EPIDEMIOLOGY OF MALARIA AND INTESTINAL HELMINTHS CO-INFECTION AMONG CHILDREN IN RURAL COMMUNITIES IN ONA-ARA LOCAL GOVERNMENT AREA, OYO STATE

BY

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CERTIFICATION

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DEDICATION

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ABSTRACT

The malaria and Intestinal Helminth (IH) parasites co-exist and are prevalent in the tropics due to favourable climatic conditions and poor sanitary practices. These parasites have adverse effects on cognitive development, educational performance and school attendance of children. The epidemiology of Malaria and Intestinal Helminths Co-infections (MIHC) among children have not been fully documented in Nigeria and community-based studies are also limited. The epidemiology of MIHC among children in Ona-Ara Local Government Area (OLGA), Oyo State was therefore investigated.

A cross-sectional survey was conducted. A two-stage cluster sampling technique was used to select 131 households having children 6 months-17 years from six settlements one from each of the six rural wards within OLGA. Information on socio-demographic characteristics, environmental hygiene, preventive practices on helminthiasis and malaria from each household was obtained from household heads using a semi-structured questionnaire. Single stool and finger prick blood samples were collected from 376 children from selected households. Kato-katz and formol-ether techniques were employed to process stool samples for microscopy while Giemsa-stained thick blood smears were used to screen for malaria parasites. Subsequently, 123 children asymptomatic with malaria parasitaemia (irrespective of the presence or absence of IH) were followed-up for 6 weeks to detect acute malaria, thereafter second blood samples were collected to confirm Malaria Parasitaemia (MP). Data were analysed using descriptive statistics, Chi-square test and Kaplan-Meier statistics at 5% level of significance.

Mean age of children was 6.5 ± 0.4 years and 52.9% were females; age distribution was 46.2%, 41.1% and 12.7% for 0-5 year, 6-11 year and 12-17 year age-groups respectively. Several (73.3%) sourced their drinking water from wells and 83.0% defecated in the bush. Only 9.0% used mosquito nets. Some (55.7%) used antihelminthic drugs to prevent worm infection, 21.0% used herbs while 23.3% did not practice deworming. Number of children who submitted both samples, blood sample only and stool sample only were 162, 212 and 2 respectively. Prevalences of asymptomatic malaria, IH infections and MIHC were

51.1%, 37.0%, and 27.8% respectively. *Ascaris lumbricoides* was the only IH species identified in stool samples. Among all age groups, the 0-5year age-group had the highest prevalence of MP (57.3%), while the 6-11year age-group had the highest prevalences of MIHC (59.5%) and IH infection (52.1%). At follow up, MP clearance rate of 7.3% was detected; 92.7% remained positive and 36.6% of these developed acute malaria while 63.4% remained asymptomatic. Incidence rate was 5.3/100 person-weeks for co-infected children and 7.3/100 person-weeks for children infected with MP only. Overall mean survival time (time from recruitment into follow-up until incidence of acute malaria) was 5.2 ± 0.3 weeks.

Intestinal helminth and its co-infection with malaria constitute a major health burden among children of 6-11 year age-group while those under five are more prone to malaria alone in the study area. In addition, modifiable risk practices which have potential for promoting malaria and intestinal helminth infections abound in the communities; hence community-based integrated control programmes among children and health education for caregivers is advocated.

Keywords: Malaria, Intestinal helminths, Parasitic co-infections, Risk practices.

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LIST OF ACRONYMS

ACTs:	Artemisinin-Based Combination Therapies
CDC:	Centers for Disease Control and Prevention
EpiData:	Epidemiological Data Software
FMoH:	Federal Ministry of Health
HIV/AIDS:	Human Immunodeficiency Virus infection / Acquired Immuno Deficiency Syndrome
KM:	Kaplan Meier
LGA:	Local Government Area
MIS:	Malaria Indicator Survey
NDHS:	Nigeria Demographic and Health Survey
NIAID:	National Institute of Allergy and Infectious Diseases
NMIS:	National Malaria Indicator Survey
NTD:	Neglected Tropical Diseases
OLGA:	Ona-am Local Government Area
PSAC:	Pre-School Age Children
RDT:	Rapid Diagnostic Test
SAC:	School Age Children
SPSS:	Statistical Package for the Social Sciences
STH:	Soil Transmitted Helminths
UNICEF:	United Nations Children's Fund
USA:	United State of America
WER:	Weekly Epidemiological Record
WHA:	World Health Assembly
WHO:	World Health Organisation

CHAPTER ONE

INTRODUCTION

1.1 Background of study

Malaria has remained an issue of public health concern, especially in the tropical regions of the world. Pregnant women and children below five years are the most vulnerable population. According to the World Health Organisation (WHO), there were an estimated 216 million episodes of malaria, of which approximately 174 million cases (81%), were from Africa; 655 000 malaria deaths: of which 91% occurred in Africa and approximately 86% of global malaria deaths were of children under 5 years of age (WHO, 2011a). Malaria in Nigeria, results in an estimated number of 3.5 malaria episodes per person-year for children under 5 years; as well as a total of 10-110 million clinical cases per year. The current malaria related annual deaths for children under five years of age are estimated at around 300,000 (285,000 – 331,000), and 11% of maternal mortality (NMCP, 2008). Malaria's economic impact is enormous with about N132 billion lost to malaria annually in form of treatment and prevention, cost and loss of man hours among others (Jimoh *et al*., 2007).

In developed countries, the availability of funds and resources has led to improved and advanced health care services evident in high quality diagnosis, affordability and accessibility of effective drugs, high-speed tele-medicine for health management information system, computerized monitoring and surveillance system which translates to wide coverage of treatment, control and early case detection, accessibility and availability of skilled health providers, application of novel and cutting-edge strategies from ongoing clinical research and trials. All these explain the wide margin in mortality and morbidity rates of these countries compared to developing countries. Countries in sub-Saharan Africa bear the heaviest burden of malaria. These countries are among the poorest in the world and widespread poverty on the continent continues to play a role in the burden of the disease (Yusuf *et al*., 2010). Also, high prevalence and morbidity of Soil Transmitted

Helminths (STHs) has been reported to occur among the poorest populations in the least-developed countries of the world (WHO 2001a, WHO 2012b). Poverty protract the conditions where diseases thrive, and is a significant factor in the escalating poor health conditions of these countries especially in their rural areas, given that majority of the poor live in such areas. The climatic condition prevalent in the tropical regions is another plausible factor responsible for the high incidence and prevalence of malaria in endemic countries. Several reasons explain why populations in developing countries are disproportionately affected by climatic changes as compared to populations in developed countries.

There is a strong correlation between climatic conditions and infectious diseases. For example, in areas holo-endemic for malaria, transmission is perennial. Temperature and surface water have important influences on the insect vector. Mosquitoes need access to stagnant water in order to breed, and the adults need humid conditions for viability. Warmer temperatures enhance vector breeding and reduce the pathogen's maturation period within the vector organism. Very hot and dry conditions can reduce mosquito survival; consequently malaria morbidity worsens during the rainy seasons and tends to decrease in the dry seasons (WHO, 2003). In tropical regions, favourable climatic conditions, poverty and unhygienic practices enhance the co-infection of malaria parasite with other protozoan and parasitic infections, especially infections with similar geographical/spatial distribution and epidemiological pattern. A typical example of such parasite is the intestinal helminth, also referred to as "Soil Transmitted Helminths (STH)", they are not foreign to tropical areas, and in fact most people resident in such communities assume their presence to be more or less normal. However, intestinal helminths have deleterious effects in the body and on other vital organs. Worse still, they can be deadly in the event of interaction with other parasitic infections like malaria (Gallagher et al., 2005, Le Hesran *et al.*, 2003, Yatich *et al.*, 2009, Adegnika *et al.*, 2010). Approximately, one-third of the almost three billion people that live on less than two US dollars per day in developing regions of sub-Saharan Africa, Asia, and the Americas, are estimated to be infected with one or more helminths (Hotez *et al.*, 2006). The most common helminth diseases worldwide are those caused by infection with ascariasis, trichuriasis, and hookworm, followed by schistosomiasis (Hotez *et al.*, 2006).

"Co-infection" is used to describe concurrent infection of a host with two or more infectious agents. It explains the simultaneous infection of a host by multiple pathogens. The global prevalence figures on co-infection among human hosts are not available, but co-infection is thought to be commonplace (Cox, 2001). Co-infections involving helminths affect about 800 million people worldwide (Crompton. 1999) and is of particular clinical importance when they interact with other pathogens within the same host. Helminths are endemic in the tropics as are the Plasmodium infections with similar geographical distribution (Keiser *et al.*, 2002). Thus the overlapping distribution of these parasites result in a high rate of co-infection (Adrienne *et al.*, 2005), which may cause synergism and antagonistic interaction between helminths and malaria parasites within the human host (Mathieu 2002, Kirsten 2005).

Both infections affect all age groups but mostly children. Studies have shown that younger children are much more predisposed to heavy infections with intestinal parasites because their immune systems are not yet fully developed and they also habitually play in faecally contaminated soil (Rao *et al.*, 2006). Age-stratified epidemiologic studies indicate that the prevalence of asymptomatic *Plasmodium* infections increases in early childhood, beginning to decline with the gradual acquisition of immunity, in contrast, the prevalence of STHs increases throughout childhood to a relatively stable plateau or show a slight decrease in adulthood. Thus school-age children, rather than pre-school children or adults, are most at risk of plasmodium-helminth co-infection, and thereby at greatest risk of the consequences of co-infection (Brooker *et al.*, 2007).

1.2 Problem statement

The implications of co-infection among children are quite grave, in addition to considerable mortality and morbidity, infection with intestinal helminths affects a child's cognitive/mental development, growth and physical fitness while also predisposing children to other infectious agents (Stephenson *et al.*, 1993, Simeon *et al.*, 1995, De Silva *et al* 1997). In turn these indirectly, have adverse effects on educational performance and school attendance of these children. Despite the plausible implications of similar

environmental and socio-economic conditions in the distribution of malaria and intestinal helminths, as well as the susceptibility of children, few studies have explicitly focused on identifying predictors of co-infection with these parasites among children. Conflicting reports also exist on the role of helminths in development of malaria. Some suggest that the ubiquity of these parasites results in high rates of co-infection (Petney and Andrews, 1998); and that co-infection of both parasites may cause various morbidities in infected individuals. (Adrienne *et al.*, 2005); others argue that worms reduce/suppress malaria (Nacher *et al.*, 2000 and Brutus *et al.*, 2007, Nacher *et al.*, 2001b).

1.3 Justification of study

Considering the possible consequence when more than one parasites co-exist in a host, the vulnerability of different people to similar infections and the prevalence of malaria, helminthiasis and their co-infection in favorable environs; this study is very important to elucidate the epidemiology of co-infections of these parasites among rural dwellers especially children since they are more prone and exposed to these infections.

1.4 Aims and Objectives of the study

1.4.1. Brond objective

To determine the burden of malaria and intestinal helminths co-infection and their determinants among children in rural communities in Ona-ara LGA, Oyo state Nigeria.

1.4.2 Specific objectives are to;

- Determine the prevalence of asymptomatic malaria, intestinal helminth infections and malaria and intestinal helminth co-infections among children in the study area.
- Determine the incidence of acute malaria among children with asymptomatic parasitaemia in the study area.
- Describe the risk practices for malaria-intestinal helminths co-infections among carers in the study area.
- Determine the association between malaria co-infection with intestinal helminthis infection and the development of acute malaria.

CHAPTER TWO

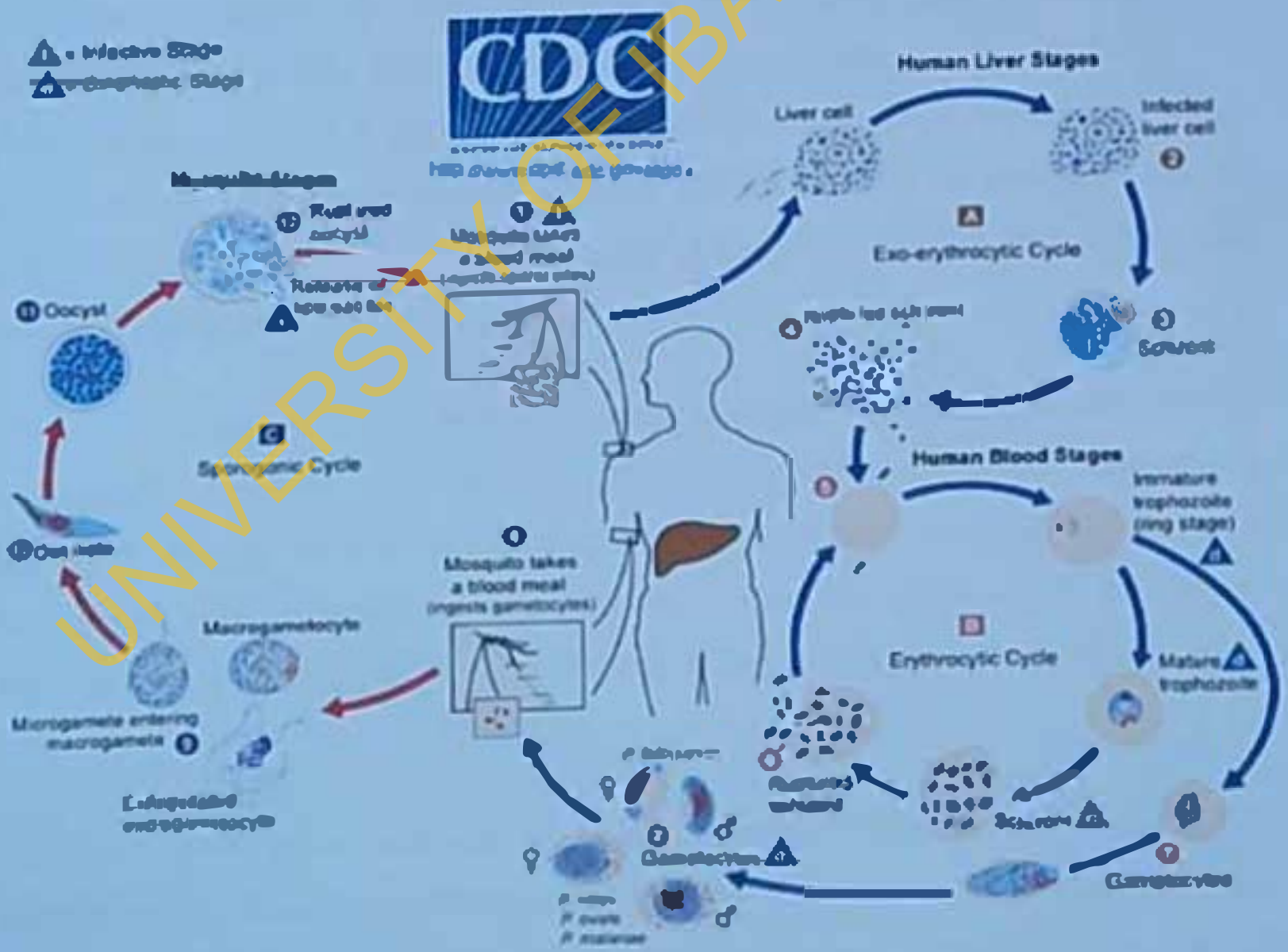
LITERATURE REVIEW

2.1 Malaria

2.1.1 Lifecycle of malaria

Malaria is caused by a parasite, called Plasmodium which infects a person's red blood cells. It is transmitted from one person to another by the bite of the female *Anopheles* mosquitoes. Five species of plasmodium affect man, these are *P.falciparum*, *P.vivax*, *P.ovale*, and *P.malariae* and *P.knowlesi*. The parasite goes through a complex cycle in both the mosquito and in humans before transmission can take place. Figure 2.1.1 gives an illustration of the lifecycle of the malaria parasite

Figure 2.1.1 Lifecycle of the malaria parasite



Scheme of the malaria life cycle, courtesy of CDC, 2006 (www.cdc.gov)

The malaria parasite life cycle involves an insect vector (mosquito) and a vertebrate (human). This begins when an infected female *Anopheles* mosquito pierces a person's skin to take a blood meal, *sporozoites* in the mosquito's saliva enter the bloodstream and migrate to the liver where they infect the liver cells multiplying asexually and asymptomatically for a some days. These *sporozoites* infect liver cells and mature into *schizonts*, which rupture and release *merozoites*, this is called exo-erythrocytic schizogony. The *merozoites* then escape into the blood and infect red blood cells to begin the erythrocytic stage of the life cycle (erythrocytic schizogony). Within the red blood cells, the parasites multiply further, again asexually, periodically breaking out of their hosts to invade fresh red blood cells. This periodic release of *merozoites* occurs simultaneously causing typical waves of fever or chills in the host. Thus blood stage parasites are responsible for the clinical manifestations of the disease. Some *merozoites* differentiate into male *(microgametocytes)* and female *(macrogametocytes)* gametocytes. This is the sexual erythrocytic stage. When a mosquito pierces the skin of an infected person, it potentially picks up gametocytes within the blood. While in the mosquito's stomach, the microgametes penetrate the macrogametes generating zygotes. This is the sporogonic cycle. The zygotes become motile and elongated *(ookinetes)* which invade the midgut wall of the mosquito where they develop into *oocysts*. The *oocysts* grow, rupture, and release new *sporozoites*. The new *sporozoites* then develop and travel to the mosquito's salivary gland, completing the cycle. Inoculation of the *sporozoites* into a new human host perpetuates the malaria life cycle.

It is worth mentioning that *P. vivax* and *P. ovale* sporozoites do not immediately develop into exoerythrocytic-phase *merozoites*, but instead produce *hypnozoites* that remain dormant for periods ranging from several months (6-12 months is typical) to as long as three years. After a period of dormancy, they reactivate and produce *merozoites*. *Hypnozoites* are responsible for long incubation and late relapses typical of *P. vivax* infections.

Also, three conditions are to be met for malaria to occur: firstly, *anopheles* mosquitoes must be present, in contact with humans, and in which the parasites can complete the "invertebrate host" half of their life cycle; secondly, humans must be present, who are in contact with *Anopheles* mosquitoes, and in whom the parasites can complete the

"vertebrate host" half of their life cycle; lastly, malaria parasites must be present (CDC, 2012). However, malaria parasites are often transmitted from one person to another without requiring passage through a mosquito (for example: from mother to child in "congenital malaria" or through transfusion, organ transplantation, or shared needles).

2.1.2 Clinical signs and symptoms of malaria

Generally, symptoms of malaria are: fever, headache, severe chills or rigor, profuse sweating and general body pains. Some patients, especially children may have vomiting, cough or diarrhoea . In persistent and recurrent infections, anaemia may be present. Malaria tends to be more severe in children under five years old. Symptoms start showing about ten days to four weeks after being bitten. For under-fives typical symptoms of malaria include: fever, shivering, cold, irritability and drowsiness, poor appetite, sleeplessness, vomiting, stomach pain and rapid breathing. Children older than five usually have similar symptoms as adults (Babycenter, 2012). The severity and course of a clinical attack depend on the species and strain of the infecting plasmodium parasite, as well as the age, genetic constitution, malaria-specific immunity, and nutritional status of the child, and previous exposure to antimalarial drugs (Caulfield *et al*., 2004 and Fowowe, 2011).

2.1.3 Clinical case definitions of malaria

a). Uncomplicated/acute malaria:

Fever or history of fever associated with symptoms such as nausea, vomiting and diarrhoea, headache, back pain, chills, myalgia, malaise, aches and body pain, weakness, tiredness, pallor, anorexia, jaundice, hepatosplenomegaly, where other infectious diseases have been excluded (WHO, 2001c and FMoH, 2008a).

b). Severe malaria:

Fever and symptoms as for uncomplicated malaria but with associated signs such as disorientation, repeated vomiting, prostration, hypoglycaemia, circulatory collapse, renal failure, hyperparasitaemia, loss of consciousness, convulsions, severe anaemia, jaundice, haemoglobinuria, spontaneous bleeding, pulmonary oedema, shock (WHO 2001c, FMoH 2008a).

c). Confirmed case: Demonstration of malaria parasites in blood films by examining thick or thin smears or by Rapid Diagnostic Test (RDT) for *P. falciparum* diagnosis (WHO 2001c, FMoH 2008a). Worthy of mention is the fact that microscopy is the gold standard

for Laboratory diagnosis of malaria. A study by Rafael *et al.*, in 2006, asserts that a highly effective RDT could avert over 100.000 malaria related deaths and about 400 million unnecessary treatments (Rafael et al., 2006). However RDTs have been reported (Murray and Bennett, 2009) to have limited sensitivity particularly in mixed infections and infections at low concentrations of parasites.. Thus microscopy remains the gold standard in the laboratory diagnosis of malaria.

2.1.4 Malaria in children: morbidity and mortality situation in Nigeria

According to the latest Malaria Indicator Survey (MIS) report for Nigeria, up to one-fourth (25%) of the malarial disease burden in Africa was from Nigeria. Malaria in Nigeria is endemic. Eleven percent (11%) of maternal mortality was related to malaria; it also contributed up to 25% of infant mortality and 30 % of under-five mortality, resulting in about 300,000 childhood deaths annually (Nigeria Malaria Indicator Survey, 2010). .

This rising burden of malaria in Nigeria calls for serious attention. The 2010 MIS reported a higher proportion (35%) of under-fives who had a fever in the two weeks before the survey compared to 16% in the 2008 survey (FMoH, 2008b). It also reported that four in ten Nigerian children (42% of children age 6-59 months) were infected with malaria and the disease was most common in South West and North Central zones where half of all children were infected and least common in South East Zone where prevalence among children was 28% (NMIS. 2010).

Young children are much more vulnerable to all forms of malaria because their immune systems are not yet fully developed, while in under -fives they have not yet developed effective resistance to the disease. Malaria can have a devastating effect on children's education. Repeated infections cause children to miss large number of school periods. Anaemia, a complication of frequent malaria attacks, interferes with children's ability to concentrate in learning and causes chronic fatigue. Repeated illnesses from malaria can also exacerbate any malnutrition, which can both decrease the effectiveness of anti-malaria drugs and increase children's susceptibility to the other main killer diseases like diarrhoea and pneumonia (Malaria Consortium. 2012)

Considering this alarming situation, it becomes very pertinent to access every possible means to combat this disease; existing strategies must be improved, new researches

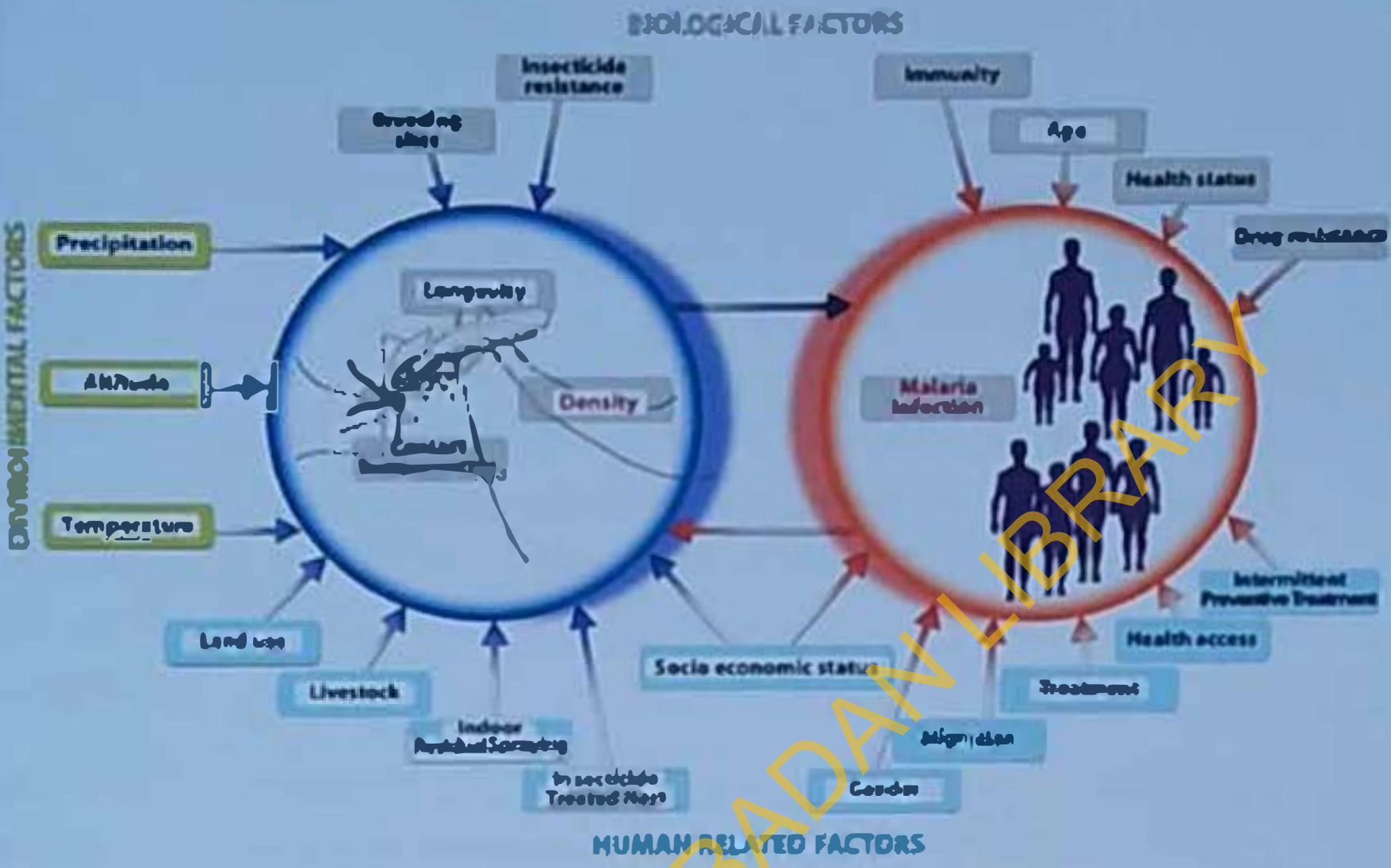
towards developing better results and policies should be encouraged, education and reorientation of the public, more especially caregivers, should be sustained, also capacity building programmes for community health workers and healthcare providers must be given priority.

It is in this context that many researches are diverging into other plausible areas that could in any way influence the malaria situation in our environments so as to proffer suitable interventions towards malaria eradication or at least minimal prevalence.

2.1.5 Risk factors associated with malaria

Various studies have investigated the relationship between risk factors and malaria transmission. Each of these factors either singly or combined influence malaria occurrence. In a prior study carried out in Africa, (Protopoff *et al.*, 2009), a conceptual model was developed to explain the necessity of understanding the influence and role of certain predictors of malaria to guide Malaria Control Efforts in African Highlands. Figure 2.1.5.1 below is the schematic diagram of the model. It highlights some of the risk factors of malaria as described in this study.

Fig 2.1.5.1 Conceptual model of important risk factors affecting malaria prevalence in the African Highlands (Protopopoff et al., 2009)



Following the model, the risk factors are divided in three areas, vis-a-vis Biological, Environmental and Human - related

Biological risk factors of malaria

The host

Age is a very significant predictor of malaria. Younger children, especially the under-fives are reported to be more prone to malaria compared to other age groups (Lusingu *et al*., 2004, Reyburn *et al*., 2005, Yazoume *et al*., 2008, Camcito *et al*., 2010)

Another important biological factor is *immunity*. Children below the age of five have low immunity against the parasite thus have greater chance of experiencing high case fatality (WHO, 2011a). Pregnant women are also among the high risk groups. Pregnancy has been reported to alter the immune response system especially in primigravidae (Okoko, 2003). During the latter stages of pregnancy, malaria infection, in combination with maternal anaemia, impairs foetal weight gain and contribute to intrauterine growth retardation or prematurity and thus result in low birth weight. This has been demonstrated most

convincingly by trials of malaria prevention strategies in which both drugs and bednets were shown to reduce these adverse outcomes (DFID, 2010, Menéndez, 2007).

The health status of an individual is another plausible biological factor. It is well established that undernutrition affects the immune system and increases the incidence, duration and severity of many infectious diseases (DFID, 2010). There is, however, reasonable evidence for a link between some aspects of both acute and chronic malnutrition and severe malaria Bejon, *et al.*, 2008b. Undernutrition prolongs the severity of malaria episodes and increases the chance of death (Caulfield et al., 2004b). Children who have severe chronic undernutrition are twice as likely to die of malaria as children of normal height (Black *et al.*, 2008). Children who are acutely undernourished (of which there are 55 million worldwide) are two to three times more likely to die of malaria (Black *et al.*, 2003).

Additionally, the influence of genetic factors cannot be over-emphasized. Persons who have the sickle cell trait (heterozygotes for the abnormal hemoglobin gene HbS) are relatively protected against *P. falciparum* malaria and thus enjoy a biologic advantage. Also, the prevalence of hemoglobin-related and blood cell disorders such as Hemoglobin C, the thalassemias and G6PD deficiency, are more prevalent in malaria endemic areas and are thought to provide protection from malarial disease (CDC, 2012).

The Vector:

Insecticide resistance:

Insecticide-based control measures include indoor spraying with insecticides and the use of insecticide treated bednets (ITNs). These are the major ways to kill mosquitoes that bite indoors. However, after prolonged exposure to an insecticide over several generations, mosquitoes, like other insects, may develop resistance, thus able to survive contact with such an insecticide. Since mosquitoes can have many generations per year, high levels of resistance can arise very quickly. The development of resistance to insecticides used for indoor residual spraying was a major impediment during the Global Malaria Eradication Campaign. Nonetheless, cautious use of insecticides for mosquito control can limit the development and spread of resistance (CDC, 2012).

Refractoriness :

Some *Anopheles* species are poor vectors of malaria, as the parasites do not develop well (or at all) within them. There is also variation within species. In the laboratory, it has been possible to select for strains of *An. gambiae* that are refractory to infection by malaria parasites. These refractory strains have an immune response that encapsulates and kills the parasites after they have invaded the mosquito's stomach wall. Thus in the areas where these strains of mosquitoes thrive, malaria prevalence will be low. Also scientists can study the genetic mechanism for this response, replicate and employ it to achieve the goal of eliminating malaria in the nearest future (CDC, 2012).

Environmental factors

Climate is a key determinant in the geographic distribution and the seasonality of malaria. studies have associated warming trends to the increase in malaria transmission (Loevinsohn *et al.*, 1994; Pascual *et al.*, 2006; Patz *et al.*, 2002) other studies show no association (Zhou, 2004., Shanks *et al.*, 2002, Small *et al.*,2003, Bonora *et al.*, 2001).

In addition, rainfall can create collections of water which become breeding sites where *Anopheles* eggs are deposited and larvae and pupae develop into adulthood, this is very common in tropical areas. To transmit malaria successfully, female *Anopheles* must survive long enough after they have become infected (through a blood meal on an infected human) to allow the parasites they now harbor to complete their growth cycle which takes about 9-21 days at 25°C or 77°F. Warmer ambient temperatures shorten the duration of this extrinsic cycle, thus increasing the chances of transmission. Conversely, below a minimum ambient of 20°C or 68°F (for *P. falciparum*), the extrinsic cycle cannot be completed and malaria cannot be transmitted. This explains in part why malaria transmission is greater in warmer areas of the globe (tropical and semitropical areas and lower altitudes), particularly for *P. falciparum* (CDC, 2012).

Climate also determines human behaviors that may increase contact with *Anopheles* mosquitoes between dusk and dawn, when the *Anopheles* are most active. Hot weather may encourage people to sleep outdoors or discourage them from using bed nets. During harvest seasons, agricultural workers might sleep in the fields or nearby locales, without protection against mosquito bites.

Human related factors

Many studies have reported a positive association between human attitude, perception, practice or behaviours and malaria transmission. For example, prevalence of malaria and socio-economic status of caregivers have been reported as having positive correlation (Olaschinde *et al.*, 2008, Klinkenberg *et al.*, 2005, Lawrence *et al.*, 2004); findings have reported that children whose caregivers have little or no education have more tendencies to have malaria compared to those whose parents are educated (Dike et al., 2006, Godwin *et al.*, 2010).

Among geo-political zones in Nigeria, the southwest zone has been reported to have the least use of insecticide-treated nets, little wonder it is also the zone with the highest prevalence of malaria. Only a few children less than five years (30%) slept under an Insecticide-Treated-Net (NMIS 2010, Ekundayo *et al.*, 2011).

The hygienic conditions of household environs has also been associated with malaria prevalence, a recent study by Adedotun in Oyo town, Oyo state (Adedotun, 2010) reported environmental hygiene as a significant predictor of malaria prevalence. Similar conclusion was obtained by Nsagha in Cameroun (Nsagha *et al.*, 2011).

The treatment seeking pattern of caregivers can also influence malaria occurrence. In a related study, the use of local herbs seemed to be a better option in many households compared to orthodox medicine despite numerous campaigns and health education (Aibinuola, 2007) on the use of effective antimalarial drugs.

Household amenities and environs have also been linked with malaria transmission. Children living in houses with mud roofs have significantly higher risk of getting *P. falciparum* infection compared to those living in iron-sheet roofed houses (Yazoumé, 2006), the study further asserted that the more affluent houses may have better sealing around doors, hence preventing entry of mosquitoes. Moreso, in the more affluent households children may be better nourished and hence less susceptible to infection (Yazoumé, 2006). Atieli in his study in Kenya proposed that ceiling modification is likely to be acceptable and is expected to be of greatest benefit when used in combination with other malaria control strategies (Atieli, 2009). In another study conducted in Cameroun, malaria parasite prevalence and parasite density were significantly higher in the individuals of wooden plank houses than those of cement brick houses

Inhabitants of houses surrounded by bushes or garbage heaps and swamps or stagnant water showed higher malaria parasite prevalence and densities compared with those from cleaner surroundings. The study also indicated that poor environmental sanitation and housing conditions may be significant risk factors for malaria parasite. (Nkuo-Akenji, 2006b).

2.1.6 Update on malaria diagnosis and case management

The Federal Ministry of Health (FMoH), Nigeria in the *Implementation Guide for Parasite-Based Diagnosis of Malaria* released in year 2011, reiterated the advocacy for early diagnosis; prompt and effective treatment as the basis for the management of malaria and key to reducing malaria morbidity and mortality. It stated that the demonstration of the presence of malaria parasites prior to treatment with antimalarial drugs is fundamental to this goal and that clinical diagnosis has limited accuracy and leads to over-diagnosis of malaria with resultant wastage of antimalarial medicines, and inappropriate treatment of non-malarial fevers (FMoH/NMCP, 2011).

Also, WHO recommended the universal use of diagnostic testing to confirm malaria infection, followed by appropriate treatment based on the results. Diagnosis was said to be increasingly important, not only to have certainty about malaria cases but also to avoid unnecessary consumption of antimalarial drugs, which increases the risk of malaria parasite resistance (WHO, 2010). Thus parasite based diagnosis is the right approach and should be the first step in the diagnosis and case management of malaria.

2.1.7 Challenges in the treatment of malaria

Prompt and effective treatment of malaria within 24 hours of fever onset with an effective antimalarial agent is necessary to prevent life threatening complications. Howbeit these are not without challenges in the third world. Firstly majority of malaria cases are seen within the informal health sectors (Childinfo, 2012), most caregivers visit drug hawkers, patent medicine sellers, herbalists, and traditional healers/attendants (Ajayi *et al*., 2002). Unfortunately, most of these care providers are not knowledgeable or well acquainted with recent guidelines and policies for treatment as stipulated by the government. Some are not educated and only sell or give out the drugs just to make a living; they are more concerned about the financial gain they will make in their sales than the health of their clients. Thus

many patients especially children die of mismanagement, some due to improper diagnosis and/or wrong prescription and others become resistant to drugs.

In many countries, parasite-based diagnosis has not yet been fully appropriated in malaria case management amidst the escalating statistics on the contribution and efforts of funding bodies in the distribution of diagnostic materials like RDTs. Furthermore, the World Health Organisation, has stipulated in its guidelines, that uncomplicated *P. falciparum* malaria (the most lethal and pervasive malaria parasite in sub-Saharan Africa) should be treated with an ACT (Childinfo, 2012). Regrettably the situation is still far from it. Drugs like chloroquine which have been discouraged are still prescribed and dispensed by many health care providers in our setting (Megan *et al.*, 2011), despite various outreach programs organized to educate caregivers on malaria case management.

2.2 Helminths

2.2.1 Epidemiology of helminths

The word *helminth* comes from Greek hélmins, meaning a kind of worm. "Worm" refers to any of a number of creeping or burrowing invertebrate animals, as those of the phyla Annelida, Nematoda, or Platyhelminthes, with long, slender, soft, flexible, rounded or flattened body and often without obvious appendages or limbs.

Helminths are a division of eukaryotic parasites that, unlike external parasites such as lice and fleas, live inside their host (Maizels *et al.*, 2003). They are worm-like organisms that live and feed off living hosts, receiving nourishment and protection while disrupting their hosts' nuuient absorption, causing weakness and disease. Those that live inside the digestive tract are called *intestinal parasitic helminths*. They can live inside humans as well as other animals. These are the type of intestinal parasite that resides in the human gastrointestinal tract. They represent one of the most prevalent forms of parasitic disease. They are also referred to as "intestinal worms" and "soil-transmitted helminths (STH)" Soil-transmitted helminth is a term referring to a group of parasitic diseases caused by nematode worms that are transmitted to humans by faecally contaminated soil. The soil-transmitted helminths of major concern to humans are *Ascaris lumbricoides*, *Trichuris trichiura*, *Necator americanus* and *Ancylostoma duodenale*. The latest estimates indicate

that more than 2 billion people are infected with these parasites. The highest prevalence occurs in areas where sanitation is inadequate and water supplies are unsafe (WHO 2012b). In medically oriented schemes the flatworms or platyhelminths (platy from the Greek root meaning "flat") include flukes (trematodes) and tapeworms (cestodes). Roundworms are nematodes (nemato from the Greek root meaning "thread"). These groups are subdivided for convenience according to the host organ in which they reside, e.g., lung flukes, extra intestinal tapeworms, and intestinal roundworms. Helminths develop through egg, larval (juvenile), and adult stages (Castro, 1996). They undergo different stages of growth and development and this is related to the epidemiology and pathogenesis of helminth diseases, as well as for the diagnosis and treatment of patients harboring these parasites.

Platyhelminths and nematodes that infect humans have similar anatomic features that reflect common physiologic requirements and functions. The outer covering of helminths is the cuticle or tegument. Prominent external structures of flukes and cestodes are acetabula (suckers) or bothria (false suckers). Male nematodes of several species possess accessory sex organs that are external modifications of the cuticle. Internally, the alimentary, excretory, and reproductive systems can be identified by an experienced observer. Tapeworms are unique in lacking an alimentary canal. This lack means that nutrients must be absorbed through the tegument. The blood flukes and nematodes are bisexual. All other flukes and tapeworm species that infect humans are hermaphroditic. With few exceptions, adult flukes, cestodes, and nematodes produce eggs that are passed in excretions or secretions of the host (Castro, 1996). Typical pictures of named helminths and their eggs are shown in Appendix H.

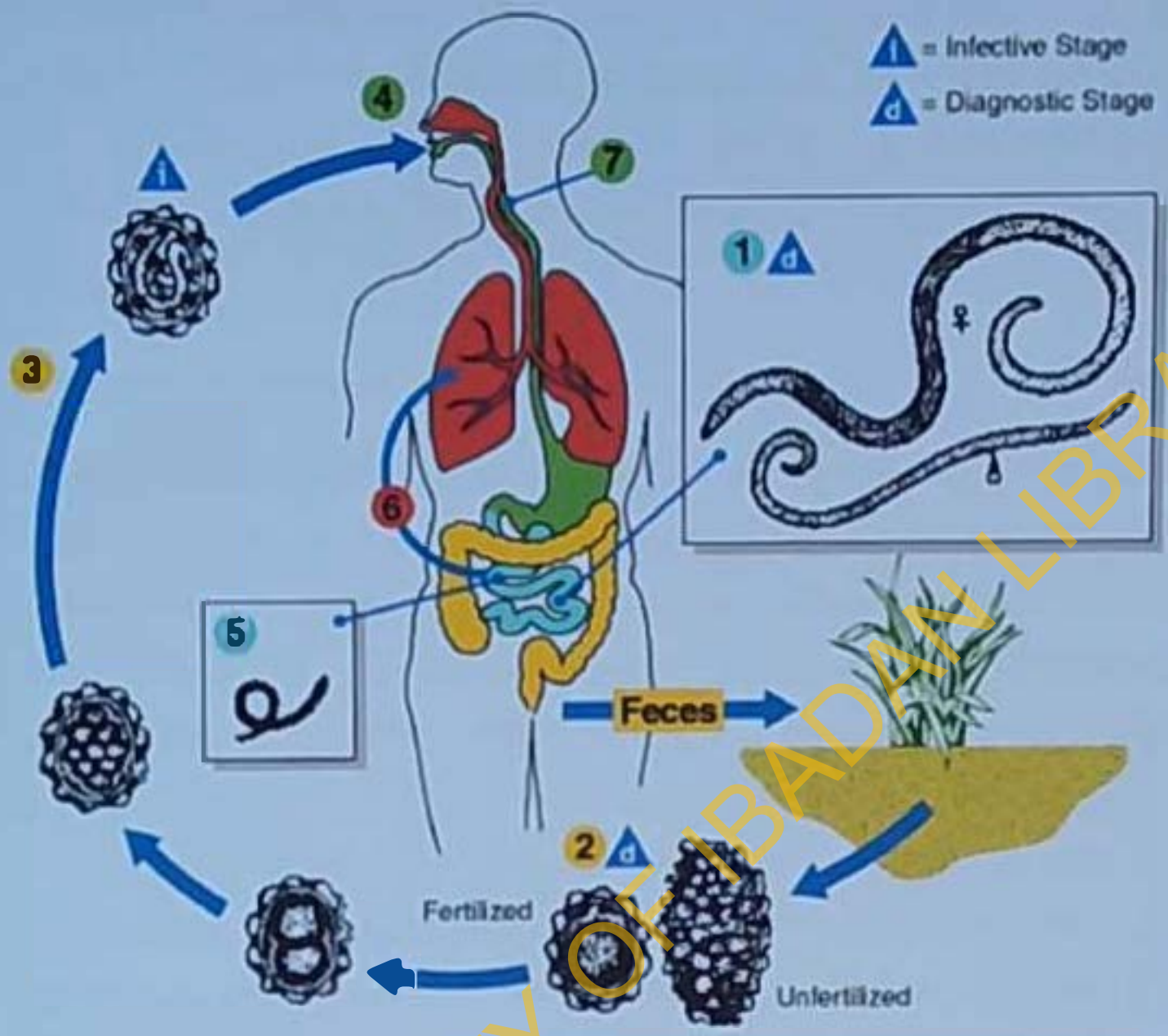
2.2.2 *Ascaris lumbricoides*: as a typical example of STHs

Ascariasis is the most common human worm infection. Infection occurs worldwide. According to the World Health Organization, severe ascaris infections cause approximately 60,000 deaths per year, mainly in children (WHO 2001b). *Ascaris lumbricoides* is the largest nematode (roundworm) parasitizing the human intestine. It is most common in tropical and subtropical areas where sanitation and hygiene are poor and causes an estimated 20,000 deaths each year (NIAID 2011). Ascariasis is caused by ingesting the eggs of ascaris. This can happen when hands or fingers that have contaminated dirt on them are put in the mouth or by consuming vegetables or fruits that

have not been carefully cooked, washed or peeled. Human faeces in streets, fields, and yards are a major source of infective eggs in heavily populated areas; also the use of human feces as fertilizer may also permit transmission of infective eggs by food that is grown in the soil and eaten without being thoroughly washed. The eggs of ascaris do not infect humans when first excreted by the worm. The eggs are very resistant to extremes of temperature and humidity and require several weeks to develop and become infective (NIAID, 2011, CDC, 2012).

Children are infected more often than adults, the most common age group being 3-8 years (WHO, 2001b). They often become infected after putting their hands to their mouths after playing in contaminated soil. The infection is likely to be more serious if nutrition is poor. Eating uncooked food grown in contaminated soil or irrigated with inadequately treated wastewater is another frequent avenue of infection. Many factors, including the large number of eggs produced by a female worm, the properties of the eggs, environmental conditions, and poor socioeconomic settings facilitate the spread of the parasite and thus determine the geographic distribution of the disease (Adeoye *et al.*, 2007. Mwangi *et al.*, 2006, Brooker *et al.*, 2007). Below is a pictorial representation of the Lifecycle of *Ascaris lumbricoides*.

Figure 2.2.2 Lifecycle of *Ascaris lumbricoides*



(Source: CDC's Parasites and Health page, http://www.dpd.cdc.gov/dpdx/HTML/Ascariasis.htm)

Mature male and female worms live and mate in small intestine of the human host. The female produces eggs. Fertilization occurs; fertilized eggs become infectious after two weeks in soil; they remain viable and can persist in soil for years. The fertile eggs develop into embryos and (depending on the environmental conditions i.e optimum being moist, warm, and shaded soil) become infective after 18 days to several weeks. These eggs are passed in the stool of an infected person.

Ascaris lumbricoides, or "roundworm", infections in humans occur when an infective egg is ingested fæco-orally by intake of contaminated food or water. The eggs hatch and develop into larvae (immature stage) in the intestines of the host. The larval worm then penetrates the wall of the duodenum and enters the blood stream where they develop further. The larvae are carried in the bloodstream to the lungs. They migrate upwards from

the lungs into the throat, where they are coughed up, swallowed, and thus returned to the small intestine. Once the larvae return to the small intestine, they develop into adult worms and mate. The female adult worm, which can grow to more than 30 cm in length, may produce up to 200,000 eggs per day. An adult ascaris may live up to 1 and a half Years. The Male and female worms mate and the females lay eggs in the intestines beginning the lifecycle all over again. The ingestion of these eggs by another person perpetuates the lifecycle.

Symptoms of Ascariasis:

Most cases of ascariasis are asymptomatic. The first sign may be the passage of a live worm, usually in the faeces. If symptoms do occur they can be light and include abdominal discomfort. The clinical effects of heavier infections include a wide range of manifestations with symptoms associated with the migration of juvenile or adult worms in infected organs. In a severe infection, intestinal blockage may cause abdominal pain, particularly in children. People may also experience cough, wheezing and difficulty in breathing, or fever this is due to migration of the worms through the body. Other common complications include pneumonitis due to passage of worms in the lungs, with pulmonary eosinophilia; and biliary and pancreatic obstruction by worms (USAID/NTD, 2009; WHO 2001b). The intensity of clinical signs is usually related to the worm burden in infected individuals. Serious, even fatal, but less common complications of ascariasis result from the infiltration of the larvae into sensitive tissues, such as the brain, and from the migration of the adult worms into various body structures, where they produce abscesses and toxic manifestations (USAID/NTD, 2009).

2.2.3 The burden and consequences of helminthiasis in children

Approximately two billion people or almost 29% of the world's population are infected with soil-transmitted helminth infections worldwide. Soil-transmitted helminth infections are widely distributed in tropical and subtropical areas, with the greatest numbers occurring in sub-Saharan Africa, the Americas, China and East Asia. Over 270 million preschool-age children and over 600 million school-age children live in areas where these parasites are intensively transmitted, and are in need of treatment and preventive

interventions (WHO, 2012b). In an earlier WHO estimate it was reported that *A. lumbricoides* infects over 1 billion people, *T. trichiura* 795 million, and hookworms (*Ancylostoma duodenale* and *Necator americanus*) 740 million (WHO 2004).

Children are particularly susceptible to the adverse effects of helminth infections due to their incomplete physical development and their greater immunological vulnerability, high mobility and lower standards of hygiene, school-age children are particularly vulnerable (Montresor *et al.*, 2002). They tend to harbor the greatest numbers of intestinal worms and schistosomes and as a result, experience growth stunting and diminished physical fitness as well as impaired memory and cognition (Crompton *et al.*, 2002). These adverse health consequences combine to impair childhood educational performance, reduce school attendance (Miguel *et al.*, 2004) and account for the observation that hookworm (and presumably other diseases caused by parasitic worms) reduces future wage-earning capacity (Bleakley, 2007).

Infection with *A. lumbricoides* may contribute substantially to child morbidity when associated with malnutrition, pneumonia, enteric diseases, and vitamin A deficiency. Ascariasis adversely affects children's growth and development. Also worth mentioning are the studies of Ezeamama *et al.*, 2005 and Sakti *et al.*, 1999 on worm burden in the Philippines and Indonesia, respectively. Both authors found significant negative impacts of helminthic infection on memory and fluency. Worms may also contribute to malnutrition by creating anorexia. A study of 459 children in Zanzibar reported that mothers noticed spontaneous increases in appetite after their children underwent a deworming regime (Stoltzfus *et al.*, 2003). Infection with STHs is particularly a problem in the developing world where food and water is usually unclean, and many people simply do not own shoes. Many walk miles barefoot only to collect contaminated water for their families, and as a result contract diseases and helminths.

People infected do not usually have symptoms except for patients with a heavy worm load. Generally conditions associated with intestinal helminth infection include intestinal obstruction, insomnia, vomiting, weakness, and stomach pains; (John *et al.*, 2006) while the natural movement of worms and their attachment to the intestine may be generally uncomfortable for their hosts. The immune response triggered by helminth infection may

drain the body's ability to fight other diseases, making affected individuals more prone to co-infection (Watkins *et al.*, 1997). One way in which intestinal helminths may impair the development of their human hosts is through their impact on nutrition. Intestinal helminth infection has been associated with problems such as vitamin deficiencies, stunting, anemia, and protein-energy malnutrition, which in turn affect cognitive ability and intellectual development (WHO, 1987) This relationship is particularly alarming because it is gradual and often relatively asymptomatic.

Studies on soil transmitted helminths in tropical regions of the world have always indicated at least 10% occurrence among any study population however school children remain the age group most vulnerable. In a study conducted in Ethiopia, nine species of intestinal helminths were identified with an overall prevalence of 27.2% among students aged 5-24 years (Tadesse, 2005), 28.6% prevalence of ascariasis among school children aged 1-16 years in Nigeria (Adefemi and Musa 2006), another study in Ogun State, Nigeria by Ekpo reported a prevalence of 54.9% in an urban government school, 63.5% in a rural government school, and 28.4% in the private school; the most common worm being *Ascaris lumbricoides* (Ekpo, 2008). In Zanzibar, Tanzania a prevalence of 73.7% in the rural and 48.9% in the peri-urban setting were recorded with school-aged children showing the highest intensities (Knobb *et al.*, 2010). More recent studies conducted among Nigerian school children, reported 40.2% intestinal helminth prevalence in Osogbo (Ojurongbe et al., 2011), 49.5% in Anambra State (Emmy-Egbe *et al.*, 2012), 46% in Bosso, North central Nigeria (Adabara *et al.*, 2011) and 75.6% prevalence for ascariasis among children aged 1-5 years in Edo State (Osazuwa, 2011).

The control of helminth infections in developing countries is of considerable public health importance and several factors have been associated with these infections.

Risk factors

Hurt and Adamu in Malaysia and Nigeria respectively identified the consumption of raw vegetable or salad as a risk factor for an infection with *A. lumbricoides* (Hurt *et al.*, 2012, Adamu *et al.*, 2012). Similar conclusions were reported in previous studies and documentations (Knobb *et al.*, 2010, Blumenthal and Peasey, 2002, Blumenthal and

Fleisher, 2001).Two studies carried out in Saudi Arabia and Turkey, indicated association between mother's educational level and awareness of parasitic infestations (Nagwa and Magda, 2010, Okyay *et al.*, 2004) although in Nepal, no significant differences were observed in parasite positivity rates in relation to low literacy rates of carers (Batu *et al.*, 2004).

Furthermore, poor sanitary conditions or contaminated water supplies were significantly associated with the transmission of Ascaris infections (Mehraj *et al.*, 2008). Some other studies reported socio-economic status, water supply, sanitary disposal of faeces and family size (Ekpeyong *et al.*, 2008, Obiukwu *et al.*, 2008, Ilechukwu *et al.*, 2010, Ngui *et al.*, 2011, Huart *et al.*, 2012) to be related with prevalence of intestinal helminth infections in humans.

A study among school-age children living in Mafia Island, Tanzania reiterated that (between 0 – 15 years of age) harbour heavy intestinal worms and are the group most responsible for contaminating the environment and transmitting these infections (Albonico *et al.*, 2002).

2.2.1 Challenges in the control, prevention and treatment of helminthiasis

At the 54th World Health Assembly 2001, a declaration was made towards attainment by 2010; a minimum target of regular administration of chemotherapy to at least 75% and up to 100% of all school-age children at risk of morbidity, this is referred to as "resolution WHA54.19". Member States were urged to:

- give high priority to implementing or intensifying control of STHs and schistosomiasis in areas of high transmission while monitoring the quality and efficacy of medicines;
- sustain successful control activities in low-transmission areas in order to eliminate STHs and schistosomiasis as a public-health problem;
- promote access to safe water, sanitation and health education through intersectoral collaboration;
- mobilize resources in order to sustain control activities for STHs and schistosomiasis.

However, current update informs that the attainment of the 75% coverage of regular administration of preventive chemotherapy to school-age children at risk of morbidity from STH and schistosomiasis by the target year has not been reached in many countries. Only a

third of all children in need have received appropriate treatment for STHs; in 2008, 16% of infected children were treated worldwide. Only three countries: Burkina Faso, Cambodia and the Lao People's Democratic Republic, were noted to have reached the World Health Assembly target (WHO, 2001a).

A likely reason for the lag in achieving this goal might be the issue of negligence. Helminthiases have often been ignored and as such receive little or no attention in the healthcare planning and budgeting of countries particularly in the tropics. Many Funding Agencies and NGOs do not have helminth infections as included in the diseases of core interest and as such very little funds are available for the support of helminth prevention, control and treatment. This neglect is possibly because of the asymptomatic presentation of the infection and the fact that these worms could be harboured for years without immediate clinical manifestations. However, the long-term effects of these worms are deleterious, sometimes causing permanent health challenges. Also the co-infection of these worms with other diseases suggests increased morbidity in the hosts. It is in this premise that the World Health Organisation included STHs as one of the Neglected Tropical Diseases (NTDs).

Secondly, the needs of populations affected by NTDs are major factors for the delay in attaining "resolution WHA 54.19". Wrecked by poverty, these populations do not have the funds to feed, they lack basic amenities like potable water and good living conditions *vis-a-vis* approved housing standards and spacing; some studies have linked access to safe water and proper sanitation to the persistence and prevalence of helminthiases (Pinheiro *et al.*, 2011, Lustigman *et al.*, 2012). In the tropics, proper sewage disposal amenities are either absent or insufficient; the people also lack sufficient funds to buy drugs for prevention and treatment when necessary. Until these problems are settled the prevalence of helminthiases will remain endemic in the populations affected.

There is also the challenge of erratic information systems. Data on STHs are always incomplete, delayed, inaccurate, insufficient or non-representative. At all levels, most of the health workers lack professional skills and lack proficiency in collection and reporting techniques particularly in current health management information system. Thus

surveillance is deficient, weakening implementation and evaluation strategies towards a helminth free populace.

Lack of Governmental support is another limitation. There is usually, lack of sufficient funds from the individual governments of the endemic countries to support institutional infrastructure, to fund medium and long-term research projects and to own responsibility of these projects. However, research capacity development remains an important endeavour and if not encouraged, evidence-based knowledge relevant to the health concerns of local communities and policy-makers for implementation of adequate practices in such nations will be lacking (Health link, 2006). Governments should be responsible for funding issues and ownership of programmes on helminthiasis control, by so doing the efforts of external donor agencies, research funding bodies and foundations, pharmaceutical companies, and non-governmental development organisations should be complemented; the national government can even take over what is already received from external sources, thus sustaining the success of control and elimination efforts made (Osei-Atweneboana *et al.*, 2012).

In disease endemic countries there is limitation in research capacity for helminthiases and other infectious diseases, especially in areas that require the application of advanced technology for disease control such as functional genomics and bioinformatics investigations. Research on NTDs and helminthiases is not considered a priority, receiving very little attention (Osei-Atweneboana *et al.*, 2012). There is also the lack of expertise in the development of new reagents, products and approaches for diagnosis, anthelmintics, vaccines, and integrated vector control, which are crucial for the sustained success of current programmes for the control and elimination of helminthiases (WHO, 2007). All these contribute to the poor management of helminthises and needs serious attention if we must achieve the goal of regular administration of chemotherapy to at least 75% and up to 100% of all school-age children at risk of morbidity.

If this condition is to be ameliorated, the procurement and distribution of essential medicines for NTDs must be given prior consideration. Quality-assured medicines must be made fully accessible and given free of charge for patients and all vulnerable persons especially children. This can be achieved by establishing a functional and sustained monitoring and evaluation system for delivery of these medicines.

More research into new diagnostic tools and medicines, coverage, compliance, acceptance and impact of interventions peculiar to STHs infections should be encouraged and funding available. This will bring out novel, evidence-based interventions and ideas towards a more effective and efficient combat against the spread of these infections.

Furthermore, control programmes in endemic countries should be encouraged as it has been demonstrated to be beneficial. This is known as preventive chemotherapy. Here, school-age children are treated through school-health programs, also preschool children and pregnant women at visits to health clinics. A study in Kenya demonstrated that deworming programs improve school attendance by 25% (Miguel and Michael, 2004); also another study in American South found that school attendance and enrollment grew significantly in the schoolage populations that benefited most from the Rockefeller Foundation's deworming programs, leading to a long-term increase in income as well as a rise in literacy rates (Bleakley, 2007). By using schools as treatment centres, Burkina Faso, Cambodia and the Lao People's Democratic Republic have achieved the target set by the World Health Assembly of treating 75% of school-aged children (WHO, 2010b).

Global changes should also be put into consideration. Planning for the development of prevention and control measures for NTDs should take into account the possible effects of porous borders, population growth and migration, the movements of livestock and vectors, and the political and geographical consequences of climate change (WHO, 2010b).

Monitoring and evaluation instruments should be devised and deployed to assess the effectiveness of research capacity building strategies in the same rigorous way they are applied to quantify the impact of control interventions. This would provide evidence-based arguments for the continuation and improvement of capacity building (WHO, 2010b).

2.3 Co-infection with malaria and intestinal helminths

There has been, an awakened research interest in recent times to explore the interaction of *Plasmodium sp* with other parasitic infections having similar epidemiological pattern, as this could unfold vital information needed for the achievement of a malaria free populace.

2.3.1 Malaria and Intestinal helminths Interactions

Co-infection is the concurrent infection of a host by more than one pathogen. It has also been expressed as the norm in nature (Haitgers *et al.*, 2008, Booth *et al.*, 2008), especially in communities endemic for helminth infections of different species and similarly exposed to infection with plasmodia (Booth *et al.*, 2006).

By distribution, over a third of the world's population, mainly those living in the tropics and sub tropics are infected by parasitic helminthes (worms) or one or more species of *Plasmodium* (De Silva *et al.*, 2003, Snow *et al.*, 2005). In sub-Saharan Africa and elsewhere, helminthiasis are frequently co-endemic with malaria (Hotez *et al.*, 2006), and HIV/AIDS (Borkow *et al.*, 2006). It is therefore not uncommon for an individual in this region to be co-infected with the malaria-causing parasite and one or more parasitic worm (Brooker *et al.*, 2006b, 2009, Druilhe *et al.*, 2005) or HIV (Kjetland *et al.*, 2006).

The ubiquity of these parasites in these areas results in high rates of co- infection (Petney and Andrews, 1998). It is also speculated that interaction with both infections within a host might have significant consequential alterations in terms of morbidity, pathology, and rate of recovery. Such co-infections have additive effects, such as severe anaemia, increased transmission of the malaria causing parasite, HIV, and/or increased susceptibility to infection with these pathogens as well as exacerbated progression of these two killer diseases (Gallagher *et al.*, 2005).

The results from the Comore study by Murray *et al.*, 1977 on the protective effects of Ascariasis first aroused the interest of many researchers in conducting researches about the association of the malaria parasite with intestinal helminth. The study reported that children with heavy infection of ascariasis had very low incidence of malaria. The authors suggested that the infestation with ascariasis could have led to nutritional deficiencies in

these children which created an unfavorable environment for the malaria parasite to thrive. For about two decades there were no other studies in that area until recently.

Since then, many studies have been conducted to elucidate the association between these two infections, however the findings have remained contradictory and conflicting. Valencia *et al.*, in 2010, conducted a correlation study and concluded that there was actually a correlation between the falciparum malaria and ascariasis, though low (R^2= 0.086) but this correlation was stronger into the clusters of towns with prevalence of *Ascaris lumbricoides* infection. Other studies suggested no relation between the two helminths and malaria (Shapiro *et al.*, 2005, Bejon *et al.*, 2008).

Some researchers assert that intestinal helminths aggravate malaria particularly severe malaria (Le Hesran *et al.*, 2003, Yatich *et al.*, 2009, Adegnika *et al.*, 2010) while so many other studies have concluded that intestinal helminths especially ascariasis have some protective effects against malaria (Nacher *et al.*, 2000 and Brutus *et al.*, 2007, Nacher *et al* 2001 b).

Studies continue to show that helminths either exacerbate (Le Hesran *et al.*, 2004) or reduce (Nacher *et al.*, 2001b, 2002) the severity of malaria.

Interaction between helminth infections and malaria is therefore of considerable public health importance, and more findings support the fact that helminth infections alter susceptibility to clinical malaria (Nacher *et al.*, 2001a, Nacher 2001, Druilhe *et al.*, 2005, Hotez *et al.*,2006, Borkow, 2006) and may result into antagonistic association in causing various morbidities in infected individuals (Adrienne *et al.*, 2005). Pierre asserts the fact that worms could constitute a confounding factor in the assessment of efficacy of malaria-control intervention, including vaccine prototypes in clinical trials. The study suggested that if it is confirmed that worms aggravate development to clinical malaria, then a novel means to control malaria would have been discovered (Druille *et al.*, 2005).

Animal models also exist to support the fact that helminth infections may increase susceptibility to malaria and the effects of co-infection may vary by malaria and helminths species and the intensity of the infections (Akhwale *et al.*, 2004). Several other reports in Kenya, Nigeria, and some other countries of Africa suggest an additive impact of co-

infection on anemia confounded by socio-economic, genetic, and nutritional factors (Brooker *et al.*, 2006a, Akhwale *et al.*, 2004, Egwunyenga 2001).

Some risk factors have also been associated with malaria-intestinal helminth, these include age, household size/clustering, educational status, knowledge of hygienic practices, socioeconomic status, residence, and toilet facilities, environment, and genetics (Brooker *et al.*, 2003, Hotez *et al.*, 2008, Yatich *et al.*, 2009).

Conversely other studies suggested that helminths were protective and could reduce the development of symptoms or curtail severity of malarial disease in a co-infected individual. Infection with A.lumbricoides was associated with a protective, dose-dependant effect against cerebral malaria and was found to hold for all helminths in a subsequent study even after controlling for nutritional status and personal protection measures against mosquito biting (Nacher *et al.*, 2002). In contrast, the risk of non-severe malaria and mixed plasmodia infections has been suggested to be increased among individuals infected with helminths compared to uninfected individuals (Nacher *et al.*, 2001a, 2002). Thus, in Thai adults, infection with helminths appears to lead to an increased risk of non-severe malaria but protect against severe malaria.

From recent co-morbidity studies

Prevalences of co-infection in recent studies continue to draw attention. In a study conducted in Cote d'Ivoire (Yapi *et al.*, 2012), the prevalence of *P. falciparum-mansoni* and *P.falciparum-hookworm* were 15.98% and 18.16%, respectively. In another study among outpatients in Ethiopia, 19.4% were infected with both *Plasmodium* and intestinal helminths (Degarege *et al.*, 2012); also a different Cote d' Ivoirien study observed a 27.9% concurrent infection with Plasmodium and hookworm in school-aged children (Righetti *et al.*, 2012). In Osun State, Nigeria, the prevalence of Plasmodium falciparum, intestinal helminth infections, and co-infection of malaria and helminth observed in a study were 25.6%, 40.2% and 4.3%, respectively. At a closer view, conclusions made from the interactions observed between these infections are contrasting. In the Ethiopian study, the likelihood of being infected with non-severe *P. falciparum* malaria was significantly higher in individuals infected with intestinal helminths, particularly in those with *A.*

lumbricoides alone. *T. trichiura* alone or *S. mansoni* alone compared to individuals without intestinal helminths. Similarly, prevalence of non-severe malaria (*P. falciparum* and/or *P. vivax*) was significantly higher in individuals infected with intestinal helminth or *A.lumbricoides* alone compared to individuals without intestinal helminths (Degarege, 2012). In the same vein co-infected children in Cote d'Ivoire had lower odds of anemia and iron deficiency than their counterparts infected with P. falciparum alone (Righetti *et al.*, 2012). Also, in the study by Ojurongbe *et al.*, geo-helminth-positive children tended to be parasitaemic and there was statistically significant association between helminth status and parasitaemia.

Contrastingly, Righetti et al., from their findings suggest that interaction between P. falciparum and light-intensity hookworm infections vary with age and, in school-aged children, may benefit the host through preventing iron deficiency anemia (Righetti *et al.*, 2012).

Participants older than five years were at higher risk of co-infection compared to their younger in Abidjan, southern Cote d'Ivoire. However, multinomial analysis of co-infection of *P. falciparum-S. mansoni* reflected no significant association of age and sex to the co-infection (Yapi *et al.*, 2012).

Another conclusion made by Adegnika *et al.*, after a review on "Epidemiology of malaria and helminth interaction: a review from 2001 to 2011" suggested a development toward a protective effect of Ascaris lumbricoides and Schistosoma hematobium, and worsening effect of hookworm and S. mansoni on the pathogenesis and incidence of malaria, respectively (Adegnika *et al.*, 2012).

From another perspective, Knowles after a meta-analysis study on the effect of helminth co-infection on malaria in mice concluded that her findings were consistent with the hypothesis that whether the immune responses elicited by helminth co-infection would promote or inhibit malarial disease depends on the existing balance of pro- and anti-inflammatory responses mounted against malaria parasites in a given host (Knowles *et al.*, 2011).

From the fore-going, the research interest into the interactions between intestinal helminths and malaria parasites continue to deepen.

A newer and interesting hypothesis was formulated by Nacher in a recent review article. He recommended that further verification should be done, since many studies, though in different epidemiological settings, suggest that helminth-infected patients have more gametocytes, and have less symptomatic malaria, longer-lasting infections, and are more attractive for vectors. Therefore if it is verified that patients co-infected by worms and malaria could be a "*transmission hub*" this would be an interesting piece of strategic information in the context of the spread of anti-malarial resistance and the malaria eradication attempts (Nacher *et al.*, 2012).

In conclusion, the conflicting reports from these studies have been linked to differences in study designs, stability of malaria transmission in the study area, sample size, study population and other factors. Therefore more studies are needed, especially prospective in design, since many observational studies have been conducted and are subject to unmeasured bias, this will provide more robust epidemiological evidence of the interactions between helminth infections and malaria.

However it remains important to understand the true role of these intestinal helminths because of the implication in management of these infections.

If truly there are some protective effects of these worms on the malaria parasite, what are the possible consequences of interventions like mass treatment on a population or the herd immunity of such a people?

If however the helminths aggravate malaria, then treatment of helminthiasis will need more attention and strategies to ensure faster and wider coverage as this might be another way to reduce the unchanging prevalence of the malaria scourge.

Other issues arising:

Are the intestinal helminths truly protective? If they are as some studies suggest, since they reduce (or rather "delay") the progression to development of symptoms, what happens to the malaria parasites in the host system? Are they actually cleared or still multiplying?

CHAPTER THREE

METHODOLOGY

3.1 Study Area

The study was conducted in Ona Ara Local Government Area, Oyo state. It is located southeast of Ibadan, the capital of Oyo state Nigeria. It covers a total land area of 425.544 square kilometers with a population density of 707 persons per square kilometer. There are about 56,406 children under the age of five years and 12,515 infants according to data from National Programme on Immunisation 2007. Older children are about 124,999 and adults are 100,630. The LGA is made up of about 400 villages which are divided into 11 wards - 3 urban, 2 peri-urban and 6 rural wards. The residents of the area are mainly Yorubas. The people are of Christianity, Islamic and Traditional religious backgrounds and are predominantly farmers and traders. Among agricultural activities practiced by the people are gari processing, oil milling, poultry, piggery and fishing. Malaria is holo-endemic in the LGA with perennial transmission. The climate is that of tropical rainforest zone.

3.2 Study design

Cross-sectional survey was carried out to obtain baseline information on characteristics of the study populations. This was complemented with the blood and stool sample collection malaria parasite test, and stool analysis to determine prevalence of asymptomatic parasitaemia, and malaria-intestinal helminth co-infection. Subsequently, a six-week longitudinal follow-up study of all consenting asymptomatic subjects was nested into the study for active case detection of progression to acute malaria. Second blood test was then conducted to confirm presence or absence of parasitaemia at instance of acute malaria symptoms during follow up period or at end of study for those still asymptomatic.

3.3 Study period

The study period was from February 2011 to June 2011.

3.4 Study population

The study population included children between the ages of 6 months and 17 years living within the study area and whose caregiver.

3.5 Inclusion criteria

The study population included any child:

- aged between 6 months and 17 years.
- who had been resident in the study area up to six months or more.
- who was supposedly healthy (had no symptoms of malaria or any apparent illness) as at the time of recruitment.
- whose caregiver provided written or verbal informed consent.

3.6 Exclusion criteria

The study population excluded any child:

- who was not within the ages of 6 months and 17 years.
- who had not lived up to six months in the study area.
- who had any symptoms of malaria or other apparent illness as at the time of recruitment.
- whose caregiver declined written or verbal informed consent.

3.7 Sample size calculation

Sample size was calculated using the Leslie Kish formula (Kish, 1965).

Using $n = \frac{Z^2pq}{d^2}$

Where n = sample size

p = proportion of children who were co-infected with malaria and intestinal helminth. this was 24.7% from a previous study in Cameroun (Nkuo-Akenji *et al*., 2006)

$q = 100 - p = (75.3\%)$, $\quad d = 5\%$

Thus $n = \dfrac{1.96^2 \times 24.7\% \times 75.3\%}{5^2} = 286$ children

Adjusting for non-response rate of 20% (considering the invasive nature (blood collection) of the study and the probability of participants changing location since it was farming season), the final sample size was calculated to be N

Where $N = \dfrac{n \times 100}{100 - r}$

And n = initial sample size

r = non response rate (20%)

Thus $N = \dfrac{286 \times 100}{100 - 20} = 358.$

3.8 Sampling technique

A two stage sampling technique was used to select 131 households from six communities of the LGA for the survey. Firstly, the six rural wards were selected purposefully (considering possibility of greater spread of helminthiasis and malaria in rural environments) out of the eleven wards in the LGA. Secondly, six communities were selected (one from each of the six rural wards) based on largest population size, accessibility of road and the informed consent/co-operation of the village head/representative.

Sample size was divided proportionately among the six communities based on population. In each of the settlements selected, the right side of the major entrance road was selected randomly; Research assistants then visited all households with eligible children in that area. In case no one was available for the survey or no one was at home when a research assistant visited, or there was no eligible child or the household head refused to give

consent, the research assistant proceeded to the next household. This was done until the sample size for the community was attained.

3.9 Data collection procedure

Five research assistants (with laboratory science background) were recruited and trained in questionnaire administration and laboratory sample collection. For every household visited, informed consent was obtained from the caregiver/head of household/adult representative then the study questionnaire was administered.

The questionnaire was developed by team members of the Epidemiology and Biostatistics Research unit (EBRU) of the Institute of Advanced Medical Research and Training (IAMRAT), University of Ibadan. It was face validated by another malaria expert, consultant physician and consultant parasitologist. Further still, the instrument was translated and administered into the local language "Yoruba". It was pre-tested also at another LGA different from the study LGA. The instrument is structured and has three sections:

Section A was on socio-demographic characteristics

Section B included questions on risk practices related to helminthiasis and malaria

Section C was an observation checklist to be used by the interviewer to observe and assess the household environs.

After administering the questionnaire, a laboratory form was filled for each eligible child; blood samples were collected and labeled appropriately.

A clean and well labeled stool container for stool collection was then given to the carer with instructions on how to collect the child's stool sample properly the next morning.

The research assistants returned very early the next day morning to collect the stool samples, these were temporarily stored in cool-packs and transported to the parasitology laboratory of the Microbiology Department of the University College Hospital, Ibadan for microscopy. This was the daily procedure for each community visited.

3.9.1 Laboratory Diagnosis

- For malaria parasites

Thick blood films were prepared from the blood samples collected by finger prick; the films were air dried and stored in slide racks. The slides were then transported to malaria laboratory of the Institute of Advanced Medical Research and Training, College of Medicine, University of Ibadan for microscopy. At the malaria laboratory, the blood smears were stained with Giemsa stain and examined under oil immersion objective (magnification x100) of the microscope. The thick smear was used to determine the presence of any asexual blood stage parasite. After reading 200 fields, smears were declared positive if asexual blood stage parasite was present and negative if none was seen.

- Microscopic examination (temporary wet mounts) of stool samples

A drop of saline was placed on slides and a small amount of faeces was placed on the microscope slide using applicator stick, this was mixed in drop and covered by cover slip. The samples were then examined microscopically at high power magnification.

- For the stool samples the formol-ether concentration and Kato-Katz thick smear techniques were employed for quantitative determination of helminths ova.

Formalin-Ether Concentration technique for stool Examination

The specimen was mixed with formalin and thoroughly stirred. A sufficient quantity was strained through gauze into a centrifuge tube to get the desired amount of sediment. Saline was mixed with it and centrifuged at about 2500 revolutions per minute. The supernatant was decanted; 10ml of 10% formalin was then added to the sediment and mixed thoroughly. About 3ml of ether was added and properly shaken in an inverted position for some seconds and then the stopper was removed carefully. The resulting solution was centrifuged at 1500 rpm for about 1 minute and four layers were produced. The three top layers were decanted carefully, and adhering debris were removed from the top with a cotton swab. The remaining sediment was mixed with the small amount of fluid that drains back from the sides of the tube or a small drop of formalin or saline was added. Finally wet mounts were prepared for microscopic examination. The presence of any helminth ova was considered positive; the absence of it, negative.

3.9.2 Follow up

Follow up usually commenced the next day, depending on the result of the malara parasite tests. Any child positive for asymptomatic malaria parasitaemia (irrespective of the presence or absence of intestinal helminths) were followed up for six weeks (to cover the incubation period of the malaria parasite in a malaria endemic zone) to determine time to development of symptoms of acute malaria.

These children were visited weekly for active detection of acute malaria using a follow up questionnaire; functional phone numbers were also given to carers to contact the research assistants in the event or development of fever (by subjective diagnosis). At each point, the carer of the child is interviewed on any clinical developments/issues arising since each last visit.

With the onset of acute malaria on or before the 6th week, second blood samples were collected to re-confirm parasitaemia; once confirmed, the patient was treated with Artemisinin Lumefantrine (AL); also Referrals were made to the nearest health center and University College Hospital for presentation with severe cases or other serious ailments not related to the outcome of interest.

At the end of the study period, those still asymptomatic and all those diagnosed with intestinal helminth were treated with AL and appropriate anti-helminthics (mebendazole and albendazole based) as the case may be.

3.9.3 Treatment/referral process for positive cases

Drugs were carried along in dry packs/cartons during the follow up period; the research assistants conducting the follow up were properly trained on how to administer the drugs. The research assistants explained the dosage thoroughly to the carer and gave him/her some health education/advice that will help in the wellness and health of his/her children including proper personal and environmental hygiene. They also followed up the children who were treated until they recovered.

Figure 3.10 FLOW CHART SHOWING STUDY PROCESS

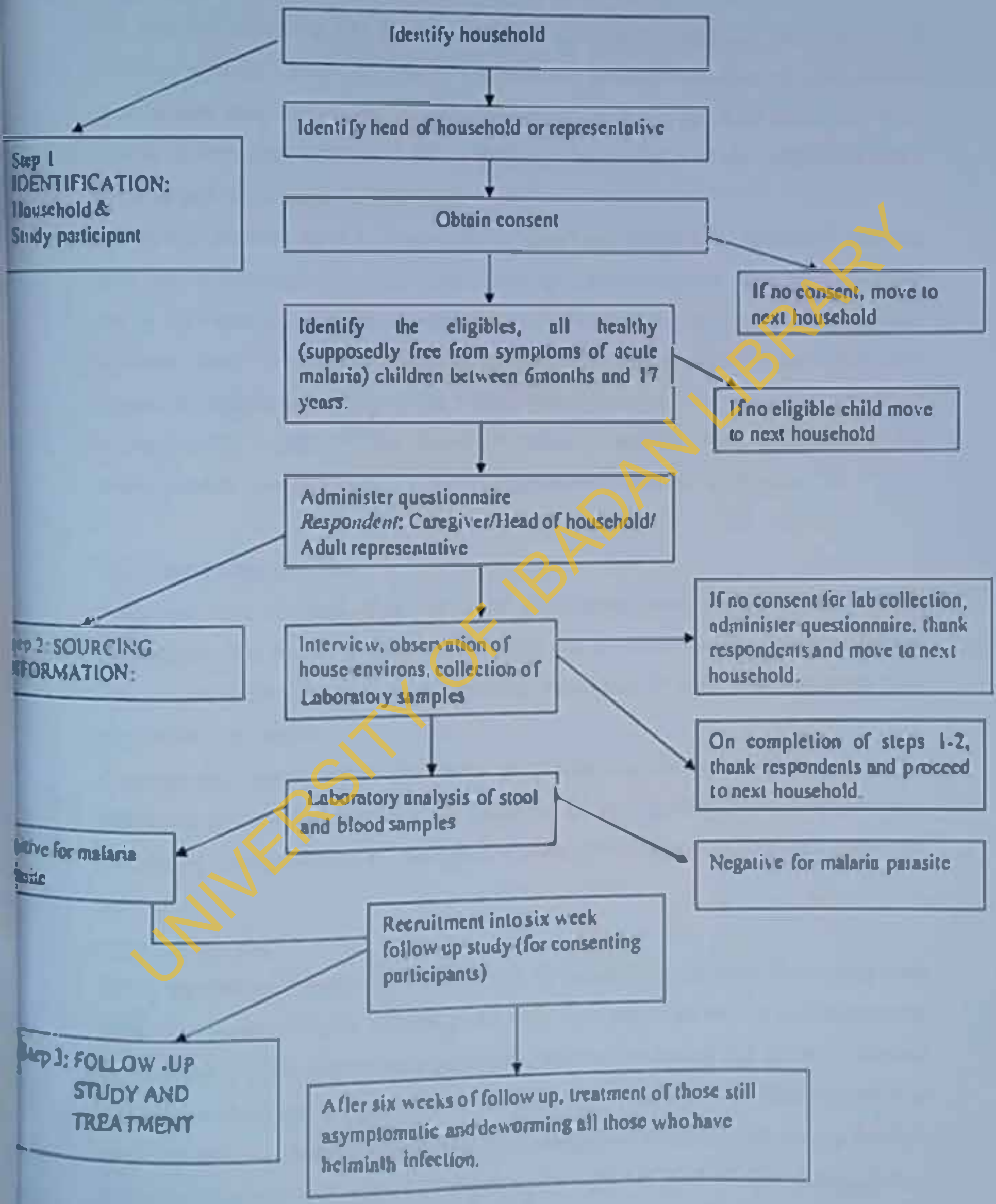
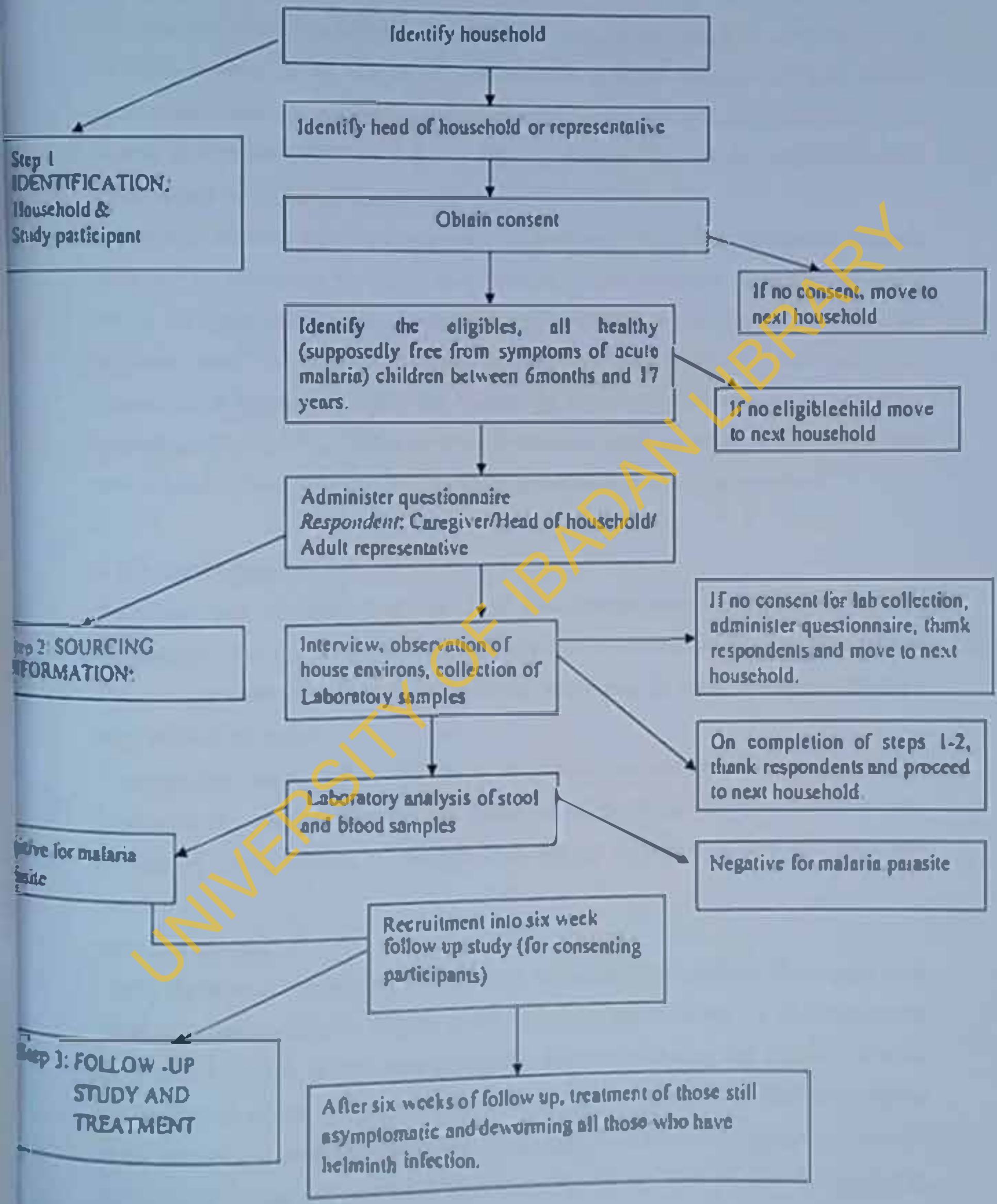


Figure 3.10 FLOW CHART SHOWING STUDY PROCESS



3.11 Data analysis

The data was entered in EPI data 3.1 statistical package and analysed using SPSS 15.0 statistical software (SPSS Inc. USA). The outcome variables measured included malaria parasitaemia, helminthinsis and co-infection with malaria and intestinal helminths, acute malaria. Independent variables included different characteristics of the children and their carers as well as the home environment.

Descriptive statistics such as frequencies, proportions, means and confidence intervals were used to summarize the data. Categorical data were compared using the Chi-square test or the Fisher's exact test, as appropriate. Person-time-at-risk was used to calculate incidence rates. The General Loglinear analysis was used to quantify the relationship between the categorical variables. The Kaplan-Meier procedure was used to estimate time-to-event models, to adjust for the presence of censored cases and estimate the survival rate at each point in time. A p-value < 0.05 was considered statistically significant.

3.12 Ethical Consideration

Permission was obtained from the local government secretariat and head of the communities. The ethical approval for the study was obtained from the Oyo State Ethical Review Committee. The findings of this study would also be made available to the Oyo State Ministry of Health.

Confidentiality: Every effort was made to protect the identity of participants. The importance of confidentiality and the protection of the identities of respondents were emphasized during training of research assistants for collection of data and laboratory samples.

Individual consent:

During the surveys, consent was obtained from the carers of the children. The consent form included an introduction, the purpose of the study, how questions were to be administered, the risks and benefits to those who participate, information stating that the data collected will be confidential and that participation is purely on a voluntary basis. Written consent or verbal consent was obtained from carers. Participants were allowed to drop out at anytime during the study and not respond to questions they did not wish to, this also applied to collection of laboratory samples.

Beneficence/Non Maleficence:

Prior to the commencement of the study, a visit was made to the Ministry of Health to request for free ACT anti-malaria and anti-helminth drug donations which were to be used for the treatment of the study participants. The Ministry of Health provided some packs of ACT anti-malaria (AL) which assisted to the case management to some extent; additional packs of ACT anti malarials and anti helminthics were later purchased to make up for insufficiency and to ensure that all the participants who needed treatment were treated appropriately.

During the study period, the carers were instructed to call some functional phone numbers given to contact the research assistants in the event of any severe cases or other serious ailments not related to the outcome of interest. Such were referred to the nearest health center and subsequently University College Hospital. Furthermore, during the follow up visitations, the carers were enlightened on personal and environmental hygiene to ensure malaria and worm free community.

3.13 Data storage

Data was collected through paper questionnaires and laboratory forms. All data collected from the survey were cleaned before and after data entry and stored on PCs and USB drives. Field notes and hard copies of the questionnaires were stored in locked filing cabinets.

CHAPTER FOUR

RESULTS

The results of this study are presented in three major sections: the survey, the laboratory tests and follow-up study.

SECTION A

4.1 Survey

4.1.1. Socio-demographic characteristics of the study participants (children)

Table 4.1.1.1 illustrates the distribution of children recruited per settlement. Among the six settlements, Gbedun had the greatest proportion 81(21.5%) of children studied, the least 52 (13.8%) was from Akanran. Table 4.1.1.2 shows the socio-demographic characteristics of the children studied. There were more females 199 (52.9%) than males 177 (47.1%). Mean age of the children was 6.5 ± 0.4 years.

Table 4.1.1.1 Distribution of children recruited per settlement

Community (N=376)	Health-ward	n (%)
Gbedun	10	81(21.5)
Badeku	3	64(17.0)
Aturomi	2	62(16.5)
Gbada	4	59(15.7)
Ajia	8	58(15.4)
Akanran	1	52(13.8)

Table 4.1.1.2 Socio-demographic characteristics of the children

Characteristics (N =376)	n (%)
Gender	
Male	177(47.1)
Female	199(52.9)
Age group in years	
6 months – 5	169(45.0)
6 – 11	152(40.4)
12 – 17	47(12.5)
No response	8(2.1)
Community (N =376)	
Gbedun	81(21.5)
Badeku	64(17.0)
Araromi	62(16.5)
Gbada	59(15.7)
Ajia	58(15.4)
Akanran	52(13.8)

4.1.2 Socio-demographic characteristics of the carers

The socio-demographic characteristics of the carers are summarized in Table 4.1.2. Three hundred and forty one carers from 131 households were interviewed. Their ages were grouped into six; the modal group was the 25 – 34 age groups and their mean age 38 ± 1.6 years. A greater number 178 (52.2%) of the respondents were of the Islamic religion, others were Christians 160 (47.0%) and very few 3 (0.8%) were traditional worshippers. Majority of them 276 (80.9%) were Yorubas. Farming 153 (44.8%) and trading (40.6%) were the major occupations of the people and about 121 (35.5%) of the respondents had no formal education. Three hundred and six (89.7%) of the carers were married while others 35 (10.3%) were either single parent or separated. About two-fifths of the carers were from Badeku (21.1%) and Gbedun (20.2%) while Akanran had the least (9.4%) proportion of the carers.

Table 4.1.2 Socio-demographic characteristics of the carers (N=341)

Characteristic	Frequency	Percentage (%)
Age group (years)		
15 – 24	47	13.6
25 – 34	155	45.4
35 – 44	77	22.6
45 – 54	31	9.2
55 – 64	19	5.6
>65	12	3.6
Religion		
Islam	178	52.2
Christianity	160	47.0
Others	3	0.8
Ethnicity		
Yoruba	276	80.9
Others	65	19.1
Marital status		
Married	306	89.7
Others	35	10.3
Occupation		
Farmer	153	44.8
Trader	138	40.6
Artisan	21	6.0
Unemployed	18	5.3
Student	11	3.2
Educational status		
No formal education	121	35.5
Primary	133	39.0
Secondary /higher	87	25.5
Community		
Badeku	72	21.1
Gbedun	69	20.2
Ajia	68	19.9
Araromi	60	17.6
Gbada	40	11.7
Akanran	32	9.4

4.1.3 Knowledge of malaria and its risk practices.

Table 4.1.3 shows the response of the carers on questions relating to their knowledge of malaria and associated risk practices. When asked about the symptoms of malaria they observe in their children, more than half of the carers mentioned high temperature 261 (79.0%), loss of apetite 240 (72.2%), rigors/chills 201 (60.9%) headache 197 (59.7%), and tiredness/child not being active 187 (56.7%).

Out of three hundred and twenty nine carers, 215 (65.3%) affirmed that malaria can be prevented; among these, majority 153 (71.2%) stated the use of mosquito coil, malaria drugs 147 (68.6%) and local herbs 116 (54.1%) as malaria preventive measures.

Only 93 (27%) of the carers reported to own Insecticide Treated Bednets (ITNs) and among those who owned ITNs, only 8 (9%) used them regularly.

Two hundred and thirty two (68.1%) of the carers reported that their children are usually inside the house between the hours of 5 and 10 pm.

Table 4.1.3 Knowledge of malaria and its prevention practices

Variables	Frequency	Percentage (%)
*Symptoms observed and suggestive of malaria (N = 330)		
High temperature/fever	261	79.0
Loss of apetite	240	72.7
Rigors/chills	201	60.9
Headache	197	59.7
Tiredness/child not active	187	56.7
Catarrh	149	45.2
Convulsion	145	43.9
Paleness/no blood/white hand	141	42.7
Vomiting	139	42.1
Cough	135	40.9
Difficulty in breathing	130	39.4
Whether malaria is preventable (N = 329)		
Yes	215	65.3
No	114	34.7
*Malaria preventive practices (N = 215)		
Burning of mosquito coils	153	71.2
Taking of malaria drugs	147	68.6
Using local herbs	116	54.1
Cutting of grass around the house	59	27.4
Making nets on windows/doors	58	27.1
Closing doors/windows	52	24.2
Using insecticide	45	21.1
Putting on cloths that cover the body	27	12.5
Using mosquito bednets	23	10.6
Burning of leaves	16	7.6
Possession of Insecticide Treated Bednets?		
Yes	93	27.3
No	248	72.7
Regularly usage of the Insecticide Treated Bednets (N = 93)		
Yes	8	9.0
No	85	91.0
Where is your child during the hours of 5-10pm?		
My child is usually outside	109	31.9
My child is usually inside the house	232	68.1

Note: * multiple responses

4.1.4 Knowledge about intestinal helminths and practices associated with their prevention

A summary of risk practices associated with intestinal helminths mentioned by the carers is shown in Table 4.1.4. One hundred and thirty two (38.7%) of the carers mentioned stomach pain as the symptoms of worm infection, others reported vomiting (19.3%), passing out worm (13.3%), diarrhea (4.0%) and malaria (1.0%). About one-fifth (23.7%) of the carers did not know any symptom for worm infection.

One hundred and ninety (55.7%) of the carers used anti-helminthics for worm prevention in their household, 21% used herbs while 23.3% did not practice deworming.

Among those who practiced deworming, about one-fifth 56 (21.3%) reported to have dewormed their children within the past two weeks; 39.1% between 2-6 months; and 12.4% more than a year; preceding the survey.

When asked about how often their children put on foot wears, about half 176 (51.7%) specified everytime, 43.2% said only when the child wants to go out, while eighteen (5.2%) reported that their children do not put on footwears at all.

About 75% of the carers washed fruits before taking them whereas one-quarter 87 (25.4%) did not; almost all 338 (99.1%) of the carers reported that they washed vegetables before consumption.

Table 4.1.4 Knowledge about intestinal helminths and practices associated with their prevention

Variables	Frequency	Percentage (%)
Symptoms of worm infection? (N = 341)		
Stomach pain	132	38.7
Vomiting	66	19.3
Passing out worm	45	13.3
Diarrhoea	14	4.0
Malaria	3	1.0
I don't know	81	23.7
Means of preventing worm infection (N = 341)		
Antihelminthic drugs	190	55.7
Herbs	72	21.0
We don't take anything	79	23.3
Last time child was dewormed (N = 262)		
Less than 2 weeks ago	56	21.3
> 2 – 6 months ago	102	39.1
> 6 – 12 months ago	21	7.9
More than 1 year now	32	12.4
I can't remember/ I don t know/it has been long	51	19.3
Use of footwears (N = 341)		
Everytime he/she is at home	176	51.7
Only when he/she wants to go out	147	43.2
Not all	18	5.2
Washing of fruits before eating (N = 341)		
Yes	254	74.6
No	87	25.4
Washing of vegetables before eating (N = 341)		
Yes	338	99.1
No	3	0.9

4.1.5 Observation of household amenities and environment.

Table 4.1.5 presents the report of the observations of the amenities in the household and environment of the house.

Most 343 (91.1%) of the children were from households who sourced their drinking water from surface water; 276 (73.3%) drank from the well, 67(17.8%) drank from any of pond/stream/river. Only thirty-three (8.9%) of them were from households who sourced drinking water from tap 5 (7.4%) or borehole 28 (1.5%).

Most of the children were from houses whose walls and floors were made of mud 290 (77.1%) and 236 (62.8%) respectively.

Many 311 (82.6%) of the children were from houses without any window or door screen/net. Three hundred and twelve (83.0%) children were from households that defecated in the bush, only three children (0.8%) were from households that had n water cistern.

A look around the house revealed that 121 (32.3%) children were from houses having overgrown vegetations around, eighteen (4.8%) of them belong to houses having water in uncovered containers of water.

Table 4.1.5: Frequency distribution of findings on Observation of household amenities and environment (N = 376).

Variables	Frequency	Percentage (%)
Source of drinking water		
Well	276	73.3
Pond/stream/river	67	17.8
Tap water	28	7.4
Borehole	5	1.5
Wall type		
Mud/not plastered	290	77.1
Cement/block	86	22.9
Floor type		
Mud	236	62.8
Cement	105	27.9
Others	35	9.3
Does the house have screen on door and/or windows?		
Yes	65	17.4
No	311	82.6
Type of toilet facility used		
Bush	312	83.0
Pit latrine	55	14.8
Water closet	3	0.8
Bucket	6	1.5
***Presence of potential mosquito breeding site**		
None	237	62.9
Overgrown vegetation	121	32.3
Uncovered containers of water	18	4.8

Note: * multiple responses

SECTION B

4.2 Laboratory procedures

A total number of 376 children were recruited for the study. Number of children who submitted both blood and stool samples, blood sample only and stool sample only were 162, 212 and 2 respectively. Thus Malaria Parasite (MP) test was conducted for 374 children, stool analysis for 164 children.

4.2.1. Malaria test results

The overall prevalence of malaria was 51.1%. The prevalence of malaria parasite according to sex, age group and settlement is shown in Table 4.2.1.1. No significant association existed between malaria and sex ($\chi^2 = 0.114$, $p = 0.736$) or malaria and settlement ($\chi^2 = 5.007$, $p = 0.400$).

There was a significant association between the children's age group and malaria ($p < 0.05$). Ages 0-5 years had the highest prevalence (56.8%) of malaria. The distribution of prevalence of malaria shows a gradual decrease as the age increases. Among all the children who tested positive for malaria, 51.6% were under 5, 41.4% were between ages 6 – 11, while 7.0% were of the 12 – 17 years age group.

Table 4.2.1.1 Prevalence of malaria parasite by child's characteristics

Characteristic	Malaria test result			χ^2	p value
	Positive n (%)	Negative n (%)	Total N (%)		
Sex					
Male	91 (52.0)	84 (48.0)	175 (100.0)		
Female	100 (50.3)	99 (49.7)	199 (100.0)	0.114	0.736
Community					
Akanran	29 (55.8)	23 (44.2)	52 (100.0)	5.007	0.400
Ajia	25 (43.1)	33 (56.9)	58 (100.0)		
Gbada	28 (47.5)	31 (52.5)	59 (100.0)		
Amaromi	38 (61.3)	24 (38.7)	62 (100.0)		
Badeku	32 (50.8)	31 (49.2)	63 (100.0)		
Gbedun	39 (48.8)	41 (51.2)	80 (100.0)		
Age group(years)					
0 – 5	96 (56.8)	73 (43.2)	169 (100.0)	12.525	0.002
6 – 11	77 (51.3)	73 (48.7)	150 (100.0)		
12 – 17	13 (27.7)	34 (72.3)	47 (100.0)		

4.2.2 Stool test result

A total of one hundred and sixty four (164) stool samples were analysed for the detection of any intestinal helminth. *Ascaris lumbricoides* was the only intestinal helminth species detected among the stool samples tested. Among all the children who tested positive for helminthiasis, 22 (36.7%) were under-5, 37 (61.7%) were between ages 6 – 11 years, while 1 (1.6%) was in the 12 – 17 years age group.

Overall prevalence of *Ascariasis* was 37.2%. The association between child's characteristics and intestinal helminth test result are shown in Table 4.2.2.2. There was a significant association between age group and helminth test results. About half of those who tested positive were from the 6 – 11 years age group. More males than females were positive for the intestinal helminth tests, however this was not significant ($\chi^2 = 1.331$, $p = 0.249$). There was no significant association between the communities and intestinal helminth test result of the children ($\chi^2 = 4.793$, $p = 0.442$).

Table 4.2.2.1 Helminth test result by child's characteristics

Characteristic	Helminth test result			χ^2	p value
	Positive N = 60 n(%)	Negative N = 101 n(%)	Total N = 161 N(%)		
Age group(years)					
0 – 5	22(29.7)	52(70.3)	74(100.0)	15.033	0.000*
6 – 11	37(52.1)	34(47.9)	71(100.0)		
12 – 17	1(6.2)	15(93.8)	16(100.0)		
Sex					
Male	35(41.2)	50(58.8)	85(100.0)	1.331	0.249
Female	26(32.5)	54(67.5)	80(100.0)		
Community					
Akanran	7(46.7)	8(53.3)	15(100.0)	4.793	0.442
Gbada	7(28.0)	11(68.8)	16(100.0)		
Araromi	5(31.2)	18(72.0)	25(100.0)		
Badeku	12(42.9)	16(57.1)	28(100.0)		
Ajia	18(46.2)	21(53.8)	39(100.0)		
Gbedun	12(28.6)	30(71.4)	42(100.0)		

*significant at 5% (fishers' exact test)

4.2.3 Co-infection with malaria and helminthiasis

A total of one hundred and sixty two (162) children submitted both blood and stool samples for laboratory tests. Of the 162 children, 54 (33.3%) tested positive for *P. falciparum* only, 15 (9.1%) tested positive for helminths only, and 45 (27.8%) were co-infected.

Children without helminth infection were more likely to test positive for malaria than those with helminth infection (OR = 2.72, CI = 1.35, 5.49).

There was no relationship between co-infection status and sex (p = 0.17) or communities (p = 0.571) as shown in Table 4.2.3.1. There was n significant association between the age groups and co-infection (p < 0.05). All the children between 12 -17 years tested were negative for co-infection (Table 4.2.3.2). More than half (56.8%) of the co-infected children were from the 6 - 11 age group whereas a greater proportion (63.8%) of the children with single infection of malaria were aged between 0 - 5 years. This association was significant, children of 6 - 11 age group were about two times more likely to be co-infected with malaria and helminthiasis compared to under-fives (OR = 2.3, CI = 1.0, 5.39).

Table 4.2.3.1 Co-infection and children's characteristics

Characteristic	Co-infection status			χ^2	p value
	Yes N = 45 n(%)	No N = 54 n(%)	Total N = 99 N(%)		
Sex					
Male	27(51.9)	25(48.1)	52(100.0)		
Female	18(38.3)	29(61.7)	47(100.0)	1.848	0.174
Community					
Ajia	3(37.5)	5(62.5)	8(100.0)		
Araromi	6(54.5)	5(45.5)	11(100.0)		
Gbada	6(50.0)	6(50.0)	12(100.0)		
Badeku	5(35.7)	9(64.3)	14(100.0)	3.848	0.571
Akanran	15(57.7)	11(42.3)	26(100.0)		
Gbedun	10(35.7)	18(64.3)	28(100.0)		
Age group(years)					
0 – 5	19(38.8)	30(61.2)	49(100.0)	8.385	0.015*
6 – 11	25(59.5)	17(40.5)	42(100.0)		
12 – 17	0(0.0)	5(100.0)	5(100.0)		

*significant at 5% (fishers' exact test)

4.3 FOLLOW UP

Of a total of 374 children whose blood samples were screened for malaria parasites, 191 children were positive; among those who had parasitaemia, 160 (83.8%) whose parents gave informed consent and expressed willingness to co-operate in the study, were recruited into a six- week follow up study to detect time to developing acute malaria. One hundred and fifty one of them were successfully followed up while nine were lost to follow up. Among all followed up successfully, 60 (39.7%) developed acute malaria while 91 (60.3%) remained asymptomatic.

Table 4.3.1 shows the number of acute malaria episodes per week. The median number of acute malaria episodes per week was 11 (range 5 – 12). During follow up 13 (21.7%), 12 (20.0%), 11 (18.3%), 11 (18.3%), 8 (13.3%) and 5 (8.3%) of the children developed acute malaria in the third, sixth, second, fourth, fifth and first weeks of follow up respectively.

Table 4.3.1 Distribution of acute malaria by follow up week

Follow up week	Number who became symptomatic n (%)
First	5 (8.3)
Second	11 (18.3)
Third	13 (21.7)
Fourth	11 (18.3)
Fifth	8 (13.3)
Sixth	12 (20.0)
Total	**60 (100.0)**

4.3.2 Symptoms reported by the children who developed acute malaria during the follow up period.

Different symptoms were reported by the children and carers (as appropriate by age). Almost all (94.9%) reported high temperature, other symptoms mentioned were headache (28.3%), yellow urine (20%) and cough (18.3%). Table 4.3.2 shows a summary of the symptoms reported.

Table 4.3.2 Symptoms reported by the children who developed acute malaria during the follow up period.

SYMPTOMS*	No of children (N = 60)	(%)
1. Fever/high temperature	57	94.9
2. Headache	17	28.3
3. Yellow urine	12	20.0
4. Cough	11	18.3
5. Catarrh	9	15.0
6. Cold/shivering	7	11.7
7. Lack/loss of opetite	6	10.0
8. Measles/Body rash/Skin infection	6	10.0
9. Vomiting	5	8.3
10. Paleness/yellowish eye	4	6.7
11. Wound	3	5.0
12. Watery stool	2	3.3
13. Stomach pain/upset	2	3.3
14. Weakness	2	3.3
15. Sneezing	1	1.7
16. Teething symptoms	1	1.7
17. Sleeping	1	1.7
18. Diarrhoea	1	1.7

*This question allowed for multiple responses from the respondents

4.3.3 Relationship between child's characteristics and development of acute malaria.

The relationship between child's characteristics and development of acute malaria is shown in Table 4.3.3; there was no significant relationship between the children's characteristics and the development of acute malaria.

Table 4.3.3 Relationship between child's characteristics and development of acute malaria

Characteristic	Symptomatic status at follow up			χ^2	p value
	No N = 91 n(%)	Yes N = 60 n(%)	Total N = 151 N(%)		
Community					
Ajia	13(72.2)	5(27.8)	18(100.0)		
Gbada	13(68.4)	6(31.6)	19(100.0)		
Akanran	18(69.2)	8(30.8)	26(100.0)	10.182	0.070
Araromi	12(46.2)	14(53.8)	26(100.0)		
Badeku	19(73.1)	7(26.90)	26(100.0)		
Gbedun	16(44.4)	20(55.6)	36(100.0)		
Age group (in years)					
0 – 5	39(51.3)	37(48.7)	74(100.0)		
6 – 11	41(68.3)	19(31.7)	60(100.0)		
12 – 17	8(72.7)	3(27.3)	11(100.0)	4.860	0.088
Co-infected					
Yes	29(64.4)	16(35.6)	45(100.0)	0.473	0.493
No	27(57.4)	20(42.6)	47(100.0)		
Sex					
Male	42(58.3)	30(41.7)	72(100.0)		
Female	49(62.0)	30(38.7)	79(100.0)	0.214	0.643

4.4 Incidence rate analysis

The 151 children enrolled contributed a total of 771.5 person-weeks of observation. The mean ± SD duration of person time contributed was 4.8 ± 0.3 weeks with a range from 0.5 to 6 weeks. Sixty (39.7%) participants developed acute malaria during the study follow-up period. The median time to development of acute malaria was 3.5 weeks and overall incidence-density rate was estimated to be at 7.78 per 100-person years (95% CI = 2.78 - 3.62).

About 40% of children (aged 0.5 – 17 years) who tested positive for malaria developed symptoms of acute malaria during the study period while 8 cases of acute malaria were observed per 100 person-weeks during the study period.

4.4.1. Incidence rates and child's characteristics

The incidence rates were further explored to study their association with child's characteristics.

4.4.1.1 Co-infection and incidence rates

Table 4.4.1.1 shows the cumulative incidence and incidence-density rate of the two groups of infected children.

Children infected with both malaria and intestinal helminths had lower risk of developing acute malaria compared to children with only malaria parasitaemia (0.32 : 0.42); also the incidence density rate for the co-infected (0.07 per 100 person-week) was lower than that of those having malaria parasitaemia alone (0.09 per 100 person-week).

Table 4.4.1.1 Co-infection and incidence rates

Co-infection status	Risk (cumulative incidence)	Incidence density rate (per person week of observation)
Co-infected (mp+, helminth +ve)	0.36	0.07
Single infection (mp+, helminth -ve)	0.42	0.09

4.4.1.2 Age specific incidence rates

Of the three age groups, children under the age of five had the highest cumulative risk and incidence density rate compared to the other age groups. This is shown in Figure 4.4.1.2. Cumulative incidence among the 6-11years (0.26) and 12 -17 years (0.27) age groups were almost the same, the incidence density rates for both age groups were 3 and 5 per 100 person-years respectively.

Figure 4.4.1.2.Age specific incidence rates

4.4.1.3. Sex specific incidence rates

Table 4.4.1.3 shows the sex specific incidence rates. The male children had greater risk (0.42) of developing acute malaria compared to the females (0.38); similarly the female children (0.07 per 100 person-weeks) had lower incidence density rate compared to the males (0.08 per 100 person-weeks).

4.5 SURVIVAL ANALYSIS

Survival analysis was conducted using the Kaplan-meier statistics to study the difference in survival times of the different age groups and infection types. However there was no sufficient data to study the median survival times of the different groups, as less than half of the follow-up cohort developed acute malaria within the study period; thus the mean survival times was appropriate (Parma and Royston, 2011, IBM, 2010).

4.5.1 Survival analysis and co-infection

Of the co-infected subjects, 16 (36%) developed acute malaria at follow up compared with 20 (43%) of the children with single infection of malaria [log-rank test of equality of survivor functions, χ^2=0.771, p= 0.380, RR (95% CI) = 0.75 (0.32-1.73)]. Mean survival time of the co-infected and those infected with malaria only was 5.16 ± 0.45 and 4.70 ± 0.54 weeks respectively. Those co-infected had a better survival curve and fewer of them developed acute malaria compared to the single - infected cohort, however this was not significant (p = 0.38). Figure 4.5.1 shows the survival curves of the two cohorts. Table 4.5.1 summarizes the difference in their mean survival times.

Table 4.5.1 Mean survival times of the two cohorts.

Cohorts	Mean Estimate	95% Confidence Interval	
		Lower Bound	Upper Bound
Co-infected	5.156	4.707	5.604
Single infection	4.702	4.165	5.239
Overall	4.924	4.570	5.278

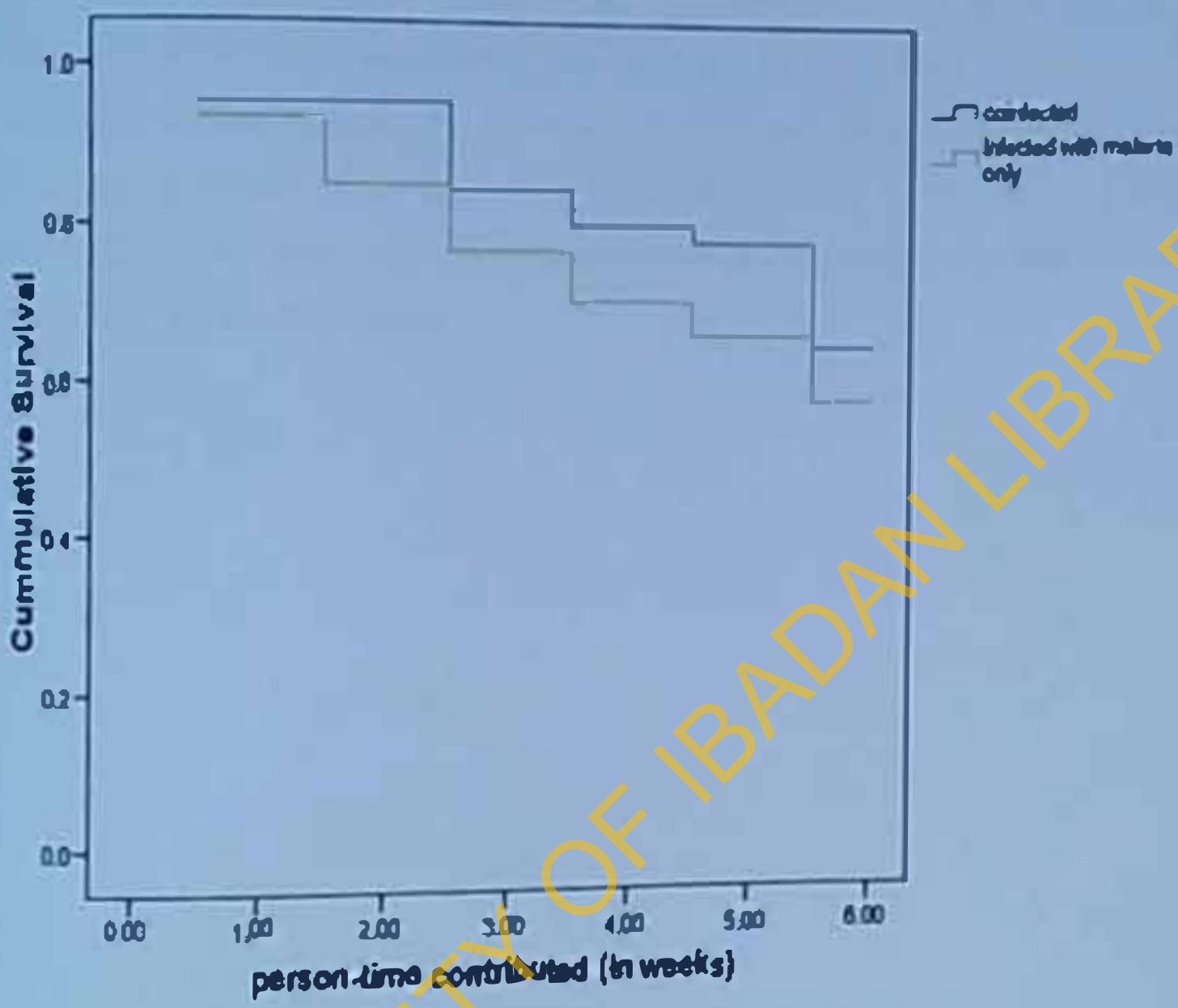


Figure 4.5.1 Survival curves of the two groups of infected children.

4.5.2 Survival times of the different age groups

For clarity considering initial results, the children's ages were regrouped into two: 0-5 years and 6 – 17 years; the difference in the survival times of the two age groups was then explored. The mean difference observed was significant ($p < 0.05$). Mean survival times of the 0 – 5 year and 6-17 year cohorts were 4.53 ± 0.43 (CI = 4.10, 4.96) and 5.21 ± 0.17 (4.89, 5.54) respectively; also the curve of the 6 -17 year cohort is above the curve for the 0 -5 age group, thus a higher proportion of children between 6 -17 year age group did not survive (did not develop acute malaria) per unit time compared to the under fives. Figure 4.5.2 shows the survival curves.

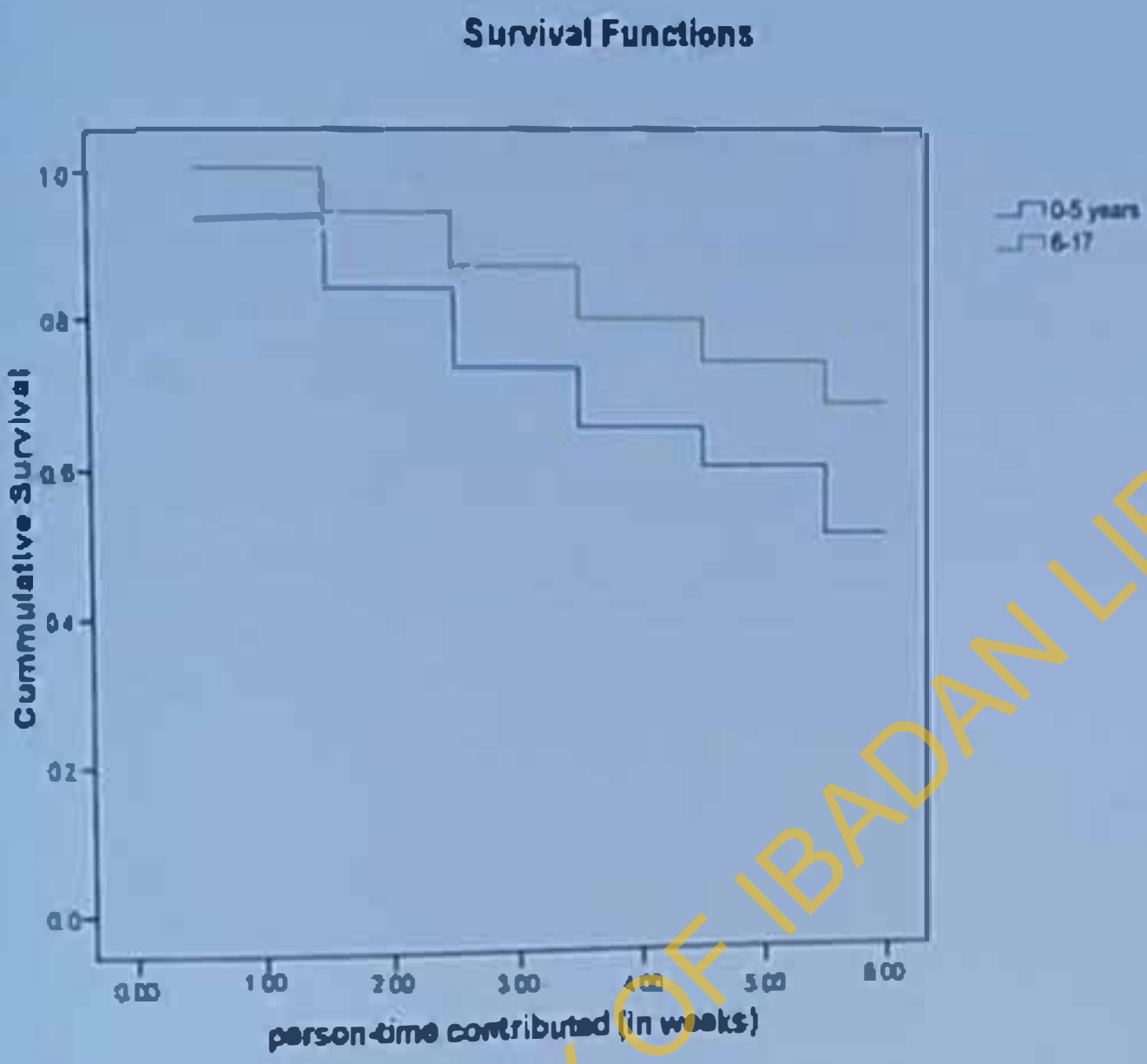


Figure 4.5.2 Survival curves of the 0-5 and 6 -17 year age groups

4.6 Second malaria test

From the initial malaria parasite (mp) test conducted, 191 had parasitaemia One hundred and fifty one of them were followed up to detect time to development of acute malaria a second test collected for malaria patasite after the follow up duration was expected for a successfully completed follow up. However, 123 (81.5%) children had the second test conducted (based on willingness/consent of their carers); of these, 114 (92.7%) remained positive for malaria while 9 (7.3%) had no parasitaemia without any drug or treatment administered.

Forty five (0.75%) of the children who were symptomatic had the second malaria parasite test conducted; among these, 41 (91.1%) tested positive for the second mp test while 4 (8.9) tested negative.

CHAPTER 5

DISCUSSION

This study showed differences in the distribution and occurrence of malaria and helminthiasis among children of different age groups in a rural setting.

The preventive practices for malaria-intestinal helminths co-infections in a typical rural setting were identified. Prevalence of asymptomatic malaria, intestinal helminths infections and malaria and intestinal helminths co-infections among children in the study area were determined. The association between intestinal helminths infection and the development of acute malaria was also explored.

5.1.1 Preventive practices for malaria-intestinal helminths co-infections

The carers' description of high temperature, loss of appetite, rigors/chills and headache as major symptoms of malaria were similar to those reported in previous studies in Swaziland, Tanzania (Warsame et al., 2007, Hlongwana et al. 2009) and the latest Malaria Indicator Survey in Nigeria (NMIS, 2010) and agrees with the description of malaria symptoms in clinical case management. The ability of mothers to recognise the symptoms associated with malaria particularly fever has important implications on child's survival (Alemseged et al., 2008). It reflects in the promptness to seek treatment for the sick child and adherence to treatment prescriptions. This study supports the findings in an earlier research (Ajayi et al., 2008b) conducted in the study location.

The study highlights the carers' perception of preventive measures and shows that coil (71.2%), drugs (68.6%) and herbs (54.1%) were used more than other malaria preventive measures. There is no gainsaying the fact that the cheap cost of these coils may have necessitated the high increase frequency of its usage.

As for ITNs, only 27% of the carers reported to own one in their households, among those who owned the nets, no more than 8 (9%) used them regularly. This is poor and

corroborates the 2010 NDHS Southwest estimates of 23.7% for ownership, 8.9% for use of bednets (NMIS, 2010). Thus, health education and campaigns should be intensified to enhance use of effective malaria preventive measures especially prophylaxis and ITNs. Costs of these measures have been reported to be impediment to ownership. The poorest socio-economic groups were less likely to own an untreated net, to purchase an ITN, and stated a lower willingness to pay for an ITN. Studies in Kenya and Tanzania have also found that poverty was an impediment to the purchase of mosquito nets (Musa et al., 2009; Kikumbih, 2002; FOSPPN, 2001; Hanson, 2003). Thus the government should subsidize their costs in order to improve accessibility and affordability especially among the rural poor. Similar conclusion was made in a related study in Nigeria (Erhun et al., 2005).

5.1.2 Risk practices associated with intestinal helminths

The symptoms of helminthiasis described by the mothers correctly reflect the WHO's scientific description of the disease (WHO, 2012). A similar observation was made in a study at Cote d'Ivoire (Acka et al., 2010) where knowledge, attitudes, and practices associated with parasitic worms had some implications for integrated control. However some carers (23.7%) stated that they did not know any symptom of helminthiases. This underscores the need for sustained public health enlightenment campaigns on knowledge of the signs and symptoms of helminthiasis among caregivers in the study location.

The caregivers' practice of deworming in the study location seems promising but the high prevalence of helminthiasis in the study population is paradoxical. A good practice of deworming should have translated into low prevalence of helminthiases. A recent study in Enugu, Nigeria observed a similar result (Chijioke et al, 2011). A possible reason might be related to drug misuse and abuse. Many of the anti-helminthics are cheap and are sold over the counter such that people purchase and use them at their own discretion without consulting qualified health workers or physicians for prescription. This might interfere with treatment course in individuals.

Other reasons include the low efficacy of single-dose mebendazole and albendazole (Adams et al., 2004; Albonico et al., 1994); high rates of post treatment reinfection for STHs in areas of high endemicity (Albonico et al., 1995); and diminished efficacy with frequent and repeated use of antihelminths (Albonico et al., 2003).

Equally, health education of the carers is very necessary as some of them still need to improve on environmental cleanliness and hygienic practices to ensure their children stay worm-free.

5.1.3 Prevalence of malaria

This is similar to previous results observed in Nigeria and Gambia (Adesina *et al.*, 2009, Obu and Ibe 2011). With an overall prevalence of 51.1%, the study area has high transmission and is therefore holo- and hyper- endemic for malaria; this is in line with the descriptions of high transmission areas according to a recent WHO policy brief on malaria (WHO, 2011).

Of more concern is the fact that the blood samples were collected in February which is not peak transmission season, and also these children were asymptomatic for malaria whereas they had parasites in their blood. Invariably, these serve as potential reservoirs for malaria transmission in the community thus malaria prevalence remains hyper-endemic.

Moreso this data can be used to predict the probable force of infections when the malaria seasons approach since the children harbor the asexual forms of the malaria parasite thereby act as potent reservoirs in the study area. This agrees with the hypotheses made from prior studies in three areas endemic for malaria transmission Southern Zambia, Eastern Sudan and Indo-Bangladesh (Sturrock *et al.*, 2010, Amel Abdel-Wahab *et al.*, 2002, Dhiman *et al.*, 2011) that targeting the reservoirs of asymptomatic malaria in a community especially in a non-malaria season will reduce incidence of malaria in the peak transmission season.

There was a significant association between the children's age group and malaria ($p < 0.05$). Children under 5 years had the highest prevalence (56.8%) of malaria, this supports existing propositions (WHO 2012, UNICEF, 2004, Olasinde *et al.*, 2010). The distribution of prevalence of malaria showed a gradual decrease as the age increases. This agrees with the fact that in an area of stable malaria, immunity develops progressively from early childhood to adolescence (Brooker *et al.*, 2007, Ojuronghe, 2011).

5.1.4 Prevalence of intestinal helminths

An overall prevalence of 37% was observed for intestinal helminth infections among the children in this study. This is comparable to a prevalence of 36.1% for a rural area in an earlier study conducted in Ife, Nigeria (Oninla *et al.*, 2007). According to WHO manual for preventive chemotherapy in human helminthiasis (Crompton, 2006), the study area falls under the Moderate-risk areas (≥ 20% and < 50% prevalence); thus the recommended frequency of once a year re-treatment should be adhered to. The relatively high prevalence of helminth infections in this study population could also be due to of poor environmental sanitation/hygiene and improper sewage disposal, as shown by the fact that 91.1% of the children were from households who sourced their drinking water from surface water (73.3% from well, 17.8% from any of pond/stream/river) and most (83%) were from households that defecated in the bush. It becomes important therefore that the needs of these rural poor be addressed. There should be provision of potable water, proper sewage disposal facilities, enforcement of environmental sanitation and approved housing standards. Until these problems are settled the prevalence of helminthiases may remain endemic in the study area.

A. lumbricoides was the only intestinal helminth identified; this observation is somewhat different from the results of a previous study in this environment (Dada-Adegbola *et al.*, 2005): Although in that study *Ascaris lumbricoides* was the most prevalent helminth but other spp of helminths were detected including hookworm. It might be that some hookworm eggs were missed due to temperature changes during transportation from the rural study sites for analysis, though the stool sample plastics were sterile and kept in cool packs before transporting them to the laboratories.

The highest proportion (61.7%) of those infected with intestinal helminth were the school age children (6 -11 year); this could be traced to their outdoor behaviors, they are more likely to walk to the bush; they are known to be more active and frequently make contact with soil and other contaminated materials (exposing them to the ingestion of ova as food contaminants) compared to the pre-school age children (0-5 year age group) who, though make contact with soil are still better protected by their carers. Similar conclusion has been

drawn from existing review articles (Bundy *et al.*, 1995; De Sylva *et al.*, 2003, Brooker *et al.*, 2007).

5.1.5 Co-infection with malaria and intestinal helminths

The prevalence of co-infection (27.8%) observed in this study is higher than that from a previous study in Osun state, Nigeria (Ojurongbe *et al.*, 2011). The reason for this is not clearly understood considering the fact that the study was conducted in high malaria season and also in a rural area. Also, of the children who had malaria, greater than 45% had intestinal helminths. Previous studies in Cameroun and Tanzania (Nkuo-Akenji *et al.*, 2006a, Mazigo *et al.*, 2010) observed lower rates.

In this study, children without intestinal helminth infections were almost three times as likely to test positive for malaria parasite compared to children with helminth infection but there was no significant difference between time to development of acute malaria between the two groups.

This does not agree with the findings of Ojurongbe (Ojurongbe *et al.*, 2011) in Osun state, Nigeria and previous related studies in Thailand and Ethiopia (Nacher M, 2001a and Bentwich *et al.*, 2000) where, a positive and statistically significant association between geohelminth and malarial infection were reported. Reason for this is not very clear.

From another point of view, a study conducted in rural area of Ghana reported helminth infection to be associated with increased levels of Interleukin- IL-10 (Hartgers *et al.*, 2009). IL-10 is an anti-inflammatory cytokine known to inhibit the protective immune responses against malaria parasites and to be involved in exacerbating parasitemia during Plasmodium infection (Nikuura *et al.*, 2011, May *et al.*, 2000, Perkins *et al.*, 2000, Ho *et al.*, 1995, Othoro *et al.*, 1999).

Results from the Ghanaian study, suggest that helminth infections may alter the antimalarial immune response through suppression of proinflammatory activity. Also animal models (Finney *et al.*, 2007, Wilson *et al.*, 2005) have shown that helminth infections can lead to the induction of regulatory T cells that have the ability to inhibit both Th1 and Th2 responses directed to other pathogens. This buttresses the fact that more research is still needed to demystify the actual course and role of helminths in their interactions with malaria parasite, this will be very relevant for a more scientific and

evidence-based approach in the prevention, control and management of malaria-helminthiases co-infections.

5.1.6 Follow-up and acute malaria incidence

The follow up study to detect acute malaria episodes were identified by a weekly active case detection. About 21% of the children eligible for the follow up study were not recruited due to lack of consent from their carers. This was mainly due to erroneous belief of the people on issues bordering on using their human excreta and blood for some evil acts. This was however corrected, and explanation made with the support of the village heads, however most of them still refused consent. Other reasons given accrue to travelling for farming activities or oil production, attendance to traditional ceremonies outside their communities. These challenges are not peculiar to this study; similar challenges were experienced in a community-based study in Benin, West Africa (Nahum *et al.*, 2010).

The overall risk (cumulative incidence) of developing acute malaria in the follow up cohort was about 40% for the study period; and 8 per 100 person years for incidence density; this is similar to 8.4/100 person months obtained from a previous study in Benin, West Africa (Nahum *et al.*, 2010). This low rate could be attributed to the fact that this study was conducted off –peak malaria season. Also, the small sample size of the follow up study could be another plausible factor for the low incidence density observed.

However the age specific incidence rate for the under fives is noteworthy. Compared with the 3.5 per person year from the NMCP/RBM business plan 2009 – 2013 (NMCP, 2008b), the incidence density of 10 per person year for under-fives in this study is much higher. This could be due to a more defined study area (rural) compared to the former which is a generalized result for the whole of Nigeria. All the same, more research on incidence rates in different locations will justify the discrepancy.

The difference in the incidence rate of malaria in the co-infected children and that of the children infected with malaria parasite alone could be traced to host characteristics,

Different people react differently to similar infections due to differences in nutrition status, immunity conditions, genetic factors, environmental exposures and others.

The symptoms reported or observed during follow up still correspond to the standard case definitions. Fever or high temperature was the most common (94.9%) symptom reported, this is similar to inferences from other studies on malaria in Nigeria and other African countries (Ajayi *et al.*, 2008a, 2008b; Uzochukwu *et al.*, 2008, Agu and Nwojiji 2005, Omole *et al.*, 2007, Sirima *et al.*, 2003). This substantiates the fact that fever or elevated temperature is a definitive symptom of malaria. This is also evident in the standard clinical case definition of malaria in major health documentaries (CDC, 2010, WHO 2001c, FMoH, 2008) where fever is defined as the primary definitive symptom of malaria.

5.1.7 Survival analysis

The survival curve obtained showed that in this study, children co-infected with malaria and intestinal helminths had a longer time to development of acute malaria symptoms compared to those infected with malaria alone although the difference was not statistically significant.

This observation as said before could be the consequence of the interplay and dynamics of non-specific characteristics of the host. This is similar to conclusion made from a meta-analysis of 42 mouse co-infection experiments used to explore the factors influencing how helminths influence malaria parasite replication and host mortality (Knowles 2011).

"Mean" survival time was used in this study as less than half of the follow-up cohort developed acute malaria within the study period. Similar method has been used in a previous study with the same challenge (Royston and Parmar, 2011, Fang *et al.*, 2006). This imposes some limitations in the interpretation of the survival analysis result since the median survival time is always preferred (IIM, 2006; Barker, 2009, Kaplan and Meier, 1958); therefore a prospective study with larger sample size and longer follow-up duration is needed to establish or refute the findings of this survival analysis.

The significant mean difference observed in the mean survival time of the 0 – 5 year and 6. 11 year cohorts, emphasizes the fact that children below the age of five years are at higher

risk of being infected with malaria parasites or developing acute malaria. This is because of their low or partially acquired immunity against malaria especially in a place of stable transmission like the study area. Other studies support this proposition (WHO 2012a, UNICEF. 2004, Olascinde *et al*., 2010). It is therefore very necessary that the policy of presumptive treatment of malaria for all febrile illnesses be implemented in the interim in Ona-ara LGA. this will ameliorate the present morbid situation pending the time the diagnostic packages are made available, accessible and affordable.

5.1.8 Limitations

An important limitation of this study is the short length of time for follow up, because it is thought that some people in endemic regions may not develop symptoms of acute malaria within the study time of 6 weeks, this could lead to only a smaller number of subject developing the symptom.

Some modifying factors, such as Blood group type and immunological interactions could have affected comparability between the children.

Also as the stool samples collected were transported to the laboratories, it is possible that some ova of hookworm which are very sensitive to heat might have been missed. Consequently, hookworm prevalence and its potential association with malaria may therefore have been missed.

Another limitation is the issue of ascertaining that among those who developed acute malaria the same parasite seen on the first smear caused the episode. However to ascertain this, PCR (Polymerase Chain Reaction) was needed; but the cost and expertise precluded its inclusion in this study.

5.2 CONCLUSION

In summary, this study showed that malaria and helminthiasis as well as mild co-infection of both are common among children in rural areas of Ona-ara LGA. Most importantly, it confirmed that age is an independent risk factor for both parasitic infections. The overall *P. falciparum* microscopy prevalence was 51.1%, with the highest parasite rates among 0-5 year olds.

Intestinal helminth and its co-infection with malaria constitute a major health burden among children of 6-11 years age-Group in the study area. Also, modifiable risk practices which have potential for promoting malaria and intestinal helminth infections abound in the communities.

Within the 6-week follow up period more than half of the children with patent parasitaemia remained asymptomatic and almost all the children who developed acute malaria were confirmed to have parasitaemia at second test.

The incidence studies have documented intense malaria transmission with median time to development of acute malaria as 3.5 weeks, cumulative risk of 0.4 and incidence-densities between 5 and 8 infections/per 100-person year among children aged 6 to 17 years living in the study area.

Results from the survival analysis suggest that intestinal helminths may influence acute malaria development depending on the interplay and dynamics of non-specific host characteristics and the influence of other socio-economic and environmental factors.

These findings may help in guiding future research on prevention and control of parasitic infections like malaria and intestinal helminths among Nigerian children. It will also be useful in designing effective and efficient interventions for malaria case management among children of different age groups.

5.3 RECOMMENDATIONS

1. Public health education on hygiene practices, environmental sanitation to prevent and reduce the rate of worm infections and malaria is strongly advocated for carers in the rural areas.
2. Modern toilet facilities and potable water should be made available in the rural areas to ensure healthier living.
3. Current prevalence and incidence rates should be employed in the planning, implementation and evaluation of health programmes to ensure efficiency and effectiveness.
4. There is need for the government and stakeholders to support this populace by subsidizing the costs of malaria preventive materials including ITNs and

prophylactics especially for the under-fives. Distribution of these materials should also be properly monitored to ensure better coverage as well as usage.

5. Further detailed investigation using larger sample size and longer follow-up period should be conducted to determine the role of intestinal helminths in the development of acute malaria in the area.
6. A school-based deworming programme should be established throughout the schools in Ona-ara LGA.
7. Health education in primary and secondary schools should be modified to train and educate school children on basic hygiene.
8. Capacity building programmes on standard case management procedures for these infections should be organized promptly among health workers in Ona-ara LGA.
9. Children especially under-fives should be given free ACTs and anti-helminthics with a local surveillance system reinforced for efficient and effective monitoring and evaluation.

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EPIDEMIOLOGY OF MALARIA AND INTESTINAL HELMINTHS CO-INFECTION AMONG CHILDREN IN ONA-ARA LOCAL GOVERNMENT AREA, OYO STATE

CONSENT FORM FOR CAREGIVERS

My name is _____ from the Department of Epidemiology, Medical Statistics and Environmental Health, Faculty of Public Health, University of Ibadan. I am carrying out a study on the "Epidemiology of Malaria and intestinal helminths co-infection among children in Ona ara LGA Ibadan Nigeria". I will be collecting blood samples (finger prick) and stool samples of your child/ward. These are simple sample collection techniques that do not cause any harm or injury to the body. Your child/ward may experience little pain or discomfort. You will also be asked some basic questions about your child/ward. The answers will be kept very confidential or secret. The information given me will be helpful to the Ministry of Health in future to know the effects of malaria and intestinal helminths co-infection among children and inform health policy makers on the need to strengthen the combined control strategies (e.g.: distribution or supply of malaria preventive materials/drugs together with deworming programs,) in management of malaria, and will contribute to ensuring optimum health of communities and the entire public.

Your child/ward will also be treated for malaria or helminth if he/she has malaria parasite or worm in his/her blood or stool samples.

You are free to decline consent for your child/ward to take part in this programme. You have the right to withdraw your child/ward also at any given time if you choose. I will appreciate your help in giving your consent for your child/ward to take part in this study.

Consent:
Now that the study has been well explained to me and I fully understand the content of the study process. I hereby allow my child/ward take part in the programme.

Name of caregiver _____ Signature/thumbprint _____
Date _____

Name of witness _____
Signature/thumbprint _____ Date _____

EPIDEMIOLOGY OF MALARIA AND INTESTINAL HELMINTHS CO-INFECTION AMONG CHILDREN IN ONA-ARA LOCAL GOVERNMENT AREA, OYO STATE

CONSENT FORM FOR CAREGIVERS (Yoruba translation)

Oruko mi ni _____, Mo n se ayewo lori bi aisan iba ati aran se wo po to larin omode ati agbalagba ni ijoba ipinle Ona-ara. Maa nilo lati mo bi omo yin se ga to ati bi o se gbe iwon to. Ma tun nilo lati gba eje die, ati igbe omo fun ayewo.

Awon ifana yi ko ni se ijamba fun ara omo yin, sugbon o le dun yin die. A o wo boya kokoro to n fa iba wa lara omoyin ati pe boya eni aran. Ofe ni awon ayewo yii eko nilo lati san owo kankan.

Ao pa esi ayewo omo yin mo, ako ni so fun elomiran afi eyin nikan. Ogun yio si wa fun omo yin ti aba ri wipe eni kokoro iba ati aran lara.

Maa fun yin ni nomba ero iba ni soro ti e le pe e ba sakiyesi o n se omo yin bi iba larin isinsin yii si ose mefa.

Awon esi iwadi yii yio se anfani fun ajo ilera ni ojo iwaju lati je ki won mo bi a se le dena aisan iba nipa sise itoju fun omo yin ti o ba ni aisan iba tabi aran eyi ti o ba wa nini eje tabi igbe re.

Ti ko ba wu yin lati je ki omo yin kopa, e leto, e si ni agbara lati da a duro nigbakugba ti o ba wu yin. Ipinu yin lati je ki omo yin kopa ninu ayewo yi, ma dun mo mi ninu.

Consent : Ni bayi ti e ti s'alaye fun mi ti o ti ye mi ohun ti ayewo yi je, mo setan lati je ki omo mi kopa ninu ayewo naa.

Oruko Olukopa/olutoju omo_____Ifi owo si iwe/te ika_____ Ojo iforowero_____

Oruko olujeri_____Ifi owo si iwe/te ika_____ Ojo iforowero_____

QUESTIONNAIRE (FOR CARERS)

EPIDEMIOLOGY OF MALARIA AND INTESTINAL HELMINTHS CO-INFECTION AMONG CHILDREN IN ONA-ARA LOCAL GOVERNMENT AREA, OYO STATE

INSTRUCTION: To be completed by the interviewer

Time Started _____

IDENTIFIERS	
1. Date of visit ___/___/___	2. Name of interviewer _____
3. Study No: _____	4. Settlement/Village name: _____
5. Compound name: _____	6. Name of Household head/adult representative/ Carer (as case may be) _____

SECTION A: SOCIODEMOGRAPHIC CHARACTERISTICS

7. Child's age: Years Months Ojo ori omo : Odun Osu	8. Sex 1 ☐ male /okunrin 2 ☐ female/obirin
9. Settlement/Abule:	
10. Age of Respondent: _____ (in years) E to omo odun melo:	11. Ethnicity/Omo du wo niyin: 1 ☐ Yoruba 2 ☐ Others/omiran
12. Religion/Esin: 1 ☐ Islam/musulmi 2 ☐ Christianity/igbagbo 3 ☐ Others	13. Marital status /Secti se ipawo: 1 ☐ married/Igbewo 2 ☐ separated/Iko lara eni 3 ☐ widowed/Se dadi wasi 4 ☐ Single/Apaun
14. Occupation/Ins ise wo lese : _____	15. Educational status/Ine melo le ka? 1 ☐ tertiary 2 ☐ secondary 3 ☐ primary 4 ☐ none 5 ☐ others Pls specify, E so eyin to baye ninu e, _____

SECTION B: PREVENTION PRACTICES ASSOCIATED WITH MALARIA AND HELMINTHIASIS

16. What symptoms do you usually observe in your child that makes you think he/she has malaria /A won omi wo ni e man rii le fi ma n ro pe omo yin ni alsanibe?

17. Do you think malaria can be prevented/Se e ro pe a le dena de alsan iba?
1☐ Yes 2☐ No

If no go to 19

18. If yes, how then can malaria be prevented/Ti o ba je beeni, bawo ni a se le dena de olsan iba?

19. Do you have Insecticide Treated Dednets/Se eni apo efon lori ibusun?
1☐ Yes 2☐ No

If no go to No 21

20. Do you use it regularly/Se e man lo deede?
1☐ Yes 2☐ No

21. Where is your child during the hours of 5-10pm? Nibo lomo yin ma n wa laart aago marun si mewa ale.
1☐ My child is usually outside/Omo mi wa ni ita
2☐ My child is usually inside the house/Omo mi ma wa ninu ile

22. What symptoms do you notice in your child that tells you he/she has worm infection/Awon ami ni e ma n rii lie ti ma mo pe omo yin ni aran?

23. What do you use to prevent worm infection in your household/Kini e man fi dena aran ninu ebi yin?
1. ☐ Antihelminthic drugs/Oogun
2. ☐ Herbs/Agbo
3. ☐ We don't take anything/A kin lo nkan kan

If you ticked 3. Go to No 25

24. When last did you deworm your child/Igba wo le lo Oogun aran fun omo yin?

25. How often does your child use footwears/Bawo ni omo yin se ma n lo bata?
1☐ Everytime he/she is at home/Ni gbogbo igba ti o wa nile
2☐ Only when he/she wants to go out/Nigba ti o ba fe jade
3☐ Not all/rara

26. Do you usually wash your hands before eating/Se e man fo eso yin ki e to je?
1☐ Yes 2☐ No

27. Do you usually wash your vegetable before eating/Se e ma n saba to efo ki e to je?
1☐ Yes 2☐ No

Time ended :

EPIDEMIOLOGY OF MALARIA AND INTESTINAL HELMINTHS CO-INFECTION AMONG CHILDREN IN ONA-ARA LOCAL GOVERNMENT AREA, OYO STATE

SECTION C OBSERVATION CHECKLIST

INSTRUCTION: To be completed by the interviewer for the child to be tested

Time Started _____

IDENTIFIERS	
1. Date of visit ____/____/_____	2. Name of interviewer _____
3. Study No: _____	4. Settlement/Village name : _____
5. Compound name: _____	6. Name of Household head/adult representative/ Carer (as case may be) _____
7. Child's age: Years Months	8. Sex: 1 ☐ male 2 ☐ female
OBSERVATIONS	
9. Source of drinking water for the family ☐ 1 Well 2 ☐ Pond/stream/river 3 ☐ Borehole 4 ☐ Tapwater	10. Wall made of : _____ 11. Floor made of: _____
12. Does the house have screen on door and/or windows? 1 ☐ Yes 2 ☐ No	13. Type of toilet facility used _____

14. Presence of potential mosquito breeding site: 1. Yes ☐ 2. ☐ o

If yes please describe in brief:

_____

Time ended: _____

EPIDEMIOLOGY OF MALARIA AND INTESTINAL HELMINTHS CO-INFECTION AMONG CHILDREN IN ONA-ARA LOCAL GOVERNMENT AREA, OYO STATE

LABORATORY INFORMATION PAPER

INSTRUCTION: To be filled by the research assistant and sent with the specimens collected to the laboratory.

Time Started_____

IDENTIFIERS	
1. Date of visit _____/_____/_____	2. Name of interviewer _____
3. Study No: _____	4. Settlement/Village name : _____
5. Compound name: _____	6. Name of Household head/adult representative/ Carer (as case may be) _____
7. Child's age: Years Months	8. Sex: 1[ ]male 2[ ]female

Laboratory Section

Sample collection

Specimen	Date collected
1. Blood/mp	
2. Blood/pcv	
3. Stool	

Laboratory diagnosis

Nature of specimen	Diagnostic test	Result	Comments/Date
Blood	Mp		
Blood	Pcv		
Stool	Stool analysis		

Time ended: _____

EPIDEMIOLOGY OF MALARIA AND INTESTINAL HELMINTHS CO-INFECTION AMONG CHILDREN IN ONA-ARA LOCAL GOVERNMENT AREA, OYO STATE

FOLLOW UP QUESTIONNAIRE

Good day. My name is _____. I am working with the research group who is looking at the Epidemiology of malaria and intestinal helminth co infection among adults and children in communities. We thank you for consenting to be part of this study. We are here to ask you few questions on your observations regarding your child/ward since he/she had your finger pricked for blood examination. We would like to know if you noticed any unusual event in your child's health. The interview will take about 15 minutes. Nothing you say will be considered wrong or right and it will not be mentioned to any one. Everything you tell us will be used strictly for the study. Thank you.

E ku ojumo o. O ruko mi ni _____. Mo je oko lara awon ti won se ayewo lori bi aisan iba ati aran se wop o larin omode ati agbaalagba ni ijoba Ipinle Ona-ara. Ao dupe lowo yin pe e daarapo mo ayewo yi. A wa lati se ibeere die lori akiyesi yin lori omo yin lati igba ti a ti gba eje e fun ayewo. A fe se iwadi boya omo yin si dubule aisan lati igba ti a ti gba eje re. Iforowero yii ko ni ju iseju medogun lo. A o pa esi ayewo omo yin mo, a ko ni so fun elomiran ati eyin nikan. A du pe lowo yin fun pe e ko pa nini iwadi yii.

IDENTIFIERS

1. Date of visit ___/___/___ b. Date enrolled into the study ___/___/___	2. Name of interviewer _____
3. Study No: _____	4. Settlement/Village name : _____
5. Compound name: _____	6. Name of Household head/adult representative/ Carer (as case may be) _____
7. Child's age: Years Months _____ __	8. Sex : 1[ ]male 2[ ] female

MALARIA HISTORY

9. Has your child had fever/ symptoms of malaria since the day his/her blood and stool samples were collected/ Se aa omo yin ti gbona tabi e ti ri ami iba lati igba ti a ti gba eje ati igbe re? 1[ ] Yes 2[ ] No

If yes proceed to other questions, if No. stop.

10. When did this illness begin/Igba wo ni aisan naa bere?

_____

11. What symptoms did your child experience /did you observe in your child/Iru arun wo lo ma se omo yin ti o mo?

_____

_____

_____

12. Have you administered any treatment since this illness started/Se o ti fun ni ogun nkankan?

1 ☐ Yes 2 ☐ No

13. When was the last time this child experienced illness before this one/Nigba wo ni arun na ti se ki to eyin?_____

_____

_____

14. What other illness does your child have apart from this one/Iru arun miran wo lo tun se?_____

_____

15. Was any one else in the family sick within the past 2 weeks/Se arun eniyan mi to tun se ninu ebi yin lose meji seyin?

1 ☐ Yes 2 ☐ No

16. Does anyone in your family, have any peculiar illness/Se ko si arun nkankan to wopo ninu ebi yin? Specify please_____(e.g. sickle cell disease, asthma etc.)

Thanks for your participation!

Ese pupo!

MINISTRY OF HEALTH

DEPARTMENT OF PLANNING, RESEARCH & STATISTICS DIVISION

PRIVATE MAIL BAG NO. 5027, OYO STATE OF NIGERIA

[redacted]

Our Ref. No: AD 13479/131 Date: 19th July, 2011

The Principal Investigator,
Department of Epidemiology, Medical Statistics
& Environmental Health,
College of Medicine,
University of Ibadan, Ibadan.

Attention: Afonne Chinenye;

Ethical Approval for the Implementation of Your Research Proposal in Oyo State

This acknowledges the receipt of the corrected version of your Research Proposal titled "*Epidemiology of Malaria – Intestinal Helminth co-infection among Children and Adults in Ona-Ara LGA, Ibadan, Nigeria*".

The Committee has noted your compliance with all the ethical concerns raised in the initial review of the proposal. In the light of this, I am pleased to convey to you, the approval of the committee for the implementation of the Research Proposal in Oyo State, Nigeria.

Please, note that the committee will monitor, closely, and follow up the implementation of the research study. However, the Ministry of Health would like to have a copy of the results and conclusions of the findings as this will help in policy making in the health sector.

Wishing you all the best

Mrs. V.A. Adejoju.
Director (Planning, Research & Statistics)
Secretary, Oyo State, Research Ethical Review Committee

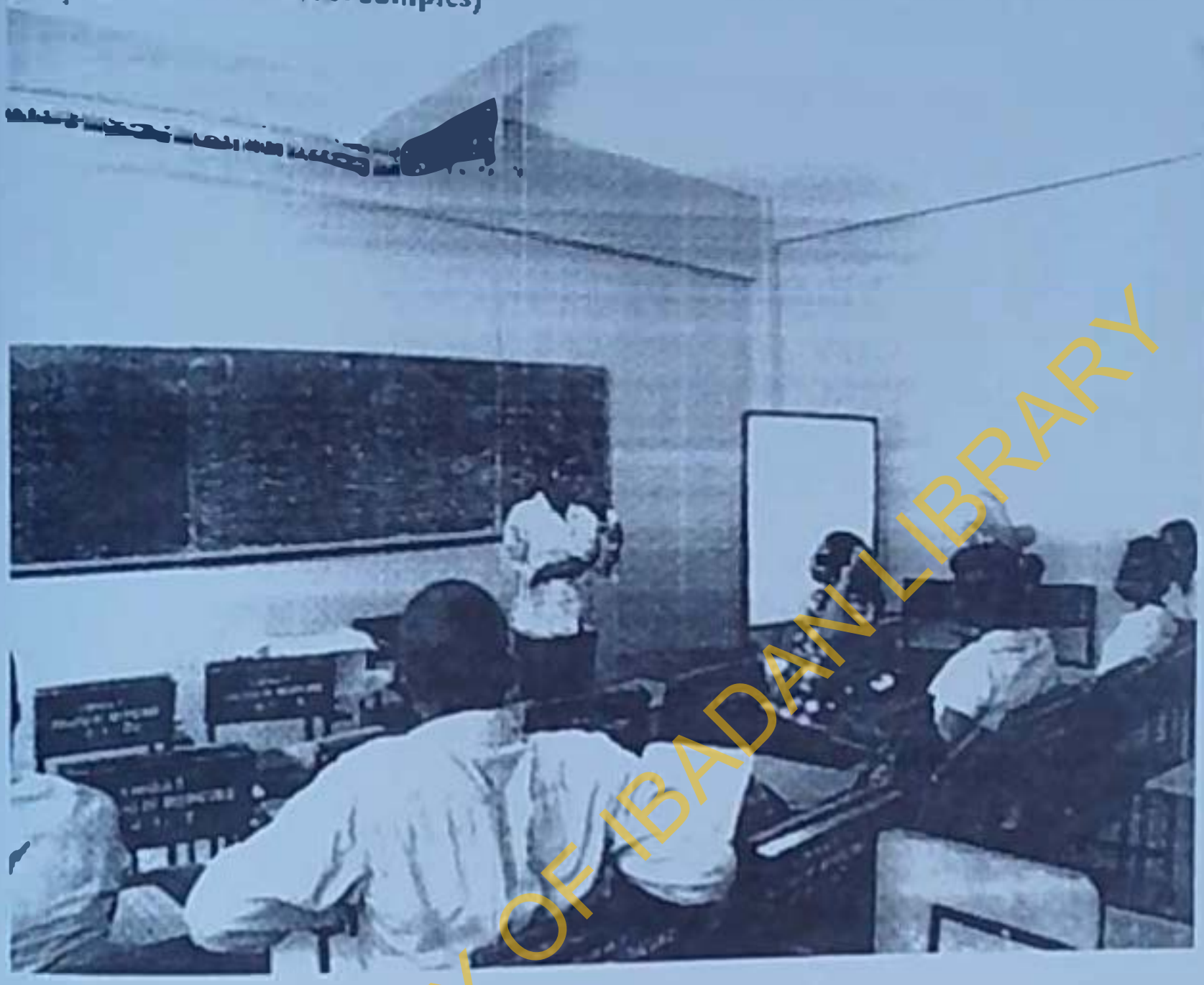
APPENDIX II: Plates showing ova and mature of roundworm

Plate 2a Mature egg of a Nematode- *Ascaris lumbricoides* (Roundworm)

Plate 2b Mature worm of a Nematode- *Ascaris lumbricoides* (Roundworm) passed out by a 5 year old girl during field work.

APPENDIX I: A cross-sectional view of research assistants during training for the study (collection of blood samples)

APPENDIX J: Cross-sectional view of research assistants during training for the study (collection of stool samples)



APPENDIX K: Field work: Student collecting blood sample for malaria test from a child

APPENDIX L: Field work: Research assistants attending to carers and their children

Operational definitions

Household:

A household refers to a group of people living in the same residence and eat separately from any other persons in the building and which have direct access from outside the building or through a common hall. The occupants here may be a single family, one person living alone, two or more families living together, or any other group of related or unrelated persons who share living arrangements (Sullivan and Steven, 2003, United States Census Bureau, 2012).

Household head:

This refers to the societal head of a household. This could be the eldest man or woman, a husband or an adult representative of a particular household who has the authority to make decisions on behalf of other members of the household. Without their informed consent no member of such a household was recruited into the study.

Carer:

This is any adult respondent, whether man or woman, interviewed during the survey and follow up visit, in order to obtain necessary information on behalf of any child recruited into the study. A carer may or may not be the household head.

Acute malaria:

In this study, acute malaria was defined as fever (axillary temperature $\geq$ 37.5°C) with a positive blood slide for Plasmodium falciparum asexual stages, regardless of parasite density.

Helminthiasis:

This refers to the infection of a child with any helminth or worm.

Co-infection:

This means the infection of a child with both malaria and intestinal helminth. In this study it refers to the condition where the first malaria test and the helminth test for a child were both positive, such a child is said to be co-infected'.

Child:

A child in this study refers to any individual between 6 months and 17 years who is still dependent on parents, guardian and adult relative.

Survival time:

This is the time from recruitment for follow-up until incidence of acute malaria.

Person-time / person-week of observation:

The time contributed by each child, for however long such a child remained in the study.

Censored cases:

These are cases for which acute malaria was not detected during the follow up study period, i.e. those that remained asymptomatic or were lost to follow up after being recruited into the follow up study.