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EXAMINING THE CO-INFECTION EFFECTS OF HELMINTHS AND MALARIA IN AN INDONESIAN COMMUNITY

A Thesis Presented

by

ANDREA C. RODRÍGUEZ-SÁNCHEZ

Submitted to the Graduate School of the
University of Massachusetts Amherst in partial fulfillment
of the requirements for the degree of

MASTER OF SCIENCE

May 2021

School of Public Health and Health Sciences

Department of Biostatistics and Epidemiology

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ABSTRACT

EXAMINING THE CO-INFECTION EFFECTS OF HELMINTHS AND MALARIA IN AN INDONESIAN COMMUNITY

MAY 2021

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Malaria is one of the most prevalent vector-borne infectious diseases with major morbidity and mortality in sub-Saharan Africa and Southeast Asia. Recent epidemiological studies have shown that co-occurrence of soil-transmitted helminth (STH) infections, or infection caused by parasitic worms, are associated with increased risk of malaria infection. However, studies of the association between STH and malaria, and the effect of antihelminth (deworming) treatments that are more commonly used in areas with high STH infection rates, are sparse. Therefore, we explored the relationship between STH and malaria infection in an Indonesian community (N=1997) with high prevalence of both STH and malaria while controlling for covariates and evaluating the role of deworming treatment as a covariate. Participants with STH infection and/or malaria infection were categorized as either infected or uninfected using PCR testing (cycle threshold count) at both baseline and end of study. Self-report, blood, and stool samples were used to assess overall STH and malaria infection from September 2008 to July 2010. Descriptive statistics were used to assess the impact of STH infection on malaria outcomes. To quantify these associations, robust Poisson regression models were

used to assess the impact of baseline infections including STH infection on malaria while adjusting for age, sex, and the use of deworming treatment. Approximately 39.5% and 19.1% of all participants were infected with *Plasmodium vivax* and *P. falciparum*, respectively, at the start, while 18.0% and 9.96%, respectively, were infected at the end. A positive association was observed between *Ascaris lumbricoides* and *P. vivax*, and between *Necator americanus* and *P. falciparum* (PR = 1.04, 95% CI = 0.53 to 2.04; PR = 2.07, 95% CI = 1.00 to 4.29, respectively). While a negative association was observed between *N. americanus* and *P. vivax*, and between *A. lumbricoides* and *P. falciparum* (PR = 0.91, 95% CI = 0.44 to 1.89; PR = 0.66, 95% CI = 0.27 to 1.65, respectively). Overall, two of these models were significant (p = 0.062; p = 0.008; p = 0.030; p = 0.062, respectively). Similarly, there was a positive association observed between the use of albendazole treatment and STH and malaria outcomes.

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CHAPTER I

BACKGROUND AND SIGNIFICANCE

A. Introduction

Malaria is considered one of the most severe public health problems in the world, despite various prevention interventions and recommendations from health professionals on the benefits of using insecticide-treated bednets (ITNs), early diagnosis and treatment, and controlling the vectors.[1] In 2019, the World Health Organization (WHO) reported that almost half of the world's population lives in high risk areas for malaria with an estimated 229 million clinical episodes and 409,000 deaths attributable to malaria infections and its complications.[2] Although the majority of cases are found in the African region, in 2019 the WHO reported an estimated 6.3 million cases in the South-East Asia region and approximately 9000 deaths.[2] Overall, an estimated 3.4 billion people in 92 countries are at risk of being infected and developing the disease.[3] Due to an efficient vector transmission, an ideal environment, scarce health resources and socioeconomic instability, malaria is an especially prevalent disease in young children, pregnant women, due to incomplete immunity, and travelers.[4]

In vulnerable populations, malaria is associated with a variety of symptoms that can range from absent/mild to life threatening disease depending on the blood stage of the parasite. In an uncomplicated infection, the disease may presents itself in three main stages, although rarely observed: a cold stage, a hot stage, and a sweating stage with

symptoms such as fever, chills, headaches, vomiting, and general malaise occurring every second or third day.[5] In contrast, in a more severe infection, symptoms may include organ failure, severe anemia, acute respiratory distress syndrome, and abnormalities in blood coagulation.[4]

These incidence rates can increase depending on region, average environmental temperature, vector reproduction, and medical access. Individuals who reside in warmer areas with humid climates that have high population of *Anopheles* mosquitos (the vector for malaria), are at higher risk of becoming infected with malaria.[6] Additionally, if the mosquitos are able to live longer and infect more people, then those within that region are also at higher risk. Other modifiable risk factors include having access to medical attention and preventative tools such as insecticide-treated bednets and indoor insecticide treatments (IRS). Without these preventative strategies, the risk of being infected increases and not getting immediate medical attention increases the likelihood of death due to malaria infection.[6] Therefore, the ability to access these resources over time is a useful predictor of health risk.

Malaria, however, is not the only vector-borne disease that is common in specific regions and climates. Soil-transmitted helminths (STH) are parasitic worms that favor similar conditions to malaria and its vector, and are found in some of the most popular malaria infected spots such as Sub-Saharan Africa and Southeast Asia.[7] Similarly to malaria cases, more than 1.5 billion people have been infected with STH worldwide, with over 500 million of those infected being school-age children.[7] More specifically, according to the US Center for Disease Control and Prevention department, over an

estimated 1.1 billion cases were seen in 2013 within the African and Southeast Asian regions.[8] Due to similar geographic ranges, and impacted populations, several studies have investigated the relationships between malaria and STH.

Similarly, to malaria, STH infections are associated with immunocompromising symptoms that can range from mild to life-threatening depending on infection intensity, (the number of parasitic worms present in an individual). In a more intense infection, the most common symptoms that are present are diarrhea, abdominal pain, nutrient deficiency, general weakness, and impaired growth and physical development.[7] In extreme cases, an infection of very high intensity could present symptoms like intestinal obstruction, requiring special surgical procedures to resolve.[7] With significant infection prevalence in communities, and with similar risk factors, this study therefore proposes a secondary analysis of data from a randomized control trial (RCT) to examine the relationship between STH, measured by PCR-based cycle threshold count (Ct) and malaria infection, as indicated by Ct of parasitemia, among a cohort of Indonesian household members using data collected between September 2008 and July 2010.

B. Physiology of the Relationship between STH and Malaria Infection

Malaria and STH are caused by two different groups of parasites, a *Plasmodium* spp. microorganism and either hookworm species or *Ascaris* species parasitic worms, respectively.[9–11] In general, both parasites require a human host in order to continue their life cycle, however, the way in which they do so is fairly different. In terms of malaria, *Plasmodium* spp. require transportation from a vector, more specifically a female

Anopheles mosquito, to penetrate into a human host's liver through the blood, and then later on, to the bloodstream.[7] Once inside the host, *Plasmodium* parasites are able to multiply and prepare for the next transmission to occur through a different *Anopheles* mosquito. In contrast, in terms of STH, helminths do not require a vector but do require a human host and access to feces. The eggs of the helminths are fertilized in feces that later are deposited on soil which allows the eggs to hatch larvae.[10,11] Once in the larval stage, humans must come into contact with the helminths either through the touch of the infected soil or through ingestion of larvae in order to become infected.[10,11] Once infected, and depending on the specific helminth, the human host begins to show symptoms and increase parasitic density. Although these parasites have very different life cycles and transmissions, these two infections may impact the host's immune system in a similar way, lowering the host's defenses and reproducing at a fast rate causing major clinical impacts. In addition, it has been found that STH infections causes an immune response in the host that suppresses T-cell activity, or a body's ability to respond to infection quickly, and renders the host more susceptible to other co-infections.[12]

Due to such an impactful effect of infection, and the fact that co-infections are common, it has been hypothesized that when one infection occurs, the human host may be more susceptible to another infection at the same time or later in life due to an impaired ability to react to subsequent infection.[13] As a result, communities are attempting to keep up with these co-infections by providing specific treatments that mainly target the controllable infection such as STH and are readily accessible. [7,14] These types of treatments are called antihelminth treatments, with albendazole being the most common. By providing a treatment that focuses on reducing the density and burden of

STH, it may influence how the host is able to fight off the remaining malaria infection, impacting the host's chances of better clinical outcomes from a co-infection.

C. Epidemiology of the Relationship between STH and Malaria Infection

Five epidemiologic studies have evaluated the co-infection between STH and malaria, all of which are cross-sectional in design.[15–19] Of these studies, two studies took place in West Africa (Ghana, and Nigeria),[16,17] two in Central Africa (Gabon and Cameroon),[15,19] and one in Ethiopia.[18] Age ranges were 0-15 years in two studies,[15,19] 0-100 years in one study,[16] 0-40 years in one study,[17] and 15-45 years in one study.[18] In all the studies, information was collected via questionnaires, along with both blood samples (both thick and thin sample slides) and stool samples,[15–19] In terms of the outcome, all the studies evaluated helminth and malaria as a co-infection, while three studies also looked at helminth and malaria infection individually.[15,16,18] Overall, all the studies included age, sex, and socioeconomic status as covariates.[14-18] Three studies found a positive association between helminth and odds of malaria infection,[17–19] one study was null,[16] and one found an inverse association.[15] In terms of a possible confounding, only two studies considered deworming treatment having an effect on infection,[16,19] with one finding evidence for a positive association.[19]

In the only study that yielded a positive association when considering a deworming treatment, Ndamukong-Nyanga et al. conducted a cross-sectional survey that involved 1138 school-aged children in Southwest Cameroon.[19] Participants consisted of children of both sexes between the ages of 4 and 15 years who had been enrolled in one of the study schools that had received parental/guardian consent between 2012 and 2014.

Questionnaires, fever assessment, blood, and stool samples were collected from eligible participants. Additionally, all individuals that were positive for either malaria or STH infection received free malarial and deworming treatments as part of a community prevention program. Overall prevalence for individual malaria and helminth infection was 38% and 2.5% respectively, however, prevalence for co-infection was significantly lower ranging from 2.6% to 0.2% depending on the location of the schools.

In summary, all five epidemiological studies were limited in regard to study design and sample size, all with a cross-sectional design and only two studies with a sample size larger than 1000 people,[16,19] and all of the studies were conducted in Africa. Out of the two studies taking into consideration deworming treatment, neither of which assessed it as a covariate, rather just focused on the infections overall.

D. Study Objectives, Significance and Innovation

This study proposes to assess the relationship between STH infection, and risk of malaria, both measured by disease infection in Indonesian communities adjusting for age, sex, and use of deworming treatment. Specifically, the aim of the study is:

> Specific Aim: Use data collected from household surveys in Indonesian villages to evaluate the relationship between STH infection and risk of malaria.

> Hypothesis 1: People with a positive STH infection will have a higher risk for malaria co-infection, as compared to people who are negative for STH infection.

This investigation will contribute to the sparse epidemiological literature on the association between STH and malaria infection among Indonesian communities.

This proposal is **innovative** in being one of the few to study the relationship between STH infection and risk of malaria infection in Indonesia as opposed to Sub-Saharan Africa, focusing on helminth co-infection affecting risk of malaria. It is also **innovative** in its power to control for covariates and ability to evaluate the role of albendazole treatment as a covariate.

This study is **significant** because co-infection rates and the use of deworming treatments are rapidly growing in places like Africa and Southeast Asia. Few studies have looked at the association between STH and malaria infection among Southeast Asian regions, and this study can contribute to a more comprehensive understanding of this relationship and its risk factors.

CHAPTER II

STUDY DESIGN AND METHODS

A. Study Design and Population

We evaluated the relationship between STH and malaria infection in Indonesian communities using data from the Resource Competition study: an ecological study conducted between September 2008 and July 2010.[13] Adult and children community members were randomly enrolled from Indonesian village households and were all initially considered as potential participants for this study. Household members were eligible to participate if they were adult males, females and children. These households were located within the Ende district of Flores Island, Indonesia with a focus on communities within Nangapanda. This particular area was chosen by the investigators due to a high prevalence for malaria and being a high endemic area for STH.[20] All individuals within a household were considered eligible. The exclusion criteria were: 1) pregnant women, 2) children younger than 2 years of age, and 3) persons with illness.[14] This left 3,491 individuals out of 4,650 eligible for this study. Of these 3,491 participants included in the dataset, 1,494 participants were excluded due to missing data. This resulted in a final analytic population of 1,997 participants.

Clinical and demographic data, stool samples for STH infection and blood samples for malaria infection analyses were collected from the enrolled household participants at baseline, at 9 months, and at 21 months follow-ups.

Ethics: This secondary analysis used data collected with approvals by the Ethical Committee of the Medical Faculty, University of Indonesia approved the overall study protocol after institutional review (ethical clearance ref; 194/PT02.FK/Etik/2006), with fully informed written consent from participants or from parents/guardians of children.[14]

B. Exposure Assessment

Overall STH infection status was obtained using a questionnaire at baseline and two years after the treatment. Stool samples were collected every year during the study period from participants in order to obtain STH infection cycle threshold count (Ct). For the purpose of this analysis, two dichotomous categorical variables were created using Ct for both *Necator americanus* and *Ascaris lumbricoides*, as these are the most common STH species found in this region of Indonesia. These variables were categorized as either "uninfected" or "infected" by taking into account that the lower the Ct detected, the higher the infection density within the individual. Any samples that failed to amplify by 50 Ct were automatically considered uninfected and those that were amplified below 50 Ct were considered infected.[13]

STH infection status was cross-checked with the information obtained from puskesmas (government-administered community health clinics) and a research team in Jakarta at the Department of Parasitology, University of Indonesia.[14] Additionally, specific helminth DNA was extracted from feces and analyzed using validated laboratory protocol and each sample was tested using real-time Polymerase Chain Reaction (PCR) to obtain accurate readings from the samples collected and a proper Ct. This specific test

was chosen to determine standard measures because PCR is the most accurate method of determining parasitic density as it correlates with visual fecal egg counts, which is a more traditional way of detecting and counting soil-transmitted helminths.[13]

C. Outcome Assessment

To obtain information on malaria status, the same questionnaire mentioned above was used. Follow-up questionnaires regarding general health and malaria related health concerns were given to each household every month. The survey questions assessed respondents had medically diagnosed malaria or if they show any malaria related symptoms. In this case, malaria symptoms are defined as fever (oral temperature greater than 37.5°C) and/or history of fever within 48 hours. In addition to malaria infection status, infection density was also obtained by collecting peripheral blood samples on randomly selected individuals over four years of age within each household at baseline, 12 months, and 24 months follow-up. Additionally, to properly assess the whole study population, those that were not chosen for venous blood collection had their finger pricked to evaluate malaria status. These samples were used to determine Ct of three species: *Plasmodium falciparum*, *P. malariae*, and *P. vivax* and used to determine the overall infection status of an individual. Any samples that failed to amplify by 50 Ct were considered uninfected.[13] For the purpose of this analysis, two dichotomous variables were created using Ct for both *Plasmodium falciparum* and *P. vivax*, as these are the most common malaria species in the Indonesia. These variables were categorized as either "uninfected" or "infected".

To assess validity of the malaria Ct, the reported values were cross-checked with the official community records mentioned above in the assessment of exposure and through proper laboratory procedures. These procedures consisted of using the blood samples collected and extracting them for DNA to test against specific polymers using multiplex PCR. The polymers selected are specifically used to detect some of the main human-infecting malaria pathogens (*P. falciparum*, *P. vivax*, and *P. malariae*).[13] Additionally, blood smears were also assessed using a laboratory protocol Giemsa stain and examined by expert microscopists.[10]

D. Covariate Assessment

Risk factors associated with both STH and malaria infection were assessed as possible confounders. These covariates included: age (in years), sex of individuals (male or female), and use of deworming treatment at baseline and end of study period.[13] They were abstracted from clinical records and questionnaires administered at baseline and monthly follow-ups. These were used to control for confounding in the potential relationship between co-infection of STH and malaria. To use deworming treatment as a covariate, this variable will be dichotomously categorized as “yes” or “no”.

CHAPTER III

DATA ANALYSIS

Specific Aim: Use data collected from households in Indonesian villages to evaluate the relationship between STH infection and risk of malaria.

All statistical analyses were conducted using RStudio version 1.2.5033. Modification such as creating new variables were made to account for STH and malaria infection outcome measures and missing data among the covariates. This modified dataset was only used for multivariable model building.

A. Descriptive Analysis

The total study population and the percent of participants who did not have a STH or malaria infection, as well as the number and percent of those missing data were assessed. The total number and percentage of those with STH or malaria infection was also calculated. The mean and SD of those with and without malaria infection were calculated for both baseline and end of study period time points.

B. Bivariate Analysis

The prevalence of STH and malaria infections were compared in regard to study population characteristics chi-square (X^2) tests and Fisher's exact tests for small cell frequencies. ANOVA was used to obtain p-values for continuous covariates.

C. Multivariable Analysis

Robust Poisson regression modeling was used to assess the relationship between STH and malaria infection. Separate models were made for each STH and malaria pathogen species at both baseline and end of study period. Covariates that caused a 10% change in the coefficient for STH infection was considered a confounding factor and included in all the final models. Prevalence ratios and 95% confidence intervals were reported for unadjusted and adjusted coefficient estimates.

CHAPTER IV

RESULTS

The final dataset consisted of 1,997 participants, as can be seen in Table 1. Of the 1,997 participants included in this analysis, 789 (39.5%) were infected with *N. americanus* at baseline and 359 (18.0%) at the end of follow-up, while 382 (19.1%) were infected with *A. lumbricoides* at baseline and 199 (9.96%) at the end of the study period. The mean age (SD) of participants infected with *N. americanus* and *A. lumbricoides* at baseline was 33.2 (19.3) and 26.5 (18.7) respectively (t-test: $p = 0.049$ and <0.001), while the mean age (SD) of participants infected with *N. americanus* and *A. lumbricoides* at the end of follow-up was 35.2 (20.1) and 27.5 (20.1) respectively (t-test for difference: $p = 0.0011$, and 0.0702 respectively). The proportion of females infected was higher in those infected with either *N. americanus* or *A. lumbricoides* at both baseline and end of study (58.7%, 42.6%, and 61.3%, 65.3% respectively) as seen in Figure 1, although this difference was not statistically significant (X^2 test: $p = 0.629$; 0.405; 0.396; and 0.07 respectively). A similar and not statistically significant increase was observed in participants who were treated with albendazole and were infected with *N. americanus* (0% vs 21.2%) or *A. lumbricoides* (0% vs 22.6%) at the end of the study when compared to the baseline (X^2 test: $p = 0.737$ and 0.779 respectively).

Results from *P. vivax* and *P. falciparum* infections are presented in Tables 2, 3, 4, and 5. Of the 1,997 participants, 122 (6.11%) were infected with *P. vivax* at baseline and 40 (2%) at the end of study, while 138 (6.91%) were infected with *P. falciparum* at baseline and 39 (1.95%) at the end of study. There was a slight increase in the number of males (50.8%) that were infected with *P. vivax* at baseline, with an inverse situation of

more females (60%) infected at end of study. On the contrary, more females were more likely to be infected with *P. falciparum* at both baseline and the end of study (58.7% and 66.7% respectively) as seen in Tables 4 and 5. The mean age (SD) of those infected with *P. vivax* at baseline and end of study was 24.1 (16.4) and 24.8 (18.3). Similarly, the mean age (SD) of those infected with *P. falciparum* at baseline and end of study was 23.2 (16.5) and 28.8 (18.8) respectively (Tables 2, 3, 4, and 5). In general, the number and percent of participants between 23 – 33 years of age that were infected with a *Plasmodium* spp. was greater at baseline than participants infected at the end of study of the study. Overall, there was significant increase in participants that received albendazole treatment and were found to be infected with either *P. vivax* (0% vs 47.5%) or *P. falciparum* (0% vs 53.8%) at the end of study when compared to those infected at baseline (p = <0.001).

Tables 6 and 7 shows the associations between dichotomized STH infection and *P. vivax* and *P. falciparum* infection. We observed a nonsignificant increase in the co-infection between *P. falciparum* and *N. americanus* in an unadjusted model but observed a significant increase in the adjusted model (PR = 1.13, 95% CI = 0.60 to 2.11, p = 0.711; PR = 2.07, 95% CI = 1.00 to 4.29, p = 0.01, respectively). Similarly, we also observed a small nonsignificant increase in *P. vivax* infection among participants infected with *A. lumbricoides* as compared to those not infected in both the unadjusted and adjusted model (PR = 0.97, 95% CI = 0.49 to 1.93, p = 0.932; PR = 1.04, 95% CI = 0.53 to 2.04, p = 0.912, respectively). On the contrary, we observed a nonsignificant decrease in *P.vivax* infection among participants infected with *N. americanus*, as well as in *P. falciparum* infection among those infected with *A. lumbricoides* as compared to those not infected in

both the unadjusted and adjusted models (PR = 0.64, 95% CI = 0.34 to 1.20, p = 0.165; PR = 0.91, 95% CI = 0.44 to 1.89, p = 0.802; PR = 0.56, 95% CI = 0.25 to 1.26, p = 0.162, respectively). However, in the adjusted model for *P. falciparum* infection among those infected with *A. lumbricoides*, there was a significant decrease observed (PR = 0.66, 95% CI = 0.27 to 1.65, p = 0.030). Furthermore, we observed some non-statistically significant collinearities between STH and malaria infection at baseline and *P. vivax* at the end of study in an adjusted robust Poisson regression model (PR = 0.11, p = 0.8272), as well as a slightly positive increase in mean age and a decrease in female participants that were infected with *P. vivax* when compared to those not infected (PR = 1.00, 95% CI = 0.97 to 1.02; PR = 0.69, 95% CI = 0.25 to 1.87, respectively), although these differences were not significant (p = 0.816; p = 0.464).

CHAPTER V

DISCUSSION

In this secondary analysis of a randomized control trial of STH and malaria co-infection in Indonesia, we observed both positive and negative associations between both STH infections and malaria parasitemia as measured by PCR. More specifically, we observed an overall decrease in participants infected with either *P. vivax* or *P. falciparum* at baseline and end of study when compared with those not infected. In other words, as STH infections were decreasing from baseline to end of study, malaria infections were also decreasing at those time points. In addition, we observed an increase in females being infected from baseline to end of study when compared to males being infected. Although statistical significant effects were not found with sex and were found with co-infection, these results are consistent with previous literature[17–19] and suggest potential for decreased malaria infection among those with STH infection. Interestingly, a positive association was also observed between the use of albendazole treatment and both STH and malaria infections, especially between *N. americanus* and *P. falciparum*. However, even though overall STH and malaria infections decreased between baseline and end of study, we observed an increase in the number of participants with malaria infections at the end of study that were treated with albendazole compared to the number of participants with malaria infection at baseline who received albendazole treatment, which is a similar result that a previous study had observed,[16] although only a few epidemiological studies have assessed the role deworming treatments may have on immune responses.

This study is not without limitations. One important limitation is loss to follow-up, since participant information was obtained from voluntary questionnaires. It is possible that individuals that developed less severe symptoms or were asymptomatic classified themselves as not infected with either STH or malaria. These individuals could have been less concerned about the outcome of the study as they might have seen it as time-consuming or a burden to participate in. In addition, it is possible that individuals might have not had the resources to participate for longer periods of time and therefore decide to leave the study early. This form of differential loss to follow-up would result in an attenuation of any measure association.

Non-differential misclassification of malaria outcome could have also occurred in our study, resulting in an underestimation of the association between STH and malaria infection. Participants were considered uninfected if samples failed to amplify by 50 Ct. Therefore, if a participant had provided samples during the incubation period, it would have been missed by the PCR. Since STH infection was also established using the same cut off Ct, this could have also misclassified participants in our study.

Regardless of the potential limitations, our study has several strengths. The prospective study design and collection of data at multiple time points limit the potential for temporal bias or recall bias which are common in other study designs that are used in previous literature. Our ability to adjust for covariates and evaluate the role of albendazole treatment as a covariate makes our study unique from other studies that also evaluated STH and malaria infection. Our study population was also a high-risk, but under-studied cohort of people in a community in Flores, Indonesia.

Overall, the present study found that those infected with *P. vivax* are negatively associated to those with an initial *A. lumbricoides* infection but positively associated to those with an initial *N. americanus* infection, while individuals infected with *P. falciparum* are positively associated to those with an initial *N. americanus* infection and negatively associated to those with an initial *A. lumbricoides* infection. Therefore, depending on the specific malaria infection, individuals can be more at risk of co-infection than those without an initial STH infection. This study provides preliminary results that lay the foundation for future studies assessing the association between STH and malaria infection among Indonesian communities. Further studies evaluating albendazole treatment as either an effect modifier or potential exposure to co-infection are warranted and will help explain the impact of co-infection has on communities at high risk such as Indonesia.

Table 1. Number and percent in final sample; n=1997

		Total	Percent
Original Study Sample		10,473	100%
Excluded	Pregnant women, children younger than 2 years, ill persons	3,491	33.33%
	Missing Data	1,494	14.26%
Final Sample Size		1,997	19.07%

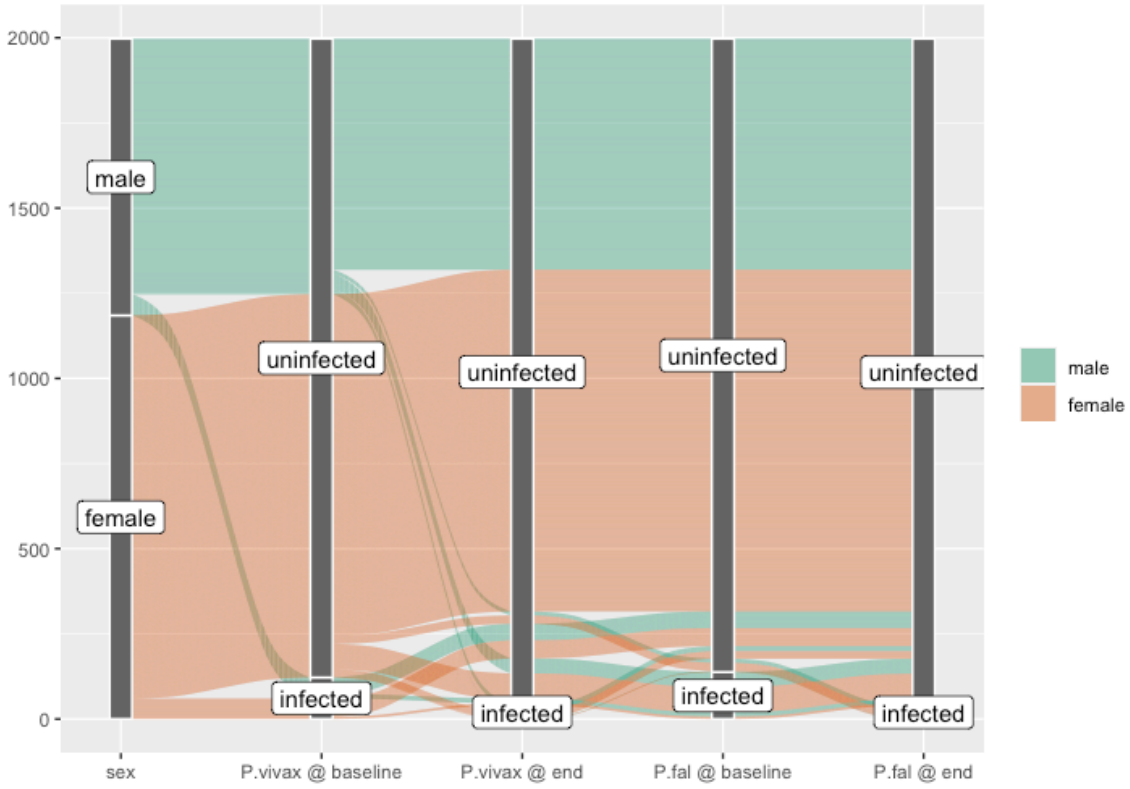

Figure 1. Malaria infection by sex

P.vivax/P.fal @ baseline = Plasmodium vivax/Plasmodium falciparum infection status at baseline; P.vivax/P.fal @ end = Plasmodium vivax/Plasmodium falciparum infection status at end of study.

Table 2. Distribution of covariates according to *Plasmodium vivax* infection at baseline

	Malaria Status			
	uninfected (N=1875)	**infected (N=122)**	**Total (N=1997)**	**p-value**
Sex				
Male	750 (40.0%)	62 (50.8%)	812 (40.7%)	0.01853
Female	1125 (60.0%)	60 (49.2%)	1185 (59.3%)	
Age (in years)				
Mean (SD)	32.6 (19.8)	24.1 (16.4)	32.1 (19.7)	<0.0001
Median [Min, Max]	33.4 [4.10, 80.1]	17.5 [4.16, 69.1]	32.7 [4.10, 80.1	
Albendazole Treatment				
No	1439 (76.7%)	122 (100%)	1561 (78.2%)	<0.0001
Yes	436 (23.3%)	0 (0%)	436 (21.8%)	

Table 3. Distribution of covariates according to *Plasmodium vivax* infection at end of study

	Malaria Status			
	uninfected (N=1957)	**infected (N=40)**	**Total (N=1997)**	**p-value**
Sex				
Male	796 (40.7%)	16 (40.0%)	812 (40.7%)	0.9315
Female	1161 (59.3%)	24 (60.0%)	1185 (59.3%)	
Age (in years)				
Mean (SD)	32.2 (19.8)	24.8 (18.3)	32.1 (19.7)	0.0106
Median [Min, Max]	32.9 [4.10, 80.1]	16.3 [5.16, 61.4]	32.7 [4.10, 80.1]	
Albendazole Treatment				
No	1540 (78.7%)	21 (52.5%)	1561 (78.2%)	<0.0001
Yes	417 (21.3%)	19 (47.5%)	436 (21.8%)	

Table 4. Distribution of covariates according to *Plasmodium falciparum* infection at baseline

	Malaria Status			
	uninfected (N=1859)	**infected (N=138)**	**Total (N=1997)**	**p-value**
Sex				
Male	755 (40.6%)	57 (41.3%)	812 (40.7%)	0.8733
Female	1104 (59.4%)	81 (58.7%)	1185 (59.3%)	
Age (in years)				
Mean (SD)	32.7 (19.8)	23.2 (16.5)	32.1 (19.7)	<0.0001
Median [Min, Max]	33.8 [4.10, 80.1]	16.7 [4.23, 72.4]	32.7 [4.10, 80.1]	
Albendazole Treatment				
No	1423 (76.5%)	138 (100%)	1561 (78.2%)	<0.0001
Yes	436 (23.5%)	0 (0%)	436 (21.8%)	

Table 5. Distribution of covariates according to *Plasmodium falciparum* infection at end of study

	Malaria Status			
	uninfected (N=1958)	**infected (N=39)**	**Total (N=1997)**	**p-value**
Sex				
Male	799 (40.8%)	13 (33.3%)	812 (40.7%)	0.347
Female	1159 (59.2%)	26 (66.7%)	1185 (59.3%)	
Age (in years)				
Mean (SD)	32.1 (19.8)	28.8 (18.8)	32.1 (19.7)	0.2677
Median [Min, Max]	32.9 [4.10, 80.1]	25.9 [8.12, 69.1]	32.7 [4.10, 80.1]	
Albendazole Treatment				
No	1543 (78.8%)	18 (46.2%)	1561 (78.2%)	<0.0001
Yes	415 (21.2%)	21 (53.8%)	436 (21.8%)	

Table 6. Multivariable association between baseline STH infection and *Plasmodium vivax* infection outcome

	Unadjusted		Adjusted	
	PR	95% CI	PR	95% CI
N. americanus				
Uninfected	-	Referent	-	Referent
Infected	0.64	(0.34, 1.20)	0.91	(0.44, 1.89)
A. lumbricoides				
Uninfected	-	Referent	-	Referent
Infected	0.97	(0.49, 1.93)	1.04	(0.53, 2.04)

Adjusted for age, sex, and deworming treatment. *p<0.05, **p<0.01
STH = Soil-Transmitted Helminths
The variable for soil-transmitted helminth infection was observed at baseline and the variable for *Plasmodium vivax* infection was observed at end of study

Table 7. Multivariate association between baseline STH infection and *Plasmodium falciparum* infection outcome

	Unadjusted		Adjusted	
	PR	95% CI	PR	95% CI
N. americanus				
Uninfected	-	Referent	-	Referent
Infected	1.13	(0.60, 2.11)	2.07	(1.00, 4.29)**
A. lumbricoides				
Uninfected	-	Referent	-	Referent
Infected	0.56	(0.25, 1.26)	0.66	(0.27, 1.65)*

Adjusted for age, sex, and deworming treatment. *p<0.05, **p<0.01
STH = Soil-Transmitted Helminths
The variable for soil-transmitted helminth infection was observed at baseline and the variable for *Plasmodium vivax* infection was observed at end of study

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