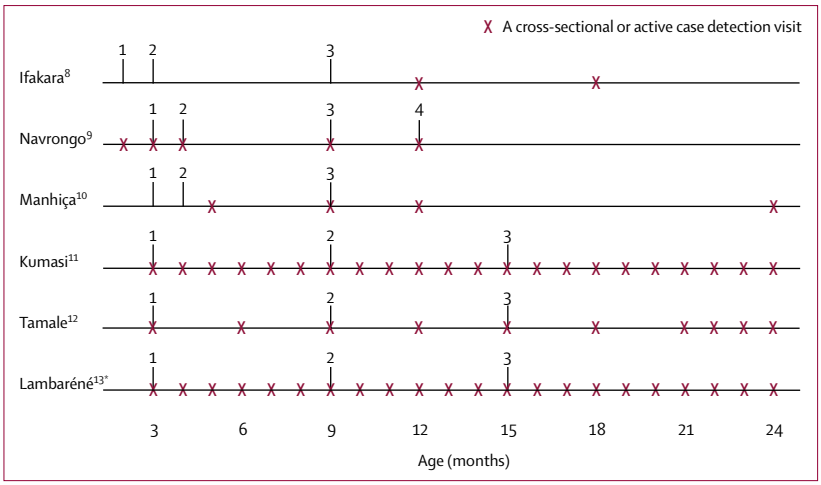

Figure 1: **Schedules of study treatment and follow-up visits**
Vertical bars represent the age when intermittent preventive treatment with sulfadoxine-pyrimethamine or placebo was given (and number of dose). *Follow-up in the trial in Lambaréné was up to 30 months of age.

analysis with random effects, and as weight for each trial the inverse of the SE of the estimated RR in the logarithmic scale. To assess the effect of an individual trial in the meta-analysis, sensitivity analyses were done in which one study at a time was removed from the analysis. Analyses were done with Stata version xx software. [A: version number?]

Standard WHO definitions were used for adverse events and for the grading of severity.[21] In all trials apart from the one in Kumasi, a serious adverse event was defined as a hospital admission or death. In the trial in Kumasi, a life-threatening event or enduring disability was also judged as a serious adverse event (in the other trials, a patient with a life-threatening event would be admitted to hospital [A: edit ok?]). Assessment of causality was made by the on-site principal investigator or physician. Causality was assessed on symptoms known to be related to sulfadoxine-pyrimethamine, apart from in the trial in Kumasi where all adverse events that occurred within 8 weeks of treatment were deemed possibly related to study drug. Serious adverse events that occurred more than 3 months after the last dose of study drug were deemed very unlikely to be related to treatment and excluded from these analyses.

The number of deaths, non-fatal hospital admissions, serious dermatological adverse events [A: why were only dermatological adverse events analysed?], total sample size, and person-time at risk were extracted by principal investigators or statisticians and reviewed by the consortium safety panel. A meta-analysis was done on the risk of mortality by use of Review Manager version 5.0 or StatsDirect version 2.7.1 software. The numerator was the number of deaths, and the denominator was the number of infants who received at least one dose of IPT or placebo [A: ok?]. The pooled rate ratio was calculated by the DerSimonian-Laird method. For the trial that was cluster randomised, the rate ratio and SE of the rate ratio were estimated by use of a robust cluster method. The cluster-adjusted SE was identical to the unadjusted SE.

Heterogeneity between trials was assessed by visual inspection of forest plots of the effects and 95% CIs for each site, calculation of a χ^2 test for heterogeneity (statistical significance at 10% level), and calculation of the I^2 statistic (which quantifies the amount of heterogeneity over and above that expected due to chance alone on a scale from 0% to 100%).[22] Fixed-effect meta-analysis was used to pool data for this outcome measure.

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.

	Start of time at risk	End of time at risk
Efficacy (clinical malaria, hospital admissions, anaemia)		
Primary	Dose 1 of IPT or placebo	12 months of age
Secondary	Dose 1 of IPT or placebo	3 months after the last dose of IPT or placebo
Prophylactic effect I	Dose of IPT or placebo at 3 months of age*	35 days after start of time at risk
Prophylactic effect II	Dose of IPT or placebo at 9 months of age†	35 days after start of time at risk
Prophylactic effect III	Dose of IPT or placebo at 12 months or 15 months of age‡	35 days after start of time at risk
Inter-dose effect	35 days after the dose of IPT or placebo at 3 or 4 months of age	Dose of IPT or placebo at 9 months of age
Potential rebound I	35 days after the dose of IPT or placebo at 9 months of age	15 months of age or the next dose of IPT or placebo§
Potential rebound II	35 days after the last dose of IPT or placebo¶	5 months after start of time at risk
Safety (deaths, adverse effects)		
Primary	Dose 1 of IPT or placebo	3 months after the last dose given or 12 months of age

IPT=intermittent preventive treatment. * Dose 2 in the trial in Ifakara, dose 1 in the other trials. †Dose 3 in the trials in Ifakara, Navrongo, and Manhiça; dose 2 in the trials in Kumasi, Tamale, and Lambaréné. ‡Dose 4 in the trial in Navrongo at 12 months; dose 3 in the trials in Kumasi, Tamale, and Lambaréné at 15 months of age. §Next dose at 12 months of age in the trial in Navrongo, and 15 months of age in the trials in Kumasi, Tamale, and Lambaréné. ¶Last dose was at 9 months of age in the trials in Ifakara and Manhiça, at 12 months of age in the trial in Navrongo, and at 15 months of age in the trials in Kumasi, Tamale, and Lambaréné. [A: "or placebo" added to all—ok?]

Table 2: **Risk periods for each analysis**

	Ifakara[8]	Navrongo[9]	Manhiça[10]	Kumasi[11]	Tamale[12]	Lambaréné[13]
From dose 1 until 12 months of age						
Clinical malaria						
Primary definition*	59·4% (41·7 to 71·7)	30·3% (17·8 to 40·9)	20·8% (3·5 to 35·0)	20·7% (8·7 to 31·2)	32·4% (19·6 to 43·2)	22·6% (−24·2 to 51·7)
Locally defined cut-off density†	61·9% (43·5 to 74·3)	32·3% (16·9 to 44·8)	30·9% (14·4 to 44·3)	22·7% (9·2 to 34·1)	27·4% (4·7 to 44·6)	29·2% (−15·1 to 56·5)
High-density cut-off‡	56·3% (25·3 to 74·5)	33·2% (14·0 to 48·1)	26·6% (6·5 to 42·4)	18·4% (−15·1 to 42·2)	26·0% (−22·0 to 55·1)	26·2% (−49·0 to 63·5)
All-cause hospital admissions	29·0% (6·6 to 46·1)	18·3% (0·3 to 33·1)	24·9% (6·6 to 39·7)	17·8% (−22·5 to 44·8)	49·8% (18·5 to 69·0)	−35·8% (−142·3 to 23·9)
Hospital admissions associated with malaria parasitaemia§	58·3% (28·4 to 75·8)	52·1% (29·5 to 67·5)	20·3% (−19·9 to 47·0)	−6·6% (−103·1 to 44·1)	44·5% (−80·1 to 82·9)	..
Anaemia (reduced risk of first or only episode)¶	49·9% (8·4 to 72·5)	46·5% (21·2 to 63·7)	5·4% (−27·5 to 29·8)	11·1% (−4·5 to 24·4)	17·0% (0·8 to 30·5)	25·2% (−2·7 to 45·5)
Against clinical malaria (primary definition) on different follow-up times						
Prophylactic effect‖						
I (after dose at 3 months of age)	77·7% (−3·0 to 95·2)	75·6% (49·6 to 88·2)	57·5% (20·6 to 77·3)	82·0% (61·8 to 91·5)	83·0% (12·8 to 96·7)	74·8% (−125·5 to 97·2)
II (after dose at 9 months of age)	91·1% (62·1 to 97·9)	79·3% (69·5 to 85·9)	65·2% (37·1 to 80·7)	47·6% (17·1 to 66·8)	97·6% (90·5 to 99·4)	72·9% (−53·2 to 95·2)
III (after dose at 12 or 15 months of age)	..	73·7% (57·6 to 83·7)	..	29·7% (−5·1 to 52·9)	90·6% (79·7 to 95·6)	77·5% (−100·9 to 97·5)
Inter-dose effect period**	42·4% (−1·2 to 67·3)	12·9% (−6·8 to 29·0)	−8·0% (−39·3 to 16·3)	11·5% (−6·1 to 26·2)	19·6% (−0·2 to 35·5)	11·2% (−62·9 to 51·6)
Potential rebound period I††	29·0% (−4·2 to 51·6)	−3·4% (−29·3 to 17·5)	7·4% (−13·4 to 24·4)	7·8% (−9·1 to 22·1)	19·6% (−2·2 to 36·7)	12·7% (−54·9 to 50·8)
Potential rebound period II‡‡						
Clinical malaria (primary definition)	30·3% (1·0 to 50·9)	0·2% (−20·3 to 17·1)	−11·0% (−45·0 to 15·0)	−5·8% (−24·0 to 9·8)	−0·3% (−18·9 to 15·4)	−36·3% (−147·3 to 24·9)
All-cause hospital admissions	−7·9% (−51·9 to 23·4)	−16·5% (−54·0 to 11·9)	8·4% (−25·6 to 33·2)	−19·8% (−108·0 to 31·0)	24·6% (−21·5 to 53·3)	−1·4% (−115·7 to 52·3)
Hospital admissions associated with malaria parasitaemia	11·3% (−74·4 to 54·9)	−8·6% (−79·5 to 34·3)	−36·1% (−117·4 to 14·8)	−47·7% (−261·2 to 39·6)	−74·5% (−496·1 to 48·9)	..
Anaemia (reduced risk of first or only episode)	40·0% (−11·8 to 67·8)	−24·2% (−105·0 to 26·3)	10·8% (−36·4 to 41·7)	−2·5% (−22·9 to 14·6)	3·4% (−9·9 to 15·1)	−15·1% (−154·3 to 47·9)

..=data not available. IPT=intermittent preventive treatment. Data are % protective efficacy (95% CI). Protective efficacy defined as (1–RR)×100. [A: ok?] *Primary definition: history of fever or measured fever with any *P falciparum* parasitaemia. History of fever included reported fever during the past 24 h in the trials in Ifakara and Manhiça, and during the past 48 h for the other four trials. Measured fever was defined as an axillary temperature 37·5°C or more for the trials in Ifakara, Navrongo, Tamale, and Manhiça; rectal or tympanic temperature 38°C or more for the trial in Kumasi, and 38·5°C or more for the trail in Lambaréné. †A history of fever, or measured fever, with a minimum *P falciparum* parasite density for each site chosen to have a specificity more than 90%; trials in Ifakara, Manhiça, and Kumasi more than 500 parasites per µL; trial in Lambaréné more than 600 parasites per µL; trial in Tamale more than 5000 parasites per µL; trial in Navrongo more than 8000 parasites per µL. ‡Episodes with a history of fever or measured fever with *P falciparum* parasitaemia more than 20 000 parasites per µL. §Admissions to a paediatric ward with any *P falciparum* parasitaemia irrespective of symptoms suggestive of malaria or a clinical diagnosis of malaria. ¶Packed-cell volume less than 25% in the trials in Ifakara, Navrongo, and Manhiça, and a haemoglobin concentration less than 80 g/L in the trials in Kumasi, Lambaréné, and Tamale. ‖See table 2 for definitions. **From 35 days after dose at 3 months or 4 months of age until dose at 9 months of age. ††From 35 days after the dose at 9 months of age up to the next dose of IPT or age 15 months. ‡‡5-month period starting 35 days after last dose. [A: please check all footnotes are cited correctly]

Table 3: **Protective efficacies of IPT with sulfadoxine-pyrimethamine in infants**

Results

[A: to conform with journal style, subheadings have been deleted from this section. Also, to avoid repetition, any data in the text that is clearly shown in the tables and figures has been deleted]

This analysis is based on data from 7930 infants (IPT, n=3958; placebo, n=3972) in all six trials of IPT with sulfadoxine-pyrimethamine in infants published up to May, 2009. Reported baseline characteristics were similar between IPT and placebo groups in all the trials. [A: please provide a table showing the baseline characteristics of the two groups]

Table 3 shows the estimates of efficacy of IPT in infants up to 12 months of age in the individual trials. The combined estimate of protective efficacy against the primary definition of clinical malaria in children aged up to 12 months was 30·3% (95% CI 19·8–39·4, p<0.0001; figure 2 and table 4). There was significant heterogeneity between trials (I^2=61·8%). Removal of the trial with the highest protective efficacy (Ifakara) reduced heterogeneity to non-significant levels, and the combined efficacy estimate to 25·9% (19·6–31·7%, p<0·001; table 4). [A: please provide exact p value unless p<0·0001] Detailed information about each analysis, including the total number of events and person-years at risk, total number of children in each site and outcome, as well as other analyses are provided in the webappendix.

The effect of IPT on the relative risk of anaemia in infants ranged from 5·4% to 49·9%, with moderate heterogeneity between trials (I^2=46·9%). The combined efficacy estimate for risk of anaemia was 21·3% (8·2–32·5, p=0·002; table 4).

IPT had protective efficacies of 22·9% (10·0–34·0, p=0·001) against all-cause hospital admissions and 38·1% (12·5–56·2, p=0·007) and for hospital admissions associated with malaria parasitaemia (table 4). The heterogeneity between trials for these two outcomes was moderate (I^2=33·5% and 49·6%, respectively); however, removing the trial with the highest protective efficacy made little difference to the estimates (table 4).

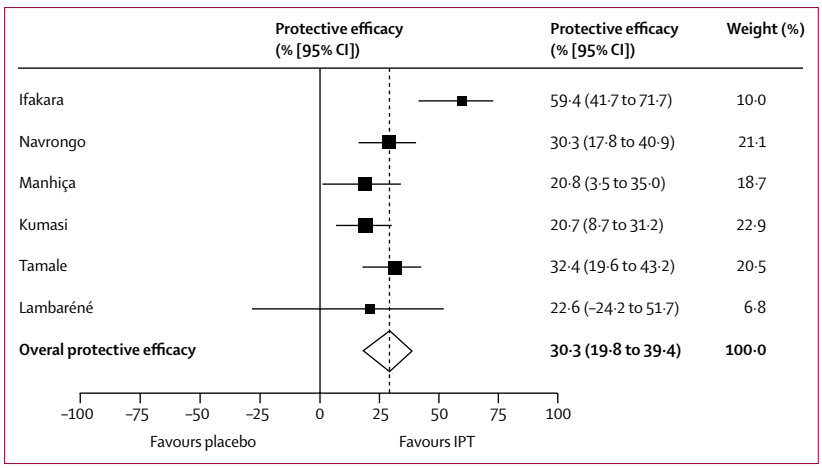

***Figure 2*: Combined estimates for the protective efficacy of IPT with sulfadoxine-pyrimethamine in infants against clinical malaria from dose 1 up to 12 months of age**
The width of the diamond represents the 95% CI interval in the overall pooled protective efficacy estimate.
[A: vertical line moved to 0%. Ok?]

Prophylactic effects I, II, and III are the 35-day intervals following the doses at 3 months, 9 months, and 12 or 15 months of age, respectively. During prophylactic effect I, the incidence of clinical malaria was between 57·5% and 83·0% lower in the IPT group than in the placebo group **[A: is this edit correct—ie, these were the % differences?]** (table 3). Malaria incidence was 47·6–97·6% and 29·7–90·6% lower in the ITP group than in the placebo group during prophylactic effects II and III, respectively. **[A: is this edit correct?]** Analyses of the inter-dose effect (35 days after the IPT or placebo dose at 3 or 4 months of age until the dose at 9 months of age) varied between trials with borderline significant efficacy in the trials in Ifakara and Tamale, but no effect was seen in the other trials.

Incidence of clinical malaria and hospital admissions and the risk of anaemia did not differ between groups in either of the potential rebound periods (tables 3 and 4, see table 2 for definitions). **[A: edit ok?]** Similar results were found in the sensitivity analysis (table 4).

There were 56 deaths (1·4%) in the IPT group compared with 53 (1·3%) in the placebo group (rate ratio 1·05, 95% CI 0·72–1·54, p=0·79). There was moderate statistical heterogeneity in the number of deaths between trials (I^2=24·6%). One death, in the IPT group of the trial in Kumasi, was classified as possibly caused by study treatment **[A: ok, rather than IPT? Were assignment groups still masked when classified?]**, since it occurred 19 days after a treatment dose (table 5). At the visit after administration of the second dose at 9 months of age, malaria was confirmed by microscopy and the infant received amodiaquine, and iron and folic acid supplementation. 2 weeks later, the infant became very weak, was admitted to hospital, given a blood transfusion for severe anaemia, and received penicillin, artesunate, paracetamol, iron, and folic acid. The infant was discharged 6 days later in an apparently satisfactory condition but died the next night at home. The most probable cause of death was sepsis with complications of recent malaria and severe anaemia.

Four of 676 non-fatal hospital admissions in the IPT group were deemed related to study treatment (assigned while the trials were masked), compared with five of 860 in the placebo group. **[A: edit ok?]** In the trial in Kumasi, causality could not be assessed for five hospital admissions (IPT, n=3; placebo, n=2) because hospital files were missing.

Three serious dermatological adverse events were reported in the IPT group; however, none of these was judged related to study treatment (table 5). Of 13 serious dermatological adverse events in the placebo group, one was classified as possibly related to study drug, since it occurred within 3 weeks after a dose. At the time of the second dose of study treatment at 9 months of age, the infant had malaria and received artesunate-amodiaquine (in addition to study treatment) but was not admitted to hospital. The infant developed bullous skin lesions 3 weeks later. Another infant in the placebo group was diagnosed with Stevens–Johnson syndrome and died at the age of 5 months from multiple organ failure, 2 months after the first dose of study treatment. The infant was HIV-positive and had been started on agents known to be associated with Stevens–Johnson syndrome (antituberculosis drugs [isoniazid, rifampicin, pyrazinamide, and ethambutol] and co-trimoxazole) 5 days before the onset of dermatological symptoms. The child had not been admitted to hospital.

Discussion

[A: any repetition of Introduction and Results sections has been deleted] This pooled analysis of six randomised, placebo-controlled trials showed that the incidence of clinical malaria and hospital admissions and the risk of anaemia were lower in infants assigned to ITP with sulfadoxine-pyrimethamine than in those assigned to placebo. Other trials of intermittent treatment were not included in this analysis because they used different drugs and did not deliver IPT at the same time as EPI vaccines,[23] used IPT as a treatment for anaemia in children,[24,25] or gave IPT with monthly intervals to schoolchildren[26] or children up to 5 years or 10 years of age in settings with highly seasonal transmission of malaria.[27–29] **[A: edit ok (ie, were the schoolchildren in ref 26 given IPT at monthly intervals)?]**

None of the individual trials had sufficient power to assess the effect of IPT on mortality. However, our meta-analysis found that the overall number of deaths did not differ between groups, suggesting that IPT does not reduce mortality compared with placebo. All the studies provided study participants with good access to curative services, which, combined with intensive follow-up in some studies, might account for the low crude mortality rates recorded in the trials. Our efficacy estimates might therefore underestimate the potential effect of IPT on

	Placebo			IPT			Combined estimates			Sensitivity analysis§		
	Events	PYAR*	Incidence per PYAR	Events	PYAR*	Incidence per PYAR	Pooled estimate of protective efficacy† (% [95% CI])	I2‡	p value	Pooled estimate of protective efficacy† (% [95% CI])	p value	Trial removed
From dose 1 until 12 months of age												
Clinical malaria												
Primary definition¶	2257	2598	0·87	1658	2625	0·63	30·3% (19·8 to 39·4)	61·8	<0·0001	25·9% (19·6, 31·7)	??	Ifakara[8]
Locally defined cut-off density‖	1473	2632	0·56	1048	2651	0·40	32·9% (21·8 to 42·4)	53·7	??	27·7% (20·2 to 34·5)	??	Ifakara[8]
High-density cut-off**	656	2671	0·25	467	2684	0·17	29·9% (19·3 to 39·1)	0	??	27·4% (16·1 to 37·3)	??	Ifakara[8]
All-cause hospital admissions	898	2776	0·32	714	2783	0·26	22·9% (10·0 to 34·0)	33·5	0·001	20·6% (9·8 to 30·1)	??	Tamale[12]
Hospital admissions associated with malaria parasitaemia††	233	2477	0·09	141	2480	0·06	38·1% (12·5 to 56·2)	49·6	0·007	31·4% (–0·4 to 53·1)	??	Ifakara[8]
Anaemia (reduced risk of first or only episode)‡‡	656	3963	0·17	526	3948	0·13	21·3% (8·2 to 32·5)	46·9	0·002	18·7% (6·2 to 29·5)	??	Ifakara[8]
Against clinical malaria (primary definition) on different follow-up times												
Prophylactic effect§§												
I (after dose at 3 months of age)	152	341	0·45	42	344	0·12	73·1% (60·9 to 81·4)	0	??	72·4% (59·6 to 81·2)	??	Tamale[12]
II (after dose at 9 months of age)	309	307	1·00	87	323	0·27	79·7% (60·1 to 89·7)	79·8	??	71·3% (51·0 to 83·2)	??	Tamale[12]
III (after dose at 12 or 15 months of age)	237	207	1·14	95	224	0·42	73·5% (31·3 to 89·8)	87·6	??	59·8% (5·4 to 82·9)	??	Tamale[12]
Inter-dose effect period¶¶	1185	1294	0·92	1054	1298	0·81	12·1% (2·2 to 21·0)	5·7	??	10·8% (1·1 to 19·6)	??	Ifakara[8]
Potential rebound period I‖‖	1264	1405	0·90	1166	1415	0·82	9·5% (0·3 to 17·8)	0	0·044	8·0% (–1·7 to 16·7)	??	Ifakara[8]
Potential rebound period II* **												
Clinical malaria (primary definition)	1491	1368	1·09	1502	1370	1·10	–1·0% (–11·9 to 8·7)	18	0·843	–3·9% (–13·9 to 5·2)	??	Ifakara[8]
All-cause hospital admissions	404	1408	0·29	413	1470	0·28	–2·7% (–20·2 to 12·1)	0	0·735	–6·6% (–25·9 to 9·6)	??	Tamale[12]
Hospital admissions associated with malaria parasitaemia	105	1308	0·08	124	1302	1·0	–20·2% (–59·3 to 9·3)	0	0·199	–28·2% (–74·7 to 6·0)	??	Ifakara[8]
Anaemia (reduced risk of first or only episode)	531	3839	0·14	522	3821	0·14	2·1% (–8·0 to 11·2)	0	0·673	0·9% (–9·5 to 10·2)	??	Ifakara[8]

PYAR=person-years at risk. IPT=intermittent preventive treatment. *Apart from anaemia, where the total number of children at risk is presented. †Protective efficacy defined as (1–RR)×100. ‡Proportion of the variation attributable to heterogeneity is presented as I2. §The sensitivity analysis removes the trial with the highest protective efficacy from table 3. ¶Primary definition: history of fever or measured fever with any *P falciparum* parasitaemia. History of fever included reported fever during the past 24 h in the trials in Ifakara and Manhiça, and during the past 48 h for the other four trials. Measured fever was defined as an axillary temperature 37·5°C or more for the trials in Ifakara, Navrongo, Tamale, and Manhiça; rectal or tympanic temperature 38°C or more for the trial in Kumasi, and 38·5°C or more for the trial in Lambaréné. ‖A history of fever, or measured fever, with a minimum *P falciparum* parasite density for each site chosen to have a specificity of more than 90%; trials in Ifakara, Manhiça, and Kumasi more than 500 parasites per µL; trial in Lambaréné more than 600 parasites per µL; trial in Tamale more than 5000 parasites per µL; trial in Navrongo more than 8000 parasites per µL. **Episodes with a history of fever or measured fever with *P falciparum* parasitaemia more than 20 000 parasites per µL. ††Admissions to a paediatric ward with any *P falciparum* parasitaemia irrespective of symptoms suggestive of malaria or a clinical diagnosis of malaria. ‡‡Packed-cell volume less than 25% in trials in Ifakara, Navrongo, and Manhiça and a haemoglobin concentration less than 80 g/L in trials in Kumasi, Lambaréné, and Tamale. §§For definitions see table 2. ¶¶From 35 days after dose at 3 months or 4 months of age until dose at 9 months of age. ‖‖From 35 days after the dose at 9 months of age up to the next dose of IPT or age 15 months. ***5-month period starting 35 days after last dose. **[A: please check all footnotes are cited correctly] [A: incidence has been added, so that readers can compare IPT and placebo more easily. Please check that these figures are correct] [A: please check p values added and provide the missing values]**

Table 4: **Combined estimates and sensitivity analysis|**

mortality in populations with poor access to curative health services. Although IPT did not affect mortality rates, it was associated with a reduced incidence of illness sufficiently severe to warrant hospital admission, reflecting a potential of IPT to save lives. A pooled analysis of safety and efficacy at 3 months after the last dose given (ie, including doses given between 12 months and 24 months) in four of the six trials showed similar safety and efficacy outcomes to the analysis at 12 months of age.

Careful assessment of safety is important when preventive interventions are being evaluated, since those given to healthy individuals need to have very high benefit-to-harm ratios. None of the serious dermatological adverse events in the IPT group was associated with study treatment. However, there was one suspected case

For more on the **pooled analysis at 3 months after the last dose given** see http://www.ipti-malaria.org

	IPT		Placebo	
	Events	Number of events possibly related to treatment	Events	Number of events possibly related to treatment
Deaths (number of deaths/number of infants [%]) [A1]				
Ifakara[8]	5/350 (0·9%)	0	10/351 (2·8%)	0
Navrongo[9]*	22/1221 (1·8%)	0	11/1225 (0·9%)	0
Manhiça[10]	20/748 (2·7%)	0	22/755 (2·9%)	0
Kumasi[11]	3/535 (0·6%)	1	3/535 (0·6%)	0
Tamale[12]	6/600 (1·0%)	0	7/599 (1·2%)	0
Lambaréné[13]	0/504 (0%)	0	0/507 (0%)	0
Total	56/3958 (1·4%)	1	53/3972 (1·3%)	0
Non-fatal hospital admissions (number of admissions/PYAR [incidence per PYAR])				
Ifakara[8]	106/248 (0·43)	0	151/251 (0·60)	0
Navrongo[9]*	248/874 (0·28)	0	309/867 (0·26)	0
Manhiça[10]	227/495 (0·46)	0	279/487 (0·57)	0
Kumasi[11]†	46/386 (0·12)	1	52/389 [A3] (0·13)	2
Tamale[12]	23/402 (0·06)	1	52/401 (0·13)	1
Lambaréné[13]	26/327 (0·08)	2	17/330 (0·05)	2
Total [A2]	676	4	860	5
Serious dermatological adverse events (number of events/PYAR [incidence per PYAR])				
Ifakara[8]	0/248	0	0/251	0
Navrongo[9]*	..		..	
Manhiça[10]	2/495 (0·004)	0	7/487 (0·01)	0
Kumasi[11]	0/386	0	2/398 [A3] (0·005)	1
Tamale[12]	0/402	0	2/401 (0·005)	0
Lambaréné[13]	1/327 (0·003)	0	2/330 (0·006)	0
Total [A2]	3	0	13	1

IPT=intermittent preventive treatment. PYAR=person-years at risk. ..=data not available. *In the trial in Navrongo, no deaths or serious dermatological adverse events were judged related to treatment, but no more details are available. †In the trial in Kumasi, three hospital admissions in the sulfadoxine-pyrimethamine group and two in the placebo group were not assessable to work out causality. [A1: percentages and incidences have been added, so that readers can compare IPT and placebo more easily. Please check that these figures are correct] [A2: why is the denominator not present?] [A3: person-years at risk differ in this trial (389 for hospital admissions, 398 for SAEs), which is correct?]

Table 5: **Deaths, non-fatal hospital admissions, and serious dermatological adverse events up to 12 months of age, or 3 months after the last dose of study treatment received, whichever is earlier**

of Stevens–Johnson syndrome in the placebo group of the trial in Kumasi. Two further possible cases of this syndrome have also been reported in children from the same site, after they received a third dose of IPT [A: please confirm they were in the IPT group and not the placebo group] at 15 months of age.[11] Both children recovered without admission to hospital and presented to the study team in the convalescent phase. The study team erred on the side of caution and reported suspected Stevens–Johnson syndrome, although the diagnosis has not been confirmed (May J, personal communication). After a review of the existing information, reports, and a photograph of one of the cases, the consortium safety panel judged these two cases as unlikely to be Stevens–Johnson syndrome. IPT data, including the pooled analyses for safety and efficacy, were reviewed by a panel of experts convened by the US Institute of Medicine. The experts also concluded that these cases were highly unlikely to be Stevens–Johnson syndrome,[30] because the syndrome is a severe disorder that requires intensive care, is associated with a high case-fatality rate, and a patient with the syndrome who is not admitted to hospital in a rural African setting is unlikely to recover.

Large-scale implementation studies of IPT with sulfadoxine-pyrimethamine in infants are being done by the IPTi Consortium in Tanzania and by UNICEF in six other African countries [A: are there references for these?]. Across these studies, more than 250 000 infants a year are receiving three doses of IPT alongside routine vaccination delivered by the EPI. So far, no serious adverse events related to IPT have been reported to the consortium safety panel (Schellenberg D, unpublished data; de Sousa A, [A: affiliation?], personal communication). Data obtained in the trials in Manhiça and Navrongo suggest that IPT with sulfadoxine-pyrimethamine has no adverse effect on serological responses to vaccines for polio, hepatitis B, measles, or diphtheria, tetanus, and pertussis (DTP),[9,10] and there are reassuring data on yellow fever vaccination [A: what do you mean here—there is less convincing evidence for yellow fever vaccines, or that the evidence is from the following report? Please rephrase to clarify] (Interim report on IPTi with SP, WHO Advisory Committee on serological responses to EPI vaccines in infants receiving IPTi, WHO Internal Report 2006 [A: is this report in the public domain? If so, we would prefer to add to the reference list]).

The individual trials reported different findings for various extended follow-up periods after the last dose of IPT or placebo. Sustained protection against clinical malaria was seen up to the age of 2 years in children assigned to IPT in the trial in Ifakara.[31] In children aged between 16 months and 24 months in Navrongo, incidence of clinical malaria with a parasite density more than 5000 per μL was higher in the IPT group than in the placebo group. In the trial in Kumasi, the number of episodes of anaemia (haemoglobin <75 g/L) during the 8-month period starting 5 weeks after the last dose at 15 months of age was higher in the ITP group than in the placebo group; however, this difference was not seen with definitions of anaemia of haemoglobin 70 g/L or 80 g/L. In the trial in Tamale, the risk of severe malarial anaemia (haemoglobin <50 g/L) during the 8-month period starting 1 month after the last IPT dose at 15 months of age in children assigned to IPT was about double the risk in children assigned to placebo. There was no evidence of either sustained protection or of increased risk during extended follow-up in the trials in Lambaréné and Manhiça. [A: this section is a little difficult to read and understand. Can you rephrase or present the results in a different way?]

Even though findings have not been consistent across different endpoints within or between trials, they have raised concerns that IPT in infants might impair the development of naturally acquired immunity to malaria.

In the 5-month period starting 35 days after the last dose (ie, after treatment completion), [A: correct?] the incidence of hospital admissions associated with malaria parasitaemia was higher in the IPT group than in the placebo group; however, the pooled effect estimate did not reach statistical significance and there were no significant increases in incidence of clinical malaria or all-cause hospital admissions, or in risk of anaemia during this period. These findings contrast with the protective effect seen against these endpoints during the intervention period and, thus, the balance of risks and benefits seem to favour IPT. Nevertheless, monitoring of morbidity should be part of studies of effectiveness and phase IV studies in which IPT in infants is implemented. A pooled analysis for a possible rebound effect was done for those trials with extended follow-up periods (Ifakara, Manhiça, Lambaréné, and Navrongo); outcomes did not differ between IPT and placebo groups in the 11-month period starting 35 days after the last dose (data not shown).

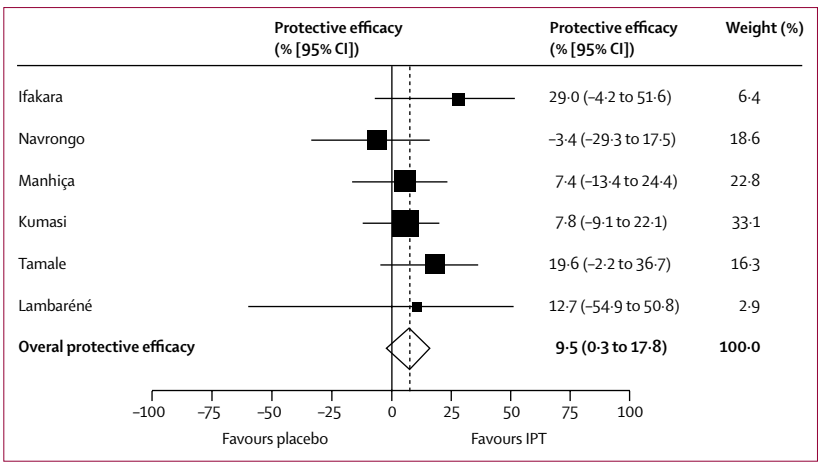

Figure 3: **Combined estimates for the protective efficacy of IPT with sulfadoxine-pyrimethamine in infants against clinical malaria from 35 days after the dose at 9 months of age until next dose or 15 months of age**
The width of the diamond represents the 95% CI interval in the overall pooled protective efficacy estimate.
[A: vertical line moved to 0%. Ok?]

The first trial of IPT in infants, undertaken in Ifakara, showed high protective efficacy of the intervention. Because of these results, additional trials were done; however, they reported lower estimates of protective efficacy. Protective efficacy against clinical malaria was similar between trials during all periods analysed, apart from during the inter-dose period, when efficacy was higher in the trial in Ifakara than in the other trials. Because of the differences in trial design between the six studies, we were unable to draw conclusions about the conditions under which IPT in infants might have the best possible effect. However, a detailed comparison between very similar trials in Ifakara and Manhiça[32] suggested that the combined use of insecticide-treated bednets and IPT might explain the higher efficacy reported in the Ifakara trial. Nevertheless, when sulfadoxine-pyrimethamine and artesunate were coadministered as IPT in a trial in western Kenya, where use of insecticide-treated bednets was very high, efficacy [A: against clinical malaria?] was less than 30% (Newman R, Slutsker L, unpublished data).

Parasite resistance to sulfadoxine-pyrimethamine has spread across Africa, which could undermine the efficacy of IPT in infants. The highest reported frequency of resistance during the trials was 31% (as measured by the WHO standard day 14 in-vivo clinical and parasitological resistance in 6–59-month-old symptomatic children). This level of resistance, which corresponds with intermediate levels as defined by ter Kuile and colleagues,[33] did not preclude protective efficacy when sulfadoxine-pyrimethamine was used for IPT in infants. Furthermore, the site with the highest level of resistance to the drug combination (Ifakara)[34] had the highest efficacy of IPT, and in all trials (apart from in Lambaréné and after the last dose of IPT in Kumasi), there was significant protection in the month after an IPT dose. These findings call into question the value of estimates of curative efficacy to inform the use of antimalarial drugs for prevention where infections might be of low density and asymptomatic [A: meaning of highlighted sentence unclear; please rephrase]. Moreover, the increasing use of artemisinin-based combination therapy will lead to a reduction in the use of sulfadoxine-pyrimethamine, reducing the spread of resistance and prolonging the duration for which this drug combination could be useful for IPT. A corresponding concern is that IPT with sulfadoxine-pyrimethamine in infants might facilitate the spread of drug resistance. Although the prevalence of markers of resistance to sulfadoxine-pyrimethamine increases after doses in infants,[35,36] mathematical models suggest that the size of such effect in the global spread of resistance will be small.[37] At present, sulfadoxine-pyrimethamine is the only antimalarial drug available for IPT in both pregnancy and infancy, in view of the combination's long half-life and prophylactic effect, established safety profile, acceptability,[7,38] and affordability. IPT seems to work by prophylaxis, with sulfadoxine-pyrimethamine providing protection for up to 6 weeks in infants.[39,40] New long-acting antimalarial drugs are urgently needed for use in IPT in infants.

Where malaria transmission is highly seasonal and severe malaria occurs rarely in infants, methods for delivering IPT to older children might be needed.[41] However, in areas with a substantial burden of malaria in infants, delivery of IPT through WHO's EPI system has been shown to be highly cost effective.[42]

[A: please provide a brief paragraph discussing the limitations of your analysis]

This pooled analysis substantiates the notion that IPT is safe and efficacious in infants. Furthermore, operational experience from Tanzania[43] and six other African countries [A: reference?] shows that rapid large-scale deployment of IPT is feasible. Thus, this intervention

For the **pooled analysis of the extended follow-up period** see http://www.ipti-malaria.org

could make an important contribution to reducing the intolerable burden of malaria in infants and should be integrated with other effective control methods.[32,44–50]

Contributors

JJA, IC, ID, RK, BL, JM, and SS developed and undertook the pooled efficacy analysis. AB, JC, AD, ZP, ES, RS-B, and PW compiled and analysed the safety information. SAd, PA, SAn, DC, BG, MPG, SI, PGK, EM, JM, CM, FM, HM, SO-A, DS, and TM were principal and co-principal investigators of the six randomised controlled clinical trials and shared the data used for the analyses presented in this report. AE was the coordinator of the IPTi Consortium, coordinated the pooled analyses, and was involved in the development of this report. PA, BG, MPG, PGK, CM, RDN, DS, LS, and MT had a key role in the development and establishment of the IPTi Consortium, providing overall leadership in the activities and development of the analyses and this report. PA, JJA, AB, JC, AE, CM, and DS wrote the manuscript. All authors saw and approved the final version of the report [A: correct?].

Conflicts of interest

We declare that we have no conflicts of interest.

Acknowledgments

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