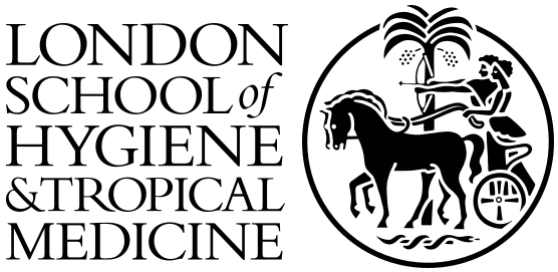

Effect of *Plasmodium falciparum* sulfadoxine-pyrimethamine resistance on the effectiveness of intermittent preventive therapy for malaria in pregnancy in Africa: a systematic review and meta-analysis

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Summary

Background Resistance of *Plasmodium falciparum* to sulfadoxine-pyrimethamine threatens the antimalarial effectiveness of intermittent preventive treatment during pregnancy (IPTp) in sub-Saharan Africa. We aimed to assess the associations between markers of sulfadoxine-pyrimethamine resistance in *P falciparum* and the effectiveness of sulfadoxine-pyrimethamine IPTp for malaria-associated outcomes.

Methods For this systematic review and meta-analysis, we searched databases (from Jan 1, 1990 to March 1, 2018) for clinical studies (aggregated data) or surveys (individual participant data) that reported data on low birthweight (primary outcome) and malaria by sulfadoxine-pyrimethamine IPTp dose, and for studies that reported on molecular markers of sulfadoxine-pyrimethamine resistance. Studies that involved only HIV-infected women or combined interventions were excluded. We did a random-effects meta-analysis (clinical studies) or multivariate log-binomial regression (surveys) to obtain summarised dose-response data (relative risk reduction [RRR]) and multivariate meta-regression to explore the modifying effects of sulfadoxine-pyrimethamine resistance (as indicated by Ala437Gly, Lys540Glu, and Ala581Gly substitutions in the *dhps* gene). This study is registered with PROSPERO, number 42016035540.

Findings Of 1097 records screened, 57 studies were included in the aggregated-data meta-analysis (including 59 457 births). The RRR for low birthweight declined with increasing prevalence of *dhps* Lys540Glu (p_{trend}=0·0060) but not Ala437Gly (p_{trend}=0·35). The RRR was 7% (95% CI 0 to 13) in areas of high resistance to sulfadoxine-pyrimethamine (Lys540Glu ≥90% in east and southern Africa; n=11), 21% (14 to 29) in moderate-resistance areas (Ala437Gly ≥90% [central and west Africa], or Lys540Glu ≥30% to <90% [east and southern Africa]; n=16), and 27% (21 to 33) in low-resistance areas (Ala437Gly <90% [central and west Africa], or Lys540Glu <30% [east and southern Africa]; n=30; p_{trend}=0·0054 [univariate], I^2=69·5%). The overall RRR in all resistance strata was 21% (17 to 25). In the analysis of individual participant data from 13 surveys (42 394 births), sulfadoxine-pyrimethamine IPTp was associated with reduced prevalence of low birthweight in areas with a Lys540Glu prevalence of more than 90% and Ala581Gly prevalence of less than 10% (RRR 10% [7 to 12]), but not in those with an Ala581Gly prevalence of 10% or higher (pooled Ala581Gly prevalence 37% [range 29 to 46]; RRR 0·5% [–16 to 14]; 2326 births).

Interpretation The effectiveness of sulfadoxine-pyrimethamine IPTp is reduced in areas with high resistance to sulfadoxine-pyrimethamine among *P falciparum* parasites, but remains associated with reductions in low birthweight even in areas where *dhps* Lys540Glu prevalence exceeds 90% but where the sextuple-mutant parasite (harbouring the additional *dhps* Ala581Gly mutation) is uncommon. Therapeutic alternatives to sulfadoxine-pyrimethamine IPTp are needed in areas where the prevalence of the sextuple-mutant parasite exceeds 37%.

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Introduction

Without pregnancy-specific protection, an estimated 45% of 32 million pregnancies in malaria-endemic sub-Saharan Africa are exposed to *Plasmodium falciparum* malaria yearly,[1] leading to 900 000 malaria-associated low birthweight deliveries[2] and associated consequences for infant health.[3] In these areas, WHO recommends intermittent preventive treatment in pregnancy (IPTp) with antimalarials. IPTp with sulfadoxine-pyrimethamine, the only antimalarial currently recommended for this strategy, is associated with major reductions in maternal anaemia, low birthweight, and neonatal mortality.[4] However, the effectiveness of sulfadoxine-pyrimethamine IPTp is threatened by resistance to this

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Research in context

Evidence before this study

We searched the Malaria in Pregnancy Library, PubMed, Web of Science, and Scopus for studies (published in English, up to March 1, 2018) in sub-Saharan Africa of the ecological relationship between molecular markers of sulfadoxine-pyrimethamine resistance and the effectiveness of sulfadoxine-pyrimethamine intermittent preventive treatment in pregnancy (IPTp) for preventing low birthweight, preterm birth, maternal malaria infection, and maternal anaemia. The following search terms were used: "Malaria AND pregnan* AND (intermittent OR IPT) AND Review". We found one prospective multi-country study (done in eight sites), two meta-analyses, and one modelling study. In the prospective study, prevalence of molecular markers of sulfadoxine-pyrimethamine resistance was strongly correlated with clearance of existing infections by the drug, and with duration of post-treatment prophylaxis, but showed no clear trend with regard to reductions in low birthweight, maternal anaemia, or plasmodium infections from this treatment. In this study, few areas with a high prevalence of the highly resistant sextuple-mutant *Plasmodium falciparum* parasite were investigated. One meta-analysis showed, based on three studies, no protective effect of sulfadoxine-pyrimethamine IPTp (*vs* placebo or no intervention) against low birthweight in areas with more than 50% *dhps* Lys540Glu mutation prevalence. By contrast, the other meta-analysis (nine studies) showed no reduced effectiveness of the treatment in areas with high sulfadoxine-pyrimethamine resistance. The modelling study did not directly investigate the relationship between the effect of sulfadoxine-pyrimethamine resistance and the effectiveness of sulfadoxine-pyrimethamine, but suggested that, even accounting for resistance, extending sulfadoxine-pyrimethamine IPTp to all women attending antenatal clinics would have a sizeable and cost-effective impact on maternal and infant health. Although this inference was valid in most malaria-endemic settings in sub-Saharan Africa, the single exception was highly resistant areas where sextuple-mutant parasites are common.

Added value of this study

This is the most comprehensive study of the effect of sulfadoxine-pyrimethamine resistance on the effectiveness of IPTp, involving 57 studies, 13 surveys, and more than 100 000 births. The aggregated data meta-analysis indicated substantial heterogeneity in effect size between studies, which might explain the contradictory findings between the two previous smaller reviews and the ongoing controversy about the continued use of sulfadoxine-pyrimethamine IPTp in areas of high resistance. We report for the first time a clear trend towards reduced effectiveness of sulfadoxine-pyrimethamine IPTp for low birthweight and *P falciparum* infection with increasing prevalence of molecular sulfadoxine-pyrimethamine resistance markers. Sulfadoxine-pyrimethamine was protective against low birthweight in areas of high resistance where parasites with the *dhfr* and *dhps* quintuple-mutant haplotype are essentially fixed. However, three observational cohort studies published elsewhere showed that these beneficial effects were not apparent in individuals infected with the highly resistant sextuple-mutant parasites (harbouring the quintuple mutant haplotype plus *dhps* Ala581Gly).

Implications of all the available evidence

Overall, evidence suggests a decline in the effectiveness of sulfadoxine-pyrimethamine IPTp for reducing malaria infection, anaemia, and low birthweight with increasing resistance. Nevertheless, use of sulfadoxine-pyrimethamine IPTp remains associated with reduced risks of low birthweight, even in areas where sulfadoxine-pyrimethamine fails to clear a third of asymptomatic infections in women receiving IPTp. These findings support WHO's recommendation to continue using sulfadoxine-pyrimethamine for IPTp in these high-resistance areas. However, an important exception is areas where sextuple mutant parasites are common (≥37% prevalence). In such areas, alternative preventive strategies are required now. The substantial heterogeneity between studies, even in areas with similar resistance levels, suggests that single observational studies of the relationship between sulfadoxine-pyrimethamine doses and low birthweight might not be informative as tools for making policy decisions. A decision tool using just two or three mutational markers in the *dhps* gene could be considered to guide sulfadoxine-pyrimethamine IPTp policy.

drug combination, particularly in east and southern Africa.

In *P falciparum*, sulfadoxine-pyrimethamine resistance results from a series of single nucleotide polymorphisms in the parasite's dihydrofolate reductase (*dhfr*) and dihydropteroate synthase (*dhps*) genes. At the ecological level, a high prevalence of quintuple-mutant *P falciparum* parasites, defined as those that harbour the five most common substitutions (*dhfr* substitutions Asn51Ile, Cys59Arg, and Ser108Asn, and *dhps* substitutions Ala437Gly and Lys540Glu), reduces the efficacy of sulfadoxine-pyrimethamine as an intermittent preventive treatment against malaria in infants and children,[5,6] undermines the ability of sulfadoxine-pyrimethamine to clear existing *P falciparum* infections in asymptomatic pregnant women,[7,8] and shortens the post-treatment prophylactic period following IPTp.[7] Sextuple-mutant *P falciparum* parasites, which harbour the additional *dhps* Ala581Gly mutation, are associated with enhanced sulfadoxine-pyrimethamine resistance in vitro, sulfadoxine-pyrimethamine treatment failure in patients with acute malaria,[9–11] and failure of the drug combination to inhibit parasite growth or prevent malaria-associated fetal growth restriction in pregnant women.[12–15]

Despite these effects, there are no guidelines on the use of molecular prevalence data to inform the use of sulfadoxine-pyrimethamine for IPTp.[16] The ecological

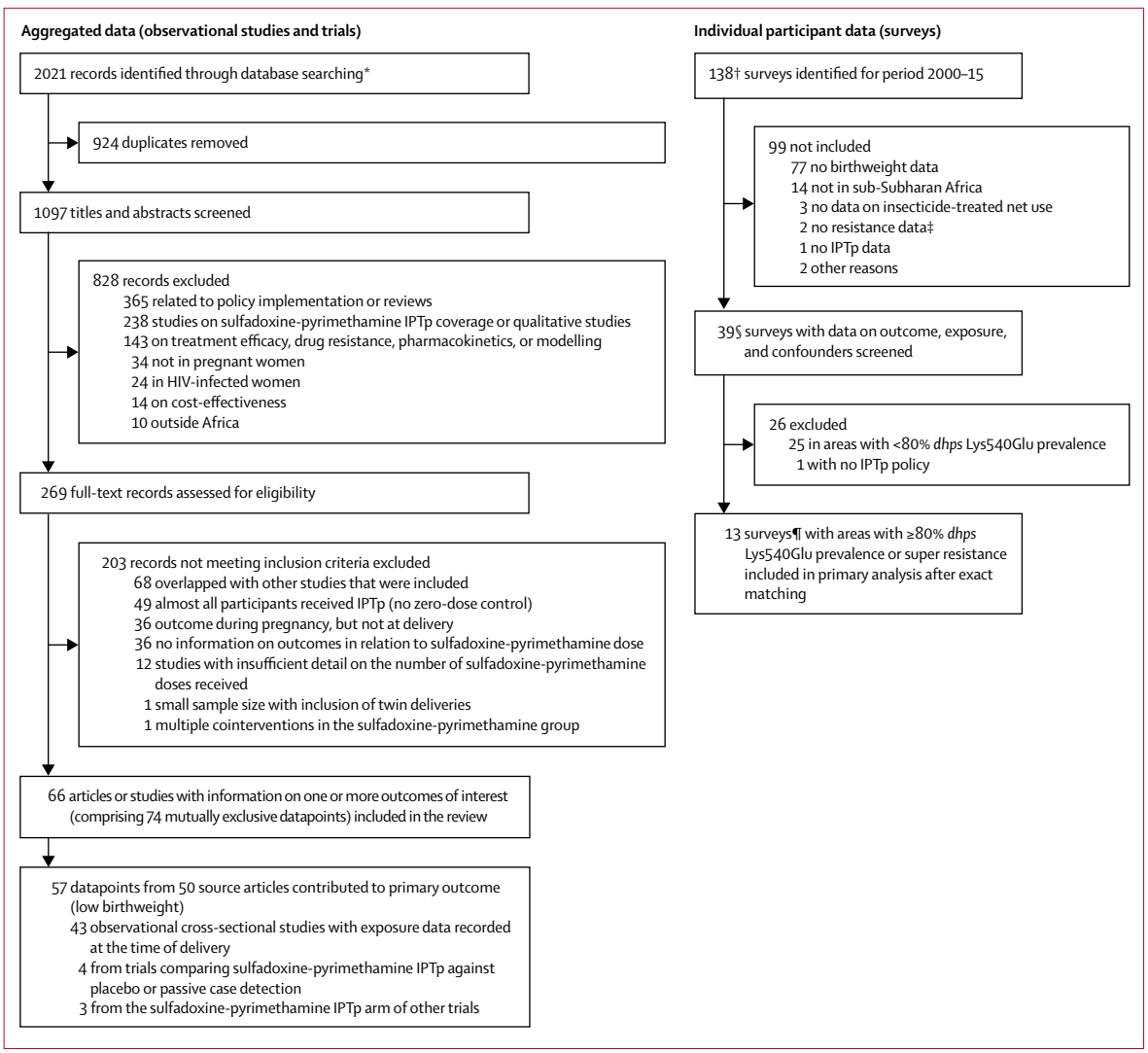


Figure 1: **Study profile**

dhps=dihydropteroate synthase. IPTp=intermittent preventive treatment in pregnancy. *561 from Malaria in Pregnancy Library, 440 from PubMed, 518 from Web of Science, and 502 from Scopus. †63 Demographic and Health Surveys, 13 Malaria Indicator Surveys, 54 Multiple Indicator Cluster Surveys (UNICEF), and eight AIDS indicator surveys. ‡Resistance data were not available for Comoros and São Tomé and Príncipe. §39 surveys with individual-level data available and information on outcomes, exposures, and potential confounders (276 383 single live births: 46% with measured birthweight available, 54% with perceived birthweight; mean birthweight 3217 g (SD 699), small birth size 14·1% of 276 383, low birthweight 9·4% of 128 347). ¶Comprising 49 481 births (of which 98·2% were singleton livebirths) before exact matching, and 42 394 singleton livebirths (19 429 with measured birthweight not available and 22 965 with measured birthweight available) after exact matching.

relationship between molecular measures of sulfadoxine-pyrimethamine resistance and the effect of sulfadoxine-pyrimethamine IPTp on clinically relevant birth outcomes, such as low birthweight, is not clear. Previous attempts to define these relationships reached conflicting conclusions,[17,18] possibly reflecting substantial between-study heterogeneity in the effect of sulfadoxine-pyrimethamine treatment on low birthweight.[14,18]

Using all available data derived from observational studies, clinical trials, and national surveys in sub-Saharan Africa, we did a meta-analysis of the ecological relationship between molecular markers of sulfadoxine-pyrimethamine resistance and the effect of sulfadoxine-pyrimethamine IPTp on low birthweight. We hypothesised that a higher prevalence of sulfadoxine-pyrimethamine resistance, as indicated by the prevalence of molecular markers of sulfadoxine resistance, would be associated with an attenuation of the sulfadoxine-pyrimethamine IPTp-associated reduction in low birthweight.

Methods

Search strategy and selection criteria

We did a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses statement (appendix, p 41). Two main sources of data regarding IPTp effectiveness were used: aggregated data from observational studies and clinical trials (henceforth

See Online for appendix

referred to collectively as clinical studies), and individual participant data from nationally representative surveys (referred to as surveys). Clinical studies were identified by two independent reviewers (AMvE and GK) by searching trial registries and electronic databases (Malaria in Pregnancy Library,[19] PubMed, Web of Science, and Scopus) for studies published between Jan 1, 1990, and March 1, 2018, without language restrictions, in addition to scanning reference lists of articles and consulting with experts in the field (appendix p 2). The search terms "Malaria AND pregnan* AND intermittent AND (prevent* OR prophyla* OR chemoprevent* OR chemoprophyla* OR IPT*) AND (sulfadoxine OR sulphadoxine OR pyrimethamine OR SP)" were used. Observational studies were included if they were done in sub-Saharan Africa, had information at delivery on the number of sulfadoxine-pyrimethamine doses received, and data on birthweight, maternal haemoglobin, or plasmodium infection at delivery. Trials were included if they were quasi-randomised or randomised trials done in sub-Saharan Africa, compared sulfadoxine-pyrimethamine IPTp against passive case detection or placebo, and otherwise fulfilled the same criteria as for the observational studies. Studies or study arms were excluded if they involved only HIV-infected women or if they combined sulfadoxine-pyrimethamine with other antimalarial drugs (such as artemisinin derivatives or azithromycin) or with other interventions (such as screening for malaria). Final study eligibility was agreed on by the reviewers. If no agreement could be reached, a third reviewer (FOtK) assessed the study and agreement was reached by consensus.

To identify surveys, one reviewer (DAL) searched all national-level datasets from surveys done in malaria-endemic countries in Africa after the year 2000 (when WHO introduced the sulfadoxine-pyrimethamine IPTp policy) and with datasets publicly available (as described in detail elsewhere;[4] search date May 31, 2015), including the Demographic and Health Surveys Program, UNICEF Multiple Indicator Cluster Surveys, and Malaria Indicator Surveys. Surveys were included if they contained data on low birthweight (perceived birth size and measured weight), measured IPTp use by number of doses among recently pregnant women, and measured insecticide-treated net coverage at the household level (appendix pp 2–3).

Data on molecular markers of sulfadoxine-pyrimethamine resistance were obtained from the clinical study reports or from the authors of those reports. If these data were not available, data were obtained from existing population prevalence maps of *P falciparum dhps* mutations by use of the molecular surveyor tool of the Worldwide Antimalarial Resistance Network (WWARN) and existing prediction surfaces of the prevalence of sulfadoxine-pyrimethamine resistance-associated mutations based on these data.[16,20–22] Malaria transmission intensity data were obtained from the Malaria Atlas Project.

For the **Demographic and Health Surveys Program** see http://dhsprogram.com/

For the **UNICEF Multiple Indicator Cluster Surveys** see http://mics.unicef.org/

For the **Malaria Indicator Surveys** see http://www.malariasurveys.org/

For the **Malaria Atlas Project** see http://www.map.ox.ac.uk/

Extraction and quality assessment of IPTp effectiveness data

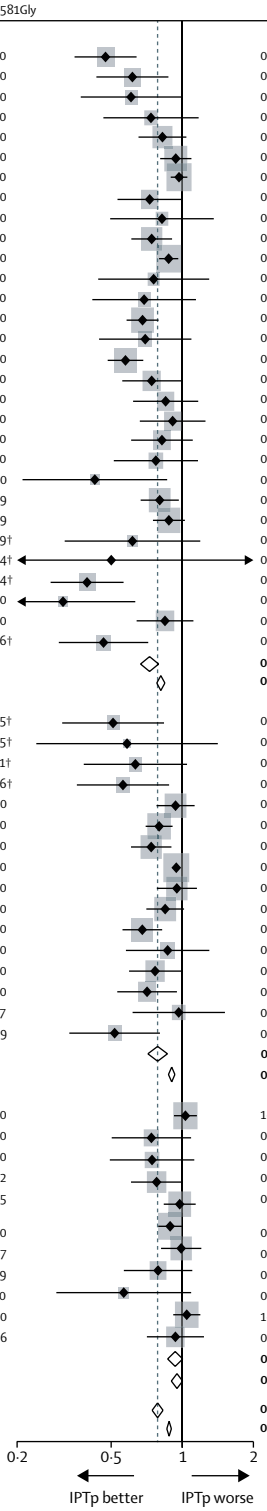
From clinical studies, extraction of summary data was done independently by two investigators (AMvE and GK or DECS). Authors of primary studies were contacted for missing information or if reported data did not fit the required format. The following information was extracted: first author, publication year, year of study start and end, study design, study and randomisation procedures (trials only), inclusion criteria (eg, any restrictions by gravidity), insecticide-treated net use, numerator and denominator per outcome per sulfadoxine-pyrimethamine dose, and details of control intervention (trials only). If available, sulfadoxine-pyrimethamine resistance data were extracted. Study quality was assessed by two reviewers (AMvE and GK or DECS) using an adaptation of the Newcastle-Ottawa Scale (appendix, p 3).[23]

From surveys, the following (individual patient-level) data were extracted: reported number of sulfadoxine-pyrimethamine doses received; composite of low birthweight (<2·5 kg) if measured birthweight was available, or perceived small birth size (very small or small) if birthweight was not available (the correlation between perceived and measured low birthweight has been described elsewhere[4]); and measured birthweight as a continuous variable.[4] Other data extracted included number of antenatal visits, tetanus vaccination, iron supplementation and insecticide-treated net ownership, household socioeconomic status, mother's education, mother's age and parity, birth spacing, newborn sex, season of birth, and whether it was a single or multiple birth.

Data on the prevalence of *dhps* Ala437Gly, Lys540Glu, and Ala581Gly mutations among *P falciparum* parasites were extracted from the clinical studies in pregnant women, the literature, and existing molecular surveyor databases (appendix p 4).[16,20–22] In areas where the

Figure 2: **Relative risk of low birthweight associated with each incremental dose of sulfadoxine-pyrimethamine IPTp in all gravidae by resistance strata**
On the basis of the estimated prevalence of *dhps* mutations in the study areas (matched as described in text and appendix p 9), resistance was stratified into low (Ala437Gly <90% [central and west Africa], or Lys540Glu <30% [east and southern Africa]; 30 studies), moderate (Ala437Gly ≥90% [central and west Africa], or Lys540Glu ≥30% to <90% [east and southern Africa]; 16 studies), and high (Lys540Glu ≥90% in east and southern Africa; 11 studies). p values following the I^2 statistics represent the χ^2 test for heterogeneity. Weights are from random effects analysis. Data marker sizes indicate the weight applied to each study using random-effects meta-analysis. Diamonds represent summary effect of studies. CW=central and west Africa. *dhps*=dihydropteroate synthase. D+L=Dersimonian-Laird method for random effects models. ES=east and southern Africa. IPTp=intermittent preventive treatment in pregnancy. I-V=inverse variance method for fixed effects models. *Reference refers to the lowest sulfadoxine-pyrimethamine dose category (0 or 0–1 dose as indicated in the sulfadoxine-pyrimethamine dose category column), and the comparison column (included for illustration only) refers to all the other exposure groups pooled (eg, if the sulfadoxine-pyrimethamine categories were 0, 1, 2+, the comparison column would reflect the data in the 1 dose group and 2+ dose groups pooled; full sample sizes per dose group and average doses are shown in the appendix (p 13). †The high prevalence of *dhps* Ala581Gly in these studies was not accompanied by a high prevalence in *dhps* Lys540Glu, so this information was not interpreted as an indication of the presence of sextuple-mutant parasites.

	Site	Region	Study period	Sulfadoxine-pyrimethamine dose category	Low birthweight prevalence, n/N (%)*		Mutation prevalence, %			Risk ratio trend (95% CI)	Study weight, % (D+L)	Low birthweight relative risk reduction per dose, % (95% CI)
					Reference	Comparison	Ala437Gly	Lys540Glu	Ala581Gly			
Low-resistance areas												
Muhammad et al, 2016, Nigeria	Nguru, Yobe	CW	2014	0–1,2+	58/104 (55·8)	10/80 (12·5)	24·5	0·0	0·0	0·47 (0·35 to 0·64)	1·67	53 (36 to 65)
Kayentao et al, 2014, Mali	San	CW	2009–10	0,1,2+	18/110 (16·4)	22/320 (6·9)	27·5	0·0	0·0	0·62 (0·43 to 0·87)	1·41	38 (13 to 57)
Kayentao et al, 2014, Mali	San	CW	2006	0,1,2+	15/135 (11·1)	14/263 (5·3)	32·6	0·0	0·0	0·61 (0·37 to 0·99)	0·89	39 (1 to 63)
Kayentao et al, 2014, Mali	Djenne	CW	2006	0,1,2+	10/110 (9·1)	13/245 (5·3)	32·7	0·0	0·0	0·74 (0·46 to 1·17)	0·96	26 (–17 to 54)
Olliaro et al, 2008, Senegal	Mlomp	CW	2000–07	0,1,2+	57/532 (10·7)	29/372 (7·8)	39·3	0·0	0·0	0·82 (0·65 to 1·04)	2·14	18 (–4 to 35)
Mbaye et al, 2006, Gambia	Farafenni	CW	2002–04	0,2+	46/716 (6·4)	40/738 (5·4)	46·8	0·0	0·0	0·94 (0·81 to 1·09)	2·81	6 (–9 to 19)
Oduro et al, 2010, Ghana	Navrongo	CW	2006–07	0,1,2,3+	76/391 (19·4)	342/1886 (18·1)	53·8	0·0	0·0	0·97 (0·89 to 1·05)	3·36	3 (–5 to 11)
Falade et al, 2007, Nigeria	Ibadan	CW	2003–04	0,1+	16/171 (9·4)	31/595 (5·2)	63·0	0·0	0·0	0·73 (0·53 to 1·00)	1·60	27 (0 to 47)
Bouyou-Akotet et al, 2016, Gabon	Libreville, Melen	CW	2011	0,1,2+	5/58 (8·6)	14/241 (5·8)	66·7	0·0	0·0	0·82 (0·50 to 1·36)	0·85	18 (–36 to 50)
Coulibaly et al, 2014, Burkina Faso	Ziniare	CW	2011–12	0,1,2+	32/155 (20·6)	106/757 (14·0)	75·3	0·0	0·0	0·74 (0·61 to 0·91)	2·42	26 (9 to 39)
Tutu et al, 2011, Ghana	Offinso	CW	2005–07	0,1,2,3+	62/499 (12·4)	250/2084 (12·0)	77·6	0·0	0·0	0·88 (0·80 to 0·96)	3·28	12 (4 to 20)
Moleins et al, 2010, Senegal	Oussouye	CW	2007–08	0–1,2+	6/55 (10·9)	6/96 (6·3)	43·0	0·1	0·0	0·76 (0·44 to 1·30)	0·76	24 (–30 to 56)
Kayentao et al, 2014, Mali	Koro	CW	2006–07	0,1,2+	13/130 (10·0)	14/221 (6·3)	44·8	0·1	0·0	0·69 (0·42 to 1·14)	0·85	31 (–14 to 58)
Sirima et al, 2006, Burkina Faso	Koupela	CW	2004	0,1,2,3+	16/66 (24·2)	119/1054 (11·3)	48·1	0·1	0·0	0·68 (0·58 to 0·79)	2·78	32 (21 to 42)
Kayentao et al, 2014, Mali	Bougouni	CW	2006–07	0,1,2+	11/101 (10·9)	17/306 (5·6)	33·8	0·2	0·0	0·70 (0·44 to 1·09)	1·01	30 (–9 to 56)
Gies et al, 2009, Burkina Faso	Boromo	CW	2004–06	0,1,2+	19/52 (36·5)	204/1220 (16·7)	71·5	0·2	0·0	0·57 (0·48 to 0·68)	2·63	43 (32 to 52)
Kayentao et al, 2014, Mali	Kita	CW	2009–10	0,1,2+	18/124 (14·5)	38/420 (9·0)	15·2	0·7	0·0	0·74 (0·56 to 0·99)	1·77	26 (1 to 44)
Famanta et al, 2011, Mali	Bamako	CW	2009	0,1,2+	16/102 (15·7)	25/257 (9·7)	15·2	0·7	0·0	0·85 (0·62 to 1·17)	1·58	15 (–17 to 38)
Hommerich et al, 2007, Ghana	Agogo	CW	2006	0,1,2,3+	8/52 (15·4)	20/173 (11·6)	84·6	1·4	0·0	0·91 (0·66 to 1·25)	1·57	9 (–25 to 34)
Ramharter et al, 2007, Gabon	Lambarene	CW	2005–06	0,1,2+	11/97 (11·3)	60/596 (10·1)	57·9	3·3	0·0	0·82 (0·61 to 1·11)	1·69	18 (–11 to 39)
Bouyou-Akotet et al, 2010, Gabon	Libreville	CW	2005–06	0,1+	24/120 (20·0)	11/83 (13·3)	69·0	6·9	0·0	0·77 (0·51 to 1·17)	1·15	23 (–17 to 49)
Likwela et al, 2012, DR Congo	Mikalayi	CW	2007	0–1,2+	35/363 (9·6)	2/114 (1·8)	76·9	11·3	0·0	0·43 (0·21 to 0·86)	0·49	57 (14 to 79)
Toure et al, 2014, Côte d'Ivoire	Abidjan, Comoe	CW	2009–10	0,1,2,3+	50/436 (11·5)	61/876 (7·0)	52·1	0·9	0·9	0·80 (0·67 to 0·97)	2·52	20 (3 to 33)
Vanga-Bosson et al, 2011, Côte d'Ivoire	National	CW	2008	0,1,2,3+	35/309 (11·3)	172/1636 (10·5)	52·1	0·9	0·9	0·88 (0·75 to 1·03)	2·78	12 (–3 to 25)
Tonga et al, 2013, Cameroon	Sanaga–Maritime	CW	2011–12	0,1,2+	7/68 (10·3)	6/127 (4·7)	76·5	0·0	5·9†	0·62 (0·32 to 1·19)	0·55	38 (–19 to 68)
Alli et al, 2013, Nigeria	Kubwa	CW	2010–11	0,1+	4/158 (2·5)	0/42 (0·0)	84·2	0·0	47·4†	0·50 (0·05 to 4·78)	0·05	50 (–379 to 95)
Aziken et al, 2010, Nigeria	Benin City	CW	2009	0,1+	61/371 (16·4)	14/370 (3·8)	84·2	0·0	47·4†	0·40 (0·28 to 0·56)	1·39	60 (44 to 72)
Suleiman et al, 2003, Sudan	Wad Medani	ES	1999–2001	0,2+	19/53 (35·8)	2/57 (3·5)	13·3	0·0	0·0	0·31 (0·15 to 0·63)	0·49	69 (37 to 85)
Challis et al, 2004, Mozambique	Maputo	ES	2001–02	0,2+	27/203 (13·3)	19/200 (9·5)	26·1	25·4	0·0	0·85 (0·64 to 1·11)	1·83	15 (–11 to 36)
Likwela et al, 2012, DR Congo	Kisangani	ES	2007	0–1,2+	16/50 (32·0)	6/87 (6·9)	74·1	27·8	5·6†	0·46 (0·30 to 0·72)	1·06	54 (28 to 70)
D+L subtotal (I^2 70·5%, p<0·0001)										**0·73 (0·67 to 0·79)**	**48·32**	**27 (21 to 33)**
I–V subtotal										**0·81 (0·78 to 0·84)**		
Moderate-resistance areas												
Tongo et al, 2011, Nigeria	Ibadan	CW	2007–08	0–1,2+	68/649 (10·5)	4/147 (2·7)	92·4	1·0	2·5†	0·51 (0·31 to 0·84)	0·87	49 (16 to 69)
Olorunda et al, 2013, Nigeria	Ibadan	CW	2010	0,1+	22/246 (8·9)	4/84 (4·8)	92·4	1·0	2·5†	0·58 (0·24 to 1·41)	0·33	42 (–41 to 76)
Kilauzi et al, 2013, DR Congo	Kinshasa	CW	2011	0,1+	21/204 (10·3)	32/501 (6·4)	100·0	18·9	8·1†	0·63 (0·38 to 1·05)	0·85	37 (–5 to 62)
Igboeli et al, 2017, Nigeria	Enugu State	CW	2013	0,1+	8/101 (7·9)	7/315 (2·2)	96·8	0·0	52·6†	0·56 (0·36 to 0·88)	1·01	44 (12 to 64)
Njagi et al, 2002, Kenya	Bondo	ES	1997–99	0,2+	51/359 (14·2)	46/369 (12·5)	42·8	31·1	0·0	0·94 (0·78 to 1·13)	2·52	6 (–13 to 22)
Parise et al, 1998, Kenya	Kisumu	ES	1994–96	0,2,3+	52/340 (15·3)	53/656 (8·1)	42·8	31·1	0·0	0·80 (0·70 to 0·91)	2·98	20 (9 to 30)
van Eijk et al, 2004, Kenya	Kisumu	ES	1999–2000	0,1,2+	112/948 (11·8)	70/925 (7·6)	42·8	31·1	0·0	0·74 (0·61 to 0·90)	2·43	26 (10 to 39)
Cassam et al, 2007, Mozambique	Gaza	ES	2005–07	0,3+	756/8650 (8·7)	488/6645 (7·3)	53·2	47·6	0·0	0·94 (0·91 to 0·98)	3·59	6 (2 to 9)
Menendez et al, 2008, Mozambique	Manhica	ES	2003–05	0,2+	49/411 (11·9)	41/382 (10·7)	62·9	68·6	0·0	0·95 (0·78 to 1·15)	2·44	5 (–15 to 22)
Yussuf et al, 2010, Tanzania	Lindi	ES	2009–10	0,1,2+	55/123 (44·7)	44/123 (35·8)	79·7	72·7	0·0	0·85 (0·70 to 1·02)	2·54	15 (–2 to 30)
Feng et al, 2010, Malawi	Blantyre	ES	1997–99	0,1,2+	49/215 (22·8)	84/697 (12·1)	63·6	74·0	0·0	0·68 (0·56 to 0·82)	2·46	32 (18 to 44)
Ndeserua et al, 2015, Tanzania	Rufiji	ES	2012	0–1,2+	12/166 (7·2)	10/184 (5·4)	75·0	76·3	0·0	0·87 (0·58 to 1·30)	1·16	13 (–30 to 42)
Feng et al, 2010, Malawi	Blantyre	ES	1999–2001	0,1,2+	20/117 (17·1)	85/719 (11·8)	80·3	84·0	0·0	0·77 (0·60 to 0·99)	1·99	23 (1 to 40)
Mace et al, 2014, Zambia	Mansa	ES	2009–10	0–1,2,3+	17/157 (10·8)	13/266 (4·9)	83·7	84·0	0·0	0·71 (0·53 to 0·95)	1·74	29 (5 to 47)
Mosha et al, 2014, Tanzania	Rufiji, Moshi	ES	2012	0–1,2+	9/169 (5·3)	9/181 (5·0)	93·2	88·3	2·7	0·97 (0·62 to 1·52)	1·01	3 (–52 to 38)
Minja et al, 2013, Tanzania	Korogwe	ES	2008–10	0–1,2+	4/17 (23·5)	43/705 (6·1)	100·0	87·5	42·9	0·52 (0·33 to 0·80)	1·04	48 (20 to 67)
D+L subtotal (I^2 66·7%, p=0·0001)										**0·79 (0·72 to 0·87)**	**28·97**	**21 (14 to 29)**
I–V subtotal										**0·90 (0·87 to 0·93)**		
High-resistance areas												
Msyamboza et al, 2009, Malawi	Chikwawa	ES	2002–04	0–1,2,3+	65/427 (15·2)	157/891 (17·6)	87·0	92·7	0·0	1·03 (0·92 to 1·15)	3·14	–3 (–15 to 8)
Tetteh-Ashong et al, 2005, Malawi	Chikwawa	ES	2005	0–1,2,3+	6/42 (14·3)	13/186 (7·0)	94·1	94·8	0·0	0·74 (0·50 to 1·09)	1·24	26 (–9 to 50)
Namusoke et al, 2010, Uganda	Kampala	ES	2004–05	0,1,2+	28/162 (17·3)	19/159 (11·9)	93·5	95·1	0·0	0·74 (0·49 to 1·12)	1·14	26 (–12 to 51)
Arinaitwe et al, 2014, Uganda	Tororo	ES	2011	0–1,2+	29/227 (12·8)	25/325 (7·7)	97·3	97·5	0·2	0·78 (0·61 to 1·00)	2·02	22 (–0 to 39)
Gutman et al, 2013, and Kalilani et al, 2014, Malawi	Southern Malawi	ES	2009–11	0–1,2,3+	28/334 (8·4)	103/1498 (6·9)	94·4	99·6	1·5	0·98 (0·83 to 1·14)	2·78	2 (–14 to 17)
Feng et al, 2010, Malawi	Blantyre	ES	2002–06	0,1,2,3+	29/234 (12·4)	212/2137 (9·9)	93·5	94·7	2·0	0·89 (0·79 to 1·00)	3·11	11 (0 to 21)
Desai et al, 2014, Kenya	Nyanza	ES	2011–12	0–1,2,3+	10/135 (7·4)	59/734 (8·0)	93·0	95·6	5·7	0·99 (0·81 to 1·20)	2·44	1 (–20 to 19)
Braun et al, 2015, Uganda	Fort Portal	ES	2013	0,1,2+	8/56 (14·3)	52/552 (9·4)	100·0	100·0	12·9	0·79 (0·57 to 1·10)	1·49	21 (–10 to 43)
Harrington et al, 2011, Tanzania	Muheza	ES	2002–05	0,1,2+	6/80 (7·5)	11/292 (3·8)	100·0	90·2	13·0	0·57 (0·29 to 1·09)	0·55	43 (–9 to 71)
Ndyomugyenyi et al, 2011, Uganda	Kabale	ES	2004–07	0,2+	99/1577 (6·3)	107/1561 (6·9)	100·0	100·0	45·0	1·04 (0·92 to 1·19)	2·98	–4 (–19 to 8)
Likwela et al, 2012, DR Congo	Rutsuhuru	ES	2007	0–1,2+	16/177 (9·0)	39/493 (7·9)	88·1	91·2	45·6	0·94 (0·71 to 1·24)	1·82	6 (–24 to 29)
D+L subtotal (I^2 31·4%, p=0·15)										**0·93 (0·87 to 1·00)**	**22·71**	**7 (0 to 13)**
I–V subtotal										**0·95 (0·90 to 1·00)**		
D+L overall (I^2 69·5%, p<0·0001)										**0·79 (0·75 to 0·83)**	**100·00**	**21 (17 to 25)**
I–V overall										**0·88 (0·86 to 0·90)**		



	n	Univariate meta-regression					Multivariate meta-regression*				
		Coefficient (95% CI)	p value	τ^2	I^2, %	R^2, %	Coefficient (95% CI)	p value	τ^2	I^2, %	R^2, %
***dhps* Ala437Gly prevalence†**											
All studies	57	1·001 (0·999–1·004)	0·35	0·02596	69·9	1·8	1·001 (0·999–1·004)	0·25	0·01645	57·7	37·8
Excluding low-quality studies‡	50	1·002 (0·999–1·004)	0·13	0·02079	67·3	7·5	1·002 (1·000–1·004)	0·08	0·01323	54·1	41·1
Restricted to largest 50% of studies§	29	1·003 (1·000–1·005)	0·06	0·01615	73·9	13·3	1·002 (1·000–1·005)	0·09	0·01137	62·1	39·0
***dhps* Lys540Glu prevalence†**											
All studies	57	1·002 (1·001–1·003)	0·0060	0·02142	66·2	19·0	1·002 (1·001–1·003)	0·0031	0·01222	53·7	53·8
Excluding low-quality studies‡	50	1·002 (1·000–1·003)	0·0090	0·01732	61·9	22·9	1·002 (1·000–1·003)	0·0160	0·01133	51·1	49·6
Restricted to largest 50% of studies§	29	1·002 (1·000–1·003)	0·0223	0·01469	70·5	21·1	1·002 (1·000–1·003)	0·0132	0·00909	58·7	51·2
Resistance strata¶											
All studies	57	1·10 (1·03–1·18)	0·0054	0·02040	65·4	22·8	1·10 (1·03–1·17)	0·0043	0·01184	52·9	55·2
Excluding low-quality studies‡	50	1·10 (1·03–1·18)	0·0075	0·01687	61·6	24·9	1·09 (1·02–1·16)	0·0095	0·01067	49·7	52·5
Restricted to largest 50% of studies§	29	1·10 (1·02–1·18)	0·0122	0·01386	69·7	25·6	1·10 (1·03–1·17)	0·0067	0·00802	55·9	56·9

dhps=*Plasmodium falciparum* dihydropteroate synthase. *Adjusted for malaria transmission intensity, average number of sulfadoxine-pyrimethamine doses, study quality, and proportion of paucigravidae in study. †In the meta-regression, the sulfadoxine-pyrimethamine resistance variable was introduced as a linear continuous variable reflecting 1% stepped increases in prevalence of the resistance marker. ‡Excludes studies with less than three of six stars for quality. §To ascertain the effect of potential bias due to small-study effect, the analysis was restricted to the largest 50% of studies, based on their standard error of the log relative risk for low birthweight. ¶Sulfadoxine-pyrimethamine resistance, defined by the prevalence of molecular markers, stratified into low (*dhps* Ala437Gly <90% in central and west Africa or *dhps* Lys540Glu <30% in east and southern Africa), moderate (*dhps* Ala437Gly ≥90% in central and west Africa, or *dhps* Lys540Glu ≥30% and <90% in east and southern Africa), and high (*dhps* Lys540Glu ≥90% in east and southern Africa).

Table: **Effect of sulfadoxine-pyrimethamine resistance on the effectiveness of sulfadoxine-pyrimethamine IPTp to prevent low birthweight in women receiving intermittent preventive treatment during pregnancy (sub-Saharan Africa, 1997–2013, aggregated data)**

prevalence of this quintuple mutant was more than 50%, the prevalence of the *dhps* Ala581Gly mutation served as a proxy for the sextuple mutant. Two areas were identified where the sextuple mutant was more than 10%: northeastern Tanzania, and the area crossing the borders of southwestern Uganda, eastern Rwanda, eastern Democratic Republic of the Congo, and northwestern Tanzania (appendix p 4). The prevalence of each point mutation and the *P falciparum* parasite prevalence in children aged 2–10 years ($Pf\mathrm{PR}_{2-10}$; using data from the Malaria Atlas Project) was matched to each study by time (the same year for $Pf\mathrm{PR}_{2-10}$ and within 2 years before or after for point mutations) and by location using latitude and longitude (within 300 km where possible).[24] For national surveys, these prevalence data were calculated for the administrative boundary of the given survey using Malaria Atlas Project data and WWARN's geospatial models (appendix p 4).[22]

Definition of resistance categories

To stratify resistance into low, moderate, and high levels, different combinations of threshold levels (at 5% step increases) of the resistance-associated mutations in *dhps* were explored in the aggregated-data meta-analysis. Because of distinct parasite populations and distributions of mutations in each region,[25] threshold analysis was done separately for central and west Africa and for east and southern Africa. Results were then combined to obtain a single categorical variable that represented the optimal thresholds based on the R^2 for each region.

Statistical analysis

The primary outcome was low birthweight. Secondary outcomes included anaemia, malaria, preterm delivery, birthweight, haemoglobin level, and gestational age. Analyses of clinical studies were done with Stata (version 14). A two-stage random-effects meta-analysis was done by use of a generalised least-squares regression for trend estimation of summarised dose-response data.[26,27] Effect sizes were expressed as relative risk reduction (RRR; 100×[1−relative risk]) for trend (appendix p 4), and were then combined across studies with use of a random-effects meta-analysis, with heterogeneity quantified using the I^2 statistic. Potential modifying effects of sulfadoxine-pyrimethamine resistance were examined with multivariate linear meta-regression, adjusting for the following prespecified covariates: malaria transmission, study quality, average number of sulfadoxine-pyrimethamine doses, and proportion of paucigravidae (defined as women in their first or second pregnancy).[28] The proportion of women using insecticide-treated nets was not found to be associated with resistance level in our analyses and was not included as covariate in the metaregression. Subgroup analyses by gravidity (paucigravidae *vs* multigravidae) were also done. For the assessment of the effect of sulfadoxine-pyrimethamine IPTp on continuous outcomes, only the no doses group versus the two or more doses group were compared. Further sensitivity analysis was done by excluding low-quality studies and exploring the presence and impact of potential small-study effects due to publication and other biases (appendix p 4).[29]

The survey analysis was done in R and restricted to the higher-resistance areas with more than 80% prevalence of *dhps* Lys540Glu. Only the most recent livebirth within the past 2 years was considered. To mitigate potential confounding of the effect of sulfadoxine-pyrimethamine dose on birthweight, exact matching was used (appendix p 4).[4] The modifying effect of sulfadoxine-pyrimethamine resistance was first assessed for each survey by use of random-effects log-binomial regression models for low birthweight and linear regression for birthweight with the matched birth strata included as a random intercept using the lme4 package in R.[30] IPTp exposures were considered as continuous variables similar to the aggregated meta-analysis. The effect measures were then further evaluated by resistance strata (quintiles) and compared by use of meta-regression.

This study is registered with PROSPERO, number 42016035540.

Role of the funding source

Except for the US Centers for Disease Control and Prevention (CDC) and WWARN, the funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. CDC and WWARN staff participated in the conduct of the study. AMvE, FOtK and DAL had full access to all the data in the study. AMvE and FOtK had final responsibility for the decision to submit for publication.

Results

For the aggregated-data meta-analysis, we identified 2021 records through database searching. After removal of duplicates, 1097 articles were assessed for eligibility, of which 66 were included in the review: 58 observational studies and eight trials (figure 1). A summary of the included studies is provided in the appendix (p 6). Of these, 50 source articles from 17 countries (appendix p 30) were included in the analysis of low birthweight, involving 57 datapoints (henceforth referred to as studies) and 59 457 births. The remaining 16 studies did not provide data on low birthweight, but contributed to the analysis of secondary outcomes. In central and west Africa (31 studies), the median prevalence of *dhps* Ala437Gly was 57·9% (IQR 39·3–77·6; range 15·2–100·0), despite a low prevalence of *dhps* Lys540Glu (0·1% [IQR 0·0–0·9; range 0·0–18·9]), whereas, in east and southern Africa (26 studies), the prevalence of *dhps* Ala437Gly (85·4% [IQR 62·9–94·1; range 13·3–100·0]) was similar to that of *dhps* Lys540Glu (85·8% [IQR 47·6–94·8; range 0·0–100·0]; appendix pp 27, 31). The *dhps* Ala581Gly mutation (used as a proxy for the sextuple mutant) mainly occurred in areas with a *dhps* Lys540Glu prevalence of more than 80% in east and southern Africa (figure 2, appendix p 27). Among sulfadoxine-pyrimethamine recipients, the median number of sulfadoxine-pyrimethamine doses received (study-level) was 1·7 (IQR 1·3–2·4; appendix p 13). The number of sulfadoxine-pyrimethamine doses received by study participants was not correlated with the prevalence of *dhps* Ala437Gly (r=–0·0295, p=0·83) or *dhps* Lys540Glu (r=0·1594, p=0·24).

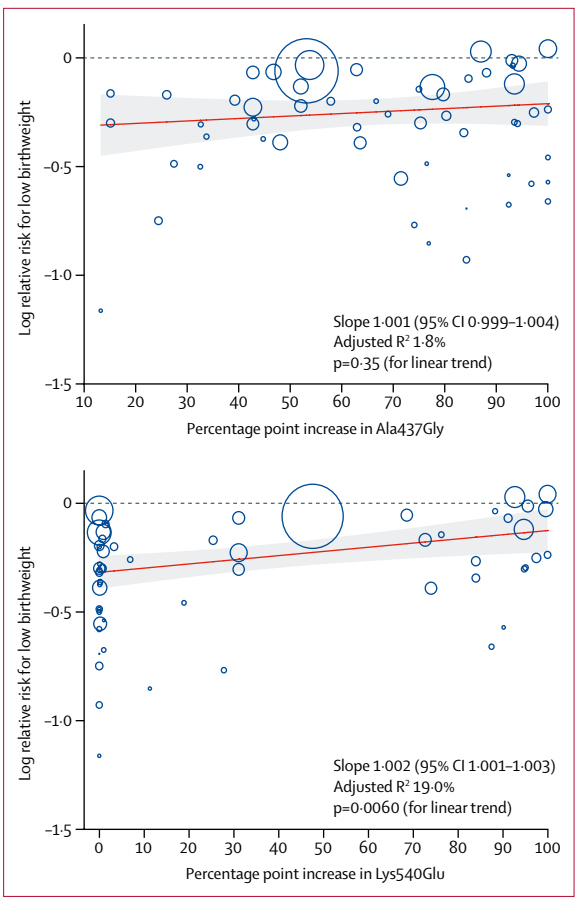


Figure 3: **Correlation between relative risk for low birthweight in women receiving IPTp and the prevalence of *dhps* Ala437Gly or *dhps* Lys540Glu mutations in 57 studies**

Meta-regression bubble plots show the log of the relative risk estimates for low birthweight across each sulfadoxine-pyrimethamine dose category, obtained by use of generalised least-squares regression for trend estimation of summarised dose-response data, with 95% CI of the regression line represented by the shaded area. The size of the bubbles for individual studies is proportional to the random effects study weights. A positive slope indicates decreasing effectiveness of sulfadoxine-pyrimethamine IPTp for averting low birthweight with increasing mutation prevalence. *dhps*=dihydropteroate synthase. IPTp=intermittent preventive treatment in pregnancy.

Overall, per dose of sulfadoxine-pyrimethamine, sulfadoxine-pyrimethamine IPTp was associated with an RRR for low birthweight of 21% (95% CI 17–25; 57 studies; figure 2). RRR was 22% (17–27; 34 studies) in paucigravidae and 18% (11–24; 31 studies) in multigravidae (appendix p 17). There was substantial heterogeneity between studies (I^2=69·5%, p<0·0001; figure 2).

Univariate and multivariate meta-regression analyses showed a linear trend towards decreasing effectiveness of sulfadoxine-pyrimethamine IPTp (as indicated by the log relative risk of low birthweight moving closer to the null) with increasing prevalence of *dhps* Lys540Glu (table, figure 3). No differences were seen by gravidity (appendix

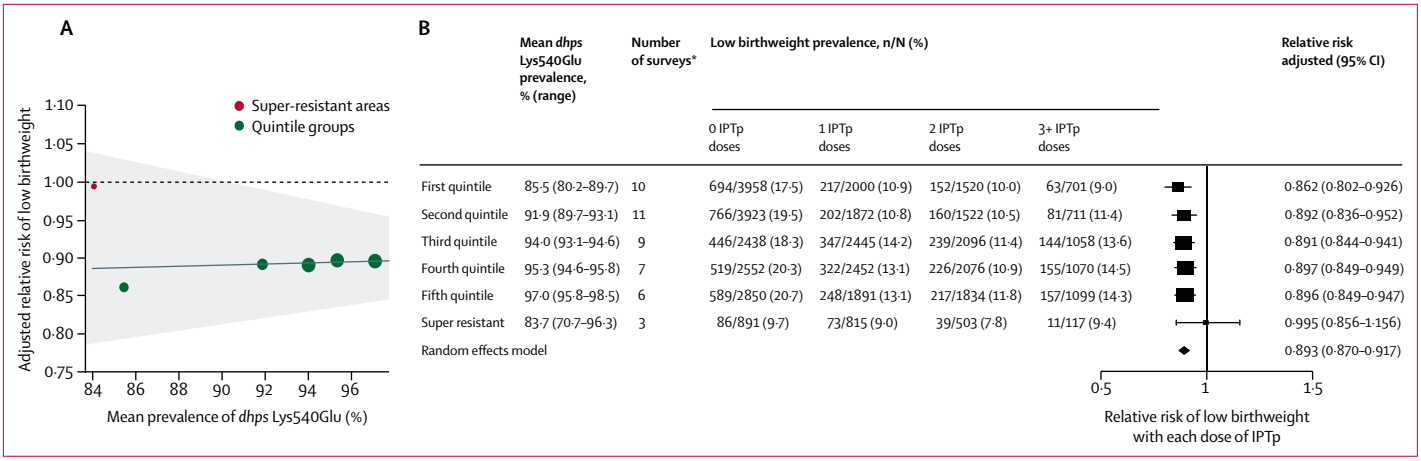


Figure 4: **Relative risk for low birthweight associated with number of sulfadoxine-pyrimethamine IPTp doses by resistance strata in areas with super resistance or *dhps* Lys540Glu of more than 80% in east and southern Africa**

(A) Linear meta-regression bubble plot with solid line representing the regression line and shaded area representing the 95% CI. (B) Forest plot. Individual observations in all areas with a *dhps* Lys540Glu prevalence of more than 80% were divided into quintiles after excluding the surveys in the super-resistant areas. Super-resistant areas were defined as those with a *dhps* Ala581Gly prevalence of more than 10% (southwestern Uganda, northern Tanzania, and eastern Democratic Republic of the Congo).[16] Overall, sulfadoxine-pyrimethamine IPTp was associated with an RRR of 11% (95% CI 8–13) for low birthweight. The RRR was 10% (7–12) in areas with a *dhps* Lys540Glu prevalence of more than 90% and Ala581Gly prevalence of less than 10%. *dhps*=dihydropteroate synthase. IPTp=intermittent preventive treatment in pregnancy. RRR=relative risk reduction. *Number of surveys (total 13) that contributed to each quintile group; surveys could contribute to more than one group.

p 16). No significant trend was observed for *dhps* Ala437Gly (table, figure 3). Of the different thresholds used to stratify resistance into low, medium, and high, the most predictive combination was low resistance defined as *dhps* Ala437Gly less than 90% in central and west Africa or *dhps* Lys540Glu less than 30% in east and southern Africa (RRR 27% [95% CI 21–33]); moderate resistance defined as *dhps* Ala437Gly 90% or higher (central and west Africa) or *dhps* Lys540Glu 30% or higher and less than 90% in east and southern Africa (RRR 21% [14–29]); and high resistance defined as *dhps* Lys540Glu 90% or higher in east and southern Africa (RRR 7% [0–13]; p=0·0054 for linear trend; table). These definitions of resistance strata explained 22·8% of the between-study variance (R^2) in univariate models and, combined with other covariates, 55·2% in multivariate models (table). Very similar results were obtained if alternative thresholds (<20% or <40%) for *dhps* Lys540Glu prevalence were used to define low resistance, or if a *dhps* Ala437Gly prevalence of less than 80% was used to define low resistance, or if the presence (≥1%) of *dhps* Ala581Gly (instead of *dhps* Lys540Glu ≥90%) was used to define high resistance (appendix p 18).

Meta-regression results were similar after the exclusion of low-quality studies (table). There was evidence for significant small-study effects (p<0·0001), but this effect was observed in all three resistance strata (appendix p 32), and restricting the analysis to the larger 50% of studies did not change the observed trend towards decreasing efficacy with increasing resistance (table). By region, multivariate meta-regression showed significant correlations between low birthweight and *dhps* Ala437Gly prevalence, *dhps* Lys540Glu prevalence, and resistance strata only in east and southern Africa (appendix p 16).

Only five studies were done in areas that had a more than 10% prevalence of sextuple-mutant *P falciparum* parasites (pooled *dhps* Ala581Gly prevalence 32% [95% CI 17 to 48]). Substantial heterogeneity in effect size was found among these studies (I^2=68·8%, p=0·012; appendix p 33): the three studies with a small sample size in the reference group had an RRR of 35% (14 to 51; pooled *dhps* Ala581Gly prevalence 21%), whereas the two remaining larger studies, both conducted in areas with the highest *dhps* Ala581Gly prevalence (pooled prevalence 46%) had an RRR of –2% (–15 to 9; p=0·0518 for subgroup difference).

When outcomes other than low birthweight were considered, we observed a linear trend towards decreasing effectiveness of IPTp with increasing prevalence of *dhps* Lys540Glu for maternal moderate-to-severe anaemia and for malaria infection (maternal, placental, or any malaria) at delivery. The RRRs at delivery for moderate-to-severe anaemia were 41% (28 to 51) in low-resistance, 20% (1 to 35) in moderate-resistance, and 13% (3 to 22) in high-resistance areas (p_{trend}=0·0049); and for any malaria infection were 20% (13 to 26) in low-resistance, 18% (10 to 26) in moderate-resistance, and 3% (–3 to 9) in high-resistance areas (p_{trend}=0·0164; appendix pp 21–26).

The analysis of individual participant data from surveys focused on areas with a more than 80% prevalence of the *dhps* Lys540Glu mutation, with the aim of ascertaining the effect of the sextuple-mutant *P falciparum* parasite in areas previously defined as super resistant (>10% *dhps* Ala581Gly prevalence).[16] Of 138 publicly available surveys, 39 met the inclusion criteria, and 13 surveys that included data from areas with a *dhps* Lys540Glu prevalence of more than 80% or with super resistance (all in east and southern Africa from 2008–15, and comprising

42 394 singleton livebirths) were included in the analysis after exact matching of probability of receiving IPTp, resistance, and malaria transmission intensity data (figure 1). Sulfadoxine-pyrimethamine IPTp in these areas was associated with an RRR of 11% (95% CI 8 to 13) for low birthweight. Even in areas with a *dhps* Lys540Glu prevalence of more than 90% and a *dhps* Ala581Gly prevalence of up to 10%, sulfadoxine-pyrimethamine IPTp was associated with significantly reduced risk of low birthweight (RRR 10% [7 to 12]; figure 4). However, in the two super-resistant areas, sulfadoxine-pyrimethamine IPTp did not protect against low birthweight (RRR 0·5% [–16 to 14]; figure 4). In these two areas, the pooled prevalence of the *dhps* Ala581Gly mutation across all contemporary molecular studies was 37% (29 to 46; appendix p 34).

Discussion

In our meta-analysis of aggregated data from 57 clinical studies, increases in the prevalence of two molecular markers of sulfadoxine resistance were associated with clear reductions in the effectiveness of sulfadoxine-pyrimethamine IPTp to avert low birthweight and other outcomes such as malaria infection at delivery and maternal anaemia. In our parallel analysis of individual participant data from nationally representative surveys, sulfadoxine-pyrimethamine IPTp was associated with a significant but modest protective effect against low birthweight in areas where the *P falciparum dhps* Lys540Glu mutation prevalence was 90% or higher and the prevalence of sextuple-mutant parasites was less than 10%.[16] However, these surveys also showed that, in areas where sextuple-mutant parasites are common (pooled prevalence estimate 37%), sulfadoxine-pyrimethamine IPTp did not protect against low birthweight. These findings are consistent with our understanding of the incremental increase in resistance to sulfadoxine-pyrimethamine with successive mutations in the *dhfr* and *dhps* genes, and with the previous studies that showed compromised efficacy of sulfadoxine-pyrimethamine in women infected with sextuple-mutant *P falciparum*.[12–15] This high resistance is currently restricted to a few foci in east Africa,[16] but its spread would have important implications for the continued use of sulfadoxine-pyrimethamine for IPTp.

Compared with other markers of sulfadoxine-pyrimethamine resistance, fewer data are available on the distribution of the *dhps* Ala581Gly mutation. Therefore, the aggregated-data meta-analysis was limited in its ability to define and validate different thresholds for the *dhps* Ala581Gly mutation. There were only five studies done in areas in east and southern Africa with a *dhps* Ala581Gly prevalence of more than 10%, and none were done in areas with a *dhps* Ala581Gly prevalence between 13% and 43%. Within these studies, there was also substantial between-study heterogeneity in the effect of treatment on low birthweight: the three smaller studies, with only four to eight low birthweight events in the reference groups,[12,15,31] showed a pooled effect size of 35% (95% CI 14 to 51), whereas the studies with larger reference groups reported an effect size of –2% (–15 to 9; appendix p 33).[32,33] The results of these larger two studies, which were done in areas with a *dhps* Ala581Gly prevalence of more than 45%, are consistent with the lack of effect on low birthweight in our analysis of survey data, which was based on much larger sample sizes and areas with an average *dhps* Ala581Gly prevalence of 37%.

Irrespective of sulfadoxine-pyrimethamine resistance, we observed large between-study heterogeneity in the treatment effect on low birthweight among the 57 clinical studies. This can be explained, in part, by the multicausal nature of low birthweight and the varying population-attributable fractions of malaria towards low birthweight, which depend on transmission intensity and uptake of interventions such as insecticide-treated nets. In the current study, insecticide-treated net use was not an effect modifier or confounder, but malaria transmission intensity was correlated with resistance (lower transmission levels were associated with higher resistance levels) and was thus a potential confounder, which is why it was important to adjust for malaria transmission in our models. Nevertheless, estimates of the effect of sulfadoxine-pyrimethamine resistance on the effectiveness of sulfadoxine-pyrimethamine IPTp for averting low birthweight (ie, the slope of the meta-regression lines) were largely unaffected by the inclusion of four covariates—malaria transmission, study quality, mean number of sulfadoxine-pyrimethamine doses, and proportion of paucigravidae—in the models, suggesting minimal confounding by these variables overall.

Although the effectiveness of IPTp for low birthweight decreased with increasing resistance, sulfadoxine-pyrimethamine IPTp remained associated with a 7–10% reduced risk of low birthweight even in areas where the resistant quintuple-mutant haplotype is fixed. This small but resilient effect on low birthweight contrasts with the lack of effect (RRR 3%) on malaria infection in high-resistance areas seen in the aggregated-data meta-analysis (appendix p 19), and with the previously observed unfavourable parasitological response in asymptomatic pregnant women receiving sulfadoxine-pyrimethamine IPTp in these areas, where clearance of parasites by day 42 was achieved in only 50% of paucigravidae.[7] That IPTp can decrease risk of low birthweight even in areas where its efficacy for clearance of infection is compromised might suggest that suppression, rather than radical clearance of parasites, is required to mitigate the adverse effects of malaria on placental function and growth, as observed in multigravidae (who acquire protective antimalarial immunity over successive pregnancies). Alternatively, sulfadoxine-pyrimethamine might have beneficial effects on birthweight that are independent of its antimalarial properties and are, therefore, unaffected by parasite resistance (eg, antimicrobial effects,[32–34] or effects related to

immunomodulation, similar to those described for co-trimoxazole[35]).

The differences in *P falciparum* parasite populations (shown in the scatter plot of the prevalence of *dhps* Ala437Gly and Lys540Glu mutations in the appendix p 31) reflect the distinct geographical origins of two or three parasite populations in east and west Africa.[25] In east and southern Africa, the combination of the resistance alleles at *dhps* codons 540 and 581 could be considered to track sulfadoxine-pyrimethamine resistance. In central and west Africa, where the *dhps* Lys540Glu mutation is absent or rare, tracking *dhps* Ala437Gly might be informative. However, other mutations have started to emerge in west Africa, such as *dhps* Ile431Val, which has been reported on a haplotype bearing mutant alleles at codons 581 and 613 but a wild-type allele at codon 540.[36,37] The clinical implications of such new haplotypes require further study.

Our analyses have important limitations. First, the potential biases associated with observational data, in which the number of sulfadoxine-pyrimethamine doses is not determined by the study, have been discussed in detail elsewhere.[4] Although the use of exact matching and multivariate models will have reduced the potential for bias in the surveys, residual confounding cannot be excluded. Second, national surveys are subject to measurement error and information bias from respondent recall and self-report.[4] Similar limitations apply to the aggregated-data analysis, which could only adjust for study-level covariates. For some studies, time-matched local resistance data were not available and were obtained from other sources, which are less precise. Some studies were considered to be of poor quality, with a trend towards greater effectiveness with decreasing study quality, but sensitivity analysis showed that these low-quality studies were equally distributed across the resistance spectrum and did not affect the conclusions. Similarly, there was evidence of a small-study effect, but this effect was also observed in all three resistance strata, and restricting the analysis to the largest 50% of studies (which are least likely to be affected by publication bias) did not alter the conclusions. In addition, the meta-analysis suffered from design and reporting variation and small numbers in the extreme dose groups (zero doses and three or more doses). This limitation was partly mitigated by use of a dose-response analysis that placed less emphasis on the extreme dose groups.

This is the most comprehensive study of the effect of sulfadoxine-pyrimethamine resistance on the effectiveness of sulfadoxine-pyrimethamine IPTp, involving 57 clinical studies, 13 nationally representative surveys, and more than 100 000 births. The data show that, despite the substantial heterogeneity between studies with regard to the effectiveness of sulfadoxine-pyrimethamine IPTp on low birthweight, increasing prevalence of molecular markers of sulfadoxine resistance is correlated with a decrease in effectiveness of sulfadoxine-pyrimethamine to prevent low birthweight and malaria infections. These findings suggest that molecular monitoring of sulfadoxine-pyrimethamine resistance is a potential policy tool to guide the use of sulfadoxine-pyrimethamine IPTp. It is reassuring that a protective association of sulfadoxine-pyrimethamine IPTp with low birthweight can be detected even in high-resistance areas where quintuple-mutant *P falciparum* parasites are almost fixed. However, sulfadoxine-pyrimethamine IPTp is not likely to reduce malaria and malaria-associated low birthweight in areas where the prevalence of sextuple-mutant parasites, with the *dhps* Ala581Gly mutation, exceed 37% (the pooled estimate in the high-resistance areas). For these areas, the search for alternative strategies or drugs to replace sulfadoxine-pyrimethamine IPTp is a pressing research priority for the control of malaria in pregnancy.

Contributors

FOtK conceived the study. AMvE, DAL, and FOtK wrote the protocol. AMvE, DAL, GK, and DECS did the literature search, acquired the aggregated data, screened records, and extracted data. AMvE, GK, and DECS assessed the quality of included studies. CK and FOtK acquired and combined the individual participant data from different observational studies. AMvE, DAL, and FOtK did the statistical analysis. KK, MD, JG, SJR, SRM, SMT, CR, and LCO provided individual level participant clinical or molecular data. CR, LCO, and CHS set up and maintained the interactive maps of the distribution of molecular resistance markers used in the analysis. AMvE, DAL, and FOtK wrote the first draft of this manuscript. All authors provided critical conceptual input, interpreted the data analysis, and critically revised and approved the final version of the manuscript.

Declaration of interests

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Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: van Eijk AM, Larsen DA, Kayentao K, et al. Effect of *Plasmodium falciparum* sulfadoxine-pyrimethamine resistance on the effectiveness of intermittent preventive therapy for malaria in pregnancy in Africa: a systematic review and meta-analysis. *Lancet Infect Dis* 2019; published online March 25. http://dx.doi.org/10.1016/S1473-3099(18)30732-1.

Appendix to 'Impact of Sulphadoxine-Pyrimethamine Resistance on the Effectiveness of Intermittent Preventive Therapy for Malaria in Pregnancy (IPTp) in Africa: A Systematic Review and Meta-Analysis'

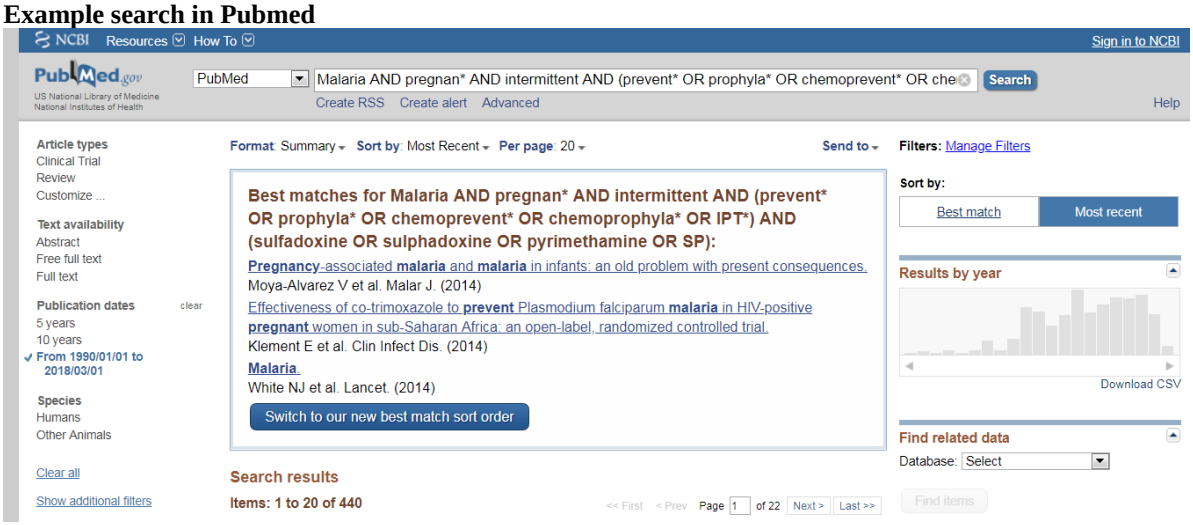
Contents

Supplemental Methods

Search terms

We used the PICOS model to design the search strategy. The following search terms were used for the aggregated data meta-analysis: "Malaria AND pregnan* AND intermittent AND (prevent* OR prophyla* OR chemoprevent* OR chemoprophyla* OR IPT*) AND (sulfadoxine OR sulphadoxine OR pyrimethamine OR SP)". The electronic databases "Malaria in Pregnancy Library",[1] PubMed, Web of Science, and Scopus were searched. The search was conducted in English but without language restriction.

Example search in Pubmed



Eligibility criteria clinical studies

Observational studies were included if they were conducted in sub-Saharan Africa, had information at delivery on the number of SP doses received, and data on birthweight, maternal haemoglobin or plasmodium infection at delivery. Trials were included if they were: quasi-randomized or randomized trials; conducted in sub-Saharan Africa; compared IPTp-SP against passive case detection or placebo and otherwise fulfilled the same criteria as for the observational studies. Studies or study arms were excluded if they involved only HIV-infected women, combined SP with other antimalarial drugs, such as artemisinin derivatives or azithromycin, or with other interventions such as screening for malaria. Surveys were included if they were conducted after the year 2000 (when IPTp-SP started to be introduced as policy) with datasets publicly available by 31 May 2015; contained data on LBW (perceived birth size and measured weight); measured IPTp use by number of doses among recently pregnant women, and ITN coverage measured at the household level.

PICOS Table

Components	Characteristics
Participants/Population	Women at the time of delivery in malarious areas in Africa with documentation (verbal or written) of the number of intermittent sulfadoxine-pyrimethamine (SP) doses received during pregnancy for the prevention of malaria and pregnancy outcome (birth weight, maternal haemoglobin, malaria). There are two components: a) women participating in trials and observational studies with this information available b) women participating in national surveys. Studies/surveys will be matched with SP molecular resistance data and indicators of malaria transmission in the same area.
Intervention/exposure	Number of SP doses received during pregnancy as part of IPTp

Comparator/control	No SP (zero doses received during pregnancy) or inadequate doses of SP (0-1 doses)
Outcomes	Primary outcome: Low birth weight (<2500 grams) Secondary outcomes: Placental parasitaemia (the presence of asexual parasites in the placenta at delivery by microscopy, Rapid diagnostic test (RDT), or histology), maternal parasitaemia (the presence of asexual parasites in the peripheral blood of mother at delivery detected by microscopy or RDT), mean maternal haemoglobin, maternal anaemia (any anaemia: <11 or 10 g/dl; moderate-to-severe anaemia: <9 or 8 or 7 g/dl), miscarriage or abortion (foetal loss <28 weeks gestation), stillbirth (foetal loss =28 weeks gestation), preterm delivery (delivery before 37 weeks of gestational age), and gestational age.
Study design	Any survey, cohort or trial among pregnant women in a malarious area in sub-Saharan Africa published from 1990 onwards without language restriction

Data extraction and quality assessment of clinical studies

For studies where time of conduct of the study was not reported or could not be obtained, the study was assumed to have been conducted two years before the publication date,[2,3] based on the analysis of the Malaria in Pregnancy library content.[4] Data from reports with multiple publications were combined into a single entry, to avoid duplication. Two independent reviewers identified studies and agreed on final study eligibility (AMvE, GK), and extracted data and assessed study quality unblinded to authors of the source study (AMvE and GK or DECS). If no agreement could be reached a third reviewer (FtK) got involved and agreement was reached by consensus.

An adaption of the Newcastle-Ottawa Scale for cohort studies was used for quality assessment both for observational studies and for the IPTp-SP arms of clinical trials, where the number of SP doses was used as the exposure variable and low birthweight (or other outcomes) as the outcome variable (see table quality assessment). Quality assessment was conducted by two persons (AMvE and GK or DECS); where disagreement occurred, a joint review of the study was conducted until agreement was reached by consensus. Follow-up or outcome was considered adequate if more than 80% of participants initially enrolled were included in the analysis. Study quality was categorized into four categories as <=2, 3, 4, >=5 stars. Studies were not excluded a-priori based on their quality score.

Quality assessment form for observational studies and trials

	Focus area	**Category options†**
1	Representativeness of the exposed group	a) truly representative of pregnant women in the community (e.g. random selection in community) * b) somewhat representative of the average pregnant woman in the community (e.g. selection in ANC) * c) selected group of pregnant women (e.g. women who deliver in a health unit) d) no description of the derivation of the group
2	Selection of the non-exposed group	a) drawn from the same community/pool as the exposed group * b) drawn from a different source c) no description of the derivation of the non-exposed group
3	Ascertainment of exposure	a) ANC record (e.g. antenatal clinic notes) b) structured interview c) combination of ANC notes and interview * d) observed and prospectively collected (trial or cohort study) * e) unsecure record f) written self-report g) no description
4	Comparability of exposed and unexposed group	a) differences examined and no differences reported in characteristics which are presented * b) differences in characteristics present but no effect on outcome, or multivariate analysis for outcome available or randomized study * c) differences in characteristic present, not shown if effect on outcome d) no description/not examined
5	Outcome assessment (low birthweight, haemoglobin, malaria)	a) independent blind assessment * b) record linkage * c) not clear d) no blind assessment e) no description
6	Attrition	a) complete - all subjects accounted for * b) Outcome not available for all subjects but unlikely to introduce bias - small number lost - <20%, or description provided of those lost * c) Outcome for less than 80% of people with exposure data and no description of those lost d) no statement

† A study could be awarded a maximum of one star for each item

Prediction surfaces of SP resistance mutation prevalence

Prevalence data of *Pfdhps*-A437G, K540E and A581G mutations were extracted from the clinical studies in pregnant women, the literature, and existing molecular surveyor databases.[5-8] These mutations in *Pfdhps* were chosen over the major resistance mutations in *dhfr* because the *Pfdhps* mutations have a more geographically heterogeneous distribution, reflecting their more recent emergence in Africa.[9] The *Pfdhps*-K540E prevalence served as a proxy for the prevalence of quintuple *Pfdhps*/*Pf*dhfr mutant genotype.[10] In areas where the prevalence of this quintuple mutant was >50%, the prevalence of *Pfdhps*-A581G mutation served as a proxy for the sextuple mutant. In West Africa, *Pfdhps*-A581G may occur independent of the *Pfdhps*-K540E mutation. These mutations were not considered sextuple mutants if the *Pfdhps*-K540E prevalence was <=50%.[7] Presence was defined as a prevalence of ≥1%. Raster files from existing point data maps from areas that had previously been defined as 'super-resistant' (>10% prevalence of sextuple mutant) were obtained from the authors.[7] Two such areas were identified: in north-eastern Tanzania, and in the area crossing the borders of Southwest Uganda and East Rwanda, eastern Democratic Republic of Congo, and north-western Tanzania.[7]

Matching IPTp effectiveness, resistance and malaria transmission intensity data

The prevalence of each point mutation and the *Pf*$PR_{2–10}$ (the *Plasmodium falciparum* parasite rate in 2-10 year olds)[11] was matched to each study by time (the same year for *Pf*$PR_{2–10}$ and +/- 2 years for point mutations) and location using latitude and longitude (within 300 km).[12] Location was defined as the site of the main research facility in the observational studies and trials, or the midpoint between study locations. The following order of preference was used to match resistance with clinical data: a) resistance data provided in the clinical study reports or by the authors for that location and time of study (data from individuals with a recent history of SP intake were excluded); b) estimates from continuous surface maps from WWARN's geospatial models for *Pfdhps*-A437G and *Pfdhps*-K540E;[8] and c) for *Pfdhps*-A581G, or for studies after 2012, data were used from existing population prevalence maps of *Pfdhps* (Table S2).[5-7] For national surveys, the mean prevalence of *Pf*$PR_{2–10}$ and *Pfdhps* mutations was calculated for the sub-national region of each given survey using Malaria Atlas Project data[11] and WWARN's geospatial models.[8] All matching for surveys was performed using the Raster-Package of R (v3.3.2).[13]

Assessment of heterogeneity and small-study effects clinical studies

The extent of heterogeneity was measured using the I^2 statistic,[14] which is a measure of the proportion of total variability explained by heterogeneity rather than chance expressed as a percentage, with 0−40% representing no or little heterogeneity, 30−60% moderate heterogeneity, 50−90% substantial heterogeneity, and 75−100% considerable heterogeneity.[15] To examine the presence of small-study effects (the tendency for the smaller studies to show larger treatment effects) due to potential publication and other bias, we used funnel plots with effect size (relative risk of LBW) as a function of study size (the standard error of the log relative risk). We used Egger's test for small study effect as statistical test for funnel plot asymmetry. To determine the impact of small-study effects we conducted sensitivity analysis by restricting the analysis to the largest 50% of studies.[16]

Further details of methods used to define the analytical population and mitigate for potential confounding of the effect of SP dose on birthweight in the individual participant data meta-analysis of survey data

In the analysis of the survey data, only the most recent live birth in the past <2 years was considered, to minimize information error on exposure to SP and details of the birth outcomes. To mitigate potential confounding of the effect of SP dose on birthweight, exact matching was employed (MatchIt package in R version 2.15.149)[17] for the following variables: neonatal tetanus vaccination (any or none), iron supplementation during pregnancy (any or none), household wealth (dichotomized at the median as rich and poor), mother's education (any or none), malaria transmission intensity (low:<25% and high:>=25% $pfPR_{2-10}$), antenatal care (any or none), and residence (urban or rural). Unmatched live births were excluded from the analyses. To further mitigate potential confounding factors of the effect of SP dose on birthweight, we used multivariate log binomial regression for LBW and linear regression for birthweight as continuous variable adjusting for the following covariates: household wealth quintile, mother's age (< 18y, 18-30y or > 30y), mother's education (none, some primary or completed primary), whether the child was a twin or not, parity and birth interval (firstborn, second born <24 months spacing, second born ≥24 months spacing, third born or later <24 months spacing, third born or later ≥24 months spacing), gender, any household ITN ownership during pregnancy, $PfPR_{2–10}$, and quarter of the year.

Generalized least square (GLST) regression for trend estimation of summarized dose-response data
The first step in generalized least square (GLST) regression for trend estimation of summarized dose-response data consisted of calculation a single summary effect estimate for each study.[18,19] This was expressed as relative risk for the trend effect and computed using the correlated log RR estimates across each of SP dose categories. The exposure value for each SP dose category represented the mean number of SP doses for that category. If the SP dose was not reported per exact dose categories (0, 1, 2, 3, etc), but as groups (2 groups [e.g. 0 vs 2+, or 0-1 vs 2+], 3 [e.g. 0,1,2 or 0,1,2+] or 4 groups [e.g. 0, 1, 2, 3+]), then the mean SP dose per dose category was calculated as the sum of the total doses received divided by the number of women contributing to each dose category; for example, if a study reported outcome data for the intervention group as a single pooled group of women who had received at least 2 doses (2+) and the study also reported that this 2+ group consisted of 70, 20 and 10 women who received 2, 3 and 4 doses respectively, then a mean was 2.4 (240 doses/100 women) was used as the number of SP doses received by the 2+ dose group. Similarly, if a study only presented pooled data for women receiving 0 or 1 dose of SP as the 'control' group, and that category consisted of 40 women who had received 0 doses and 60 who had received 1 dose, then a mean of 0.6 SP doses (60 doses/100 women) was used to define exposure to SP in that group (Table S2). We also combined SP-dose groups when the sample size was low in a specific group with the aim to obtain at least 30-40 women in any SP-dose strata, but this was not achieved for all studies (e.g. Minja 2013, or in analyses by gravidity group). For the same reason, we pooled data from 2 studies conducted in Malawi in 2010 that used the same design and protocol.[20,21] For studies with a continuous outcome, we used the weighted mean difference between the outcome among women who had not received SP versus women who had received 2 or 2+ doses of SP, and the outcomes were pooled using random effects meta-analysis.

Meta-regression
Meta-regression graphs of log transformed relative risks (RR) for low birthweight (LBW) are presented. Study specific estimates are depicted as circles proportional to their precision (inverse of the variance of the log[RR]). The solid line indicated fitted values by random-effects meta-regression. The RRtrend value indicated the reduction in risk associated with each incremental dose of SP calculated obtained using generalized least square (GLST) regression for trend estimation of summarized dose-response data.[18,19]

Pooled mutation prevalence by resistance strata or study area using MetaProp
The pooled mutation prevalence by resistance strata or study area were obtained with Metaprop: a Stata command to perform meta-analysis of binomial data.[22]

Supplemental Results

In univariate meta-regression, study quality was more predictive of the effectiveness of IPT on LBW (p=0.05) than study design (P=0.14), and because the two variables were correlated (i.e. trials tend to have higher quality scores than observational studies), only study quality (rather than both or study design alone) was considered as co-variate in further multivariate models.

Although we intended to look at birth outcomes such as miscarriage, abortion, or stillbirth, these outcomes were not frequently reported and were not examined further. The dose of folic acid could not be used in the analyses of potential effect modifiers or confounders because this data was available from only 20 of the 57 studies (35.1%) included in the birth weight analysis; furthermore, some authors reported that not all included women received folic acid.[23] The use antenatal clinic or the number of antenatal clinic visits could not be included as confounder or effect modifier because this was reported for only 31 of 57 studies (54.4%); for 28 studies ANC uptake (at least one ANC visit) was >90%, and for 3 studies this ranged from 65 to 87%. Other authors reported that lower SP uptake was associated with lower or later antenatal attendance.[24-28]

Supplemental Tables

Table S1: Study characteristics of observational studies and trials with information on outcomes[a] by SP doses

	Author and Publication Year	Country	Time period	Design	# of sites	LBW (all) %	Pauci-gravidae % [b]	Definition pauci-gravidae	ITN use % [c]	HIV % [d]	Folate dose (mg)[e]	ANC % [f]	*Pf*Pr$_{2-10}$[11]	Quality score
1	Aduloju 2013[29]	Nigeria	2011-2011	Survey	1	NA	20.7	G1	10.3	4.1 (UNAIDS)	NA	100.0	39.3	2
2	Alli 2013[30]	Nigeria	2010-2011	Survey	1	2.0	35.0	G1	19.5	4.1 (UNAIDS)	NA	100.0	50.6	3
3	Anchang Kimbi 2009[31]	Cameroon	2007-2007	Survey	1	NA	31.0	G1	6.6	5.6	NA	NA	51.6	3
4	Apinjoh 2015[32]	Cameroon	2008-2010	Survey	1	NA	32.0	G1	9.8	4.0	NA	100.0	51.6	4
5	Arinaitwe 2013[33] [g,h]	Uganda	2011-2011	Survey	1	9.8	32.4	G1	87.8	0.0	5.0	NA	38.2	4
6	Aziken 2011[34]	Nigeria	2009-2009	Cohort	1	10.1	18.9	G1	0.0	0.0	NA	100.0	62.3	2
7	Bouyou-Akotet 2010[35]	Gabon	2005-2006	Survey	1	17.2	77.3	G1	37.0	5.4 (UNAIDS)	NA	NA	37	3
8	Bouyou-Akotet 2016[36] [g]	Gabon	2011-2011	Survey	2	6.0	19.1	G1	16.2	0.0	NA	100.0	43.5	4
9	Braun 2015[37] [g]	Uganda	2013-2013	Survey	1	9.6	31.7	G1	65.1	0.0	NA	NA	24.5	4
10	Cassam 2007[38]	Mozambique	2005-2007	Survey	50	8.1	27.5	G1	43.7	36.4	NA	100.0	54.7	4
11	Challis 2004[39]	Mozambique	2001-2002	Trial (IPTp)	2	11.4	100	G1/G2	1.0	10.0	NA	100.0	43.1	5
12	Chukwuocha 2016[40]	Nigeria	2014-2014	Survey	1	NA	36.5	G1	19.7	3.2 (UNAIDS)	NA	100.0	62.8	0
13	Coulibaly 2014[41] [g,h]	Burkina Faso	2010-2012	Survey	5	15.1	20.6	G1	80.3	0.0	0.4	NA	63.8	4
14	Desai 2015[42] [g,h]	Kenya	2011-2012	Survey	3	7.9	40.0	G1	98.0	0.0	0.4	NA	61.5	4
15	Douamba 2014[43]	Burkina Faso	2013-2014	Survey	1	NA	21.3	G1 [g]	86.6	.9 (UNAIDS)	NA	NA	54.5	2
16	Falade 2007[44]	Nigeria	2003-2004	Survey	1	6.1	23.5	G1	1.1	2.0	5.0	NA	50.5	3
17	Famanta 2011[45] [g]	Mali	2009-2009	Survey	1	11.4	27.5	G1	80.7	1.3 (UNAIDS)	NA	72.8	34.9	2
18	Fehintola 2016[46]	Nigeria	2013-2013	Survey	2	NA	40.3	G1	27.0	4.0	NA	85.3	44.7	2
19	Feng 2010[47] [g]	Malawi	1997-1999	Survey	1	14.6	46.4	G1/G2	10.0	16.6 (UNAIDS)	NA	NA	27.7	2
	Feng 2010[47] [g]	Malawi	1999-2001	Survey	1	12.7	48.4	G1/G2	23.0	16.5 (UNAIDS)	NA	NA	27.7	2
	Feng 2010[47] [g]	Malawi	2002-2006	Survey	1	10.1	47.5	G1/G2	51.0	14.5 (UNAIDS)	NA	NA	24.4	2
20	Gies 2009[48]	Burkina Faso	2004-2006	Trial (cluster)	12	17.5	100	G1/G2	5.3	1.4 (UNAIDS)	NA	95.3	51.1	5
21 22	Gutman 2013[21]/ Kalilani 2014[20] [g,h]	Malawi	2009-2011	Survey	4	7.2	31.6	G1	67.0	0.0	0.4	NA	43.5	4
23	Harrington 2011[49] [g]	Tanzania	2002-2005	Survey	1	4.6	29.2	G1	15.5	6.9 (UNAIDS)	NA	100.0	17.4	4
24	Hommerich 2007[25]	Ghana	2006-2006	Survey	1	12.4	32.7	G1	8.0	3.0	NA	NA	39.6	3
25	Igboeli 2017[50]	Nigeria	2013-2013	Survey	1	3.6	30.2	G1	20.0	3.4 (UNAIDS)	NA	100.0	33.5	3
26	Inyang-Etho 2011[51]	Nigeria	2008-2008	Cohort	1	NA	24.4	G1 [g]	7.2	3.1 (UNAIDS)	NA	100.0	35.6	3
27	Kayentao 2014[52] [g]	Mali: Koro	2006-2007	Survey	1	7.7	27.8	G1	58.7	1.3 (UNAIDS)	0.4	NA	48.2	4
	Kayentao 2014[52] [g]	Mali: San	2006-2006	Survey	1	7.3	23.6	G1	61.3	1.3 (UNAIDS)	0.4	NA	64.7	4
	Kayentao 2014[52] [g]	Mali: Bougouni	2006-2007	Survey	1	6.9	23.5	G1	35.9	1.3 (UNAIDS)	0.4	NA	52.6	4
	Kayentao 2014[52] [g]	Mali: Djenne	2006-2006	Survey	1	6.5	22.1	G1	67.9	1.3 (UNAIDS)	0.4	NA	50.5	4
	Kayentao 2014[52] [g,h]	Mali: Kita	2009-2010	Survey	1	10.3	25.8	G1	88.3	1.3 (UNAIDS)	0.4	NA	39.5	4

Table S1: Study characteristics of observational studies and trials with information on outcomes[a] by SP doses

	Author and Publication Year	Country	Time period	Design	# of sites	LBW (all) %	Pauci-gravidae % [b]	Definition pauci-gravidae	ITN use %[c]	HIV % [d]	Folate dose (mg)[e]	ANC % [f]	*Pf*Pr$_{2-10}$[11]	Quality score
	Kayentao 2014[52] [g,h]	Mali: San	2009-2010	Survey	1	9.3	20.2	G1	94.5	1.3 (UNAIDS)	0.4	NA	66.6	4
28	Kilauzi 2013[53]	DRC	2011-2011	Survey	1	7.5	20.0	G1 [g]	43.8	1.1 (UNAIDS)	NA	NA	29.7	3
29	Likwela 2012[54]	DRC: Mikalayi	2007-2007	Survey	1	16.1	17.2	G1	6.5	1.5 (UNAIDS)	NA	100.0	33.2	4
	Likwela 2012[54]	DRC: Kisangani	2007-2007	Survey	1	7.8	29.2	G1	4.7	1.5 (UNAIDS)	NA	100.0	40.2	4
	Likwela 2012[54]	DRC: Rutshuru	2007-2007	Survey	1	8.2	16.4	G1	11.3	1.5 (UNAIDS)	NA	100.0	36.8	4
30	Mace 2015[55] [g,h]	Zambia	2009-2010	Survey	2	7.1	36.7	G1	55.5	0.0	5.0	NA	20.6	4
31	Mbaye 2006[56]	The Gambia	2002-2004	Trial (IPTp)	14	5.9	0.0	G1	70.3	0.5	0.4	100.0	16.5	6
32	Menendez 2008[57]	Mozambique	2003-2005	Trial (IPTp)	1	11.3	25.7	G1	91.5	23.9 (UNAIDS)	0.4	100.0	47.2	6
33	Minja 2013[58]	Tanzania	2008-2010	Cohort	1	6.5	21.6	G1	94.9	5.8 (UNAIDS)	NA	100.0	11.3	3
34	Moleins 2010[26]	Senegal	2007-2008	Survey	1	7.9	27.3	G1 [g]	45.7	0.8 (UNAIDS)	NA	100.0	26.6	3
35	Mosha 2014[59]	Tanzania	2012-2012	Survey	2	5.1	37.4	G1	94.6	3.4	NA	100.0	18.8	4
36	Msyamboza 2009[60] [g]	Malawi	2002-2004	Cohort	26	16.8	29.4	G1	10.2	15.2 (UNAIDS)	NA	87.3	27.4	4
37	Muhammad 2016[61]	Nigeria	2014-2014	Survey	1	37.0	62.0	G1/G2	89.7	3.2 (UNAIDS)	NA	100.0	40.8	4
38	Mwangi 2015[62]	Kenya	2011-2013	Trial (Iron)	4	NA	18.1	G1	15.5	21.1	NA	NA	61	6
39	Mwapasa 2004[63]	Malawi	2000-2002	Survey	1	NA	42.2	G1	22.3	0.0	5.0	NA	24.4	4
40	Namusoke 2010[64] [g]	Uganda	2004-2005	Survey	1	14.6	49.4	G1	32.0	11.0	NA	96.8	19.3	4
41	Ndeserua 2015[65]	Tanzania	2012-2012	Survey	1	6.3	33.1	G1	97.7	1.7	NA	NA	28.2	4
42	Nduka 2011[3]	Nigeria	2009-2009	Survey	3	NA	35.5	G1	12.0	4 (UNAIDS)	NA	NA	61.6	2
43	Ndyomugyenyi 2011[66]	Uganda	2004-2007	Trial (IPTp)	10	6.6	21.1	G1	97.0	6.5 (UNAIDS)	5.0	100.0	24.9	6
44	Nganda 2004[67]	Tanzania	2003-2003	Survey	1	NA	42.3	G1	48.1	6.8 (UNAIDS)	NA	100.0	17.5	3
45	Njagi 2002[68]	Kenya	1997-1999	Trial (IPTp)	1	13.3	100	G1/G2	50.0	22.4 (UNAIDS)	5.0	100.0	22.9	5
46	Oduro 2010[27]	Ghana	2006-2007	Survey	6	18.4	24.2	G1	53.6	2.2 (UNAIDS)	NA	97.0	63.3	3
47	Olliaro 2008[69]	Senegal	2000-2007	Survey	1	9.5	21.7	G1 [g]	12.4	.8 (UNAIDS)	NA	100.0	26.6	4
48	Olorunda 2013[28]	Nigeria	2010-2010	Survey	1	7.9	37.2	G1	13.9	4.1 (UNAIDS)	NA	100.0	37.9	4
49	Onyebuchi 2014[70]	Nigeria	2012-2012	Survey	1	NA	45.2	G1/G2	100.0	3.4 (UNAIDS)	NA	100.0	54.0	0
50	Orobaton 2016[71]	Nigeria	2014-2015	Survey	4	NA	18.3	G1	56.1	3.1 (UNAIDS)	NA	56.6	33.5	0
51	Parise 1998[72]	Kenya	1994-1996	Trial (IPTp)	1	10.5	100	G1/G2	1.0	26.9	5.0	100.0	22.6	4
52	Ramharter 2007[73]	Gabon	2005-2006	Survey	3	10.2	28.7	G1	38.1	7.9	NA	NA	45.9	3
53	Rogawski 2012[74]	Malawi	1997-2006	Survey	1	NA	47.8	G1	37.0	15.5 (UNAIDS)	NA	NA	27.7	4
54	Rogerson 2000[75]	Malawi	1997-1999	Survey	1	NA	46.0	G1	7.0	16.6 (UNAIDS)	0.25	100.0	27.7	2
55	Sirima 2006[76] [g]	Burkina Faso	2004-2004	Survey	2	12.1	31.1	G1	35.3	1.6 (UNAIDS)	0.25	NA	33.9	3
56	Suleiman 2003[77]	Sudan	1999-2001	Cohort	2	19.1	100	G1	1.0	0.1 (UNAIDS)	NA	100.0	3.2	4
57	Tetteh-Ashong 2005[78]	Malawi	2005-2005	Survey	1	8.3	27.6	G1	17.6	0.1 (UNAIDS)	0.25	NA	27.4	3

Table S1: Study characteristics of observational studies and trials with information on outcomes[a] by SP doses

	Author and Publication Year	Country	Time period	Design	# of sites	LBW (all) %	Pauci-gravidae % [b]	Definition pauci-gravidae	ITN use %[c]	HIV % [d]	Folate dose (mg)[e]	ANC % [f]	*Pf*Pr$_{2-10}$[11]	Quality score
58	Tonga 2013[79]	Cameroon	2011-2012	Survey	5	16.7	22.5	G1	19.3	6.0	NA	NA	55.4	2
59	Tongo 2011[80]	Nigeria	2007-2008	Survey	2	9.0	11.6	G1	20.1	3.1 (UNAIDS)	NA	NA	50.8	2
60	Toure 2014[24]	Cote d'Ivoire	2009-2010	Survey	6	8.5	24.0	G1	16.7	4.0	NA	98.6	55.5	4
61	Tutu 2011[81]	Ghana	2005-2007	Survey	6	12.1	24.3	G1	26.5	2.3 (UNAIDS)	NA	NA	30.9	4
62	Vanga-Bosson 2011[82]	Cote d'Ivoire	2008-2008	Survey	6	10.6	16.1	G1	48.0	5.4	NA	97.8	65.4	5
63	van Eijk 2004[23] [g]	Kenya	1999-2000	Survey	1	9.7	50.2	G1	7.4	14.8 (UNAIDS)	5.0	100.0	7.0	5
64	Van Spronsen 2012[83]	Ghana	2010-2010	Survey	1	NA	34.0	G1	26.5	0.0	NA	NA	57.4	1
65	Verhoeff 1998[84]	Malawi	1993-1994	Survey	1	NA	30.0	G1	1.0	0.0	NA	100.0	27.4	3
66	Yussuf 2010[85]	Tanzania	2009-2010	Survey	1	40.2	50.4	G1	91.5	4.0	NA	65.0	29.5	4

Abbreviations (alphabetical order): *dhps*=dihydropteroate synthetase. G1, G2: first and second pregnancies. G3+ =3 or more previous pregnancies. NA=not available. *Pf*Pr2-10=*P. falciparum* parasite prevalence in children aged 2-10 years. NP=not published. SP=sulfadoxine-pyrimethamine. UNAIDS=Joint United Nations Programme on HIV and AIDS.

Notes:

a: Outcomes considered: Low birthweight, birth weight, maternal anaemia (<11 g/dl), maternal moderate to severe anaemia (<7-9 g/dl), haemoglobin, maternal malaria at the time of delivery (any test), placental malaria (any test), cord malaria, neonatal malaria, preterm delivery, gestational age

b: The proportion of primigravidae among the study population was not reported in some studies; a best estimate was obtained from a Demographic and Health Survey (DHS) close in time and location for the following studies: Douambo *et al*. (2014):[43] DHS 2010 Burkina Faso, Inyang-Etoh *et al*. (2011):[51] DHS 2008 Nigeria, Kilauzi *et al.* (2013):[53] DHS DRC 2007 DRC & DHS 2013-2014 (midpoint), Moleins *et al.* (2010):[26] DHS 2005 Senegal, and Olliaro *et al.* (2008):[69] DHS 2005 Senegal.

c: If ITN data was not reported in the study sample, DHS or MIS survey data were used instead matched closest in time and location. If survey data for a particular year was not available, the nearest value was recorded. If data from two surveys were available (i.e. the nearest survey before and after the start and completion of the study), a linear trend was assumed between the two coverage estimates of the two surveys. If ITN data was not available, then bed net data was used. Information on ITN or bednet use was commonly not reported for studies conducted prior to 2001 and if so, coverage of 1% was assumed in the analyses.

d: Where data was not available for HIV-negative women only, the HIV status prevalence was reported as available in the study. If this was not available, HIV prevalence data among adult women was obtained from UNAIDS for year and country among female adults 15-49 years.[86]

e: Folic acid dose used in the antenatal clinic as reported in the article

f: Proportion of the study population who had visited an antenatal clinic during pregnancy

g: Data was supplemented with information from the authors.

h: These studies were part of the 'IPTp-Mon' study, a multi-country observational study specifically designed to address the relationship between the population level of SP resistance and IPTp-effectiveness.[42] The study used a common protocol and data sets were available to the current study.

Table S2: Matching of studies with information on SP resistance markers (*Pfdhps*-A437G, *Pfdhps*-K540E and *Pfdhps*-A581G)

	IPTp study Author, Publication Year	Study site, country	Time period study	*Pfdhps* A437G %	Distance in km (location match)	Years difference (study period match)	*Pfdhps* K540E %	Distance in km (location match)	Years difference (study period match)	*Pfdhps* A581G %	Distance in km (location match)	Years difference (study period match)	N
1	Aduloju 2013[29]	Ado Ekiti, Nigeria	2011-2011	84.2[87]	~400 (Enugu)	-1 (2010)	0.0[87]	~400 (Enugu)	-1 (2010)	47.4[87]	~400 (Enugu)	-1 (2010)	38[87]
2	Alli 2013[30]	Kubwa, Nigeria	2010-2011	84.2[87]	~400 (Enugu)	0 (2010)	0.0[87]	~400 (Enugu)	0 (2010)	47.4[87]	~400 (Enugu)	0 (2010)	38[87]
3	Anchang Kimbi 2009[31]	Mutengene, Cameroon	2007-2007	85.5[88]	0 (Mutengene)	-1 (2004-2006)	0.5[88]	0 (Mutengene)	-1 (2004-2006)	2.0[88]	0 (Mutengene)	-1 (2004-2006)	200[88]
4	Apinjoh 2015[32]	Mutengene, Cameroon	2008-2010	85.5[88]	0 (Mutengene)	-2 (2004-2006)	0.5[88]	0 (Mutengene)	-2 (2004-2006)	2.0[88]	0 (Mutengene)	-2 (2004-2006)	200[88]
5	Arinaitwe 2013[33]	Tororo, Uganda	2011-2011	97.3[42]	0 (Tororo)	0	97.5[42]	0 (Tororo)	0	0.2[42]	0 (Tororo)	0	100[42]
6	Aziken 2011[34]	Benin City, Nigeria	2009-2009	84.2[87]	~260 (Enugu)	+1 (2010)	0.0[87]	~260 (Enugu)	+1 (2010)	47.4[87]	~260 (Enugu)	+1 (2010)	38[87]
7	Bouyou-Akotet 2010[35]	Libreville, Gabon	2005-2006	69.0[89]	0	0	6.9[89]	0	0	0.0[89]	0	0	29[90]
8	Bouyou-Akotet 2016[36]	Libreville, Melen, Gabon	2011-2011	66.7[89]	0	0	0.0[89]	0	0	0.0[89]	0	0	18[90]
9	Braun 2015[37]	Fort Portal, Uganda	2013-2013	100[91]	~130 (Kihurura)	0 (2012-2014)	100[91]	~130 (Kihurura)	0 (2012-2014)	12.9[91]	~130 (Kihurura)	0 (2012-2014)	62[91]
10	Cassam 2007[38]	Gaza, Maputo, Mozambique	2005-2007	53.2[8]	0	0	47.6[8]	0	0	0.0[92,93]	0 (Gaza, Maputo)	0 (2006-2007)	~ 2700[92,93]
11	Challis 2004[39]	Matola, Boane, Mozambique	2001-2002	26.1[94]	0 (peri-urban Maputo)	0 (2001)	25.4[94]	0 (peri-urban Maputo)	0 (2001)	0.0[95]	0 (Maputo)	0 (1999-2004)	134[94] ~1000[95]
12	Chukwuocha 2016[40]	Owerri, Nigeria	2014-2014	96.8[87]	~230 (Benin City)	0 (2014-2015)	0.0[87]	~230 (Benin City)	0 (2014-2015)	52.6[87]	~230 (Benin City)	0 (2014-2015)	95[87]
13	Coulibaly 2014[41]	Ziniare, Burkina Faso	2010-2012	75.3[42]	0	0	0.0[42]	0	0	0.0[42]	0	0	273[42]
14	Desai 2015[42]	Siaya, Kenya	2011-2012	93.0[42]	0	0	95.6[42]	0	0	5.7[42]	0	0	53[42]
15	Douamba 2014[43]	Ouagadougou, Burkina Faso	2013-2014	75.3[42]	~ 30 (Ziniare)	-1 (2010-12)	0.0[42]	~ 30 (Ziniare)	-1 (2010-12)	0.0[42]	~ 30 (Ziniare)	-1 (2010-12)	273[42]
16	Falade 2007[44]	Ibadan, Nigeria	2003-2004	63.0[87]	0 (Ibadan)	0 (2003)	0.0[87]	0 (Ibadan)	0 (2003)	0.0[87]	0 (Ibadan)	0 (2003)	36[87]
17	Famanta 2011[45]	Bamako, Mali	2009-2009	15.2[42]	~190 (Kita)	0 (2009-2010)	0.7[42]	~190 (Kita)	0 (2009-2010)	0.0[42]	~190 (Kita)	0 (2009-2010)	117[42]
18	Fehintola 2016[46]	Ile Ife, Nigeria	2013-2013	96.8[87]	~230 (Benin City)	+1 (2014-2015)	0.0[87]	~230 (Benin City)	+1 (2014-2015)	52.6[87]	~230 (Benin City)	+1 (2014-2015)	95[87]
19	Feng 2010[47]	Blantyre, Malawi	1997-1999	63.6[8]	0	0	74.0[8]	0	0	0.0[96]	0 (Ndirande)	0 (1997-1999)	149[96]
	Feng 2010[47]	Blantyre, Malawi	1999-2001	80.3[8]	0	0	84.0[8]	0	0	0.0[97]	0 (Ndirande)	0 (1999-2001)	550[97]
	Feng 2010[47]	Blantyre, Malawi	2002-2006	93.5[8]	0	0	95.0[97]	0 (Ndirande)	+1 (2007-2009)	2.0[97]	0 (Ndirande)	+1 (2007-2009)	556
20	Gies 2009[48]	Boromo, Burkina Faso	2004-2006	71.5[8]	0	0	0.2[8]	0	0	0.0[42]	210 (Ziniare)	+4 (2010)	273[42]
21 22	Gutman 2013[21]/ Kalilani 2014[20]	Blantyre & Machinga, Malawi	2009-2011	94.4[42]	0	0	99.6[42]	0	0	1.5[42]	0	0	134[42]
23	Harrington 2011[49]	Muheza, Tanzania	2002-2005	100.0[98]	0	0	90.2[98]	0	0	13.0[98]	0	0	540 & 581: 17[98]*
24	Hommerich 2007[25]	Agogo, Ghana	2006-2006	84.6[8]	0	0	1.4[8]	0	0	0.0[99]	~90 (Bekwai)	+1 (2007-2008)	35[99]
25	Igboeli 2017[50]	Enugu State, Nigeria	2013-2013	96.8[87]	~ 260 (Benin City)	+1 (2014-2015)	0.0[87]	~ 260 (Benin City)	+1 (2014-2015)	52.6[87]	~ 260 (Benin City)	+1 (2014-2015)	95[87]
26	Inyang-Etho 2011[51]	Calabar, Nigeria	2008-2008	84.2[87]	~ 260 (Enugu)	+2 (2010)	0.0[87]	~ 260 (Enugu)	+2 (2010)	47.4[87]	~ 260 (Enugu)	+2 (2010)	38[87]

Table S2: Matching of studies with information on SP resistance markers (*Pfdhps*-A437G, *Pfdhps*-K540E and *Pfdhps*-A581G)

	IPTp study Author, Publication Year	Study site, country	Time period study	*Pfdhps* A437G %	Distance in km (location match)	Years difference (study period match)	*Pfdhps* K540E %	Distance in km (location match)	Years difference (study period match)	*Pfdhps* A581G %	Distance in km (location match)	Years difference (study period match)	N
27	Kayentao 2014[52]	Koro, Mali	2006-2007	44.8[8]	0	0	0.1[8]	0	0	0.0[42]	~200 (San)	+3 (2010)	130[42]
	Kayentao 2014[52]	San, Mali	2006-2006	32.6[8]	0	0	0.0[8]	0	0	0.0[42]	0 (San)	+4 (2010)	130[42]
	Kayentao 2014[52]	Bougouni, Mali	2006-2007	33.8[8]	0	0	0.2[8]	0	0	0.0[42]	~650 (San)	+3 (2010)	130[42]
	Kayentao 2014[52]	Djenne, Mali	2006-2006	32.7[8]	0	0	0.0[8]	0	0	0.0[42]	~130 (San)	+4 (2010)	130[42]
	Kayentao 2014[52]	Kita, Mali	2009-2010	15.2[42]	0	0	0.7[42]	0	0	0.0[42]	0	0	117[42]
	Kayentao 2014[52]	San, Mali	2009-2010	27.5[42]	0	0	0.0[42]	0	0	0.0[42]	0	0	130[42]
28	Kilauzi 2013[53]	Kinshasa, DRC	2011-2011	100.0[91]	0 (Kinshasa)	+1 (2012-2014)	18.9[91]	0 (Kinshasa)	+1 (2012-2014)	8.1[91]	0 (Kinshasa)	+1 (2012-2014)	37[91]
29	Likwela 2012[54]	Mikalayi, DRC	2007-2007	76.9[8]	0	0	11.3[8]	0	0	0.0[12]			
	Likwela 2012[54]	Kisangani, DRC	2007-2007	74.1[8]	0	0	27.8[100]	0 (Kisangani)	0 (2007)	5.6[100]	0 (Kisangani)	0 (2007)	18[100]
	Likwela 2012[54]	Rutshuru, DRC	2007-2007	88.1[101]	~280 (Rukara & Mashesa, Rwanda)	-1 (2005-2006)	91.2[101]	~280 (Rukara & Mashesa, Rwanda)	-1 (2005-2006)	45.6[101]	~280 (Rukara & Mashesa, Rwanda)	-1 (2005-2006)	Mean†: 776[101]
30	Mace 2015[55]	Mansa, Zambia	2009-2010	83.7[42]	0	0	84.0[42]	0	0	0.0[42]	0	0	97[42]
31	Mbaye 2006[56]	Farafenni, The Gambia	2002-2004	46.8[8]	0	0	0.02[8]	0	0	0.0[102]	~260 (Thies & Tambacounda Senegal)	0 (2003)	22[102]
32	Menendez 2008[57]	Manhica district, Mozambique	2003-2005	62.9[103]	0 (Manhica)	0 (2002-2005)	68.6[103]	0 (Manhica)	0 (2002-2005)	0.0[92]	50 (Magude)	0 (2004-2005)	70[103]‡ ~500[92]
33	Minja 2013[58]	Korogwe, Tanzania	2008-2010	100[58]	0	0	87.5[58]	0	0	42.9[58]	0	0	581: 28[58]
34	Moleins 2010[26]	Oussouye, Senegal	2007-2008	43.0[8]	0	0	0.06[8]	0	0	0.0[104]	~440 (Thies)	0 (2008)	93[104]
35	Mosha 2014[59]	Moshi & Rufiji, Tanzania	2012-2012	93.2[8]	0	0	88.3[105]	0-500 (Rufiji, Misungwi)	-1 (2010-2011)	2.7[105]	0-500 (Rufiji, Misungwi)	-1 (2010-2011)	Mean†: 224[105]
36	Msyamboza 2009[60]	Chikwawa, Malawi	2002-2004	87.0[8]	0	0	92.7[8]	0	0	0.0[106]	~70 (Chileka)	0 (2003-2005)	95[106]
37	Muhammad 2016[61]	Nguru, Yobe state, Nigeria	2014-2014	24.5[107]	~ 1200 (Parakou, Benin)	-2 (2012)	0.0[107]	~ 1200 (Parakou, Benin)	-2 (2012)	0.0[12]			192[107]
38	Mwangi 2015[62]	South West Kisumu, Nyanza, Kenya	2011-2013	93.0[42]	~70 (Siaya county)	0 (2011-2012)	95.6[42]	~70 (Siaya county)	0 (2011-2012)	5.7[42]	~70 (Siaya county)	0 (2011-2012)	53[42]
39	Mwapasa 2004[63]	Blantyre, Malawi	2000-2002	80.2[8]	0	0	85.3[8]	0	0	0.0[97]	0 (Ndirande)	0 (1999-2001)	550[97]
40	Namusoke 2010[64]	Kampala, Uganda	2004-2005	93.5[8]	0	0	95.1[8]	0	0	0.0[108]	~200 (Tororo)	0 (2003-2006)	55[108]§
41	Ndeserua 2015[65]	Rufiji, Tanzania	2012-2012	75.0[109]	0	-1 (2010-2011)	76.3[105]	0	-1 (2010-2011)	0.0[105]	0	-1 (2010-2011)	96-97[105,109]
42	Nduka 2011[3]	Umuahia, Afikpo, Okigwe, Nigeria	2009-2009	84.2[87]	~130 (Enugu)	+1 (2010)	0.0[87]	~130 (Enugu)	+1 (2010)	47.4[87]	~130 (Enugu)	+1 (2010)	38[87]
43	Ndyomugyenyi 2011[66]	Kabale district, Uganda	2004-2007	100.0[110]	~70 (Bufundi)	0 (2005)	100.0[110]	~70 (Bufundi)	0 (2005)	45.0[110]	~70 (Bufundi)	0 (2005)	60[110]
44	Nganda 2004[67]	Kibaha, Tanzania	2003-2003	19.8[111]	~20 (Mlandizi)	-1 (2002)	23.6[111]	~20 (Mlandizi)	-1 (2002)	0.0[111]	~20 (Mlandizi)	-1 (2002)	106[111]
45	Njagi 2002[68]	Bondo, Kenya	1997-1999	42.8[112]	~60 (Kisumu)	0 (1996-2000)	31.1[112]	~60 (Kisumu)	0 (1996-2000)	0.0[112]	~60 (Kisumu)	0 (1996-2000)	180[112]
46	Oduro 2010[27]	Navrongo, Ghana	2006-2007	53.8[99]	0	0 (2007-2008)	0.0[99]	0	0 (2007-2008)	0.0[99]	0	0 (2007-2008)	39[99]
47	Olliaro 2008[69]	Mlomp, Senegal	2000-2007	39.3[8]	0	0	0.03[8]	0	0	0.0[102]	~410 (Thies)	0 (2003 & 2008)	108[104]

Table S2: Matching of studies with information on SP resistance markers (*Pfdhps*-A437G, *Pfdhps*-K540E and *Pfdhps*-A581G)

	IPTp study Author, Publication Year	Study site, country	Time period study	*Pfdhps* A437G %	Distance in km (location match)	Years difference (study period match)	*Pfdhps* K540E %	Distance in km (location match)	Years difference (study period match)	*Pfdhps* A581G %	Distance in km (location match)	Years difference (study period match)	N
48	Olorunda 2013[28]	Ibadan, Nigeria	2010-2010	92.4[87]	0 (Ibadan)	-2 (2007-2008)	1.0[87]	0 (Ibadan)	-2 (2007-2008)	2.5[87]	0 (Ibadan)	-2 (2007-2008)	198[87]
49	Onyebuchi 2014[70]	Abakaliki, Nigeria	2012-2012	84.2[87]	~70 (Enugu)	-2 (2010)	0.0[87]	~70 (Enugu)	-2 (2010)	47.4[87]	~70 (Enugu)	-2 (2010)	38[87]
50	Orobaton 2016[71]	Sokoto State, Nigeria	2014-2015	47.4[107]	~620 (Parakou, Benin)	-2 (2012)	0.0[107]	~620 (Parakou, Benin)	-2 (2012)	0.0[12,113]			192[107]
51	Parise 1998[72]	Kisumu, Kenya	1994-1996	42.8[112]	0 (Kisumu)	0 (1996-2000)	31.1[112]	0 (Kisumu)	0 (1996-2000)	0.0[112]	0 (Kisumu)	0 (1996-2000)	180[112]
52	Ramharter 2007[73]	Lambarene, Libreville, Gabon	2005-2006	57.9[114]	0 (Lambarene)	0 (2005-2007)	3.3[114]	0 (Lambarene)	0 (2005-2007)	0.0[114]	0 (Lambarene)	0 (2005-2007)	121[114]
53	Rogawski 2012[74]	Blantyre	1997-2006	80.2[8]	0	0	85.3[8]	0	0	0.0[97]	0 (Ndirande)	0 (1999-2001)	550[97]
54	Rogerson 2000[75]	Blantyre, Malawi	1997-1999	63.6[8]	0	0	74.0[8]	0	0	0.0[97]	0 (Ndirande)	0 (1999-2001)	550[97]
55	Sirima 2006[76]	Koupela district, Burkina Faso	2004-2004	48.1[8]	0	0	0.1[8]	0	0	0.0[41]	~120 (Ziniare)	+6 (2010-2011)	273[41]
56	Suleiman 2003[77]	Wad Medani, Sudan	1999-2001	13.3[115]	~190 (Khartoum)	-2 (1996-1997)	0.0[115]	~190 (Khartoum)	-2 (1996-1997)	0.0[115]	~190 (Khartoum)	-2 (1996-1997)	45[115]
57	Tetteh-Ashong 2005[78]	Chikwawa, Malawi	2005-2005	94.1[8]	0	0	94.8[8]	0	0	0.0[106]	~70 (Chileka)	0 (2003-2005)	95[106]
58	Tonga 2013[79]	Sanaga-Maritime, Cameroon	2011-2012	76.5[116]	~180 (Yaounde)	0 (2010-2011)	0.0[116]	~180 (Yaounde)	0 (2010-2011)	5.9[116]	~180 (Yaounde)	0 (2010-2011)	51[116]
59	Tongo 2011[80]	Ibadan, Nigeria	2007-2008	92.4[87]	0 (Ibadan)	0 (2007-2008)	1.0[87]	0 (Ibadan)	0 (2007-2008)	2.5[87]	0 (Ibadan)	0 (2007-2008)	198[87]
60	Toure 2014[24]	Abidjan and Comoe districts, Cote d'Ivoire	2009-2010	52.1[117]	0 (Abidjan)	-1 (2008)	0.9[117]	0 (Abidjan)	-1 (2008)	0.9[117]	0 (Abidjan)	-1 (2008)	94[117]
61	Tutu 2011[81]	Offinso district, Ghana	2005-2007	77.6[118]	~60 (Sunyani)	0 (2005-2008)	0.0[118]	~60 (Sunyani)	0 (2005-2008)	0.0[99]	~60 (Sunyani)	0 (2007-2008)	85[118] 49[99]
62	Vanga-Bosson 2011[82]	Cote d'Ivoire	2008-2008	52.1[117]	0 (Abidjan)	0 (2008)	0.9[117]	0 (Abidjan)	0 (2008)	0.9[117]	0 (Abidjan)	0 (2008)	94[117]
63	van Eijk 2004[23]	Kisumu, Kenya	1999-2000	42.8[112]	0 (Kisumu)	0 (1996-2000)	31.1[112]	0 (Kisumu)	0 (1996-2000)	0.0[112]	0 (Kisumu)	0 (1996-2000)	180[112]
64	Van Spronsen 2012[83]	Gushegu, Ghana	2010-2010	73.0[8]	0	0	0.7[8]	0	0	0.0[99]	~ 200 (Navrongo)	-2 (2008)	39[99]
65	Verhoeff 1998[84]	Chikwawa, Malawi	1993-1994	34.4[8]	0	0	34.2[8]	0	0	0.0[97]	~50 (Ndirande)	+7 (1999-2001)	550[97]
66	Yussuf 2010[85]	Lindi, Tanzania	2009-2010	79.7[8]	0	0	72.7[105]	~150 (Nachingwea)	0 (2010-2011)	0.0[105]	~150 (Nachingwea)	0 (2010-2011)	88[105]

*581: SP-negative women. (info supplemented with tables from Okell)
†mean of two sites: Rukara & Mashesa for Rutsuhuru (Likwela *et al*. 2012), Rufiji and Misungwi for Rufiji and Moshi (Mosha *et al.* 2014, Dr. Alifrangis, University of Copenhagen, personal communication)
‡Placebo arm
§Non-users of cotrimoxazole

Matching: The following order of preference was used to match resistance with clinical data: 1) resistance data provided in the clinical study reports or by the authors of these reports for that location and time of study, where data from individuals with a recent history of SP intake were excluded; 2) estimates from continuous surface maps from WWARN's geospatial models for *Pfdhps*-A437G and *Pfdhps*-K540E;[8] and 3) for *Pfdhps*-A581G, or for studies after 2012, data were used from existing population prevalence maps of *Pfdhps* (Table S2).[5-7,9]

Prevalence was defined as the proportion of infected humans carrying at least one mutant clone with the specific haplotype. If contemporaneous molecular data was not available, but the local prevalence of a molecular marker was 0% in studies conducted >2 years after the clinical study, a value of 0% was assumed (e.g. Mali). If a high *Pfdhps*-A581G (>15%) was encountered, the *Pfdhps*-K540E prevalence of the same source study was used.

Matches for the following studies involved distances over 300 km: 1) Aduloju *et al.* (2013),[29] Ado Ekiti, Nigeria in 2011; reference Oguike et al. (2016),[87] Enugu, Nigeria, 2010, ~400 km away; 2) Alli *et al.* (2013),[30] Kubwa, Nigeria in 2010-2011; reference Oguike et al. (2016),[87] Enugu, Nigeria, 2010, ~400 km away, 3) Muhammad *et al*. (2016),[61] Nguru, Yobe State, Nigeria in 2014; reference Ogouyemi-Hounto *et al*. (2013)[107] Parakou,Benin, 2012, ~1200 km away; 4) Orobaton *et al.* (2016),[71] Sokoto, Nigeria in 2014-15; reference Ogouyemi-Hounto *et al*. (2013)[107] ~620 km away. For Moshi in Tanzania in 2012 (Mosha *et al.* 2014)[59] Mwanza was used as reference site (~600 km, 2010-2011), after consultation with local experts (Dr. Alifrangis, personal communication), instead of Muheza (~320 km).

Table S3: SP dose categories used and low birthweight across categories and mean SP doses where known, for studies with information on low birthweight

Study (First author and publication year, country)	Site	Study Period	SP dose groups	LBW n/N (%) 1st SP group (reference)	Mean # SP doses reference group	LBW n/N (%) 2nd SP group	Mean # SP doses 2nd SP group	LBW n/N (%) 3rd SP group	Mean # SP doses 3rd SP group	LBW n/N (%) 4th SP group	Mean # SP doses 4th SP group	Notes
Alli 2013,[30] Nigeria	Kubwa	2010-2011	0,1+	4/158 (2.5)	0	0/42 (0.0)	1.3					
Arinaitwe 2014,[33] Uganda	Tororo	2011-2011	01,2+	29/227 (12.8)	0.9	25/325 (7.7)	2					
Aziken 2010,[34] Nigeria	Benin City	2009-2009	0,1+	61/371 (16.4)	0	14/370 (3.8)	1.6					
Bouyou-Akotet 2010,[35] Gabon	Libreville	2005-2006	0,1+	24/120 (20.0)	0	11/83 (13.3)	1.6					a
Bouyou-Akotet 2016,[36] Gabon	Libreville, Melen	2011-2011	0,1,2+	5/58 (8.6)	0	5/81 (6.2)	1	9/160 (5.6)	2.1			
Braun 2015,[37] Uganda	Fort Portal	2013-2013	0,1,2+	8/56 (14.3)	0	20/186 (10.8)	1	32/366 (8.7)	2			b
Cassam 2007,[38] Mozambique	Gaza	2005-2007	0,3+	756/8650 (8.7)	0	488/6645 (7.3)	3					c
Challis 2004,[39] Mozambique	Maputo	2001-2002	0,2+	27/203 (13.3)	0	19/200 (9.5)	2					
Coulibaly 2014,[42] Burkina Faso	Ziniare	2011-2012	0,1,2+	32/155 (20.6)	0	54/308 (17.5)	1	52/449 (11.6)	2			
Desai 2014,[42] Kenya	Nyanza	2011-2012	01,2,3+	10/135 (7.4)	0.9	22/246 (8.9)	2	37/488 (7.6)	3.3			
Falade 2007,[44] Nigeria	Ibadan	2003-2004	0,1+	16/171 (9.4)	0	31/595 (5.2)	1.8					
Famanta 2011,[45] Mali	Bamako	2009-2009	0,1,2+	16/102 (15.7)	0	8/107 (7.5)	1	17/150 (11.3)				b
Feng 2010,[47] Malawi	Blantyre	1997-1999	0,1,2+	49/215 (22.8)	0	55/412 (13.3)	1	29/285 (10.2)	2.2			
Feng 2010, [47] Malawi	Blantyre	1999-2001	0,1,2+	20/117 (17.1)	0	56/426 (13.1)	1	29/293 (9.9)	2.1			
Feng 2010, [47] Malawi	Blantyre	2002-2006	0,1,2,3+	29/234 (12.4)	0	71/623 (11.4)	1	85/867 (9.8)	2	56/647 (8.7)	3.2	
Gies 2009,[48] Burkina Faso	Boromo	2004-2006	0,1,2+	19/52 (36.5)	0	100/408 (24.5)	1	104/812 (12.8)	2			
Gutm'&Kali' 2014,[42] Malawi	Southern Malawi	2009-2011	01,2,3+	28/334 (8.4)	0.9	70/1099 (6.4)	2	33/399 (8.3)	3.1			
Harrington 2011,[49] Tanzania	Muheza	2002-2005	0,1,2+	6/80 (7.5)	0	8/156 (5.1)	1	3/136 (2.2)	2			b
Hommerich 2007,[25] Ghana	Agogo	2006-2006	0,1,2,3+	8/52 (15.4)	0	6/60 (10.0)	1	9/59 (15.3)	2	5/54 (9.3)	3	c
Igboeli 2017,[50] Nigeria	Enugu State	2013-2013	0,1+	8/101 (7.9)	0	7/315 (2.2)	2.2					d
Kayentao 2014,[52] Mali	San	2006-2006	0,1,2+	15/135 (11.1)	0	10/177 (5.6)	1	4/86 (4.7)	2			
Kayentao 2014, [52] Mali	Koro	2006-2007	0,1,2+	13/130 (10.0)	0	10/131 (7.6)	1	4/90 (4.4)	2			
Kayentao 2014,[42] Mali	Kita	2009-2010	0,1,2+	18/124 (14.5)	0	14/121 (11.6)	1	24/299 (8.0)	2			
Kayentao 2014,[42] Mali	San	2009-2010	0,1,2+	18/110 (16.4)	0	12/165 (7.3)	1	10/155 (6.5)	2.1			
Kayentao 2014, [52] Mali	Bougouni	2006-2007	0,1,2+	11/101 (10.9)	0	10/182 (5.5)	1	7/124 (5.6)	2			
Kayentao 2014, [52] Mali	Djenne	2006-2006	0,1,2+	10/110 (9.1)	0	6/106 (5.7)	1	7/139 (5.0)	2			
Kilauzi 2013,[53] DRC	Kinshasa	2011-2011	0,1+	21/204 (10.3)	0	32/501 (6.4)	1					
Likwela 2012,[54] DRC	Mikalayi	2007-2007	01,2+	35/363 (9.6)	0.5	2/114 (1.8)						e
Likwela 2012,[54] DRC	Rutsuhuru	2007-2007	01,2+	16/177 (9.0)	0.5	39/493 (7.9)						e
Likwela 2012,[54] DRC	Kisangani	2007-2007	01,2+	16/50 (32.0)	0.5	6/87 (6.9)						e

Table S3: SP dose categories used and low birthweight across categories and mean SP doses where known, for studies with information on low birthweight

Study (First author and publication year, country)	Site	Study Period	SP dose groups	LBW n/N (%) 1st SP group (reference)	Mean # SP doses reference group	LBW n/N (%) 2nd SP group	Mean # SP doses 2nd SP group	LBW n/N (%) 3rd SP group	Mean # SP doses 3rd SP group	LBW n/N (%) 4th SP group	Mean # SP doses 4th SP group	Notes
Mace 2015,[55] Zambia	Mansa	2009-2010	01,2,3+	17/157 (10.8)	0.8	9/138 (6.5)	2	4/128 (3.1)			3	
Mbaye 2006,[56] Gambia	Farafenni	2002-2004	0,2+	46/716 (6.4)	0	40/738 (5.4)	2.7					
Menendez 2008,[57] Mozambique	Manhica	2003-2005	0,2+	49/411 (11.9)	0	41/382 (10.7)	2					
Minja 2013,[58] Tanzania	Korogwe	2008-2010	01,2+	4/17 (23.5)	0.5	43/705 (6.1)	2					
Moleins 2010,[26] Senegal	Oussouye	2007-2008	01,2+	6/55 (10.9)	0.2	6/96 (6.3)	1.9					
Mosha 2014,[59] Tanzania	Rufiji/Moshi	2012-2012	01,2+	9/169 (5.3)	0.8	9/181 (5.0)	2					b
Msyamboza 2009,[60] Malawi	Chikwawa	2002-2004	01,2,3+	65/427 (15.2)	0.9	118/620 (19.0)	2	39/271 (14.4)	3			
Muhammad 2016,[61] Nigeria	Nguru, Yobe State	2014-2014	01,2+	58/104 (55.8)	0.9	10/80 (12.5)	2					b
Namusoke 2010,[64] Uganda	Kampala	2004-2005	0,1,2+	28/162 (17.3)	0	15/118 (12.7)	1	4/41 (9.8)	2			
Ndeserua 2015,[65] Tanzania	Rufiji	2012-2012	01,2+	12/166 (7.2)	0.9	10/184 (5.4)	2					
Ndyomugyenyi 2011,[66] Uganda	Kabale	2004-2007	0,2+	99/1577 (6.3)	0	107/1561 (6.9)	2					
Njagi 2002,[68] Kenya	Bondo	1997-1999	0,2+	51/359 (14.2)	0	46/369 (12.5)	2					
Oduro 2010,[27] Ghana	Navrongo	2006-2007	0,1,2,3+	76/391 (19.4)	0	89/515 (17.3)	1	132/640 (20.6)	2	121/731 (16.6)	3	c
Olliaro 2008,[69] Senegal	Mlomp	2000-2007	0,1,2+	57/532 (10.7)	0	7/63 (11.1)	1	22/309 (7.1)	2			
Olorunda 2013,[28] Nigeria	Ibadan	2010-2010	0,1+	22/246 (8.9)	0	4/84 (4.8)	1.2					
Parise 1998,[72] Kenya	Kisumu	1994-1996	0,2,3+	52/340 (15.3)	0	27/325 (8.3)	2	26/331 (7.9)	3.2			
Ramharter 2007,[73] Gabon	Lambarene	2005-2006	0,1,2+	11/97 (11.3)	0	24/181 (13.3)	1	36/415 (8.7)	2			b
Sirima 2006,[76] Burkina Faso	Koupela	2004-2004	0,1,2,3+	16/66 (24.2)	0	30/163 (18.4)	1	48/362 (13.3)	2	41/529 (7.8)	3	
Suleiman 2003,[77] Sudan	Wad Medani	1999-2001	0,2+	19/53 (35.8)	0	2/57 (3.5)	2					
Tetteh-Ashong 2005,[78] Malawi	Chikwawa	2005-2005	01,2,3+	6/42 (14.3)	0.9	10/139 (7.2)	2	3/47 (6.4)	3			
Tonga 2013,[79] Cameroon	Sanaga-Maritime	2011-2012	0,1,2+	7/68 (10.3)	0	4/75 (5.3)	1	2/52 (3.8)	2.2			
Tongo 2011,[80] Nigeria	Ibadan	2007-2008	01,2+	68/649 (10.5)	0.1	4/147 (2.7)	2					b
Toure 2014,[24] Cote d'Ivoire	Cote d'Ivoire	2009-2010	0,1,2,3+	50/436 (11.5)	0	19/306 (6.2)	1	39/483 (8.1)	2	3/87 (3.4)	3	c
Tutu 2011,[81] Ghana	Offinso	2005-2007	0,1,2,3+	62/499 (12.4)	0	57/314 (18.2)	1	91/676 (13.5)	2	102/1094 (9.3)	3	
Vanga-Bosson 2011,[82] Cote d'Ivoire	National	2008-2008	0,1,2,3+	35/309 (11.3)	0	79/653 (12.1)	1	80/792 (10.1)	2	13/191 (6.8)	3	c
Yussuf 2010,[85] Tanzania	Lindi	2009-2010	0,1,2+	55/123 (44.7)	0	18/35 (51.4)	1	26/88 (29.5)	2			
van Eijk 2004,[23] Kenya	Kisumu	1999-2000	0,1,2+	112/948 (11.8)	0	48/606 (7.9)	1	22/319 (6.9)	2			

Note: SP dose groups 01 represent data from the combined 0 and 1 dose groups

a. No data was provided in source manuscript on the mean number of doses for the 1+ dose group. The mean number of doses was therefore based on data from malaria indicator survey 2008 Gabon, from Table 5 which has data from 2006

b. No data was provided in source manuscript on the mean number of doses for the 2+ dose group: a mean of 2 doses was assumed for analysis
c. No data was provided in source manuscript on the mean number of doses in the 3+ dose group: a mean of 3 doses was assumed for analysis
d. No data was provided in source manuscript on the mean number of doses in the 1+ dose group: the mean was based on data from the DHS Nigeria 2013
e. No data was provided in source manuscript on the mean number of doses in the 01 and 2+ dose groups: a mean of 0.5 and 2 doses were assumed respectively

Table S4: The effect of SP resistance on the effectiveness of IPTp on LBW by region and by gravidity, sub-Saharan Africa, 1997-2013

			Univariate meta-regression					Multivariate*				
		N	Coefficient (95% CI)	p	T^2	I^2 %	R^2 %	Coefficient (95% CI)	p	T^2	I^2 %	R^2 %
West and Central Africa												
Pfdhps-437	All studies	31	0.998 (0.994, 1.002)	0.38	0.03072	68.4	0.0	0.998 (0.995, 1.002)	0.39	0.01528	40.0	48.2
	Excluding 7 low quality studies	27	1.001 (0.996, 1.005)	0.78	0.02282	65.2	0.0	1.001 (0.997, 1.005)	0.53	0.00647	16.1	70.4
Pfdhps-540	All studies	31	0.991 (0.963, 1.021)	0.55	0.03005	67.7	0.0	1.013 (0.983, 1.045)	0.38	0.01380	40.3	53.2
	Excluding 7 low quality studies	27	0.989 (0.961, 1.017)	0.42	0.02199	63.9	0.0	1.012 (0.982, 1.044)	0.41	0.00570	14.2	74.0
Resistance strata†	All studies	31	0.76 (0.54, 1.07)	0.12	0.0269	65.9	8.8	0.82 (0.58, 1.16)	0.25	0.01434	40.1	51.4
	Excluding 7 low quality studies	27	0.78 (0.53, 1.15)	0.19	0.02068	63.1	5.5	0.87 (0.59, 1.29)	0.47	0.00625	15.5	71.4
East and southern Africa												
Pfdhps-437	All studies	26	1.002 (0.998, 1.005)	0.34	0.01453	64.4	2.1	1.004 (1.000, 1.008)	0.07	0.00688	44.4	53.6
	Excluding 7 low quality studies	23	1.001 (0.998, 1.005)	0.43	0.01430	61.8	0.3	1.005 (1.000, 1.009)	0.0385	0.00858	43.0	40.1
Pfdhps-540	All studies	26	1.002 (0.999, 1.005)	0.12	0.01383	64.0	6.8	1.004 (1.002, 1.007)	0.0044	0.00363	31.8	75.5
	Excluding 7 low quality studies	23	1.002 (0.999, 1.005)	0.11	0.01167	60.0	18.6	1.005 (1.002, 1.008)	0.0046	0.00559	28.0	61.0
Resistance strata†	All studies	26	1.16 (1.03, 1.30)	0.0158	0.00942	61.6	36.5	1.19 (1.08, 1.31)	0.0011	0.00159	24.9	89.3
	Excluding 7 low quality studies	23	1.15 (1.01, 1.31)	0.0321	0.00867	58.0	39.6	1.21 (1.09, 1.35)	0.0017	0.00313	19.2	78.1
Paucigravidae												
Pfdhps-437	All studies	34	1.000 (0.997, 1.003)	0.89	0.01500	49.1	0.0	1.000 (0.997, 1.003)	0.94	0.01782	51.5	0.0
	Excluding 7 low quality studies	30	1.000 (0.996, 1.003)	0.86	0.01901	53.3	0.0	0.999 (0.996, 1.003)	0.77	0.02288	55.4	0.0
Pfdhps-540	All studies	34	1.001 (0.999, 1.003)	0.29	0.01290	46.5	7.0	1.001 (0.999, 1.003)	0.33	0.01562	48.6	0.0
	Excluding 7 low quality studies	30	1.001 (0.999, 1.003)	0.46	0.01743	52.1	0.8	1.000 (0.998, 1.003)	0.77	0.02296	54.6	0.0
Resistance strata†	All studies	34	1.07 (0.98-1.16)	0.14	0.01202	45.1	13.4	1.07 (0.97-1.18)	0.19	0.01517	47.5	0.0
	Excluding 7 low quality studies	30	1.06 (0.96-1.18)	0.26	0.01667	51.2	5.1	1.06 (0.95-1.19)	0.29	0.02234	53.9	0.0
Multigravidae												
*Pf*dhsp-437	All studies	31	1.001 (0.997, 1.005)	0.60	0.02107	48.4	0.0	1.001 (0.997, 1.005)	0.66	0.01445	37.2	27.1
	Excluding 7 low quality studies	27	1.001 (0.997, 1.005)	0.59	0.01667	45.1	0.0	1.000 (0.996, 1.005)	0.82	0.01767	43.0	0.0
Pfdhps-540	All studies	31	1.000 (0.998, 1.002)	0.82	0.02207	47.7	0.0	1.000 (0.998, 1.002)	1.00	0.01537	37.7	22.4
	Excluding 7 low quality studies	27	1.000 (0.998, 1.002)	0.95	0.01796	45.4	0.0	1.000 (0.998, 1.002)	0.83	0.01804	42.8	0.0
Resistance strata†	All studies	31	1.01 (0.91-1.11)	0.92	0.02232	48.2	0.0	1.01 (0.92-1.11)	0.81	0.01513	37.5	23.6
	Excluding 7 low quality studies	27	1.01 (0.91-1.12)	0.90	0.01791	45.4	0.0	0.99 (0.89-1.11)	0.91	0.01802	42.9	0.0

Pooled summary estimate from meta-analysis of the risk of LBW associated with each incremental dose of IPTp-SP for each subgroup (RR, 95% CI): West and Central Africa: 0.73 (0.67, 0.79) I^2 67.5%; East and southern Africa: 0.85 (0.80, 0.90) I^2 63.1%; Paucigravidae: 0.78 (0.73, 0.83) I^2 47.5% RRR 22% (17-27); Multigravidae: 0.82 (0.76, 0.89) I^2 46.8% RRR 18% (11-24).

*Multivariate meta-regression: adjusted for malaria transmission intensity, number of SP courses, proportion of paucigravidae (only in models by region) and study quality

†Low resistance: *Pfdhps*-A437G <90% in Central and West Africa or *Pfdhps*-K540E <30% in East and southern Africa; moderate: *Pfdhps*-A437G ≥90% in Central and West Africa or *Pfdhps*-K540E ≥30% and *Pfdhps*-K540E <90% in East and southern Africa; high: *Pfdhps*-K540E ≥90% in East and southern Africa

Table S5: Sensitivity analysis of the effect of the thresholds used to categorise SP resistance into low, moderate and high on the primary endpoint (LBW)

	N by resistance strata	RRR % by resistance strata	Metaregression †									
			Univariate					Multivariate†				
	All (L|M|H)	All (L|M|H)	Coefficient (95% CI)	p-value	Tau^2	I^2 %	R^2 %	Coefficient (95% CI)	p-value	Tau^2	I^2 %	R^2 %
Definition 1 (primary analysis)												
All studies	57 (30|16|11)	21 (27|21|7)	1.10 (1.03, 1.18)	0.0054	0.02040	65.4	22.8	1.10 (1.03, 1.17)	0.0043	0.01184	52.9	55.2
Excluding 7 low quality studies	50 (27|13|10)	20 (26|18|6)	1.10 (1.03, 1.18)	0.0075	0.01687	61.6	24.9	1.09 (1.02, 1.16)	0.0095	0.01067	49.7	52.5
Alternative lower threshold for Pfdhps-A437G to define low and moderate resistance in East and southern Africa												
Definition 2 (sensitivity analysis)												
All studies	57 (27|19|11)	21 (26|24|7)	1.09 (1.02, 1.17)	0.0140	0.02152	66.2	18.6	1.09 (1.02, 1.16)	0.0097	0.01259	54.0	52.4
Excluding 7 low quality studies	50 (25|15|10)	20 (26|17|6)	1.10 (1.03, 1.18)	0.0054	0.01668	61.5	25.7	1.10 (1.03, 1.17)	0.0060	0.01048	49.3	53.3
Definition 3 (sensitivity analysis)												
All studies	57 (22|24|11)	21 (25|26|7)	1.08 (1.00, 1.17)	0.0373	0.02307	67.9	12.8	1.07 (1.00, 1.15)	0.0433	0.01458	56.5	44.9
Excluding 7 low quality studies	50 (21|19|10)	20 (25|21|6)	1.09 (1.01, 1.18)	0.0203	0.01876	64.5	16.5	1.08 (1.01, 1.16)	0.0345	0.01225	52.7	45.4
Alternative lower threshold for Pfdhps-K540E to define low and moderate resistance in East and southern Africa												
Definition 4 (sensitivity analysis)												
All studies	57 (28|18|11)	21 (27|23|7)	1.10 (1.02, 1.18)	0.0090	0.02091	65.9	20.9	1.09 (1.03, 1.17)	0.0072	0.01197	53.2	54.7
Excluding 7 low quality studies	50 (25|15|10)	20 (25|20|6)	1.09 (1.02, 1.17)	0.0139	0.01746	62.3	22.2	1.09 (1.02, 1.16)	0.0147	0.01076	50.1	52.1
Definition 5 (sensitivity analysis)												
All studies	57 (33|13|11)	21 (26|24|7)	1.09 (1.02, 1.17)	0.0107	0.02093	64.7	20.8	1.09 (1.02, 1.15)	0.0101	0.01287	54.6	51.3
Excluding 7 low quality studies	50 (30|10|10)	20 (24|19|6)	1.09 (1.02, 1.17)	0.0119	0.01688	60.0	24.8	1.07 (1.01, 1.14)	0.0324	0.01194	52.4	46.8
Alternative definition using Pfdhps-A581G to define high resistance in East and southern Africa												
Definition 6 (sensitivity analysis)												
All studies	57 (30|18|9)	21 (27|19|9)	1.10 (1.02, 1.19)	0.0112	0.02144	66.2	18.9	1.09 (1.02, 1.17)	0.0157	0.01354	55.8	48.8
Excluding 7 low quality studies	50 (27|15|8)	20 (26|15|9)	1.10 (1.02, 1.19)	0.0145	0.01771	62.3	21.2	1.08 (1.00, 1.17)	0.0405	0.01237	53.4	44.9
Definition 7 (sensitivity analysis)												
All studies	57 (30|25|2)	21 (27|17|-2)	1.14 (1.03, 1.25)	0.0102	0.02154	64.9	18.5	1.12 (1.02, 1.23)	0.0178	0.01430	57.0	45.9
Excluding 7 low quality studies	50 (27|21|2)	20 (26|14|-2)	1.13 (1.03, 1.25)	0.0087	0.01876	61.1	22.4	1.12 (1.02, 1.23)	0.0227	0.01213	53.0	46.0
Alternative definition using four categories (two categories for Pfdhps-A581G)												

Definition 8 (sensitivity analysis)	**All (L|M|H|VH)**	**All (L|M|H|VH)**										
All studies	57 (30|18|7|2)	21 (27|19|12|-2)	1.10 (1.03, 1.17)	0.0068	0.02087	66.0	21.1	1.08 (1.02, 1.15)	0.0147	0.01365	55.4	48.4
Excluding 7 low quality studies	50 (27|15|6|2)	20 (26|15|15|-2)	1.09 (1.02, 1.16)	0.0094	0.01737	62.4	22.7	1.07 (1.00, 1.14)	0.0354	0.01230	52.7	45.2

Definitions

Primary analysis

Definition 1: Low: *Pfdhps*-A437G <90% (West/Central) or *Pfdhps*-K540E <30% (East/southern)
Moderate: *Pfdhps*-A437G ≥90% (West/Central) or *Pfdhps*-K540E ≥30% & *Pfdhps*-K540E <90% (East/southern)
High: *Pfdhps*-K540E ≥90% (East/southern)

Alternative lower threshold for *Pfdhps*-A437G to define low and moderate resistance in West and Central Africa

Definition 2: Low: *Pfdhps*-A437G <80% (West/Central) or *Pfdhps*-K540E <30% (East/southern)
Moderate: *Pfdhps*-A437G ≥80% (West/Central) or *Pfdhps*-K540E ≥30% & *Pfdhps*-K540E <90% (East/southern)
High: *Pfdhps*-K540E ≥90% (East/southern)

Definition 3: Low: *Pfdhps*-A437G <70% (West/Central) or *Pfdhps*-K540E <30% (East/southern)
5906 Moderate: *Pfdhps*-A437G ≥70% (West/Central) or *Pfdhps*-K540E ≥30% & *Pfdhps*-K540E <90% (East/southern)
High: *Pfdhps*-K540E ≥90% (East/southern)

Alternative lower threshold for *Pfdhps*-K540E to define low and moderate resistance in East and southern Africa

Definition 4: Low: *Pfdhps*-A437G <90% (West/Central) or *Pfdhps*-K540E <20% (East/Southern)
20574 Moderate: *Pfdhps*-A437G ≥90% (West/Central) or *Pfdhps*-K540E ≥20% & *Pfdhps*-K540E <90% (East/southern)
High: *Pfdhps*-K540E ≥90% (East/southern)

Definition 5: Low: *Pfdhps*-A437G <90% (West/Central) or *Pfdhps*-K540E <40% (East/southern)
20528 Moderate: *Pfdhps*-A437G ≥90% (West/Central) or *Pfdhps*-K540E ≥40% & *Pfdhps*-K540E <90% (East/southern)
High: *Pfdhps*-K540E ≥90% (East/southern)

Alternative thresholds for *Pfdhps*-A581G to define resistance in East and southern Africa

Definition 6: Low: *Pfdhps*-A437G <90% (West/Central) or *Pfdhps*-K540E <30% (East/southern)
20102 Moderate: *Pfdhps*-A437G ≥90% (West/Central) or *Pfdhps*-K540E ≥30% & *Pfdhps*-A581G <1% (East/southern)
High: *Pfdhps*-A581G ≥1% (East/southern)

Definition 7: Low: *Pfdhps*-A437G <90% (West/Central) or *Pfdhps*-K540E <30% (East/southern)
20183 Moderate: *Pfdhps*-A437G ≥90% (West/Central) or *Pfdhps*-K540E ≥30% & *Pfdhps*-A581G <45% (East/southern)
High: *Pfdhps*-A581G ≥45% (East/southern)

Alternative definition using a total of four categories including two categories for *Pfdhps*-A581G

Definition 8: Low: *Pfdhps*-A437G <90% (West/Central) or *Pfdhps*-K540E <30% (East/southern)
20652 Moderate-1: *Pfdhps*-A437G ≥90% (West/Central) or *Pfdhps*-K540E ≥30% & *Pfdhps*-A581G <1% (East/southern)
Moderate-2: *Pfdhps*-A581G ≥1% & *Pfdhps*-A581G <45% (East/southern)
High: *Pfdhps*-A581G ≥45% (East/southern)

Abbreviations: L=Low resistance. M=Moderate resistance. H=High resistance. VH=very high resistance. CI=confidence interval. *Pfdhps*=dihydropteroate synthase *P. falciparum*. RRR=relative risk reduction.

†. Metaregression parameters from a model with the variable for SP-resistance introduced as a linear variable. Multivariate models adjusted for malaria transmission, number of SP courses received, proportion of paucigravidae, and study quality.

Table S6 Meta-analysis of the effectiveness of IPTp on other outcomes than low birthweight, sub-Saharan Africa, 1997-2015

Outcome and resistance category*	Number of studies	Pooled protective effectiveness† % Relative Risk Reduction (RRR) (95% CI)	*P*‡	I^2, %	*P-trend over resistance categories*
Anaemia (<11 g/dl)					
All studies	28	14.5 (9.2, 19.5)	<0.0001	83.8	
Low resistance	10	29.9 (17.7, 40.3)	<0.0001	83.6	
Moderate resistance	11	8.5 (3.0, 13.6)	0.0028	63.3	0.0352
High resistance	7	9.7 (-1.5, 19.7)	0.0879	89.1	
Excluding low quality studies	22	13.8 (8.2, 19.0)	<0.0001	79.9	
Low resistance	7	25.2 (14.2, 34.8)	<0.0001	75.7	
Moderate resistance	9	7.9 (1.1, 14.3)	0.0231	70.1	0.01793
High resistance	6	11.7 (0.0, 22.0)	0.0499	83.2	
***Moderate anaemia* §**					
All studies	14	21.1 (12.3, 29.0)	<0.0001	34.3	
Low resistance	3	40.9 (28.4, 51.3)	<0.0001	0	
Moderate resistance	6	19.8 (1.3, 34.9)	0.0376	0	0.0049
High resistance	5	13.0 (3.3, 21.7)	0.0095	21.1	
Excluding low quality studies	11	23.8 (12.8, 33.4)	0.0001	46.3	
Low resistance	3	40.9 (28.4, 51.3)	<0.0001	0	
Moderate resistance	4	21.2 (-1.9, 39.0)	0.07	0	0.0118
High resistance	4	13.3 (-0.3, 25.1)	0.06	40.8	
Placental malaria (any test)					
All studies	45	17.2 (11.7, 22.3)	<0.0001	71.0	
Low resistance	22	19.4 (10.8, 27.1)	<0.0001	73.5	
Moderate resistance	14	23.3 (17.9, 28.3)	<0.0001	19.3	0.07
High resistance	9	3.4 (-4.6, 10.8)	0.40	28.1	
Excluding low quality studies	37	17.5 (10.8, 23.7)	<0.0001	73.9	
Low resistance	18	19.4 (9.6, 28.1)	0.0002	74.7	
Moderate resistance	11	28.6 (23.4, 33.4)	<0.0001	0	0.10
High resistance	8	1.6 (-7.3, 9.7)	0.72	22.3	
Maternal malaria (any test)					
All studies	40	15.0 (9.1, 20.6)	<0.0001	71.2	
Low resistance	20	22.7 (14.6, 30.0)	<0.0001	59.2	
Moderate resistance	13	11.6 (0.1, 21.7)	0.0476	77.8	0.0090
High resistance	7	2.1 (-5.0, 8.8)	0.55	13.8	
Excluding low quality studies	32	14.7 (7.2, 21.7)	0.0002	73.7	
Low resistance	16	21.9 (12.1, 30.6)	<0.0001	65.2	
Moderate resistance	10	11.8 (-4.1, 25.4)	0.14	78.3	0.0251
High resistance	6	-1.1 (-8.7, 6.0)	0.77	0	
Any malaria at delivery*					
All studies	54	16.5 (11.9, 20.9)	<0.0001	74.7	
Low resistance	29	20.0 (13.3, 26.2)	<0.0001	73.6	
Moderate resistance	16	17.9 (9.6, 25.5)	0.0001	72.6	0.0164
High resistance	9	3.0 (-3.0, 8.6)	0.32	27.5	
Excluding low quality studies	44	16.9 (11.5, 22.1)	<0.0001	77.9	

Low resistance	23	20.8 (13.0, 27.9)	<0.0001	76.2	
Moderate resistance	13	19.5 (8.6, 29.1)	0.0008	77.5	0.0228
High resistance	8	1.8 (-4.6, 7.8)	0.58	25.5	
Preterm delivery					
All studies	26	18.1 (11.5, 24.3)	<0.0001	54.6	
Low resistance	13	24.9 (13.1, 35.0)	0.0001	60.6	
Moderate resistance	6	20.1 (4.3, 33.4)	0.0151	64.9	0.12
High resistance	7	10.6 (3.5, 17.3)	0.0043	6.6	
Excluding low quality studies	21	17.1 (9.1, 24.3)	0.0001	57.6	
Low resistance	11	23.0 (9.6, 34.4)	0.0014	61.6	
Moderate resistance	4	23.3 (-1.9, 42.3)	0.07	76.2	0.21
High resistance	6	8.9 (0.6, 16.6)	0.0366	7.9	
Continuous variables		**Pooled weighted mean difference (95% CI, 2 vs. 0 doses)**			
Haemoglobin (g/dl)					
Overall	20	0.43 (0.25, 0.60)	<0.0001	55.2	
Low resistance	6	0.71 (0.51, 0.90)	<0.0001	0.0	
Moderate resistance	7	0.32 (0.14, 0.51)	0.0008	7.2	0.0209
High resistance	7	0.28 (-0.03, 0.59)	0.08	50.5	
Excluding low quality studies	16	0.58 (0.43, 0.74)	<0.0001	7.1	
Low resistance	5	0.74 (0.53, 0.94)	<0.001	0	
Moderate resistance	5	0.53 (0.25, 0.82)	0.0003	0	0.06
High resistance	6	0.39 (0.05, 0.73)	0.0255	30.6	
Gestational age (weeks)					
Overall	21	0.25 (0.11, 0.39)	0.0004	55.1	
Low resistance	10	0.25 (0.06, 0.45)	0.0104	50.6	
Moderate resistance	5	0.38 (-0.09, 0.85)	0.11	69.8	0.78
High resistance	6	0.09 (-0.10, 0.27)	0.35	16.0	
Excluding low quality studies	19	0.19 (0.06, 0.32)	0.0032	46.2	
Low resistance	9	0.23 (0.04, 0.43)	0.0172	51.6	
Moderate resistance	4	0.25 (-0.32, 0.83)	0.39	54.8	0.62
High resistance	6	0.09 (-0.10, 0.27)	0.35	16.0	
Birthweight (grams)					
Overall	41	93.1 (60.4, 125.9)	<0.0001	70.1	
Low resistance	18	100.9 (39.3, 162.4)	0.0013	78.0	
Moderate resistance	13	96.2 (54.8, 137.5)	<0.001	46.1	0.50
High resistance	10	28.7 (-11.3, 68.6)	0.16	15.8	
Excluding low quality studies	36	93.3 (56.8, 129.8)	<0.0001	71.6	
Low resistance	17	103.4 (39.3, 167.5)	0.0016	79.2	
Moderate resistance	10	81.0 (35.1, 127.0)	0.0005	40.9	0.56
High resistance	9	40.7 (-12.2, 93.7)	0.13	21.1	
Birthweight Paucigravidae (grams)					
Overall	26	119.4 (69.9, 168.8)	<0.0001	69.5	
Low resistance	12	153.1 (60.6, 245.5)	0.0012	69.9	
Moderate resistance	6	123.6 (84.5, 162.6)	<0.0001	0.0	0.0453
High resistance	8	25.7 (-35.2, 86.6)	0.41	35.7	
Excluding low quality studies	22	127.9 (71.4, 184.3)	<0.0001	71.3	
Low resistance	11	167.4 (73.1, 261.7)	0.0005	69.8	0.07

Moderate resistance	4	113.1 (69.7, 156.5)	<0.0001	0.0	
High resistance	7	40.6 (-41.1, 122.3)	0.33	44.9	
Birthweight Multigravidae (grams)					
Overall	20	50.1 (6.6, 93.6)	0.0240	36.5	
Low resistance	9	52.1 (-0.61, 104.9)	0.05	0.0	
Moderate resistance	4	75.8 (-62.7, 214.2)	0.28	60.1	0.94
High resistance	7	58.4 (-30.1, 146.9)	0.20	52.1	
Excluding low quality studies	16	46.8 (-1.8, 95.4)	0.06	38.1	
Low resistance	8	47.0 (-7.1, 101.1)	0.09	0.0	
Moderate resistance	2	141.9 (-157.9, 441.6)	0.35	70.9	0.98
High resistance	6	63.0 (-46.6, 172.7)	0.26	57.2	

* Low resistance: *Pfdhps*-A437G <90% in Central and West Africa or *Pfdhps*-K540E <30% in East and southern Africa; moderate: *Pfdhps*-A437G ≥90 in Central and West Africa or *Pfdhps*-K540E ≥30% and *Pfdhps*-K540E <90% in East and southern Africa; high: *Pfdhps*-K540E ≥90% in East and southern Africa.

†Pooled effect per incremental SP dose obtained by meta-analysis

‡ P-value for Z-test that the risk reduction or the weighted mean difference is 0

§ Moderate anaemia: Haemoglobin<9 g/dl or <8 g/dl or <7 g/dl

** Any test of any blood compartment at delivery

Table S7: Meta-regression of the effect of SP resistance on the effectiveness of IPTp on other outcomes than low birthweight in sub-Saharan Africa, 1997-2015

			Univariate meta-regression					Multivariate meta-regression*				
		N	Coefficient (95% CI)	p	Tau^2	I^2 %	R^2 %	Coefficient (95% CI)	p	Tau^2	I^2 %	R^2 %
Anaemia (<11 g/dl)												
Pfdhps-437	All studies	28	1.003 (0.996, 1.009)	0.40	0.03031	83.9	0.0	1.001 (0.995, 1.007)	0.71	0.01590	76.3	46.4
	Excluding low quality studies	22	1.003 (0.998, 1.008)	0.23	0.01807	80.6	0.0	1.001 (0.997, 1.005)	0.72	0.00708	64.3	60.1
Pfdhps-540	All studies	28	1.002 (1.000, 1.004)	0.0208	0.02346	81.7	20.9	1.001 (1.000, 1.003)	0.11	0.01191	73.6	59.8
	Excluding low quality studies	22	1.002 (1.000, 1.003)	0.0482	0.01618	79.3	8.9	1.001 (1.000, 1.002)	0.17	0.00590	60.0	66.8
Resistance strata†	All studies	28	1.12 (1.01, 1.25)	0.0352	0.02582	82.6	12.9	1.08 (0.99, 1.19)	0.09	0.01159	73.2	60.9
	Excluding low quality studies	22	1.08 (0.98, 1.19)	0.10	0.01793	80.6	0.0	1.05 (0.97, 1.13)	0.22	0.00633	61.6	64.4
Moderate anaemia ‡												
Pfdhps-437	All studies	14	1.006 (1.001, 1.011)	0.0238	0.00415	0.0	73.9	1.008 (1.000, 1.016)	0.0399	0.00000	0.0	100.0
	Excluding low quality studies	11	1.006 (1.000, 1.012)	0.0492	0.01001	16.7	58.1	1.009 (0.999, 1.020)	0.07	0.00000	0.0	100.0
Pfdhps-540	All studies	14	1.004 (1.002, 1.007)	0.0040	0.00000	0.0	100.0	1.004 (0.999, 1.009)	0.08	0.00000	0.0	100.0
	Excluding low quality studies	11	1.004 (1.001, 1.007)	0.0112	0.00304	0.0	87.3	1.004 (0.998, 1.010)	0.14	0.00199	0.0	91.7
Resistance strata†	All studies	14	1.20 (1.07, 1.34)	0.0049	0.00000	0.0	100.0	1.16 (0.96, 1.39)	0.10	0.00000	0.0	100.0
	Excluding low quality studies	11	1.20 (1.05, 1.38)	0.0118	0.00264	0.0	89.0	1.15 (0.92, 1.44)	0.17	0.00264	0.0	89.0
Placental malaria (any test)												
Pfdhps-437	All studies	45	1.002 (1.000, 1.005)	0.06	0.02114	65.1	10.8	1.002 (1.000, 1.005)	0.09	0.01738	55.0	26.7
	Excluding low quality studies	37	1.003 (1.000, 1.005)	0.07	0.02491	67.7	10.2	1.002 (0.999, 1.005)	0.15	0.01849	55.8	33.4
Pfdhps-540	All studies	45	1.001 (1.000, 1.003)	0.06	0.02122	65.1	10.4	1.002 (1.000, 1.003)	0.0291	0.01504	49.4	36.5
	Excluding low quality studies	37	1.002 (1.000, 1.003)	0.09	0.02492	66.5	10.1	1.002 (1.001, 1.004)	0.0142	0.01401	46.1	49.5
Resistance strata†	All studies	45	1.07 (0.99, 1.16)	0.07	0.02174	65.9	8.3	1.09 (1.01, 1.18)	0.0273	0.01513	48.9	36.1
	Excluding low quality studies	37	1.08 (0.98, 1.18)	0.10	0.02592	68.3	6.6	1.12 (1.03, 1.23)	0.0127	0.01386	44.7	50.0
Maternal malaria (any test)												
Pfdhps-437	All studies	40	1.004 (1.001, 1.006)	0.0061	0.02469	65.6	20.7	1.004 (1.001, 1.007)	0.0035	0.02575	64.1	17.4
	Excluding low quality studies	32	1.004 (1.001, 1.007)	0.0048	0.02601	62.7	31.5	1.004 (1.000, 1.007)	0.0048	0.02662	61.2	29.8
Pfdhps-540	All studies	40	1.002 (1.001, 1.004)	0.0057	0.02212	61.9	29.0	1.002 (1.001, 1.004)	0.0006	0.00473	33.1	84.8
	Excluding low quality studies	32	1.002 (1.000, 1.004)	0.0386	0.03223	68.0	15.1	1.002 (1.000, 1.004)	0.0183	0.00992	38.1	73.9
Resistance strata†	All studies	40	1.13 (1.03, 1.24)	0.0090	0.02525	66.0	19.0	1.13 (1.06, 1.22)	0.0011	0.00832	38.3	73.3
	Excluding low quality studies	32	1.13 (1.02, 1.27)	0.0251	0.03261	69.4	14.1	1.12 (1.04, 1.22)	0.0064	0.00816	33.6	78.5
Any malaria at delivery §												
Pfdhps-437	All studies	54	1.003 (1.001, 1.005)	0.0093	0.01974	69.9	17.3	1.002 (1.000, 1.004)	0.0180	0.01556	59.0	35.8
	Excluding low quality studies	44	1.003 (1.001, 1.006)	0.0116	0.02290	72.7	19.0	1.003 (1.000, 1.005)	0.0228	0.01702	61.0	40.9

Pfdhps-540	All studies	54	1.002 (1.000, 1.003)	0.0068	0.01900	67.2	20.4	1.002 (1.001, 1.003)	0.0007	0.01195	51.6	50.6
	Excluding low quality studies	44	1.002 (1.001, 1.003)	0.0081	0.02190	69.4	22.5	1.002 (1.001, 1.004)	0.0013	0.01301	54.0	54.8
Resistance strata†	All studies	54	1.09 (1.02, 1.16)	0.0164	0.02047	69.9	14.2	1.11 (1.04, 1.18)	0.0024	0.01375	55.4	43.2
	Excluding low quality studies	44	1.10 (1.01, 1.18)	0.0228	0.02426	73.0	14.2	1.12 (1.04, 1.20)	0.0040	0.01519	58.3	47.3
Preterm delivery												
Pfdhps-437	All studies	26	1.001 (0.997, 1.005)	0.59	0.02057	56.4	0.0	1.002 (0.997, 1.007)	0.53	0.02059	55.5	0.0
	Excluding low quality studies	21	1.002 (0.997, 1.006)	0.41	0.02524	59.7	0.0	1.002 (0.996, 1.008)	0.54	0.03519	62.4	0.0
Pfdhps-540	All studies	26	1.001 (0.999, 1.003)	0.14	0.01630	53.6	3.2	1.001 (0.998, 1.003)	0.62	0.01919	55.1	0.0
	Excluding low quality studies	21	1.001 (0.999, 1.004)	0.36	0.02183	58.6	0.0	1.000 (0.997, 1.004)	0.95	0.03377	62.4	0.0
Resistance strata†	All studies	26	1.08 (0.98, 1.19)	0.12	0.01634	53.3	2.9	1.05 (0.92, 1.20)	0.44	0.01782	53.8	0.0
	Excluding low quality studies	21	1.08 (0.96, 1.21)	0.21	0.02023	57.3	0.0	1.04 (0.88, 1.23)	0.61	0.03316	62.0	0.0
	Continuous variables											
Birthweight (grams)												
Pfdhps-437	All studies	41	-0.79 (-2.17, 0.60)	0.26	7026	64.3	6.0	-0.53 (-2.04, 0.98)	0.48	6455	60.3	13.5
	Excluding low quality studies	36	-0.76 (-2.33, 0.80)	0.33	8339	64.9	4.8	-0.10 (-1.77, 1.57)	0.91	7380	61.5	15.8
*Pf*dhsp-540	All studies	41	-0.16 (-1.06, 0.75)	0.73	7659	66.6	0.0	-0.23 (-1.17, 0.70)	0.62	6630	61.4	11.2
	Excluding low quality studies	36	-0.13 (-1.19, 0.93)	0.81	9061	67.7	0.0	0.20 (-0.92, 1.32)	0.72	7455	63.0	14.9
Resistance strata†	All studies	41	-15.7 (-61.9, 30.5)	0.50	7490	65.9	0.0	-22.0 (-69.8, 25.8)	0.36	6311	60.1	15.5
	Excluding low quality studies	36	-15.0 (-67.0, 37.1)	0.56	8884	67.2	0.0	-6.9 (-63.3, 49.5)	0.80	7293	61.9	16.7
Birthweight (grams) Paucigravidae												
Pfdhps-437	All studies	26	-1.55 (-3.24, 0.14)	0.07	7912	58.8	22.6	-1.76 (-3.52, 0.10)	0.05	8242	59.6	19.4
	Excluding low quality studies	22	-1.30 (-3.23, 0.62)	0.17	9788	62.5	14.0	-1.36 (-3.32, 0.60)	0.16	9599	61.9	15.6
Pfdhps-540	All studies	26	-0.92 (-2.13, 0.28)	0.13	8344	59.7	18.4	-1.55 (-2.83, -0.26)	0.0208	6995	56.5	31.6
	Excluding low quality studies	22	-1.07 (-2.46, 0.31)	0.12	9062	59.7	20.3	-1.47 (-2.91, -0.02)	0.0466	7544	56.7	33.7
Resistance strata†	All studies	26	-58.9 (-116.5, -1.3)	0.0453	7003	54.5	31.5	-103.5 (-160.0, -47.0)	0.0010	3789	42.3	62.9
	Excluding low quality studies	22	-60.1 (-126.0, 5.9)	0.07	8225	56.9	27.7	-94.2 (-159.8, -28.6)	0.0074	4824	45.6	57.6
Birthweight (grams) Multigravidae												
Pfdhps-437	All studies	20	0.11 (-1.57, 1.78)	0.89	2947	36.5	0.0	0.32 (-1.50, 2.14)	0.72	2605	32.4	0.0
	Excluding low quality studies	16	0.21 (-1.63, 2.05)	0.81	3304	38.9	0.0	0.57 (-1.42, 2.55)	0.55	2604	32.6	0.0
Pfdhps-540	All studies	20	0.04 (-1.02, 1.10)	0.94	2904	35.3	0.0	0.31 (-0.96, 1.58)	0.61	2758	32.4	0.0
	Excluding low quality studies	16	0.19 (-1.04, 1.43)	0.74	3573	37.6	0.0	0.62 (-0.79, 2.04)	0.36	2573	31.0	0.0
Resistance strata†	All studies	20	-2.0 (-55.3, 51.3)	0.94	2729	34.5	0.0	14.7 (-49.4, 78.8)	0.63	2482	32.5	0.0
	Excluding low quality studies	16	0.9, (-59.3, 61.0)	0.98	3057	36.5	0.0	26.5 (-47.0, 100.1)	0.45	2078	31.5	8.5

Haemoglobin (g/dl)												
Pfdhps-437	All studies	20	-0.009 (-0.020, 0.001)	0.08	0.04726	40.3	28.3	-0.009 (-0.017, -0.001)	0.0315	0	0.0	100
	Excluding low quality studies	16	-0.009 (-0.018, 0.000)	0.06	0	0.0	100	-0.006 (-0.018, 0.005)	0.26	0	0.0	100
Pfdhps-540	All studies	20	-0.005 (-0.008, -0.002)	0.0041	0.01583	14.9	76.0	-0.002 (-0.006, 0.002)	0.37	0.00624	0.0	90.6
	Excluding low quality studies	16	-0.003 (-0.007, 0.000)	0.08	0	0.0	100	0.000 (-0.005, 0.004)	0.82	0	0.0	100
Resistance strata†	All studies	20	-0.23 (-0.42, -0.04)	0.0209	0.02865	23.1	55.6	-0.13 (-0.30, 0.05)	0.15	0.00078	0.0	98.8
	Excluding low quality studies	16	-0.18 (-0.36, 0.01)	0.06	0	0.0	100	-0.06 (-0.28, 0.17)	0.58	0	0.0	100
Gestational age (weeks)												
Pfdhps-437	All studies	21	0.001 (-0.005, 0.007)	0.70	0.05536	55.5	0.0	0.001 (-0.005, 0.007)	0.71	0.02659	34.0	44.4
	Excluding low quality studies	19	0.000 (-0.006, 0.005)	0.86	0.03330	44.5	0.0	0.000 (-0.007, 0.007)	0.98	0.02748	37.4	0.0
Pfdhps-540	All studies	21	0.000 (-0.004, 0.003)	0.87	0.05308	50.6	0.0	0.001 (-0.004, 0.006)	0.66	0.02742	34.5	42.6
	Excluding low quality studies	19	0.000 (-0.003, 0.004)	0.92	0.03630	44.6	0.0	0.000 (-0.005, 0.006)	0.86	0.02658	37.4	1.8
Resistance strata†	All studies	21	-0.03 (-0.22, 0.17)	0.78	0.05289	51.5	0.0	-0.03 (-0.26, 0.21)	0.80	0.02847	35.6	40.4
	Excluding low quality studies	19	-0.04 (-0.22, 0.13)	0.62	0.02779	41.8	0.0	-0.08 (-0.34, 0.19)	0.55	0.02147	35.3	20.7

Abbreviations: N=number of studies. CI=confidence interval.

* Multivariate metaregression: adjusted for malaria transmission intensity, number of SP courses, study quality and proportion of paucigravidae; for continuous variables number of SP courses not included (comparison is 0 vs. 2 doses of SP). For birthweight by gravidity, proportion of paucigravidae was not included.

† Resistance strata: Definition of SP resistance using molecular markers: Low resistance: *Pfdhps*-A437G <90% in Central and West Africa or *Pfdhps*-K540E <30% in East and southern Africa; moderate: *Pfdhps*-A437G ≥90 in Central and West Africa or *Pfdhps*-K540E ≥30% and *Pfdhps*-K540E <90% in East and southern Africa; high: *Pfdhps*-K540E ≥90% in East and southern Africa. This variable was introduced as a continuous variable.

‡ Haemoglobin<9 g/dl or <8 g/dl or <7 g/dl

§ Any test of any blood compartment at delivery

Table S8: Prevalence of *Pfdhps* resistance markers by resistance category and region, 57 settings in sub-Saharan Africa with low birthweight information, 1994-2014

Resistance level	Region	N	Median (interquartile range)		
			***Pfdhps*-A437G**	***Pfdhps*-K540E**	***Pfdhps*-A581G**
Any level	West & Central	31	57.9 (39.3-77.6)	0.1 (0.0-0.9)	0.0 (0.0-0.9)
	East & southern	26	85.4 (62.9-94.1)	85.8 (47.6-94.8)	0.0 (0.0-5.6)
	Overall	57	74.1 (44.8-92.4)	3.3 (0.0-84.0)	0.0 (0.0-2.5)
Low*	West & Central	27	52.1 (33.8-75.3)	0.0 (0.0-0.7)	0.0 (0.0-0.0)
	East & southern	3	26.1 (13.3-74.1)	25.4 (0.0-27.8)	0.0 (0.0-5.6)
	Overall	30	52.1 (32.7-74.1)	0.1 (0.0-0.9)	0.0 (0.0-0.0)
Moderate*	West & Central	4	94.6 (92.4-98.4)	1.0 (0.5-10.0)	5.3 (2.5-30.4)
	East & southern	12	69.3 (48.0-82.0)	73.4 (39.4-84.0)	0.0 (0.0-0.0)
	Overall	16	80.0 (58.1-92.8)	58.1 (25.0-80.2)	0.0 (0.0-2.6)
High*	West & Central	0	NA	NA	NA
	East & southern	11	94.1 (93.0-100.0)	95.1 (92.7-99.6)	2.0 (0.0-13.0)
	Overall	11	94.1 (93.0-100.0)	95.1 (92.7-99.6)	2.0 (0.0-13.0)

NA: not applicable.

* Low resistance: *Pfdhps*-A437G <90% in Central and West Africa or *Pfdhps*-K540E <30% in East and southern Africa; moderate: *Pfdhps*-A437G ≥90% in Central and West Africa or (*Pfdhps*-K540E ≥30% and *Pfdhps*-K540E <90%) in East and southern Africa; high: *Pfdhps*-K540E ≥90% in East and southern Africa.

Table S9: Characteristics of included surveys by country showing the number of LBW events of women exposed to varying levels of malaria prevention in pregnancy before matching

Country	Year	Survey	Year IPTp adopted as policy	Proportion women sleeping under an ITN[1]	Proportion of women receiving 2+ doses SP[1]	Mean % prevalence of A437G	Mean % prevalence of K540E	LBW / live birth no IPTp	LBW / live births 1 dose IPTp	LBW / live births 2 doses IPTp	LBW / live births 3+ doses iptp
Benin	2006	DHS	2005	19.6%	3.0%	77.03%	3.16%	1,310 / 10,003	24 / 142	18 / 163	12 / 117
Benin	2011	DHS	2005	75.8%	22.8%	72.45%	2.31%	636 / 4,816	95 / 813	148 / 1,217	137 / 935
Burkina Faso	2003	DHS	2005	3.0%	0.0%	62.95%	0.07%	1,235 / 7,212	0/0	0/0	1/9
Burkina Faso	2010	DHS	2005	44.5%	38.5%	58.31%	0.21%	440 / 2,947	407 / 3,223	428 / 3,306	94 / 851
Burundi	2010	DHS	No policy	49.9%	NA	88.80%	87.03%	604 / 4,821	0 / 5	0 / 3	0 / 8
Cameroon	2011	DHS	2004	19.8%	25.6%	52.71%	0.45%	615 / 4,127	110 / 1,250	118 / 1,075	87 / 1,024
Cote d'Ivoire	2011	DHS	2005	40.2%	17.6%	60.62%	0.73%	546 / 3,626	80 / 560	91 / 662	55 / 385
DRC	2007	DHS	2004	7.1%	6.9%	77.19%	29.92%	355 / 4,316	29 / 467	12 / 224	18 / 168
DRC	2013	DHS	2004	60.9%	14.3%	77.66%	25.55%	663 / 7,425	163 / 2,004	69 / 977	50 / 601
Gabon	2012	DHS	2003	28.7%	2.6%	79.51%	2.45%	526 / 3,642	12 / 83	16 / 95	10 / 68
Ghana	2003	DHS	2003	2.7%	1.0%	79.98%	0.55%	427 / 2,592	0 / 1	0 / 5	0 / 26
Ghana	2008	DHS	2003	27.4%	45.5%	81.04%	1.20%	135 / 966	32 / 240	42 / 335	59 / 537
Guinea	2005	DHS	2005	1.4%	3.6%	46.04%	0.31%	486 / 3,789	2 / 14	2 / 16	6 / 98
Guinea	2012	DHS	2005	28.0%	17.8%	39.32%	0.39%	378 / 2,927	45 / 400	57 / 543	48 / 552
Kenya	2003	DHS	1999	5.4%	6.8%	63.83%	62.74%	438 / 3,371	37 / 271	19 / 130	11 / 123
Kenya	2008	DHS	1999	49.0%	15.1%	95.41%	92.21%	300 / 2,205	88 / 814	38 / 319	17 / 255
Liberia	2013	DHS	2004	37.1%	47.6%	56.80%	1.05%	428 / 1,950	177 / 861	248 / 1,533	176 / 964
Madagascar	2008	DHS	2004	46.2%	6.7%	45.45%	0.30%	1,338 / 7,433	62 / 394	49 / 379	20 / 156
Malawi	2004	DHS	1993	14.7%	46.5%	84.19%	89.66%	251 / 1,392	328 / 2,331	255 / 2,240	143 / 1,047
Malawi	2010	DHS	1993	35.2%	55.0%	95.26%	95.12%	274 / 1,535	591 / 4,691	490 / 4,688	299 / 2,310
Mali	2006	DHS	2003	28.9%	11.2%	38.03%	0.11%	1,403 / 7,458	64 / 294	77 / 526	76 / 513
Mali	2012	DHS	2003	73.2%	19.9%	26.71%	0.11%	488 / 2,750	177 / 1,251	158 / 1,136	125 / 928
Mozambique	2011	DHS	2006	34.3%	18.6%	76.32%	56.74%	545 / 4,187	172 / 1,431	123 / 830	89 / 757
Namibia	2006	DHS	2005	8.8%	10.6%	66.74%	5.96%	404 / 2,621	38 / 302	11 / 121	109 / 786
Niger	2006	DHS	2005	13.3%	0.3%	42.20%	0.30%	1,296 / 5,801	0 / 0	1 / 4	2 / 21
Niger	2012	DHS	2005	19.9%	34.8%	41.98%	0.28%	748 / 2,762	399 / 1,875	415 / 2,022	133 / 685
Nigeria	2008	DHS	2004	4.8%	6.5%	51.01%	1.29%	2,461 / 15,496	60 / 673	47 / 576	69 / 567
Nigeria	2013	DHS	2004	16.4%	14.6%	50.39%	1.19%	2,275 / 14,487	236 / 1,908	207 / 1,903	148 / 1,351
Rwanda	2005	DHS	2005[2]	17.2%	0.9%	80.87%	83.24%	530 / 5,233	2 / 50	3 / 23	1 / 27
Senegal	2005	DHS	2004	8.6%	13.2%	44.72%	0.03%	1,506 / 5,759	149 / 532	111 / 518	58 / 243
Senegal	2010	DHS	2004	36.0%	38.6%	40.28%	0.05%	567 / 2,559	527 / 2,341	347 / 2,030	184 / 1,021
Sierra Leone	2007	DHS	2004	27.2%	12.0%	48.81%	0.58%	504 / 2,845	39 / 298	40 / 290	36 / 227
Sierra Leone	2013	DHS	2004	52.6%	45.1%	47.46%	0.42%	459 / 2,775	143 / 1,520	237 / 2,141	194 / 1,781
Tanzania	2005	DHS	2001	15.6%	21.7%	57.43%	51.88%	355 / 3,380	134 / 1,264	73 / 830	10 / 146
Tanzania	2010	DHS	2001	56.9%	27.2%	88.18%	81.69%	128 / 1,548	112 / 1,766	104 / 1,523	10 / 166
Uganda	2006	DHS	2000	10.0%	17.6%	93.97%	93.71%	580 / 2,931	107 / 815	69 / 485	38 / 259
Uganda	2011	DHS	2000	46.9%	26.7%	96.02%	93.64%	429 / 2,462	161 / 1,062	102 / 753	67 / 476
Zambia	2007	DHS	2001	32.7%	65.7%	66.20%	50.42%	69 / 569	91 / 878	94 / 897	137 / 1,767
Zimbabwe	2005	DHS	2004	3.2%	6.8%	29.95%	25.54%	408 / 3,587	12 / 168	4 / 79	12 / 137

Zimbabwe	2010	DHS	2004	9.6%	7.8%	60.63%	39.01%	35 / 3,643	19 / 242	9 / 125	22 / 246

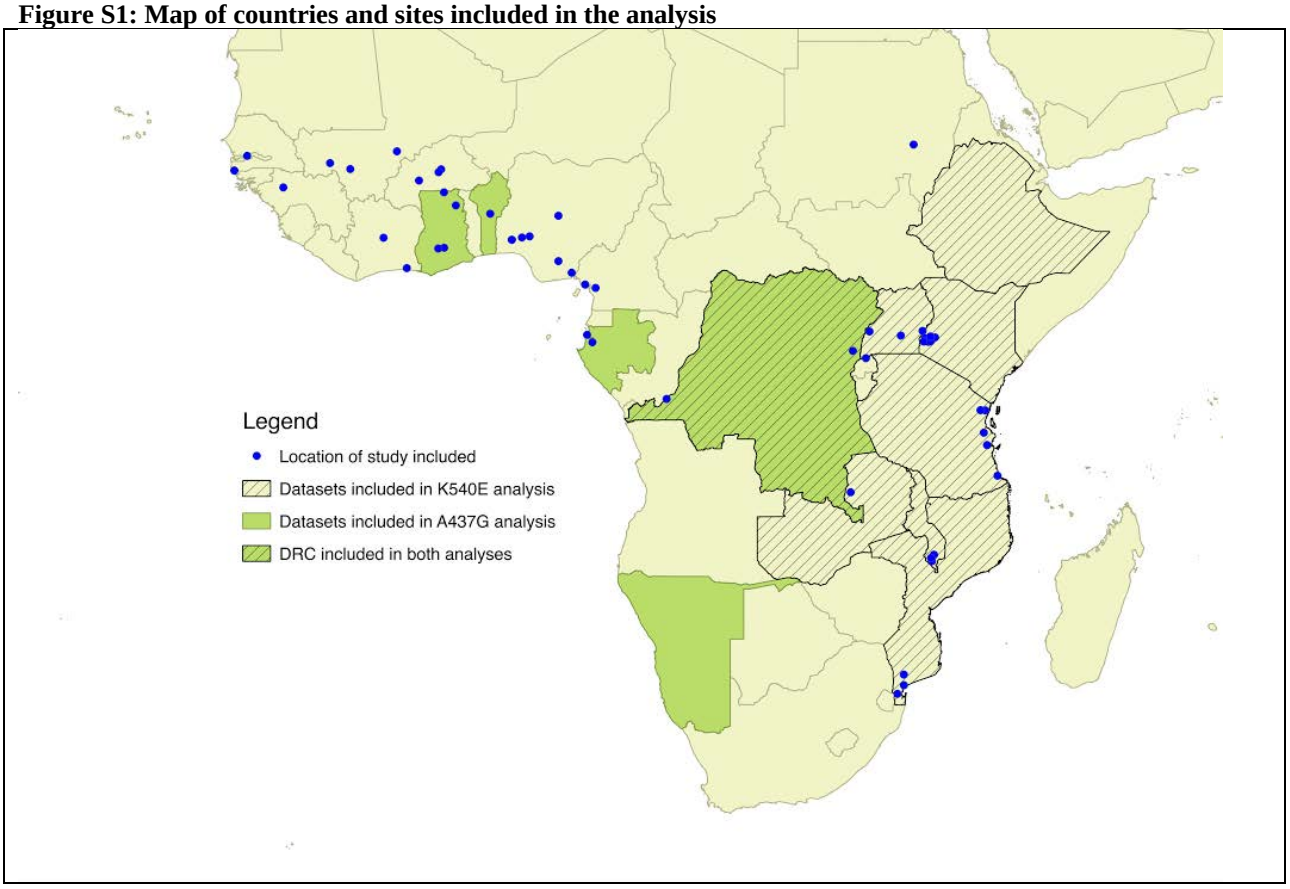
Abbreviations: DRC=Democratic Republic of the Congo.

[a]Coverage estimates derived from publications

[b]Rwanda ended IPTp as national policy in 2008

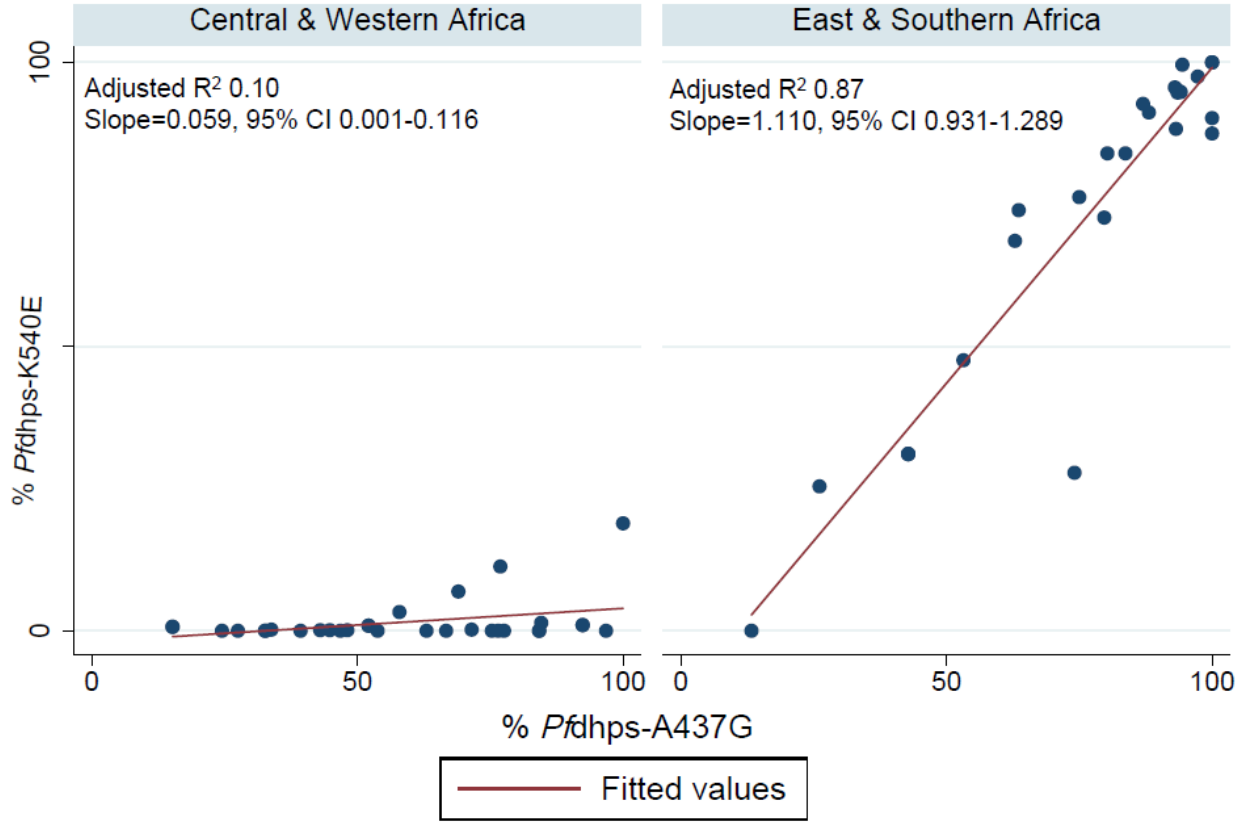
Supplemental Figures

Figure S1: Map of countries and sites included in the analysis



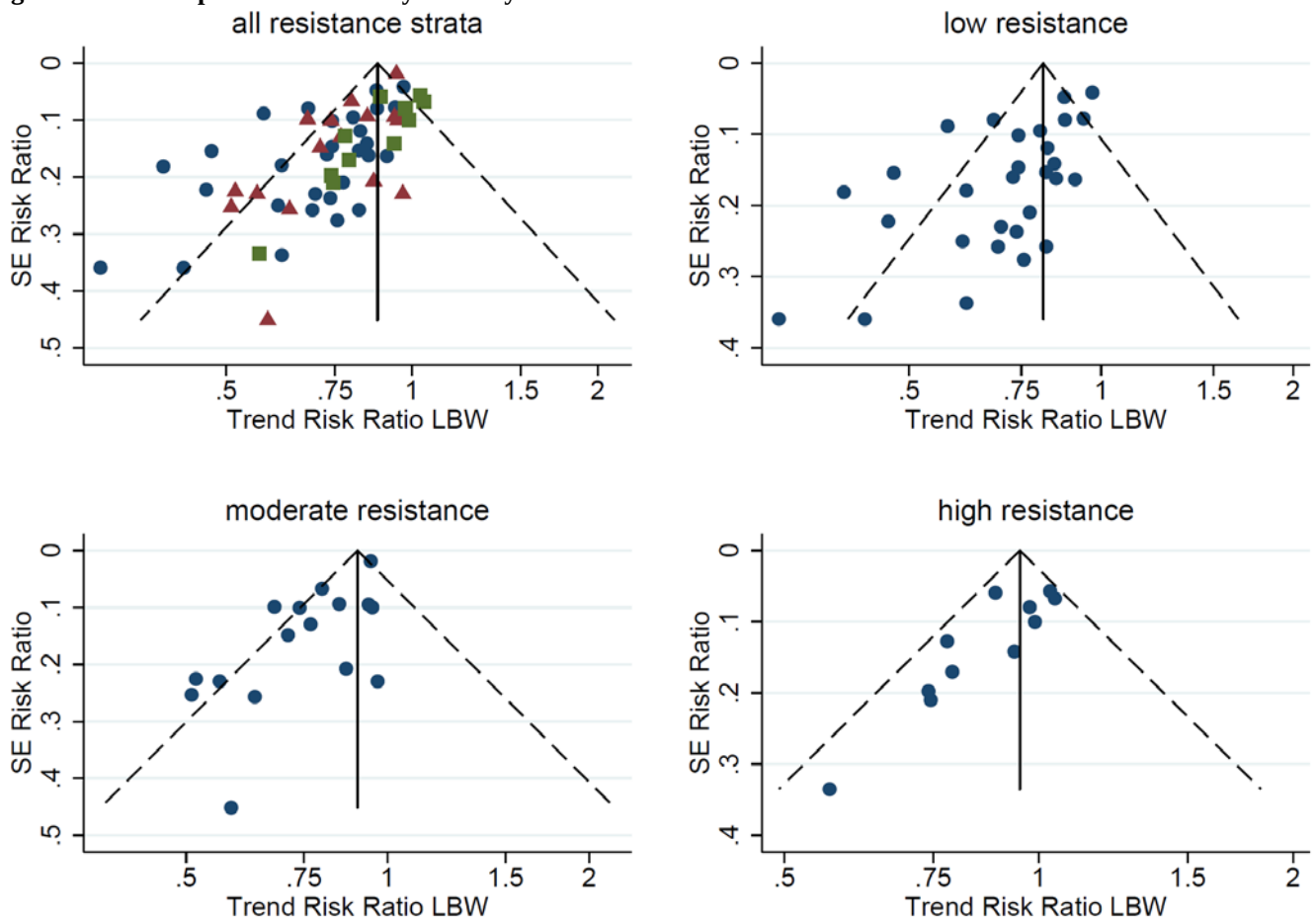
Blue dots represent the location of studies included in the aggregated data meta-analysis. Green and shaded areas represent countries with national survey data included in the individual participant data meta-analysis.

Figure S2: Relationship between the prevalence of the *Pfdhps*-A437G and *Pfdhps*-K540E mutation in the study locations in Central and West Africa and East and southern Africa



Pfdhps=Plasmodium falciparum dihydropteroate synthetase

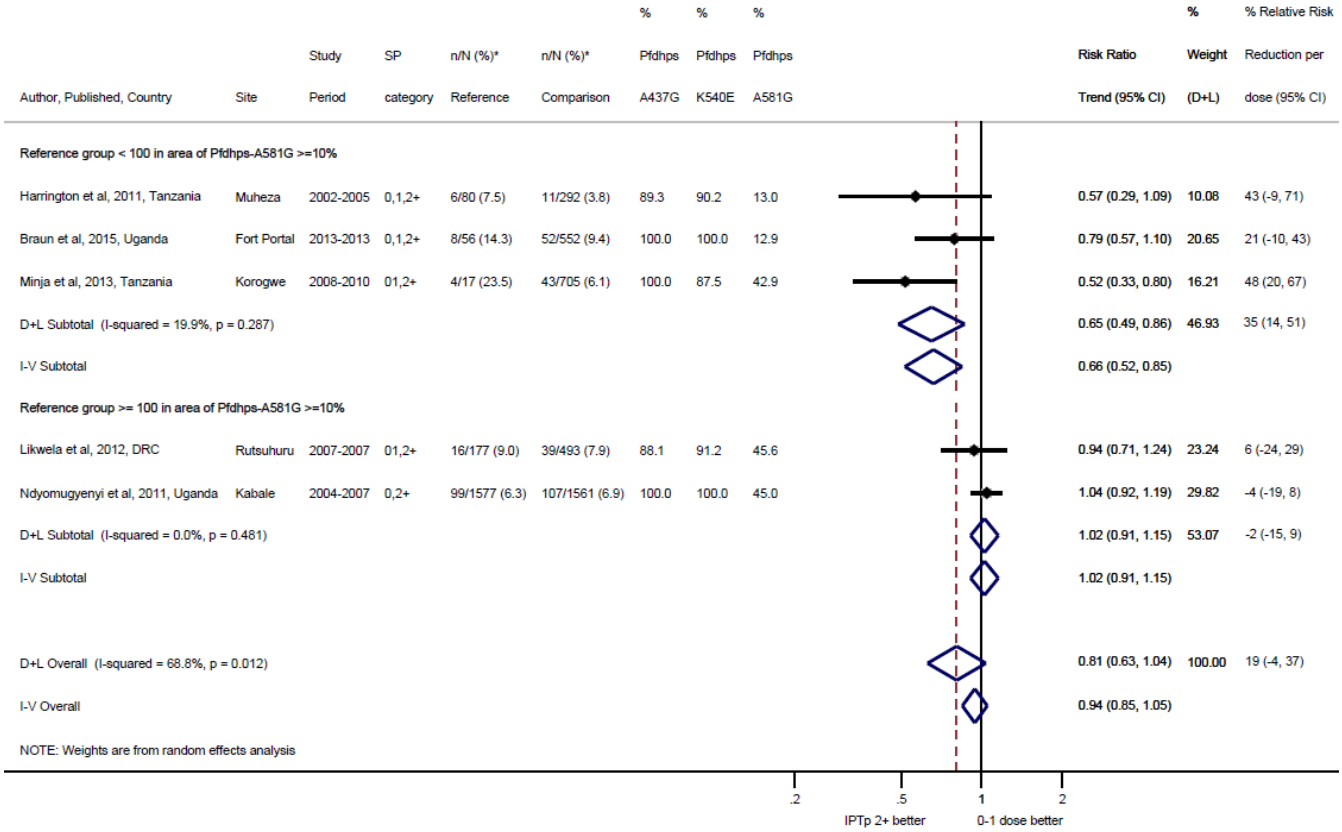
Figure S3: Funnel plots of small study effect by resistance strata



SE=standard error, LBW=low birth weight. Low resistance=*Pfdhps*-A437G <90% in Central and West Africa or *Pfdhps*-K540E <30% in East and southern Africa; moderate=*Pfdhps*-A437G ≥90% in Central and West Africa or (*Pfdhps*-K540E ≥30% and *Pfdhps*-K540E <90%) in East and southern Africa; high=*Pfdhps*-K540E ≥90% in East and southern Africa.

Funnel plot of the effect size (X-axis, the risk ratio of LBW associated with each incremental dose of IPTp-SP) and the standard error of the risk ratio (Y-axis). In the top left graph for all resistance strata, the dark blue circles, dark red triangles and green squares represent studies in low, moderate and high resistance areas respectively. One study with zero events in the intervention arm was excluded in the graphs. The asymmetry suggests a potential for small-study effect with smaller studies (larger standard errors) showing greater treatment effects. This can be observed overall (top left) and in each of the three resistance strata. The two-sided p-values for asymmetry of the funnel plot by Egger's test were P<0.0001, P<0.0001, P<0.0001 and P=0.0103 for all strata combined, and for low, moderate and high resistance respectively.

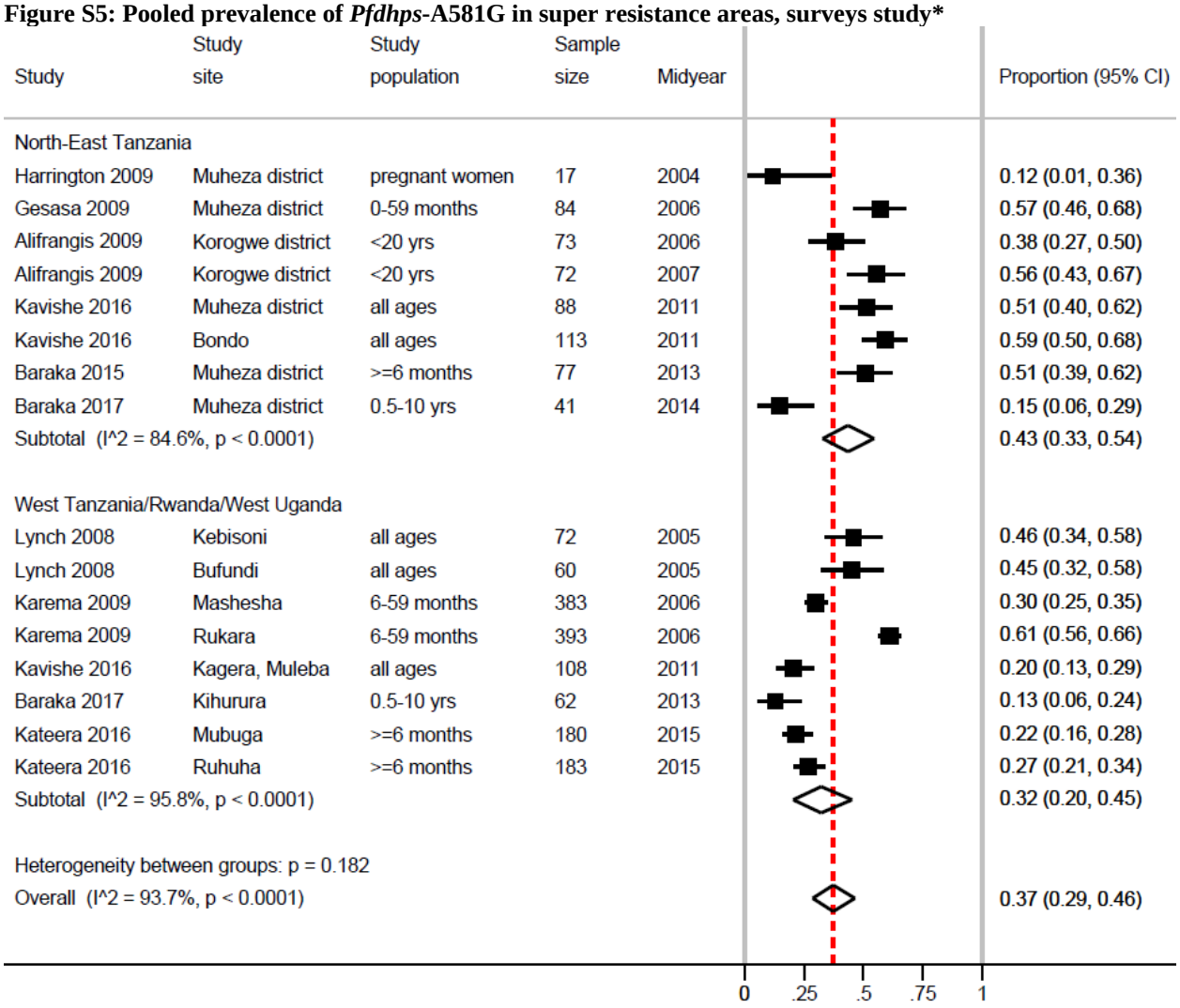
Figure S4: Meta-analysis of the risk of low birthweight associated with each incremental dose of IPTp-SP in all gravidae by sample size in areas with a high prevalence of *Pfdhps*-A581G, clinical studies



Pfdhps=Plasmodium falciparum dihydropteroate synthetase

* Reference refers to the group with 0 doses SP or 0 combined with 1 dose SP, and comparison refers to the other dose groups combined. For full sample size per dose-group, and average dose, see Table S2.

Figure S5: Pooled prevalence of *Pfdhps*-A581G in super resistance areas, surveys study*



The pooled mutation prevalence were obtained with Metaprop: a Stata command to perform meta-analysis of binomial data.[22]

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Prisma checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Main text Page 1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Main text Page 2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Main text Page 5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Main text Page 5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	Page 5 (Prospero CRD42016035540)
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Main text Page 5 Appendix Page 2
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Main text Page 5 Appendix Page 2
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix Page 2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Figure 1, Appendix Page 2
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Main text page 5-6 Appendix Page 2
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Main text page 5-6 Appendix Page 2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Main text page 7 Appendix Page 4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Main text page 7 Appendix Page 4
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	Main text page 7 Appendix Page 4

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Main text Page 7 Appendix Page 4
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	Main text page 7 Appendix Page 4
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Figure 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Appendix Table S1 & S9
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table S1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Figure 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	Figure 2-4, Appendix Tables S4-S7
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Appendix Figure S3-S4
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Appendix Tables S4-S7 Figure S4, S5
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Main text page 9
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Main text page 10
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Main text page 9-10
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Main text page 10

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097[119]

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