ESTIMATING THE ASSOCIATION BETWEEN TYPES OF BED NET USAGE AND MALARIA INCIDENCE IN A COHORT OF CHILDREN IN KINTAMPO, GHANA

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INTRODUCTION

- Ghana faces one of the highest malaria burdens in the world.[1] In 2021, there were about 5.4 million reported cases of malaria and 12,500 malaria deaths.[1]
- The phase III trial of the RTS,S/AS01 malaria vaccine was a double-blind, randomized controlled trial conducted between March 27, 2009, and January 31, 2014, at 11 sites across seven sub-Saharan countries.[2] Previous research analyzing phase III trial data in Lilongwe, Malawi, revealed that bed net use was associated with a 38.68% reduction in malaria incidence (95% CI: 9.27% to 58.56%).[3] The study also suggested that combining the RTS,S/AS01 vaccine with bed nets was more effective in preventing malaria cases than using the vaccine alone.[3] However, the specific impact of bed net use alone on reducing malaria cases in Ghana during this trial has not been clearly established. It is also not clear whether the types of bed net usage, including imperfect use or perfect use, had different association with malaria incidence.
- **Purpose:** To estimate the association between types of bed net usage and malaria incidence among children in the control group of the phase III trial of RTS,S/AS01 in Kintampo, Ghana.

METHODS

Follow-up Segmentation and Malaria Episode Counting:
- The extension phase after the dose 3 was divided into three time periods, as depicted in Figure 1. The usage of the bed nets were documented during three home visits: at 12 months and 29 months after the third vaccine dose was given to the child, and one month before the trial ended.[4] Each measurement within an interval serves as a proxy for bed net usage during that time period. We counted the number of malaria episodes within each interval for every child.
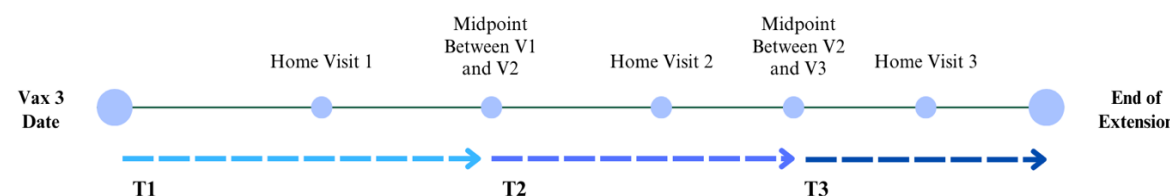

Figure 1. Timeline of Follow-up Home Visits and Data Collection Intervals.

Exposure:
- We coded bed net usage categories as follows: 0 - No bed net was observed on the child's bed, 1 - The bed net was either untreated, had at least one hole large enough to admit three fingers, or both, 2 - The bed net was treated and had no holes large enough to admit three fingers.

Outcome of Interest:
- Clinical malaria, defined in the trial as an illness accompanied by an axillary temperature of at least 37.5°C and *P. falciparum* asexual parasitemia (> 5000 parasites per mm³).[2]

Confounding Variables:
- Based on the literature, the age of the child, background malaria transmission intensity, and household socioeconomic status (SES) were identified as potential confounders that are likely to influence both a child's bed net usage and the number of malaria cases experienced.[3, 5-7]

➢ Household SES Index
- We used principal component analysis (**PCA**).[8] Roof type, wall type, floor type, and nighttime lights were included for PCA based on literature.[9-11] We scaled the variables and extracted the first principal component, PC_1, to generate the household SES index, with higher values indicating more advantages in living condition and resource access.

$$PC_1 = a_{11}X_1 + a_{12}X_2 + a_{13}X_3 + a_{14}X_4$$

➢ Background Malaria Incidence
- We used two machine learning (ML) algorithms—a random forest (**RF**) model and an artificial neural network (**ANN**). Our training and test data consist of data from control-group infants across three study sites—Lilongwe, Malawi; Kintampo, Ghana; and Lambaréné, Gabon (total n = 419). Twelve ecological variables were selected based on a study by Bell et al.[12] We also included the study site as a predictor to account for transmission heterogeneity across the sites. To tune the hyperparameters, we utilized the random search approach with 10-fold cross-validation. Finally, the model having the lowest root mean-square error (RMSE) and the highest predictive R-squared was used for estimating the background malaria incidence for each child in our study cohort.

➢ Baseline Age
- Time from the child's birth date to the first day of the corresponding follow-up.

Statistical Analysis: All analyses were done in RStudio for Windows, version 2023.09.1. We started with a **univariate analysis** that estimated the association between types of bed net usage and malaria incidence without adjusting for any confounders. We then conducted a **multivariate analysis,** adjusting for potential confounders, to see if and how the estimates would change. We added a random intercept to account for within-subject correlation since each child could have more than one observation. For both analyses, we used a mixed-effects Poisson regression model.

1) $\ln(E[Y]) = \beta_0 + \beta_1 * Imperfect\ Bed\ Net\ Use + \beta_2 * Perfect\ Bed\ Net\ Use + \ln(Follow\ up\ Days) + b_{pid[i]}$

2) $\ln(E[Y]) = \beta_0 + \beta_1 * Imperfect\ Bed\ Net\ Use + \beta_2 * Perfect\ Bed\ Net\ Use + \beta_3 * Age + \beta_4 * Household\ SES + \beta_5 * Background\ Malaria\ Incidence + \ln(Follow\ up\ Days) + b_{pid[i]}$

RESULTS

After removing incomplete data, 666 records from 242 children were included in the final analysis.
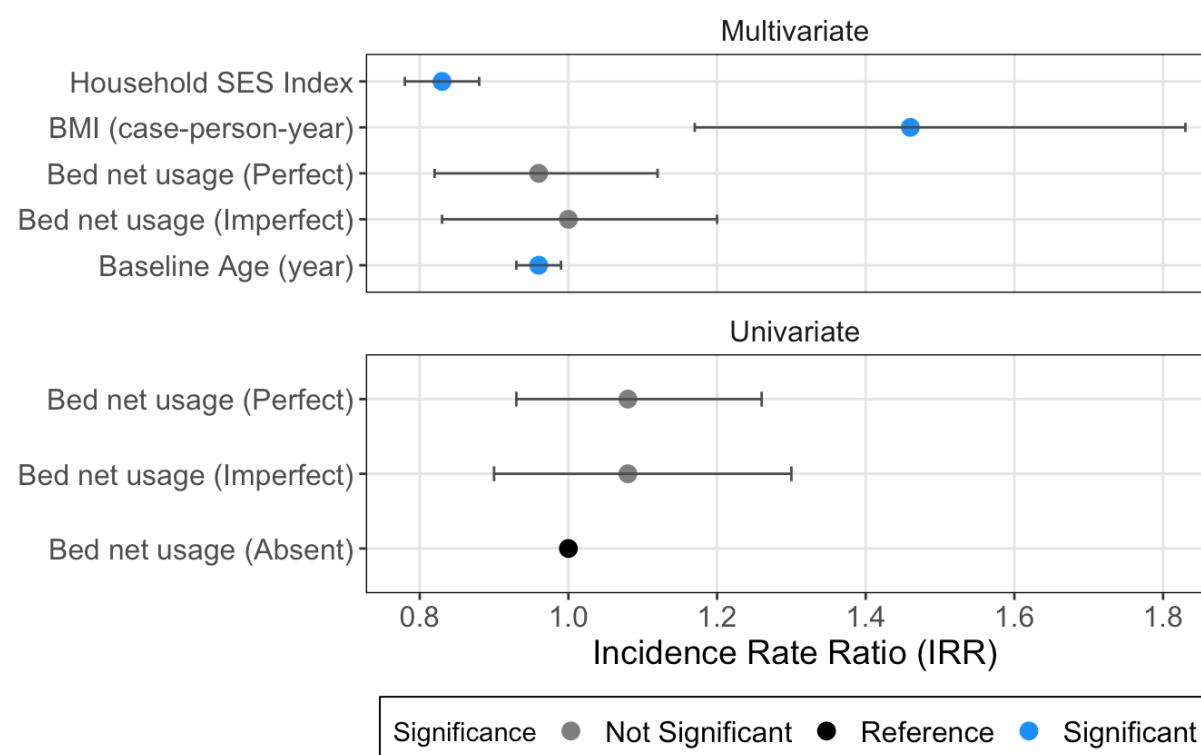

Figure 2. Incidence Rate Ratios of Malaria by Bed Net Usage and Control Variables.

Variable	Loading
Wall Type	0.595
Roof Type	0.590
Floor Type	0.324
Nighttime Lights	0.439

Figure 3. Loadings of Household Characteristics on the First Principal Component.
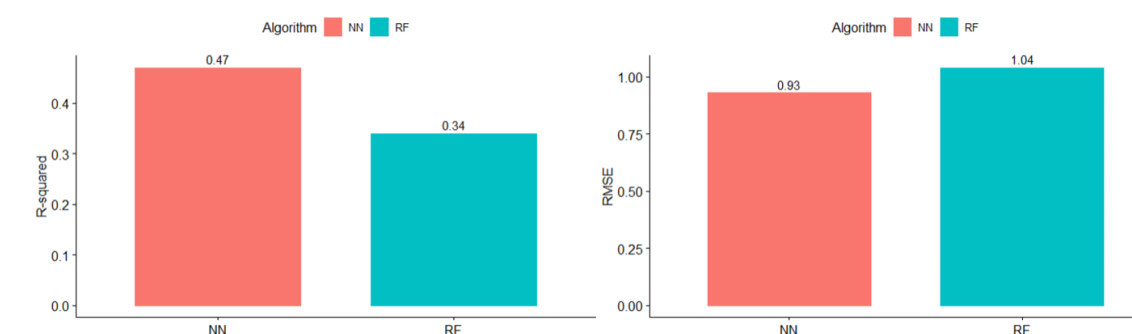

Figure 4. Comparison of Performance Between Machine Learning Algorithms.
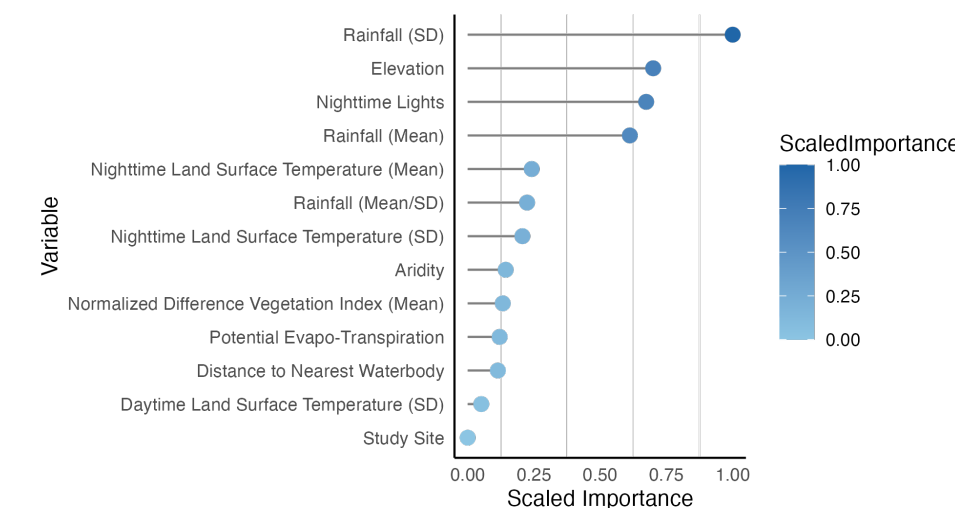

Figure 5. Permutation Feature Importance Plot for the Neural Network Model.

- We conducted a sensitivity analysis by varying the way of segmenting the extension phase. We employed the same unadjusted mixed-effects Poisson model and the results remained consistent.

CONCLUSIONS

- Our univariate and multivariate analyses did not reveal a significant impact of bed net use, whether perfect or imperfect, on malaria incidence in either model. Future studies could benefit from data with more consistent measurements of bed net usage.
- Our analysis suggests that targeted interventions in Ghana should prioritize resources and support for younger children and households with lower socioeconomic status, as well as for children living in areas with higher estimated background malaria transmission intensity. This will allow us to enhance the overall effectiveness of existing interventions and reduce the burden of this disease among the most vulnerable populations.

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