Supplementary appendix

Supplement to: Gutman et al., Intermittent screening and treatment with artemisinin-combination therapy versus intermittent preventive treatment with sulphadoxine-pyrimethamine for malaria in pregnancy: a systematic review and individual participant data meta-analysis of randomised clinical trials

Supplemental methods

Supplement 1: Eligibility criteria for trials

Trials were included if they were randomised controlled trials conducted in sub-Saharan Africa comparing intermittent preventive treatment with sulphadoxine-pyrimethamine (IPTp-SP) versus intermittent screening and treatment in pregnancy with an artemisinin-based therapy (ACT) (ISTp-ACT). Studies or study arms were excluded if they involved only HIV-infected women, used SP only for ISTp (because ACTs replaced SP as treatment drug in the general population and the 2nd and 3rd trimester of pregnancy), combined SP with other antimalarial drugs for IPTp, such as artemisinin derivatives or azithromycin, or with other interventions such IPTp with antimalarials other than SP.

Supplement 2: Quality and risk of bias assessment of trials

The risk of bias assessment for each included trial was conducted by two persons (JG and CK) using version 2 of the Cochrane risk-of-bias tool for randomised trials (RoB 2), which is structured into a fixed set of domains of bias, focusing on different aspects of trial design, conduct and reporting. A judgement about the risk of bias arising from each domain is proposed by an algorithm and can be overwritten by the authors with justification. Judgements can be 'Low', or 'High' risk of bias, or can express 'Some concerns'.[1] Where disagreement occurred, a joint review of the study was conducted until agreement was reached by consensus. Studies were not excluded a-priori based on their quality score.

Supplement 3: Definition of outcomes

Primary outcomes

- Malaria at delivery: Any *Plasmodium* infection detected in peripheral or placental blood by PCR, microscopy, RDT or histopathology (acute and/or chronic infections)
- Adverse pregnancy outcome: A composite of low birth weight (<2500 grams), small-for-gestational-age (SGA, <10th percentile relative to INTERGROWTH-21st gender-specific chart),[2] or and preterm delivery (<37 weeks gestation).

Secondary maternal outcomes

- Clinical malaria: The definition was based on the definition used in the source studies, as this defined when treatment was given. In Tagbor 2010, clinical malaria was defined as any positive RDT documented in a woman who presented with a history of fever or other features suggestive of malaria.[3] In Desai and Madanitsa,[4,5] clinical malaria was defined by a positive RDT or smear in conjunction with documented fever (>37.5 °C) or reported fever in the past 24 hours. In Tagbor 2015, any positive RDT plus documented fever (>37.5 °C) was considered clinical malaria.[6] Esu did not report on clinical malaria and was not included in the analysis of this outcome.[7]
- Subpatent malaria during pregnancy: *Plasmodium* infection during pregnancy identified in the maternal peripheral blood by positive PCR, with negative microscopy and/or RDT
- Subpatent malaria at delivery: *Plasmodium* infection at delivery identified in the maternal peripheral blood by positive PCR with negative microscopy and/or RDT
- Patent malaria at delivery: *Plasmodium* infection during pregnancy identified in the maternal peripheral blood by positive microscopy or RDT, with PCR either positive or missing

The analyses of the impact of ISTp versus IPTp excluded enrolment and delivery time points from the incidence data during pregnancy. For the analysis of the impact of patent and subpatent infection on adverse pregnancy outcomes, the enrolment and delivery time points were included.

Secondary newborn outcomes

- Low birth weight (LBW): A birthweight < 2,500g measured. All birthweights in the analyses refer to corrected birthweights taken within seven days (168 hours) after birth. Birthweights taken more than 24 hours after delivery were corrected for the physiological fall in birth weight in breastfed infants occurring in the first days following delivery.[8,9] Birth weights taken 24-48h hours, 48-72 hours, 72-96 hours, 96-120 hours, 120-144 hours and 144-168 hours after delivery were corrected by a factor +5%, +5.4%, +3.4%, +1.3%, +0% and -1.2%, respectively to obtain the estimated weight at birth.[10,11]
- Preterm birth (PTD): A gestational age at birth of < 37 weeks. Gestational age at birth was defined as follows: In the trial in Malawi, gestational age at birth was based on the gestational age at enrolment assessed by ultrasound.[5] In the three other IPD studies in Kenya[4] and West-Africa[3,6] gestational at birth was based on physical parameters assessed at birth using the Ballard score.[12]
- Small-for-gestational-age: A birthweight <10th percentile of the INTERGROWTH-21st reference standard which is derived from a multi-ethnic cohort of low-risk, well-nourished mothers with uncomplicated pregnancies.[2,13] Infants with a gestational age >42 weeks were classified as SGA if they were lighter than the 42-week reference standard; those who were heavier than the cut-off for SGA at 42 weeks were excluded from the analysis.
- Spontaneous miscarriage: Loss of foetus before 28 weeks gestational age
- Stillbirth: Loss of foetus at or after 28 weeks gestation or birth of foetus showing no signs of life
- Foetal loss: Stillbirth or miscarriage
- Perinatal death: stillbirths and deaths in the first week of life
- Neonatal death: death within 28 days of birth
- Infant mortality: Death of a live-born infant by 6-8 weeks of age
- Congenital anomalies: Physical abnormality of infant detected at delivery or newly noted abnormality during the infant visits.

Risk ratios were measured for the binary outcomes, and mean differences for continuous outcomes. Missing outcomes were not imputed, nor missing covariates.

Supplement 4: Model selected and assessment of heterogeneity

Fixed-effect models were used because only five trials contributed, and heterogeneity cannot be reliably estimated with a small number of studies (3 to 4 for most outcomes), resulting in poor precision of the estimate of the between-studies variance.[14-16] The extent of heterogeneity was measured using the I^2 statistic,[17] 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.[18]

Supplement 5: Analytic methods for assessing the effect of exposure to subpatent malaria on pregnancy outcomes

The effect of exposure to subpatent malaria on pregnancy outcomes was examined using fixed-effect models with Poisson regression for binary outcomes and linear regression for continuous outcomes, accounting for study and number of subpatent and patent tests conducted. Data from patients in both ISTp and IPTp-SP were included in the analysis as long as there was data from at least one test for subpatent infection and one for patent infection. Robust Huber/White/sandwich estimate of variance was used. Poisson regression is a generalized linear model with a log link and a

Poisson distribution. When the outcome is binary, the exponentiated coefficients are risk ratios instead of incidence-rate ratios.[19] The two exposure variables of interest, the number of patent infections and the number of subpatent infections, were modelled as continuous variables. In the binary models, risk ratios for these variables correspond to the change in the risk of the adverse outcome associated with one additional positive test (malaria infection) during pregnancy. In models with continuous outcomes, the mean difference in the outcome measure associated with each additional positive test (malaria infection) was estimated. Fractional polynomials were also used to explore nonlinear relationships between number of patent and subpatent infections and pregnancy outcomes and were considered if the reduction in deviance compared to the linear model was significant at $p<0.05$. The results of linear models are presented throughout because the differences with non-linear models were non-significant for both variables and all outcomes.

Crude models included the two exposures of interest and study arm. Adjusted models also included gestational age at enrolment, maternal age, gravidity (G1-G2/G3+) and the number of sick visits. Adjusted models were used as the primary analysis to assess the impact of patent and subpatent infections because the exposure groups of interested were not randomised.

A previous analysis of the study in Malawi[20] looked at the effect of subpatent infections among the women enrolled in the ISTp arm and found that among women of all gravidities, cumulative subpatent infections were not associated with an increased risk of LBW (RR= 0.78, 95% CI: 0.38–1.60) nor preterm delivery (RR=1.35, 95% CI: 0.87-2.1) compared to women with no infection. By contrast, the current analysis found that subpatent infections were associated with an increased risk of LBW and preterm delivery (aRR= 1.13, 95% CI: 1.07-1.19 and aRR= 1.35, 95% CI: 1.15-1.57, respectively). The previous analysis had less power to detect the effect of subpatent infections. In addition to the smaller sample size, it included only RDT positives and defined subpatent infection as 'any woman with at least one RDT-negative and PCR-positive infection' vs no infection. The current analysis used both RDT and microscopy to define patent and sub patent infections. Furthermore, in the previous analysis, only women in the ISTp arm were included, whereas, in the current analysis, both arms were included in the analysis of the impact of patent and subpatent infections.

Supplement 6: Sensitivity analysis of the impact of the method of assessment for gestational age

We conducted a sensitivity analysis to explore whether the method of assessment influenced the effect of subpatent parasitaemia because the definition of preterm and SGA depends on the accuracy of gestational age assessment and because of the substantially higher accuracy of gestational age dating by ultrasound compared to other methods (i.e., fundal height, Ballard scores[12], last menstrual period).[21] This could be done using the data from the study in Malawi, which had used both early ultrasound measurement at enrolment and the Ballard score at delivery.[5] For this study, we used the INTERGROWTH-21st reference group[22] to assess SGA, while the original publications used Schmiegelow[23] (for Desai, 2015 and Madanitsa, 2016) and Landis[24] (for Tagbor, 2015).

Supplemental results

Supplement 7: List of excluded studies

1. Community-based Malaria Screening and Treatment for Pregnant Women Receiving Standard Intermittent Preventive Treatment With Sulfadoxine-Pyrimethamine: A Multicenter (The Gambia, Burkina Faso, and Benin) Cluster-randomized Controlled Trial. Clin Infect Dis 2019; 68(4): 586-96.

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17. Chaponda EB. The epidemiology of malaria, curable sexually transmitted and reproductive tract infections and their coinfection among pregnant women in a catchment area in Nchelenge District, Zambia; 2017.

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Supplement 8: Sensitivity analysis of method of assessment for gestational age

A comparison between the Ballard score at delivery[12] and dating ultrasound (at enrolment) showed that the Ballard methods underestimated the mean gestational age at delivery by an average of 2.54 days (95% CI 1.67-3.41, p <0.001) overall. This was 1.64 days (95% CI 0.04-3.25, p=0.04) for women who had any evidence of malaria infection during pregnancy (either patent or subpatent), and 2.66 days (0.43-4.89, p=0.021) in women without any malaria. The corresponding figures were 3.52 days

(1.62-5.41, p<0.001) and 2.78 days (1.28-4.28, p=0.001) for women with patent infections only and for women who had subpatent infections only, respectively (Table S5). The impact of the method of assessment on the mean gestational age estimates at birth between patent and subpatent infection were modest (3.52 vs 2.78 days), and the conclusions of the meta-analyses were the same regardless of whether ultrasound or the Ballard score were used to assess gestational age.

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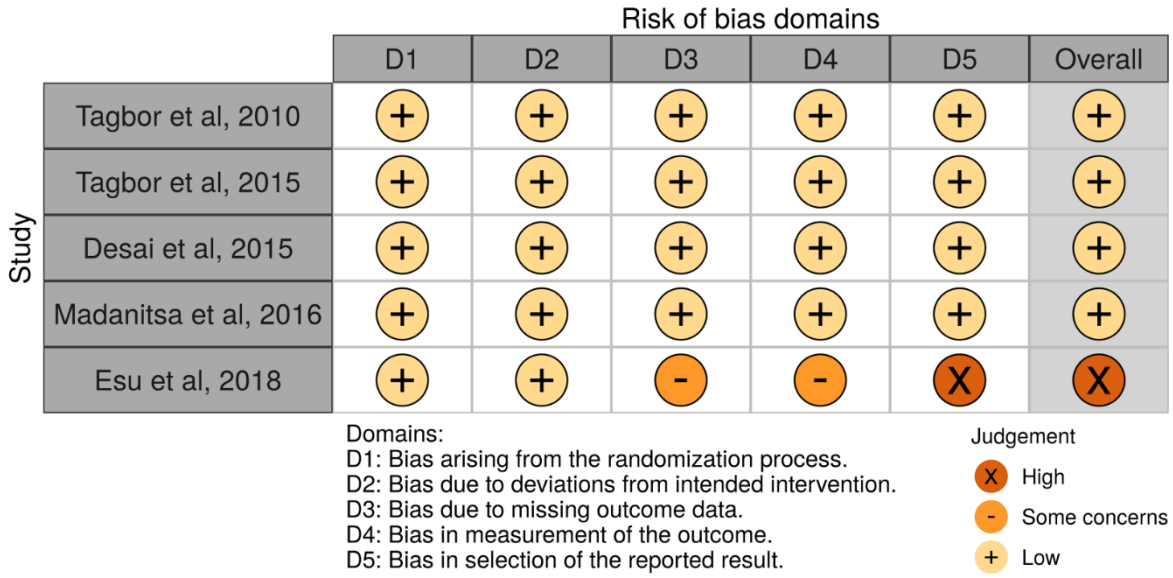
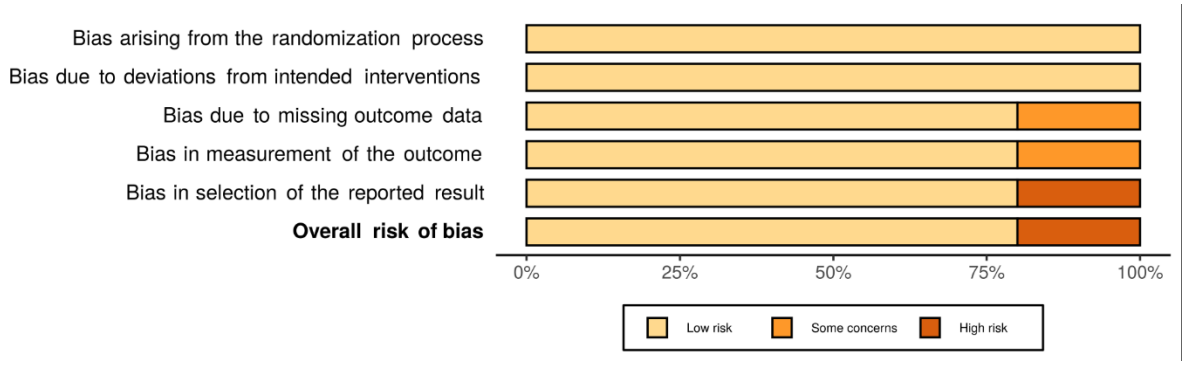
Supplemental figures

FIGURE S1: RISK OF BIAS ASSESSMENT

TRAFFIC LIGHT PLOT



SUMMARY PLOT



Esu et al., 2018 was scored as 'Some concern' for domain 3 (D3) because the primary outcome (haemoglobin concentration in the third trimester) was missing in 48.1% of participants, and the key secondary outcomes, malaria microscopy in the third trimester and birthweight, were missing in 54.7% and 29.2% of participants, respectively. It was also scored as 'Some concern' for domain 4 (D4) because only one preterm delivery was recorded, which is much lower than the expected background rate, potentially biasing the effect size towards the null. Domain 5 (D5) was scored as 'High' because not all outcomes were reported for the per-protocol or intention to treat analysis and because the p-value of the relative risk for LBW was P=0.7 in the main text, but the effect on the risk difference in LBW is reported as being significant elsewhere (p <0.001) and in the abstract.

The plots were generated using the Risk of Bias visualisation tool obtained from McGuinness, LA, Higgins, JPT. Risk-of-bias Visualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments. Res Syn Meth. 2020; 1- 7. https://doi.org/10.1002/jrsm.1411

Supplemental tables

TABLE S1: STUDY CHARACTERISTICS OF INCLUDED TRIALS

Author and Publication Year	**Tagbor et al., 2010**	**Tagbor et al., 2015**	**Desai et al., 2015**	**Madanitsa et al., 2016**	**Esu et al., 2018**
Country	Ghana	The Gambia, Mali, Burkina Faso and Ghana	Kenya	Malawi	Nigeria
Recruitment	March 2007 – September 2007	May 2010 – October 2011	August 2012 – June 2014	July 2011 – March 2013	October 2013 – November 2014*
Design	Non-inferiority	Non-inferiority	Superiority	Superiority	Non-inferiority
Number of sites	1	6†	4	3	1
SP resistance ‡ (Ala437Gly | Lys540Glu | Ala581Gly)	No molecular data available, but generally low SP resistance	BF: 75.3 |0.0|0.0 Ghana: 77.4 |0.0|0.0 Gambia: 9.1 |0.0|0.0 Mali: 21.4 |0.37|0[10]	93.0 |95.6|5.7[16]	94.4 |99.6|1.5[16]	No molecular data available, but generally low SP resistance
Gravidity groups	All	G1/G2 only	All	All; enrolment stratified by G1/2 and G3+	All
Gestational age at enrolment	16-24	16-30	16-32	16-28	16-24
Method of gestational age assessment	Ballard	Ballard	Ballard	Ultrasound	
Intervention frequency	IPTp or IST up to 3 times depending on GA at enrolment	IPTp up to 2 times in The Gambia, Mali, Burkina Faso and up to 3 times in Ghana as per national policy. ISTp up to 3 times depending on GA at enrolment	IPTp or ISTp up to 4 times depending on GA at enrolment	IPTp or ISTp up to 4 times depending on GA at enrolment	IPTp-SP or ISTp administered up to 3 times (at enrolment and 24 and 32 weeks GA)
Drug used for ISTp	SP or AQ+AS[§]	AL	DP	DP	AL
RDT used for ISTp	DiaMed OptiMAL-IT, pLDH based RDT (Cressier, Switzerland)	First Response Malaria pLDH/HRP2 Combo Test (Premier Medical Corporation Ltd., Mumbai, India)	First Response Malaria pLDH/HRP2 Combo Test (Premier Medical Corporation Ltd., Mumbai, India)	First Response Malaria pLDH/HRP2 Combo Test (Premier Medical Corporation Ltd., Mumbai, India)	SD Bioline malaria antigen HRP2/pLDH (Pan) RDT
Primary outcome	Third trimester anaemia	Low birth weight	Malaria infection at delivery	Muligravidae: Malaria infection at delivery Paucigravidae: SGA/ LBW/ preterm composite	Third trimester haemoglobin concentration
Proportion contributing to study primary outcome (ITT)	80.0%	86.9%	88.5%	SGA/LBW/preterm: 90.9% Malaria infection:88.3%	52.1%

Baseline malaria prevalence (%) by microscopy and seasonality	17.4%, perennial transmission with marked seasonality	30.8%, all sites had marked seasonality	17.3%, perennial transmission	15.9%, perennial transmission with marked seasonality	7.0%, perennial transmission with marked seasonality
Folate dose (mg/day)	4	0.4	0.4	0.4	4
Number of women that received at least one course of artemether-lumefantrine or amodiaquine-artesunate	ISTp: 252 (22.8%) IPTP: 2 (0.2%)	ISTp: 1334 (50.4%) IPTP: 18 (0.7%)	ISTp: 61 (11.9%) IPTP: 45 (8.9%)	ISTp: 0 (0%) IPTP: 144 (15.6%)	N/A
Number of courses of artemether-lumefantrine received for ISTp¶	252, 1.2 (0.5) [1-4]	1334, 1.3 (0.6) [1-3]	195, 1.8 (0.8) [1-4]	473, 1.3 (0.5) [1-3]	N/A
Number of SP courses received for IPTp¶	1098, 2.3 (1.0) [1-6]	2634, 2.1 (0.5) [1-4]	506, 4.4 (1.2) [2-7]	916, 3.3 (0.9) [1-4]	N/A

Values are mean (SD) or percentages unless otherwise indicated.

GA=gestational age. ISTp=intermittent screening and treatment in pregnancy. IPTp=intermittent preventive treatment in pregnancy. AQ+AS=amodiaquine+artesunate. AL=artesunate-lumefantrine. DP=dihydroartemisinin-piperaquine. SP=sulfadoxine-pyrimethamine. BF Burkina-Faso. EIR=Entomological inoculation rate (infectious bites/person/year). ITN=insecticide treated nets. SES=Socioeconomic status. ITT=Intention to treat population.

* Esu: Dates reported correspond to recruitment and follow-up.

† One site in Burkina Faso, the Gambia, and Ghana, and three sites in Mali. All sites contributed to efficacy analysis comparing ISTp vs IPTp (except for outcomes requiring PCR data). Only Ghana had serial PCR data and contributed to the subpatent IPD meta-analysis.

‡ Prevalence of Ala437Gly, Lys540Glu, and Ala581Gly substitutions in the parasite dihydropteroate synthase gene

§ Only data from the ISTp arm with amodiaquine+artesunate was used in this analysis

¶ Values are N, mean (SD) [range].

TABLE S2: BASELINE CHARACTERISTICS OF PARTICIPANTS

	Tagbor et al., 2010	Tagbor et al., 2015	Desai et al., 2015	Madanitsa et al., 2016	Esu et al., 2018
N	**2205**	**5292**	**1021**	**1844**	**459**
Maternal characteristics					
Maternal age (years)	26.5 (6.0)	20.4 (3.3)	23.4 (5.9)	22.5 (5.1)	28.2 (5.0)
Used a bednet previous night	1133 (71.5%)	3063 (58.8%)	730 (71.5%)	350 (19.0%)	67 (14.6%)
Schooling level*					
Low	438 (27.4%)	4537 (86.4%)	235 (23.1%)	565 (30.7%)	13 (2.8%)
Medium	1125 (70.4%)	635 (12.1%)	452 (44.4%)	980 (53.3%)	195 (42.5%)
High	34 (2.1%)	78 (1.5%)	330 (32.4%)	295 (16.0%)	251 (54.7%)
SES index score (median, range)	0.1 (-7.9; 4.1)	0.4 (-6.0; 4.9)	-0.2 (-8.3; 19.6)	-1.0 (-1.8; 14.7)	N/A
Pregnancy number (gravidity)					
First	505 (22.9%)	2904 (55.1%)	353 (34.6%)	627 (34.1%)	216 (47.0%)
Second	486 (22.1%)	2363 (44.9%)	204 (20.0%)	513 (27.9%)	137 (29.9%)
Third or higher	1210 (55.0%)	0 (0.0%)	464 (45.4%)	704 (38.2%)	106 (23.1%)
Gestational age (weeks)	19.8 (2.7)	20.5 (3.3)	22.9 (4.8)	20.9 (3.1)	N/A
Weight (kg)	59.5 (10.7)	N/A	61.3 (8.7)	55.1 (7.4)	N/A
Height (cm)	155.3 (8.2)	N/A	164.2 (6.9)	154.0 (5.0)	N/A
BMI	24.6 (4.0)	N/A	22.7 (3.0)	23.2 (3.0)	N/A
Laboratory findings					
Haemoglobin (g/dL)	10.7 (1.4)	10.4 (2.3)	10.5 (1.6)	11.0 (1.5)	11.5 (1.4)
Malaria infection					
RDT†	189 (15.2%)	1045 (40.2%)	111 (22.9%)	385 (38.4%)	26 (11.3%)‡
Microscopy	368 (17.4%)	1595 (30.8%)	167 (17.3%)	291 (15.9%)	32 (7.0%)
PCR		1216 (40.8%)	330 (34.1%)	788 (43.6%)	29 (6.3%)
Subpatent		331 (9.2%)	171 (20.0%)	360 (27.4%)	

Values are mean (SD) or percentages unless otherwise indicated.

SES=Socioeconomic status. N/A=Not available. RDT=Rapid diagnostic test for malaria. PCR=Polymerase chain reaction. BMI=Body mass index.

* Schooling: Low: no schooling or primary school not completed, Medium: Primary school completed, High: Junior high school completed, Highest: Senior High school or academy completed. For Esu et al., Low corresponds to primary school attainment, medium to secondary school, and high to tertiary school.

† RDT were only conducted in symptomatic women in the IPTp arms, but among all women in the ISTp arm. ‡ The RDT data reported for Esu represent the ISTp-AL arm only (n=230).

TABLE S3: FIXED VERSUS RANDOM-EFFECTS MODELS OF THE COMPARISON BETWEEN ISTP-ACT VS IPTP-SP

Outcome	# studies	Fixed-effect*	Random-effects*	
		RR (95%CI), P-value	RR (95%CI), P-value	I^2 (%)
Adverse pregnancy outcome (co-primary outcome)†				
Low resistance	2	1.01 (0.97;1.06), 0.637	1.01 (0.97;1.06), 0.637	0.0
High resistance	2	0.94 (0.83;1.07), 0.341	1.07 (0.71;1.61), 0.760	81.3
Overall	4	1.00 (0.96;1.05), 0.916	1.00 (0.92;1.09), 0.968	54.5
Any Plasmodium infection at delivery (placental or peripheral) (co-primary outcome)‡				
Low resistance	1	1.00 (0.90;1.10), 0.960	1.00 (0.90;1.10), 0.960	0.0
High resistance	2	1.20 (1.06;1.35), 0.003	1.20 (1.06;1.35), 0.003	0.0
Overall	3	1.08 (1.00;1.16), 0.063	1.09 (0.94;1.28), 0.253	67.0
Any subpatent Plasmodium infection at delivery (placental or peripheral)§				
Low resistance	1	1.08 (0.61;1.89), 0.795	1.08 (0.61;1.89), 0.795	0.0
High resistance	2	1.17 (0.99;1.39), 0.066	1.05 (0.68;1.61), 0.831	65.7
Overall	3	1.17 (0.99;1.37), 0.066	1.10 (0.84;1.43), 0.488	33.3
Any patent Plasmodium infection at delivery (placental or peripheral)§				
Low resistance	1	0.81 (0.55;1.19), 0.283	0.81 (0.55;1.19), 0.283	0.0
High resistance	2	1.28 (1.00;1.64), 0.048	1.28 (1.00;1.64), 0.048	0.0
Overall	3	1.12 (0.91;1.38), 0.278	1.10 (0.81;1.49), 0.533	51.4
Any placental Plasmodium infection (patent or subpatent)¶				
Low resistance	1	0.98 (0.88;1.09), 0.764	0.98 (0.88;1.09), 0.764	0.0
High resistance	2	1.18 (1.02;1.37), 0.022	1.18 (1.02;1.37), 0.022	0.0
Overall	3	1.05 (0.96;1.14), 0.268	1.08 (0.93;1.25), 0.319	53.7
Subpatent placental Plasmodium infection||				
Low resistance	0	---	---	
High resistance	2	1.12 (0.90;1.41), 0.311	1.11 (0.85;1.44), 0.441	11.3
Overall	2	1.12 (0.90;1.41), 0.311	1.11 (0.85;1.44), 0.441	11.3
Patent placental Plasmodium infection||				
Low resistance	0	---	---	
High resistance	2	1.30 (1.00;1.70), 0.051	1.30 (1.00;1.70), 0.051	0.0
Overall	2	1.30 (1.00;1.70), 0.051	1.30 (1.00;1.70), 0.051	0.0
Any maternal peripheral blood Plasmodium infection at delivery (patent or subpatent)**				
Low resistance	2	1.09 (0.95;1.26), 0.227	1.09 (0.95;1.26), 0.227	0.0
High resistance	2	1.30 (1.11;1.52), 0.001	1.30 (1.11;1.52), 0.001	0.0
Overall	4	1.18 (1.06;1.31), 0.002	1.18 (1.06;1.31), 0.002	0.0
Subpatent maternal peripheral blood Plasmodium infection at delivery††				
Low resistance	1	1.12 (0.63;1.97), 0.707	1.12 (0.63;1.97), 0.707	0.0
High resistance	2	1.34 (1.06;1.69), 0.013	1.34 (1.06;1.69), 0.013	0.0
Overall	3	1.31 (1.05;1.62), 0.015	1.31 (1.05;1.62), 0.015	0.0
Patent maternal peripheral blood Plasmodium infection at delivery††				
Low resistance	1	0.83 (0.57;1.23), 0.358	0.83 (0.57;1.23), 0.358	0.0
High resistance	2	1.15 (0.86;1.54), 0.354	1.15 (0.86;1.54), 0.354	0.0
Overall		1.02 (0.81;1.29), 0.853	1.02 (0.81;1.29), 0.853	0.0
Any anaemia in the third trimester/delivery (Hb<11 g/dL)‡‡				
Low resistance	3	1.02 (0.96;1.08), 0.510	1.02 (0.96;1.08), 0.510	0.0
High resistance	2	0.91 (0.81;1.03), 0.133	0.92 (0.78;1.09), 0.315	47.4
Overall	5	1.00 (0.95;1.05), 0.962	0.98 (0.91;1.06), 0.606	38.4

Outcome	# studies	Fixed-effect*	Random-effects*	
		RR (95%CI), P-value	RR (95%CI), P-value	I^2 (%)
Moderate-to-severe anaemia in the third trimester/delivery (Hb<9 g/dL)‡‡				
Low resistance	2	1.18 (0.96;1.46), 0.108	1.18 (0.96;1.46), 0.108	0.0
High resistance	2	1.02 (0.68;1.53), 0.918	1.02 (0.68;1.53), 0.918	0.0
Overall	4	1.15 (0.96;1.38), 0.139	1.15 (0.96;1.38), 0.139	0.0
Clinical malaria during pregnancy§§				
Low resistance	2	1.44 (1.13;1.85), 0.004	1.44 (1.13;1.85), 0.004	0.0
High resistance	2	1.08 (0.88;1.32), 0.453	1.09 (0.84;1.42), 0.499	37.2
Overall	4	1.21 (1.04;1.42), 0.016	1.23 (1.00;1.51), 0.054	37.2
Any Plasmodium infection during pregnancy (patent or subpatent)¶¶				
Low resistance	3	1.32 (1.22;1.43), <.001	1.32 (1.22;1.43), <.001	0.0
High resistance	2	1.10 (1.02;1.19), 0.017	1.14 (0.95;1.36), 0.166	75.8
Overall	5	1.20 (1.14;1.28), <.001	1.21 (1.06;1.38), 0.005	74.0
Patent Plasmodium Infection during pregnancy‖‖‖				
Low resistance	3	1.47 (1.34;1.60), <.001	1.39 (1.14;1.70), 0.001	56.3
High resistance	2	1.21 (1.05;1.41), 0.011	1.22 (0.94;1.59), 0.133	67.8
Overall	5	1.40 (1.29;1.50), <.001	1.31 (1.11;1.55), 0.001	67.7
Subpatent Plasmodium infection during pregnancy‖‖‖				
Low resistance	1	0.87 (0.63;1.21), 0.409	0.87 (0.63;1.21), 0.409	0.0
High resistance	2	1.01 (0.90;1.13), 0.898	1.01 (0.90;1.13), 0.898	0.0
Overall	3	0.99 (0.89;1.10), 0.885	0.99 (0.89;1.10), 0.885	0.0
Low birth weight (<2,500g)				
Low resistance	3	1.04 (0.93;1.17), 0.489	1.04 (0.93;1.17), 0.489	0.0
High resistance	2	1.28 (0.99;1.64), 0.055	1.28 (0.99;1.64), 0.055	0.0
Overall	5	1.08 (0.97;1.20), 0.154	1.09 (0.97;1.23), 0.146	7.5
Preterm birth (<37 weeks)				
Low resistance	3	0.99 (0.92;1.07), 0.818	0.99 (0.92;1.07), 0.818	0.0
High resistance	2	1.04 (0.88;1.24), 0.620	1.18 (0.74;1.88), 0.481	57.3
Overall	5	1.00 (0.93;1.07), 0.999	1.00 (0.93;1.07), 0.999	0.0
Small-for-gestational-age				
Low resistance	2	1.03 (0.95;1.11), 0.528	1.03 (0.95;1.11), 0.528	0.0
High resistance	2	0.83 (0.67;1.04), 0.111	0.94 (0.47;1.89), 0.856	88.1
Overall	4	1.00 (0.93;1.08), 0.962	0.99 (0.80;1.21), 0.892	74.9
Spontaneous miscarriage (<28 weeks gestation)				
Low resistance	3	0.80 (0.46;1.39), 0.424	0.80 (0.46;1.39), 0.424	0.0
High resistance	2	2.02 (0.60;6.77), 0.257	2.02 (0.60;6.77), 0.257	0.0
Overall	5	0.94 (0.57;1.55), 0.797	0.94 (0.57;1.55), 0.797	0.0
Stillbirth (>=28 weeks gestation)				
Low resistance	3	1.15 (0.87;1.51), 0.331	1.15 (0.87;1.51), 0.331	0.0
High resistance	2	1.06 (0.60;1.88), 0.834	1.10 (0.35;3.45), 0.872	74.8
Overall	5	1.13 (0.88;1.45), 0.334	1.14 (0.84;1.53), 0.396	14.1
Fetal loss (spontaneous abortion or stillbirth)				
Low resistance	3	1.08 (0.83;1.39), 0.573	1.08 (0.83;1.39), 0.573	0.0
High resistance	2	1.19 (0.71;2.00), 0.505	1.16 (0.37;3.63), 0.793	79.4
Overall	5	1.10 (0.87;1.38), 0.424	1.09 (0.79;1.51), 0.586	34.8

Outcome	# studies	Fixed-effect*	Random-effects*	
		RR (95%CI), P-value	RR (95%CI), P-value	I^2 (%)
Perinatal death				
Low resistance	2	1.07 (0.84;1.36), 0.589	1.07 (0.84;1.36), 0.589	0.0
High resistance	2	0.98 (0.63;1.50), 0.914	0.98 (0.37;2.62), 0.971	80.7
Overall	4	1.05 (0.85;1.29), 0.675	1.05 (0.74;1.50), 0.777	46.4
Neonatal death (<28 days)				
Low resistance	1	1.03 (0.69;1.53), 0.887	1.03 (0.69;1.53), 0.887	0.0
High resistance	2	0.93 (0.48;1.79), 0.824	0.90 (0.31;2.59), 0.846	61.2
Overall	3	1.00 (0.71;1.40), 0.994	0.99 (0.63;1.54), 0.949	24.5
Infant mortality by end of follow-up(6-8 weeks of age)				
Low resistance	1	1.07 (0.73;1.56), 0.743	1.07 (0.73;1.56), 0.743	0.0
High resistance	2	0.91 (0.49;1.68), 0.752	0.85 (0.29;2.52), 0.767	67.1
Overall	3	1.02 (0.74;1.41), 0.910	0.98 (0.60;1.60), 0.929	38.1
Fetal loss or infant death by 6-8 weeks				
Low resistance	1	1.10 (0.88;1.39), 0.404	1.10 (0.88;1.39), 0.404	0.0
High resistance	2	1.07 (0.72;1.58), 0.742	1.02 (0.34;3.06), 0.976	87.3
Overall	3	1.09 (0.90;1.34), 0.376	1.06 (0.64;1.75), 0.821	74.7
Congenital anomalies				
Low resistance	2	1.28 (0.68;2.41), 0.438	1.28 (0.68;2.41), 0.438	0.0
High resistance	2	0.81 (0.48;1.34), 0.409	0.81 (0.48;1.34), 0.409	0.0
Overall	4	0.97 (0.65;1.44), 0.879	0.97 (0.65;1.44), 0.879	0.0
Maternal Hb (g/dL)(last visit)				
Low resistance	3	-0.01 (-0.08;0.06), 0.822	0.01 (-0.10;0.11), 0.905	42.5
High resistance	2	0.06 (-0.05;0.17), 0.275	0.04 (-0.14;0.21), 0.686	50.7
Overall	4	0.01 (-0.05;0.07), 0.688	0.02 (-0.06;0.10), 0.635	39.3
Fetal haemoglobin (g/dL) (cord blood)				
Low resistance	0	---	---	
High resistance	2	-0.08 (-0.27;0.11), 0.411	-0.11 (-0.41;0.19), 0.464	56.1
Overall	2	-0.08 (-0.27;0.11), 0.411	-0.11 (-0.41;0.19), 0.464	56.1
Birth weight (grams)				
Low resistance	3	-24.7 (-46.2;-3.2), 0.024	-24.7 (-46.2;-3.2), 0.024	0.0
High resistance	2	-36.9 (-71.5;-2.3), 0.037	-36.9 (-71.5;-2.3), 0.037	0.0
Overall	5	-28.1 (-46.4;-9.8), 0.003	-28.1 (-46.4;-9.8), 0.003	0.0
Birthweight for gestational age (Z-score)				
Low resistance	2	-0.05 (-0.15;0.05), 0.311	-0.05 (-0.15;0.05), 0.311	0.0
High resistance	2	-0.02 (-0.11;0.07), 0.628	-0.02 (-0.11;0.07), 0.628	0.0
Overall	4	-0.03 (-0.10;0.03), 0.303	-0.03 (-0.10;0.03), 0.303	0.0
Gestational age at birth (weeks)				
Low resistance	2	-0.03 (-0.20;0.14), 0.708	-0.03 (-0.20;0.14), 0.708	0.0
High resistance	2	-0.17 (-0.33;-0.01), 0.04	-0.17 (-0.33;-0.01), 0.04	0.0
Overall	4	-0.10 (-0.22;0.01), 0.082	-0.10 (-0.22;0.01), 0.082	0.0
Asexual parasite density (log) (delivery)				
Low resistance	2	1.11 (0.81;1.52), 0.505	1.11 (0.81;1.52), 0.505	0.0
High resistance	2	1.78 (0.70;4.49), 0.224	1.78 (0.70;4.49), 0.224	0.0
Overall	4	1.17 (0.87;1.57), 0.307	1.17 (0.87;1.57), 0.307	0.0

RR=relative risk, CI=confidence interval

* Fixed-effect using inverse-variance estimation method, Random-effects using the DerSimonian–Laird method.

Outcome	# studies	Fixed-effect*	Random-effects*	
		RR (95%CI), P-value	RR (95%CI), P-value	I^2 (%)

† Adverse live-birth (co-primary outcome) defined as the composite of low birth weight (<2500 grams), small-for-gestational-age (SGA, <10th percentile relative to INTERGROWTH-21st gender-specific chart), or and preterm delivery (<37 weeks gestation).
‡ Any malaria at delivery (co-primary outcome) defined as any maternal plasmodium infection detected in peripheral or placental blood by any diagnostic method (PCR, microscopy, RDT or histopathology (acute and/or chronic infections)).
§Any patent *Plasmodium* infection in peripheral or placental blood detected by PCR or histopathology (acute and/or chronic infections) and positive by microscopy or RDT. Any subpatent infection at delivery is defined as a microscopy and RDT negative infection detected by PCR or histopathology.
¶Any placental malaria infection detected in the placental blood by any diagnostic method (PCR, microscopy, RDT or histopathology (acute and/or chronic infections)).
||Patent placental malaria infection defined as any infection in the placental blood detected by PCR or histopathology positive by RDT or microscopy. Subpatent placental malaria infection is defined as microscopy and RDT negative infections detected by PCR or histopathology (acute and/or chronic infections).
**Any maternal plasmodium infection detected in peripheral blood by PCR, microscopy, or RDT.
††Patent maternal plasmodium infection in peripheral blood detected by PCR and by microscopy or RDT. Subpatent maternal plasmodium infection detected in peripheral blood by PCR, but not by microscopy or RDT.
‡‡Maternal anaemia (Hb <11 g/dL) and moderate to severe anaemia (Hb <9 g/dL) at delivery or otherwise in the third trimester if values at delivery were not available.
§§Clinical malaria, defined as documented fever or recent history of fever in the presence of microscopy or RDT confirmed malaria infection.
¶¶Any maternal peripheral blood *Plasmodium* infection during pregnancy, detected by microscopy or RDT, or PCR.
||||Patent maternal peripheral blood *Plasmodium* infection during pregnancy detected by PCR and by microscopy or RDT. Subpatent Plasmodium infection during pregnancy, defined as PCR positive but microscopy and RDT negative infections.

TABLE S4: CONTINUOUS OUTCOMES COMPARING ISTP TO IPTP

Outcome	Study	Number of women, mean (SD) IST	Number of women, mean (SD) IPT	Unadjusted mean difference (95% CI), p-value*	I^2 (%)	Adjusted mean Difference (95% CI), p-value
Maternal Hb (g/dL) (delivery or last visit in 3rd trimester)						
Low resistance	Tagbor, 2010	888, 11.0 (1.2)	881, 11.0 (1.3)	-0.03 (-0.14;0.09), 0.666		-0.02 (-0.15;0.11), 0.816
	Tagbor, 2015	1621, 10.9 (1.4)	1588, 11.0 (1.4)	-0.02 (-0.12;0.07), 0.654		-0.00 (-0.09;0.09), 0.976
	Esu, 2018	124, 11.7 (1.2)	115, 11.4 (1.4)	0.30 (-0.03;0.63), 0.076		
	Subgroup, IV (I^2=42.5%, p=0.175)			-0.01 (-0.08;0.06), 0.822	42.5	-0.01 (-0.08;0.07), 0.875
High resistance	Desai, 2015	307, 11.1 (1.3)	294, 11.1 (1.5)	-0.08 (-0.31;0.14), 0.480		-0.06 (-0.27;0.16), 0.614
	Madanitsa, 2016	670, 11.7 (1.2)	665, 11.6 (1.2)	0.11 (-0.02;0.23), 0.099		0.11 (-0.02;0.23), 0.091
	Subgroup, IV (I^2=50.7%, p=0.155)			0.06 (-0.05;0.17), 0.275	50.7	0.07 (-0.04;0.17), 0.218
Overall	Heterogeneity between subgroups: p=0.299			0.01 (-0.05;0.07), 0.688	39.3	0.02 (-0.04;0.08), 0.565
Fetal haemoglobin (g/dL) (cord blood)						
Low resistance	Tagbor, 2010	0, . (.)	0, . (.)	. (.;.), .		. (.;.), .
	Tagbor, 2015	0, . (.)	0, . (.)	. (.;.), .		. (.;.), .
	Subgroup, IV (I^2=0.0%, p=.)			. (.;.), .		. (.;.), .
High resistance	Desai, 2015	399, 14.1 (2.4)	403, 14.4 (2.6)	-0.30 (-0.63;0.04), 0.087		-0.29 (-0.63;0.05), 0.089
	Madanitsa, 2016	769, 14.9 (2.4)	761, 14.9 (2.2)	0.02 (-0.21;0.24), 0.884		0.02 (-0.21;0.24), 0.885
	Subgroup, IV (I^2=56.1%, p=0.131)			-0.08 (-0.27;0.11), 0.411	56.1	-0.08 (-0.26;0.11), 0.415
Overall	Heterogeneity between subgroups: p cannot be computed			-0.08 (-0.27;0.11), 0.411	56.1	-0.08 (-0.26;0.11), 0.415
Birth weight (grams)						
Low resistance	Tagbor, 2010	858, 2951.4 (475.1)	850, 2987.0 (485.5)	-28 (-72;17), 0.227		-18 (-72;35), 0.497
	Tagbor, 2015	2282, 2830.3 (450.6)	2314, 2857.1 (436.4)	-23 (-48;2), 0.071		-23 (-48;2), 0.073
	Esu, 2018	167, 3170 (0.53)	158, 3210 (0.53)	-40 (-156;76), 0.498		
	Subgroup, IV (I^2=0.0%, p=0.951)			-25 (-46;-3), 0.024	0.0	-35 (-69;-0), 0.048
High resistance	Desai, 2015	412, 3226.5 (493.8)	412, 3275.7 (467.9)	-57 (-120;7), 0.082		-51 (-114;12), 0.113
	Madanitsa, 2016	830, 2919.2 (439.1)	826, 2947.2 (447.6)	-29 (-70;13), 0.174		-28 (-69;13), 0.184
	Subgroup, IV (I^2=0.0%, p=0.470)			-37 (-72;-2), 0.037	0.0	-22 (-45;1), 0.056
Overall	Heterogeneity between subgroups: p=0.558			-28 (-46;-10), 0.003	0.0	-26 (-45;-7), 0.007

Birthweight for gestational age (Z-score)						
Low resistance	Tagbor, 2010	759, 0.15 (1.83)	763, 0.22 (1.78)	-0.06 (-0.24;0.13), 0.546		-0.04 (-0.27;0.18), 0.705
	Tagbor, 2015	2012, 0.04 (2.00)	2009, 0.10 (2.02)	-0.05 (-0.17;0.07), 0.415		-0.05 (-0.18;0.07), 0.382
	Subgroup, IV (I^2=0.0%, p=0.960)			-0.05 (-0.15;0.05), 0.311	0.0	-0.01 (-0.10;0.07), 0.771
High resistance	Desai, 2015	410, 0.13 (1.05)	412, 0.18 (1.00)	-0.07 (-0.20;0.07), 0.321		-0.06 (-0.19;0.08), 0.413
	Madanitsa, 2016	815, 0.05 (1.18)	814, 0.04 (1.24)	0.01 (-0.10;0.13), 0.829		0.02 (-0.10;0.13), 0.749
	Subgroup, IV (I^2=0.0%, p=0.371)			-0.02 (-0.11;0.07), 0.628	0.0	-0.05 (-0.16;0.06), 0.343
Overall	Heterogeneity between subgroups: p=0.656			-0.03 (-0.10;0.03), 0.303	0.0	-0.03 (-0.10;0.04), 0.411
Gestational age at birth (weeks)						
Low resistance	Tagbor, 2010	909, 38.7 (3.5)	924, 38.6 (3.4)	0.08 (-0.23;0.40), 0.617		-0.01 (-0.39;0.36), 0.953
	Tagbor, 2015	2466, 38.3 (3.7)	2463, 38.4 (3.8)	-0.08 (-0.28;0.12), 0.443		-0.08 (-0.28;0.12), 0.445
	Subgroup, IV (I^2=0.0%, p=0.404)			-0.03 (-0.20;0.14), 0.708	0.0	-0.06 (-0.24;0.11), 0.484
High resistance	Desai, 2015	450, 39.1 (1.8)	451, 39.1 (1.8)	-0.10 (-0.33;0.13), 0.386		-0.11 (-0.34;0.12), 0.352
	Madanitsa, 2016	871, 38.0 (2.4)	864, 38.2 (2.3)	-0.23 (-0.45;-0.00), 0.04		-0.23 (-0.45;-0.01), 0.04
	Subgroup, IV (I^2=0.0%, p=0.451)			-0.17 (-0.33;-0.01), 0.04	0.0	-0.17 (-0.33;-0.01), 0.03
Overall	Heterogeneity between subgroups: p=0.262			-0.10 (-0.22;0.01), 0.082	0.0	-0.12 (-0.24;-0.01), 0.04
Asexual parasite density maternal blood at delivery (geometric mean, 95% CI)						
Low resistance	Tagbor, 2010	108, 341 (235;493)	85, 365 (240;555)	0.99 (0.57;1.70), 0.958		0.80 (0.44;1.45), 0.459
	Tagbor, 2015	207, 3467 (2,600;4,623)	186, 2,699 (2,074;3,511)	1.18 (0.80;1.74), 0.395		1.17 (0.80;1.73), 0.417
	Subgroup, IV (I^2=0.0%, p = 0.594)			1.11 (0.81;1.52), 0.505	0.0	1.05 (0.76;1.45), 0.779
High resistance	Desai, 2015	57, 493 (228;1,066)	45, 427 (191;957)	1.89 (0.63;5.64), 0.254		1.82 (0.61;5.42), 0.284
	Madanitsa, 2016	16, 3,861 (1,039;14,345)	18, 2,984 (992;8,979)	1.52 (0.27;8.71), 0.637		0.85 (0.18;3.92), 0.836
	Subgroup, IV (I^2=0.0%, p = 0.836)			1.78 (0.70;4.49), 0.224	0.0	1.41 (0.58;3.42), 0.452
Overall	Heterogeneity between subgroups: p=0.348			1.17 (0.87;1.57), 0.307	0.0	1.08 (0.80;1.47), 0.601

ISTp=intermittent screening and treatment in pregnancy. IPTp=intermittent preventive treatment in pregnancy. I^2=I-squared measure for heterogeneity, based on unadjusted values. I-V=inverse variance method for fixed-effect. Heterogeneity between subgroups represents the difference between the effect in low and high SP resistance areas. When there is considerable heterogeneity observed (I^2 >=75%) in one or more subgroups the tests for heterogeneity between subgroups are likely to be invalid and should be interpreted with caution. Values are mean (SD) unless indicated otherwise. The mean difference for asexual parasite densities at delivery represents the geometric mean ratio.

*The unadjusted mean difference reflects models that include the stratification factor gravidity (primigravidae vs secundigravidae vs multigravidae), which was used in some of the source studies, as well as site. Adjusted models also include anaemia at enrolment (haemoglobin < 11 g/dL), gestational age (binary, study-specific median), and maternal ITN use at enrolment

TABLE S5: COMPARISON OF GESTATIONAL AGE ASSESSMENT BY ULTRASOUND VS BALLARD

	N	Gestational age in days		Mean difference (95% CI) between Ultrasound and Ballard (days)	p-value
		Ultrasound	Ballard		
Overall	921	268.3	265.7	2.5 (1.7-3.4)	<0.001
No malaria	137	267.8	265.2	2.7 (0.4-4.9)	0.02
Patent only	193	269.8	266.3	3.5 (1.6-5.4)	0.001
Subpatent only	288	268.9	266.1	2.8 (1.3-4.3)	0.001
Any malaria	303	266.9	265.3	1.6 (0.0-3.2)	0.04