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Association of *Schistosoma haematobium* and *Plasmodium falciparum* Infection in Nigerian Children

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An abstract of

A thesis submitted to the Faculty of the Rollins School of

Public Health of Emory University

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Methods

This study examined the association between these two parasitic infections in Nigerian children using a combination of univariate and multivariate regression analysis. Independent variables were selected using a Chi Squared Test of Independence. Chosen variables included age, gender, residence type, residence zone, wealth quintile, mosquito net ownership, and the variable of interest, schistosomiasis symptoms.

Results

Data from the 2008 Nigeria DHS survey were analyzed to find variables affecting the prevalence of malaria infection. The analysis showed a significant protective effect of schistosomiasis infection on malaria infection (OR=0.85, 95% CI= 0.79 - 0.91, $p<0.01$). Gender was also found to have an effect on symptoms of schistosomiasis, with males having a higher prevalence than females ($p<0.001$).

Discussion

Children showing symptoms of a schistosomiasis infection are 1.17 times less likely to have an active malaria infection than those who do not show signs of a schistosomiasis infection. The data may have under reported true schistosomiasis infection rates, as only symptoms were recorded and not verified parasite loads. This should be considered when evaluating both schistosomiasis and malaria interventions in sub-Saharan Africa.

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Background

Malaria and helminth infections comprise two of the largest causes of morbidity and mortality in sub-Saharan Africa. Coinfection of parasites is not uncommon to the region, as both *Plasmodium spp.* and *Schistosoma spp.* are endemic to the tropics and sub-tropics. (1) Both parasites cause an abundance of social and economic burden in the affected areas. These diseases are major contributors to disease burden globally and have a serious effect on low-income countries where the climate is suitable for their vector to thrive. (1)

Of the Malaria causing species, *Plasmodium falciparum* and *Plasmodium vivax* are the two most common species with *Plasmodium falciparum* considered the deadliest. (2) Malaria transmitted by *Plasmodium falciparum* remains a major cause of mortality and morbidity in the tropics and subtropics. According to the 2009 world report, over half of the global population find themselves at risk of contracting malaria. That report saw 247 million cases that led to roughly 863,000 deaths mostly among African children. (3) This population made malaria the dominant parasitic disease of the tropics and one of the deadliest communicable diseases. (1) Malaria slows regional development in several ways: it affects fertility, population growth, investment, worker productivity, and causes premature mortality. Malaria may also affect fetal development due to the loss of immunity in the mother. (4) It is, however, curable if treatment and prevention measures are employed quickly after infection.

Plasmodium has two developmental life cycles consisting of a mosquito cycle and a primate host cycle. When gametocytes, both male and female, from a currently infected human are ingested during a mosquito blood meal, a process called exflagellation

occurs to the male gametocytes, resulting in the formation of microgametes. (5) Following fertilization of the female gametocyte, the macrogamete, a zygote is formed, which elongates to produce a motile organism called an ookinete. This ookinete penetrates the midgut wall surrounding the blood meal that brought the gametocytes into the *Anopheles* mosquito. There, under the basal membrane, an oocyst develops. After two to three weeks, many hundreds of sporozoites are produced within each oocyst. The oocysts rupture and the sporozoites are released into the hemocoel of the mosquito. The sporozoites are carried via circulation to the salivary glands, where they accumulate in the *Anopheles* salivary enzyme producing cells. During a subsequent blood meal, sporozoites are introduced into the salivary duct and injected into humans, infecting them. (5)

In the human, following the infectious blood meal, the sporozoites rapidly invade the liver, where, within a parenchymal cell, the parasite matures in approximately 15 days into a malarial nursery known as a schizont. Each schizont will produce thousands of infectious malarial cells called merozoites. Upon release, these merozoites invade erythrocytes via multiple receptor-ligand interactions and initiate the aptly named erythrocytic cycle. There is no evidence of a dormant liver stage in *Plasmodium falciparum* as there is in *Plasmodium vivax*. However, not all liver stage forms will mature on the same day, creating a pseudo-dormancy stage where parasites will be released over the course of several days. This uptake cycle takes as little as 60 seconds, leaving very little time for the immune system to respond to the presence of the merozoites. *P. vivax* invades only Duffy blood group-positive blood cells, blood cells that are released during inflammation, using the Duffy-binding protein found mostly on

the immature red blood cells, reticulocytes. The more virulent *Plasmodium falciparum* uses several different receptors that are highly redundant to allow for an almost guarantee of infection. Varieties of Duffy binding-like (DBL) homologous proteins and the reticulocyte binding-like proteins of *Plasmodium falciparum* recognize different red blood cell receptors other than the Duffy blood group or the reticulocyte receptors.

This approach allows *Plasmodium falciparum* to infect either immature reticulocytes in the same manner as *Plasmodium vivax* or any other red blood cell. The genome for *Plasmodium vivax* contains only one Duffy/erythrocyte binding gene whereas *Plasmodium falciparum* contains four such genes. Following a developmental cycle in the erythrocyte that lasts 3 days, merozoites go through a ring stage and trophozoite stage that assemble the infected red blood cell to degrade proteins into amino acids and increase the permeability of the cell. The trophozoites again form schizonts inside of vacuoles. However, these schizonts only form around eight additional merozoites. The merozoite count will eventually reach numbers high enough for the red blood cell to rupture, releasing the parasites into the bloodstream. The released merozoites will then infect additional red blood cells. Some of the merozoites develop into the male and female gametocytes, now called sporocytes, and will remain in the blood stream until an *Anopheles* mosquito takes a blood meal, thus ingesting the sporocytes and starting the *Anopheles* life cycle. (6)

The symptoms of a malaria infection occur following the erythrocyte cycle. The merozoites are released by the lysis of infected red blood cells and along with them, numerous waste substances, such as red blood cell membrane products and toxic factors such as glycosylphosphatidylinositol (GPI) are also released. These waste

products, particularly the GPI, activate macrophages and endothelial immune response to secrete cytokines and inflammatory proteins such as tumor necrosis factor, interferon-γ, interleukins-1, -6, and -8, lymphotoxin, as well as superoxide and nitric oxide.

Many studies have implicated the GPI tail, common to several merozoite surface proteins (MSP) such as MSP-1, MSP-2, and MSP-4, as a hallmark of parasitic infections. (5) The systemic symptoms of malaria such as headache, fever, nausea and vomiting, diarrhea, anorexia, immunosuppression, coagulopathy, tiredness, aching joints and muscles, thrombocytopenia, and central nervous system manifestations have been largely attributed to the cytokines released in response to these waste products. In addition to these factors, *Plasmodium spp.* DNA is also highly proinflammatory and can induce cytokinemia and fever. This DNA interacts intracellularly with the Toll-like receptor-9, leading to a cytokine storm that will, in turn, induce COX-2-upregulating prostaglandins leading to the induction of fever. (5) It has also been linked to apoptosis in bone marrow of developing erythrocytes and reticulocytes, leading to anemia. (6)

Schistosomiasis, or bilharziasis, is a parasitic disease prevalent in the developing world, predominantly Africa, South America, and Asia, with about 650 million people living in these areas. Roughly 207 million people are infected, with 180 million of those living in underdeveloped regions of Africa. This results in about 15,000 deaths per year, primarily in children below the age of 14. (8) The acute cause of the illness is an immune response predicated by the eggs laid by the schistosomes in the patient. *Schistosoma mansoni, Schistosoma japonicum,* and *Schistosoma haematobium* are the major species that are found in the developing world. *Schistosoma haematobium* is

found primarily in Africa and causes intense symptoms with the urinary tract, kidneys, and reproductive systems. *Schistosoma mansoni* and *Schistosoma japonicum* are typically found through areas of the Middle East and Southeast Asia, respectively. They each cause a type of intestinal fibrosis as well as hepatic diseases. (9)

Transmission of all three is dependent on contact with contaminated freshwater in which the intermediary snail hosts live. The snails contain Schistosoma eggs, which hatch and mature into cercariae. These cercariae penetrate the skin of the human host and become schistosomulae, a tailless version of the cercariae. The schistosomulae migrate to the hepatic portal via circulation and mature into adults. Adults then migrate in mating pairs to either the bowels or bladder depending on the species and reproduce sexually, sending out eggs in urine or feces. If these eggs are in freshwater containing the snail host, they will hatch into miracidia and infect the snails, restarting the cycle. This process takes a number of weeks and will typically not show symptoms until the eggs are released from the schistosomes. Eggs shed by the adult worms that do not pass out of the body can become lodged in the intestine or bladder causing inflammation. Repeated infection in children leads to anemia and malnutrition. The parasite will also damage the liver, intestinal system, lungs, and any other area of the circulatory system where the veins and arteries are small, allowing schistosomes to become lodged. These complications can appear even several years after the infection subsides. (9)

Both malaria and schistosomiasis are recognized as major factors contributing to the burden of disease and decreased development of the countries to which they are endemic. (10) The interactive pathology between *Plasmodium spp.* and *S. mansoni* has received a significant increase in research as a result of their overlapping endemic

regions; however, parasitic coinfection is a new area of research. Existing data often contradicts each other on the impact of a helminth infection on a malarial disease. At a clinical level, these infections have been shown to exist together frequently due to similarities in the habitats of their vectors and sanitation practices that have shown to increase the rates of infection for both infections independently. (11, 26) There is evidence to suggest that a helminth infection may offer a protective effect on transmission of malaria and is associated with a decrease in *Plasmodium spp.* density within the host. (11-14, 19-23) However, there is also evidence that suggests the contrary. Due to the nature of the specific helminths, the outcome may be helminth specific, with a difference of effect between Ascaris worms, hookworms, and schistosomes. (15-16)

The pathology of these infections is shown to affect different sectors of the immune system, thus stretching the resources more thinly. A typical *Plasmodium spp.* infection is associated with proinflammatory cytokine production, activation of cytotoxic T cells, and the use of IGG1 and IGG3 antibody isotopes. (24) To contrast this, a helminth infection is combated by the production of Th2 T helper cells and the production of IGE and IGG4 antibodies. The Th2 activation pathway is part of an immunoregulatory network which leads to downregulation of cytokine production, one of the key factors in combating a new *Plasmodium spp.* infection. (13) The helminth must downregulate the immune response pathway to survive in the host, which may also lead to the ability for other parasites to proliferate unhindered by the other branches of the host's immune system. (14)

There is biological plausibility that an interaction between these two parasites can occur, but the results of the interaction is not well known. The studies that have been previously published used mice and lab work to identify specific areas of the immune system that may be affected by coinfection. (19) However, to address the gaps in knowledge of the true effects of parasitic coinfection in sub-Saharan Africa, we have reported the results of a multiple regression analysis considering the data collected by Demographic and Health Surveys (DHS).

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Introduction

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Methods

This study examined the association between these two parasitic infections in Nigerian children using a combination of univariate and multivariate regression analysis. Independent variables were selected using a Chi Squared Test of Independence. Chosen variables included age, gender, residence type, residence zone, wealth quintile, mosquito net ownership, and the variable of interest, schistosomiasis symptoms.

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Data from the 2008 Nigeria DHS survey were analyzed to find variables affecting the prevalence of malaria infection. The analysis showed a significant protective effect of schistosomiasis infection on malaria infection (OR=0.85, 95% CI= 0.79 - 0.91, $p<0.01$). Gender was also found to have an effect on symptoms of schistosomiasis, with males having a higher prevalence than females ($p<0.001$).

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Children showing symptoms of a schistosomiasis infection are 1.17 times less likely to have an active malaria infection than those who do not show signs of a schistosomiasis infection. The data may have under reported true schistosomiasis infection rates, as only symptoms were recorded and not verified parasite loads. This should be considered when evaluating both schistosomiasis and malaria interventions in sub-Saharan Africa.

Introduction

Malaria and helminth infections make up the two of the largest causes of morbidity and mortality in sub-Saharan Africa. (1,3) Coinfection of parasites is not uncommon to the region, as both *Plasmodium spp.* and *Schistosoma spp.* are endemic to the tropics and sub-tropics. These two parasites cause an abundance of social and economic burden in the affected areas. (1)

Areas of Africa with >80% of Population at Risk for Malaria Infection

Areas of Africa with Endemic Schistosomiasis

Parasitic coinfection is a new area of research. Existing data often contradicts on the impact of a helminth infection on a malarial disease. At a clinical level, these infections have been shown to exist together frequently due to similarities in the habitats of their vectors and sanitation practices that have shown to increase the rates of infection for both infections independently. (11) There is evidence to suggest that a helminth infection may offer a protective effect on transmission of malaria and is associated with a decrease in *Plasmodium spp.* density within the host (11-14); however, there is also evidence that suggests the contrary. Due to the nature of the specific helminths, the outcome may be helminth specific, with a difference of effect between Ascaris worms, hookworms, and schistosomes. (15-16)

The pathology of these infections is shown to affect different sectors of the immune system, thus stretching the resources more thinly. (27) A typical *Plasmodium spp.* infection is associated with proinflammatory cytokine production, activation of cytotoxic T cells, and the use of IGG1 and IGG3 antibody isotopes. To contrast this, a helminth

infection is combated by the production of Th2 T helper cells and the production of IGE and IGG4 antibodies. (35) The Th2 activation pathway is part of an immunoregulatory network which leads to downregulation of cytokine production, one of the key factors in combating a new *Plasmodium spp.* Infection. (13) The helminth must downregulate the immune response pathway to survive in the host, which may also lead to the ability for other parasites to proliferate unhindered by the other branches of the host's immune system. (14)

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Methods

This analysis used data from the Nigeria 2008 DHS to conduct a series of univariate and multivariate regressions. This is a nationally representative and population-based household survey conducted by the DHS Program. (17) The 2008 Nigeria Survey is an expansion of the national survey series started in 1990, and 2008 was the first year that data on Neglected Tropical Diseases (NTDs) such as Schistosomiasis was included. The survey is designed to provide information on background characteristics of the respondents, fertility levels, nuptiality, sexual activity, fertility preferences, awareness and use of family planning methods, breastfeeding practices, nutritional status of

mothers and young children, early childhood mortality and maternal mortality, maternal and child health, and awareness and behavior regarding HIV/AIDS and other sexually transmitted infections.

The survey is targeted towards men and women aged 15 – 49 in selected households across Nigeria; however, family data of children between age 0 and 17 were also collected for NTDs. The specific focus of this analysis concerns the data from the 49,061 children that background, family, and NTDs data were collected on. (17)

Study Area

Nigeria is in West sub-Saharan Africa and is bordered by Benin, Chad, Cameroon, and Niger. The southern coast is in the Gulf of Guinea. Nigeria comprises 36 states and a territory that serves as a Federal Capital, Abuja. Within these states, there are a total of 774 federally recognized local governments. Culturally, Nigeria has more than 260 unique ethnic groups. The largest and most influential of these groups are Hausa, Igbo, and Yoruba. Nigeria is the most populous country in Africa with a population of more than 160 million.

Data Collection

The 2008 Nigeria DHS sample was selected using a cluster design consisting of 888 clusters total, 286 urban clusters and 602 rural clusters. Within these clusters, 36,800 households distributed proportionally between urban and rural were selected. There was a minimum target of 950 completed interviews per state established.

Household interviews were conducted with the head of household or another consenting adult in the case that the head of household was unable to respond. For

cultural considerations, the surveys were translated and prepared in both Hausa and Igbo languages. The adult chosen for the interview was asked about household demographic information, standard socio-economic indicators, educational level, household construction, and malaria indicators such as mosquito net ownership.

A men's questionnaire was administered to all men aged 15 – 59 in every second household. This questionnaire collected more specific data on background characteristics, birth history, family planning, malaria prevention and treatment, and awareness of HIV/AIDS.

In addition to this, a woman of reproductive age within the household, established by DHS to be 15 – 49 years of age, was selected at random to answer the women's questionnaire. This additional survey included similar questions to the men's questionnaire as well as additional questions related to fertility preferences, delivery and postnatal care, vaccinations and childhood illness, marriage, mortality, and domestic violence. The women's questionnaire also included questions about children including neglected tropical diseases and children's nutrition/health.

All children ten years old and younger as well as individuals of all ages in every third household were eligible to receive testing for *Plasmodium spp.*by rapid diagnostic test and microscopy. Rapid diagnostic tests were used for on-site diagnosis and treatment. Blood films were prepared by laboratory technologists and read by certified laboratory scientists in The Carter Center laboratories. Positive rapid diagnostic tests were offered on-site treatment. Pregnant individuals were offered prophylactic treatment. To ensure maximum participation for testing and sampling, households with absentee members were revisited at a later time to recruit the missing members.

Statistical Analysis

Data were downloaded directly from DHS and imported into SAS 9.1 for analysis. Exploratory analyses were conducted between the chosen independent variables using Chi Squared Test of Independence. A univariate analysis was also conducted between the independent variables and malaria status. Those variables that showed independence and an association with $p \leq 0.10$ were included in the final multivariate modeling procedure. Categorical variables were encoded using a dummy binary variable for each category. For each categorical variable, a reference category was chosen. Odds Ratios (ORs) at 95% Confidence Intervals (CIs) were also computed.

The multivariate modeling procedure consisted of creating multiple regression models adding more independent variables in each subsequent model. This was done to examine the effects of the additional variables on the hypothesis that having a Schistosomiasis infection affects the chance that the subject has a Plasmodium infection.

Independent Variables

Gender

Gender was determined in the household schedule in the household questionnaire with the questions "*Please give me the names of the persons who usually live in your household and guests of the household who slept here last night, starting with the head of the household,"* and *"Is (NAME) male or female?"* In the original dataset, this variable is named Sex. However, this variable was referred to as Gender in the analysis for sensitivity reasons.

Age Group

Age was determined in a similar way to gender. The follow up question was instead "*How old was (NAME) as of last birthday?"*

Zone of Residence

Zone of Residence was determined using GPS data along with the predetermined zones laid out by the researchers when choosing household/zone inclusion.

Residence

Residence was determined by the research cluster that the household falls within.

Wealth Quintile

Wealth quintile was determined by questions concerning the household's ownership of various consumer goods such as a television, car, radio, or kitchen equipment, dwelling characteristics such as flooring/housing material, water source, toilet facilities, as well as other characteristics related to wealth status.

Mosquito Net

Presence of at least one mosquito net was determined using the question "*Does your household have any mosquito nets that can be used while sleeping?"*

Symptoms of Schistosomiasis

Symptoms of Schistosomiasis was used as a surrogate for laboratory confirmed infection of *Schistosoma spp.* A laboratory analysis was not conducted at the time of questioning. However, respondents were asked the questions, *In the last 12 months, has (NAME) taken any drug for bilharazia [LOCAL TERM], which causes blood in the urine,"* and *"Have you noticed any blood in (NAME'S) urine in the last month?"* The

second question was specifically asked about Schistosomiasis infection and is therefore believed to be a good surrogate for infection. In addition to this, answers to the second question were chosen as a surrogate for infection as the first question did not pass a test of independence with Wealth Quintile (χ^2=17.56, p=.0015).

Results

A total of 49,061 children between ages 5 and 17 were included in the analysis. Of these, 25,005 were male and 24,056 were female. (Table 1) Gender was found to have an associate with malaria infection (χ^2=83.7, p<.0001) with females being more likely to have a positive test results for a *Plasmodium spp.* infection. Roughly 1% of children aged 5 to 17 reported having symptoms of schistosomiasis infection in the previous 30 days. The prevalence of these symptoms was higher in males than females and was found to have some association (χ^2=21.9, p<.001). This would normally disqualify it from inclusion in the multivariate analysis; however, the association with malaria infection was stronger. Thus gender was included in only the last two multivariate models. Schistosomiasis symptoms were also more common in Northern zones of Nigeria compared to the Southern zones (χ^2=309, p<.001).

An association existed between the zone of residence and malaria infection that was slightly stronger (χ^2=464.00, p<.001). For this reason, the variable was included only in a single multivariate analysis. Urban clusters within the zones had a higher proportion of households in the fourth and highest wealth quintiles (30%, 47%) compared with rural clusters (15%, 7%). Conversely, rural areas had a higher proportion of households in the lowest and second lowest wealth quintiles (29%, 27%) than urban areas (3%, 5%). An association was found between living in the South West zone and being in the

highest quintile (χ^2=8, p=.018). This result was expected, as the southern zones are more urbanized. Of the children with symptoms of schistosomiasis, 66 children also had a malaria infection (10.8%).

Table 1: Demographic Information of Nigerian Children Included in the Multivariate Analysis To Determine Association Between Malaria and Schistosomiasis Infection, 2020

Variable	Characteristics	n (%)	Symptoms of Schistosomiasis Infection	Positive for Malaria
Gender	Male	25005 (50.9%)	425 (1.7%)	3676 (14.7%)
	Female	24056 (49.1%)	188 (0.8%)	3904 (16.2%)
Age Group	5-9	23118 (47.1%)	231 (1%)	4046 (17.5%)
	10-14	18042 (36.8%)	271 (1.5%)	2598 (14.4%)
	15-17	7901 (16.1%)	111 (1.4%)	936 (11.9%)
Zone of Residence	North Central	7670 (15.6%)	161 (2.1%)	721 (9.4%)
	North East	7266 (14.8%)	240 (3.3%)	1482 (20.4%)
	North West	13610 (27.7%)	163 (1.2%)	2273 (16.7%)
	South East	5061 (10.3%)	20 (0.4%)	997 (19.7%)
	South Central	6705 (13.7%)	13 (0.2%)	1381 20.6%)
	South West	8751 (17.8%)	18 (0.2%)	726 (8.3%)
Residence	Urban	15257 (31.1%)	153 (1%)	1867 (12.2%)
	Rural	33805 (68.9%)	473 (1.4%)	5713 (16.9%)
Wealth Quintile	Lowest	10473 (21.3%)	272 (2.6%)	1812 (17.3%)
	Second	10408 (21.2%)	167 (1.6%)	1759 (16.9%)
	Middle	10116 (20.6%)	91 (0.9%)	1598 (15.8%)
	Fourth	9345 (19.0%)	65 (0.7%)	1346 (14.4%)
	Highest	8720 (17.8%)	26 (0.3%)	1065 (12.2%)
At Least One Mosquito Net	Yes	8340 (17.0%)	100 (1.2%)	1025 (12.3%)
	No	40721 (83%)	367 (0.9%)	7492 (18.4%)

Risk Factors for Malaria

Coding of the independent variables considered for multivariate analysis was done as a set of dummy variables to represent each category within the variable. (Table 2) The number of dummy variables were *n-1* where *n* represents the number of categories of the variable. They are presented as a set of 0 and 1, where each represented the value of the dummy variable. A reference category was chosen for each variable based on

literature research and the result of Chi Square tests between the independent variable and malaria infection.

Table 2: Dummy Variable Encoding of the Independent Variables Included in the Multivariate Analysis, 2020

Variable	Characteristics	Coding
Gender	Male	0 (referent)
	Female	1
Age Group	5-9	0, 0 (referent)
	10-14	1, 0
	15-17	0, 1
Zone of Residence	North Central	0, 0, 0, 0, 0 (referent)
	North East	1, 0, 0, 0, 0
	North West	0, 1, 0, 0, 0
	South East	0, 0, 1, 0, 0
	South Central	0, 0, 0, 1, 0
	South West	0, 0, 0, 0, 1
Residence	Urban	0 (referent)
	Rural	1
Wealth Quintile	Lowest	0, 0, 0, 0 (referent)
	Second	1, 0, 0, 0
	Middle	0, 1, 0, 0
	Fourth	0, 0, 1, 0
	Highest	0, 0, 0, 1
At Least One Mosquito Net	Yes	0 (referent)
	No	1
Symptoms of Schistosomiasis	No	0 (referent)
	Yes	1

Results of the univariate analysis for the association of malaria with the chosen independent variables showed a significant association between malaria and age group (17.5%, 14.4%, and 11.9%, $p<.001$). (Table 3) Moreover, there was a highly significant association when comparing rates of malaria infection between urban and rural residences (12.2%, 16.9%, $p<.001$). This was consistent with the literature as the improved housing and infrastructure in urban areas tends to produce a lower prevalence of malaria. (28) Showing symptoms of schistosomiasis infection showed an

association with malaria infection, but just outside of the p<.05 range. Having symptoms of schistosomiasis produced a lower OR than those that did not (OR = 0.81, p = .053). In total, five variables showed a significant association (p<0.05) with the prevalence of malaria infection. The remaining two variables showed an association at the p<0.10 level and were thus also included in the multivariate analysis at a later stage.

Table 3: Results of Univariate Analysis Testing for Association Between Chosen Independent Variables and Malaria, 2020

Variable	Characteristics	Positive for Malaria	OR (95% CI)	P Value
Gender	Male	3676 (14.7%)	1	
	Female	3904 (16.2%)	1.07 (0.75 - 1.39)	0.062
Age Group	5-9	4046 (17.5%)	1	
	10-14	2598 (14.4%)	2.42 (1.89 - 3.20)	<0.001
	15-17	936 (11.9%)	1.84 (1.43 - 2.95)	<0.001
Zone of Residence	North Central	721 (9.4%)	1	
	North East	1482 (20.4%)	2.56 (2.35 - 2.77)	0.025
	North West	2273 (16.7%)	2.21 (2.05 - 2.37)	0.031
	South East	997 (19.7%)	2.14 (1.93 - 2.35)	0.027
	South Central	1381 20.6%)	2.61 (2.37 - 2.85)	0.015
	South West	726 (8.3%)	0.88 (0.73 - 1.04)	0.009
Residence	Urban	1867 (12.2%)	1	
	Rural	5713 (16.9%)	1.27 (1.12 - 1.42)	<0.001
Wealth Quintile	Lowest	1812 (17.3%)	1	
	Second	1759 (16.9%)	1.02 (0.91 - 1.13)	0.033
	Middle	1598 (15.8%)	0.91 (0.80 - 1.02)	0.031
	Fourth	1346 (14.4%)	0.99 (0.85 - 1.13)	0.012
	Highest	1065 (12.2%)	0.55 (0.42 - 0.68)	<0.001
At Least One Mosquito Net	Yes	1025 (12.3%)	1	
	No	7492 (18.4%)	2.72 (2.60 - 2.83)	<0.001
Symptoms of Schistosomiasis	No	6346 (13.1%)	1	
	Yes	66 (10.8%)	0.81 (0.62 - 1.00)	0.053

Multivariate Analysis

A multivariate analysis was conducted in a stepwise-like fashion. Seven regression models were made, adding variables in order of their statistical significance and plausibility according to the literature. (Table 4) Each included Symptoms of

Schistosomiasis, as it is the primary variable of interest. Subsequent models added Residence, Mosquito Net, Wealth Quintile, Age Group, Gender, and Zone of Residence, respectively. Overall, Symptoms of Schistosomiasis became significant at the $p<0.05$ level in model 2, and significant at the $p<0.01$ level in model 5. Within model 5, those with symptoms of schistosomiasis were 0.85 times less likely to also have a positive result for malaria infection (OR = 0.85, 95% CI: 0.79 - 0.91, $p<0.01$). Household ownership of a mosquito net was also significant in every model it was included in (OR = 2.36 - 2.55, $p<0.01$) showing that those participants living in a household that did not have at least one mosquito net were roughly 2.4 times more likely to have a malaria infection than those that did own at least one mosquito net. While urban compared to rural residence was significantly associated with the prevalence of malaria, when considering age group, it was no longer significant at the $p<.05$ level but was significant at the $p<0.1$ level (OR = 1.30, 95% CI: 1.18 - 1.42, $p=0.054$).

Table 4: Results of Stepwise-Like Multivariate Analysis Between Chosen Independent Variables and Malaria, 2020

		Model 1	Model 2	Model 3	Model 4	Model 5	Model 6	Model 7
Variable	Characteristics	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio
Symptoms of Schistosomiasis	No	REF	REF	REF	REF	REF	REF	REF
	Yes	0.81	0.83*	0.91*	0.87*	0.85**	0.85*	0.84**
Residence	Urban		REF	REF	REF	REF	REF	REF
	Rural		1.21	1.23	1.31*	1.30	1.31**	1.32*
At Least One Mosquito Net	Yes			REF	REF	REF	REF	REF
	No			2.55**	2.54**	2.55***	2.43***	2.36***
Wealth Quintile	Lowest				REF	REF	REF	REF
	Second				0.99	1.00	1.01	0.99
	Middle				0.92	0.90	0.95	0.91*
	Fourth				0.87	0.81	0.86*	0.88**
	Highest				0.70***	0.62***	0.71***	0.68***
Age Group	5-9					REF	REF	REF
	10-14					2.38	2.25	2.26
	15-17					1.78	1.69*	1.69*
Gender	Male						REF	REF
	Female						1.04	1.04
Zone of Residence	North Central							REF
	North East							2.45*
	North West							2.26*
	South East							2.1
	South Central							2.66
	South West							0.85**

Note: *p<.05, **p<0.01, ***p<.001

Discussion

Both schistosomiasis and malaria continue to be a major public health concern in sub-Saharan Africa. There are approximately 29 million Nigerians infected with schistosomiasis with an additional 101 million at risk for infection out of a total population of 201 million. (18) In comparison, there are 100 million Nigerians infected with malaria with 195 million at risk of infection. (2)

Our modeling procedure tested the seven selected independent variables to compare their effects on malaria prevalence. With the results of the univariate analyses, we are suggesting that model 5, which included Symptoms of Schistosomiasis, Residence Type, Mosquito Net Ownership, Wealth Quintile, and Age Group, to be the best fit model. Gender and Zone of Residence were found as potential confounders with the

other independent variables. Within model 5, we found there to be a significant negative association in children with symptoms of schistosomiasis and malaria infection (OR 0.85, $p<0.01$).

In this study, we focused on the interaction between having a schistosomiasis infection and a malaria infection with symptoms of schistosomiasis being a surrogate for the infection. Several previous studies focusing on the biological interactions have shown a synergistic effect of a *Plasmodium spp.* and *Schistosoma spp.* infection. Wilson, *et* al. concluded through a combination of a Southeast Asian biological and a mouse model studies that the IL-4 and IL-5 response generated by schistosoma infection lowers general antibody response and increases specific Th2 antibody response. This then lead to an increased chance for *Plasmodium spp.* to infect the host and survive without detection due to decreased Pfs-IgG3 production. (34) Their hypothesis is that children infected with schistosomiasis may still have a malaria infection, but it is not PCR-detectable due to the decreased antibody production. (29) However, there are also a number of studies conducted in the same manner that suggest a Schistosoma infection may prime the host's immune system to better respond to the presence of Plasmodium. (13, 14, 30-32) For example, Lyke, *et* al. conducted a matched pair analysis of 338 schistosomiasis positive and negative Malian children between ages 4 and 14. These children were followed for a malaria transmission season and their serologic cytokine levels were measured at each instance of positive malaria screen. Their results showed that children who were positive for schistosomiasis infection had lower levels of IL-6 and IL-10 cytokines, both associated with acute malaria. They hypothesized that the increased levels of Th2 induced by schistosomiasis infection protected subjects from a

cytokine storm of IL-6 and IL-10, creating a more difficult environment for *Plasmodium spp.* Furthermore, Diallo, *et* al. followed 79 children in Senegal infected with schistosomiasis, malaria, both, and neither and compared their immune responses to the two parasites. Their data was analyzed using a combination of the Mann-Whitney U-test and Spearman's rank correlation. (36)

Lemaitre, *et* al. performed a similar analysis to ours in Senegalese children. They compared *S. haematobium* egg loads and parasite densities in these children over a 2-year period to consider the malaria transmission season. Their results showed that children with a *S. haematobium* egg load between 1 and 9 eggs/10mL of urine had lower *P. falciparum* densities than children that are not infected with schistosomiasis ($p=0.04$). In a discussion of their results, Lemaitre, *et* al. concluded to better understand the true relationship between the two infections an analysis that included additional variables to adjust for confounding factors. (14)

Our study was designed to account for confounding factors but was limited by specific parasite and egg densities. In addition to this, there may also be an overestimate of children with schistosomiasis due to the use of blood in urine as a surrogate. A future study taking these additional variables into consideration as well as having laboratory confirmed schistosomiasis egg loads and malaria parasite densities could further improve the clarity of the association between schistosomiasis and malaria infection.

In conclusion, our findings, considering biological plausibility and previous related studies, suggested that schistosomiasis infection in Nigerian children had a protective effect on malaria infection. Thus, children with a schistosomiasis infection are less likely to also have an active malaria infection.

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Tables

Table 1: Demographic Information of Nigerian Children Included in the Multivariate Analysis To Determine Association Between Malaria and Schistosomiasis Infection, 2020

Variable	Characteristics	n (%)	Symptoms of Schistosomiasis Infection	Positive for Malaria
Gender	Male	25005 (50.9%)	425 (1.7%)	3676 (14.7%)
	Female	24056 (49.1%)	188 (0.8%)	3904 (16.2%)
Age Group	5-9	23118 (47.1%)	231 (1%)	4046 (17.5%)
	10-14	18042 (36.8%)	271 (1.5%)	2598 (14.4%)
	15-17	7901 (16.1%)	111 (1.4%)	936 (11.9%)
Zone of Residence	North Central	7670 (15.6%)	161 (2.1%)	721 (9.4%)
	North East	7266 (14.8%)	240 (3.3%)	1482 (20.4%)
	North West	13610 (27.7%)	163 (1.2%)	2273 (16.7%)
	South East	5061 (10.3%)	20 (0.4%)	997 (19.7%)
	South Central	6705 (13.7%)	13 (0.2%)	1381 20.6%)
	South West	8751 (17.8%)	18 (0.2%)	726 (8.3%)
Residence	Urban	15257 (31.1%)	153 (1%)	1867 (12.2%)
	Rural	33805 (68.9%)	473 (1.4%)	5713 (16.9%)
Wealth Quintile	Lowest	10473 (21.3%)	272 (2.6%)	1812 (17.3%)
	Second	10408 (21.2%)	167 (1.6%)	1759 (16.9%)
	Middle	10116 (20.6%)	91 (0.9%)	1598 (15.8%)
	Fourth	9345 (19.0%)	65 (0.7%)	1346 (14.4%)
	Highest	8720 (17.8%)	26 (0.3%)	1065 (12.2%)
At Least One Mosquito Net	Yes	8340 (17.0%)	100 (1.2%)	1025 (12.3%)
	No	40721 (83%)	367 (0.9%)	7492 (18.4%)

Table 2: Dummy Variable Encoding of the Independent Variables Included in the Multivariate Analysis, 2020

Variable	Characteristics	Coding
Gender	Male	0 (referent)
	Female	1
Age Group	5-9	0, 0 (referent)
	10-14	1, 0
	15-17	0, 1
Zone of Residence	North Central	0, 0, 0, 0, 0 (referent)
	North East	1, 0, 0, 0, 0
	North West	0, 1, 0, 0, 0
	South East	0, 0, 1, 0, 0
	South Central	0, 0, 0, 1, 0
	South West	0, 0, 0, 0, 1
Residence	Urban	0 (referent)
	Rural	1
Wealth Quintile	Lowest	0, 0, 0, 0 (referent)
	Second	1, 0, 0, 0
	Middle	0, 1, 0, 0
	Fourth	0, 0, 1, 0
	Highest	0, 0, 0, 1
At Least One Mosquito Net	Yes	0 (referent)
	No	1
Symptoms of Schistosomiasis	No	0 (referent)
	Yes	1

Table 3: Results of Univariate Analysis Testing for Association Between Chosen Independent Variables and Malaria, 2020

Variable	Characteristics	Positive for Malaria	OR (95% CI)	P Value
Gender	Male	3676 (14.7%)	1	
	Female	3904 (16.2%)	1.07 (0.75 - 1.39)	0.062
Age Group	5-9	4046 (17.5%)	1	
	10-14	2598 (14.4%)	2.42 (1.89 - 3.20)	<0.001
	15-17	936 (11.9%)	1.84 (1.43 - 2.95)	<0.001
Zone of Residence	North Central	721 (9.4%)	1	
	North East	1482 (20.4%)	2.56 (2.35 - 2.77)	0.025
	North West	2273 (16.7%)	2.21 (2.05 - 2.37)	0.031
	South East	997 (19.7%)	2.14 (1.93 - 2.35)	0.027
	South Central	1381 20.6%)	2.61 (2.37 - 2.85)	0.015
	South West	726 (8.3%)	0.88 (0.73 - 1.04)	0.009
Residence	Urban	1867 (12.2%)	1	
	Rural	5713 (16.9%)	1.27 (1.12 - 1.42)	<0.001
Wealth Quintile	Lowest	1812 (17.3%)	1	
	Second	1759 (16.9%)	1.02 (0.91 - 1.13)	0.033
	Middle	1598 (15.8%)	0.91 (0.80 - 1.02)	0.031
	Fourth	1346 (14.4%)	0.99 (0.85 - 1.13)	0.012
	Highest	1065 (12.2%)	0.55 (0.42 - 0.68)	<0.001
At Least One Mosquito Net	Yes	1025 (12.3%)	1	
	No	7492 (18.4%)	2.72 (2.60 - 2.83)	<0.001
Symptoms of Schistosomiasis	No	6346 (13.1%)	1	
	Yes	66 (10.8%)	0.81 (0.62 - 1.00)	0.053

Table 4: Results of Stepwise-Like Multivariate Analysis Between Chosen Independent Variables and Malaria, 2020

		Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**	**Model 7**
Variable	Characteristics	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio	Odds Ratio
Symptoms of Schistosomiasis	No	REF	REF	REF	REF	REF	REF	REF
	Yes	0.81	0.83*	0.91*	0.87*	0.85**	0.85*	0.84**
Residence	Urban		REF	REF	REF	REF	REF	REF
	Rural		1.21	1.23	1.31*	1.30	1.31**	1.32*
At Least One Mosquito Net	Yes			REF	REF	REF	REF	REF
	No			2.55**	2.54**	2.55***	2.43***	2.36***
Wealth Quintile	Lowest				REF	REF	REF	REF
	Second				0.99	1.00	1.01	0.99
	Middle				0.92	0.90	0.95	0.91*
	Fourth				0.87	0.81	0.86*	0.88**
	Highest				0.70***	0.62***	0.71***	0.68***
Age Group	5-9					REF	REF	REF
	10-14					2.38	2.25	2.26
	15-17					1.78	1.69*	1.69*
Gender	Male						REF	REF
	Female						1.04	1.04
Zone of Residence	North Central							REF
	North East							2.45*
	North West							2.26*
	South East							2.1
	South Central							2.66
	South West							0.85**

Note: *p<.05, **p<0.01, ***p<.001

Summary, Public Health Implications, Possible Future Directions

The results of this analysis show that schistosomiasis infection has a protective effect on malaria infection. I believe that this information could potentially lead to reexamining the way that researchers account for malaria infections. It is possible that the protective effect could lead to under reporting true malaria infections. Furthermore, this could prove useful in explaining why efforts to eradicate NTDs in sub-Saharan Africa could lead to increased prevalence of malaria.

If I were to continue this research, I would like to incorporate data on parasite loads in subjects. This could give a more specific association between schistosome egg loads and plasmodium infection counts. This could potentially show a positive association between certain egg loads and malaria infection. I would also like to expand the study to encompass more NTDs such as guinea worm disease, hookworm, lymphatic filariasis, and onchocerciasis. These parasitic infections represent a significant burden of disease in sub-Saharan Africa but are not as heavily funded as malaria or HIV/AIDS research. It is biologically plausible that these parasitic infections affect the immune response to malaria. Potentially, they could show a positive association with malaria infection. If this were to be the case, eradicating these NTDs could become a sub-focus of malaria eradication. Some NTD organizations within Africa speculate that eradication of these parasites is feasible given a large enough budget in the same way that the Gates Foundation has all but eradicated guinea worm disease.