Impact of IPTp Regimen on Pregnancy Outcomes in a Malaria-Endemic Setting

**Authors**

* Asmith Joseph (ORCID: 0009-0004-6875-0868)

**Author affiliations**

1. College of Public Health, University of Georgia, Athens, GA, USA.

Corresponding author: asmith.joseph@uga.edu

Disclaimer: The opinions expressed in this article are the author’s own and don’t reflect their employer.

# 1. Summary/Abstract

*Write a summary of your project.*

# 2. Introduction

## 2.1 General Background Information

Malaria remains a major public health challenge worldwide, particularly in Sub-Saharan Africa, where the disease disproportionately affects vulnerable populations. Caused by Plasmodium parasites transmitted through the bite of infected Anopheles mosquitoes, malaria accounted for an estimated 249 million cases globally in 2022, marking an increase of five million cases compared to the previous year. Uganda alone reported over 597,000 malaria cases during this period, reflecting the country’s substantial malaria burden (World Health Organization, 2023; Talapko et al., 2019). Pregnant women represent one of the most vulnerable groups to malaria infection, facing an increased risk of severe clinical symptoms and poor pregnancy outcomes. Malaria during pregnancy has been associated with a range of adverse outcomes, including miscarriage, fetal loss, preterm birth, low birth weight, and neonatal mortality (Chua et al., 2021).

Efforts to mitigate the impact of malaria in pregnancy have centered on preventive strategies such as the use of insecticide-treated bed nets (ITNs) and chemoprophylaxis through intermittent preventive treatment during pregnancy (IPTp). Two widely used IPTp regimens are sulfadoxine-pyrimethamine (SP) and dihydroartemisinin-piperaquine (DP). While these preventive measures have shown significant benefits in reducing the risk of malaria-related complications, the effectiveness of these regimens may not be uniform across all contexts. In particular, emerging evidence suggests that the choice of IPTp regimen may influence how malaria episodes affect pregnancy outcomes. However, this potential effect modification remains underexplored in current literature. Additionally, maternal characteristics such as gravidity—the number of times a woman has been pregnant—may also play a role in shaping birth outcomes. Prior research has suggested that previous pregnancy experience may offer protective benefits against adverse outcomes, possibly due to improved physiological adaptation or better health-seeking behavior.

This study addresses two research questions. First, it examines whether the type of IPTp regimen modifies the association between malaria episode frequency and adverse birth outcomes in Ugandan pregnant women. Preliminary analyses suggest a potential interaction between malaria episodes and the SP regimen, indicating that the impact of malaria may differ by treatment. Second, the study investigates whether increased gravidity reduces the risk of adverse birth outcomes among younger pregnant women under 25 years. Early findings point to a protective effect of prior pregnancies in this subgroup. By addressing these questions, this study aims to clarify how preventive treatment strategies and maternal reproductive history influence birth outcomes in malaria-endemic settings. The results may inform targeted interventions to improve maternal and neonatal health in Uganda and similar contexts

By addressing these two research questions, this study aims to contribute meaningful insights into how preventive treatment strategies and maternal reproductive history influence pregnancy outcomes in malaria-endemic settings. The findings have the potential to guide more effective, equitable, and context-specific interventions to improve the health of pregnant women and their infants in Uganda and similar settings.

# 3. Methods

This study analyzed data from a double-blind randomized controlled trial conducted in Uganda, obtained from ClinEpiDB (Release #24, August 30, 2022). The trial evaluated IPTp with either sulfadoxine-pyrimethamine (SP) or dihydroartemisinin-piperaquine (DP) among HIV-uninfected pregnant women. The dataset comprised 782 observations, including maternal, pregnancy, and infant health information. Multiple births were recorded separately, and variable definitions adhered to original trial protocols.

The analysis focused on two primary objectives: (1) to assess whether the IPTp regimen modifies the association between malaria episode frequency and adverse birth outcomes (preterm birth, low birth weight, and stillbirth), and (2) to evaluate whether increased gravidity is associated with lower risk of adverse outcomes among women under 25 years.

Data preparation and analysis were performed using R. Date fields were standardized, and categorical variables were coded as factors. Variables with more than 20% missing data were excluded; those with lower missingness were retained and imputed where appropriate. Descriptive statistics and visual inspection were used to assess data integrity.

For the first research question, multivariable logistic regression models were fitted to examine the association between malaria episodes and adverse outcomes, including an interaction term for IPTp regimen. Covariates included maternal age, gravidity, and socioeconomic status. Predicted probabilities were calculated to facilitate interpretation of interaction effects.

For the second question, a subgroup analysis restricted to women under 25 years assessed the association between gravidity and adverse birth outcomes, using logistic regression and adjusting for relevant covariates. Gravidity was treated as a continuous variable, and sensitivity analyses were performed to assess robustness.

All statistical analyses were conducted using the most recent version of R (version 4.3.2).

# 4. Statistical analysis

## 4.1 Exploratory/Descriptive analyses

Descriptive analyses were conducted to summarize key maternal and clinical characteristics, including maternal age, gravidity, treatment assignment (SP or DP), and malaria episode frequency. Standard summary statistics were used for continuous variables, and proportions were reported for categorical variables. Distributions were visually assessed to identify potential outliers, and missing data were handled through imputation or exclusion based on the extent of missingness.

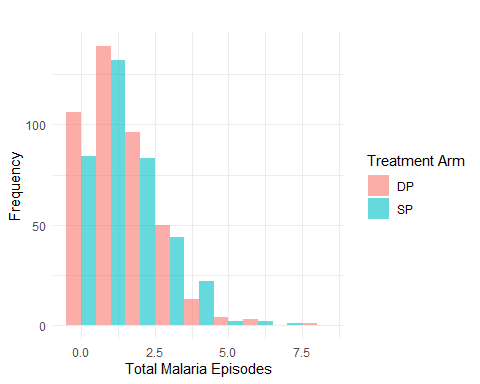
For the first research question, we evaluated whether the IPTp regimen modified the association between malaria episode frequency and adverse birth outcomes (preterm birth, low birth weight, and stillbirth). Multivariable logistic regression models were fitted, including an interaction term between malaria episodes and IPTp regimen. Models were adjusted for potential confounders, including maternal age, gravidity, and socioeconomic status. Predicted probabilities were estimated to facilitate interpretation of interaction effects.

For the second research question, we conducted a subgroup analysis among pregnant women under 25 years of age to assess the association between gravidity and adverse birth outcomes. Logistic regression models were used, adjusting for relevant covariates, including maternal age, malaria episode frequency, and treatment regimen. Gravidity was treated as a continuous variable.

**Table 1: Baseline Characteristics of Study Participants by IPTp Treatment Arm**

| Characteristic | Subcategory | DP (N=4121) | SP (N=3701) |
| --- | --- | --- | --- |
| Age (years) |  | 25.0 (5.0) | 25.0 (4.9) |
| Gestational Age (weeks) |  | 15.24 (1.97) | 14.97 (1.94) |
| Maternal Education Level (%) |  |  |  |
|  | Primary | 262 (66.7%) | 258 (66.4%) |
|  | Tertiary | 65 (16.5%) | 61 (15.7%) |
|  | University | 66 (16.8%) | 70 (18.0%) |
| Gravidity |  |  |  |
|  | 1 | 91 (22%) | 56 (15%) |
|  | 2–3 | 167 (41%) | 166 (45%) |
|  | ≥4 | 154 (37%) | 148 (40%) |
| Parity |  |  |  |
|  | 0 | 79 (19%) | 77 (21%) |
|  | 1–2 | 175 (42%) | 158 (43%) |
|  | ≥3 | 158 (38%) | 135 (36%) |
| Total Malaria Episodes |  |  |  |
|  | 1 | 245 (59%) | 216 (58%) |
|  | 2–3 | 146 (35%) | 127 (34%) |
|  | ≥4 | 21 (5.1%) | 27 (7.3%) |
| Total Malaria Episodes During Pregnancy |  |  |  |
|  | 1 | 179 (43%) | 165 (45%) |
|  | 2–3 | 138 (33%) | 120 (32%) |
|  | ≥4 | 95 (23%) | 85 (23%) |
| Malaria Infection Rate During Pregnancy |  | 1.01 (0.58) | 1.05 (0.58) |
| Placental Malaria (Rogerson Criteria) |  | 75 (18%) | 72 (19%) |
| Preterm Births Count |  |  |  |
|  | 1 | 391 (95%) | 348 (94%) |
|  | 2 | 21 (5.1%) | 22 (5.9%) |
| Stillbirth bin |  | 37 (9.0%) | 50 (14%) |
| Birthweight |  | 2.79 (0.64) | 2.81 (0.62) |
| History of Previous Malaria Episodes (%) |  | 40 (10%) | 35 (9%) |

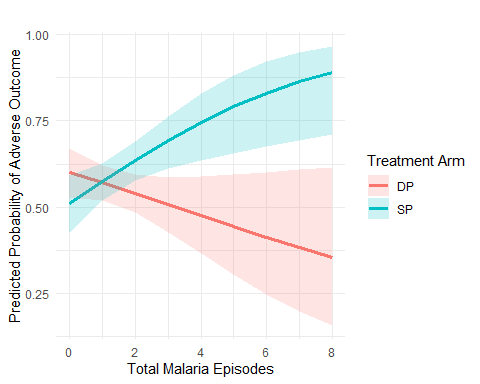
**Figure 1: Distribution of Total Malaria Episodes by IPTp Treatment Arm**



**Table 2: Outcome Measures and Malaria Exposure Variables Stratified by IPTp Regimen**

|  | **DP** N = 412*1* | **SP** N = 370*1* | **p-value***2* |
| --- | --- | --- | --- |
| Malaria Infection Rate During Pregnancy | 1.01 (0.58) | 1.05 (0.58) | 0.3 |
| Placental Malaria (Rogerson Criteria) | 75 (18%) | 72 (19%) | 0.7 |
| Preterm Births Count |  |  | 0.6 |
| 1 | 391 (95%) | 348 (94%) |  |
| 2 | 21 (5.1%) | 22 (5.9%) |  |
| Stillbirth bin | 37 (9.0%) | 50 (14%) | 0.044 |
| Birthweight | 2.79 (0.64) | 2.81 (0.62) | 0.7 |
| Composite Adverse Outcome | 232 (56%) | 219 (59%) | 0.4 |
| *1*Mean (SD); n (%) | | | |
| *2*Wilcoxon rank sum test; Pearson's Chi-squared test | | | |

*Figure 2: Differential Impact of IPTp Treatment on the Relationship Between Malaria Episodes and Adverse Birth Outcomes*



**Table 2: Outcome Measures and Malaria Exposure Variables Stratified by IPTp Regimen**

|  | **DP** N = 412*1* | **SP** N = 370*1* | **p-value***2* |
| --- | --- | --- | --- |
| Malaria Infection Rate During Pregnancy | 1.01 (0.58) | 1.05 (0.58) | 0.3 |
| Placental Malaria (Rogerson Criteria) | 75 (18%) | 72 (19%) | 0.7 |
| Preterm Births Count |  |  | 0.6 |
| 1 | 391 (95%) | 348 (94%) |  |
| 2 | 21 (5.1%) | 22 (5.9%) |  |
| Stillbirth bin | 37 (9.0%) | 50 (14%) | 0.044 |
| Birthweight | 2.79 (0.64) | 2.81 (0.62) | 0.7 |
| Composite Adverse Outcome | 232 (56%) | 219 (59%) | 0.4 |
| *1*Mean (SD); n (%) | | | |
| *2*Wilcoxon rank sum test; Pearson's Chi-squared test | | | |

# 5. Results

## 5.1 Basic statistical analysis

Baseline characteristics were similar between IPTp treatment arms, with comparable age, gestational age at enrollment, education, gravidity, and parity distributions (Table 1). Although overall malaria exposure measures were similar, the stillbirth rate was significantly higher in the SP arm compared to DP (14% vs. 9%; p = 0.044) (Table 2).

In our multivariable logistic regression analysis—adjusting for maternal age, gravidity, and education—the main effects of total malaria episodes (OR = 0.88, 95% CI: 0.75–1.03, p = 0.121) and treatment arm (OR = 0.69, 95% CI: 0.44–1.08, p = 0.102) were not significant. However, adding an interaction term between total malaria episodes and treatment arm significantly improved model fit (ΔDeviance = 10.11, p = 0.00148), with the interaction itself reaching significance (OR = 1.47, 95% CI: 1.16–1.88, p = 0.002). Notably, higher gravidity was protective (OR = 0.89, 95% CI: 0.80–0.98, p = 0.023), underscoring the potential benefit of prior pregnancy experience. Sensitivity analyses confirmed that these findings were robust, and model diagnostics (VIFs < 2) indicated no concerning multicollinearity. Collectively, these results suggest that the impact of malaria exposure on adverse birth outcomes is modified by the IPTp regimen, highlighting the importance of tailoring preventive strategies based on maternal risk profiles.

**Table 3: Interaction Between Malaria Exposure and IPTp Treatment Arm in Predicting Adverse Birth Outcomes**

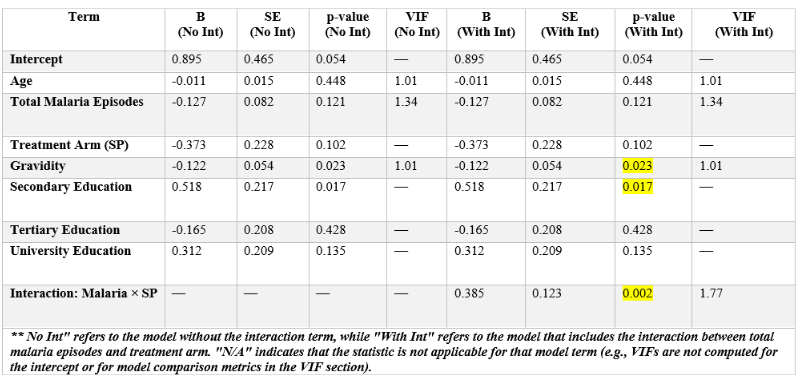
|  | Odds Ratio | Std. Error | z value | p-value | 95% CI Lower | 95% CI Upper |
| --- | --- | --- | --- | --- | --- | --- |
| Total Malaria Episodes | 0.88 | 0.08 | -1.55 | 0.121 | 0.75 | 1.03 |
| Treatment Arm (SP) | 0.69 | 0.23 | -1.64 | 0.102 | 0.44 | 1.08 |
| Age at Enrollment (years) | 0.99 | 0.01 | -0.76 | 0.448 | 0.96 | 1.02 |
| Gravidity | 0.89 | 0.05 | -2.27 | 0.023 | 0.80 | 0.98 |
| Secondary Education | 1.68 | 0.22 | 2.39 | 0.017 | 1.10 | 2.57 |
| Tertiary Education | 0.85 | 0.21 | -0.79 | 0.428 | 0.56 | 1.27 |
| University Education | 1.37 | 0.21 | 1.49 | 0.135 | 0.91 | 2.06 |
| Interaction: Malaria Episodes × SP | 1.47 | 0.12 | 3.13 | 0.002 | 1.16 | 1.88 |

**Table 4: Regression Diagnostics for IPTp Treatment Effect**

| Model | Residual Df | Residual Dev | Df | Deviance | p-value |
| --- | --- | --- | --- | --- | --- |
| No Interaction | 774 | 1045.674 | NA | NA | NA |
| With Interaction | 773 | 1035.565 | 1 | 10.10871 | 0.0014757 |

|  | Variable | GVIF | Df (VIF) | GVIF^(1/(2\*Df)) |
| --- | --- | --- | --- | --- |
| total\_malaria\_episodes | Total Malaria Episodes | 1.798086 | 1 | 1.340927 |
| study\_arm | Treatment Arm | 2.368263 | 1 | 1.538916 |
| age\_at\_enrollment\_years | Age at Enrollment | 1.005887 | 1 | 1.002939 |
| gravidity | Gravidity | 1.010161 | 1 | 1.005068 |
| education\_level | Education Level | 1.020210 | 3 | 1.003340 |
| total\_malaria\_episodes:study\_arm | Interaction: Malaria Episodes × SP | 3.119000 | 1 | 1.766069 |

**Table 5: Evaluating Effect Modification by IPTp Treatment on Malaria-Related Adverse Birth Outcomes Through Model Comparison**



**Table 4: “Incidence Rate Ratios for Malaria Episode Occurrence among Pregnant Women**

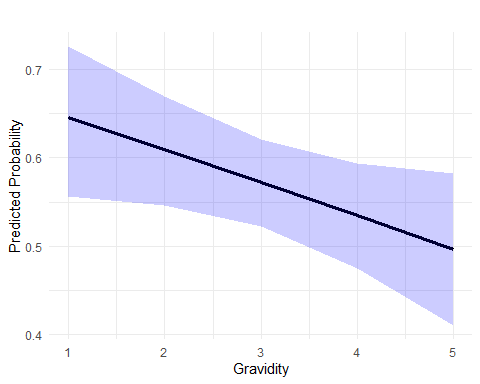
| Variable | IRR | X95..CI.Lower | X95..CI.Upper | p.value |
| --- | --- | --- | --- | --- |
| Intercept | 1.6081682 | 1.1297705 | 2.280714 | 0.0080210 |
| Treatment Arm (SP vs. DP) | 1.0552044 | 0.9382987 | 1.186523 | 0.3693644 |
| Age at Enrollment (years) | 0.9942737 | 0.9825662 | 1.006133 | 0.3422319 |
| Gravidity | 1.0095680 | 0.9675647 | 1.053391 | 0.6604499 |
| Education Level: Secondary | 0.9884423 | 0.8348897 | 1.170522 | 0.8926618 |
| Education Level: Tertiary | 0.8900707 | 0.7505115 | 1.055600 | 0.1805472 |
| Education Level: University | 1.0363703 | 0.8805393 | 1.220799 | 0.6680350 |

To investigate whether increased gravidity is associated with a reduced risk of adverse birth outcomes among young pregnant women (<25 years), we restricted our analysis to this subgroup. Adverse birth outcome was defined as the occurrence of any one of the following: preterm birth, stillbirth, or low birth weight (<2.5 kg). A logistic regression model was then fitted with gravidity, total malaria episodes, study arm, and education level as predictors. As shown in Table 6 and illustrated in Figure 3, increased gravidity was significantly associated with lower odds of adverse outcomes (OR = 0.86, 95% CI: 0.74–1.00, p = 0.044), suggesting that each additional pregnancy reduced the risk by approximately 14%. In contrast, total malaria episodes (OR = 0.97, 95% CI: 0.83–1.15, p = 0.745), treatment arm (SP vs. DP; OR = 0.96, 95% CI: 0.64–1.44, p = 0.841), and education level (secondary: OR = 1.39, 95% CI: 0.77–2.53, p = 0.270; tertiary: OR = 1.01, 95% CI: 0.57–1.80, p = 0.967; university: OR = 1.30, 95% CI: 0.73–2.30, p = 0.371) were not statistically significant predictors. These findings indicate that prior pregnancy experience is the primary protective factor against adverse birth outcomes in this population.

*Table 6: Adjusted Odds Ratios for Adverse Birth Outcomes Among Young Pregnant Women (<25 Years)*

| Variable | Odds Ratio (95% CI) | p-value |
| --- | --- | --- |
| Gravidity | 0.86 (0.74, 1) | 0.0444419 |
| Total Malaria Episodes | 0.97 (0.83, 1.15) | 0.7447399 |
| Treatment Arm (SP) | 0.96 (0.64, 1.44) | 0.8412639 |
| Secondary Education | 1.39 (0.77, 2.53) | 0.2697874 |
| Tertiary Education | 1.01 (0.57, 1.8) | 0.9668397 |
| University Education | 1.3 (0.73, 2.3) | 0.3709861 |

*Figure 3: Predicted Probability of Adverse Outcome by Gravidity (Age < 25)*



For the primary analysis focused on women under 25, our logistic regression model revealed a statistically significant protective effect of gravidity on adverse birth outcomes. Although we generated additional diagnostic figures—such as ROC curves and calibration plots—to assess overall model performance, these figures indicated only modest discriminative ability (with AUC values near 0.55–0.60) and calibration issues. Given that our key finding is the significant association between increased gravidity and reduced risk of adverse outcomes, we present the adjusted odds ratios in Table 6 as the main results. Detailed model diagnostics and alternative model evaluations are provided in the supplementary materials to demonstrate our comprehensive application of analysis techniques.

# 6. Discussion

## 6.1 Summary and Interpretation

*Summarize what you did, what you found and what it means.*

## 6.2 Strengths and Limitations

*Discuss what you perceive as strengths and limitations of your analysis.*

## 6.3 Conclusions

*What are the main take-home messages?*

*Include citations in your Rmd file using bibtex, the list of references will automatically be placed at the end*

This paper (1) discusses types of analyses.

These papers (2,3) are good examples of papers published using a fully reproducible setup similar to the one shown in this template.

Note that this cited reference will show up at the end of the document, the reference formatting is determined by the CSL file specified in the YAML header. Many more style files for almost any journal [are available](https://www.zotero.org/styles). You also specify the location of your bibtex reference file in the YAML. You can call your reference file anything you like.

# 7. References

1. Leek JT, Peng RD. [Statistics. What is the question?](https://doi.org/10.1126/science.aaa6146) *Science (New York, N.Y.)*. 2015;347(6228):1314–1315.

2. McKay B, Ebell M, Billings WZ, et al. [Associations Between Relative Viral Load at Diagnosis and Influenza A Symptoms and Recovery.](https://doi.org/10.1093/ofid/ofaa494) *Open forum infectious diseases*. 2020;7(11):ofaa494.

3. McKay B, Ebell M, Dale AP, et al. [Virulence-mediated infectiousness and activity trade-offs and their impact on transmission potential of influenza patients.](https://doi.org/10.1098/rspb.2020.0496) *Proceedings. Biological sciences*. 2020;287(1927):20200496.