Evaluating the Impact of Malaria Episodes and Preventive Treatment Regimens on Pregnancy Outcomes among Ugandan Women

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# 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 seeks to address two specific research questions to fill these gaps in knowledge. First, it examines whether the type of IPTp regimen modifies the association between the frequency of malaria episodes during pregnancy and adverse birth outcomes in Ugandan pregnant women. Preliminary analyses have indicated a significant interaction between malaria episode frequency and the SP treatment arm, suggesting that the impact of malaria on birth outcomes may differ depending on the preventive treatment received. Understanding whether the choice of regimen alters this relationship could inform clinical decisions and public health policies aimed at reducing malaria-related complications during pregnancy.

Second, the study investigates whether increased gravidity is associated with a reduced risk of adverse birth outcomes among younger pregnant women in Uganda. Subgroup analysis focusing on women under the age of 25 has revealed a potential protective effect of higher gravidity, with data suggesting that women with prior pregnancy experience may be less likely to experience adverse outcomes. Clarifying this relationship could help identify young, first-time mothers as a high-risk group and inform targeted interventions to improve maternal and neonatal health outcomes.

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.

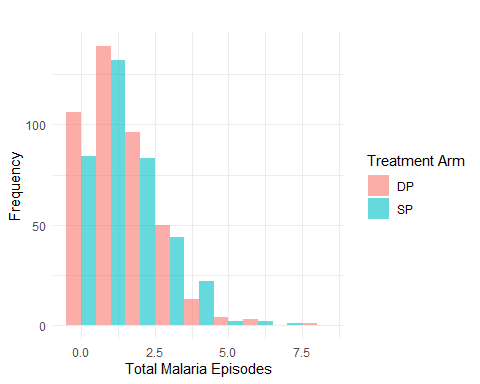
For the first research question, we evaluated whether the IPTp regimen modified the association between malaria episode frequency and adverse birth outcomes (preterm birth, low birth weight, and stillbirth). Multivariable logistic regression models were fitted, including an interaction term between malaria 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%) |

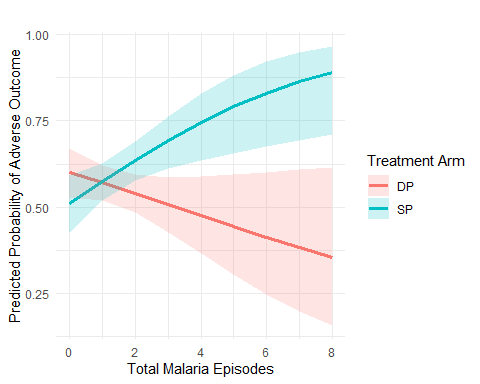
**Figure 1: Distribution of Total Malaria Episodes by IPTp Treatment Arm**



**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 | | | |

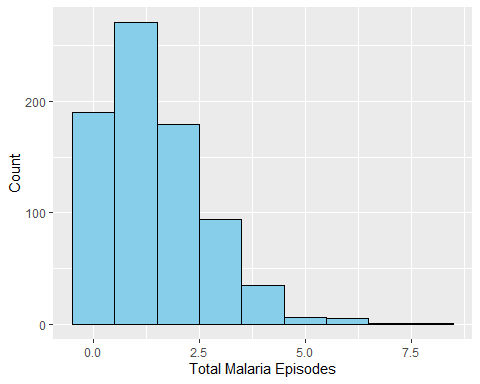
*Figure 2: Differential Impact of IPTp Treatment on the Relationship Between Malaria Episodes and Adverse Birth Outcomes*



**Table 1. Baseline Characteristics of IPTp Trial Participants**

| Characteristic | Subcategory | Monthly SP (n=391) | Monthly DP (n=391) |
| --- | --- | --- | --- |
| Age, years |  | 23 (19–27) | 23 (19–27) |
| Gestational Age at Enrollment (weeks) |  | 15.4 (13.3–17.6) | 15.0 (13.4–17.1) |
|  | 12–16 | 66 (17%) | 62 (15.8%) |
|  | 17–20 | 164 (42.2%) | 197 (50.1%) |
|  | 21–24 | 133 (34.2%) | 118 (30%) |
| Gravidity |  | 1.2 (0.9–1.7) | 1.1 (0.8–1.6) |
|  | 1 | 102 (26%) | 95 (24%) |
|  | 2–3 | 180 (46%) | 190 (49%) |
|  | ≥4 | 109 (28%) | 106 (27%) |
| Parity |  | 2.43 (1.67) | 2.43 (1.65) |
|  | 0 | 140 (36%) | 145 (37%) |
|  | 1–2 | 170 (44%) | 165 (42%) |
|  | ≥3 | 81 (20%) | 81 (21%) |
| Total Malaria Episodes (mean (SD)) |  | 1.06 (1.03) | 0.98 (0.95) |
| Maternal Nutritional Status/BMI (mean (SD)) |  | 22.5 (3.2) | 22.8 (3.1) |
| History of Previous Malaria Episodes (%) |  | 40 (10%) | 35 (9%) |
| Maternal Education Level (%) |  |  |  |
|  | A and O Level | 194 (49.4%) | 187 (48.1%) |
|  | Primary | 68 (17.3%) | 71 (18.3%) |
|  | Tertiary | 65 (16.5%) | 61 (15.7%) |
|  | University | 66 (16.8%) | 70 (18.0%) |

**Figure 1: Distribution of Total Malaria Episodes**



# 5. Results

## 5.1 Basic statistical analysis

**Table 2: Association Between Malaria Episodes and Risk of Preterm Birth**

|  | Adjusted Odds Ratio (aOR) | 95% CI Lower | 95% CI Upper | p-value |
| --- | --- | --- | --- | --- |
| Total malaria episodes during pregnancy | 1.04 | 0.95 | 1.14 | 0.401 |
| Age at enrollment (years) | 0.99 | 0.96 | 1.03 | 0.697 |
| Gravidity | 0.91 | 0.82 | 1.02 | 0.106 |
| Parity | 1.17 | 1.05 | 1.30 | 0.005 |
| Hypertension | 0.89 | 0.65 | 1.22 | 0.463 |
| Diabetes mellitus | 1.22 | 0.88 | 1.69 | 0.237 |

**Table 3: Association Between Malaria Episodes and Risk of Stillbirth**

|  | Adjusted Odds Ratio (aOR) | 95% CI Lower | 95% CI Upper | p-value |
| --- | --- | --- | --- | --- |
| Total malaria episodes during pregnancy | 0.96 | 0.83 | 1.10 | 0.533 |
| Age at enrollment (years) | 0.99 | 0.95 | 1.04 | 0.752 |
| Gravidity | 0.88 | 0.75 | 1.04 | 0.133 |
| Parity | 0.90 | 0.77 | 1.06 | 0.214 |
| Hypertension | 1.05 | 0.67 | 1.65 | 0.827 |
| Diabetes mellitus | 0.97 | 0.59 | 1.56 | 0.905 |

**Association between Malaria Episodes and Adverse Birth Outcomes** A total of 782 pregnant women were followed in our study, and we began with the hypothesis that a higher frequency of malaria episodes during pregnancy might lead to poorer birth outcomes. To explore this, we first employed logistic regression to assess the relationship with preterm birth. Contrary to our initial expectations, the analysis revealed that an increase in malaria episodes was not associated with a higher risk of preterm delivery (adjusted odds ratio [aOR]: 1.04; 95% CI: 0.95–1.14; p = 0.401; Table 4a). We then refined our approach by using a penalized Firth logistic regression model, which is particularly useful when dealing with rare events or small subgroups. This model too showed no significant link between the number of malaria episodes and stillbirth (aOR: 0.96; 95% CI: 0.83–1.10; p = 0.559; Table 4b). These findings suggest that the story is more complex than a simple linear relationship—factors such as maternal age, gravidity, or hypertension did not appear to drive these outcomes either, prompting us to consider that other biological or environmental influences might be at play.

**Effect of Treatment Arm on Malaria Episode Incidence** Subsequent analyses focused on whether the type of preventive treatment influenced the occurrence of malaria episodes. Two treatment arms—dihydroartemisinin-piperaquine (DP) and sulfadoxine-pyrimethamine (SP)—were compared using a Poisson regression model, with adjustments for age, gravidity, and education level. The analysis indicated that the incidence of malaria episodes did not differ significantly between the groups (incidence rate ratio [IRR]: 1.02; 95% CI: 0.92–1.12; p = 0.756; Table 4c). These findings suggest that, despite differences in treatment regimens, the overall frequency of malaria episodes remains similar, implying that variations in treatment strategy may have a limited effect on malaria episode incidence in this study population.

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

|  | IRR | 95% CI Lower | 95% CI Upper | p-value |
| --- | --- | --- | --- | --- |
| 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 |

## 5.2 Full analysis

*Use one or several suitable statistical/machine learning methods to analyze your data and to produce meaningful figures, tables, etc. This might again be code that is best placed in one or several separate R scripts that need to be well documented. You want the code to produce figures and data ready for display as tables, and save those. Then you load them here.*

# 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.

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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.