

SCHOOL OF PUBLIC HEALTH

COLLEGE OF HEALTH SCIENCES

UNIVERSITY OF GHANA

**REPORTED MALARIA CASES AT THE WAR MEMORIAL HOSPITAL: PRE AND
POST MASS ADMINISTRATION OF IVERMECTIN IN THE KASSENANANKANA
EAST AND WEST DISTRICTS OF GHANA**

BY

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**THIS DISSERTATION IS SUBMITTED TO THE UNIVERSITY OF GHANA, LEGON
IN PARTIAL FULFILMENT OF THE REQUIREMENT FOR THE AWARD OF
MSc. CLINICAL TRIALS DEGREE**

SEPTEMBER, 2015

DECLARATION

I **NZOLO BOMENE Didier** of admission number **10509581**, hereby declare that except for the other people's investigations which have been duly acknowledged, this work is the result of my own original research, and that this dissertation, either in whole or in part has not been presented elsewhere for another degree.

I also declare that this dissertation has been reviewed by my supervisor and is submitted to the University of Ghana, Legon in partial fulfilment of the requirement for the award of Master of Science in Clinical Trials Degree.

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DEDICATION

This work is dedicated to all African children who are still bearing the burden of malaria infection, to all my family for their love, to all the staff of Clinical Pharmacology and Pharmacovigilance Unit for their support.



ACKNOWLEDGEMENT

I want to first and foremost acknowledge my supervisor, Dr. Francis Anto for his guidance and inputs during the design, conduct and writing of this work.

Also, I would like to thank Mr. Victor Asoala of the Navrongo Health Research Service for his guidance in the field to make the work possible. I am also grateful to Mr. Dominic Apio of the War Memorial Hospital for mobilizing his team as research assistants and to Mr. Martin Adjuik for his advice on statistical methods.



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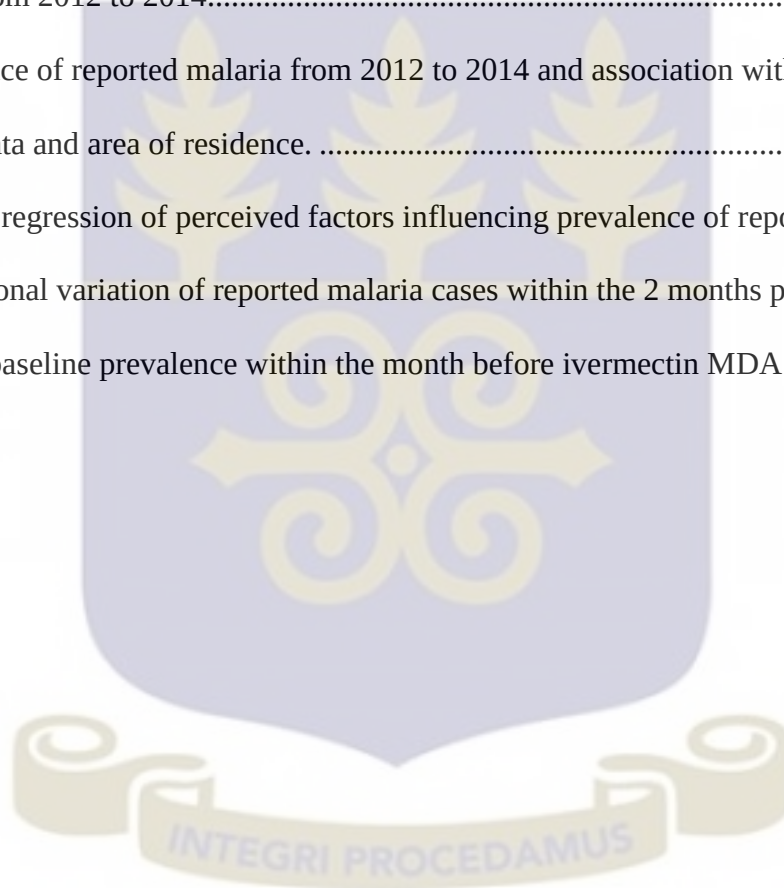
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LIST OF ABBREVIATIONS

ACT: Artemisinin-based Combination Therapies

CI: Confidence Interval

EIR: Entomological Inoculation Rate

GABA: γ -aminobutyric acid

HDSS: Health and Demographic Surveillance System

IPD: Inpatient Department

IPT: Intermittent Preventive Therapy

IPTi: Intermittent Preventive Therapy in Infants

IRS: Indoor Residual Spraying

IVM: Ivermectin

LLINs: Long-Lasting Insecticidal Nets

MDA: Mass Drug Administration

MSAT: Mass Screening and Treatment

OPD: Outpatient Department

DEFINITION OF TERMS

Given that the study relied on secondary data where the diagnosis was already available, the following operational definitions were used for the definition of malaria:

Reported malaria:

Refers to patients registered with a diagnosis of malaria (uncomplicated or severe). This definition includes confirmed and unconfirmed or suspected malaria cases. It excludes patients diagnosed as malaria cases but with negative laboratory result.

Confirmed malaria:

Refers to patients registered with a diagnosis of a malaria (uncomplicated or severe) and confirmed with an available laboratory result (RDT or microscopy)

Unconfirmed or suspected malaria

Refers to patients registered with a diagnosis of a malaria (uncomplicated or severe) but without a laboratory result (RDT or microscopy) confirming this diagnosis



ABSTRACT

Development and spread of resistance to current antimalarial strategies underline the necessity to develop innovative strategies. Recent studies suggest that ivermectin has a mosquitocidal effect and ivermectin mass administration might become an effective and complementary strategy in malaria elimination and eradication. However, ivermectin has been in use in many African Countries for over 25 years in Mass Drug Administration for onchocerciasis and lymphatic filariasis control.

The purpose of the current study was to investigate whether there has been a change in malaria prevalence in the months following ivermectin mass administration during the past three years.

A retrospective study was undertaken in the Navrongo War Memorial Hospital between May and June 2015. Data from 2,652 randomly selected patients were extracted from consulting room registers and admission and discharge books for the past three years. Variable of interest included date of visit, diagnoses, age, sex and area of residence. Dates of ivermectin mass drug administration were considered as point of reference. Malaria prevalence was compared three months before and after ivermectin MDA using two-group test of proportions. Pearson Chi-square and logistic regression were used to determine factors associated with malaria prevalence and strength of association.

On the whole, malaria prevalence was 24.8% (329/1,327, 95% CI: 22.5 - 27.1) before ivermectin mass administration and 26.3% (349/1,325, 95% CI: 24.0 - 28.8) after ivermectin mass administration with not statistically significant difference (-1.5%, 95% CI: -4.9 - 1.8; $p = 0.361$). On annual basis, malaria prevalence after ivermectin mass administration significantly increased during the year 2013 from 27 to 42% ($p < 0.001$) and decreased in 2014 from 20 to 14% ($p =$

0.016). Sex, age groups, source of data and year of ivermectin mass administration were found to be significantly associated with malaria prevalence ($p < 0.01$). A stabilization or decrease was observed when malaria baseline prevalence during the month preceding ivermectin mass administration was low and lasted for about two months.

We hypothesize that ivermectin administered in MDA can be used as an effective tool to reduce malaria prevalence. But its effectiveness will depend on the baseline prevalence before ivermectin distribution and may last about two months. Further studies are needed to confirm these findings.



CHAPTER ONE

1.0. INTRODUCTION

1.1. Background

Malaria Burden

According to the World Health Organization, Malaria is a life-threatening disease caused by parasites that are transmitted to people through the bites of infected mosquitoes. It is an entirely preventable and treatable mosquito-borne illness. But the last estimates showed that in 2012, there were 207 million cases of malaria (uncertainty range: 135 - 287 million) and 627 000 deaths (uncertainty range 473 000 - 789 000) [WHO, 2014]. Most malaria deaths (90%) occur in sub-Saharan Africa. Malaria kills one African child almost every minute. Nigeria and the Democratic Republic of Congo are two African countries with the highest malaria specific mortality rates. These two countries account for about 40% of global malaria death (WHO, 2013). The target 6C of the millennium development goals aim to 'have halted by 2015 and begun to reverse the incidence of malaria and other major diseases' and its first indicator is related to prevalence and death rates associated with malaria. The objectives of the Roll Back Malaria are to reduce malaria deaths to near zero, to reduce global malaria cases by 75% (from 2000 levels) and to eliminate malaria in 10 new countries by 2015 (RBM, 2008). To reach these objectives a set of strategies including curative and preventive measures are used.

Curative strategies to rollback malaria

In curative strategies, the objective of treating uncomplicated malaria is to cure the infection as rapidly as possible in order to prevent the progression to severe disease. From the public health point of view, the goal of treatment is to reduce infection, transmission and spread of resistance. For severe malaria, the objective is to prevent death and all other concerns associated with severe

malaria. To reach these objectives, WHO recommended the use of Artemisinin-based Combination Therapies (ACT) for the treatment of uncomplicated *P. falciparum* malaria; artesunate or quinine plus tetracycline or doxycycline or clindamycin as Second-line for treatment failure; and parenteral treatment with quinine and artemisinin derivatives for severe malaria, with preference in using intravenous artesunate.

Concerning ACTs, the artemisinin derivatives produce rapid clearance of parasitaemia and rapid resolution of symptoms. Its gametocytocidal action is necessary to reach the public health goal of reducing malaria transmission by decreasing the gametocyte carriage. The association with another effective schizonticidal antimalarial drug which is slowly eliminated allows just 3 days administration and the mutual protection of the two associated drugs against resistance development.

However, the weakness of curative strategies is the occurrence and the spread of resistance. This occurred with most of the antimalarial drugs used in therapy and now because of the risk of resistance to artemisinin derivatives, the WHO has created the global plan for artemisinin resistance containment (GPARC). Resistance in artemisinin derivatives is a real and very dangerous issue because currently there are no other antimalarial drugs offering the same level of efficacy and tolerability as ACTs (WHO and RBM, 2011). Resistance to artemisinin was first reported and is confirmed in Asia. But the bad news is the report of the first case of resistance in Angola, which is a sub-Saharan African country (Van Hong et al., 2014). So the best solution should be to contain this resistance and to promote development and implementation of preventive strategies.

Preventive strategies to rollback malaria

Considering the malaria morbidity and mortality rates and the threat to existing curative strategies, efforts are concentrated in effective preventive strategies to control, eliminate and/or eradicate malaria. Currently, there are several preventive methods including the use of Long-Lasting Insecticidal Nets (LLINs), Indoor Residual Spraying of insecticide (IRS) and administration of some drugs for preventive purposes among vulnerable groups including intermittent preventive therapy (IPT) for pregnant woman and infants (IPTi). The aim of these methods is to reduce malaria transmission from mosquitoes to human, as well as from human reservoir to mosquitoes.

Between 2000 and 2012, the association of all these existing interventions contributed to reduce malaria incidence by 25% globally and 31% in the WHO African Region (WHO Global Malaria Programme, 2013). During the same period, malaria mortality rate was reduced by 42% globally and 49% in the WHO African region and an estimated 3 million children under-five in sub-Saharan Africa were saved.

Vector control in malaria prevention is one of the most important targets of donors. For example, in 2010, the United States President's Malaria Initiative (PMI) dedicated 56% of its expenditures to LLINs and IRS which are the most important and cost-effective antivectorial methods. Unfortunately, IRS and LLINs are based only in the use of four classes of recommended insecticides (pyrethroids, organochlorines, organophosphates and carbamates). Only pyrethroids are currently recommended for use in LLINs and organochlorines and pyrethroids are preferred for IRS.

Since 2009, there has been an increase in reported insecticide resistance cases. According to the Global plan for insecticide resistance management in malaria vectors (GPIRM), resistance has been identified in 64 countries with ongoing malaria transmission, mainly to pyrethroids. Resistance to DDT is also prevalent, and there are increasing reports of resistance to organophosphates and carbamates. In the WHO African Region, there are several areas of critical concern because of particularly widespread resistance to pyrethroids or to multiple insecticide classes. This spread of resistance is a real threat against all the effort made at global level in order to control and eliminate malaria (WHO global malaria programme, 2012).

1.2. Problem statement

Considering the threat to existing curative strategies and the development and spread of resistance to current insecticides used as preventive strategies, innovative strategies are badly needed in the effort of malaria elimination and eradication.

Recent studies suggest that mass administration of ivermectin might become an effective and complementary strategy in malaria elimination and eradication (Slater et al., 2014). The drug is known to have properties that address three main challenges related to malaria vector control. These are: (1) its mode of action is different from the four currently used insecticides (pyrethroids, organochlorines, organophosphates and carbamates) for malaria vector control, thus it could circumvent the issue of emerging insecticide resistance; (2) as a systemic drug, it is ingested by all biting mosquitoes and so it will equally target indoor and outdoor-biting mosquitoes, as well as those with crepuscular activity; and, (3) the activity of the drug targets four out of the five variables of vectorial capacity, especially the most influential variable, the daily probability of mosquito survival (malERA Consultative Group on Vector Control., 2011; Chaccour et al., 2013). Considering this finding, a call for further studies was made to assess the

possibility of using ivermectin as an antimalarial intervention that can contribute to malaria elimination and eradication (Chaccour et al., 2013). Ivermectin is not a new drug as it has been in use in many African Countries including Ghana for over 25 years in Mass Drug Administration (MDA) for onchocerciasis and lymphatic filariasis control. However, malaria is still endemic and the leading cause of morbidity and mortality, despite the administration of ivermectin once or twice a year in many African countries. It would however, be worthwhile looking backwards and exploring whether malaria morbidity has been influenced by the administration of ivermectin. The purpose of the current study therefore is to determine whether there has been a change in malaria prevalence in the months following ivermectin mass administration during the past three years in the Kassena-Nankana districts.

1.3. Conceptual framework

The conceptual framework describes the different factors that can influence malaria prevalence in the context of our study. Four factors may be involved in the increase or decrease of malaria prevalence: individual factors, environmental factors, antimalarial interventions and ivermectin mass administration.

The individual factors include age, sex and level of exposure to *P. falciparum*. Malaria is more prevalent in children under five and in pregnant women who constitute a vulnerable group. People who are less exposed to *P. falciparum* such as travelers also constitute a vulnerable group.

The environmental factors include climate and factors related to humans. The variation in rain fall and temperature during dry and rainy season can contribute to change in malaria prevalence.

Construction of irrigation dams and a bad waste management can lead to stagnant water which is necessary for the reproduction of mosquito and the spread of malaria.

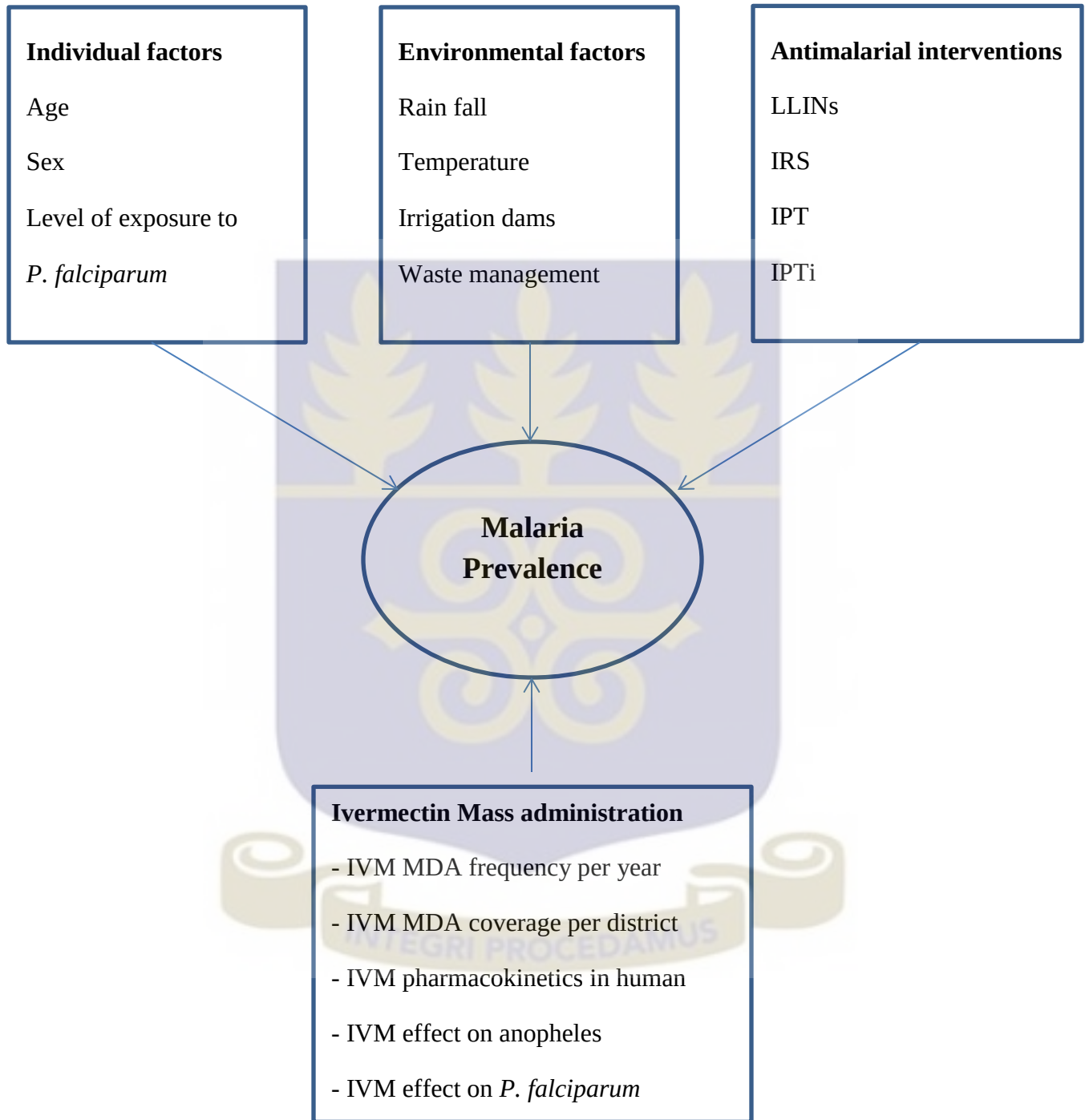
Antimalarial interventions such as implementation of LLINs, IRS, IPT, and IPTi can play an important role in the reduction of mosquito survival and/or malaria transmission and then contribute to the reduction of malaria prevalence.

Mass administration of ivermectin is now identified as a potential tool to decrease malaria prevalence. But the success of ivermectin in the reduction of malaria transmission depends on the number of MDA per year, the coverage of each MDA at district level, and the inherent properties of the drug related to human pharmacokinetics, and its action on anopheles and on *P. falciparum*.

In this study we did not focused on the effect of all the factors mentioned above but only on the effect of ivermectin on malaria prevalence.



Figure 1: Factors involved in malaria prevalence



Abbreviations: IPT, Intermittent Preventive Therapy; IPTi, Intermittent Preventive Therapy in Infants; IRS, Indoor Residual Spraying; IVM, Ivermectin; IVM MDA, Ivermectin Mass Drug Administration; LLINs, Long-Lasting Insecticidal Nets

1.4. Justification

This study is relevant because several studies are needed before introducing a new tool for disease control and elimination. Considering that there are few clinical data on the effect of ivermectin on clinical malaria in human, this study can provide data from the field, which will help to create accurate modeling or to ameliorate existing theoretical modeling that are created based not on clinical data but on data from the effect of ivermectin on anopheles and *P. falciparum*. Such a study could also provide further information about confounding factors which may influence the trend of malaria incidence after ivermectin MDA in real live and may also be useful to provide hypothesis for further prospective studies and clinical trials.

1.5. Objectives

1.5.1. General objective

To determine whether mass administration of ivermectin in the control of lymphatic filariasis in the Kassena-Nankana districts influenced malaria prevalence.

1.5.2. Specific objectives

1. To determine the prevalence of malaria three months pre and post mass ivermectin administration over the past three years
2. To determine any short term change in malaria prevalence following mass administration of ivermectin

CHAPTER TWO

2.0. LITERATURE REVIEW

2.1. Malaria epidemiology

Malaria is a life-threatening disease caused by parasites that are transmitted to people through the bites of infected mosquitoes. The disease is transmitted in tropical and subtropical areas where *Anopheles* mosquitoes can survive longer for parasites to complete their growth cycle, especially in Africa, Latin America, Asia, and the South Pacific (Hay et al., 2010). In 2012, there were 207 million cases of malaria and 627 000 deaths. Most malaria deaths (90%) occur in sub-Saharan Africa where malaria kills one child almost every minute (WHO, 2013). This makes mosquito *Anopheles* the first killing animal in the world and malaria a top global public health disease with high priority.

In Ghana, malaria accounts for about 38% of out-patient attendance, 36% of all admissions and 33% of all deaths among children aged under 5-year.

Understanding of malaria parasite transmission and lifecycle may be important for the development of new drugs and new strategies aiming at malaria elimination and eradication.

2.2. Malaria transmission

The parasite, *Plasmodium*, is spread to people through the bites of infected *Anopheles* mosquitoes, called "malaria vectors". The intensity of transmission depends on factors related to the parasite, the vector, the environment and the human host.

Malaria is caused by protozoa of the genus *Plasmodium*. To date, there are five *Plasmodium* species known to cause malaria in humans: *P. falciparum*, *P. vivax*, *P. malariae*, *P. ovale* and *P.*

knowlesi recently reported in South-East Asia (Cox-singh & Singh, 2008). *Plasmodium falciparum* is the most common of the four human malaria parasites across most of Sub-Saharan Africa and is the most deadly. In Africa, *P. vivax* is concentrated in the Horn of Africa, covering Djibouti, Eritrea, Ethiopia, Somalia, and Sudan (Mueller et al., 2007).

About 20 different *Anopheles* species are locally important around the world. The four species that transmit human malaria are *An. funestus*, *An. gambiae*, *An. arabiensis* and *An. Melas*. *An. funestus* and *An. gambiae* are the principal ones involved in malaria transmission (Fontenille & Simard, 2004). Transmission is more intense in places where the mosquito lifespan is longer and where it prefers to bite humans rather than other animals. For example, the long lifespan and strong human-biting habit of the African vector species is the main reason why about 90% of the world's malaria deaths are in Africa.

Climatic conditions that may affect the number and survival of mosquitoes are rainfall, temperature and humidity. Temperature is particularly important for malaria transmission. For instance, temperatures below 20°C (68°F) are not favorable for *Plasmodium falciparum* to complete its growth cycle in the *Anopheles* mosquito, and thus cannot be transmitted. *P. vivax* is more tolerant to lower ambient temperatures. In many places, transmission is seasonal, with the peak during and just after the rainy season.

Other environmental factors involved in malaria transmission include those related to human behavior such as waste disposal, stagnant waters, outdoor working and sleeping, deforestation, etc.

Human immunity is another important factor in areas of moderate or intense transmission conditions. Partial immunity can be developed over years of exposure and help reduce the risk of severe disease. The specific population at risk with low immunity includes: young children in stable transmission areas; pregnant women; people with HIV/AIDS; non-immune international travelers (World Health Organization, 2010)

2.3. Malaria life cycle

a. Human liver stage (exo-erythrocytic cycle)

When an infective female *Anopheles* mosquito bites its victim, it injects saliva that contains sporozoites of *Plasmodium* into the blood. The parasites are then carried to the hepatocytes (human liver cells) where they multiply through hepatic schizogony phase. About 1 to 2 weeks later, merozoites are released into the blood.

b. Human blood stage (erythrocytic cycle)

The merozoites attack the red blood cells, enter and multiply in them. Then the parasites develop through stages of rings, trophozoites, schizonts containing thousands of merozoites. After 2 or 3 days the attacked red blood cells break up, releasing the merozoites which go on to infect other red blood cells. It is during this process of cell break up that symptoms of malaria are noticed (Vanderberg, 2014).

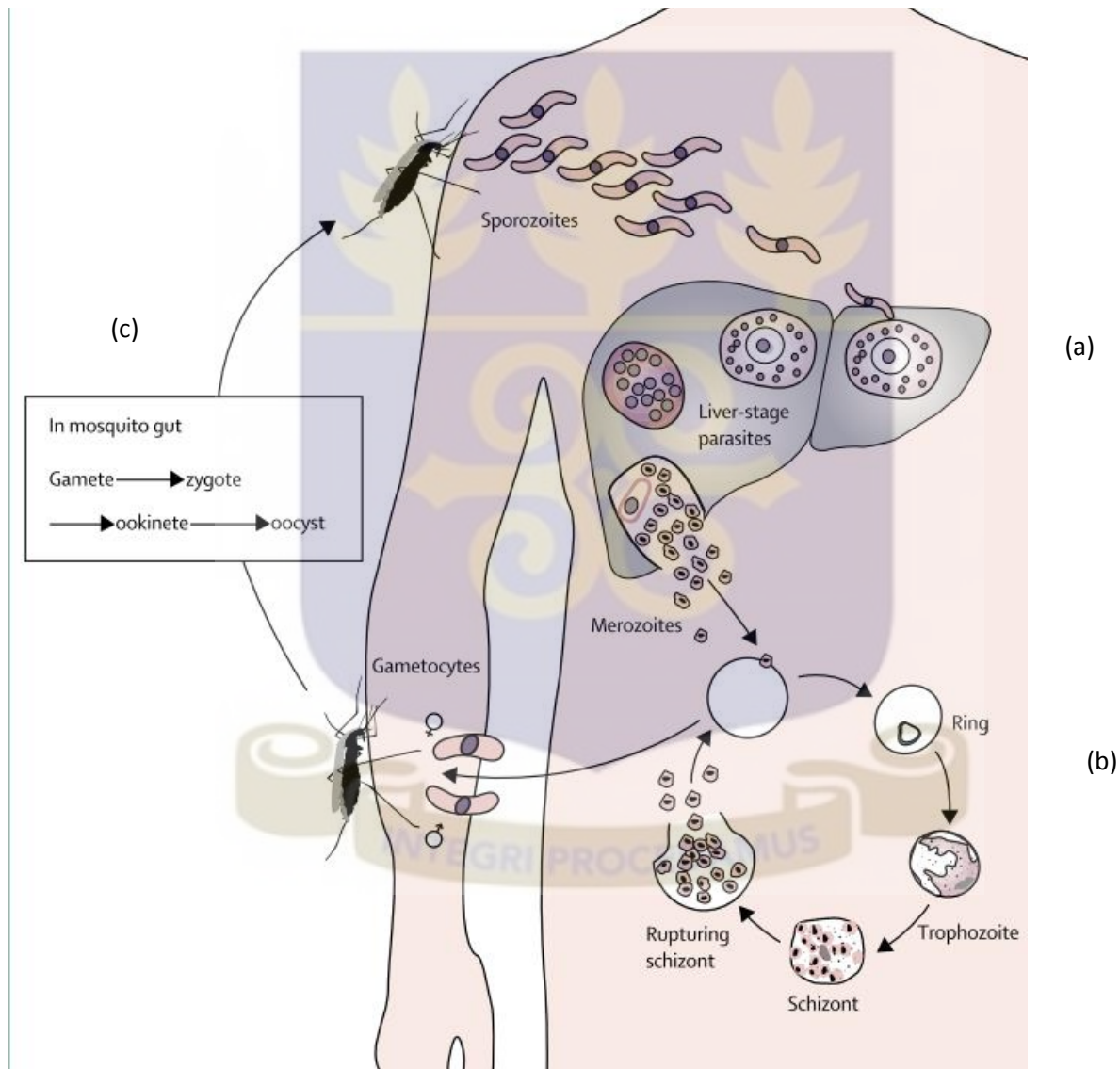
Some of the parasites differentiate into sexual stages called gametocytes in human blood, which need about ten days for maturation (Khan et al., 2005). These gametocytes are the ones with capacity of infecting biting mosquitoes that take a blood meal from infected patients.

c. Mosquito stage (sporogonic cycle)

One male (microgametocyte) and one female (macrogametocyte) are required to start the process in mosquito that will lead to further human infection. Once into the mosquito midgut,

macrogametocyte and microgametocyte produce successively, gamete, zygote, ookinete and oocyst that will differentiate into sporozoite in the salivary gland of the mosquito and will be injected into a human being during a blood meal that female *Anopheles* takes for the maturation of its egg (Greenwood et al., 2005).

Figure 2: Life cycle of the malaria parasite



(a) Human liver stage; (b) Human blood stage; (c) Mosquito stage.

Source: adapted from Greenwood et al., 2005

2.4. Management of malaria based on malaria parasite lifecycle

Management of malaria infection targets one of the phases of plasmodium lifecycle. Some preventive measures target phases that occur in mosquitoes. Indoor residual sprays of insecticide aim to kill mosquitoes, thus suppressing *Plasmodium* development in its vector. Long-Lasting Insecticidal Nets aim both to kill mosquitoes and to limit the number of human bites per night and thus sporozoite transmission to human by infected mosquitoes. Malaria vaccine RTS,S which is the most evolved candidate vaccine in clinical trials target the trophozoite injected by the mosquito by stimulating production of antibodies against the circumsporozoite protein that allow the entrance of the sporozoite into the hepatocytes for further development (Agnandji et al., 2012).

Curative methods target one part of parasite life cycle in human cells. Clinical manifestations occur after red blood cells break up that release merozoite contained in schizonts. Transmission of infection becomes possible once differentiation in gametocyte occur. This is one of the reasons why ACTs are adopted as first line for the treatment of uncomplicated malaria. The artemisinin derivatives produce rapid clearance of parasitaemia, rapid resolution of symptoms and have a gametocytocidal action. The association with another effective schizonticidal antimalarial drug slowly eliminated ensures mutual protection of the two associated drugs against resistance development (World Health Organization, 2010).

2.5. History of ivermectin

Ivermectin is a macrocyclic lactone endectocide discovered in the mid-1970s. It is a semi-synthetic derivative of avermectine B1, the fermentation products of *Streptomyces avermectinus*. It was first licensed in 1981 as a veterinary drug. By 1985, the impact of ivermectin on veterinary medicine was already apparent. It helped to prevent heartworm infections in dogs and also provided protection from infection with *Dirofilaria immitis*. Hundreds of millions of large animals including cattle, sheep, swines and horses have been treated and protected from a broad variety of insect and nematode parasites. In 1987, ivermectin was registered for human use for the control of onchocerciasis and later for lymphatic filariasis (Geary, 2005; Meredith & Dull, 1998; Sylla et al., 2010).

Global control of onchocerciasis became feasible since October 1987, when Merck & Co., Inc. announced a plan to donate its safe and effective microfilaricide Mectizan™ to treat onchocerciasis. Since then, several programmes have used Ivermectin for the control of onchocerciasis and/or lymphatic filariasis. Among them are Onchocerciasis Control Programme in West Africa (OCP), Onchocerciasis Elimination Programme in the Americas (OEPA), African Programme for Onchocerciasis Control (APOC) and Global Programme for Elimination of Lymphatic Filariasis (GPELF) [Remme, 1995].

Now in many countries, there are ivermectin distribution programmes and more than one billion treatments have been delivered over the last 25 years for controlling onchocerciasis and lymphatic filariasis (Chaccour et al., 2013). Community-directed distribution (CDT) in hyperendemic and mesoendemic areas is a strategy to reach a high coverage.

2.6. Ivermectin pharmacology

2.6.1. Pharmacokinetics

Ivermectin is generally presented as tablet of 3 mg but oral solution and capsules also exist. The average effective dosage is 150 micrograms/kg (range from 50 to 200 micrograms/kg) per dose. The frequency of administration for onchocerciasis ranges from one to three times yearly. In scabies, oral single doses of 200µg/kg may be repeated twice or three times, separated by interval of 1 or 2 weeks. After oral administration, peak plasma levels is reached at about 4 hours and should correspond to an average of 46.6 ± 21.9 ng/ml. Entero-hepatic recycling could explain the second rise in plasma levels mostly occurring between 6 and 12 hours after administration. Because of its high lipid solubility, ivermectin is widely distributed within the body; 93% are strongly bound to plasma proteins, specifically serum albumin; the volume of distribution is 3 to 3.5L/Kg but in onchocerciasis patients, it may reach 9.9 L/kg with a mean residence time of 3.7 days.

It does not cross the blood-brain barrier because of its size and its affinity with P glycoprotein, a pump that restricts the entry of many drugs and other chemicals into the central nervous system. Its metabolism is hepatic and enzymes known to be involved are Cytochrome P450 and principally CYP3A4. Its elimination half-life is around one day (mean 18 hours, ranging to 12 to 28 hours). Ivermectin and its metabolites are mainly excreted in faeces and only 1% in urine. In the milk of healthy women administered 150 µg/kg, the maximum concentration was 14.1 ng/ml reached in 6.5 hours and the average dose ingested through milk by a breast-fed child is estimated to be 2.75 µg/kg (González Canga et al., 2008).

2.6.2. Pharmacodynamics

Ivermectin principally agonizes the glutamate-gated chloride channels. Some other chloride channels may also be involved such as the γ -aminobutyric acid (GABA)-gated chloride channels. Glutamate-gated Chloride channels are found in invertebrates but not in human. GABA is known to be the primary inhibitory neuro- transmitter in the nematode somatic neuromuscular system. Humans also possess GABA-gated chloride channels located in the central nervous system but the effect of ivermectin in humans is less perceived because it has limited access to the mammalian central nervous system, probably because of its size and its affinity for P-glycoprotein. The agonism of chloride channels lead to body-wall muscle paralysis which may be associated with pharyngeal muscle paralysis. Flaccid paralysis is the main cause of organism's death (Geary, 2005).

Out of agonizing chloride channels, another action mode has been identified for ivermectin, more specifically in virus. Ivermectin has been shown to inhibit replication of HIV-1 and Dengue virus by blocking the shuttling of nuclear proteins mediated by importin α/β (Wagstaff et al., 2012).

2.7. Effect of ivermectin on anopheles

Studies on effect of ivermectin on mosquitoes were first performed in vitro and in animals. Tesh (1990) found that mosquito (*Aedes* and *Culex*) died within 48-72 hours and the lethal dose (LD50) varied from 126 to 698 ng/ml. Kobylinski et al. (2010) used in vitro blood feeds and found that, at concentrations of 26.21 and 11.73 ng/ml, there was a delay in re-feeding frequency and blood digestion in *An. gambiae* s.s. and two successive ivermectin-spiked blood meals compounded mortality effects compared to controls. Gardner et al. (1993) who used canine

blood found there was a significant increase in mortality of *An. quadrimaculatus* within 24 hours and a significant decrease in number of eggs per female and egg hatchability.

Concerning experiences in human, Chacourt et al. (2010) compared survivorship in mosquitoes feeding on 25 randomized volunteers who receive ivermectin or not and found that on day 9 after feeding, the mortality in the ivermectin group was significantly higher than in the control (96% vs 73%). No difference was found when mosquitoes fed 14 days after treatment.

In the field, Sylla et al. (2010) who collected mosquitoes from huts in 3 villages before and after ivermectin MDA and 3 control villages without ivermectin MDA, found that *An gambiae* s.s. caught 1-6 days after MDA in treated villages had significantly reduced survival compared to control (38% reduction, $P = 0.0003$), as well as those caught pre-MDA ($P < 0.0001$) and >7 days post-MDA ($P < 0.0001$). The daily probability of mosquito survival dropped $>10\%$ for the six days following MDA.

2.8. Effect of ivermectin on Plasmodium

Kobylinski et al. (2011) found that there was a 79% reduction in the mean proportion of *P. falciparum* sporozoite in *An. gambiae* s.s. which survived and were collected from 3 to 12 days following ivermectin MDA whereas there was a significant increase in the control villages at the same time. The effect of ivermectin was sustained for at least 2 weeks.

In 2012, Kobylinski et al. carried out another study with *An. gambiae* which ingested human blood infected with *P. falciparum* and containing ivermectin. It was found out that ivermectin at sub-lethal concentrations inhibits the sporogony of *P. falciparum* in *An. Gambiae*.

In 2014, Alout et al. evaluated ivermectin mass drug administration for malaria transmission control across different West African environments and found that *Anopheles gambiae*

survivorship was reduced by 33.9% for one week following MDA and Sporozoite rates were significantly reduced by more than 77.5% for 15 days following the MDAs in treatment villages during the middle of intense transmission seasons.

Panchal et al. (2014) recently studied the effect of ivermectin on *P. falciparum* *in vitro*. They found that ivermectin can inhibit the nuclear import of *P. falciparum* signal recognition particle (PfSRP) polypeptides at submicromolar concentration, thereby killing the parasites. The effect was more at 25µM concentration of ivermectin than 10µM. It was pronounced 24 hours after the treatment and was irreversible. This effect occurred even in chloroquine and mefloquine resistant *P. falciparum*. In mice infected with *P. berghei*, the administration of ivermectin alone suppressed day four parasitemias by about 40%.

2.9. Ivermectin safety profile

Ivermectin proved an excellent safety and tolerability profile over the last 25 years of its use in Africa and other continents where more than one billion treatments have been delivered in human mass drug administration campaigns for onchocerciasis and lymphatic filariasis control. Even repeated MDA or high doses of ivermectin have not shown any safety concern (Chaccour et al., 2013). The cumulative incidence of serious adverse events reported with ivermectin is 1 per 800,000 reported treatments, mostly in areas which are co-endemic for onchocerciasis and *Loa loa*, especially in Central Africa. The major problem reported to date with ivermectin is a very rare and fatal serious adverse events so-called *Loa-loa* encephalopathy. 97% of the 65 cases reported from 1981 to 2001 came from the southern part of Cameroon, where the incidence of *Loa loa* encephalopathy is 1 per 10,000 treatments administered in an onchocerciasis mass treatment program (Twum-Danso, 2003a; Twum-Danso, 2003b);. This serious adverse event is not directly attributed to ivermectin but to the effect of dying *Loa loa* microfilaria on the central

nervous system and seems to be correlated with high microfilaria load (Boussinesq et al., 2003). Ouedraogo et al. (2014) recently showed in a clinical trial that administration of one dose of ivermectin (200µg/kg) or two doses spaced 48 hours has an excellent safety profile, even when co-administered with artemether-lumefantrine.

2.10. Summary of the literature review

Based on the different articles mentioned above, ivermectin presents an excellent profile to be incorporated among the strategies for malaria elimination and eradication. However, most of the findings were based on preclinical studies to assess the action of ivermectin on mosquitoes (anopheles) or on *P. falciparum* (sporozoites). Other studies on animal model are screening for slow-release formulations that can sustain mosquito-killing levels of ivermectin for months and that may be more suitable for malaria vector control (Chaccour et al., 2015). But, there is still little evidence on the effect of ivermectin mass administration in reducing malaria prevalence based on the decrease of mosquito density and sporozoite rate. The first clinical trial in malaria-infected individuals assessed safety and some pharmacokinetic aspects in humans and efficacy on mosquito mortality and *Plasmodium* infection rates among surviving mosquitoes (Ouédraogo et al., 2014). To date, authors are designing modeling and proposing agenda for further clinical trials, which led to the establishment of an Ivermectin Research for Malaria Elimination Network (Slater et al. 2014; Chaccour et al., 2013; Chaccour et al., 2015). Existing data from malaria endemic countries where ivermectin MDA is carried out should be important for the design of accurate modeling, close to the reality on the field.

CHAPTER THREE

3.0. METHODS

3.1. Type of study

This was a retrospective study undertaken in the Navrongo War Memorial Hospital. Data on patients who visited the hospital for care over the past three years were reviewed. Date of start of ivermectin mass administration during these three year periods was used as points of reference. Data covering three months pre and post mass administration of ivermectin was collected. Assuming that mass administration of ivermectin leads to protection against malaria at the community level, data collection covered all patients regardless of whether or not they had received ivermectin. Data were extracted from both consulting room registers and admission and discharge books. Focus was placed on the medical male, female and pediatric wards. Variable of interest included date of visit, diagnoses, age, sex and area of residence. Malaria prevalence was compared three months before and after ivermectin MDA.

3.2. Study location

Kassena Nankana District (KND) is one of the eight districts of the Upper East Region located in the northern part of Ghana. It shares boundaries with Burkina Faso to the north, the Bongo and Boltagatanga districts to the east, Builsa and Sisala (upper west Region) districts to the west and Mamprusi in the northern district (northern region) to the south. KND covers an area of about 1,675 km² and its population is about 152,000 people, (Dalaba et al., 2014). It lies in the Sahelian savannah with mean daily temperature ranging from 20°C to 40°C and annual rainfall averages of 850 mm. It has two main seasons, a dry season from about October to April and the wet season from approximatively May to September. Malaria transmission is perennial with distinct seasonal patterns. The highest Entomological Inoculation Rate (EIR) is observed in the month of

September, ranging from June to November while the lowest value is observed in February or March (Kasasa et al., 2013). In 2001, an all-age point prevalence surveys undertaken in KND showed that Malaria infection prevalence was 22% in May which is the end of low malaria transmission and 61% in November which is the end of high malaria transmission, (Koram et al., 2003).

The KND has a hospital located in Navrongo that serves as a referral point, seven health centers, one private clinic, 27 Community-Based Health Planning and Services (CHPS) compounds, two community clinics jointly run by the Catholic Diocesan Development Office and the District Health Administration and a Health and Demographic Surveillance System (HDSS) run by the Navrongo Health Research Centre. Navrongo is the capital city of the District. The Navrongo War Memorial Hospital is a 140-bed district hospital collaborating with the Navrongo Health Research Centre. It is the hospital where our study was undertaken.

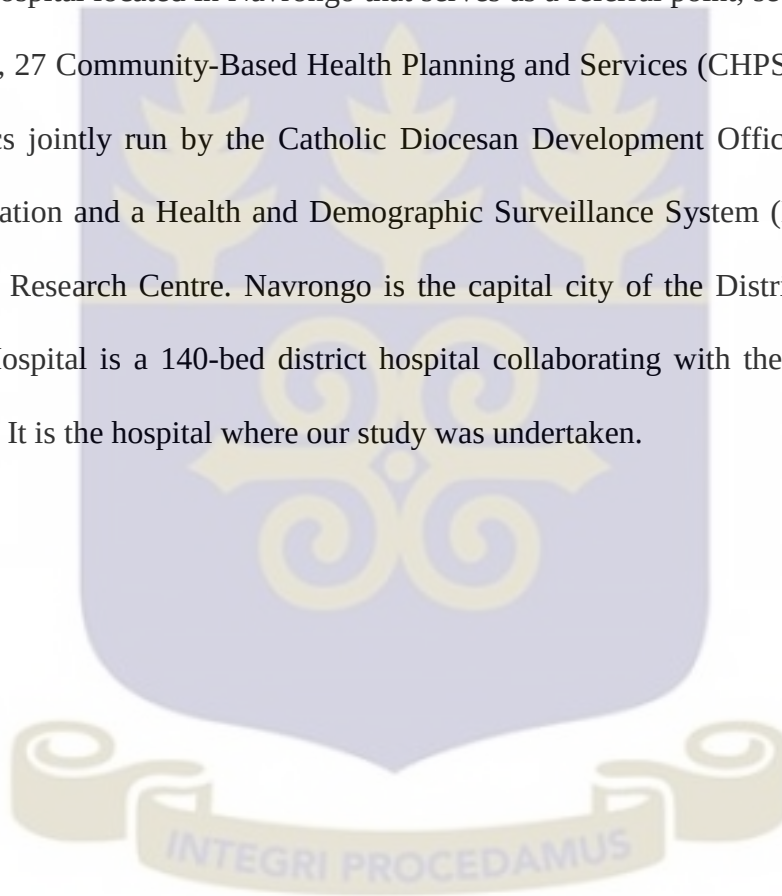
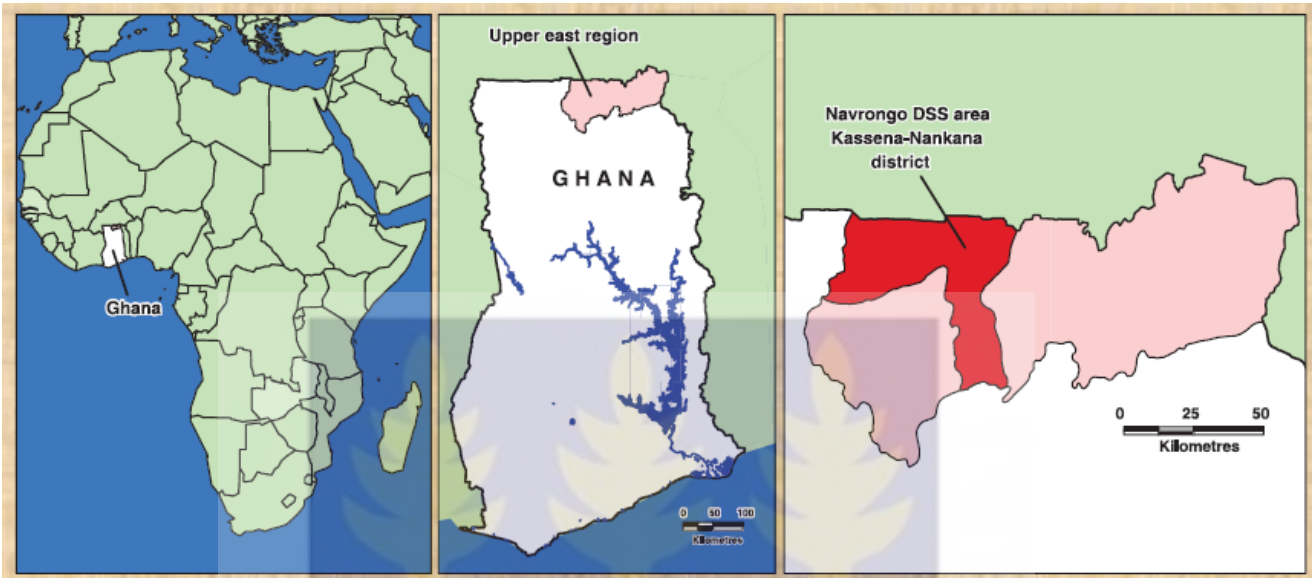
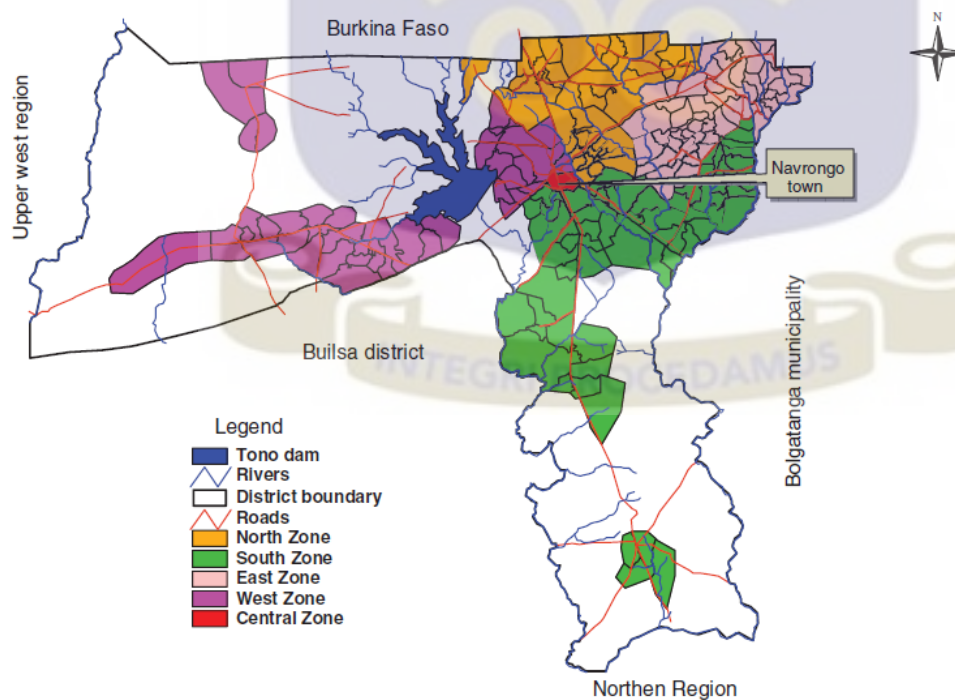


Figure 3: Location of Ghana in Africa, the Upper East Region in Ghana and the Navrongo HDSS area in the Kassena-Nankana districts of the upper east region



Source: Oduro et al., 2012.

Figure 4: A map of the Kassena-Nankana district showing the district boundaries, the five zones and other physical landmarks within the district



Source: Oduro et al., 2012.

3.3. Variables

Table 1: Description of variables

Variables	Operational definitions	Type of variable/ Possible value
Independent variables		
Date	Date of first visit for care in the hospital	
Area of residence	Refers to village of the patient. These information were coded according to the Navrongo Health and Demographic Surveillance System (NHDSS) clusters	Categorical <u>Values:</u> East, West, North, South, Central and Outside
Age	Refers to the age registered at first visit	Quantitative continuous
Sex	Sex of patient, as mentioned in the register	Categorical dichotomous <u>Values:</u> Male or Female
Dependent variables		
Diagnosis	Diagnosis written in the register in relationship with the patient consultation for the specified date	Categorical nominal <u>Value:</u> Free test
Laboratory results	Result from the laboratory (RDT or microscopy) for patients whose diagnosis is malaria	Categorical dichotomous <u>Values:</u> Positive or Negative
Outcome variables		
Reported Malaria Prevalence	Number of person with the diagnosis of malaria (confirmed or suspected) over the total of person who consulted during the corresponding 3 months period	Proportion

3.4. Study Population

The study population was made up of patients who attended the Navrongo War Memorial Hospital during the study period and whose information was available either in consulting room registers or in admission and discharge books.

3.5. Sampling

3.5.1. Sample size calculation

According to Koram et al. (2003), the lowest malaria infection prevalence is 22% and the highest is 61%. According to Slater et al. (2014), the impact on the vector population of treating 90% of the population aged ≥ 5 with 3 daily doses of ivermectin alone will result in a reduction of the infectious vector population by 68% (2/3) for approximately 60 days. Assuming that 80% MDA coverage of the population aged ≥ 5 years with one daily dose of ivermectin alone should lead at least to 1/3 reduction of clinical malaria from the baseline prevalence for approximately three months, the sample size necessary to detect 1/3 reduction on malaria prevalence using 80% power, 5% as the probability to have a type I error was calculated using the formula for determining differences in proportions for two samples $n = [z_{\alpha/2} \sqrt{2p^*q^*} + z_{\beta} \sqrt{(p_1q_1 + p_2q_2)}]^2 / \Delta^2$.

Where:

p_1 = the lowest estimated malaria prevalence = 22% = 0.22

p_2 = estimated prevalence, assuming 1/3 reduction after MDA = $p_1 \times (1 - 1/3) = 0.22 \times 2/3 = 0.147$

Δ = difference being measured = $p_1 - p_2 = 0.22 - 0.147 = 0.073$

p^* = mean estimated prevalence = $(p_1 + p_2)/2 = (0.22 + 0.147)/2 = 0.1835$

$q_1 = 1 - p_1 = 1 - 0.22 = 0.78$

$$q_2 = 1 - q_1 = 1 - 0.147 = 0.853$$

$$q^* = (q_1 + q_2)/2 = (0.78 + 0.853)/2 = 0.8165$$

α = significance level = 0.05, then $Z_{\alpha/2} = 1.96$ (z value for a two-sided test corresponding to 0.05)

Power = 80%, then $\beta = 0.20$ and $z_{\beta} = 0.84$ (z value for a one-sided test corresponding to 0.20)

Thus,

$$n = [1.96 \sqrt{(2 \times 0.1835 \times 0.8165)} + 0.84 \sqrt{(0.22 \times 0.78 + 0.147 \times 0.853)}]^2 / (0.073)^2$$

At least 441 patients three months before ivermectin mass administration and 441 patients three months after ivermectin mass administration was needed to be able to reject the null hypothesis that malaria prevalence is equal pre and post each ivermectin mass administration.

3.5.2. Sampling procedure

A total of 441 patients were randomly selected three months before and three months after each ivermectin MDA. To have an idea on monthly evolution of malaria prevalence during this period, 147 patients were selected per month. As clinical malaria includes uncomplicated and severe malaria and generally there are more cases of uncomplicated malaria than severe malaria, patients were selected in a proportion of two to one, which corresponded approximately to 100 patients from OPD and 48 admitted patients. For a given month, the total patients registered were first obtained. In OPD, the 100 patients were selected from four different consulting rooms, giving 25 patients from each consulting room. The number of patients registered during a given period of one month in a consulting room was divided by 25 to have the sampling frame and the first patient was randomly selected. The 48 admitted patients were divided into 16 from the medical pediatric ward, 16 from the medical female ward and 16 from the medical male ward

registers. Selection of the admitted patients was done as described for OPD using a calculated sampling frame and randomly selecting the first patient.

3.6. Data collection techniques and tools

At the district level, information concerning ivermectin MDA during the last three years was collected. Mass administration of ivermectin occurred from 15th to 20th March 2012, from 19th to 23rd June 2013 and from 23rd to 27th June 2014. These periods were usually followed by an additional one week for mop-up. Data was collected three months before and three months after the start of ivermectin mass administration. In 2012, data were collected from 15th December 2011 to 14th June 2012. In 2013, data were collected from 19th March to 18th September. In 2014, data were collected from 23rd March to 22nd September.

At the hospital level, data was collected from registers. Data was extracted from both consulting room registers and admission and discharge books. Data on admitted cases was collected from medical pediatric ward, female ward and male ward. Data on outpatients was collected from the four consulting rooms of the War Memorial Hospital. Data were collected according to the sampling procedure.

A Case Record Form (CRF) was designed for collection of variables of interest. It included general information, patient's information and disease information. The general information included the date of consultation and the source of information (OPD or IPD). Patient's information included ID number, area of residence, age and sex. Disease information included clinical diagnosis and laboratory results.

An electronic form was designed using Microsoft Excel. It was designed according to the CRF and contained the same variables. Data from the CRF was entered into the electronic form which was used to generate a database as an MS Excel spreadsheet for data analysis.

3.7. Quality control

Data was collected by staffs from the statistics office who were trained on the sampling procedure but not informed about interest of malaria cases to avoid any bias. Data entry was made by the principal investigator. An edit check system was included in the electronic form. As the principal investigator could not have access to the registers for confidentiality issue, data check was made by comparing all the data from the database with the corresponding CRF. The database was assessed for completeness, consistency and accuracy of information in comparison with the CRF. When needed, the source documents were requested for correction.

3.8. Data processing and analysis

Data was analyzed using STATA version 12. The main analysis was on the prevalence of malaria. Age which was the only continuous variable was grouped into 7 categories: 1 – 4 years, 5 – 9 years, 10 – 19 years, 20 – 29 years, 30 – 39 years, 40 – 49 years and ≥ 50 years.

In descriptive statistics, categorical variables were summarized as frequencies and cross tabulations were done. In analytic statistics, comparison of malaria prevalence within variables before and after ivermectin MDA was performed using two-group test of proportions. Determination of factors significantly associated with malaria prevalence was done using Pearson Chi-square test. The difference was considered statistically significant if p-value was less than 0.05. To test the strength of association of risk factors with malaria prevalence, the logistic model was used. Univariate logistic regression was used first and variables showing a p-

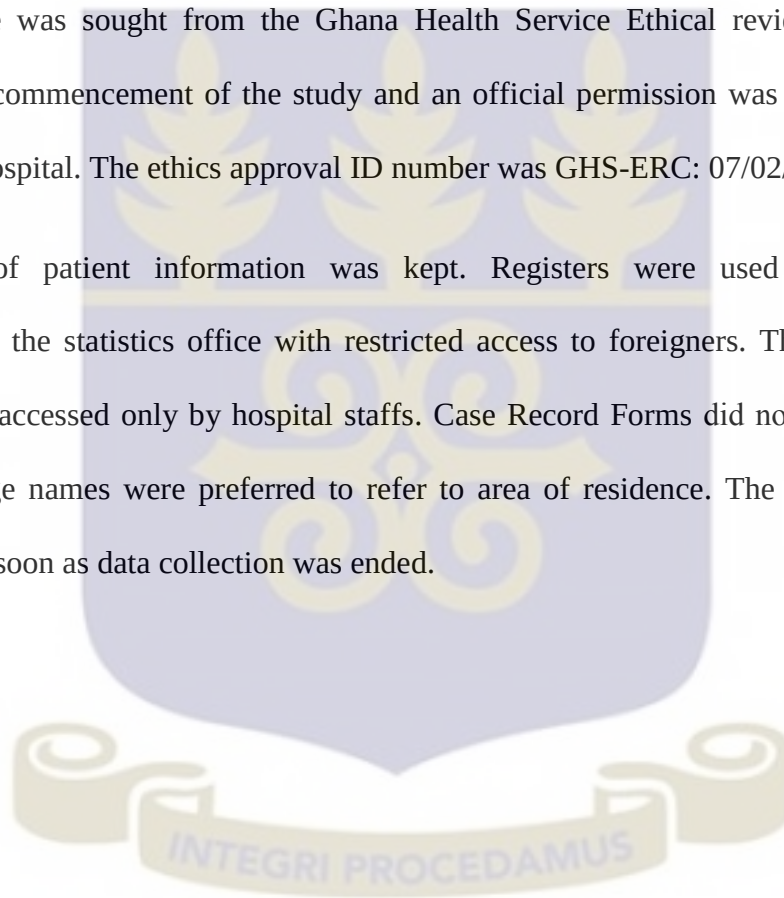
value less than 0.25 were included in multivariate logistic regression. The measure of association was the Odds Ratio with the corresponding 95% Confidence Interval.

Figures were drawn to show the trends of malaria prevalence over time from 2012 to 2014. Trends of malaria prevalence before and after ivermectin mass administration were also shown.

3.9. Ethical consideration

Ethical clearance was sought from the Ghana Health Service Ethical review committee for approval before commencement of the study and an official permission was obtained from the War Memorial hospital. The ethics approval ID number was GHS-ERC: 07/02/15.

Confidentiality of patient information was kept. Registers were used in respect with confidentiality in the statistics office with restricted access to foreigners. The whole patients' information was accessed only by hospital staffs. Case Record Forms did not include patients' names and village names were preferred to refer to area of residence. The source documents were returned as soon as data collection was ended.



CHAPTER FOUR

4.0. RESULTS

4.1. Study participants

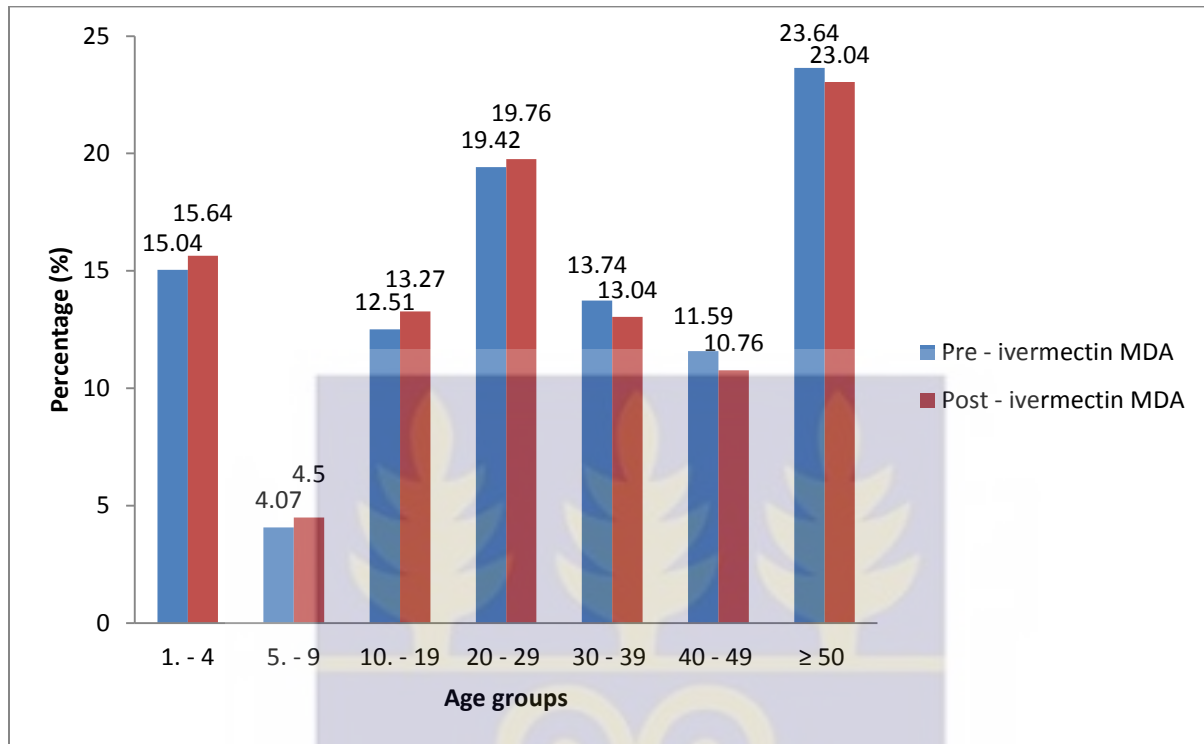
A total of 2,652 registered patients were randomly selected out of 204,989 total attendance for the period 2012 to 2014. This was made up of 1.03% (1,793/ 173,300) outpatients and 2.71% (859/ 31,689) in-patients. Among them, 1,327 were patients who sought care before the time of ivermectin mass administration and 1,325 sought care after ivermectin mass administration (table 2). The demographic characteristics including sex, age and area of residence were similar for patients before the mass administration of ivermectin and those patients after the administration of the drug. In all, there were more females than males (58.15%; 767/1,319 females versus 41.85%; 552/1,319 males before the mass administration of ivermectin and 58.60%; 770/1,314 females versus 41.40%; 544/1,314 males after the mass administration of ivermectin). Most of the study participants were aged ≥ 50 -years (23.64%; 308/1,303 pre-ivermectin and 23.04%; 302/1,314 post-ivermectin), those between 20 and 29 years formed 19.42% (253/1,303) pre-ivermectin and 19.76% (259/1,314) post-ivermectin and under-five children formed 15.04% (196/1,303) pre-ivermectin distribution and 15.64% (205/1,314) post-ivermectin distribution (table 2 and figure 5). More patients came from the central and the southern parts of the district (Central 30.48%; 363/1,191 pre-ivermectin MDA and 35.37%; 423/1,196 post-ivermectin MDA; Southern 35.43%; 422/1,191 pre-ivermectin MDA and 32.19%; 385/1,196 post-ivermectin MDA).

Table 2: Demographic characteristics of patients before and after ivermectin mass administration

Variables	Pre IVM MDA n (%)	Post IVM MDA n (%)
Year	n = 1,327	n = 1,325
2012	444 (33.46)	443 (33.43)
2013	442 (33.31)	441 (33.28)
2014	441 (33.23)	441 (33.28)
Source of data	n = 1,327	n = 1,325
OPD	897 (67.60)	896 (67.62)
IPD	430 (32.40)	429 (32.38)
Sex	n = 1,319	n = 1,314
Male	552 (41.85)	544 (41.40)
Female	767 (58.15)	770 (58.60)
Age groups (years)	n = 1,303	n = 1,311
1 - 4	196 (15.04)	205 (15.64)
5 - 9	53 (4.07)	59 (4.50)
10 - 19	163 (12.51)	174 (13.27)
20 - 29	253 (19.42)	259 (19.76)
30 - 39	179 (13.74)	171 (13.04)
40 - 49	151 (11.59)	141 (10.76)
≥ 50	308 (23.64)	302 (23.04)
Area of residence	n = 1,191	n = 1,196
Centre	363 (30.48)	423 (35.37)
East	46 (3.86)	54 (4.52)
West	124 (10.41)	131 (10.95)
North	223 (18.72)	197 (16.47)
South	422 (35.43)	385 (32.19)
Outside	13 (1.09)	6 (0.5)

Abbreviations: IVM MDA, Ivermectin Mass Drug Administration; OPD, Outpatient Department; IPD, Inpatient Department.

Figure 5: Proportion of the different age groups pre- and post-ivermectin MDA from 2012 to 2014



4.2. Reported malaria cases pre and post ivermectin mass administration

The comparison of the prevalence of reported malaria cases before and after mass administration of ivermectin revealed that on the whole, malaria was reported by 329 out of 1,327 (24.8%, 95% CI: 22.5 - 27.1) patients registered before ivermectin mass administration and by 349 out of 1,325 (26.3%, 95% CI: 24.0 - 28.8) patients registered after ivermectin mass administration. The difference in malaria prevalence within the three months before and after ivermectin mass administration was not statistically significant (-1.5%, 95% CI: -4.9 - 1.8; $p = 0.361$).

The two-group test of proportions used to compare malaria prevalence pre- and post-ivermectin MDA within variables showed that the difference in malaria prevalence before and after ivermectin administration was statistically significant only in the age group of 5 to 9-year-old, during the year 2013 and during the year 2014. In 2013, there was an increase in malaria prevalence from 26.7% (118/ 442, 95% CI: 22.6 - 30.8) pre-ivermectin distribution to 42.0% (185/441, 95% CI: 37.3 - 46.6) post-ivermectin distribution (difference: -15.3%, 95% CI: -21.4 - -9.1; $p < 0.001$). In 2014 however, there was a decrease in prevalence from 20.4% (90/441, 95% CI: 16.6 - 24.2) to 14.3% (63/441, 95% CI: 11.0 -17.6) (difference: 6.1%, 95% CI: 1.1 - 11.1; $p = 0.016$). For the other variables, the difference in malaria prevalence before and after ivermectin mass drug administration was not statistically significant (Table 3).

Table 3: Comparing prevalence of reported malaria cases pre- and post-ivermectin mass administration from 2012 to 2014

Variables	Malaria prevalence Pre IVM MDA [%] (95% CI)	Malaria prevalence Post IVM MDA [%] (95% CI)	Difference in Prevalence [%] (95% CI)	P-value
Pre-post	24.8 (22.5 - 27.1)	26.3 (24.0 - 28.8)	-1.5 (-4.9 - 1.8)	0.361
Sex				
Male	22.1 (18.6 - 25.6)	24.3 (20.7 - 27.9)	-2.2 (-7.2 - 2.8)	0.396
Female	27.0 (23.8 - 30.1)	27.8 (24.6 - 31.0)	-0.8 (-5.3 - 3.7)	0.724
Age groups (year)				
1 - 4	42.9 (35.9 - 49.8)	44.4 (37.6 - 51.2)	-1.5 (-11.2 - 8.2)	0.757
5 - 9 *	50.9 (37.5 - 64.4)	30.5 (18.8 - 42.3)	20.4 (2.6 - 38.3)	0.028
10 - 19	25.8 (19.1 - 32.5)	32.2 (25.2 - 39.1)	-6.4 (-16.1 - 3.2)	0.195
20 - 29	20.6 (15.6 - 25.5)	22.4 (17.3 - 27.5)	-1.8 (-9.0 - 5.2)	0.612
30 - 39	20.7 (14.7 - 26.6)	24.6 (18.1 - 31.0)	-3.9 (-12.7 - 4.9)	0.384
40 - 49	13.9 (8.4 - 19.4)	15.6 (9.6 - 21.6)	-1.7 (-9.8 - 6.4)	0.683
≥ 50 years	19.8 (15.4 - 24.3)	19.5 (15.1 - 24.0)	0.3 (-6.0 - 6.6)	0.934
Year				
2012	27.3 (23.1 - 31.4)	22.8 (18.9 - 26.7)	4.5 (-1.2 - 10.1)	0.126
2013*	26.7 (22.6 - 30.8)	42.0 (37.3 - 46.6)	-15.3 (-21.4 - -9.1)	0.000
2014*	20.4 (16.6 - 24.2)	14.3 (11.0 - 17.6)	6.1 (1.1 - 11.1)	0.016
Source of data				
OPD	22.0 (19.3 - 24.7)	24.3 (21.5 - 27.1)	-2.4 (-6.3 - 1.5)	0.235
IPD	30.7 (26.3 - 35.1)	30.5 (26.2 - 34.9)	0.2 (-06.0 - 6.3)	0.959
Area of residence				
Centre	28.1 (23.5 - 32.7)	26.7 (22.5 - 30.9)	1.4 (-4.9 - 7.6)	0.664
East	21.7 (9.8 - 33.7)	24.1 (12.7 - 35.5)	-2.3 (-18.8 - 14.2)	0.782
West	21.0 (13.8 - 28.1)	29.0 (21.2 - 36.8)	-8.0 (-18.6 - 2.5)	0.139
North	20.2 (14.9 - 25.4)	25.4 (19.3 - 31.5)	-5.2 (-13.2 - 2.8)	0.204
South	27.3 (23.0 - 31.5)	24.7 (20.4 - 29.0)	2.6 (-3.5 - 8.6)	0.405
Outside	23.1 (0.2 - 46.0)	16.7 (-13.2 - 46.5)	6.4 (-31.2 - 44.0)	0.750

*Statistically significant difference between prevalence pre- and post-ivermectin mass distribution;
Abbreviations: IVM MDA, Ivermectin Mass Drug Administration; OPD, Outpatient Department; IPD, Inpatient Department.

4.3. Factors associated with prevalence of reported malaria

Table 4 shows the overall prevalence of reported malaria irrespective of time of ivermectin administration. Malaria prevalence was 23.18% (254/1,096) in males and 27.39% (421/1,537) in females. Among the age groups, malaria was reported most in children under five years (43.64%, 175/401) with a gradual decrease to 14.73% (43/292) in the age group 40 – 49 years. Malaria prevalence was 25.03% (222/887) in 2012, 34.31% (303/883) in 2013 and 17.35% (153/882) in 2014. A higher proportion of admissions was due to malaria (30.62, 263/859) compared to the proportion of OPD cases (23.15, 415/1,793). Concerning area of residence, there were 27.35% (215/786) of malaria cases in the central, 26.02% (10/807) in the southern and 25.10% (64/255) in the western parts of the districts.

Sex, age groups, year of ivermectin mass administration, source of data were found to be significantly associated with a Pearson P-value <0.01 but not area of residence ($p = 0.564$). Based on this analysis, sex, age groups, year and source of data were considered as potential confounding factors associated with reported malaria prevalence. Area of residence was then excluded from the logistic model.

A test of the strength of the association of risk factors to the prevalence of malaria was performed using logistic model.

Table 4: Prevalence of reported malaria from 2012 to 2014 and association with sex, age groups, year, source of data and area of residence.

Variables	N	Malaria (%)	No Malaria (%)	Pearson Chi ²	P – value
Sex					
Male	1,096	254 (23.18)	842 (76.82)	5.9647	0.015
Female	1,537	421 (27.39)	1,116 (72.61)		
Age groups (year)					
1 - 4	401	175 (43.64)	226 (56.36)	118.6902	0.000
5 - 9	112	45 (40.18)	67 (59.82)		
10 - 19	337	98 (29.08)	239 (70.92)		
20 - 29	512	110 (21.48)	402 (78.52)		
30 - 39	350	79 (22.57)	271 (77.43)		
40 - 49	292	43 (14.73)	249 (85.27)		
≥ 50 years	610	120 (19.67)	490 (80.33)		
Year					
2012	887	222 (25.03)	665 (74.97)	66.9614	0.000
2013	883	303 (34.31)	580 (65.69)		
2014	882	153 (17.35)	729 (82.65)		
Source of data					
OPD	1,793	415 (23.15)	1,378 (76.85)	17.0364	0.000
IPD	859	263 (30.62)	596 (69.38)		
Area of residence					
Centre	786	215 (27.35)	571 (72.65)	3.8995	0.564
East	100	23 (23.00)	77 (77.00)		
West	255	64 (25.10)	191 (74.90)		
North	420	95 (22.62)	325 (77.38)		
South	807	210 (26.02)	597 (73.98)		
Outside	19	4 (21.05)	15 (78.95)		

Abbreviations: IVM MDA, Ivermectin Mass Drug Administration; OPD, Outpatient Department; IPD, Inpatient Department.

A univariate logistic model showed that there were strong evidence of association between the sex, age groups, year, source of data and the prevalence of malaria ($p < 0.001$) [see table 5].

In univariate analysis, the odds of having malaria was 25% higher in females compared with males (OR: 1.25, 95% CI: 1.04 - 1.50; $p = 0.015$), lower in all age groups compared with 1- 4-year-old. The prevalence of the disease was 56% higher in 2013 (OR: 1.56, 95% CI: 1.27 - 1.92; $p < 0.001$) and 37% lower in 2014 (OR: 0.63, 95% CI: 0.50 - 0.79; $p < 0.001$) compared to 2012. The prevalence was also 47% higher among the admitted cases compared with the OPD (OR: 1.47, 95% CI: 1.22 - 1.76; $p < 0.001$).

Multivariate logistic regression analysis which adjusted for the effects of all the possible factors found to be significantly associated with malaria prevalence showed that sex, age groups, year and source of data were independently associated with malaria prevalence (Table 5).

When adjusted for all possible risk factors, the odds of having malaria was 53% higher in females compared with males (OR: 1.53, 95% CI: 1.27 - 1.86; $p < 0.001$), lower in all age groups compared with those 1 to 4-year-old. The prevalence of the disease was 50% higher in 2013 (OR: 1.50, 95% CI: 1.21 - 1.86; $p < 0.001$) and 42% lower in 2014 (OR: 0.58, 95% CI: 0.46 - 0.74; $P < 0.001$) compared to 2012. The prevalence was also 61% higher among the admitted cases compared with the OPD (OR: 1.61, 95% CI: 1.33- 1.95; $p < 0.001$).

In univariate and in multivariate logistic models, the odds of reported malaria three months after ivermectin mass administration compared with three months before was almost similar and not statistically significant. It was 8% (Crude OR: 1.08, 95% CI: 0.91 - 1.29; $p = 0.361$) and 7% (Adjusted OR: 1.07, 95% CI: 0.89 - 1.28; $p = 0.498$) higher in univariate and multivariate analysis respectively after the mass administration of ivermectin.

Table 5: Logistic regression of perceived factors influencing prevalence of reported malaria

Variables	Malaria/ No malaria	Crude OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value
Pre-IVM MDA	329/998	1.00		1.00	
Post-IVM MDA	349/976	1.08 (0.91 - 1.29)	0.361	1.07 (0.89 - 1.28)	0.498
Sex					
Male	421/1,116			1.00	
Female	254/842	1.25 (1.04 - 1.50)	0.015	1.53 (1.27 - 1.86)	0.000
Age groups (year)					
1 - 4	175/226	1.00	-	1.00	
5 - 9	45/67	0.87 (0.57 - 1.33)	0.513	0.92 (0.59 - 1.42)	0.705
10 - 19	98/239	0.53 (0.39 - 0.72)	0.000	0.48 (0.35 - 0.67)	0.000
20 - 29	110/402	0.35 (0.26 - 0.47)	0.000	0.33 (0.24 - 0.44)	0.000
30 - 39	79/271	0.38 (0.27 - 0.52)	0.000	0.34 (0.25 - 0.48)	0.000
40 - 49	43/249	0.22 (0.15 - 0.33)	0.000	0.20 (0.13 - 0.29)	0.000
≥ 50	120/490	0.32 (0.24 - 0.42)	0.000	0.29 (0.22 - 0.39)	0.000
Year					
2012	222/665	1.00	-	1.00	-
2013	303/580	1.56 (1.27 - 1.92)	0.000	1.50 (1.21 - 1.86)	0.000
2014	153/729	0.63 (0.50 - 0.79)	0.000	0.58 (0.46 - 0.74)	0.000
Source of data					
OPD	415/1,378	1.00	-	1.00	-
IPD	263/596	1.47 (1.22 - 1.76)	0.000	1.61 (1.33- 1.95)	0.000

Abbreviations: IVM MDA, Ivermectin Mass Drug Administration; OPD, Outpatient Department; IPD, Inpatient Department.

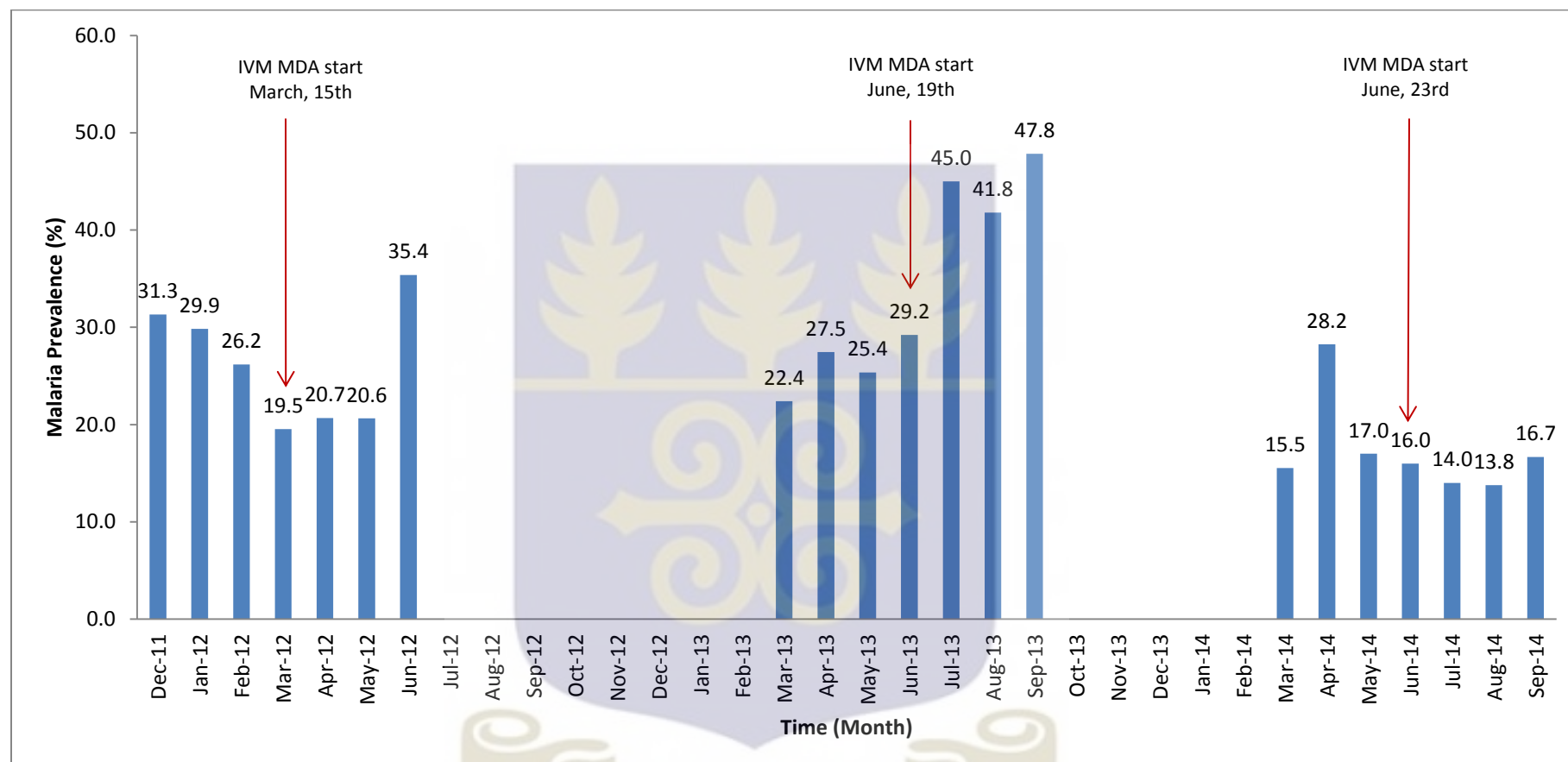
4.4. Trends of malaria prevalence from December 2011 to September 2014

Figure 6 shows trends in malaria prevalence in a monthly basis from 2012 to 2014 as captured in our sample and specify for each year the day and the month when ivermectin distribution started. During the period corresponding to 2012, reported malaria prevalence decreased from December

2011 (31.3%; 26/83) to March 2012 (19.5%; 25/128), remained stable in April and May around 21% before rising to 35.4 (23/65) in June. In 2013, reported malaria cases increased from March (22.4%; 15/67) to June (29.2%; 45/154) and further increased in July, August and September, to a peak of 47.8% (44/92) in September. In 2014, a peak of 28.2% (37/131) was observed in April. In June the prevalence decreased to 16.0% (23/144), was stable around 14% in July and August before rising in September (16.7%; 18/108). Ivermectin mass administration started on 15th March 2012, 19th July 2013 and 23rd June 2014.

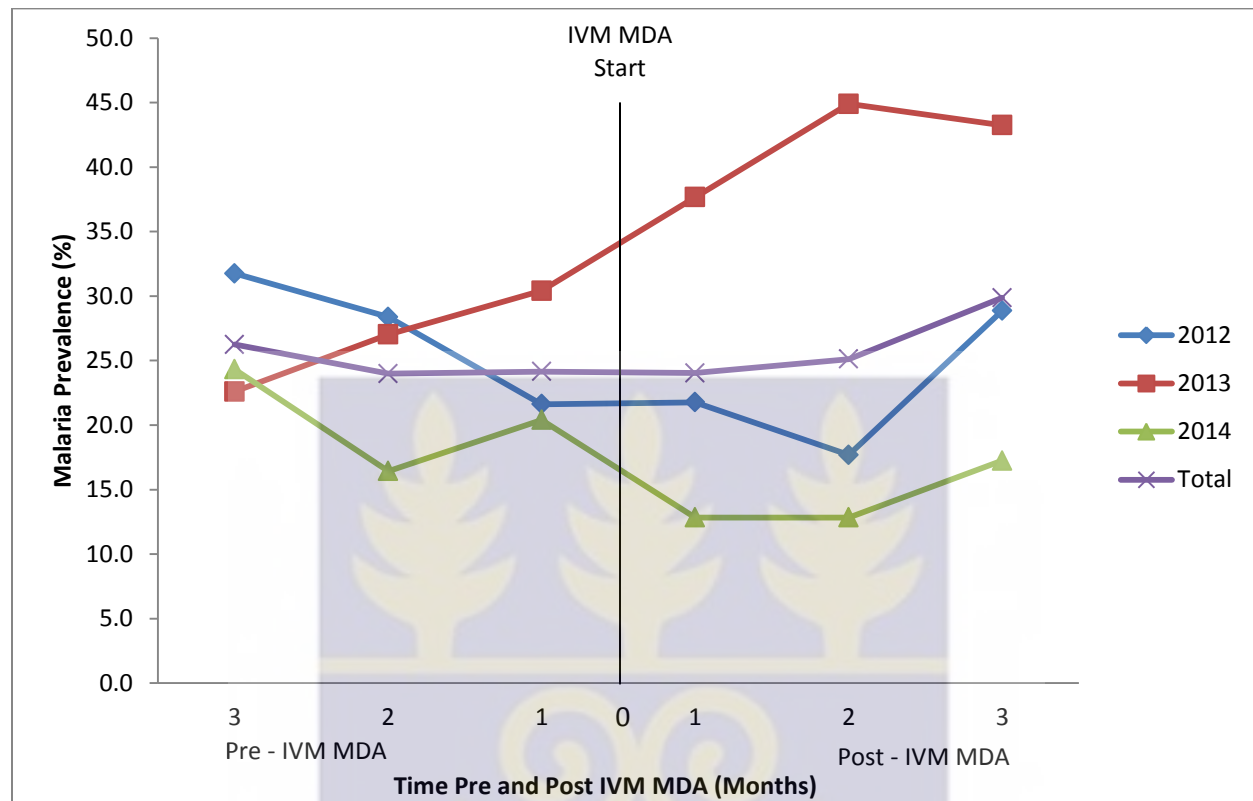
In figure 7, the days when ivermectin mass distribution started during the three study periods were all considered as time zero, one month was considered as approximately 30 days from time zero and trends of malaria prevalence was shown during the three months pre- and post-ivermectin. In 2012, malaria prevalence was decreasing during the three months preceding the start from 31.8% (47/148) to 21.6% (32/148). After the ivermectin mass administration, the prevalence remained low (21.8%, 32/147 and 17.7%, 26/147) during the two months succeeding the drug administration before rising during the third month (28.9%; 43/149). In 2013, malaria prevalence was increasing during the three months before the MDA from 22.6% (33/146) to 30.4% (45/148) and still increased (37.7%, 55/146 to 44.9%, 66/147) during the three months post-ivermectin. In 2014, malaria prevalence varied during the three months pre-ivermectin mass administration and was 20.4% (30/147) within the month (31 days) preceding the start of MDA. It decreased to 12.8% (19/148) within the two months (61 days) succeeding the period of MDA before rising to 17.2% (25/145) in the third month. Cumulatively, malaria prevalence appear to remain stable two months after ivermectin mas administration (24.0%, 106/441 and 25.1%, 111/442) before starting to rise (29.9%, 132/442) in the third month.

Figure 6: Monthly malaria prevalence during the study period from December 2011 to September 2014



Abbreviations: IVM MDA, Ivermectin Mass Drug Administration.

Figure 7: Trends of malaria prevalence pre- and post-ivermectin mass administration



Abbreviations: IVM MDA, Ivermectin Mass Drug Administration.

4.5. Impact of ivermectin mass administration on malaria prevalence

Analysis of figure 6 showed that the effect of ivermectin MDA seemed to depend on malaria prevalence during the month preceding the distribution and to last two months. So, in table 6, malaria prevalence within 29 to 31 days (1 month) before the start of ivermectin mass distribution was considered as baseline prevalence and the prevalence within the first two months, before the rise, was reported. When baseline prevalence was 30.41% (45/148) as in 2013, ivermectin mass administration was followed by an increase of 26.37% of the baseline prevalence. When the baseline prevalence was 24.15% (107/443) as seen in the cumulative data, the increase was 1.72%. When the baseline prevalence was 21.62% (32/148) as in 2012, there

was a decrease of 8.76%. With a baseline prevalence of 20.41 (30/147) as in 2014, a decrease of 37.09% was observed.

Table 6: Proportional variation of reported malaria cases within the 2 months post ivermectin MDA, based on baseline prevalence within the month before ivermectin MDA

Year	Baseline prevalence within 1 month Pre- ivermectin MDA	Prevalence within 2 months Post- ivermectin MDA	Proportional variation (%)	Observation
2013	30.41 (45/148)	41.30 (121/293)	26.37	Increase
Total	24.15 (107/443)	25.58 (217/883)	1.72	Increase
2012	21.62 (32/148)	19.73 (58/294)	8.76	Decrease
2014	20.41 (30/147)	12.84 (38/296)	37.09	Decrease



CHAPTER FIVE

5.0. DISCUSSION

5.1. Main findings

A retrospective study was undertaken in the Navrongo War Memorial Hospital between May and June 2015. Data from 2,652 randomly selected patients were extracted from consulting room registers and admission and discharge books for the past three years. Variables were compared three months before and three months after ivermectin mass drug administration.

On the whole the difference in malaria prevalence within the three months pre- and post-ivermectin mass administration was not statistically significant. In 2013 there was a significant increase and in 2014 there was a significant decrease in malaria prevalence after ivermectin mass administration. The decrease observed in 2012 was not statistically significant. Concerning the years when some level of decrease was observed, it occurred during the two months following ivermectin administration, followed with an increase during the third month. The impact of ivermectin mass administration seemed to be related to the baseline prevalence, the lower the baseline prevalence, the higher the proportional reduction observed.

5.2. Prevalence of reported malaria pre and post ivermectin mass administration

When adjusted for sex, age groups, year and source of data, the odds of reported malaria increased slightly three months after ivermectin mass administration compared to the preceding three months. According to different authors, the dry season in the Kassena Nankana District (KND) starts towards the ends of October and ends in March or April and the wet season may start in May or June (Kasasa et al., 2013; Oduro et al., 2012; Oduro et al., 2007). In 2012, the pre-ivermectin period was from December 2011 to March 2012 and the post-ivermectin was

from March to June whilst in 2013 and 2014, the pre-ivermectin period was from March to June and the post-ivermectin was from June to September. So generally, the pre-ivermectin period was mostly during the dry season and the post-ivermectin period was mostly during the rainy season. According to Kasasa et al. (2013), *An. gambiae* and *An. funestus* mean biting rates per month varied with seasonal changes in KND with most bites observed from July to November and almost no infective bites in the dry season, especially in February or March. Other studies identified that in KND the heaviest transmission occurred from June to October (Appawu et al., 2004). The non-significant increase observed in this study is not in conformity with the seasonal pattern of malaria transmission reported. We should expect a more important and significant increase of the odds when comparing these two periods pre- and post-ivermectin mass administration which coincide with the dry and the wet season. The mass administration of ivermectin can be a possible explanation of the not significant increase of malaria observed.

5.3. Trends in malaria prevalence before and after ivermectin mass administration

Data from the years 2012 and 2014 as well as aggregated data from all the three years showed that after ivermectin mass administration, prevalence of reported malaria was either stable or reduced for two months before an increase is observed during the third month. As mentioned by the authors cited above (Kasasa et al., 2013; Appawu et al., 2004), the number of mosquito bites and infective bites starts increasing with the onset of rains in May to reach the maximum in September or October when the wet season ends and infective bites rise from the lowest in February or March to the maximum in September. The year 2013 shows a classic seasonal evolution of malaria prevalence, gradually increasing from March and April to reach the peak around August and September towards the end of the rainy season. In 2012, the three months post-ivermectin administration were April, May and June. Classically an increase was expected

at least from the second month post ivermectin distribution. The absence of an increase during the first month post-ivermectin administration, the decrease during the second month and the increase during the third month may be due to the action of the drug during the first two months and also by a seasonal variation in malaria transmission. The year 2014 should have evolved as 2013 because ivermectin mass administration occurred during the same period. Having the trends of malaria prevalence similar to 2012 should be unusual. The lowest malaria prevalence observed in 2014 could have been explained by indoor residual spray (IRS) which was carried out during that year. The rational explanation would be that IRS decreased malaria transmission and ivermectin was administered during a period of low transmission, which led to a further decrease in malaria prevalence regardless of the rainfall, temperature and humidity that were favorable to malaria transmission during the wet season. In 2014, even though malaria prevalence was increasing first during the two months pre-ivermectin distribution, it decreased from 20 to 13% after ivermectin mass administration. This suggests that there should be a defined limit or baseline prevalence which allows for ivermectin to show its efficacy in preventing malaria transmission and IRS helped to reach this limit. This combined action of both IRS and ivermectin MDA has been predicted by Steketee and Kuile (2015) who said that the addition of ivermectin as population-wide treatment in conjunction with LLIN and IRS campaigns may produce dramatic transmission reduction, as each of the three interventions addresses a different component of the vector feeding and resting biology.

5.4. Impact of ivermectin mass administration on malaria prevalence

When comparing the baseline prevalence one month (29 -31 days) before the start of ivermectin MDA and the two months after the start (suggested to be the duration of the effect), it appeared that the lower the baseline prevalence, the higher the impact. With a baseline prevalence of 20%,

a decrease of 37% was observed. The proportional reduction seems to be in conformity with Slater et al. (2014) who predicted that when using ivermectin alone the total vector population should be reduced by a maximum of 35% from its precontrol level and the infectious vector population should be reduced by 68%. Ouédraogo et al. (2014) observed that a single dose of ivermectin administered alongside with artemether-lumefantrine resulted in 27% reduction in estimated malaria transmission potential.

Slater et al. (2014) also showed that the impact of ivermectin mass administration alongside with artemether lumefantrine depended on the baseline prevalence. The reduction of the prevalence and the duration of this reduction should be more important with a baseline prevalence of 5% compared with 30%. Their prediction is similar to these results concerning the principle of reduction based on baseline prevalence but not the duration. The difference in duration could be explained by the operational definition of malaria. In their prediction, malaria diagnosis was based on RDT or PCR whilst this work focused on reported malaria, mostly based on suspicion. This underlines the necessity for further study to confirm the baseline prevalence needed to allow ivermectin mass administration to be more effective and to determine the duration of this effect.

5.5. Limitation of the study

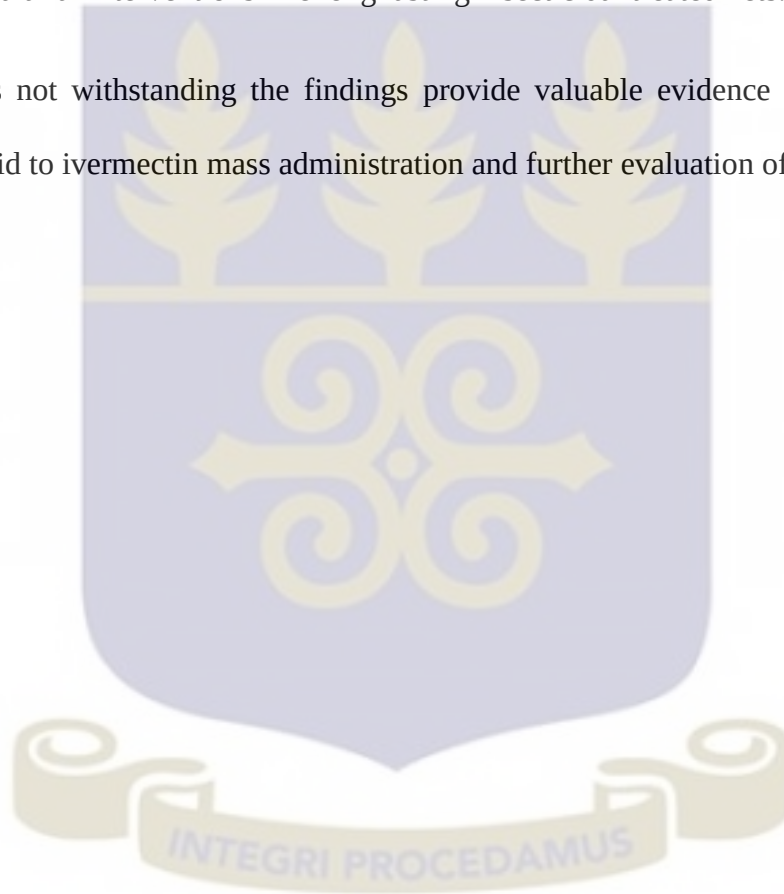
Consulting room registers and admission and discharge books offer a limited amount of variables like age, sex, address, diagnosis and condition on discharge. The study was limited only to these few variables available from the registers. Other social, demographic, economic and cultural variables were not available in the registers.

According to the operational definition, malaria cases included patients with a diagnosis of malaria, suspected or confirmed with laboratory results. But for most of the patients the

laboratory results were not available, this would have contributed to information bias by misclassification of malaria cases because it was possible to have suspected cases who truly did not have malaria infection.

Other factors that may influence malaria prevalence was not available at the hospital level. Among them are meteorological data like trends of rainfall, temperature and humidity and data about other antimalarial interventions like long lasting insecticidal treated nets.

These limitations notwithstanding the findings provide valuable evidence required for more attention to be paid to ivermectin mass administration and further evaluation of its impact.



CHAPTER SIX

6.0. CONCLUSIONS AND RECOMMENDATIONS

6.1. Conclusions

This study was undertaken to determine whether the mass distribution of ivermectin in the control of lymphatic filariasis in the Kassena-Nankana districts was associated with change in the prevalence of malaria. Malaria prevalence was compared before and after ivermectin mass administration. Trends in malaria prevalence were also assessed during the study period.

The study found that on the whole there were no difference in malaria prevalence malaria before ivermectin MDA, which corresponded to the dry season, and after ivermectin MDA, which corresponded to the rainy season. A stabilization or decrease was observed when malaria baseline prevalence during the month preceding ivermectin mass administration was low (as in 2014) and lasted for about two months.

We hypothesize that ivermectin administered in MDA can be used as a tool to reduce malaria prevalence. But its effectiveness depends on the baseline prevalence before ivermectin distribution. Other antimalarial interventions that can reduce malaria transmission and baseline prevalence to the lowest level may be important to increase this effectiveness. The duration of the action of Ivermectin mass administration on malaria prevalence would be about two months. In the context where there are almost no studies available on the effect of ivermectin on malaria prevalence, the results obtained from this work may be used to generate hypotheses for the design of further studies.

6.2. Recommendations

Based on these results, the best moment to perform ivermectin mass administration that target both control of lymphatic filariasis and prevention of malaria transmission should be at the end of the dry season (as the plan of the control programme is) when malaria transmission and prevalence is at the lowest level.

Association of ivermectin mass drug administration with other antimalarial interventions is necessary to enhance the effect of ivermectin in reducing malaria transmission and prevalence.

Further studies should be carried out to explore the effectiveness of ivermectin in the reduction of malaria prevalence after MDA in order to help generate sufficient elements for the design of future clinical trials. Based on these results, different kinds of studies that may be suggested in countries endemic for malaria where ivermectin is given in MDA for the control of lymphatic filariasis include:

- 1) Repeating the same retrospective study but increasing the power with a greater sample size pre and post ivermectin MDA; increasing the period of observation to at least the five past years with the aim of confirming these findings and addressing the main limitations.
- 2) A retrospective cohort of two or more communities with the same profile of malaria transmission and the same baseline prevalence but differing by implementation of ivermectin MDA with the aim of determining if there was a difference in malaria prevalence after ivermectin mass administration
- 3) A prospective cohort of different communities in terms of implementation of ivermectin MDA with the objective of determining malaria incidence after ivermectin mass

administration and to determine the trends of malaria infection and the duration of community protection

- 4) A prospective cohort following communities with the same profile of malaria transmission and the same baseline prevalence who have implemented ivermectin MDA one or two times per year to assess the effect of repeated doses of ivermectin on malaria incidence.



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APPENDICES**QUESTIONNAIRE**

Form Serial Number:

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	Questions	Codes							
1	Source of Information: 1. OPD 2. Ward	source							
2	Date of Consultation/ Admission: <table border="1" style="display: inline-table; vertical-align: middle;"><tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table>								datecons
3	Patient ID/NHIS/IP No:	hospid							
4	Age (in year): <table border="1" style="display: inline-table; vertical-align: middle;"><tr><td></td><td></td></tr></table>			age					
5	Sex: 1. Male 2. Female	gender							
6	Address:	adress							
7	Final/Principal Diagnosis:	diagn1							
8	Additional diagnosis:	diagn2							
9	COD (Condition on Discharge): 1. Alive 2. Died	cod							
10	If the patient had malaria, was the lab test available? 1. No 2. Yes 3. Not applicable	labav							
	If yes, please provide the result of RDT or microscopy								
11	Result RDT: 1. Negative 2. Positive	labrdt							
12	Result Microscopy: 1. Negative 2. Positive	labmic							

ETHICS APPROVAL

