ANTIMALARIAL USAGE IN PREGNANCY:
A CROSS-SECTIONAL STUDY IN SELECTED HEALTH FACILITIES IN THE BRONG AHAFO REGION OF GHANA

By

Francis Fordjour, B. Pharm (Hons.)

A Thesis submitted to the Department of Clinical and Social Pharmacy, Kwame Nkrumah University of Science and Technology Kumasi, in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE IN CLINICAL PHARMACY

Faculty of Pharmacy and Pharmaceutical Sciences,

College of Health Sciences.

March 2015

Declaration

I declare that the work described in the thesis is my own work. To the best of my knowledge, it contains no material previously published by another person nor a material that has been accepted for the award of a degree in any other University, except where due acknowledgement has been made in the text.

Francis Fordjour	……	…….
(Student ID: 20251926)	Signature	Date

Certified by:

Dr. Kwame Ohene Buabeng	…..……	……
Supervisor and Head of Department	Signature	Date

Dedication

I dedicate this piece of work to my two kids: Dave and Jessie

Acknowledgements

To God be the glory and honour for the knowledge and strength I had to cross this hurdle successfully. I am grateful to my family especially my wife and my children Dave and Jessie for the patience they had with me for the several times I absented myself from the house when I needed a quiet place to study or do assignments in the course of the programme.

I am also grateful to all Lecturers at the Department of Clinical and Social Pharmacy from 2011 to 2014, for the time they made out of their tight schedules to take us through the programme. To Dr. Kwame Ohene Buabeng; my supervisor, I express my heartfelt gratitude to you for your patience, assistance, guidance and making yourself available anytime I needed your input.

To my course mates, I thank you all for sharing your knowledge with me, especially Daniel Appiah of KATH, Cecilia Tabiri of North Suntreso Gov. Hospital and Benjamin Amoasi Rockson of WA Regional Hospital.

Abstract

Back ground: Malaria in pregnancy could be life threatening and has serious health implication for both the mother and the foetus if not managed well. In search of effective therapeutic regimen for malaria in pregnancy, the medicines used should be able to treat the disease without inducing any harm on the mother or developing foetus. Ghana has gone through policy changes regarding malaria treatment in pregnancy with a shift from chloroquine to quinine since 2004. The current policy recommendation faces an implementation challenge, because some prescribers are sceptical and thus reluctant to use quinine during pregnancy because of the reported risk of bleeding and abortions associated with its use. This study was aimed at assessing prescribers' awareness of the national policy for malaria in pregnancy, the depth of knowledge of the prescribers on the policy and the pattern of use of antimalarials in pregnancy.

Material and methods: This was a cross-sectional study involving three selected health facilities in the Brong Ahafo region of Ghana that were purposively selected. These include: the Regional hospital in Sunyani, the Holy Family hospital in Techiman and the Nkoranza Health Centre. Sixty prescribers from these facilities were systematically sampled to complete a structured questionnaire designed for data. The prescribers answered questions related to their knowledge on the national policy for malaria treatment in pregnancy and their experience with the use of quinine and the Artemisinin Combined Therapies (ACTs) in pregnancy. In addition, 310 prescriptions issued to pregnant women at the study sites with malaria were also reviewed and documented. The data obtained was coded, stored and analysed using SPSS version 16.

Results: Eighty-five percent of prescribers (n=51) knew that quinine was a policy recommended medicine for malaria in the 1st trimester of pregnancy. Only 5% (n=3)

identified both oral quinine with clindamycin as an alternative. Forty-three percent (n=26) knew that both oral quinine and the ACTs are recommended for malaria in the 2nd trimester of pregnancy. Thirty-seven percent (n=22) also knew that oral quinine and the ACTs are recommended medicines for malaria in the 3rd trimester of pregnancy. Fifty-one percent (n=31) had observed bleeding in early pregnancy and associated it with the use of quinine. Fifty-three percent (n=31) refused to prescribe quinine for malaria in pregnancy. Fifty-six percent (n=34) indicated that artemether-lumefantrine is tolerable and safer than quinine for uncomplicated malaria in pregnancy. Seventy-six percent of 1st trimester pregnant women with malaria (n=62) were prescribed artemether-lumefantrine. Ten percent in their 1st trimester (n=8) were prescribed quinine. 86.4% of pregnant women with malaria (n=197) in their 2nd and 3rd trimesters were prescribed artemether-lumefantrine. 3% (n=7) in their 2rd and 3rd trimesters were also prescribed quinine.

Conclusion: Prescribers were aware of the national policy for malaria therapy in pregnancy but few knew that oral quinine plus clindamycin is also endorsed for malaria in early pregnancy. Reports of quinine induced bleeding in early pregnancy was confirmed by most of the prescribers interviewed. More than half of the prescribers refused to give quinine for malaria in pregnancy due to the risk of quinine induced bleeding or abortion (p=0.003). There was widespread use of parenteral artemisinins and artemether-lumefantrine in early pregnancy for uncomplicated malaria. To reduce non-adherence to quinine treatment regimen in pregnancy, prescribers should be educated and encouraged to use the 3-days treatment of quinine-clindamycin combination for uncomplicated malaria in pregnancy.

TABLE OF CONTENTS **PAGE**

List of Tables **Page**

List of Figures **Page**

Abbreviations and Definitions

ACTs - Artemisinin Based Combination Therapies

ANC - Antenatal Clinic

CI - Confidence Interval

FDA - Food and Drugs Authority

SPSS - Statistical Package for Social Sciences

WHO - World Health Organization

- A prescriber was defined as a clinician involved in the management of malaria in pregnancy at the study facilities.
- First trimester pregnancy was a pregnancy with a gestational age of 1 up to 12 weeks.
- Second trimester pregnancy was a gestational age of 13 weeks up to 27 weeks.
- Third trimester pregnancy was a gestational age of 28 weeks up to delivery.

CHAPTER 1 General Introduction

1.1. Background

Malaria in pregnancy is a serious health issue which threatens the life of the mother and the foetus if not managed properly. In Ghana, malaria is common and therefore pregnant women are at risk of the infection. About 28% of OPD attendance by pregnant women in the country is due to maternal malaria [1]. Appropriate management of the infection in pregnancy is therefore crucial in order to save the lives of mothers and their unborn children.

At the Brong Ahafo regional annual health facility review in 2012, there were reports about problems encountered with the use of quinine for malaria in pregnancy in some of the health facilities. For example, from the Kintampo Government Hospital, it was reported that some pregnant women suffering from malaria bled and aborted when given quinine for malaria. Meanwhile, Physicians from St. Theresa's Hospital in Nkoranza had reported at clinical meetings in 2011 about some pregnant women who bled after taking quinine for malaria in their first trimesters.

The 2010 edition of the standard treatment guidelines for Ghana recommend seven days of oral quinine therapy for uncomplicated malaria during the first trimester of pregnancy [2]. However, due to the above listed observations, it appears some clinicians in the region feel reluctant to recommend or prescribe quinine for malaria in pregnancy.

The Food and Drugs Authority (FDA) through a circular to healthcare professionals also announced the increased recurrence of suspected oral quinine induced bleeding leading to incomplete abortion in some pregnant women who took the drug for malaria

treatment [3]. Thus it is possible that prescribers who have experienced this or heard about the news from FDA are likely to prescribe other antimalarial drugs that may not be indicated for malaria treatment in the first trimester of pregnancy. It is also possible that other prescribers who stick to quinine for malaria in the first or second trimesters may prescribe low doses for fear that they might induce bleeding or abortion in their clients.

It is against this background that this research seeks to study and analyse the pattern of usage of antimalarials in pregnancy for the purpose of generating data to inform policy makers about current practices in the pharmacological management of malaria in pregnancy. The study will look at the situation in the facilities selected; the antimalarial drug choices of prescribers in the different trimesters of pregnancy and compare with protocols mentioned in standard treatment guidelines.

1.2. **Main Objective**

To assess prescribers' awareness of the national policy for malaria in pregnancy, the depth of knowledge of the prescribers on the policy and the pattern of use of antimalarials in pregnancy.

1.3 Specific Objectives

1. To assess the knowledge of prescribers on the national policy for malaria therapy in pregnancy.
2. To verify reports of quinine induced bleeding in early pregnancy at the study sites.

3. To determine the proportion of prescribers who do not prescribe quinine for malaria in pregnancy because of its bleeding threat.
4. To assess the pattern of medicines used in the management of malaria in pregnancy at the study sites.

CHAPTER 2 Literature Review

Malaria is an infectious disease which approximately kills over one million people worldwide annually [4]. In 2009, malaria was rated second to tuberculosis as the most common cause of infectious disease-related death in the world [4]. Its devastating effects are felt more in sub-Saharan Africa which has over 90% of the world's malaria deaths burden. Pregnant women are among the group of people with the highest morbidity and mortality in Africa [5]. It is reported that approximately, four fifth of malaria deaths in Africa occur in maternal women and children under five years [6].

In sub-Saharan Africa, between the year 2000 and 2011, available evidence suggest that the prevalence of malaria in pregnant women attending antenatal clinic was 35.1% in West and Central Africa and 29.5% in East and South Africa [5]. In sub-Saharan Africa, malaria is thought to be responsible for as high as 10,000 mortalities in pregnancy annually [5].

In Ghana, malaria is hyper endemic and pregnant women are a major vulnerable group for the infection. About 9% of maternal deaths are due to malaria whilst 13.7% of pregnant women admitted in the hospitals is due to malaria. *Plasmodium falciparium (P. falciparum)* species is the most mentioned cause of malaria in Ghana [1].

Humans are infected with malaria when they are bitten by an infected female anophiline mosquito. The mosquito is the vector that carries the *Plasmadium* parasite responsible for the infection. Among the four species of *Plasmodium, i.e. vivax, ovale, malariae and falciparum, Plasmodium falciparum*, is the most virulent and known to cause the highest rate of complications and mortalities [7]. Geographically, *P.*

falciparum is more common in Africa than other areas of the world [8]. In its vector (mosquito), *P. falciparum* resides within the salivary glands. As human gets a bite from an infected female Anopheles mosquito, sporozoites of *Plasmodium falciparum* are injected from the salivary gland of the mosquito into the broken skin before it sucks blood from its victim. Saliva injection is necessary during feeding in a mosquito since it contains enzymes that prevent blood clotting and inflammation that will initiate pain in the victim [9]. The sporozoites get into the blood stream and enter the liver invading hepatocytes. The sporozoites differentiate and undergo asexual multiplication resulting in thousands of merozoites that burst out of the hepatocytes. Merozoites released invade the red blood cells (RBC) and replicate further[10]. Clinically, the malaria infection initially manifests as chills and fever when the invaded RBCs rupture synchronously and release merozoites or schizonts and toxins into the blood. Subsequently, headache, nausea, vomiting, myalgias, anaemia, low blood glucose levels, sequestration of RBCs, occlusion of capillaries which can result in organ damages such as kidney, lungs and gastrointestinal tract ensue [11]. In falciparum malaria, haemozoin and fluid can accumulate in the lungs and cause severe acute respiratory syndrome [12].

The existence of parasitaemia that may result in a bout of malaria attack in the body of a pregnant woman could have an ill effect on both the mother and the foetus [13]. The prognosis in the mother ranges from miscarriage or intrauterine death, preterm delivery, severe anaemia and maternal death. To the foetus or neonate, there could be under weight neonate, neonatal death or congenital malaria [5, 14].

Pregnant women are more prone to malaria than non-pregnant women and other individuals in the population [13]. When they are attacked by the infection, they are

more likely to suffer from the disease complications or die out of it [13]. In pregnancy, presentation of malaria tends to be atypical since changes in haematological, hormonal and immunological factors may mask the signs and symptoms of the infection [6]. Because of these hormonal and immunological challenges and the development of the placenta [6], parasitaemia may increase with the resulting complications before it is noticed in pregnant women for treatment to be initiated. The placenta of infected patients could be sequestered by *P. falciparum* which can impede the transport of nutrients and oxygen to the foetus as well [6].

Treatment of pregnant women with malaria can be more difficult due to restrictions of some drugs in pregnancy. There is fear that the foetus could be affected and malformed. In a study in Mozambique to look at drug exposure and its relation to pregnancy outcome, pregnant women exposed to drugs experienced more stillbirths and malformations like polydactyly compared with those who had no exposure [15].There is scant information on the safety and efficacy of most antimalarial drugs in pregnancy, especially for exposure in the first trimester since pregnant women are mostly not included in a lot of clinical trials. Due to this exclusion, most medicines are licensed for use with limited information on their safety during pregnancy [16].

In pregnancy, organogenesis starts in the period of 14 to 60 days after fertilization [17]. The major organ systems appear and begin to develop during this embryonic stage. The embryo at this stage is susceptible to malformation if it is exposed to some drugs. Reference could be made to the case of thalidomide inducing phocomelia in babies exposed to it in early pregnancy [18].

The sixth editions of both the standard treatment guidelines of Ghana and the essential medicine's list mention the following medicines for managing malaria: oral products; Artemether-Lumifantrine, Artesunate-Amodiaquine, Dihydroartemisinin-Piperaquine, Quinine and Clindamycin. Injectables; Artemether, Quinine and finally suppository Artesunate [2, 19]. It is out of these products that protocols have been formulated in Ghana to treat malaria in pregnancy.

The safety profiles of these antimalarials in pregnancy and their effect on the foetus, have to be considered before they are prescribed. Medicines listed in the WHO guidelines as being safe in the first trimester pregnancy includes: chloroquine, quinine, clindamycin and proguanil. In the current national policy in Ghana, quinine either alone or in combination with clindamycin are the drugs recommended for malaria in the first trimester of pregnancy [14].

2.1. Quinine as a national policy medicine for malaria in pregnancy

There have been conflicting issues regarding the safety of quinine in early pregnancy. The World Health Organisation's guidelines state that treatment with oral quinine is believed not to be toxic to the foetus irrespective of the trimester of use [14]. Studies in 1996 by Phillips-Howard et al showed that standard doses of quinine do not increase the chances of abortion or preterm delivery [20]. Mcgready and others in 2002 also reported that therapeutic doses of quinine and chloroquine were safer to be used in the first trimester of pregnancy [21]. In a similar study carried out by Adam et al in 2004, the safety profile of quinine in first trimester pregnant women in eastern Sudan was examined. Pregnant women put on standard doses of quinine were monitored until

delivery and it was reported that 3.8% of the pregnant women bled per vagina intensely and aborted whilst 7.7% had threatened abortions with mild vaginal bleeding but sustained their pregnancies until term delivery. In the absence of congenital malformations in the remaining infants at birth or after 1 year, Adam et al concluded that quinine may be safe in the first trimester of pregnancy [22]. The South African guideline for malaria also mentions that quinine is safe when administered in normal therapeutic doses even though it recognises that quinine and malaria itself may have oxytocic effects [23].

There have been other official reports that state that quinine is a potential abortifacient and teratogen when used in early pregnancy. Between 1938 and 1983, quinine was published to have caused damage to the auditory and optic nerve in the foetus when used at higher doses [24, 25]. Quinine was also reported to have the potential to induce labour [26]. Again, quinine has been mentioned in literature, to cause thrombocytopenia, coagulopathy, hypoprothrombinaemia and dissiminated intravascular coagulation in some patients who took the drug for therapy [27-29]. It is not quinine alone that has been implicated in thrombocytopenia, malaria infection itself has also been associated with low platelet count when it affects the adult [30], thus both could contribute to bleeding in pregnancy as has been reported. For instance in Ghana, it was reported by the Food and Drug's Authority (FDA) in 2011 that it had received reports of bleeding and incomplete abortion cases suspected to be caused by the use of oral quinine by some clients who had malaria in pregnancy [3].

The mechanism of quinine-induced thrombocytopenia is suspected to be the result of a formation of drug-antibody complexes with an affinity for some component of the

platelet membrane [27-29] . In the coagulation pathway, platelet release and aggregation is a prerequisite for the assembly of coagulation factor enzyme complexes. Again, in the process, prothrombin is required to be converted to thrombin which will hydrolyse peptide bonds in fibrinogen and release fibrinopeptides molecules. Polymerisation of fibrinopeptide molecules yield fibrin which forms the clot [31]. It is therefore possible that in some pregnant women with malaria exposed to quinine in early cyesis, the subsequent thrombocytopenia, hypoprothrombinaemia and inherent oxytocic effect of quinine may trigger bleeding and abortion. As a result of complications associated with quinine, its use in pregnancy is contraindicated in the United States according to the American Hospital Formulary Service (AHFS) Drug Information book [27].

2.2. Artemisinin Combination Products as national policy medicines for malaria in pregnancy

The World Health Organization reported in 2003 that the artemisinins in animal studies, have caused death of embryos in early exposures [32]. In a study in rats and rabbits, Clark et al. found out that artesunate could induce embryo loss, cardiovascular malformations and skeletal system defects in animals [33]. In a similar *in vitro* study by Longo et al on a metabolite of the artemisinins; dihydroartemisinin, on rat embryos, it was reported that dihydroartemisinin could affect yolk sac haematopoiesis and that higher concentrations and prolonged exposure of the embryo to dihydroartemisinin could inhibit the growth of new blood vessels [34].

The lethal effect of the artemisinins to the embryo is reported to be a class effect among the known derivatives [35]. This embryo-toxic mechanism of artemisinins in early pregnancy is thought to occur as a result of the depletion of early embryonic erythroblasts, resulting in severe anaemia in the embryo leading to hypoxia, cell damage and death [36]. In humans, the most

critical period for this embryo-toxic event to occur may be between week four and week ten, when early erythroblasts in circulation have not yet been fully replaced by definitive erythrocytes [35, 36]. On the contrary, published data on 607 human pregnancies in which artemisinin compounds were administered during 2nd or 3rd trimesters showed no sign of adverse pregnancy outcomes [32]. In 1st trimester, normal outcomes were observed in 124 pregnancies exposed to the artemisinins. Although pregnancy outcomes in 1st trimester exposures were normal, WHO stated that the number of exposures were too small to provide an adequate safety profile of these drugs for malaria treatment in early pregnancy [32].

2.2.1. Artesunate-Amodiaquine

Artesunate-amodiaquine is an artemisinin based product which is recommended for malaria treatment in the second and third trimesters of pregnancy. It is a combination of derivatives of an artemisinin and a 4-aminoquinoline. This combined product is water soluble but less soluble in fat thus limiting its ability to cross the placenta in excess.

The safety and efficacy of artesunate-amodiaquine in the second and third trimesters of pregnancy has been approved by WHO and supported by studies done by Tagbor et al. and Mutabingwa et al. [37, 38]. The use of this product in the second and third trimesters for malaria therapy has not been doubted. However, its use in the first three months of pregnancy raises several safety concerns. For several years, specific studies on the effect of the amodiaquine component on the developing mammalian fetus during the first three months of pregnancy have been lacking, thus, making it difficult to get data on teratogenicity associated with amodiaquine [39]. Among researchers, there was no consensus on the use of amodiaquine in pregnancy as some contraindicated its use whiles others recommended a cautious use in pregnancy if alternatives were unavailable [39]. The WHO, finds no sufficient documented evidence to warn against amodiaquine's

use during late pregnancy, although it calls for further research on amodiaquine's toxicity.

2.2.2. Artemether –Lumefantrine

Artemether-lumefantrine is another recommended artemisinin based product for malaria in the second and third trimesters of pregnancy. It is made of a fluorene derivative of aminoalcohol (lumefantrine) and artemether. Both components are insoluble in water but highly soluble in fat suggesting that the product is likely to cross the placenta.

Guidelines from WHO state that artemether-lumefantrine is safe for use in treating malaria in the second and third trimester pregnancies. Its efficacy and safety has been compared to quinine in treating maternal malaria in these trimesters and has been reported to be equally effective, safe and more tolerated than quinine [40, 41]. In the first trimester, there have been some assuring reports from a Zambian study in 2010 that artemether-lumefantrine does not necessarily increase the risk of specific perinatal abnormalities in pregnancy [42]. However there were reports of few cases of abortion, neonatal death and malformations in 9.69% pregnant women exposed to the drug in the first trimester of pregnancy.

2.2.3. Dihydroartemisinin-Piperaquine

Dihydroartemisinin-piperaquine phosphate is an artemisinin derivative combined with a *bis* 4-aminoquinolone (piperaquine). This product is lipid soluble but poorly soluble in water suggesting that it may cross the placenta. It is on the essential medicine's list for malaria treatment in the general population in Ghana but not included

in the policy for maternal malaria. Because of issues with insufficient trials and inexperience with the use of dihydroartemisinin-piperaquine phosphate in pregnancy, the WHO cautions against its use in pregnancy. In spite of this, few studies in which it was used for malaria in pregnancy did not report any birth defects. In 2008, Rijken et al used dihydroartemisinin-piperaquine to treat pregnant women with resistant falciparum malaria who had failed on quinine and artesunate and the treatment was effective, well tolerated with no evidence of toxicity to the mothers or the foetus [43]. Again, in 2010, a foetal toxicological study of piperaquine in mice did not report any birth defects in the mice [44] even though it was recommended that a larger scale trial is needed to buttress its findings.

2.3. Pharmacotherapy of maternal malaria in Ghana

Guidelines for the management of maternal malaria in Ghana have gone through several reviews. Between 1990 and the year 2003, the prophylaxis and treatment of malaria in pregnant women was done with chloroquine [45, 46]. In the year 2004 up to 2009 there was a review; oral sulfadoxine-pyrimethamine was used to substitute oral chloroquine for the prophylaxis of malaria in pregnancy owning to widespread resistance to chloroquine whilst quinine was used for treatment [47]. The year 2010 and upwards saw some modifications to the protocol in the line of the WHO recommendations. Sulfadoxine-pyrimethamine was still chosen as the prophylactic drug. For first trimester pregnancy, oral quinine was recommended alone for seven days or oral quinine plus clindamycin for three days. The ACTs were not recommended in first trimester pregnancy but where they are considered to be live-saving or when other antimalarial drugs are not suitable, they could be used. For second and third trimesters of

pregnancy, oral quinine alone, artesunate-amodiaquine or artemether-lumefantrine was recommended. For severe malaria in pregnancy, parenteral quinine followed with oral quinine was recommended for all the trimesters or parenteral artemether for the second and third trimesters [2].

The Nigerian antimalarial treatment guidelines and policy recommends oral quinine as first line agent in all trimesters. ACTs are recommended as second line agents in second and third trimesters. However, the ACT are used in first trimester where there are no suitable alternatives [48].

The South African guidelines for the treatment of uncomplicated malaria in pregnancy recommends quinine in first trimester followed by a course of clindamycin for all pregnant women. The artemisinins are only prescribed in pregnancy when no effective antimalarial medicine is available [23]. In severe malaria in pregnancy, it recommends intravenous quinine.

In 1998, a study was carried out in Mali on the use of antimalarial medicines; comparing the policy to reality and it was concluded that in pregnancy, non-recommended treatments for malaria was practised and where recommended regimens were used, suboptimal treatments were given in the study villages [49].

In 2011, patterns of antimalarial medicines treatment in pregnant women was studied in Uganda. This study concluded that a contraindicated antimalarial drug (Sulfadoxine-Pyrimethamine or Artemether-Lumefantrine) was used in 70% of first trimester pregnancy. That recommended antimalarials were used according to guidelines in only 30% of all second and third trimester episodes. It was concluded that adherence to

treatment guidelines in Uganda for the management of malaria in pregnancy was poor [50].

In 2012, Okoro and Nwambu assessed physician's prescribing patterns of antimalarial medicines during pregnancy in Nigeria. They found inappropriate antimalarial prescribing patterns in pregnancy. Sulfadoxine-pyrimethamine was prescribed for treatment in pregnancy instead of intermittent preventive therapy use. Also it was observed that chloroquine was still prescribed for use despite its withdrawal. Only 3.75% of antimalarial drug prescribed was quinine in the first and second trimesters of pregnancy whilst 88.7% was artemisinin derivatives alone or combination for all the three trimesters of pregnancy [51].

In Ghana, in the wake of reports of quinine suspected to be inducing bleeding and abortions when used in maternal malaria treatment in some clients, it is believed that this may affect the prescription patterns of antimalarial drugs in pregnancy. But, to what extent will the effect be on malaria treatment in pregnancy? This study intends to find out.

Table 2.1. Antimalarials recommended by the Standard treatment guideline (6th edition, 2010) for uncomplicated malaria in pregnancy.

Trimester of pregnancy	**Recommended medicines**
1st Trimester	Oral Quinine alone for 7 days Or Oral Quinine plus Clindamycin for 3 days
2nd and 3rd Trimester	Oral Quinine alone for 7 days Or Oral Artesunate-Amodiaquine for 3 days Or Oral Artemether-Lumefantrine for 3 days

Note: ACTs are not recommended for use in first trimester. However, in cases where ACTs are considered to be live saving, or where other antimalarials are not suitable, the ACTs should not be withheld.

CHAPTER 3 Material and Methods

3.1. **Study Setting**

This study was conducted in Brong Ahafo Region which lies in the middle belt of Ghana, sharing borders with Northern region to the north and mainly Ashanti region to the south (Figure 3.1).

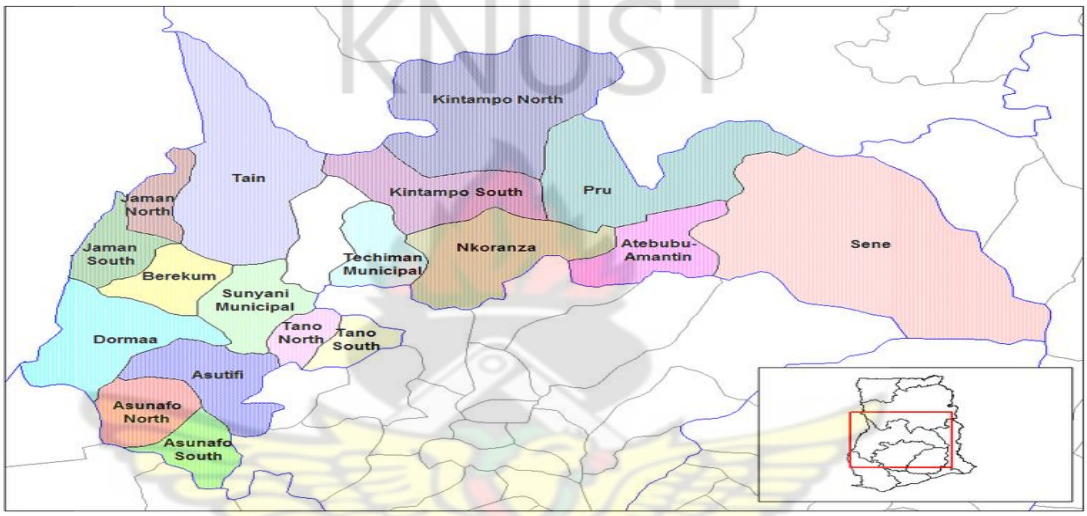

Figure 3.1. Map of Brong Ahafo region of Ghana (http://en.wikipedia.org/wiki/Brong-Ahafo_Region#mediaviewer/File:Brong_Ahafo_districts.png (Accessed 26/6/14)

The study was carried out in three health facilities. There are tertiary, secondary and primary care health facilities in the region which are either under Ghana Health Service (GHS) or Christian Health Association of Ghana (CHAG). In order to have results that will reflect practices in all the different categories of facilities in the region, the three study sites were purposively selected. The Regional hospital in Sunyani; a tertiary health facility in an urban setting was selected. The Holy Family hospital in Techiman which is a secondary health facility that has both rural and urban clientele and a CHAG hospital was also selected. Sunyani is a commercial city located in the south-western part of

Brong Ahafo (Figure 3.1). It is the capital city of the region. Techiman also lies at the north-eastern part of Sunyani with a distance of 81.5 km apart. It is the district capital of Techiman Municipality in the region and well known for its commercial activities in food stuffs. These two hospitals were selected because they were among the leading and well resourced facilities in the region. The third study site was Nkoranza health centre, a primary care facility in a rural setting. Nkoranza is a district capital town which lies in the eastern part of Techiman with a distance of 32.1 km apart. It is a farming community with yam and maize being the main crops produced.

3.2. **Study Design**

The study was cross-sectional in design and it involved prescribers in the selected facilities and pregnant women attending those facilities who were diagnosed with malaria and given antimalarials.

3.3. **Data Collection Tools**

Two different data collection tools were employed. The first tool was a structured questionnaire meant for prescribers in the selected facilities. The questionnaire was made of both closed and open ended questions which sought to test prescribers' knowledge of the national antimalarial policy for malaria in pregnancy and which medicines each prescriber prefers for his or her maternal patients with malaria.

The second tool was a data collection sheet designed to extract the relevant data from the folders and ANC cards which targeted pregnant women diagnosed of malaria and received antimalarial prescription or therapy. The purpose was to identify the real

trend in the usage of the different antimalarial drugs in the different trimesters of pregnancy.

3.4. **Ethical Clearance**

Ethical clearance for the study was obtained from the Committee on Human Research Publications and Ethics (CHRPE) at the KNUST medical school in Kumasi-Ghana (Clearance reference: CHRPE/AP/081/14, Appendix 1). Approval to use the study facilities in the region was obtained from the Regional Director of Health Services at the regional health directorate in Brong Ahafo and consent was also given by the Medical Directors or Administrators of the study facilities. Consent was also obtained from prescribers and patients who were involved in the study.

3.5. **Study Participants**

The study targeted prescribers involved in the management of malaria in pregnancy, i.e. Gyaenecologists, Physicians, Physician assistants and Midwives who have managed maternal malaria cases in the selected facilities. The study participants were pregnant women given treatment for malaria who consented to take part in the study. In all, there were 101 prescribers in the three facilities selected: 62 at the regional hospital in Sunyani, 36 at the Holy Family Hospital in Techiman and 3 at the Nkoranza Health Center. Using the Creative Research Systems Survey software, (confidence level: 95%, confidence interval: 8.96, population: 101) a sample size of 55 participants was calculated but this was increased to 60. A proportionate sampling procedure was used to select the number of prescribers in each facility to be involved in the study: 37 of the prescribers were selected from the regonal hospital, 21 prescribers were selected from

the Holy Family Hospital in Techiman and 2 from Nkoranza Health center based on the ratio of 21:12: 1 in the order of Regional hospital, Holy Family and Nkoranza health center respectively. Thereafter, the systematic random sampling was used to select the required number of prescribers from each health facilities at clinical meetings.

Based on the 2013 Antenatal Clinic (ANC) registrants at the study sites (Regional Hospital 1661, Holy Family Hospital 2202 and Nkoranza Health Center 1460), a population size of 5,323 pregnant women was calculated. Using the Out Patient Department (OPD) prevalence rate of malaria among pregnant women as 28.1 %, (95% CI) and a precision level of 0.05, a sample size of 302 was estimated but increased to 310. Again, based on the 2013 ANC registrants at the study sites, a ratio of 17:22:15 in the order of Regional hospital, Holy Family hospital and Nkoranza Health centre respectively was used to estimate the proportion of the sample size (310) to be taken in each facility. One hundred and twenty six (126) maternal malaria cases were selected at the Holy Family hospital in Tachiman, 98 cases were selected at the Regional hospital and 86 cases were picked at Nkoranza health centre.

Data collection started in March 2014 and ended in June 2014 a period during which the rains were frequent in the region and malaria transmission considered to be on the ascendency.

3.6. **Data on knowledge of prescribers on national policy for malaria management in pregnancy and their practices**

A structured questionnaire was designed and administered to each prescriber who consented to take part in the study. The questionnaire had closed and open ended questions (appendix 2) for the prescribers to answer. Prescribers were asked whether they have ever managed a maternal malaria case and those who responded they have, proceeded with the rest of the questions. The questionnaire had sections on prescribers' knowledge of the current national policy for selecting antimalarials for pregnant women in the 1st, 2nd and 3rd trimesters of pregnancy. Assessment was also made whether the prescribers adhere to the protocol for maternal malaria treatment. Regardless of the policy, prescribers were also required to name which medicines they would prescribe for pregnant women in the different trimesters. Again, prescribers were required to confirm whether they have ever experienced bleeding in early pregnancy when quinine was prescribed for a pregnant woman with malaria and whether they still prescribe quinine in early pregnancy, in spite of reports that it may cause abortion. Prescribers who do not prescribe quinine in early pregnancy were asked to give their reasons and then name which antimalarials they prefer to prescribe instead. Sixty prescribers were targeted in the survey and at the end, 60 questionnaires were filled and analysed. Prescribers in the selected facilities who had managed a maternal malaria case in recent times in Ghana and consented to be part were included. Prescribers who were students on attachment or foreigners on educational exchange programmes were excluded.

3.7. **Prescription data collection from folders of pregnant women**

At the antenatal clinics (ANC) and hospital pharmacies: folders, ANC cards and prescriptions of pregnant women currently attending the health facilities were examined for the diagnosis made or the type of medicines prescribed for them by their clinicians. Data was taken from those pregnant women who were diagnosed with malaria and prescriptions offered for antimalarial medicines. The data captured included: the gestational age or trimester of pregnancy, type of malaria diagnosed, i.e. uncomplicated or complicated and the antimalarial medicines prescribed for the clients (Appendix 2). The data on trimester of pregnancy and antimalarial medicines prescribed was to enable the assessment of the appropriateness of such antimalarials in the trimesters in which they were used and to identify a trend in the usage of such medicines in pregnancy. Prescribers at the clinic were not made aware of this part of the study because of its associated Hawthorne effect. Three hundred and ten maternal malaria cases were captured. Pregnant women not diagnosed of malaria were excluded.

3.8. **Statistical Analysis**

The data obtained was coded appropriately, entered, stored and analysed using Statistical Package for Social Sciences (SPSS) version 16. Data presentation was done using tables and bar graphs with percentages.

CHAPTER 4 Results and Analysis

4.1. **Distribution of prescribers in the study**

Sixty prescribers were involved in the study; 50% (n=30) were General Medical Officers, 30% (n=18) were Physician Assistants, 8% (n=5) Gyaenecologists, 7% (n=4) Midwives and 5% (n=3) were Physician Specialists

4.2. **Number of years that prescribers have practised**

Forty-five percent of prescribers (n=27) had practised from 6 to 10 years; 30% (n=18), 2 to 5 years; 17% (n=10), more than 10 years whilst 8% (n=5) had practised for less than 1 year (Figure 4.1).

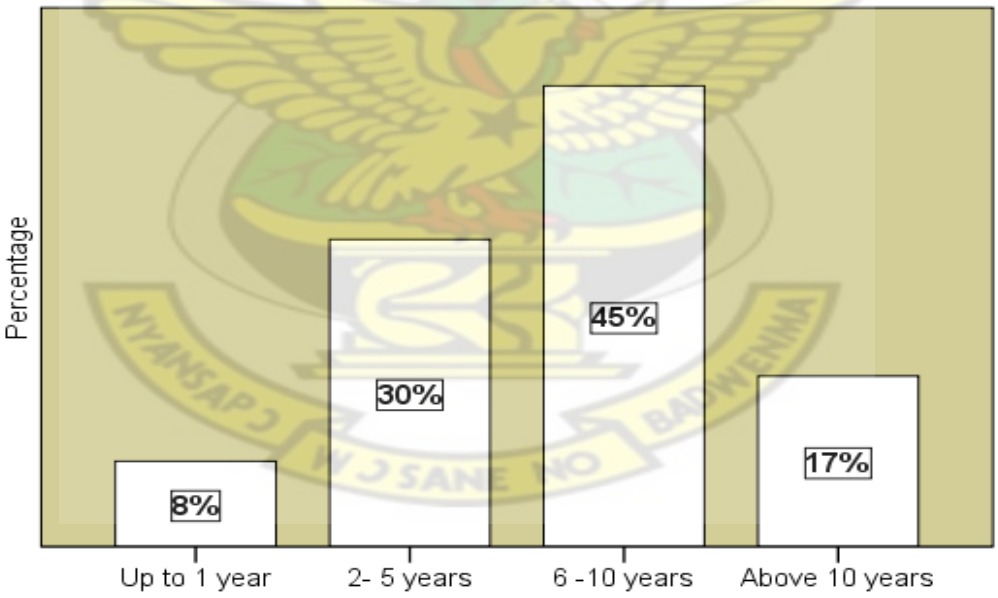

Figure 4.1. Number of years that prescribers have practised

All the prescribers sampled from the facilities had treated malaria in pregnancy.

4.3. **Prescriber's awareness of a national policy for managing malaria in pregnancy**

Majority of prescribers (88%) were aware that there is a national policy for managing malaria in pregnancy (Table 4.1).

Table 4.1. Prescribers who were aware of the national policy for managing malaria in pregnancy.

Response	**Prescribers n(%)**
Yes	53(88)
No	7(12)
Total	**60(100)**

Of the prescribers who responded that they were not aware of the national policy for malaria in pregnancy, 3 were General Medical Officers, 3 were Physician Assistants and 1 was a Physician Specialist.

4.4. **National antimalarial policy for malaria in pregnancy and its knowledge by prescribers**

Eighty-five percent of prescribers (n=51) indicated that oral quinine alone is recommended for uncomplicated malaria in the first trimester of pregnancy; 8% (n=5) indicated oral ACT; 5% (n=3), oral quinine plus clindamycin whilst one prescriber indicated that both oral quinine or oral ACT are recommended for malaria in the first trimester of pregnancy (Figure 4.2).

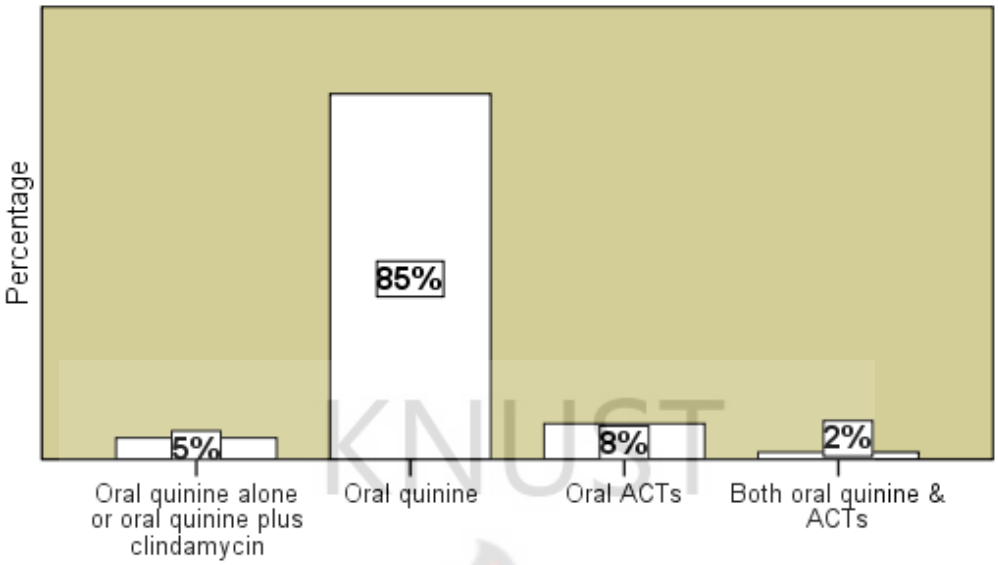

Figure 4.2. Prescribers' knowledge of policy antimalarials recommended for uncomplicated malaria in the 1st trimester of pregnancy

For uncomplicated malaria in the second trimesters of pregnancy (Figure 4.3), 43% (n=26) of prescribers indicated that both oral quinine and an ACT are recommended; 40% (n=24), indicated oral ACTs only; 15% (n=9) indicated oral quinine only whilst one prescriber mentioned parenteral artemisinin continued with oral ACT.

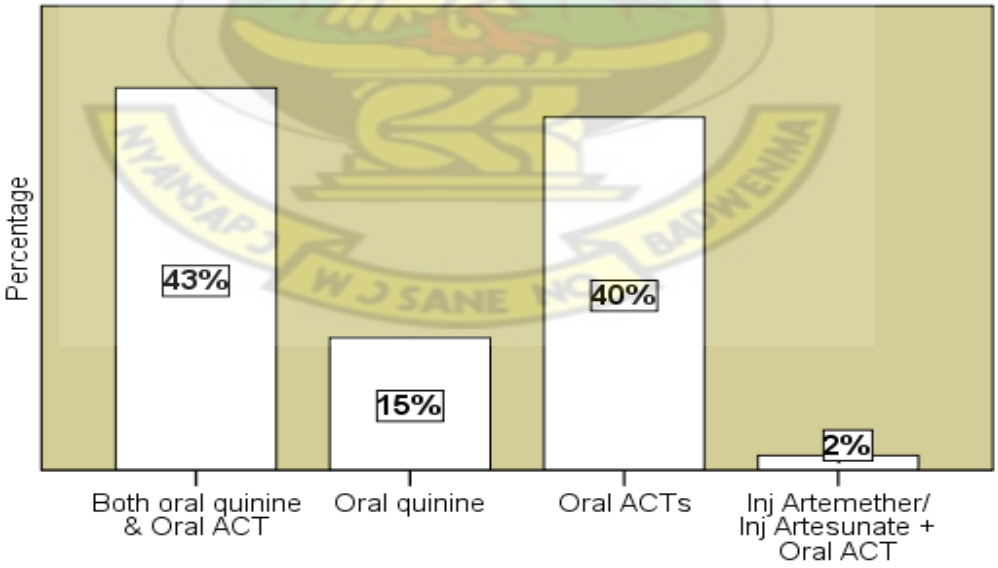

Figure 4.3. Prescribers' knowledge of policy antimalarials recommended for uncomplicated malaria in the 2nd trimester of pregnancy

For third trimester of pregnancy (Figure 4.4), 45 % (n=27) of prescribers indicated that oral ACTs only are recommended by the national policy; 37 % (n=22) indicated both oral quinine and oral ACTs; 10 % (n=6) mentioned oral quinine only; 7 % (n=4), parenteral artemisinins continued with oral ACTs, whilst one prescriber indicated an ACT and doxycycline together.

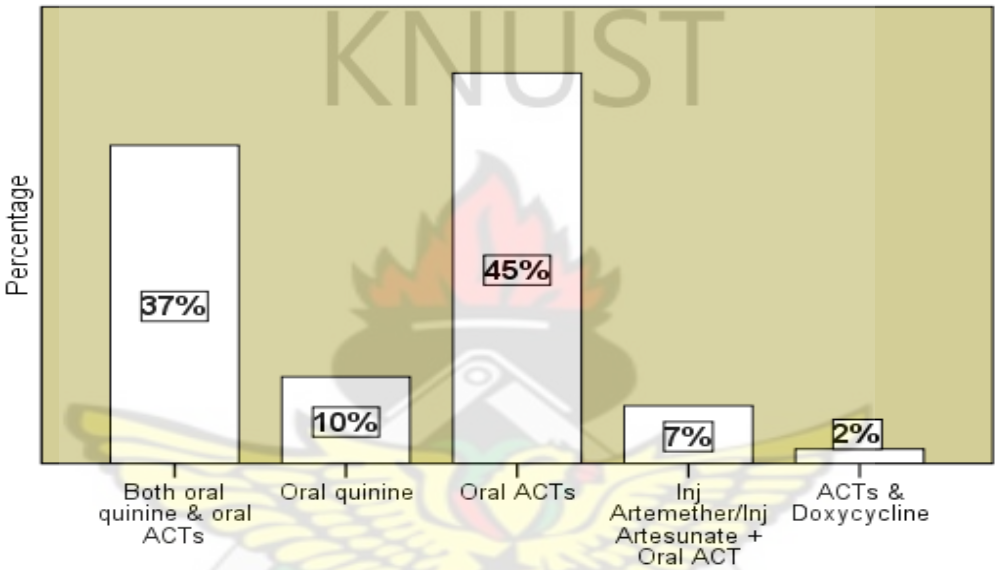

Figure 4.4 Prescribers' knowledge of policy antimalarials recommemded for uncomplicated malaria in the 3rd trimester of pregnancy

4.5. **Individual prescribers' choices of medicines for malaria in the first trimester of pregnancy regardless of policy recommendations**

Forty-two percent of prescribers mentioned that oral quinine is their 1st choice drug; 37% mentioned oral ACT; 7%, oral quinine or ACT; 5%, full course of artemisinin injection, another 5%, artemisinin injection continued with oral ACT and 1 prescriber mentioned oral quinine combined with clindamycin (Table 4.2).

Table 4.2. Individual prescribers' choices of medicines for malaria in the first trimester of pregnancy regardless of policy recommendations.

Antimalarials	**Prescribers n (%)**
Oral quinine only	25(42)
Oral ACT only	22(37)
Oral quinine or ACT	4(7)
Full course of Artemisinin injection	3(5)
Artemisinin injection stat + Oral ACT	3(5)
Rx will depend on antimalarial available	2(3)
Oral quinine plus clindamycin	1(2)
Total	**60(100)**

4.6. **Individual prescribers' choices of medicines for malaria in the second and third trimesters of pregnancy**

Seventy-eight percent of prescribers mentioned oral artemether-lumefantrine as their 1st choice drug for uncomplicated malaria in the second and third trimesters of pregnancy; 7% mentioned parenteral artemisinin continued with oral ACT; another 7 %, oral quinine or oral ACT; 5 %, oral quinine only and 3 % preferred full course of parenteral artemisinin (Table 4.3).

Table 4.3. Individual prescribers' choices of antimalarials for uncomplicated malaria in the 2nd and 3rd trimesters of pregnancy regardless of policy recommendations

Antimalarials	**Prescribers n(%)**
Oral ACT only	47(78)
Artemisinin injection stat + oral ACT	4(7)
Oral quinine or oral ACT	4(7)
Oral quinine only	3(5)
Full course of Artemisinin injection	2(3)
Total	**60(100)**

4.7. **Antimalarial prescriptions data**

Of the 310 antimalarial prescriptions reviewed, 82 were prescriptions for clients in their 1st trimester of pregnancy diagnosed with uncomplicated malaria whilst 228 were clients in their 2nd or 3rd trimesters of pregnancy. For 1st trimester pregnant women diagnosed with malaria, 76 % (n=62) were prescribed oral artemether-lumefantrine; 12 % (n=10) were prescribed parenteral artemisinins and continued with oral artemether-lumefantrine (Figure 4.5); 10% (n=8) were prescribed oral quinine; one patient had oral quinine plus clindamycin and another patient had oral artesunate-amodiaquine. This prescription data reveals something different from prescribers' responses (Table 4.2) in relation to what is known and what is practised.

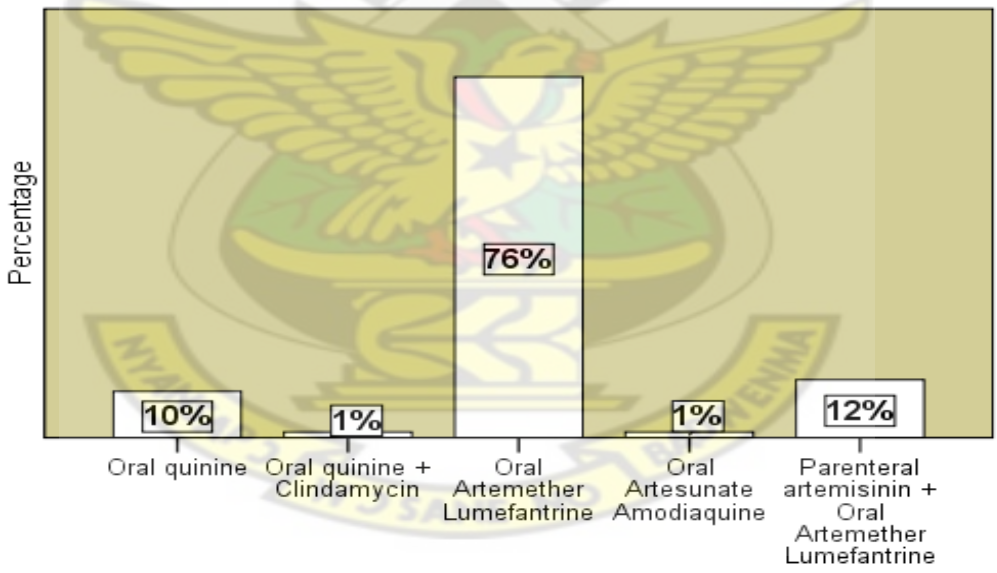

Figure 4.5. Antimalarial medicines assessed on prescriptions for pregnant women in their 1st trimester with uncomplicated malaria

For pregnant women in their second and third trimesters diagnosed with uncomplicated malaria, artemether-lumefantrine was the most prescribed (86.4 %) (n=197) followed by parenteral artemisinin continued with oral artemether-lumefantrine

(9.6 %) (n=22). In addition, 3.1% (n=7) of the second and third trimester pregnant women had oral quinine, one pregnant woman had oral artesunate-amodiaquine and another pregnant woman was prescribed dihydroartemisinin-piperaquine (Figure 4.6).

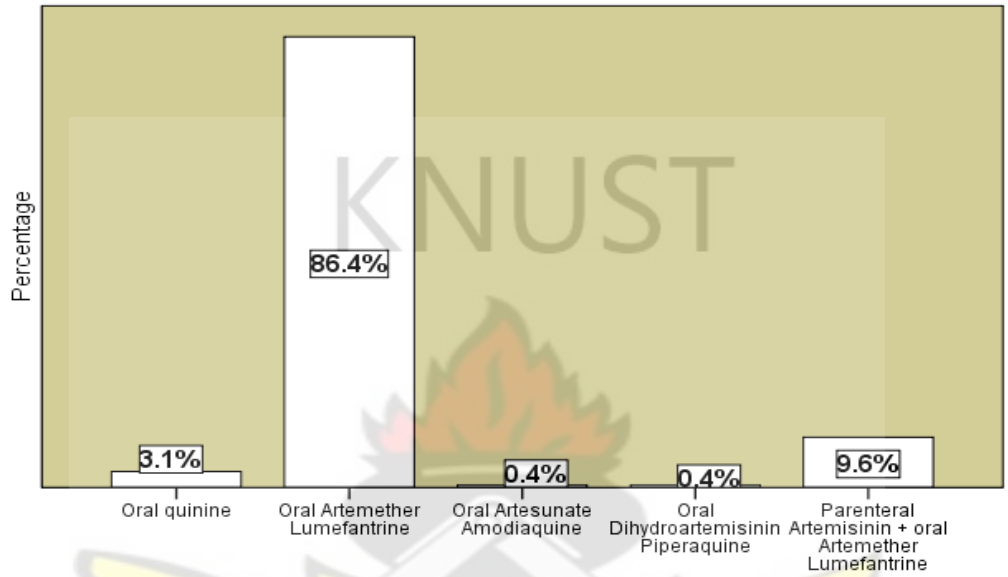

Figure 4.6. Antimalarial medicines assessed on prescriptions for pregnant women in their 2nd and 3rd trimesters with uncomplicated malaria

4.8. **Reasons why some prescribers do not like quinine for uncomplicated malaria in early pregnancy**

Seventy-eight percent of prescribers were reluctant to prescribe quinine for pregnant women diagnosed with malaria (Table 4.4).

Table 4.4. Prescribers who feel reluctant to prescribe quinine for uncomplicated malaria in the first trimester of pregnancy

Response	**Prescribers n(%)**
Yes	47(78)
No	13(22)
Total	**60(100)**

For prescribers who were reluctant to prescribe quinine, reasons were provided (Table 4.5).

Table 4.5. Reasons why some prescribers are reluctant to prescribe quinine for uncomplicated malaria in the first trimester of pregnancy

Reason	**Prescribers n(%)**
Risk of inducing bleeding, abortion or miscarriage.	36(77)
Due to the hypoglycaemic, bleeding and abortion threat.	4(9)
Poor compliance to therapy and its abortion risk.	3(6)
Because G6PD deficient clients may react to quinine.	2(4)
Due to side effects of quinine (unspecified).	2(4)
Total	**47(100)**

4.9. **Prescribers who have observed bleeding in early pregnancy when they prescribed quinine for their clients having malaria**

Fifty-one percent of prescribers had seen bleeding per vagina in their clients when they prescribed quinine for them to treat malaria in pregnancy (Table 4.6).

Table 4.6. Prescribers who have observed bleeding in early pregnancy when quinine was prescribed for malaria

Response	**Prescribers n(%)**
Yes	31(51)
No	29(49)
Total	**60(100)**

Eighty-eight percent of prescribers had heard the news about quinine causing bleeding and abortion in some early pregnancies (Table 4.7).

Table 4.7. Prescribers who have heard the news that quinine in early pregnancy may cause abortion

Response	**Prescribers n(%)**
Yes	53(88)
No	7(12)
Total (N)	**60(100)**

4.10. **Prescribers who still prescribe quinine for malaria in pregnancy regardless of its abortifacient effect**

Of the 59 prescribers who responded to this question, 47 % still prescribe quinine for malaria in pregnancy regardless of its abortion risk. (Table 4.8)

Table 4.8. Prescribers who still prescribe quinine for malaria in early pregnancy

Response	**Prescribers n(%)**
Yes	28(47)
No	31(53)
Total	**59(100)**

4.11. **Antimalarials regarded by prescribers to be tolerable and safer than quinine for malaria in the 1st trimester of pregnancy**

Fifty-six percent of prescribers (n=24) consider oral artemether-lumefantrine to be safer than quinine for malaria in early pregnancy; 23% (n=10) consider parenteral artemisinin to be safer than quinine; 5 % (n=2) consider artesunate-amodiaquine to be safer whiles another 5 % consider dihydroartemisin-piperaquine to be safer than quinine for malaria in early pregnancy (Figure 4.7).

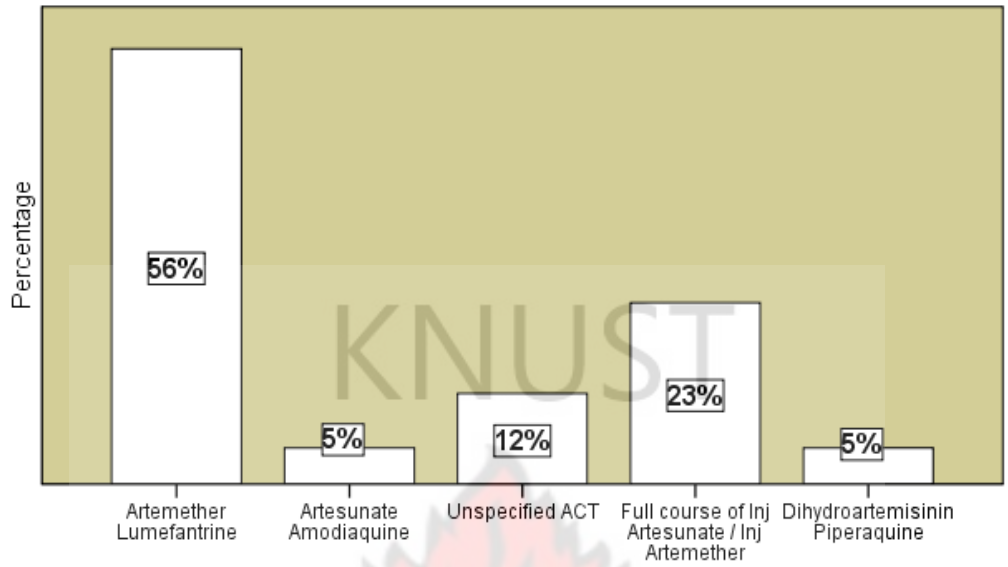

Figure 4.7. Antimalarials observed by prescribers to be safer than quinine for malaria in the 1st trimester of pregnancy

Seventy-six percent of prescribers advocated for a policy change to substitute oral quinine with a different antimalarial in the treatment of uncomplicated malaria in the first three months of pregnancy (Table 4.9).

Table 4. 9. Prescribers who advocated for a policy review to substitute oral quinine in the current national policy for malaria in pregnancy

Response	**Prescribers n(%)**
Yes	45(76)
No	14(24)
Total	**59(100)**

Table 4.10. Cross tabulation of prescribers' reluctance to prescribe quinine for malaria in early pregnancy and prescribers who have observed bleeding with the use of quinine in pregnancy.

		Prescribers who have observed bleeding in early pregnancy when quinine was prescribed		
Prescribers who feel reluctant to prescribe quinine for malaria in the first trimester of pregnancy		YES	NO	TOTAL
	YES	29	18	47
	NO	2	11	13
	TOTAL	31	29	60

Table 4.11. Chi-Square of cross tabulating prescribers' reluctance to prescribe quinine for malaria in early pregnancy and prescribers who have observed bleeding with the use of quinine in pregnancy.

Chi-Square Tests

	Value	df	Asymp. Sig. (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	8.748[a]	1	.003		
Continuity Correction[b]	6.992	1	.008		
Likelihood Ratio	9.391	1	.002		
Fisher's Exact Test				.004	.003
Linear-by-Linear Association	8.602	1	.003		
N of Valid Cases[b]	60				

a. 0 cells (.0%) have expected count less than 5. The minimum expected count is 6.28.

b. Computed only for a 2x2 table

CHAPTER 5 **Discussion**

The study revealed that more than four fifth of the prescribers were aware of the national policy for managing maternal malaria in Ghana. About a tenth of prescribers were however found not to be aware of the policy even though they have been managing malaria in pregnancy. Such uninformed prescribers may use any available antimalarial in pregnancy without recourse to its appropriateness in the trimester of the pregnancy because their choices of antimalarial medicines may not be guided by any policy.

To be assured of safe and efficient use of antimalarials in pregnancy, for best patient outcomes, prescribers have to be abreast of the existing evidence based protocols for malaria in pregnancy. In this study, majority of the prescribers (85%) identified oral quinine as a policy recommended medicine for malaria treatment in the first trimester of pregnancy. Most prescribers were not aware that clindamycin could be combined with oral quinine for malaria therapy in the first three months of pregnancy. This is a 3-day treatment regimen which is simplified and endorsed by WHO and adapted in the national treatment guidelines of Ghana. More awareness creation among prescribers about this regimen needs to be done through education. When prescribers' attention is drawn to this alternative regimen, their knowledge on antimalarials recommended in early pregnancy will not be limited to oral quinine. Some of the prescribers (8%) thought that ACTs are recommended for malaria in the first trimester of pregnancy. This knowledge is inaccurate since the national policy for malaria in pregnancy does not indicate ACTs as first choice medicines in early pregnancy. Results obtained in this study suggest that some of the prescribers may be using these ACTs as first line

medicines for first trimester pregnant women which may put the lives of some unborn babies at risk of adverse effects.

Oral quinine or ACTs are the recommendations in the national protocol for malaria in the second and third trimesters of pregnancy. Less than half of the prescribers identified quinine and ACTs for malaria in the second trimester. Also, less than half of the prescribers knew that quinine and the ACTs could be used in the third trimester. Most of the prescribers knew about single medicines i.e., oral quinine only or ACTs only for 2nd or 3rd trimesters pregnancy; a response which was considered inadequate. In addition, few of the prescribers held the wrong view that paraenteral artemisinins were recommended for use in treating malaria in second or third trimesters. The lack of refresher workshops on the management of malaria in pregnancy could account for these deficiencies in the knowledge of prescribers on the policy for malaria in pregnancy. Inadequate reference materials and non display of protocols for treating malaria in pregnancy could also account for the deficiencies observed. These may narrow the antimalarial options of most prescribers and affect the quality of care for pregnant women with malaria. It is likely that non recommended treatments for malaria in pregnancy may be practised by most of the prescribers at the study sites; a situation which was observed by Djimde et al. in Mali [49].

A gap was observed between prescribers' knowledge of the national policy and prescribers' actual practice when selecting medicines for malaria in pregnancy. The knowledge of quinine as the first line recommended medicine for malaria in early pregnancy by prescribers did not reflect when prescriptions for pregnant women with malaria at the study sites were reviewed. Most pregnant women (76%) with

uncomplicated malaria in their first trimesters were prescribed artemether-lumefantrine against the recommended medicines: oral quinine alone which was prescribed for only one tenth of clients or oral quinine combined with clindamycin which was prescribed for only one pregnant woman. The unfamiliarity of the quinine-clindamycin combination regimen among prescribers at the study facilities may have contributed to it been under prescribed for pregnant women in their first trimesters. Instead of prescribing artemther-lumefantrine with its uncertainties in the first three months of pregnancy, the simplified and evidence based quinine-clindamycin combination therapy should rather be promoted and prescribed. This treatment regimen might not cause compliance problems as compared to the seven days of oral quinine which is not preferred by most prescribers. The quinine-clindamycin regimen has been adopted successfully for the treatment of uncomplicated malaria in pregnancy by the South Africans [23] and could be practised in Ghana if prescribers are well informed about it.

The trend of prescriptions for malaria observed among the second or third trimester pregnant women was not different from that observed among those in their first trimesters of pregnancy. Most of the patients in their second or third trimesters were prescribed artemether-lumefantrine with only one receiving artesunate-amodiaquine. Though artesunate-amodiaquine and artemether-lumefantrine are equally indicated for malaria in the second or third trimesters, there was low preference for artesunate-amodiaquine compared to artemether-lumefantrine. Scientifically, artesunate is more water soluble and less fat soluble compared to artemether [52]. Therefore, the ability of artesunate-amodiaquine to cross the placenta may be minimal and less likely to have negative effects on the foetus compared to artemether-lumefantrine. The use of

artesunate-amodiaquine for malaria in pregnancy where ACTs are recommended should be preferred to the use of the lipid soluble artemether-lumefantrine. Dihydroartemisinin-piperaquine which is yet to be listed in the national treatment guideline for malaria in pregnancy because of insufficient safety data in pregnancy [14], should also not be encouraged for use in pregnancy.

The Ghanaian policy for malaria in pregnancy considers that where the first line medicines are not available or suitable in the first trimester of pregnancy, the ACTs should not be withheld [2]. It was observed that artemether-lumefantrine was rather used as first line antimalarial in early pregnancy by most of the prescribers, throwing an implementation challenge to the existing policy. At the study sites, quinine and clindamycin for malaria treatment in the first trimester of pregnancy were available; however, the ACTs/parenteral artemisinins were the ones being prescribed in both early and late trimesters. This may be a deliberate practice on the part of some prescribers to avoid the use of oral quinine in pregnancy. The simplified regimen of artemether-lumefantrine and its ease of administration may also favour its use in pregnancy by most prescribers over the 7-days duration of quinine therapy. The WHO reported the efficacy and safety of the artemisinins in 124 first trimester pregnant women who had malaria [32]. Manyando et al. also reported the safety of artemether-lumefantrine in the first trimester of pregnancy though there were few cases of malformation, abortion and neonatal death in some of the first trimester pregnancies studied [42]. Little is however known about the subsequent developments of children exposed to the artemisinins or ACTs in early pregnancy. It is therefore difficult to make sound judgment on the effect of these drugs on the growth and development of children. In earlier studies involving

the artemisinins in animals, Clark et al. reported embryo losses, skeletal system defects [33] and Longo et al. reported defects in yolk sac haematopoiesis [34]. These embryo-toxic effects of the artemisinins is reported to be a class effect among the known derivatives [36]. This has prevented the WHO and the national policy from endorsing the use of the ACTs/artemisinins in the first three months of pregnancy. Widespread use of artemether-lumfantrine and parenteral artemisinins in the first trimester of pregnancy may therefore not be safe because of developmental toxicity effects previously reported.

The use of non recommended medicines for malaria in early pregnancy has been observed in other African countries. Uganda and Nigeria have observed similar inappropriate prescribing patterns in pregnancy. Sangare et al. reported that 70% of first trimester pregnant women with malaria in Uganda were prescribed contraindicated antimalarials [50] whilst Okoro and Nwambu in Nigeria reported that 88.7% of antimalarials prescribed in pregnancy were artemisinin derivatives alone or in combination in all the trimesters of pregnancy [51]. In this study, the rate at which artemether-lumefantrine was prescribed for malaria in the first trimester of pregnancy (76%) was above the findings reported by Sangare et al. but below the findings of Okoro and Nwambu. If the inappropriate prescribing patterns are not checked, disease endermic countries may be at risk of having artemisinin resistant parasite causing malaria in pregnancy.

More than two fifth of the prescribers indicated that oral quinine is their first choice medicine for malaria in early pregnancy but this response was at variance with the data obtained from prescriptions reviewed. Quinine was less prescribed for pregnant women who received antimalarial therapy which may be linked to reports of adverse effects

associated with its use in pregnancy. The FDA in Ghana reported of bleeding and abortions in some pregnancies that were attributed to the use of oral quinine to treat maternal malaria in some hospitals [3]. This was confirmed by more than half of prescribers in this study who had observed bleeding in their clients when they prescribed quinine to treat malaria in pregnancy. The news of quinine suspected abortions in some pregnancies in Ghana was widespread among prescribers interviewed as 88% of them have heard or read about it. This news together with the experience of some prescribers observing the incident in clients themselves might have accounted for the avoidance of oral quinine for malaria in the first trimesters of pregnancy.

The World Health Organisation considers standard doses of oral quinine to be safe in pregnancy irrespective of the trimester of use [14]. Bleeding and abortions in some early pregnancies attributed to oral quinine have been reported by Phillips-Howard et al., McGready et al. and Adams et al. [20-22]. However, these studies did not disapprove of the use of quinine in pregnancy because the bleeding cases recorded, were nearly at par with the number of spontaneous abortions in pregnant women who never had any antimalarials in pregnancy. This suggests that if prescribers will stick to the right doses of oral quinine, the oxytocic and abortifacient effect of quinine in pregnancy may be minimal.

The effect of quinine induced bleeding in pregnancy affected the prescription pattern of Clinicians in using quinine for malaria in pregnancy ($p=0.003$). More than half of the prescribers involved in this study averred that they do not prescribe quinine for their maternal clients and this is a challenge to the antimalarial policy in pregnancy.

Checking the platelet count before prescribing quinine for malaria in pregnancy may be beneficial to pregnant women. Quinine and malaria infection have both been reported to induce thrombocytopenia and hypoprothrombinaemia in some patients [27-30]. Quinine is suspected to form a drug-antibody complex which has an affinity for components of the platelet membrane and therefore destroying platelet cells [27]. Some pregnant women with malaria might have suffered from this drug-antibody reaction after taking quinine which resulted in bleeding and abortion. If a baseline platelet count could be established for pregnant women before they are put on quinine therapy, so that below that level they are not given quinine, it may save some pregnant women from having miscarriages as a result of quinine therapy.

The problems of quinine in pregnancy were not limited to its bleeding or abortion effects only. Some of the prescribers raised the issue of quinine's hypoglycaemic effect. Others complained about reactions of glucose-6-phosphate dehydrogenase (G6PD) deficiency patients to quinine whilst some also talked about poor compliance to the seven days duration of therapy due to quinine induced adverse effects. The side effects of the quinine, coupled with the symptoms of discomfort seen in early pregnancy may affect compliance of patients to seven days quinine therapy. Almost four fifth of the prescribers in the study advocated for a review of the decision to use quinine for malaria in early pregnancy. If prescribers are reluctant to treat malaria in pregnancy for seven days with oral quinine, then the second option may be considered, i.e. oral quinine with clindamycin for three days.

The data obtained from both prescribers and pregnant women suggest that most prescribers were not adhering to the national policy for malaria in pregnancy. Some

prescribers selected artemether-lumefantrine for early pregnancy because of perceived tolerability compared to quinine. Exposure of the unborn children to this unrecommended antimalarial in pregnancy may put them at risk of adverse effects or developmental complications that may affect them in later life.

CHAPTER 6 Conclusions and Recommendations

6.1. **Conclusions**

Majority of prescribers involved in the study were aware of the national policy for malaria therapy in pregnancy. Very few prescribers knew that oral quinine with clindamycin could be used as an alternative for malaria in the first trimester of pregnancy. Reports of quinine induced bleeding in early pregnancy was confirmed by most of the prescribers. More than half of the prescribers did not prescribe quinine for malaria in pregnancy due to its perceived effects on the patient or pregnancy. There was widespread use of artemether-lumefantrine and the artemisinin injectables in early pregnancy for uncomplicated malaria.

6.2. **Recommendations**

- The antimalarial drugs recommended for malaria in pregnancy and the trimesters in which they are indicated should be printed at the back of the ANC cards so that prescribers could easily refer to them and prescribe appropriately when in doubt.
- Prescribers should be educated on the 3-days simplified regimen of quinine based clindamycin so that its prescription for malaria in the first three months of pregnancy is enforced instead of artemether-lumefantrine /parenteral artemisinins being prescribed.
- Prescribers must change their practice of using the fat soluble artemether-lumefantrine to treat malaria in the first three months of pregnancy because it is more likely to cross the placenta and affect the foetus.

6.3 Suggestions for further studies

Based on this study, it is suggested that:

- Future studies with more robust design should investigate the safety of ACTs/artemisinin in early pregnancies and the long term effect on the unborn child.
- Effect of quinine on platelet count was done in the US, future studies should evaluate the effect of quinine on platelet count in sub-Saharan Africa or Ghana.
- Pregnancy exposure registers should be made available at selected health facilities in the country so that exposed babies to the ACTs/parenteral artemisimins in the first trimesters of pregnancy can be traced and monitored**.**

REFERENCES

1. Ministry of Health-GHS (2009). The Republic of Ghana, Guidelines for malaria in Pregnancy (The President's initiative): p. 1. (http://www.ghanahealthservice.org/includes/upload/publications/GUIDELINES%20ON%20MALARIA%5B1%5D.pdf)

2. Ministry of Health (2010). Republic of Ghana Standard Treatment Guidelines: 6th Edition, p 374. (http://apps.who.int/medicinedocs/documents/s18015en/s18015en.pdf)

3. Food and Drug's Authority-Ghana (2011). FDA/SMD/SMU 25/VOL 1/11. (http://www.fdaghana.gov.gh/images/stories/pdfs/Dear%20Helthcare%20Prof/SUSPECTED%20ORAL%20QUININE%20SULPHATE%20INDUCED%20BLEEDING%20AND%20INCOMPLETE%20ABORTION.pdf). (Accessed 2013 October 11)

4. Schantz-Dunn, J. and Nour, N. M. (2009). *Malaria and Pregnancy: A Global Health Perspective.* Rev Obstet Gynecol; summer vol. 2(3): p. 186-192. (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2760896/)

5. Takem, E.N. and D'Alessandro, U. (2013). *Malaria in pregnancy.* Mediterr J Hematol Infect Dis; vol 5(1). (http://www.mjhid.org/article/view/11076)

6. Kakkilaya, B.S. (2011). *Malaria in Pregnancy: Double Trouble*. (http://malariasite.com/malaria/Pregnancy.htm). (Accessed 2014 July 28)

7. Olliaro, P. (2008). *Mortality Associated with Severe Plasmodium falciparum Malaria Increases with Age.* Clin Infect Dis; vol 47 (2): p. 158-160. (http://cid.oxfordjournals.org/content/47/2/158.long)

8. World Health Organisation; World Malaria Report (2008). p. 10. (http://whqlibdoc.who.int/publications/2008/9789241563697_eng.pdf)

9. Hills D. (2000). *Arthropod Vector Saliva and Disease Transmission*.(Accessed 2014 July 28) (http://www.sfu.ca/~roitberg/lab/people/resources/d_hill/MainPage.html)

10. National Institute of Allergy and Infectious Diseases, Life Cycle of the Malaria Parasite. (http://www.niaid.nih.gov/topics/malaria/pages/lifecycle.aspx) (Accessed 2014 July 28).

11. Pearson, R.D. (2007). Malaria Parasitic Infections, Merck Manual Home edition.htm. http://www.merckmanuals.com/home/infections/parasitic_infections/malaria.html. (Accessed 2013 October 29)

12. Deroost, K. Tyberghein, A. L. Noppen, S. Schwarzer, E. et al. (2013). *Hemozoin induces lung inflammation and correlates with malaria-associated acute respiratory distress syndrome.* Am J Respir Cell Mol Biol; vol 48(5): p589-600. (http://www.ncbi.nlm.nih.gov/pubmed/23328641)

13. Knott, L. (2014). Malaria in pregnancy, Egton Medical InformationSystems Limited, ID 2418 (v 24). *http://www.patient.co.uk/doctor/malaria-in-pregnancy* (Accessed 2014 July 28).

14. World Health Organization: Guidelines for the treatment of malaria, 2nd edition, Geneva, Switzerland. 2010: p. 27-28. http://whqlibdoc.who.int/publications/2010/9789241547925_eng.pdf?ua=1.

15. Sevene, E. Bardají, A. Mariano, A. Machevo, S. et al. (2012). *Drug exposure and pregnancy outcome in Mozambique.* Paediatr Drugs: vol 14(1): p. 43-49. (http://www.ncbi.nlm.nih.gov/pubmed/?term=Drug+exposure+and+pregnancy+outcome+in+Mozambique)

16. Dellicour, S. Kuile Ter, F. O. Stergachis, A. (2008). *Pregnancy exposure registries for assessing antimalarial drug safety in pregnancy in malaria-endemic countries.* PLoS Med: vol 5(9):187. (http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.0050187)

17. Tate, P. (2012). Seeley's Principles of Anatomy and Physiology, *2nd edition*: McGraw -Hill Press, p. 811-827. (http://kickass.to/tate-seeleys-principles-of-anatomy-and-physiology-2nd-c2012-t6332204.html)

18. Kim, J.H. and Scialli, A.R. (2011). *Thalidomide: The Tragedy of Birth Defects and the Effective Treatment of Disease.* Toxicological Sciences: vol 122(1): p. 1-6. (http://toxsci.oxfordjournals.org/content/122/1/1.abstract)

19. Ministry of Health (2010). Republic of Ghana Essential Medicines List: p. 8-9. http://www.moh-ghana.org/UploadFiles/Publications/eml2010140204051145.pdf

20. Phillips-Howard, P. A. and Wood, D. (1996). The safety of antimalarial drugs in pregnancy. Drug Saf; 14(3): p. 131-145.(http://www.ncbi.nlm.nih.gov/pubmed/8934576)

21. McGready, R. T. Kyaw, L. C, Thein, S. Looareesuwan, S. W. et al (2002). *The effects of quinine and chloroquine antimalarial treatments in the first trimester of pregnancy.* Transactions of the Royal Society of Tropical Medicine and Hygiene: vol 96(2) p. 180-184. (http://www.sciencedirect.com/science/article/pii/S003592030290297X)

22. Adam, I. Idris, H. M. Elbashir, M. I. (2004). *Quinine for Chloroquine-resistant falciparum malaria in pregnant Sudanese women in the first trimester.* Eastern Mediterranean Health Journal: vol10, No 4/5: p. 560-565. (http://sjph.net.sd/files/v1i1p7-12.pdf)

23. Republic of South African, Ministry of Health (2009). *Guidelines for the Treatment of Malaria*: p. 16-17. (http://whqlibdoc.who.int/publications/2008/9789241563697_eng.pdf)

24. West, R.A. (1938). *Effect of Quinine upon Auditory Nerve.* American Journal of Obstetrics and Gynecology: vol 36: p. 241-248. (http://www.ajog.org/article/S0002-9378%2838%2990993-7/abstract.)

25. Mckinna, A.J. (1966). *Quinine Induced Hypoplasia of Optic Nerve.* Canadian Journal of Ophthalmology: vol. 1(4): p. 261-266. (www.ncbi.nlm.gov/m/pubmed/5977436)

26. Mukherijgee, S. Bohse, L. N. (1968). *Induction of Labour and Abortion with Quinine infusion in the Intrauterine Fetal Death.* Am J Obst Gyn: vol 101: p. 853-854. (http://www.ncbi.nlm.nih.gov/pubmed/5660986)

27. American Hospital Formulary Service (AHFS) Drug Information. (2003). p. 759-760. (http://www.worldcat.org/title/ahfs-drug-information-2003/oclc/51626492)

28. Bougie, D.W.Wilker, P. R. Aster, R. H. (2006) *"Patients with quinine-induced immue thrombocytopenia have both "drug-dependent" and "drug-specific" antibodies". Blood*, vol 108, no. 3: p. 922-927. www.ncbi.nlm.nih.gov/pubmed/16861345?dopt=AbstractPlus.

29. Mintzer, D.M. Billet, S. N. Chmielewski, L. (2009) *"Drug-Induced Hematologic Syndromes".* Advances in Hematology, vol 2009, Article ID 495863, 11 pages. http://dx.doi.org/10.1155/2009/495863.

30. Khan, S. J. Abbass, Y. Marwat, M. A. (2012). *Thrombocytopenia as an Indicator of Malaria in Adult Population.* Malaria Research and Treatment: vol 2012(2012) p. 4. (http://dx.doi.org/10.1155/2012/405981).

31. Kumar, P. Clark, M. (2009). Clinical Medicine. 7th edition: Elsevier Health Sciences Press, p. 431-433. (http://www.us.elsevierhealth.com/internal-medicine/kumar-and-clark-clinical-medicine-paperback/9780702029936/)

32. Bosman, A. (2003). *Safety profile of antimalarial medicines with specific emphasis on the artemisinin derivatives.* WHO Training Workshop on Pharmacovigilance: Basic Introduction and Specifics for Malaria Programmes, 23rd March - 2nd April 2003 , Lusaka, Zambia, p. 18-22. (http://www.who.int/medicines/areas/quality_safety/safety_efficacy/trainingcourses/safety.pdf.)

33. Clark, R. L. White, T. E. K.A. Clode, S. G. Ian, W. Ward, P. et al (2004). *Developmental toxicity of artesunate and an artesunate combination in the rat and rabbit.* Birth Defects Research Part B: Developmental and Reproductive Toxicology: vol 71(6): p. 380-394. (http://onlinelibrary.wiley.com/doi/10.1002/bdrb.20027)

34. Longo, M. Zanoncelli, S. Manera, D. Brughera, M. et al (2006). *Effects of the antimalarial drug dihydroartemisinin (DHA) on rat embryos in vitro.* Reproductive Toxicology: vol 21(1): p. 83-93. (http://www.sciencedirect.com/science/article/pii/S0890623805001218).

35. World Health Organization, Assessment of the safety of artemisinin compounds in pregnancy: Report of two joint informal consultations convened in 2006 & 2007. WHO/CDS/MAL/2003.1094. **(**http://whqlibdoc.who.int/publications/2007/9789241596114_eng.pdf**)**

36. White, T.E.K. and Clark, R. L. (2008) *Sensitive periods for developmental toxicity of orally administered artesunate in the rat.* Birth Defects Res B Dev Reprod Toxico: 83: p. 407 - 417.(http://www.ncbi.nlm.nih.gov/pubmed/18615704)

37. Tagbor, H. Bruce, J. Browne, E. Randal, A. et al (2006). *Efficacy, safety, and tolerability of amodiaquine plus sulphadoxine-pyrimethamine used alone or in combination for malaria treatment in pregnancy: a randomised trial.* The Lancet: vol 368**,** (Issue 9544): p. 1349 - 1356. (http://www.thelancet.com/journals/lancet/article/PIIS0140-6736%2806%2969559-7/fulltext.)

38. Mutabingwa, T.K. Muze, K. Ord, R. Briceno, M. et al. (2009). *Randomized Trial of Artesunate-Amodiaquine, Sulfadoxine Pyrimethamine + Amodiaquine,*

Chlorproguanal-Dapsone and SP for malarial in Pregnancy in Tanzania. PLOS ONE, 4(4). (http://www.journals.plos.org/plosone/article?id=10.1371/journal.pone.0005138)

39. Thomas, F. Erhart, A. D'Alessandro, U. (2004). *Can amodiaquine be used safely during pregnancy?* The Lancet Infectious Diseases: vol 4(4): p. 235-239. (http://www.sciencedirect.com/science/article/pii/S1473309904009740)

40. Piola, P. Nabasumba, C. Turyakira, E. Dhorda, M. (2010). *Efficacy and safety of artemether-lumefantrine compared with quinine in pregnant women with uncomplicated Plasmodium falciparum malaria: an open-label, randomised, non-inferiority trial.* Lancet Infect Dis: vol 10: p. 762 - 769. (http://msf.openrepository.com/msf/bitstream/10144/116337/1/101006_Piola_preg-coartem-v-quinine_LID-2010-10-762.pdf)

41. Rulisa, S. Kaligirwa, N. Agaba, S. Karema, C. et al (2012). *Pharmacovigilance of artemether-lumefantrine in pregnant women followed until delivery in Rwanda.* Malaria Journal: vol. 11: p. 225. (http://www.malariajournal.com/content/11/1/225)

42. Manyando, C. Mkandawire, R. Puma, L. Sinkala, M. et al (2012). *Safety of artemether-lumefantrine in pregnant women with malaria: results of a prospective cohort study in Zambia.* Malar J: 9: p. 249. (http://www.malariajournal.com/content/9/1/249)

43. Rijken, M. J. McGready, R. Boel, M. E. Barends, M. et al (2008). *Dihydroartemisinin—Piperaquine Rescue Treatment of Multidrug-resistant Plasmodium falciparum Malaria in Pregnancy: A Preliminary Report.* The American Journal of Tropical Medicine and Hygiene: vol 78(4): p. 543-545. (http://www.ncbi.nlm.nih.gov/pubmed/18385345)

44. Batty, K. T. Moore, B. R. Stirling, V. Ilett, K. F. et al (2010). *Investigation of reproductive toxicity of piperaquine in mice.* Reproductive Toxicology: vol 29(2): p. 206-213. (http://www.sciencedirect.com/science/article/pii/S0890623809003153).

45. Ministry of Health (1995). Republic of Ghana Standard Treatment Guidelines: p. 61. ISBN 9988-75-09-3-5.

46. Ministry of Health (2000). Republic of Ghana Standard Treatment Guidelines: p. 252. ISBN: 9988-0-046-9.

47. Ministry of Health (2004). Republic of Ghana Standard Treatment Guidelines: p. 374-375.(http://apps.who.int/medicinedocs/documents/s16434e/s16434e.pdf).

48. Federal Ministry of Health (2005). National Malaria and Vector Control Division, National Antimalarial Treatment guidelines and Policy, Abuja-Nigeria. (http://apps.who.int/medicinedocs/documents/s18401en/s18401en.pdf)

49. Djimde, A. Plowe, C. V. Diop, S. Dicko, A. et al, (1998). *Use of Antimalarial Drugs in Mali: Policy versus Reality.* Am J. Trop. Med. Hyg: vol 59(3): p. 376-379. (http://www.researchgate.net/publication/13535556_Use_of_antimalarial_drugs_in_Mali_policy_versus_reality)

50. Sangare', L. R. Weiss, N. S. Brentlinger, P. E. Richardson, B. A. et al, (2011). *Patterns of anti-malarial drug treatment among pregnant women in Uganda.* Malar J: vol **10**: p. 152. (http://www.malariajournal.com/content/10/1/152).

51. Okoro, R. N. Nwambu, J. O. (2012). *Evaluation of physicians' prescribing patterns of antimalaria drugs during pregnancy at obstetrics and gynaecology department of teaching hospital in Maiduguri, Borno state, Nigeria.* Int J Pharm Biomed Sci: vol 3(2): p. 39-46. (http://www.pharmainterscience.com/Docs/IJPBS-2012-03-37.pdf)

52. Pogány, Janos. (January 2006). Pharmaceutical quality by design and development, WHO Training Workshop on Pharmaceutical Quality, GMP and Bioequivalence with a focus on artemisinines, Guilin, China.

APPENDIX 1- ETHICAL CLERANCE APPROVAL

KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY
COLLEGE OF HEALTH SCIENCES
SCHOOL OF MEDICAL SCIENCES / KOMFO ANOKYE TEACHING HOSPITAL
COMMITTEE ON HUMAN RESEARCH, PUBLICATION AND ETHICS

Our Ref: CHRPE/AP/081/14

21st March, 2014.

Mr. Francis Fordjour
Post Office Box 30
Nkoranza
BRONG AHAFO.

Dear Sir,

LETTER OF APPROVAL

Protocol Title *"Antimalarials Usage in Pregnancy- A Cross Sectional Study in Health Facilities in Brong Ahafo."*

Proposed Site: *Regional Hospital, Sunyani, Holy Family, Techiman and Nkoranza Health Centre.*

Sponsor: *Principal Investigator.*

Your submission to the Committee on Human Research, Publications and Ethics on the above named protocol refers.

The Committee reviewed the following documents:

- A notification letter of 5th December, 2013 from the Brong Ahafo Regional Health Directorate (study site) indicating approval for the conduct of the study in the Hospital.
- A completed CHRPE Application Form.
- Participant Information Leaflet and Consent Form.
- Research Proposal.
- Questionnaire.

The Committee has considered the ethical merit of your submission and approved the protocol. The approval is for a fixed period of one year, renewable annually thereafter. The Committee may however, suspend or withdraw ethical approval at anytime if your study is found to contravene the approved protocol.

Data gathered for the study should be used for the approved purposes only. Permission should be sought from the Committee if any amendment to the protocol or use, other than submitted, is made of your research data.

The Committee should be notified of the actual start date of the project and would expect a report on your study, annually or at the close of the project, whichever one comes first. It should also be informed of any publication arising from the study.

Thank you Sir, for your application.

Yours faithfully,

Osomfuor Prof. Sir J. W. Acheampong MD, FWACP
Chairman

Room 7 Block J, School of Medical Sciences, KNUST, University Post Office, Kumasi, Ghana
Phone: +233 3220 63248 Mobile: +233 20 5453785 Email: chrpe.knust.kath@gmail.com / chrpe@knust.edu.gh

APPENDIX 2-DATA COLLECTION TOOLS

ANTIMALARIALS USAGE IN PREGNANCY RESEARCH

(Please tick or fill in with answers where appropriate and use generic names of medicines where required)

1) Have you ever treated a pregnant woman with malaria?

   1. YES……
   2. NO……

   If your answer is yes, then proceed.

2) Are you aware of the current national guidelines for malaria therapy in pregnancy?

   1. Yes……
   2. NO……

3) Can you mention which antimalarial medicines have been listed in the treatment guideline for treating uncomplicated malaria in:

   1 First trimester pregnancy?_____

   _____

   2 Second trimester pregnancy?

   _____

   _____

   3 Third trimester pregnancy?_____

   _____

4) In your consulting room currently, which antimalarial medicines do you prescribe for the following clients with simple malaria who come to you based on your clinical experience?

   1 First trimester pregnant women who have malaria?

   _____

   _____

   2 Second trimester pregnant women who have malaria?

   _____

   _____

3 Third trimester pregnant women who have malaria?

_____

_____

5) For Severe or complicated malaria, which antimalarial medicine is your first choice in pregnancy?

_____

_____

6) Do you feel uncomfortable prescribing quinine to treat malaria for your clients who are pregnant in the first or second trimesters? 1YES…….
2 No……

7) If your answer to question 6 is yes, can you provide a reason for being reluctant to prescribe quinine to treat malaria for first or second trimester pregnancy?

_____

_____

_____

8) Has a pregnant woman you prescribed quinine to treat malaria bled before?
1 YES…….
2 No……..

9) If you have not experienced it yourself, have you heard the news that quinine has induced bleeding or caused abortion in some pregnant women before?
1 YES…..
2 NO…...

10) Do you still prescribe quinine for malaria in first or second trimester pregnancy regardless of its abortifacient effect? 1 YES……
2 NO……

11) If you are uncomfortable to prescribe quinine for a pregnant woman who has malaria because it can induce bleeding or abortion, what alternative antimalarial medicine do you prescribe instead of quinine for first and second trimester pregnancy?

_____

_____

12) From your clinical experience, do you see any other antimalarial medicine that is safer and effective than quinine for malaria in the first and second trimester pregnancy?
1 Yes……..
2 NO……..

13) If yes to question 13, can you mention it?_____

14) From your experience with managing malaria in pregnancy, especially with the use of quinine, will you advocate for a review of the current antimalarial policy in pregnancy to exclude quinine?

1 Yes…….
2 NO…….

15) Please indicate your profession. 1 Medical doctor……(Specialty?……..
2 Physician assistant……
3 Midwife……

16) How many years have you been practising? .....

Thank you.

Data capturing sheet for pregnant women diagnosed of malaria and the antimalarial drug prescribed

Serial number	Type of malaria diagnosed? (complicated or uncomplicated malaria)	Trimester of pregnancy	Antimalarial drug prescribed