Supplementary Content

Title: Supplemental information to Desai et al, ‘Impact of sulfadoxine-pyrimethamine on the effectiveness of intermittent preventive therapy for malaria in pregnancy at clearing infections and preventing low birth weight: A prospective, multi-country observational study across Africa’

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# Supplementary Methods

## Power and sample size calculations

Sample size calculations were conducted using the PASS sample size module in NCSS software (version 2006).

### Therapeutic efficacy

The sample size was calculated using standard statistical methods for calculating sample size in a population survey. Because it was expected that the failure rate in multigravidae was at least half that in primi,-and secundigravidae, studies used a stratified design. The primary endpoint was the expected parasitological failure rate by day 42. Sample sizes were calculated to estimate the frequency of parasitological failure by day 42 (reinfection or recrusdescence) within 5% to 10% of the true value (precision=0.05 to 0.1) with 95% confidence, allowing for 15% loss to follow-up. A total of 248 women (162 primi,- and secundi gravidae and 86 multigravidae) per study would allow detection of a 10% failure rate in primi,- and secundigravidae and 5% in multigravidae, both with 5% precision. If the true failure rates were 50% and 25% in primi,- and secundigravidae and multigravidae, the corresponding precisions would be approximately 8% and 10% respectively.

### Delivery Endpoints

Placental malaria was used as the primary outcome because it was a malaria-specific end-point and more likely to reflect changes in SP-resistance. The sample size at delivery was based on detecting a 2-fold difference in the prevalence of placental malaria in pregnant women who had received at least 2 courses of SP versus women who received <2 courses of IPTp (test statistic two-sided Fisher's Exact test, alpha level 0.05, 80% power). Since this was a cross-sectional survey, no adjustment was made for loss-to follow-up. The total sample size to be recruited also depended on the anticipated ratio of women who had received ≥2 vs <2 courses of SP. For example, in areas where the coverage of ≥2 courses of IPTp-SP was estimated at 50%, sample size calculation were conducted using a 1:1 ratio and in areas where the coverage was estimated at 66.7%, or 75% a ratio of 2:1 and 3:1 was used respectively, etc..

To detect a 2-fold difference in placental malaria from 10% to 5% in areas with 50% coverage of ≥2 course IPTp-SP, a sample size of 948 women (474 in each group) was required. Similarly, 336 women (168 in each group) were required to detect a 2-fold difference from 25% to 12.5% in areas with higher malaria transmission. In areas with 66.7% coverage of ≥2 course SP, a sample size of 1104 women (736 ≥2 courses and 368 with <2 courses of SP) would be needed to detect a 2-fold differences from 10% to 5%, or 390 women (260 ≥2 courses and 130 with <2 courses of SP) to detect a difference between 25% and 12.5%. Similar methods were used for sample size calculations using other coverage estimates of ≥2 course SP and other estimates of the prevalence of placental malaria in <2 course group.

## Data analyses delivery module

### Propensity score models

In observational data, exposure groups may vary in their mean levels of demographics, behaviours, lab measurements, or other variables. If means differ on covariates that may influence outcomes, this may confound the relationship between the exposure of interest and outcomes. The use of propensity scores in observational studies have been shown to decrease confounding to allow for an unbiased treatment effect either through matching,[39] stratification,[40] or weighting. [41] In our study, propensity score is defined as the probability a patient receives a particular dose of SP during pregnancy. The approach we used in these analysis involved two steps: estimate the propensity scores and use these to calculate weights; and use the weights in outcome models.

Prior to propensity score estimation, predictor variables in the propensity score models were recoded to allow for as much cross-site comparability and retain as many participants as possible. When at least one site had a category with a small sample size, that category was lumped with others for all sites to arrive at robust estimates.

Our exposure of interest is the number of doses of IPTp-SP taken during pregnancy. For propensity score models, we treated this as a categorical exposure with the categories defined as zero, one, two, and three or more doses of doses of IPTp-SP. Propensity scores were estimated using generalized boosted models in the twang package of R version 3.0.0.[42], which use multiple non-parametric tree-based regression models to estimate inverse probability treatment weights for a categorical exposure.[41] Outcome models used the weights derived from these models as sampling weights and included site as a cluster-level term. These generalized boosted models have been shown to perform well in two-group treatment analyses, and results are promising in the multi-group method where a series of generalized boosted models are used in place of a multinomial logistic regression model.[42, 43] Variable selection is not as crucial to the model in generalized boosted models as it is in parametric models, [41] hence we included all available and relevant data. Since each site collected different subsets of data, we fit generalized boosted models at the site level and then aggregated the data for analyses. This approach has been found to exhibit the best performance for analyses that match on the propensity score,[44] though we are unaware of similar research with weighted analyses. A list of the variables used in propensity score estimation is included (Table S1). Any participant with incomplete covariate data was dropped and we fit propensity scores for each outcome due to differences in the percentage of missing data in each outcome. Propensity score models produce weights designed for the average treatment effect, which is the effect of everyone taking one more dose of IPTp-SP.

Balance between groups was assessed using standardized bias between each groups as well as population standardized bias (PSB) and population Kolmogorov-Smirnov (PKS) statistics. For each covariate, the PSB is calculating by taking the difference in absolute value between the propensity score weighted mean and the unweighted mean of the pooled sample across all treatments and divides that by the pooled standard deviation estimate. Since there are *M* treatments, there will be *M* PSB estimates: the final PSB is the maximum of the *M* estimates. PKS is calculated by finding the difference in absolute value between the weighted empirical distribution function for a treatment as compared to the unweighted empirical distribution function for the pooled sample across all treatment. This is done at all values of the covariate and the supremum of those values is taken as the PKS for that treatment. As with PSB, the maximum of the *M* PKS values is taken as the final PKS value. Further details on both statistics can be found in McCaffrey et al. [42]. Though, since we ran propensity score models for each site and outcome, balance is difficult to assess. We feel this is due to a few differ causes. First, is the challenge of assessing balance with multiple groups and how to distil estimates into a single number. Second, we ran propensity score models for each site and outcome, which also increases the dimensionality. Hence, for each outcome, this requires aggregating the balance assessments for four categories in eight models with approximately 20-30 variables for each site. Thus, there are models where balance on some covariates improved, but others where balance did not improve. Finally, some sites have small numbers of people with some SP dose categories, which may have an influence on the population assessments, such as PSB and PKS, and lead to biased assessments of balance. Outcome models

Outcome models were implemented in the survey package of R.[45] To account for any site-level differences, site was included as a covariate in models as well as designate as strata in a stratified random sample. Models were fit with the raw, unweighted data and then after incorporating the propensity score weights. Both used the survey package and treated the data as a stratified sample. Results for models fit on the whole dataset are reported in the “Overall” rows of the forest plots. Models were fit for subsets of sites based on the level of *Pf*DHPS K540E resistance and are reported on the “Low” (Burkina Faso and Mali), “Moderate” (Zambia), and “High” (Kenya, Malawi, and Uganda) rows of the forest plots. For binary outcomes, we took a similar approach to Zou[46] by assuming a Poisson distribution, except we used survey regression instead of generalized estimating equations (GEE). Thus, we report prevalence ratios (PRs) and corresponding 95% confidence intervals (CIs) for each incremental dose of IPTp-SP. For continuous variables, results are reported as the mean difference (95% CI) (MD) for each incremental dose of IPTp-SP. In all models, the relationship between the outcome and dose is assumed to be linear. Forest plots report the sample sizes, summary statistics, and PRs and 95% CIs.

The analyses can be broken into two sets: set one (Figures 3-4 and S2-S11) and set two (Figures S12-S24). In both sets, the “All” section contains results from models where site (when appropriate), gravidity, ITN use, and IPTp-SP dose are included as independent variables and the PRs and MDs reported are from the IPTp-SP term.

Two-way interaction term models by both gravidity and ITN use (Figure 2s to Figure 11s): For set one, other sections are derived from a model with terms for site (when appropriate), IPTp-SP doses, gravidity, ITN use last night, and interactions between IPTp-SP doses and gravidity and IPTp-SP doses and ITN use last night. (The three-way interaction was never helpful and was dropped from all analyses). Results reported in the forest plots are taken from linear combinations of necessary terms to estimate the effect of one additional dose of IPTp-SP for primi- and secundi-gravidae who did not use an ITN last night (G1/2, No ITN), multigravidae who did not use an ITN last night (G3+, No ITN), primi- and secundi-gravidae who used an ITN last night (G1/2, ITN), and multigravidae who used an ITN last night (G3+, ITN).

Two-way interaction term models by either gravidity or ITNs (Figure 12s to Figure 23s): In set two, all sections except the “All” section are calculated by running separate models for gravidity and ITN use. In the gravidity models, site (when appropriate), IPTp-SP doses, gravidity, and ITN use last night are included as main effects but only IPTp-SP doses and gravidity are interacted. In ITN use last night models, the same is true but only IPTp-SP doses and ITN use last night are interacted. Thus results are reported broken down by whether or not an ITN was used last night and whether or not the women were multigravidae. As opposed to the first set of models, these give us a clearer picture of the effect of ITNs and gravidity since these omit the other two-way interaction and, hence, assume the effect of IPTp-SP is not dependent on both gravidity and ITN use.

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# Supplementary Tables

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| Table 1s: Variables used in propensity score estimation. | | | | | | |
| Variable | Burkina Faso | Kenya | Malawi | Mali | Uganda | Zambia |
| Demographics |  |  |  |  |  |  |
| Age | X | X | X | X | X | X |
| Gravidity | X | X | X | X | X | X |
| Marital status | X | X | X | X |  | X |
| School level | X | X | X | X | X | X |
| Occupation | X | X | X | X |  | X |
| Husband’s occupation | X | X | X | X |  | X |
|  |  |  |  |  |  |  |
| Malaria Interventions |  |  |  |  |  |  |
| ITN use last night | X | X | X | X | X | X |
| IRS spraying |  | X |  |  | X | X |
|  |  |  |  |  |  |  |
| Birth-related |  |  |  |  |  |  |
| Hospital birth | X |  |  |  |  |  |
| Delivery by midwife | X | X | X | X |  | X |
|  |  |  |  |  |  |  |
| Wealth |  |  |  |  |  |  |
| Electricity | X | X | X | X | X | X |
| Television | X | X | X | X | X | X |
| Mobile Phone | X | X | X | X | X | X |
| Paraffin Lamp | X | X | X |  |  | X |
| Sofa set | X | X | X |  |  | X |
| Radio | X | X | X | X | X | X |
| Freezer or refrigerator | X |  | X | X | X | X |
| Bed with mattress | X | X | X |  | X | X |
| Table and chairs | X | X | X |  |  | X |
| Water source | X | X | X |  |  | X |
| Toilet | X | X | X |  | X | X |
| Fuel | X | X | X | X |  | X |
| Floor type | X | X | X | X |  | X |
| Roof type | X | X | X | X |  | X |
| Bicycle | X | X | X | X | X | X |
| Motorcycle | X | X |  | X | X | X |
| Car or truck | X | X |  | X | X | X |
| Ox or horse cart | X | X |  | X |  |  |
| Self-reported wealth status | X | X | X |  |  | X |
| Sleeping rooms | X | X | X |  |  | X |
| Household members | X | X | X |  |  | X |

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| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Table 2s: Baseline frequencies of mutant P. falciparum dhfr and dhps alleles that confer sulfadoxine and pyrimethamine resistance | | | | | | | | |
| N. of specimens pooled | San, Mali | Kita, Mali | Ziniare, Burkina Faso | Mansa, Zambia | Blantyre, Malawia | Tororo, Ugandab | Machinga, Malawi | Siaya, Kenya |
| 130 | 117 | 273 | 97 | 34 | 100 | 100 | 53 |
| % *dhfr* alleles (95% CI) | | |  |  |  |  |  |  |
| 51I | 38.5 | 28.04 | 49.08 | 93.66 | 92.42 | 100 | 99.95 | 99.31 |
| (37.72–39.28) | (27.42–28.66) | (47.94–50.23) | (93.13–94.19) |  |  | (99.92–99.98) | (99.22-99.41) |
| 59R | 22.33 | 29.07 | 50.44 | 90.65 | 96.97 | 95.99 | 68.59 | 98.19 |
| (21.66–22.99) | (28.44–29.7) | (49.3–51.58) | (90.01–91.28) |  | (95.80–96.18) | (68–69.18) | (98.04-98.34) |
| 108N | 38.44 | 24.34 | 57.75 | 99.58 | 98.48 | 100 | 99.95 | 99.97 |
| (37.66–39.21) | (23.75–24.94) | (56.62–58.87) | (99.44–99.72) |  |  | (99.92–99.99) | (99.95-99.99) |
| 164L | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| % *dhps* alleles (95% CI) | | |  |  |  |  |  |  |
| 436A | 36.97 | 70.35 | 77.71 | 0.45 |  | 2.6 | 0 | 7.05 |
| (35.26–37.69) | (69.75–70.95) | (76.88–78.54) | (0.36–0.55) |  | (1.95–3.26) |  | (6.67 – 7.43) |
| 436Y | 6.29 | 0 | 2.07 | 0 |  | 0 | 0 | 0 |
| (5.93–6.65) |  | (1.79–2.35) |  |  |  |  |  |
| 436F | 1.22 | 6.4 | 1.42 | 0 |  | 0 | 0 | 0 |
| (1.06–1.39) | (6.08–6.72) | (1.18–1.65) |  |  |  |  |  |
| 436H | 0 | 0 | 0 | 0 |  | 0 | 0 | 1.17 |
|  |  |  |  |  |  |  | (1.01 – 1.32) |
| 437G | 27.49 | 15.24 | 75.34 | 83.65 | 88.71 | 97.35 | 100 | 92.96 |
| (26.82–28.15) | (14.77–15.71) | (74.49–76.20) | (83.12–84.18) |  | (96.69–98.01) |  | (92.58 – 93.34) |
| 540E | 0 | 0.73 | 0 | 84.03 | 100 | 97.54 | 99.23 | 95.61 |
|  | (0.58–0.87) |  | (83.45–84.61) |  | (97.12–97.96) | (99.12–99.33) | (95.29 – 95.93) |
| 581G | 0 | 0 | 0 | 0 | 1.61 | 0.24 | 1.46 | 5.74 |
|  |  |  |  |  | (0.1–0.37) | (1.3–1.62) | (5.33 – 6.16) |
| 613S | 0 | 13.2 | 23.96 | 0 |  | 0 | 0 | 0 |
|  | (12.27–14.13) | (22.95–24.97) |  |  |  |  |  |
| 613T | 0 | 0 | 0.19 | 0 |  | 0 | 0 | 0 |
|  |  | (0.09–0.29) |  |  |  |  |  |
| Estimates generated by second-generation sequencing of dhfr and dhps loci in pools of parasites from each site, except where indicated. Frequencies below 0.1% are reported as zero. Values in parentheses are 95% confidence intervals computed based upon the read coverage at that locus. Sites were classified in one of three groups based upon the frequencies of dhps mutations A437**G**, K540**E**, and A581**G**: high resistance if all 3 mutations were present (Kenya, Uganda, and both sites in Malawi); moderate resistance if A581**G** was absent but both K540**E** and A437**G** were present at high frequency (Zambia); or low resistance if A581**G** was absent but K540**E** was present at low frequency (Mali and Burkina Faso).  a *dhfr* allele proportions are prevalence of mixed or mutant alleles as measured by Sanger sequencing of individual parasites.  b Samples in Uganda were collected from febrile children with acute uncomplicated malaria. | | | | | | | | |

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| Table 3s: Treatment response and hazard ratios for SP failure by SP resistance stratum | | | | | | | | | | | | | | | | | | | |
| SP resistance stratum | Day | Failure rates (95% CI)a | | | | |  | Crude HR (95% CI) | | | | |  | Adjusted HRb (95% CI) | | | | |
| PCR uncorrected | |  | PCR corrected | |  | PCR uncorrected | |  | PCR corrected | |  | PCR uncorrected | |  | PCR corrected | |
| High | 28 | 30.5% | (26.7%; 34.8%) |  | 15.8% | (12.7%; 19.4%) |  | 2.88 | (1.47; 5.64) |  | 2.46 | (0.98; 6.20) |  | 3.10 | (1.58; 6.10) |  | 2.67 | (1.03; 6.93) |
| Moderate |  | 14.1% | (8.0%; 24.2%) |  | 7.0% | (3.0%; 16.0%) |  | 1.42 | (0.59; 3.42) |  | 1.15 | (0.32; 4.07) |  | 1.38 | (0.57; 3.35) |  | 1.14 | (0.31; 4.19) |
| Low |  | 1.6% | (0.8%; 3.1%) |  | 0.9% | (0.4%; 2.1%) |  | ref |  |  | ref |  |  | ref |  |  | ref |  |
|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| High | 42 | 39.7% | (35.5%; 44.2%) |  | 21.1% | (17.5%; 25.2%) |  | 10.09 | (6.74; 15.10) |  | 20.56 | (8.12; 52.09) |  | 10.89 | (7.27; 16.32) |  | 22.96 | (9.05; 54.79) |
| Moderatec |  | 21.0% | (13.1%; 32.7%) |  | 10.7% | (5.2%; 21.4%) |  | 5.29 | (2.80; 9.97) |  | 10.83 | (3.09; 37.91) |  | 4.66 | (2.46; 8.82) |  | 9.58 | (2.86; 32.06) |
| Low |  | 4.9% | (3.4%; 7.1%) |  | 1.1% | (0.5%; 2.4%) |  | ref |  |  | ref |  |  | ref |  |  | ref |  |
| Resistance strata assigned based upon the frequencies of *pfdhps* mutations A437G, K540E, and A581G (see Results). High resistance: Siaya, Kenya, and Machinga and Blantyre, Malawi; moderate resistance: Mansa, Zambia; low resistance: San and Kita, Mali, and Ziniaré, Burkina Faso.  a Kaplan-Meier product limit estimates of failure by day 28 and day 42  b Adjusted for use of bednet and gravidity.  c Follow-up in Mansa, Zambia was limited to 35 days, after which women received their second dose of SP | | | | | | | | | | | | | | | | | | | |

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| Table 4s: Assessment for effect modification by Gravidity and ITN use in delivery module analyses | | | | | | | |
|  |  | Gravidity by dose interaction | | | ITN use by dose interaction | | |
| Outcome | Resistance class | F | df | p | F | df | p |
| Birthweight in grams | High | 0.12 | (1, 3255) | 0.72 | 0.09 | (1, 3255) | 0.77 |
|  | Moderate | 0.64 | (1, 332) | 0.42 | 5.53 | (1, 332) | 0.02 |
|  | Low | 2.01 | (1, 2174) | 0.16 | 0.61 | (1, 2174) | 0.44 |
|  | Overall | 1.53 | (1, 5769) | 0.22 | 0.78 | (1, 5769) | 0.38 |
| Low birthweight | High | 0.07 | (1, 3255) | 0.79 | 0.24 | (1, 3255) | 0.62 |
| (< 2,500 g) | Moderate | 0.44 | (1, 332) | 0.51 | 4.24 | (1, 332) | 0.04 |
|  | Low | 0.01 | (1, 2174) | 0.90 | <0.01 | (1, 2174) | 0.98 |
|  | Overall | 0.78 | (1, 5769) | 0.38 | <0.01 | (1, 5769) | 0.93 |
| Mean gestational age, | High | 0.24 | (1, 3188) | 0.62 | 0.68 | (1, 3188) | 0.41 |
| weeks | Moderate | 0.63 | (1, 326) | 0.43 | 2.29 | (1, 326) | 0.13 |
|  | Low | 0.42 | (1, 1889) | 0.52 | 0.43 | (1, 1889) | 0.51 |
|  | Overall | 0.75 | (1, 5411) | 0.39 | 0.53 | (1, 5411) | 0.47 |
| Preterm ( < 37 weeks | High | 1.19 | (1, 3188) | 0.27 | 2.82 | (1, 3188) | 0.09 |
| gestational age) | Moderate | 2.05 | (1, 326) | 0.15 | 0.73 | (1, 326) | 0.39 |
|  | Low | 0.11 | (1, 1889) | 0.74 | 0.65 | (1, 1889) | 0.42 |
|  | Overall | 0.69 | (1, 5411) | 0.41 | 2.67 | (1, 5411) | 0.10 |
| Small for gestational age | High | 0.29 | (1, 3170) | 0.59 | 0.17 | (1, 3170) | 0.68 |
|  | Moderate | 0.05 | (1, 326) | 0.83 | 2.36 | (1, 326) | 0.13 |
|  | Low | 0.33 | (1, 1883) | 0.56 | 0.03 | (1, 1883) | 0.87 |
|  | Overall | 0.05 | (1, 5387) | 0.82 | <0.01 | (1, 5387) | 0.97 |
| Any smear positive | High | 0.64 | (1, 3274) | 0.42 | 0.61 | (1, 3274) | 0.44 |
|  | Moderate | 3.09 | (1, 332) | 0.08 | <0.01 | (1, 332) | 0.96 |
|  | Low | <0.01 | (1, 2248) | 0.99 | 1.77 | (1, 2248) | 0.18 |
|  | Overall | 0.74 | (1, 5862) | 0.39 | 0.99 | (1, 5862) | 0.32 |
| Maternal smear positive | High | 0.29 | (1, 3267) | 0.59 | 1.44 | (1, 3267) | 0.23 |
|  | Moderate | 0.85 | (1, 332) | 0.36 | 0.15 | (1, 332) | 0.70 |
|  | Low | 0.03 | (1, 2232) | 0.86 | 2.76 | (1, 2232) | 0.10 |
|  | Overall | 0.27 | (1, 5839) | 0.61 | 2.01 | (1, 5839) | 0.16 |
| Placental smear positive | High | 0.05 | (1, 3249) | 0.82 | 0.03 | (1, 3249) | 0.86 |
|  | Moderate | 0.39 | (1, 332) | 0.53 | 0.48 | (1, 332) | 0.49 |
|  | Low | 0.40 | (1, 2175) | 0.53 | 2.31 | (1, 2175) | 0.13 |
|  | Overall | 0.58 | (1, 5764) | 0.45 | 0.14 | (1, 5764) | 0.71 |
| Acute or chronic | High | 2.70 | (1, 3208) | 0.10 | 0.05 | (1, 3208) | 0.83 |
| infection by histology | Moderate | 0.29 | (1, 332) | 0.59 | 0.39 | (1, 332) | 0.53 |
|  | Low |  |  |  |  |  |  |
|  | Overall | 2.80 | (1, 3544) | 0.09 | 0.05 | (1, 3544) | 0.83 |
| Haemoglobin (g/dL) | High | 0.75 | (1, 3263) | 0.39 | 0.60 | (1, 3263) | 0.44 |
|  | Moderate | 0.25 | (1, 331) | 0.62 | 0.52 | (1, 331) | 0.47 |
|  | Low | 1.87 | (1, 2037) | 0.17 | 2.89 | (1, 2037) | 0.09 |
|  | Overall | <0.01 | (1, 5639) | 0.99 | 1.15 | (1, 5639) | 0.28 |
| Any anemia (Hb < 11) | High | <0.01 | (1, 3263) | 0.93 | 14.81 | (1, 3263) | <0.001 |
|  | Moderate | <0.01 | (1, 331) | 0.996 | 4.06 | (1, 331) | 0.04 |
|  | Low | 3.00 | (1, 2037) | 0.08 | 1.95 | (1, 2037) | 0.16 |
|  | Overall | 0.02 | (1, 5639) | 0.88 | 9.92 | (1, 5639) | 0.002 |
| Moderate-to-severe | High | 2.52 | (1, 3263) | 0.11 | 0.05 | (1, 3263) | 0.83 |
| anemia (Hb < 9) | Moderate | 2.31 | (1, 331) | 0.13 | 0.99 | (1, 331) | 0.32 |
|  | Low | 0.08 | (1, 2037) | 0.78 | 0.55 | (1, 2037) | 0.46 |
|  | Overall | 1.06 | (1, 5639) | 0.30 | 0.01 | (1, 5639) | 0.90 |

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| Table 5s: Meta-regression of the relationship between the prevalence of PfDHPS-K540E and PfDHPS-A437G and mean difference or log RR-trend for IPTp based on matched data (GBM method) | | | | | | | |
| **Outcome** | **PfDhpsK540E** | | |  | **PfDhpsA437G** | | |
| **Slope** | **(95%CI)** | **P-value** |  | **Slope** | **(95%CI)** | **P-value** |
| Low birth weight | 0.999 | (0.991-1.008) | 0.870 |  | 0.998 | (0.986-1.011) | 0.744 |
| Mean birth weight | 1.300 | (0.650-2.600) | 0.391 |  | 1.270 | (0.424-3.798) | 0.613 |
| Malaria infection | 0.999 | (0.995-1.003) | 0.606 |  | 0.999 | (0.994-1.005) | 0.796 |
| Placental infection | 0.997 | (0.993-1.001) | 0.108 |  | 0.997 | (0.990-1.004) | 0.331 |
| Mean HB | 1.000 | (0.997-1.003) | 0.976 |  | 1.001 | (0.996-1.006) | 0.750 |
| Anaemia | 1.000 | (0.998-1.002) | 0.865 |  | 0.999 | (0.997-1.001) | 0.318 |
| Severe anaemia | 1.001 | (0.996-1.005) | 0.804 |  | 0.999 | (0.992-1.006) | 0.737 |
| Mean gestational age | 1.002 | (1.000-1.005) | 0.093 |  | 1.002 | (0.998-1.007) | 0.229 |
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# Supplementary Figures

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| Figure 1s: Flowchart *in-vivo* studies |
| **mITT (n=1222)**  Burkina Faso (n=307)  Mali (n=266)  Kenya (n=58)  Zambia (n=92)  Malawi Blantyre (n=253)  Malawi Machinga (n=246)  **Day 28 (n=1078)**  Burkina Faso (n=293)  Mali (n=254)  Kenya (n=55)  Zambia (n=61)  Malawi Blantyre (n=217)  Malawi Machinga (n=198)  **Lost (n=144)**  Burkina Faso (n=14)  Mali (n=12)  Kenya (n=3)  Zambia (n=31)  Malawi Blantyre (n=36)  Malawi Machinga (n=48)  **Contribute to analysis**  **by day 42 (n=1064, 87.1%)**  Burkina Faso (n=290, 94.5%)  Mali (n=253, 95.1%)  Kenya (n=54, 93.1%)  Zambia\* (n=61, 66.3%)  Malawi Blantyre (n=215, 85.0%)  Malawi Machinga (n=191, 77.6%)  **Lost (n=14)**  Burkina Faso (n=3)  Mali (n=1)  Kenya (n=1)  Zambia (n=0)  Malawi Blantyre (n=2)  Malawi Machinga (n=7)  **Women eligible (n=1435)**  Burkina Faso (n=312)  Mali (n=268)  Kenya (n=62)  Zambia (n=208)  Malawi Blantyre (n=283)  Malawi Machinga (n=302)  **Early refusals & no follow up (n=213)**  Burkina Faso (n=5)  Mali (n=2)  Kenya (n=4)  Zambia (n=116)  Malawi Blantyre (n=30)  Malawi Machinga (n=56)  **Kenya**  Recurrences (n=25)  - Recrudescences (n=11)  - Reinfections (n=11)  - Inconclusive PCR (n=0)  - Missing PCR (n=3)  **Zambia**  Recurrences (n=15)  - Recrudescences (n=7)  - Reinfections (n=7)  - Inconclusive PCR (n=0)  - Missing PCR (n=1)  **Malawi Blantyre**  Recurrences (n=84)  - Recrudescences (n=32)  - Reinfections (n=36)  - Inconclusive PCR (n=0)  - Missing PCR (n=16)  **Mali**  Recurrences (n=8)  - Recrudescences (n=2)  - Reinfections (n=4)  - Inconclusive PCR (n=1)  - Missing PCR (n=1)  **Burkina Faso**  Recurrences (n=19)  - Recrudescences (n=4)  - Reinfections (n=14)  - Inconclusive PCR (n=1)  - Missing PCR (n=0)  **Malawi Machinga**  Recurrences (n=87)  - Recrudescences (n=51)  - Reinfections (n=17)  - Inconclusive PCR (n=0)  - Missing PCR (n=19) |

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| \*Duration of follow-up in Zambia was 35 days after which the second dose of SP was given. |

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| **Two-way interaction term models by both gravidity and ITN use (**Figure 2**s to** Figure 11**s)** |
| Figure s: Mean gestational age, weeksa; effect estimates of each incremental dose of IPTp-SP among all women and modified by gravidity and ITN use. |
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| \\cdc.gov\private\M117\fwk2\mb\iptp_mon\iptp.mon.s.figures.set1.ga.20150827.tif |
| a Gestational age, determined by Ballard or where unavailable by LMP, was missing from a variable number of individuals at each site, data completeness varied from 76-100%. |

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| Figure 3s: Preterm birtha; effect estimates of each incremental dose of IPTp-SP among all women and modified by gravidity and ITN use. |
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| \\cdc.gov\private\M117\fwk2\mb\iptp_mon\iptp.mon.s.figures.set1.preterm.20150827.tif |
| a Preterm birth defined as a gestational age < 37 weeks. |

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| Figure 4s: Small for gestational age (SGA)a; effect estimates of each incremental dose of IPTp-SP among all women and modified by gravidity and ITN use. |
| \\cdc.gov\private\M117\fwk2\mb\iptp_mon\iptp.mon.s.figures.set1.sga.20150827.tif |
| a Small for gestational age defined as birth weight for gestational age less than 10th percentile using an ultrasound-derived fetal size nomogram for a sub-Saharan African population.[47] |

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| Figure 5s: Any smear positivea; effect estimates of each incremental dose of IPTp-SP among all women and modified by gravidity and ITN use. |
| \\cdc.gov\private\M117\fwk2\mb\iptp_mon\iptp.mon.s.figures.set1.any.smear.20150827.tif |
| a Malaria infection defined as either a positive peripheral smear (maternal malaria) or a positive placental impression smear (composite endpoint). |

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| Figure 6s: Maternal smear positivea; effect estimates of each incremental dose of IPTp-SP among all women and modified by gravidity and ITN use. |
| \\cdc.gov\private\M117\fwk2\mb\iptp_mon\iptp.mon.s.figures.set1.matsmear.20150827.tif |
| a Malaria infection defined as a positive peripheral smear (maternal malaria). |

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| Figure 7s: Placental smear positivea; effect estimates of each incremental dose of IPTp-SP among all women and modified by gravidity and ITN use. |
| \\cdc.gov\private\M117\fwk2\mb\iptp_mon\iptp.mon.s.figures.set1.placsmear.20150827.tif |
| a Malaria infection defined as a positive placental impression smear. |

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| Figure 8s: Acute or chronic infection by histologya; effect estimates of each incremental dose of IPTp-SP among all women and modified by gravidity and ITN use. |
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| \\cdc.gov\private\M117\fwk2\mb\iptp_mon\iptp.mon.s.figures.set1.histopos.20150827.tif  a Active placental infection (acute or chronic) by placental histology, classified on a 5 point scale as described by Rogerson et al.[48]  Placental histology was not done in the 3 sites in west-Africa (low resistance strata). |

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| Figure 9s: Mean haemoglobin (g/dL)a; effect estimates of each incremental dose of IPTp-SP among all women and modified by gravidity and ITN use. |
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| \\cdc.gov\private\M117\fwk2\mb\iptp_mon\iptp.mon.s.figures.set1.hb.20150827.tif  a Haemoglobin in g/dL assessed by haemocue at delivery |

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| Figure 10s: Anaemia (Hb<11 g/dL)a; effect estimates of each incremental dose of IPTp-SP among all women and modified by gravidity and ITN use. |
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| \\cdc.gov\private\M117\fwk2\mb\iptp_mon\iptp.mon.s.figures.set1.any.anemia.20150827.tif  a Haemoglobin <11 g/dL assessed by haemocue at delivery |

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| Figure 11s: Moderate to severe Anaemia (Hb<9 g/dL)a; effect estimates of each incremental dose of IPTp-SP among all women and modified by gravidity and ITN use. |
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| \\cdc.gov\private\M117\fwk2\mb\iptp_mon\iptp.mon.s.figures.set1.mod.anemia.20150827.tif  a Haemoglobin <9 g/dL assessed by haemocue at delivery |

## **Two-way interaction term models by either gravidity or ITNs (Figure 12s to** Figure 24**s)**

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| Figure 12s: LBWa; effect estimates of each incremental dose of IPTp−SP among all women and modified by either gravidity or ITN use. |
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| \\cdc.gov\private\M117\fwk2\mb\iptp_mon\iptp.mon.s.figures.set2.lbw.20150827.tif  a LBW Low birthweight <2500 gr |

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| Figure 13s: Mean birthweighta; effect estimates of each incremental dose of IPTp−SP among all women and modified by either gravidity or ITN use. |
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| \\cdc.gov\private\M117\fwk2\mb\iptp_mon\iptp.mon.s.figures.set2.bw.20150827.tif  a birthweight in grams |

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| Figure 14s: Mean gestational age, weeksa; effect estimates of each incremental dose of IPTp−SP among all women and modified by either gravidity or ITN use. |
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| \\cdc.gov\private\M117\fwk2\mb\iptp_mon\iptp.mon.s.figures.set2.ga.20150827.tif  a Gestational age, determined by Ballard or where unavailable by LMP, was missing from a variable number of individuals at each site, data completeness varied from 76-100%. |

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| Figure 15s: Preterm birtha; effect estimates of each incremental dose of IPTp−SP among all women and modified by either gravidity or ITN use. |
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| \\cdc.gov\private\M117\fwk2\mb\iptp_mon\iptp.mon.s.figures.set2.preterm.20150827.tif |

a Preterm birth defined as a gestational age < 37 weeks.

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| Figure 16s: Small for gestational age (SGA)a; effect estimates of each incremental dose of IPTp−SP among all women and modified by either gravidity or ITN use. |
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| \\cdc.gov\private\M117\fwk2\mb\iptp_mon\iptp.mon.s.figures.set2.sga.20150827.tif  a Small for gestational age defined as birth weight for gestational age less than 10th percentile using an ultrasound-derived fetal size nomogram for a sub-Saharan African population.[47] |

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| Figure 17s: Any smear positivea; effect estimates of each incremental dose of IPTp−SP among all women and modified by either gravidity or ITN use. |
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| \\cdc.gov\private\M117\fwk2\mb\iptp_mon\iptp.mon.s.figures.set2.any.smear.20150827.tif  a Malaria infection defined as either a positive peripheral smear (maternal malaria) or a positive placental impression smear (composite endpoint). |

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| Figure 18s: Maternal smear positivea; effect estimates of each incremental dose of IPTp−SP among all women and modified by either gravidity or ITN use. |
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| \\cdc.gov\private\M117\fwk2\mb\iptp_mon\iptp.mon.s.figures.set2.matsmear.20150827.tif  a Malaria infection defined as a positive peripheral smear (maternal malaria). |

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| Figure 19s: Placental smear positivea; effect estimates of each incremental dose of IPTp-SP among all women and modified by either gravidity or ITN use. |
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| \\cdc.gov\private\M117\fwk2\mb\iptp_mon\iptp.mon.s.figures.set2.placsmear.20150827.tif  a Malaria infection defined as a positive placental impression smear. |

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| Figure 20s: Acute or chronic infection by histologya; effect estimates of each incremental dose of IPTp-SP among all women and modified by either gravidity or ITN use. |
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| \\cdc.gov\private\M117\fwk2\mb\iptp_mon\iptp.mon.s.figures.set2.histopos.20150827.tif  a Active placental infection (acute or chronic) by placental histology, classified on a 5 point scale as described by Rogerson et al.[48]  Placental histology was not done in the 3 sites in west-Africa (low resistance strata). |

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| Figure 21s: Mean haemoglobin (g/dL)a; effect estimates of each incremental dose of IPTp-SP among all women and modified by either gravidity or ITN use. |
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| \\cdc.gov\private\M117\fwk2\mb\iptp_mon\iptp.mon.s.figures.set2.hb.20150827.tif  a Haemoglobin in g/dL assessed by haemocue at delivery |

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| Figure 22s: Anaemia (Hb<11 g/dL)a; effect estimates of each incremental dose of IPTp-SP among all women and modified by either gravidity or ITN use. |
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| \\cdc.gov\private\M117\fwk2\mb\iptp_mon\iptp.mon.s.figures.set2.any.anemia.20150827.tif  a Haemoglobin <11 g/dL assessed by haemocue at delivery |

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| Figure 23s: Moderate to severe Anaemia (Hb<9 g/dL)a; effect estimates of each incremental dose of IPTp-SP among all women and modified by either gravidity or ITN use. |
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| \\cdc.gov\private\M117\fwk2\mb\iptp_mon\iptp.mon.s.figures.set2.mod.anemia.20150827.tif  a Haemoglobin <9 g/dL assessed by haemocue at delivery |

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| Figure s: Associations between each incremental dose of IPTp-SP and all secondary outcomes with all resistance class groupings included (a version with only the overall numbers is included in the main paper) |
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| \\cdc.gov\private\M117\fwk2\mb\iptp_mon\iptp.mon.figure5.full.20150827.tif |
| a Gestational age, determined by Ballard or where unavailable by LMP, was missing from a variable number of individuals at each site, data completeness varied from 76-100%.  b Haemoglobin in g/dL assessed by haemocue at delivery  c Small for gestational age defined as birth weight for gestational age less than 10th percentile using an ultrasound-derived fetal size nomogram for a sub-Saharan African population.[47]  d Malaria infection defined as either a positive peripheral smear (maternal malaria) or a positive placental impression smear (composite endpoint).  e Active placental infection (acute or chronic) by placental histology, classified on a 5 point scale as described by Rogerson et al.[48]  Placental histology was not done in the 3 sites in west-Africa (low resistance strata). |

## Meta-regression of the relationship between the prevalence of resistance markers and mean difference or log RR-trend for IPTp based on weighted data

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| Figure 25s: Meta-regression of the relationship between the prevalence of *Pf*DHPS-K540E and mean difference or log RR-trend for IPTp based on matched data (GBM method) |
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| Figure 26s: Meta-regression of the relationship between the prevalence of PfDHPS-A437G and mean difference or log RR-trend for IPTp based on matched data (GBM method) |
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