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'

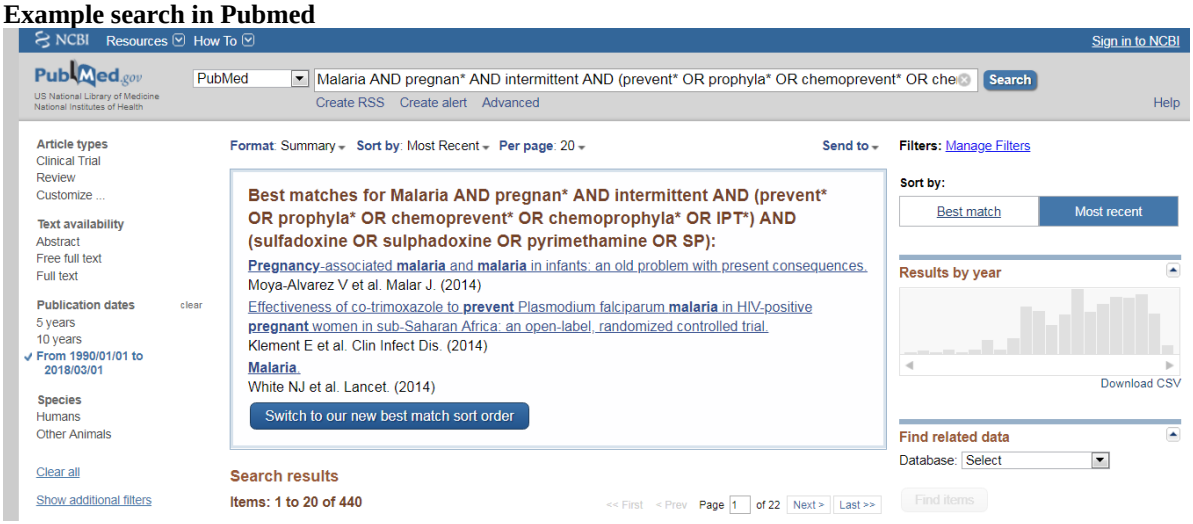
Contents

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

Assessment of heterogeneity and small-study effects clinical studies
The extent of heterogeneity was measured using the I^2 statistic,[5] 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.[6] 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.[7]

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)[8] 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.[9,10] 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.[11,12] 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.[9,10]

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.[13]

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.[14] The use of antenatal care 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.[15-19]

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$_{2-10}$[20]	Quality score
1	Aduloju 2013[21]	Nigeria	2011-2011	Survey	1	NA	20.7	G1	10.3	4.1 (UNAIDS)	NA	100.0	39.3	2
2	Alli 2013[22]	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[23]	Cameroon	2007-2007	Survey	1	NA	31.0	G1	6.6	5.6	NA	NA	51.6	3
4	Apinjoh 2015[24]	Cameroon	2008-2010	Survey	1	NA	32.0	G1	9.8	4.0	NA	100.0	51.6	4
5	Arinaitwe 2013[25] [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[26]	Nigeria	2009-2009	Cohort	1	10.1	18.9	G1	0.0	0.0	NA	100.0	62.3	2
7	Bouyou-Akotet 2010[27]	Gabon	2005-2006	Survey	1	17.2	77.3	G1	37.0	5.4 (UNAIDS)	NA	NA	37	3
8	Bouyou-Akotet 2016[28] [g]	Gabon	2011-2011	Survey	2	6.0	19.1	G1	16.2	0.0	NA	100.0	43.5	4
9	Braun 2015[29] [g]	Uganda	2013-2013	Survey	1	9.6	31.7	G1	65.1	0.0	NA	NA	24.5	4
10	Cassam 2007[30]	Mozambique	2005-2007	Survey	50	8.1	27.5	G1	43.7	36.4	NA	100.0	54.7	4
11	Challis 2004[31]	Mozambique	2001-2002	Trial (IPTp)	2	11.4	100	G1/G2	1.0	10.0	NA	100.0	43.1	5
12	Chukwuocha 2016[32]	Nigeria	2014-2014	Survey	1	NA	36.5	G1	19.7	3.2 (UNAIDS)	NA	100.0	62.8	0
13	Coulibaly 2014[33] [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[34] [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[35]	Burkina Faso	2013-2014	Survey	1	NA	21.3	G1 [g]	86.6	.9 (UNAIDS)	NA	NA	54.5	2
16	Falade 2007[36]	Nigeria	2003-2004	Survey	1	6.1	23.5	G1	1.1	2.0	5.0	NA	50.5	3
17	Famanta 2011[37] [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[38]	Nigeria	2013-2013	Survey	2	NA	40.3	G1	27.0	4.0	NA	85.3	44.7	2
19	Feng 2010[39] [g]	Malawi	1997-1999	Survey	1	14.6	46.4	G1/G2	10.0	16.6 (UNAIDS)	NA	NA	27.7	2
	Feng 2010[39] [g]	Malawi	1999-2001	Survey	1	12.7	48.4	G1/G2	23.0	16.5 (UNAIDS)	NA	NA	27.7	2
	Feng 2010[39] [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[40]	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[12]/ Kalilani 2014[11] [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[41] [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[16]	Ghana	2006-2006	Survey	1	12.4	32.7	G1	8.0	3.0	NA	NA	39.6	3
25	Igboeli 2017[42]	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[43]	Nigeria	2008-2008	Cohort	1	NA	24.4	G1 [g]	7.2	3.1 (UNAIDS)	NA	100.0	35.6	3
27	Kayentao 2014[44] [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[44] [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[44] [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[44] [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[44] [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$_{2\text{-}10}$[20]	Quality score
	Kayentao 2014[44] [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[45]	DRC	2011-2011	Survey	1	7.5	20.0	G1 [g]	43.8	1.1 (UNAIDS)	NA	NA	29.7	3
29	Likwela 2012[46]	DRC: Mikalayi	2007-2007	Survey	1	16.1	17.2	G1	6.5	1.5 (UNAIDS)	NA	100.0	33.2	4
	Likwela 2012[46]	DRC: Kisangani	2007-2007	Survey	1	7.8	29.2	G1	4.7	1.5 (UNAIDS)	NA	100.0	40.2	4
	Likwela 2012[46]	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[47] [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[48]	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[49]	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[50]	Tanzania	2008-2010	Cohort	1	6.5	21.6	G1	94.9	5.8 (UNAIDS)	NA	100.0	11.3	3
34	Moleins 2010[17]	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[51]	Tanzania	2012-2012	Survey	2	5.1	37.4	G1	94.6	3.4	NA	100.0	18.8	4
36	Msyamboza 2009[52] [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[53]	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[54]	Kenya	2011-2013	Trial (Iron)	4	NA	18.1	G1	15.5	21.1	NA	NA	61	6
39	Mwapasa 2004[55]	Malawi	2000-2002	Survey	1	NA	42.2	G1	22.3	0.0	5.0	NA	24.4	4
40	Namusoke 2010[56] [g]	Uganda	2004-2005	Survey	1	14.6	49.4	G1	32.0	11.0	NA	96.8	19.3	4
41	Ndeserua 2015[57]	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[58]	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[59]	Tanzania	2003-2003	Survey	1	NA	42.3	G1	48.1	6.8 (UNAIDS)	NA	100.0	17.5	3
45	Njagi 2002[60]	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[18]	Ghana	2006-2007	Survey	6	18.4	24.2	G1	53.6	2.2 (UNAIDS)	NA	97.0	63.3	3
47	Olliaro 2008[61]	Senegal	2000-2007	Survey	1	9.5	21.7	G1 [g]	12.4	.8 (UNAIDS)	NA	100.0	26.6	4
48	Olorunda 2013[19]	Nigeria	2010-2010	Survey	1	7.9	37.2	G1	13.9	4.1 (UNAIDS)	NA	100.0	37.9	4
49	Onyebuchi 2014[62]	Nigeria	2012-2012	Survey	1	NA	45.2	G1/G2	100.0	3.4 (UNAIDS)	NA	100.0	54.0	0
50	Orobaton 2016[63]	Nigeria	2014-2015	Survey	4	NA	18.3	G1	56.1	3.1 (UNAIDS)	NA	56.6	33.5	0
51	Parise 1998[64]	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[65]	Gabon	2005-2006	Survey	3	10.2	28.7	G1	38.1	7.9	NA	NA	45.9	3
53	Rogawski 2012[66]	Malawi	1997-2006	Survey	1	NA	47.8	G1	37.0	15.5 (UNAIDS)	NA	NA	27.7	4
54	Rogerson 2000[67]	Malawi	1997-1999	Survey	1	NA	46.0	G1	7.0	16.6 (UNAIDS)	0.25	100.0	27.7	2
55	Sirima 2006[68] [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[69]	Sudan	1999-2001	Cohort	2	19.1	100	G1	1.0	0.1 (UNAIDS)	NA	100.0	3.2	4
57	Tetteh-Ashong 2005[70]	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$_{2-10}$[20]	Quality score
58	Tonga 2013[71]	Cameroon	2011-2012	Survey	5	16.7	22.5	G1	19.3	6.0	NA	NA	55.4	2
59	Tongo 2011[72]	Nigeria	2007-2008	Survey	2	9.0	11.6	G1	20.1	3.1 (UNAIDS)	NA	NA	50.8	2
60	Toure 2014[15]	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[73]	Ghana	2005-2007	Survey	6	12.1	24.3	G1	26.5	2.3 (UNAIDS)	NA	NA	30.9	4
62	Vanga-Bosson 2011[74]	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[14] [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[75]	Ghana	2010-2010	Survey	1	NA	34.0	G1	26.5	0.0	NA	NA	57.4	1
65	Verhoeff 1998[76]	Malawi	1993-1994	Survey	1	NA	30.0	G1	1.0	0.0	NA	100.0	27.4	3
66	Yussuf 2010[77]	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):[35] DHS 2010 Burkina Faso, Inyang-Etoh *et al*. (2011):[43] DHS 2008 Nigeria, Kilauzi *et al.* (2013):[45] DHS DRC 2007 DRC & DHS 2013-2014 (midpoint), Moleins *et al.* (2010):[17] DHS 2005 Senegal, and Olliaro *et al.* (2008):[61] 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.[78]

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.[34] 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[21]	Ado Ekiti, Nigeria	2011-2011	84.2[79]	~400 (Enugu)	-1 (2010)	0.0[79]	~400 (Enugu)	-1 (2010)	47.4[79]	~400 (Enugu)	-1 (2010)	38[79]
2	Alli 2013[22]	Kubwa, Nigeria	2010-2011	84.2[79]	~400 (Enugu)	0 (2010)	0.0[79]	~400 (Enugu)	0 (2010)	47.4[79]	~400 (Enugu)	0 (2010)	38[79]
3	Anchang Kimbi 2009[23]	Mutengene, Cameroon	2007-2007	85.5[80]	0 (Mutengene)	-1 (2004-2006)	0.5[80]	0 (Mutengene)	-1 (2004-2006)	2.0[80]	0 (Mutengene)	-1 (2004-2006)	200[80]
4	Apinjoh 2015[24]	Mutengene, Cameroon	2008-2010	85.5[80]	0 (Mutengene)	-2 (2004-2006)	0.5[80]	0 (Mutengene)	-2 (2004-2006)	2.0[80]	0 (Mutengene)	-2 (2004-2006)	200[80]
5	Arinaitwe 2013[25]	Tororo, Uganda	2011-2011	97.3[34]	0 (Tororo)	0	97.5[34]	0 (Tororo)	0	0.2[34]	0 (Tororo)	0	100[34]
6	Aziken 2011[26]	Benin City, Nigeria	2009-2009	84.2[79]	~260 (Enugu)	+1 (2010)	0.0[79]	~260 (Enugu)	+1 (2010)	47.4[79]	~260 (Enugu)	+1 (2010)	38[79]
7	Bouyou-Akotet 2010[27]	Libreville, Gabon	2005-2006	69.0[81]	0	0	6.9[81]	0	0	0.0[81]	0	0	29[82]
8	Bouyou-Akotet 2016[28]	Libreville, Melen, Gabon	2011-2011	66.7[81]	0	0	0.0[81]	0	0	0.0[81]	0	0	18[82]
9	Braun 2015[29]	Fort Portal, Uganda	2013-2013	100[83]	~130 (Kihurura)	0 (2012-2014)	100[83]	~130 (Kihurura)	0 (2012-2014)	12.9[83]	~130 (Kihurura)	0 (2012-2014)	62[83]
10	Cassam 2007[30]	Gaza, Maputo, Mozambique	2005-2007	53.2[84]	0	0	47.6[84]	0	0	0.0[85,86]	0 (Gaza, Maputo)	0 (2006-2007)	~ 2700[85,86]
11	Challis 2004[31]	Matola, Boane, Mozambique	2001-2002	26.1[87]	0 (peri-urban Maputo)	0 (2001)	25.4[87]	0 (peri-urban Maputo)	0 (2001)	0.0[88]	0 (Maputo)	0 (1999-2004)	134[87] ~1000[88]
12	Chukwuocha 2016[32]	Owerri, Nigeria	2014-2014	96.8[79]	~230 (Benin City)	0 (2014-2015)	0.0[79]	~230 (Benin City)	0 (2014-2015)	52.6[79]	~230 (Benin City)	0 (2014-2015)	95[79]
13	Coulibaly 2014[33]	Ziniare, Burkina Faso	2010-2012	75.3[34]	0	0	0.0[34]	0	0	0.0[34]	0	0	273[34]
14	Desai 2015[34]	Siaya, Kenya	2011-2012	93.0[34]	0	0	95.6[34]	0	0	5.7[34]	0	0	53[34]
15	Douamba 2014[35]	Ouagadougou, Burkina Faso	2013-2014	75.3[34]	~ 30 (Ziniare)	-1 (2010-12)	0.0[34]	~ 30 (Ziniare)	-1 (2010-12)	0.0[34]	~ 30 (Ziniare)	-1 (2010-12)	273[34]
16	Falade 2007[36]	Ibadan, Nigeria	2003-2004	63.0[79]	0 (Ibadan)	0 (2003)	0.0[79]	0 (Ibadan)	0 (2003)	0.0[79]	0 (Ibadan)	0 (2003)	36[79]
17	Famanta 2011[37]	Bamako, Mali	2009-2009	15.2[34]	~190 (Kita)	0 (2009-2010)	0.7[34]	~190 (Kita)	0 (2009-2010)	0.0[34]	~190 (Kita)	0 (2009-2010)	117[34]
18	Fehintola 2016[38]	Ile Ife, Nigeria	2013-2013	96.8[79]	~230 (Benin City)	+1 (2014-2015)	0.0[79]	~230 (Benin City)	+1 (2014-2015)	52.6[79]	~230 (Benin City)	+1 (2014-2015)	95[79]
19	Feng 2010[39]	Blantyre, Malawi	1997-1999	63.6[84]	0	0	74.0[84]	0	0	0.0[89]	0 (Ndirande)	0 (1997-1999)	149[89]
	Feng 2010[39]	Blantyre, Malawi	1999-2001	80.3[84]	0	0	84.0[84]	0	0	0.0[90]	0 (Ndirande)	0 (1999-2001)	550[90]
	Feng 2010[39]	Blantyre, Malawi	2002-2006	93.5[84]	0	0	95.0[90]	0 (Ndirande)	+1 (2007-2009)	2.0[90]	0 (Ndirande)	+1 (2007-2009)	556
20	Gies 2009[40]	Boromo, Burkina Faso	2004-2006	71.5[84]	0	0	0.2[84]	0	0	0.0[34]	210 (Ziniare)	+4 (2010)	273[34]
21 22	Gutman 2013[12]/ Kalilani 2014[11]	Blantyre & Machinga, Malawi	2009-2011	94.4[34]	0	0	99.6[34]	0	0	1.5[34]	0	0	134[34]
23	Harrington 2011[41]	Muheza, Tanzania	2002-2005	100.0[91]	0	0	90.2[91]	0	0	13.0[91]	0	0	540 & 581: 17[91]*
24	Hommerich 2007[16]	Agogo, Ghana	2006-2006	84.6[84]	0	0	1.4[84]	0	0	0.0[92]	~90 (Bekwai)	+1 (2007-2008)	35[92]
25	Igboeli 2017[42]	Enugu State, Nigeria	2013-2013	96.8[79]	~ 260 (Benin City)	+1 (2014-2015)	0.0[79]	~ 260 (Benin City)	+1 (2014-2015)	52.6[79]	~ 260 (Benin City)	+1 (2014-2015)	95[79]
26	Inyang-Etho 2011[43]	Calabar, Nigeria	2008-2008	84.2[79]	~ 260 (Enugu)	+2 (2010)	0.0[79]	~ 260 (Enugu)	+2 (2010)	47.4[79]	~ 260 (Enugu)	+2 (2010)	38[79]

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[44]	Koro, Mali	2006-2007	44.8[84]	0	0	0.1[84]	0	0	0.0[34]	~200 (San)	+3 (2010)	130[34]
	Kayentao 2014[44]	San, Mali	2006-2006	32.6[84]	0	0	0.0[84]	0	0	0.0[34]	0 (San)	+4 (2010)	130[34]
	Kayentao 2014[44]	Bougouni, Mali	2006-2007	33.8[84]	0	0	0.2[84]	0	0	0.0[34]	~650 (San)	+3 (2010)	130[34]
	Kayentao 2014[44]	Djenne, Mali	2006-2006	32.7[84]	0	0	0.0[84]	0	0	0.0[34]	~130 (San)	+4 (2010)	130[34]
	Kayentao 2014[44]	Kita, Mali	2009-2010	15.2[34]	0	0	0.7[34]	0	0	0.0[34]	0	0	117[34]
	Kayentao 2014[44]	San, Mali	2009-2010	27.5[34]	0	0	0.0[34]	0	0	0.0[34]	0	0	130[34]
28	Kilauzi 2013[45]	Kinshasa, DRC	2011-2011	100.0[83]	0 (Kinshasa)	+1 (2012-2014)	18.9[83]	0 (Kinshasa)	+1 (2012-2014)	8.1[83]	0 (Kinshasa)	+1 (2012-2014)	37[83]
29	Likwela 2012[46]	Mikalayi, DRC	2007-2007	76.9[84]	0	0	11.3[84]	0	0	0.0[93]			
	Likwela 2012[46]	Kisangani, DRC	2007-2007	74.1[84]	0	0	27.8[94]	0 (Kisangani)	0 (2007)	5.6[94]	0 (Kisangani)	0 (2007)	18[94]
	Likwela 2012[46]	Rutshuru, DRC	2007-2007	88.1[95]	~280 (Rukara & Mashesa, Rwanda)	-1 (2005-2006)	91.2[95]	~280 (Rukara & Mashesa, Rwanda)	-1 (2005-2006)	45.6[95]	~280 (Rukara & Mashesa, Rwanda)	-1 (2005-2006)	Mean†: 776[95]
30	Mace 2015[47]	Mansa, Zambia	2009-2010	83.7[34]	0	0	84.0[34]	0	0	0.0[34]	0	0	97[34]
31	Mbaye 2006[48]	Farafenni, The Gambia	2002-2004	46.8[84]	0	0	0.02[84]	0	0	0.0[96]	~260 (Thies & Tambacounda Senegal)	0 (2003)	22[96]
32	Menendez 2008[49]	Manhica district, Mozambique	2003-2005	62.9[97]	0 (Manhica)	0 (2002-2005)	68.6[97]	0 (Manhica)	0 (2002-2005)	0.0[85]	50 (Magude)	0 (2004-2005)	70[97]‡ ~500[85]
33	Minja 2013[50]	Korogwe, Tanzania	2008-2010	100[50]	0	0	87.5[50]	0	0	42.9[50]	0	0	581: 28[50]
34	Moleins 2010[17]	Oussouye, Senegal	2007-2008	43.0[84]	0	0	0.06[84]	0	0	0.0[98]	~440 (Thies)	0 (2008)	93[98]
35	Mosha 2014[51]	Moshi & Rufiji, Tanzania	2012-2012	93.2[84]	0	0	88.3[99]	0-500 (Rufiji, Misungwi)	-1 (2010-2011)	2.7[99]	0-500 (Rufiji, Misungwi)	-1 (2010-2011)	Mean†: 224[99]
36	Msyamboza 2009[52]	Chikwawa, Malawi	2002-2004	87.0[84]	0	0	92.7[84]	0	0	0.0[100]	~70 (Chileka)	0 (2003-2005)	95[100]
37	Muhammad 2016[53]	Nguru, Yobe state, Nigeria	2014-2014	24.5[101]	~ 1200 (Parakou, Benin)	-2 (2012)	0.0[101]	~ 1200 (Parakou, Benin)	-2 (2012)	0.0[93]			192[101]
38	Mwangi 2015[54]	South West Kisumu, Nyanza, Kenya	2011-2013	93.0[34]	~70 (Siaya county)	0 (2011-2012)	95.6[34]	~70 (Siaya county)	0 (2011-2012)	5.7[34]	~70 (Siaya county)	0 (2011-2012)	53[34]
39	Mwapasa 2004[55]	Blantyre, Malawi	2000-2002	80.2[84]	0	0	85.3[84]	0	0	0.0[90]	0 (Ndirande)	0 (1999-2001)	550[90]
40	Namusoke 2010[56]	Kampala, Uganda	2004-2005	93.5[84]	0	0	95.1[84]	0	0	0.0[102]	~200 (Tororo)	0 (2003-2006)	55[102]§
41	Ndeserua 2015[57]	Rufiji, Tanzania	2012-2012	75.0[103]	0	-1 (2010-2011)	76.3[99]	0	-1 (2010-2011)	0.0[99]	0	-1 (2010-2011)	96-97[99,103]
42	Nduka 2011[3]	Umuahia, Afikpo, Okigwe, Nigeria	2009-2009	84.2[79]	~130 (Enugu)	+1 (2010)	0.0[79]	~130 (Enugu)	+1 (2010)	47.4[79]	~130 (Enugu)	+1 (2010)	38[79]
43	Ndyomugyenyi 2011[58]	Kabale district, Uganda	2004-2007	100.0[104]	~70 (Bufundi)	0 (2005)	100.0[104]	~70 (Bufundi)	0 (2005)	45.0[104]	~70 (Bufundi)	0 (2005)	60[104]
44	Nganda 2004[59]	Kibaha, Tanzania	2003-2003	19.8[105]	~20 (Mlandizi)	-1 (2002)	23.6[105]	~20 (Mlandizi)	-1 (2002)	0.0[105]	~20 (Mlandizi)	-1 (2002)	106[105]
45	Njagi 2002[60]	Bondo, Kenya	1997-1999	42.8[106]	~60 (Kisumu)	0 (1996-2000)	31.1[106]	~60 (Kisumu)	0 (1996-2000)	0.0[106]	~60 (Kisumu)	0 (1996-2000)	180[106]
46	Oduro 2010[18]	Navrongo, Ghana	2006-2007	53.8[92]	0	0 (2007-2008)	0.0[92]	0	0 (2007-2008)	0.0[92]	0	0 (2007-2008)	39[92]
47	Olliaro 2008[61]	Mlomp, Senegal	2000-2007	39.3[84]	0	0	0.03[84]	0	0	0.0[96]	~410 (Thies)	0 (2003 & 2008)	108[98]

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[19]	Ibadan, Nigeria	2010-2010	92.4[79]	0 (Ibadan)	-2 (2007-2008)	1.0[79]	0 (Ibadan)	-2 (2007-2008)	2.5[79]	0 (Ibadan)	-2 (2007-2008)	198[79]
49	Onyebuchi 2014[62]	Abakaliki, Nigeria	2012-2012	84.2[79]	~70 (Enugu)	-2 (2010)	0.0[79]	~70 (Enugu)	-2 (2010)	47.4[79]	~70 (Enugu)	-2 (2010)	38[79]
50	Orobaton 2016[63]	Sokoto State, Nigeria	2014-2015	47.4[101]	~620 (Parakou, Benin)	-2 (2012)	0.0[101]	~620 (Parakou, Benin)	-2 (2012)	0.0[93,107]			192[101]
51	Parise 1998[64]	Kisumu, Kenya	1994-1996	42.8[106]	0 (Kisumu)	0 (1996-2000)	31.1[106]	0 (Kisumu)	0 (1996-2000)	0.0[106]	0 (Kisumu)	0 (1996-2000)	180[106]
52	Ramharter 2007[65]	Lambarene, Libreville, Gabon	2005-2006	57.9[108]	0 (Lambarene)	0 (2005-2007)	3.3[108]	0 (Lambarene)	0 (2005-2007)	0.0[108]	0 (Lambarene)	0 (2005-2007)	121[108]
53	Rogawski 2012[66]	Blantyre	1997-2006	80.2[84]	0	0	85.3[84]	0	0	0.0[90]	0 (Ndirande)	0 (1999-2001)	550[90]
54	Rogerson 2000[67]	Blantyre, Malawi	1997-1999	63.6[84]	0	0	74.0[84]	0	0	0.0[90]	0 (Ndirande)	0 (1999-2001)	550[90]
55	Sirima 2006[68]	Koupela district, Burkina Faso	2004-2004	48.1[84]	0	0	0.1[84]	0	0	0.0[33]	~120 (Ziniare)	+6 (2010-2011)	273[33]
56	Suleiman 2003[69]	Wad Medani, Sudan	1999-2001	13.3[109]	~190 (Khartoum)	-2 (1996-1997)	0.0[109]	~190 (Khartoum)	-2 (1996-1997)	0.0[109]	~190 (Khartoum)	-2 (1996-1997)	45[109]
57	Tetteh-Ashong 2005[70]	Chikwawa, Malawi	2005-2005	94.1[84]	0	0	94.8[84]	0	0	0.0[100]	~70 (Chileka)	0 (2003-2005)	95[100]
58	Tonga 2013[71]	Sanaga-Maritime, Cameroon	2011-2012	76.5[110]	~180 (Yaounde)	0 (2010-2011)	0.0[110]	~180 (Yaounde)	0 (2010-2011)	5.9[110]	~180 (Yaounde)	0 (2010-2011)	51[110]
59	Tongo 2011[72]	Ibadan, Nigeria	2007-2008	92.4[79]	0 (Ibadan)	0 (2007-2008)	1.0[79]	0 (Ibadan)	0 (2007-2008)	2.5[79]	0 (Ibadan)	0 (2007-2008)	198[79]
60	Toure 2014[15]	Abidjan and Comoe districts, Cote d'Ivoire	2009-2010	52.1[111]	0 (Abidjan)	-1 (2008)	0.9[111]	0 (Abidjan)	-1 (2008)	0.9[111]	0 (Abidjan)	-1 (2008)	94[111]
61	Tutu 2011[73]	Offinso district, Ghana	2005-2007	77.6[112]	~60 (Sunyani)	0 (2005-2008)	0.0[112]	~60 (Sunyani)	0 (2005-2008)	0.0[92]	~60 (Sunyani)	0 (2007-2008)	85[112] 49[92]
62	Vanga-Bosson 2011[74]	Cote d'Ivoire	2008-2008	52.1[111]	0 (Abidjan)	0 (2008)	0.9[111]	0 (Abidjan)	0 (2008)	0.9[111]	0 (Abidjan)	0 (2008)	94[111]
63	van Eijk 2004[14]	Kisumu, Kenya	1999-2000	42.8[106]	0 (Kisumu)	0 (1996-2000)	31.1[106]	0 (Kisumu)	0 (1996-2000)	0.0[106]	0 (Kisumu)	0 (1996-2000)	180[106]
64	Van Spronsen 2012[75]	Gushegu, Ghana	2010-2010	73.0[84]	0	0	0.7[84]	0	0	0.0[92]	~ 200 (Navrongo)	-2 (2008)	39[92]
65	Verhoeff 1998[76]	Chikwawa, Malawi	1993-1994	34.4[84]	0	0	34.2[84]	0	0	0.0[90]	~50 (Ndirande)	+7 (1999-2001)	550[90]
66	Yussuf 2010[77]	Lindi, Tanzania	2009-2010	79.7[84]	0	0	72.7[99]	~150 (Nachingwea)	0 (2010-2011)	0.0[99]	~150 (Nachingwea)	0 (2010-2011)	88[99]

*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;[84] and 3) for *Pfdhps*-A581G, or for studies after 2012, data were used from existing population prevalence maps of *Pfdhps* (Table S2).[113-116]

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),[21] Ado Ekiti, Nigeria in 2011; reference Oguike et al. (2016),[79] Enugu, Nigeria, 2010, ~400 km away; 2) Alli *et al.* (2013),[22] Kubwa, Nigeria in 2010-2011; reference Oguike et al. (2016),[79] Enugu, Nigeria, 2010, ~400 km away, 3) Muhammad *et al*. (2016),[53] Nguru, Yobe State, Nigeria in 2014; reference Ogouyemi-Hounto *et al*. (2013)[101] Parakou,Benin, 2012, ~1200 km away; 4) Orobaton *et al.* (2016),[63] Sokoto, Nigeria in 2014-15; reference Ogouyemi-Hounto *et al*. (2013)[101] ~620 km away. For Moshi in Tanzania in 2012 (Mosha *et al.* 2014)[51] 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,[22] Nigeria	Kubwa	2010-2011	0,1+	4/158 (2.5)	0	0/42 (0.0)	1.3					
Arinaitwe 2014,[25] Uganda	Tororo	2011-2011	01,2+	29/227 (12.8)	0.9	25/325 (7.7)	2					
Aziken 2010,[26] Nigeria	Benin City	2009-2009	0,1+	61/371 (16.4)	0	14/370 (3.8)	1.6					
Bouyou-Akotet 2010,[27] Gabon	Libreville	2005-2006	0,1+	24/120 (20.0)	0	11/83 (13.3)	1.6					a
Bouyou-Akotet 2016,[28] 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,[29] 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,[30] Mozambique	Gaza	2005-2007	0,3+	756/8650 (8.7)	0	488/6645 (7.3)	3					c
Challis 2004,[31] Mozambique	Maputo	2001-2002	0,2+	27/203 (13.3)	0	19/200 (9.5)	2					
Coulibaly 2014,[34] 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,[34] 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,[36] Nigeria	Ibadan	2003-2004	0,1+	16/171 (9.4)	0	31/595 (5.2)	1.8					
Famanta 2011,[37] Mali	Bamako	2009-2009	0,1,2+	16/102 (15.7)	0	8/107 (7.5)	1	17/150 (11.3)				b
Feng 2010,[39] 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, [39] 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, [39] 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,[40] 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,[34] 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,[41] 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,[16] 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,[42] Nigeria	Enugu State	2013-2013	0,1+	8/101 (7.9)	0	7/315 (2.2)	2.2					d
Kayentao 2014,[44] Mali	San	2006-2006	0,1,2+	15/135 (11.1)	0	10/177 (5.6)	1	4/86 (4.7)	2			
Kayentao 2014, [44] Mali	Koro	2006-2007	0,1,2+	13/130 (10.0)	0	10/131 (7.6)	1	4/90 (4.4)	2			
Kayentao 2014,[34] Mali	Kita	2009-2010	0,1,2+	18/124 (14.5)	0	14/121 (11.6)	1	24/299 (8.0)	2			
Kayentao 2014,[34] 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, [44] Mali	Bougouni	2006-2007	0,1,2+	11/101 (10.9)	0	10/182 (5.5)	1	7/124 (5.6)	2			
Kayentao 2014, [44] Mali	Djenne	2006-2006	0,1,2+	10/110 (9.1)	0	6/106 (5.7)	1	7/139 (5.0)	2			
Kilauzi 2013,[45] DRC	Kinshasa	2011-2011	0,1+	21/204 (10.3)	0	32/501 (6.4)	1					
Likwela 2012,[46] DRC	Mikalayi	2007-2007	01,2+	35/363 (9.6)	0.5	2/114 (1.8)						e
Likwela 2012,[46] DRC	Rutsuhuru	2007-2007	01,2+	16/177 (9.0)	0.5	39/493 (7.9)						e
Likwela 2012,[46] 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,[47] 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,[48] Gambia	Farafenni	2002-2004	0,2+	46/716 (6.4)	0	40/738 (5.4)	2.7					
Menendez 2008,[49] Mozambique	Manhica	2003-2005	0,2+	49/411 (11.9)	0	41/382 (10.7)	2					
Minja 2013,[50] Tanzania	Korogwe	2008-2010	01,2+	4/17 (23.5)	0.5	43/705 (6.1)	2					
Moleins 2010,[17] Senegal	Oussouye	2007-2008	01,2+	6/55 (10.9)	0.2	6/96 (6.3)	1.9					
Mosha 2014,[51] Tanzania	Rufiji/Moshi	2012-2012	01,2+	9/169 (5.3)	0.8	9/181 (5.0)	2					b
Msyamboza 2009,[52] 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,[53] Nigeria	Nguru, Yobe State	2014-2014	01,2+	58/104 (55.8)	0.9	10/80 (12.5)	2					b
Namusoke 2010,[56] Uganda	Kampala	2004-2005	0,1,2+	28/162 (17.3)	0	15/118 (12.7)	1	4/41 (9.8)	2			
Ndeserua 2015,[57] Tanzania	Rufiji	2012-2012	01,2+	12/166 (7.2)	0.9	10/184 (5.4)	2					
Ndyomugyenyi 2011,[58] Uganda	Kabale	2004-2007	0,2+	99/1577 (6.3)	0	107/1561 (6.9)	2					
Njagi 2002,[60] Kenya	Bondo	1997-1999	0,2+	51/359 (14.2)	0	46/369 (12.5)	2					
Oduro 2010,[18] 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,[61] Senegal	Mlomp	2000-2007	0,1,2+	57/532 (10.7)	0	7/63 (11.1)	1	22/309 (7.1)	2			
Olorunda 2013,[19] Nigeria	Ibadan	2010-2010	0,1+	22/246 (8.9)	0	4/84 (4.8)	1.2					
Parise 1998,[64] 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,[65] 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,[68] 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,[69] Sudan	Wad Medani	1999-2001	0,2+	19/53 (35.8)	0	2/57 (3.5)	2					
Tetteh-Ashong 2005,[70] 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,[71] 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,[72] Nigeria	Ibadan	2007-2008	01,2+	68/649 (10.5)	0.1	4/147 (2.7)	2					b
Toure 2014,[15] 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,[73] 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,[74] 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,[77] 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,[14] 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)
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)
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)
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)
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)
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)
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, %
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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
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

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
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
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 (range)		
			***Pfdhps*-A437G**	***Pfdhps*-K540E**	***Pfdhps*-A581G**
Any level	West & Central	31	57.9 (15.2-100.0)	0.1 (0.0-18.9)	0.0 (0.0-52.6)
	East & southern	26	85.4 (13.3-100.0)	85.8 (0.0-100)	0.0 (0.0-45.6)
	Overall	57	74.1 (13.3-100.0)	3.3 (0.0-100.0)	0.0 (0.0-52.6)
Low*	West & Central	27	52.1 (15.2-84.6)	0.0 (0.0-11.3)	0.0 (0.0-47.4)
	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 (13.3-84.6)	0.1 (0.0-27.8)	0.0 (0.0-47.4)
Moderate*	West & Central	4	94.6 (92.4-100.0)	1.0 (0.0-18.9)	5.3 (2.5-52.6)
	East & southern	12	69.3 (42.8-100.0)	73.4 (31.1-88.3)	0.0 (0.0-42.9)
	Overall	16	80.0 (42.8-100.0)	58.1 (0.0-88.3)	0.0 (0.0-52.6)
High*	West & Central	0	NA	NA	NA
	East & southern	11	94.1 (87.0-100.0)	95.1 (90.2-100.0)	2.0 (0.0-45.6)
	Overall	11	94.1 (87.0-100.0)	95.1 (90.2-100.0)	2.0 (0.0-45.6)

* 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

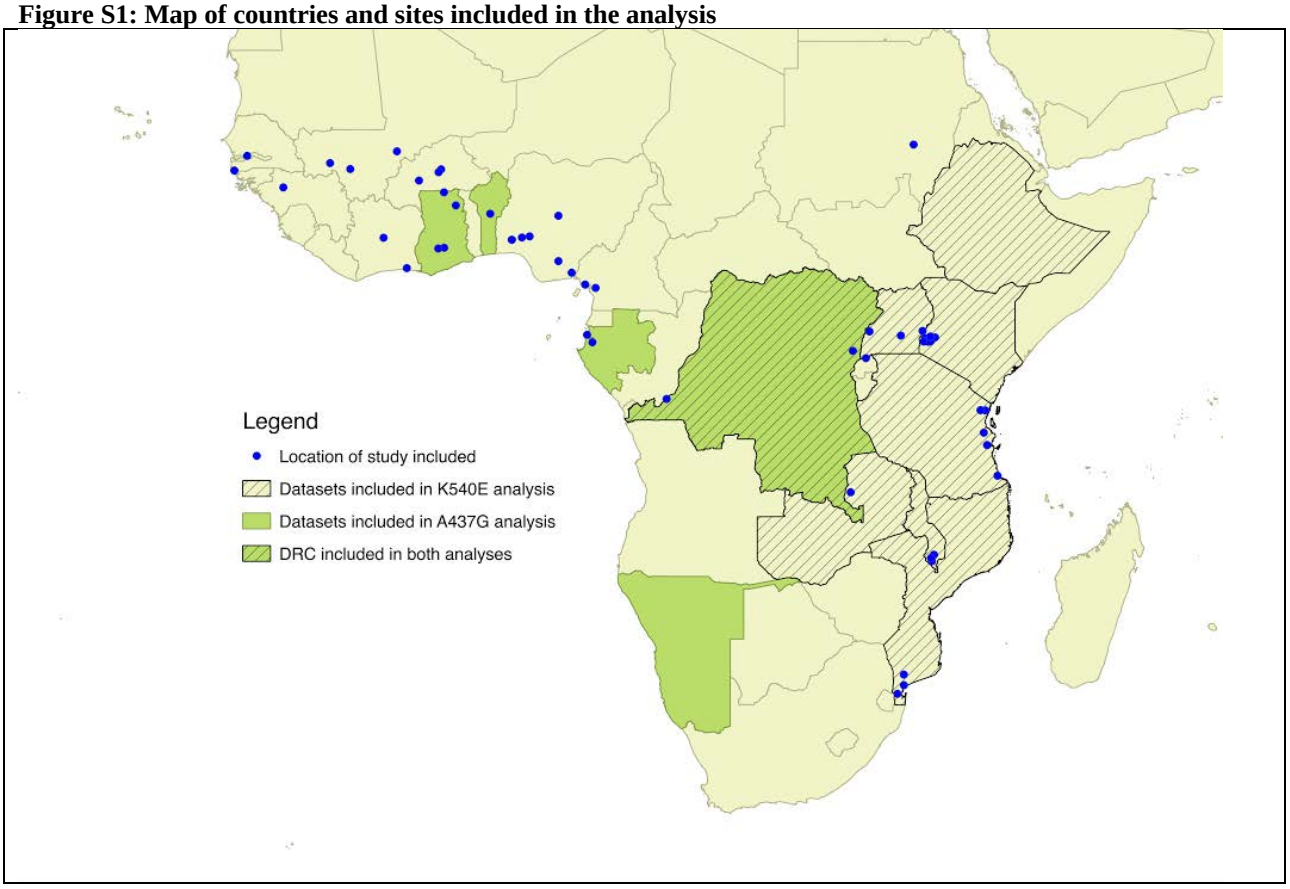
Abbreviations: DRC=Democratic Republic of the Congo.

[a]Coverage estimates derived from publications

[b]Rwanda ended IPTp as national policy in 2008

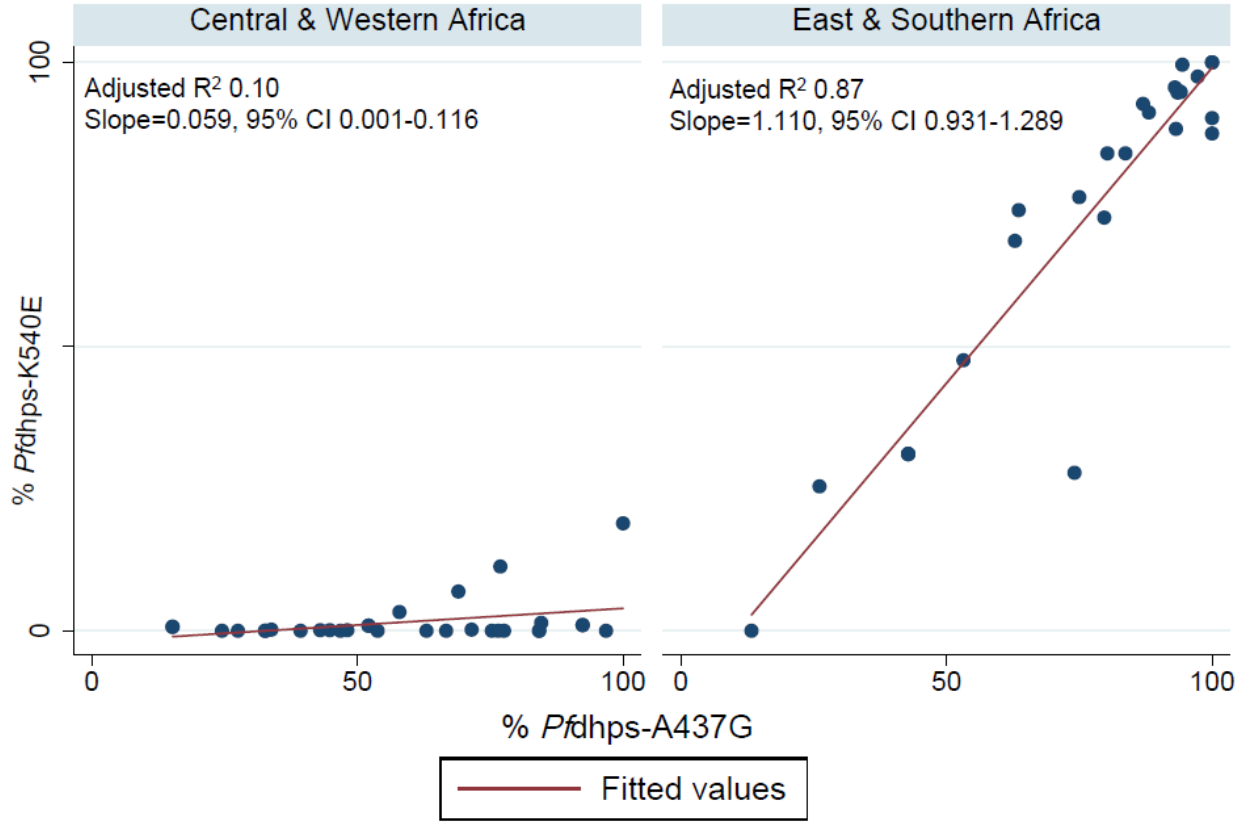
Supplemental Figures

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



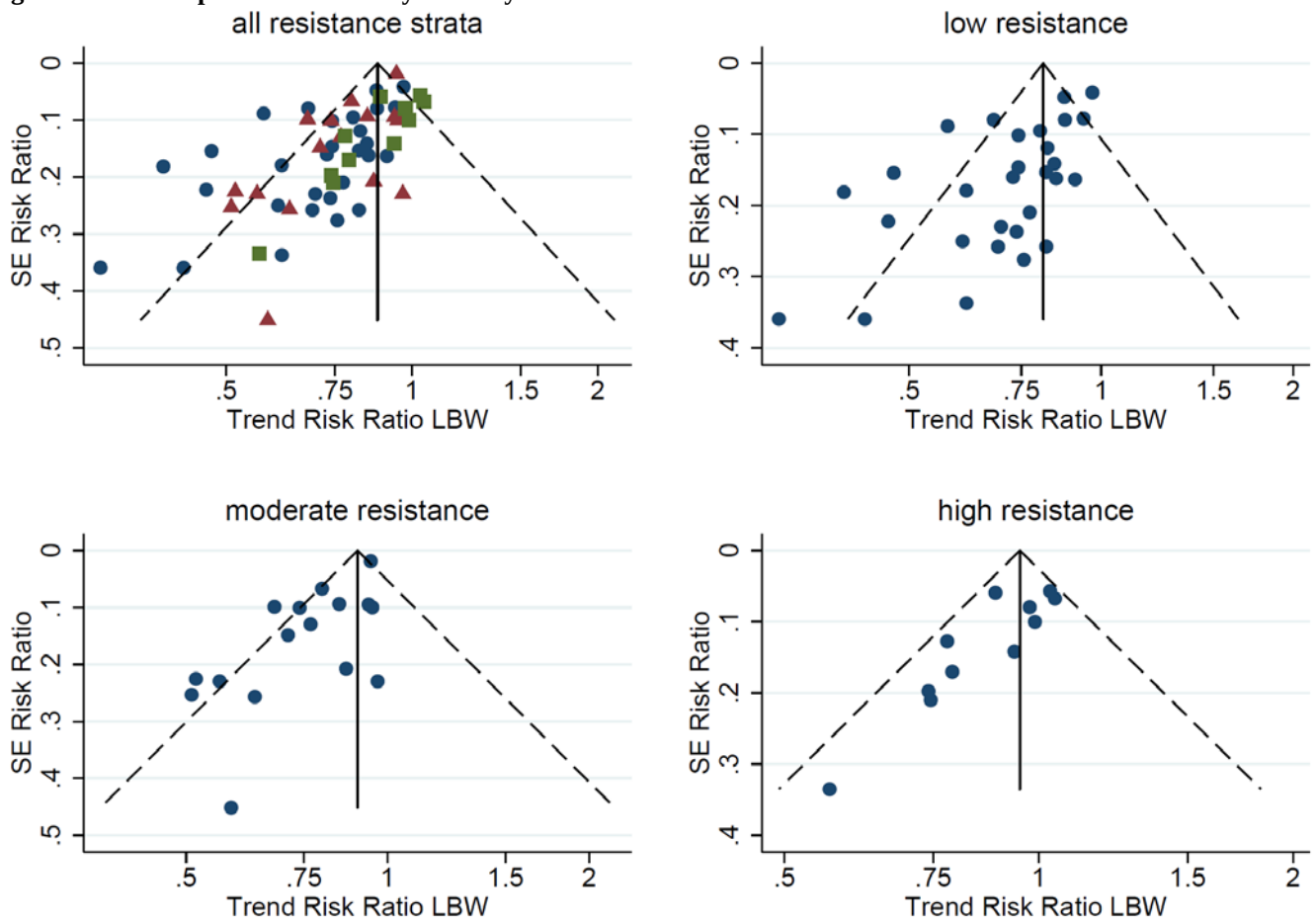
Blue dots represent the location of studies included in the aggregated data meta-analysis. Green and shaded areas represent countries with national survey data included in the individual participant data meta-analysis.

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

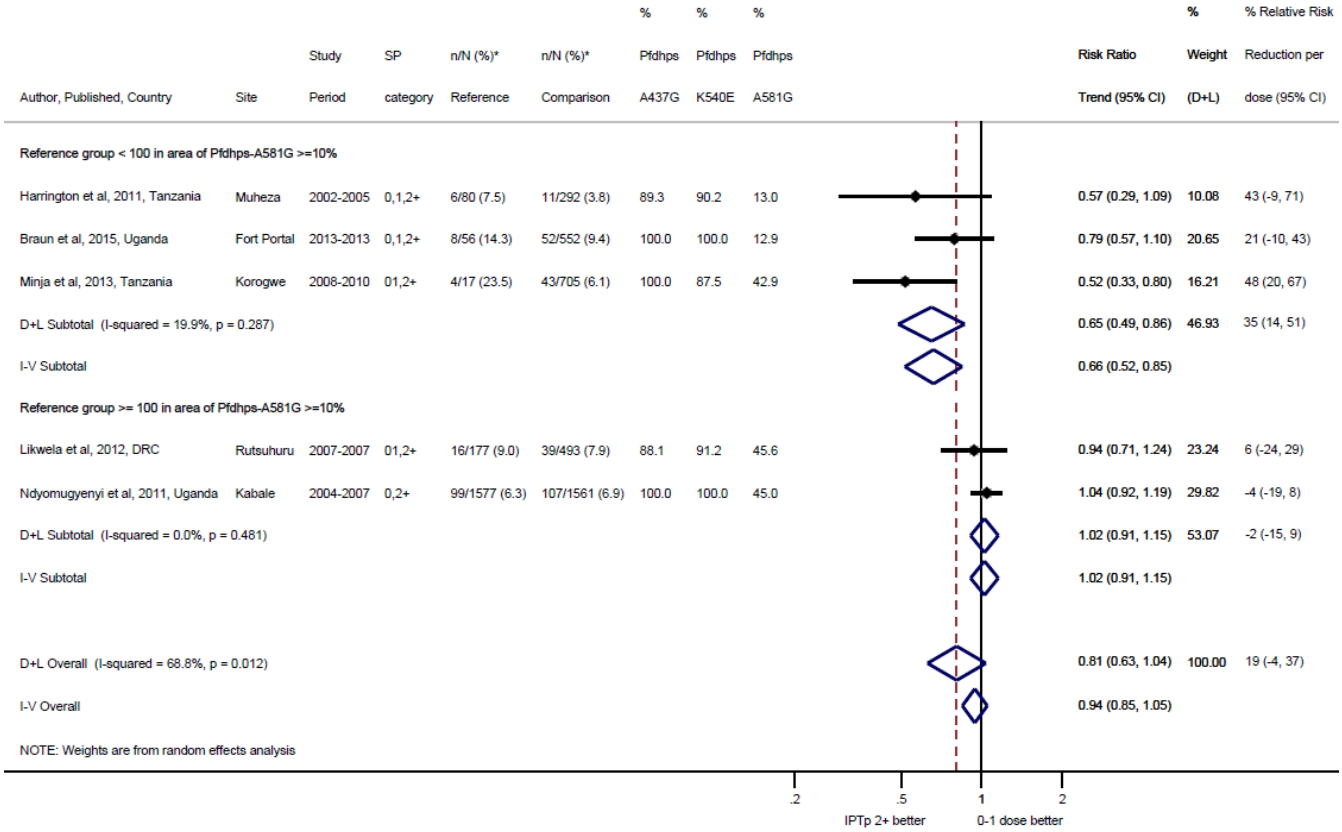
Figure S3: Funnel plots of small study effect by resistance strata



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.

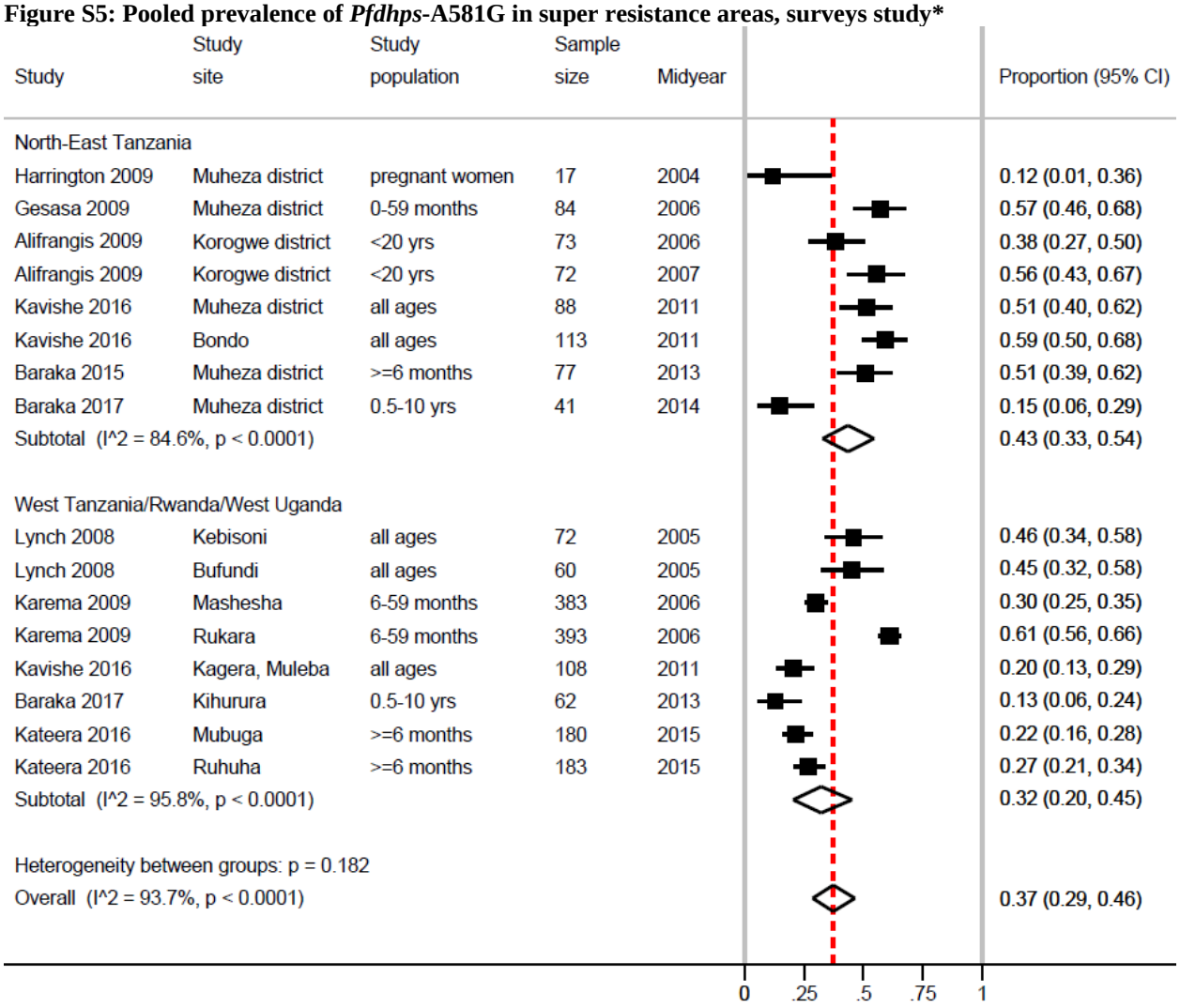
Figure S4: Meta-analysis of the risk of low birthweight associated with each incremental dose of IPTp-SP in all gravidae by sample size in areas with a high prevalence of *Pfdhps*-A581G, clinical studies



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.[13]

Supplemental References

1. Malaria in Pregnancy Consortium. Malaria in Pregnancy Library. 2018. http://library.mip-consortium.org (accessed September 18, 2018).
2. Fehintola AO, Fehintola FO, Loto OM, Fasubaa OB, Bakare B, Ogundele O. Pregnancy and fetal outcome of placental malaria parasitemia in Ile-Ife, Nigeria. *Trop J Obstet Gynaecol* 2016; **33**: 310–6.
3. Nduka FO, Nwosu E, Oguariri RM. Evaluation of the effectiveness and compliance of intermittent preventive treatment (IPT) in the control of malaria in pregnant women in south eastern Nigeria. *Ann Trop Med Parasitol* 2011; **105**: 599–605.
4. van Eijk AM, Hill J, Povall S, Reynolds A, Wong H, Ter Kuile FO. The Malaria in Pregnancy Library: a bibliometric review. *Malar J* 2012; **11**: 362.
5. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003; **327**: 557–60.
6. Deeks JJ, Higgins JP, Altman DG. Analysing data and undertaking meta-analyses. In: Higgins JP, Green S, editors. Cochrane handbook for systematic reviews of interventions (version 5.1.0): The Cochrane Collaboration; 2011.
7. Borenstein M, Hedges LS, Higgens JPT, Rothstein HR. Chapter 30 Publication Bias. Introduction to meta-analysis. Chichester, United Kingdom: John Wiley & Sons, Ltd; 2009.
8. Eisele TP, Larsen DA, Anglewicz PA, et al. Malaria prevention in pregnancy, birthweight, and neonatal mortality: a meta-analysis of 32 national cross-sectional datasets in Africa. *Lancet Infect Dis* 2012; **12**: 942–9.
9. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. *Am J Epidemiol* 1992; **135**: 1301–9.
10. Orsini N, Li R, Wolk A, Khudyakov P, Spiegelman D. Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software. *Am J Epidemiol* 2012; **175**: 66–73.
11. Kalilani L, Taylor S, Madanitsa M, et al. Waning effectiveness of intermittent preventive treatment in pregnancy (IPTp) with sulphadoxine-pyrimethamine (SP) in the presence of high SP Resistance in Malawi. *Am J Trop Med Hyg* 2011; **85**: 354-5 (abstr).
12. Gutman G, Mwandama D, Wiegand RE, Ali D, Mathanga DP, Skarbinski J. Effectiveness of intermittent preventive treatment with sulfadoxine-pyrimethamine in pregnancy on maternal and infant birth outcomes in Machinga District, Malawi. *J Infect Dis* 2013; **208**: 907–16.
13. Nyaga VN, Arbyn M, Aerts M. Metaprop: a Stata command to perform meta-analysis of binomial data. *Arch Public Health* 2014; **72**: 39.
14. van Eijk AM, Ayisi JG, ter Kuile FO, et al. Effectiveness of intermittent preventive treatment with sulphadoxine-pyrimethamine for control of malaria in pregnancy in western Kenya: a hospital-based study. *Trop Med Int Health* 2004; **9**: 351–60.
15. Toure OA, Kone PL, Coulibaly ML, et al. Coverage and efficacy of intermittent preventive treatment with sulphadoxine pyrimethamine against malaria in pregnancy in Cote d'Ivoire five years after its implementation. *Parasit Vectors* 2014; **7**: 495.
16. Hommerich L, von Oertzen C, Bedu-Addo G, et al. Decline of placental malaria in southern Ghana after the implementation of intermittent preventive treatment in pregnancy. *Malar J* 2007; **6**: 144.
17. Moleins I, Agnamey P. Malaria and pregnancy: impact of ontermittent preventive treatment with sulfadoxine-pyrimethamine on weight at birth at the Oussouye maternity (Casamance, Senegal). *Revue Sage-Femme* 2010; **9**: 123–7.
18. Oduro AR, Fryauff DJ, Koram KA, et al. Sulfadoxine-pyrimethamine-based intermittent preventive treatment, bed net use, and antenatal care during pregnancy: demographic trends and impact on the health of newborns in the Kassena Nankana District, northeastern Ghana. *Am J Trop Med Hyg* 2010; **83**: 79–89.
19. Olorunda DC, Ajayi IO, Falade CO. Do frequent antenatal care visits ensure access and adherence to intermittent preventive treatment of malaria in pregnancy in an urban hospital in South West Nigeria? *Afr J Biomed Res* 2013; **16**: 153–61.
20. Oxford Big Data Institute, University of Oxford. The Malaria Atlas Project. 2018. http://www.map.ox.ac.uk/ (accessed September 18, 2018).
21. Aduloju OP, Ade-Ojo IP, Olaogun OD, Olofinbiyi BA, Akintayo AA. Effect of intermittent preventive treatment of malaria on the outcome of pregnancy among women attending antenatal clinic of a Nigerian Teaching Hospital. *Trop J Obstet Gynaecol* 2013; **30**: 7–15.
22. Alli LA, Isah AY, Jamda MA, Adesokan AA. Use of intermittent preventive treatment for malaria among pregnant women in Kubwa, Abuja, Nigeria. *Int J Trop Dis Health* 2013; **3**: 339–45.

23. Anchang-Kimbi JK, Achidi EA, Nkegoum B, Sverremark-Ekstrom E, Troye-Blomberg M. Diagnostic comparison of malaria infection in peripheral blood, placental blood and placental biopsies in Cameroonian parturient women. *Malar J* 2009; **8**: 126.
24. Apinjoh TO, Anchang-Kimbi JK, Mugri RN, et al. Determinants of infant susceptibility to malaria during the first year of life in South Western cameroon. *Open Forum Infect Dis* 2015; **2**: ofv012.
25. Arinaitwe E, Ades V, Walakira A, et al. Intermittent preventive therapy with sulfadoxine-pyrimethamine for malaria in pregnancy: a cross-sectional study from Tororo, Uganda. *PLoS One* 2013; **8**: e73073.
26. Aziken ME, Akubuo KK, Gharoro EP. Efficacy of intermittent preventive treatment with sulfadoxine-pyrimethamine on placental parasitemia in pregnant women in midwestern Nigeria. *Int J Gynaecol Obstet* 2011; **112**: 30–3.
27. Bouyou-Akotet MK, Nzenze-Afene S, Ngoungou EB, et al. Burden of malaria during pregnancy at the time of IPTp/SP implementation in Gabon. *Am J Trop Med Hyg* 2010; **82**: 202–9.
28. Bouyou-Akotet MK, Mawili-Mboumba DP, Kendjo E, et al. Decrease of microscopic *Plasmodium falciparum* infection prevalence during pregnancy following IPTp-SP implementation in urban cities of Gabon. *Trans R Soc Trop Med Hyg* 2016; **110**: 333–42.
29. Braun V, Rempis E, Schnack A, et al. Lack of effect of intermittent preventive treatment for malaria in pregnancy and intense drug resistance in western Uganda. *Malar J* 2015; **14**: 372.
30. Cassam Y. The effect of falciparum malaria prevalence on the effectiveness of intermittent preventive treatment with sulfadoxine-pyrimethamine during pregnancy in reducing low birth weight in southern Mozambique. Pretoria, South Africa: University of Pretoria; 2007. https://repository.up.ac.za/handle/2263/29732 (accessed September 18, 2018).
31. Challis K, Osman NB, Cotiro M, Nordahl G, Dgedge M, Bergstrom S. Impact of a double dose of sulphadoxine-pyrimethamine to reduce prevalence of pregnancy malaria in southern Mozambique. *Trop Med Int Health* 2004; **9**: 1066–73.
32. Chukwuocha UM, Nwakwuo GC, Alinnor LO. Knowledge and utilization of preventive measures in the control of neonatal malaria in south-eastern Nigeria. *Tanzan J Health Res* 2016; **18**: 1–8.
33. Coulibaly SO, Kayentao K, Taylor S, et al. Parasite clearance following treatment with sulphadoxine-pyrimethamine for intermittent preventive treatment in Burkina-Faso and Mali: 42-day in vivo follow-up study. *Malar J* 2014; **13**: 41.
34. Desai M, Gutman J, Taylor SM, et al. Impact of sulfadoxine-pyrimethamine resistance on effectiveness of intermittent preventive therapy for malaria in pregnancy at clearing infections and preventing low birth weight. *Clin Infect Dis* 2016; **62**: 323–33.
35. Douamba Z, Dao NG, Zohoncon TM, et al. Mother-to-children *Plasmodium falciparum* asymptomatic malaria transmission at Saint Camille Medical Centre in Ouagadougou, Burkina Faso. *Malar Res Treat* 2014; **2014**: 390513.
36. Falade CO, Yusuf BO, Fadero FF, Mokuolu OA, Hamer DH, Salako LA. Intermittent preventive treatment with sulphadoxine-pyrimethamine is effective in preventing maternal and placental malaria in Ibadan, south-western Nigeria. *Malar J* 2007; **6**: 88.
37. Famanta A, Diakite M, Diawara SI, et al. Prevalence of maternal and placental malaria and of neonatal low birth weight in a semi-urban area of Bamako (Mali). *Sante* 2011; **21**: 3–7.
38. Fehintola AO. Prevalence and risk factors for placental parasitaemia at delivery among pregnant women in Ile Ife, Nigeria. *Int J Clin Med Cancer Res* 2015.
39. Feng G, Simpson JA, Chaluluka E, Molyneux ME, Rogerson SJ. Decreasing burden of malaria in pregnancy in Malawian women and its relationship to use of intermittent preventive therapy or bed nets. *PLoS One* 2010; **5**: e12012.
40. Gies S, Coulibaly SO, Ouattara FT, D'Alessandro U. Individual efficacy of intermittent preventive treatment with sulfadoxine-pyrimethamine in primi- and secundigravidae in rural Burkina Faso: impact on parasitaemia, anaemia and birth weight. *Trop Med Int Health* 2009; **14**: 174–82.
41. Harrington WE, Mutabingwa TK, Kabyemela E, Fried M, Duffy PE. Intermittent treatment to prevent pregnancy malaria does not confer benefit in an area of widespread drug resistance. *Clin Infect Dis* 2011; **53**: 224–30.
42. Igboeli NU, Ukwe CV, Aguwa CN. Effect of antimalarial prophylaxis with sulphadoxine-pyrimethamine on pregnancy outcomes in Nsukka, Nigeria. *MalariaWorld J* 2017; **8**: 3.
43. Inyang-Etoh EC, Agan TU, Etuk SJ, Inyang-Etoh PC. The role of prophylactic antimalarial in the reduction of placental parasitemia among pregnant women in Calabar, Nigeria. *Niger Med J* 2011; **52**: 235–8.
44. Kayentao K. Burden of malaria in pregnancy in Mali and impact of dosing frequency and antimalarial drug resistance on the effectiveness of intermittent preventive therapy in pregnancy in Africa.

Liverpool, UK: Liverpool School of Tropical Medicine; 2014. https://livrepository.liverpool.ac.uk/17795/ (accessed September 18, 2018).
45. Kilauzi AL, Mulumba JGT, Matindii BA, Tamfum JJM, Ngongo LO, Mengema B. Field utilization patterns of insecticide-treated net and intermittent preventive treatment with sulphadoxine-pyrimethamine in a resource poor endemic area: Patterns' associations with adverse mother or birth outcomes. *Ann Trop Med Public Health* 2013; **6**: 603–7.
46. Likwela JL, D'Alessandro U, Lokwa BL, Meuris S, Dramaix MW. Sulfadoxine-pyrimethamine resistance and intermittent preventive treatment during pregnancy: a retrospective analysis of birth weight data in the Democratic Republic of Congo (DRC). *Trop Med Int Health* 2012; **17**: 322–9.
47. Mace KE, Chalwe V, Katalenich BL, et al. Evaluation of sulphadoxine-pyrimethamine for intermittent preventive treatment of malaria in pregnancy: a retrospective birth outcomes study in Mansa, Zambia. *Malar J* 2015; **14**: 69.
48. Mbaye A, Richardson K, Balajo B, et al. A randomized, placebo-controlled trial of intermittent preventive treatment with sulphadoxine-pyrimethamine in Gambian multigravidae. *Trop Med Int Health* 2006; **11**: 992–1002.
49. Menendez C, Bardaji A, Sigauque B, et al. A randomized placebo-controlled trial of intermittent preventive treatment in pregnant women in the context of insecticide treated nets delivered through the antenatal clinic. *PLoS One* 2008; **3**: e1934.
50. Minja DT, Schmiegelow C, Mmbando B, et al. *Plasmodium falciparum* mutant haplotype infection during pregnancy associated with reduced birthweight, Tanzania. *Emerg Infect Dis* 2013; **19**: 1446–54.
51. Mosha D, Chilongola J, Ndeserua R, Mwingira F, Genton B. Effectiveness of intermittent preventive treatment with sulfadoxine-pyrimethamine during pregnancy on placental malaria, maternal anaemia and birthweight in areas with high and low malaria transmission intensity in Tanzania. *Trop Med Int Health* 2014; **19**: 1048–56.
52. Msyamboza KP, Savage EJ, Kazembe PN, et al. Community-based distribution of sulfadoxine-pyrimethamine for intermittent preventive treatment of malaria during pregnancy improved coverage but reduced antenatal attendance in southern Malawi. *Trop Med Int Health* 2009; **14**: 183–9.
53. Muhammad HU, Giwa FJ, Olayinka AT, et al. Malaria prevention practices and delivery outcome: a cross sectional study of pregnant women attending a tertiary hospital in northeastern Nigeria. *Malaria Journal* 2016; **15**: 326.
54. Mwangi MN, Roth JM, Smit MR, et al. Effect of daily antenatal iron supplementation on Plasmodium infection in Kenyan women: A randomized clinical trial. *JAMA* 2015; **314**: 1009–20.
55. Mwapasa V. The interactions between *Plasmodium falciparum* malaria and HIV-1 in pregnant Malawian women. Chapel Hill, Michigan: University of Michigan; 2004. https://deepblue.lib.umich.edu/handle/2027.42/124143 (accessed September 18, 2018).
56. Namusoke F, Rasti N, Kironde F, Wahlgren M, Mirembe F. Malaria burden in pregnancy at Mulago National Referral Hospital in Kampala, Uganda. *Malar Res Treat* 2010: Article ID 913857.
57. Ndeserua R, Juma A, Mosha D, Chilongola J. Risk factors for placental malaria and associated adverse pregnancy outcomes in Rufiji, Tanzania: a hospital based cross sectional study. *Afr Health Sci* 2015; **15**: 810–8.
58. Ndyomugyenyi R, Clarke SE, Hutchison CL, Hansen KS, Magnussen P. Efficacy of malaria prevention during pregnancy in an area of low and unstable transmission: an individually-randomised placebo-controlled trial using intermittent preventive treatment and insecticide-treated nets in the Kabale Highlands, southwestern Uganda. *Trans R Soc Trop Med Hyg* 2011; **105**: 607–16.
59. Nganda RY, Drakeley C, Reyburn H, Marchant T. Knowledge of malaria influences the use of insecticide treated nets but not intermittent presumptive treatment by pregnant women in Tanzania. *Malar J* 2004; **3**: 42.
60. Njagi JK. The effects of sulfadoxine-pyrimethamine intermittent treatment and pyrethroid impregnated bed nets on malaria morbidity in pregnancy and birth weight in Bondo district, Kenya. Nairobi, Kenya: University of Nairobi; 2002. http://uonlibrary.uonbi.ac.ke/content/effects-sulfadoxine-pyrimethamine-intermittent-treatment-and-pyrethroid-impregnated-bed-nets (accessed September 18, 2018).
61. Olliaro PL, Delenne H, Cisse M, et al. Implementation of intermittent preventive treatment in pregnancy with sulphadoxine/pyrimethamine (IPTp-SP) at a district health centre in rural Senegal. *Malar J* 2008; **7**: 234.
62. Onyebuchi AK, Lawani LO, Iyoke CA, Onoh CR, Okeke NE. Adherence to intermittent preventive treatment for malaria with sulphadoxine-pyrimethamine and outcome of pregnancy among parturients in South East Nigeria. *Patient Prefer Adherence* 2014; **8**: 447–52.
63. Orobaton N, Austin AM, Abegunde D, et al. Scaling-up the use of sulfadoxine-pyrimethamine for the preventive treatment of malaria in pregnancy: results and lessons on scalability, costs and programme impact from three local government areas in Sokoto State, Nigeria. *Malar J* 2016; **15**: 533.

64. Parise ME, Ayisi JG, Nahlen BL, et al. Efficacy of sulfadoxine-pyrimethamine for prevention of placental malaria in an area of Kenya with a high prevalence of malaria and human immunodeficiency virus infection. *Am J Trop Med Hyg* 1998; **59**: 813–22.
65. Ramharter M, Schuster K, Bouyou-Akotet MK, et al. Malaria in pregnancy before and after the implementation of a national IPTp program in Gabon. *Am J Trop Med Hyg* 2007; **77**: 418–22.
66. Rogawski ET, Chaluluka E, Molyneux ME, Feng G, Rogerson SJ, Meshnick SR. The effects of malaria and intermittent preventive treatment during pregnancy on fetal anemia in Malawi. *Clin Infect Dis* 2012; **55**: 1096–102.
67. Rogerson SJ, Chaluluka E, Kanjala M, Mkundika P, Mhango C, Molyneux ME. Intermittent sulfadoxine-pyrimethamine in pregnancy: effectiveness against malaria morbidity in Blantyre, Malawi, in 1997-99. *Trans R Soc Trop Med Hyg* 2000; **94**: 549–53.
68. Sirima SB, Cotte AH, Konate A, et al. Malaria prevention during pregnancy: assessing the disease burden one year after implementing a program of intermittent preventive treatment in Koupela District, Burkina Faso. *Am J Trop Med Hyg* 2006; **75**: 205–11.
69. Suleiman IEDE, Mohamadani AAA, Mirgani OA. Malaria propylaxis during pregnancy in primigravidae using sulfadoxine/pyimethamine in Wad Medani - Sudan. *Gezira J Health Sci* 2003; **1**: 1–9.
70. Tetteh-Ashong E. Evaluation of a screening method to assess the efficacy of intermittent preventive treatment with SP in pregnant women in Malawi. Liverpool, UK: Liverpool School of Tropical Medicine; 2005. (accessed September 18, 2018).
71. Tonga C, Kimbi HK, Anchang-Kimbi JK, Nyabeyeu HN, Bissemou ZB, Lehman LG. Malaria risk factors in women on intermittent preventive treatment at delivery and their effects on pregnancy outcome in Sanaga-Maritime, Cameroon. *PLoS One* 2013; **8**: e65876.
72. Tongo OO, Orimadegun AE, Akinyinka OO. Utilisation of malaria preventive measures during pregnancy and birth outcomes in Ibadan, Nigeria. *BMC Pregnancy Childbirth* 2011; **11**: 60.
73. Tutu EO, Browne E, Lawson B. Effect of sulphadoxine-pyrimethamine on neonatal birth weight and perceptions on its impact on malaria in pregnancy in an intermittent preventive treatment programme setting in Offinso District, Ghana. *Int Health* 2011; **3**: 206–12.
74. Vanga-Bosson HA, Coffie PA, Kanhon S, et al. Coverage of intermittent prevention treatment with sulphadoxine-pyrimethamine among pregnant women and congenital malaria in Cote d'Ivoire. *Malar J* 2011; **10**: 105.
75. van Spronsen JH, Schneider TA, Atasige S. Placental malaria and the relationship to pregnancy outcome at Gushegu District Hospital, Northern Ghana. *Trop Doct* 2012; **42**: 80–4.
76. Verhoeff FH, Brabin BJ, Chimsuku L, Kazembe P, Russell WB, Broadhead RL. An evaluation of the effects of intermittent sulfadoxine-pyrimethamine treatment in pregnancy on parasite clearance and risk of low birthweight in rural Malawi. *Ann Trop Med Parasitol* 1998; **92**: 141–50.
77. Yussuf SM. Effect of intermitent preventive treatment (IPTp) using sulphadoxine pyrimethamine (SP) on birth weight, Lindi region, 2009. Dar es Salaam, Tanzania: Muhimbili University of Health and Allied Sciences; 2010. http://ir.muhas.ac.tz:8080/jspui/handle/123456789/1059 (accessed September 18, 2018).
78. UNAIDS. AIDSinfo. 2017. http://aidsinfo.unaids.org (accessed September 18, 2018).
79. Oguike MC, Falade CO, Shu E, et al. Molecular determinants of sulfadoxine-pyrimethamine resistance in *Plasmodium falciparum* in Nigeria and the regional emergence of dhps 431V. *Int J Parasitol Drugs Drug Resist* 2016; **6**: 220–9.
80. Mbacham WF, Evehe MS, Netongo PM, et al. Efficacy of amodiaquine, sulphadoxine-pyrimethamine and their combination for the treatment of uncomplicated Plasmodium falciparum malaria in children in Cameroon at the time of policy change to artemisinin-based combination therapy. *Malar J* 2010; **9**: 34.
81. Bouyou-Akotet MK, Tshibola ML, Mawili-Mboumba DP, et al. Frequencies of dhfr/dhps multiple mutations and Plasmodium falciparum submicroscopic gametocyte carriage in Gabonese pregnant women following IPTp-SP implementation. *Acta Parasitol* 2015; **60**: 218-25.
82. Bouyou-Akotet MK, Mawili-Mboumba DP, Tchantchou TD, Kombila M. High prevalence of sulfadoxine/pyrimethamine-resistant alleles of Plasmodium falciparum isolates in pregnant women at the time of introduction of intermittent preventive treatment with sulfadoxine/pyrimethamine in Gabon. *J Antimicrob Chemotherapy* 2010; **65**: 438-41.
83. Baraka V, Delgado-Ratto C, Nag S, et al. Different origin and dispersal of sulfadoxine-resistant Plasmodium falciparum haplotypes between Eastern Africa and Democratic Republic of Congo. *Int J Antimicrob Agents* 2017; **49**: 456-64.
84. Flegg JA, Patil AP, Venkatesan M, et al. Spatiotemporal mathematical modelling of mutations of the dhps gene in African *Plasmodium falciparum*. *Malar J* 2013; **12**: 249.

85. Raman J, Little F, Roper C, et al. Five years of large-scale dhfr and dhps mutation surveillance following the phased implementation of artesunate plus sulfadoxine-pyrimethamine in Maputo Province, Southern Mozambique. *Am J Trop Med Hyg* 2010; **82**: 788-94.
86. Raman J, Mauff K, Muianga P, Mussa A, Maharaj R, Barnes KI. Five years of antimalarial resistance marker surveillance in Gaza Province, Mozambique, following artemisinin-based combination therapy roll out. *PLoS One* 2011; **6**: e25992.
87. Pearce RJ, Pota H, Evehe MS, et al. Multiple origins and regional dispersal of resistant dhps in African *Plasmodium falciparum* malaria. *PLoS Med* 2009; **6**: e1000055.
88. Raman J, Sharp B, Kleinschmidt I, et al. Differential effect of regional drug pressure on dihydrofolate reductase and dihydropteroate synthetase mutations in southern Mozambique. *Am J Trop Med Hyg* 2008; **78**: 256-61.
89. Kublin JG, Dzinjalamala FK, Kamwendo DD, et al. Molecular markers for failure of sulfadoxine-pyrimethamine and chlorproguanil-dapsone treatment of Plasmodium falciparum malaria. *J Infect Dis* 2002; **185**: 380-8.
90. Artimovich E, Schneider K, Taylor TE, et al. Persistence of Sulfadoxine-Pyrimethamine Resistance Despite Reduction of Drug Pressure in Malawi. *J Infect Dis* 2015; **212**: 694-701.
91. Harrington WE, Mutabingwa TK, Muehlenbachs A, et al. Competitive facilitation of drug-resistant *Plasmodium falciparum* malaria parasites in pregnant women who receive preventive treatment. *Proc Natl Acad Sci U S A* 2009; **106**: 9027–32.
92. Alam MT, de Souza DK, Vinayak S, et al. Selective sweeps and genetic lineages of Plasmodium falciparum drug -resistant alleles in Ghana. *J Infect Dis* 2011; **203**: 220-7.
93. Okell LC, Griffin JT, Roper C. Mapping sulphadoxine-pyrimethamine-resistant Plasmodium falciparum malaria in infected humans and in parasite populations in Africa. *Sci Rep* 2017; **7**: 7389.
94. Taylor SM, Antonia AL, Parobek CM, et al. Plasmodium falciparum sulfadoxine resistance is geographically and genetically clustered within the DR Congo. *Sci Rep* 2013; **3**: 1165.
95. Karema C, Imwong M, Fanello CI, et al. Molecular correlates of high-level antifolate resistance in Rwandan children with Plasmodium falciparum malaria. *Antimicrob Agents Chemother* 2010; **54**: 477-83.
96. Ndiaye D, Daily JP, Sarr O, et al. Mutations in Plasmodium falciparum dihydrofolate reductase and dihydropteroate synthase genes in Senegal. *Trop Med Int Health* 2005; **10**: 1176-9.
97. Mayor A, Serra-Casas E, Sanz S, et al. Molecular markers of resistance to sulfadoxine-pyrimethamine during intermittent preventive treatment for malaria in Mozambican infants. *J Infect Dis* 2008; **197**: 1737-42.
98. Ndiaye D, Dieye B, Ndiaye YD, et al. Polymorphism in dhfr/dhps genes, parasite density and ex vivo response to pyrimethamine in Plasmodium falciparum malaria parasites in Thies, Senegal. *Int J Parasitol Drugs Drug Resist* 2013; **3**: 135-42.
99. Kavishe RA, Kaaya RD, Nag S, et al. Molecular monitoring of Plasmodium falciparum super-resistance to sulfadoxine-pyrimethamine in Tanzania. *Malar J* 2016; **15**: 335.
100. Bell DJ, Nyirongo SK, Mukaka M, et al. Sulfadoxine-pyrimethamine-based combinations for malaria: a randomised blinded trial to compare efficacy, safety and selection of resistance in Malawi. *PLoS One* 2008; **3**: e1578.
101. Ogouyemi-Hounto A, Ndam NT, Fadegnon G, et al. Low prevalence of the molecular markers of Plasmodium falciparum resistance to chloroquine and sulphadoxine/pyrimethamine in asymptomatic children in Northern Benin. *Malar J* 2013; **12**: 413.
102. Malamba S, Sandison T, Lule J, et al. Plasmodium falciparum dihydrofolate reductase and dihyropteroate synthase mutations and the use of trimethoprim-sulfamethoxazole prophylaxis among persons infected with human immunodeficiency virus. *Am J Trop Med Hyg* 2010; **82**: 766-71.
103. Matondo SI, Temba GS, Kavishe AA, et al. High levels of sulphadoxine-pyrimethamine resistance Pfdhfr-Pfdhps quintuple mutations: a cross sectional survey of six regions in Tanzania. *Malar J* 2014; **13**: 152.
104. Lynch C, Pearce R, Pota H, et al. Emergence of a dhfr mutation conferring high-level drug resistance in Plasmodium falciparum populations from southwest Uganda. *J Infect Dis* 2008; **197**: 1598-604.
105. Kidima W, Nkwengulila G, Premji Z, Malisa A, Mshinda H. Dhfr and dhps mutations in Plasmodium falciparum isolates in Mlandizi, Kibaha, Tanzania: association with clinical outcome. *Tanzania Health Research Bulletin* 2006; **8**: 50-5.
106. Iriemenam NC, Shah M, Gatei W, et al. Temporal trends of sulphadoxine-pyrimethamine (SP) drug-resistance molecular markers in Plasmodium falciparum parasites from pregnant women in western Kenya. *Malar J* 2012; **11**: 134.

107. van Schalkwyk DA, Burrow R, Henriques G, et al. Culture-adapted Plasmodium falciparum isolates from UK travellers: in vitro drug sensitivity, clonality and drug resistance markers. *Malar J* 2013; **12**: 320.
108. Mombo-Ngoma G, Oyakhirome S, Ord R, et al. High prevalence of dhfr triple mutant and correlation with high rates of sulphadoxine-pyrimethamine treatment failures in vivo in Gabonese children. *Malar J* 2011; **10**: 123.
109. Khalil IF, Ronn AM, Alifrangis M, et al. Response of Plasmodium falciparum to cotrimoxazole therapy: relationship with plasma drug concentrations and dihydrofolate reductase and dihydropteroate synthase genotypes. *Am J Trop Med Hyg* 2005; **73**: 174-7.
110. Chauvin P, Menard S, Iriart X, et al. Prevalence of *Plasmodium falciparum* parasites resistant to sulfadoxine/pyrimethamine in pregnant women in Yaounde, Cameroon: emergence of highly resistant pfdhfr/pfdhps alleles. *J Antimicrob Chemother* 2015; **70**: 2566–71.
111. Ako AAB, Johansson M, Traore R, et al. Sulphadoxine-Pyrimethamine resistant haplotypes in asymptomatically and symptomatically malaria infected individuals in Cote d'Ivoire. *Malaria Chemotherapy Control and Elimination* 2014; **3**.
112. Duah NO, Quashie NB, Abuaku BK, Sebeny PJ, Kronmann KC, Koram KA. Surveillance of molecular markers of Plasmodium falciparum resistance to sulphadoxine-pyrimethamine 5 years after the change of malaria treatment policy in Ghana. *Am J Trop Med Hyg* 2012; **87**: 996-1003.
113. World Wide Antimalarial Resistance Network (WWARN). Molecular Surveyor. 2018. http://www.wwarn.org/dhfr-dhps-surveyor/#0 (accessed September 18, 2018).
114. London School of Hygiene and Tropical Medicine. Drug resistance maps. Mapping the distribution of resistance genes of malaria in Africa. 2010. http://www.drugresistancemaps.org/ (accessed September 18, 2018).
115. Naidoo I, Roper C. Drug resistance maps to guide intermittent preventive treatment of malaria in African infants. *Parasitology* 2011; **138**: 1469–79.
116. Naidoo I, Roper C. Mapping 'partially resistant', 'fully resistant', and 'super resistant' malaria. *Trends Parasitol* 2013; **29**: 505–15.
117. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ* 2009; **339**: b2535.

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[117]

For more information, visit: **www.prisma-statement.org**.