Patients adherence to artesunate-amodiaquine combination therapy in the Berekum District, Ghana

Simon Nyovuura Antara

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DECLARATION

This thesis is my original work and has not been presented for a degree in any other University.

Signature…….Date.....

Simon Nyovuura Antara

This thesis has been submitted for examination with our approval as University Supervisors.

Signature……Date.....

Dr. Joseph Kangangi Gikunju

JKUAT, Kenya

Signature……  …Date.....

Prof. Edwin Afar

UG, Ghana

Signature……Date.....

Dr. Myat Htoo Razak

CDC, Kenya

DEDICATION

To my loving wife, Mrs. Winifred Antara and children, Bevelyn Antara, Bestus Antara and Simon Antara Jr

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One man plants, another waters but the LORD alone provides the increase. I salute the planters and all those who watered the seed. Above all, I am highly indebted to the Almighty God who loves me a mere mortal that he gave me the strength and all the resources required for this work.

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Dr Simon Nyovuura Antara.

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LIST OF ACRONYMS

ACT:	Artemesinin-based Combination Therapy
DHMT:	District Health Management Team
ITN:	Insecticide Treated Nets
MOH:	Ministry of Health
NMCP:	National Malaria Control Program

ABSTRACT

Malaria is a serious public health problem particularly in Africa. Over the years, the situation has worsened because of the development of drug resistance to many of the previously efficacious and affordable antimalarial drugs. Following the emergence of chloroquine resistance, Ghana changed her antimalarial drug policy in 2005 opting for artesunate-amodiaquine combination as first line treatment for uncomplicated malaria. Following the implementation of the new policy, there have been several complaints of various side effects. This study was done to determine the level of adherence to the combination therapy and to identify the various factors militating against it so as to provide the basis for intervention.

It was a cross sectional study. Patients who reported to any of the district health facilities and were diagnosed as having malaria and put on artesunate-amodiaquine combination therapy were selected by convenience sampling. Their addresses were obtained from their medical records. They were traced to their homes on the fourth day of treatment and the remaining tablets were counted and semi-structured questionnaires administered to them to collect data on various issues on adherence. Data was analyzed using *E*pi-*Info version 3.3.2;* 2005. Simple proportions, odds ratios and P-values were calculated.

In total, 326 subjects were studied. It was found that only 154(47.2%) adhered to the treatment. One hundred and ten (33.3%) of the 326 participants did not adhere

because of side effects. Side effects were significant reasons for non-adherence ($P<0.05$)

The following health system related factors were associated with improved adherence: instructed to take drugs after meals ($P=0.05$), telling patients the names of the drugs ($P <0.05$); advised to sleep under insecticide treated bednet ($P<0.05$). Prescribing other drugs concurrently with the combination therapy was associated with non-adherence ($P<0.05$)

The conclusions were that the proportion of patients who adhere to the combination therapy is low; that side effect is the major reason for non-adherence; service provider factors such as inadequate counseling of patients plays an important role in non-adherence.

The recommendations are that public health education on the need to adhere to the combination therapy be intensified; health care providers be retrained to provide adequate and appropriate information; prescribers should avoid polypharmacy. Finally, more of these studies should be conducted in other districts to provide information on the national situation of adherence in the country.

CHAPTER ONE

INTRODUCTION

1.1 Background

Malaria is a serious public health problem particularly in Africa. In Ghana, malaria accounts for almost half of outpatient visits and is a leading cause of admission (Ghana Health Service, 2004). Over the years, the malaria crisis in Africa has worsened because of the development of resistance by the malarial parasites to most of the commonly used drugs (Hastings *et al.,* 2000). In most countries; chloroquine has been the drug of choice for treating *Plasmodium falciparum* malaria for more than 50 years (Menard *et al.*, 2005). It was administered mainly as monotherapy. However, the efficacy of chloroquine has become compromised as drug-resistant *Plasmodium falciparum* parasites have become increasingly prevalent in recent decades (Bloland *et al.,* 1998). Indeed resistance has developed against most of the antimalarial drugs currently available in the market (WHO, 2001). Antimalarial drug resistance undermines efforts to reduce the public health burden in most places where malaria transmission occurs (Kachur *et al.,* 2004).

With the rising drug resistance levels to conventional monotherapy, there are strong arguments for a move to combination treatment for all malaria in Africa, especially artemisinin based combination therapies (WHO, 2001).

Ghana until recently was using chloroquine as the first line treatment for uncomplicated malaria. Following various research findings that indicated various levels of resistance to chloroquine, a national task force was set up in 2002 to review the evidence on its efficacy and make the necessary recommendations. In 2004, the committee submitted a report that indicated that chloroquine resistance was as high as 25% in some parts of the country.

Based on World Health Organization guidelines, Ghana changed her treatment policy and in 2005, introduced a combination therapy of artesunate and amodiaquine as first line treatment for uncomplicated malaria. The combination therapy has the potential to improve therapeutic effectiveness, delay spread of drug resistance, and reduce gametocyte carriage *(*White, 1999).

In response to the policy change, some local pharmaceuticals produced a co-formulation of the two drugs containing 600mg of amodiaquine and 200mg of artesunate to be taken once daily for three days. The WHO pre-qualified one is however a co-administered dose containing separate tablets of artesunate (100 mg) and amodiaquine (300 mg) blistered together and to be taken twice daily. The WHO pre-qualified drug was the one distributed by the National Malaria Control Programme, while the local pharmaceuticals had distributed the co-formulated one in the open market. The dosage is weight based and is to be taken as follows: artesunate-4mg/kg body weight, amodiaquine-10mg/kg body weight in two daily divided doses.

1.2 Justification of the Study

Adherence is a critical component of the overall effectiveness of a drug (Amin *et al.,* 2004). However, following the introduction of artesunate- amodiaquine combination therapy in Ghana in 2005 as the first line treatment for uncomplicated malaria, several public concerns were raised regarding the safety of the drugs. There were many media publications alleging various adverse effects experienced by people put on the new combination therapy. These side effects were said to be more associated with the co-formulated drug (containing 600mg of amodiaquine and 200mg of artesunate) produced by local pharmaceuticals. It was thought that the high amount of amodiaquine contained in the co-formulated drug was responsible. The Ministry of Health responded to the huge public outcry by ordering the withdrawal of the co-formulated products from the market. The WHO pre-qualified one remains the first line drug for the treatment of uncomplicated malaria.

Many prescribers however are still complaining that their patients refuse to take the amodiaquine in the co-administered dose. They end up taking only the artesunate leaving the amodiaquine for fear of side effects. Adherence to treatment is essential to ensure treatment effectiveness and to delay the development of resistance to artemisin-based combination treatments. If the observation by the prescribers is true, then most of these patients are on monotherapy with artesunate. The intended purpose of the combination therapy to improve therapeutic

effectiveness, delay the development and spread of drug resistance and reduce gametocyte carriage is at risk of being defeated. This has huge public health implications especially when we consider the fact that there are only a few efficacious drugs against malaria.

It is therefore important to determine the level of adherence among patients put on the combination therapy and to address the various factors and reasons for non-adherence if the new policy must succeed. Since the introduction of the combination therapy, there has not been any such known study in the district and in the country and therefore information from this study constitutes baseline information that would be useful to the National Malaria Control Programme in implementing the new drug policy.

The information would also be useful for prescribers and other service providers to improve upon adherence with the goal of improving treatment effectiveness and delaying the development of drug resistance.

1.3 Hypothesis

Patients in the Berekum District of Ghana are not adhering to artesunate-amodiaquine combination.

1.4 Research Questions:

1. Are patients put on artesunate-amodiaquine combination therapy adhering to the treatment regimens?

2. What are the reasons for non-adherence?
3. Do prescribers and dispensers give patients enough information on the combination drugs that would improve adherence?

1.5 Objectives

1.5.1 General Objective:

To assess patients adherence to artesunate–amodiaquine combination therapy for malaria in the Berekum District of Ghana

1.5.2 Specific Objectives:

1. To determine the proportion of malaria patients put on artesunate –amodiaquine combination treatment in the Berekum District who complete the full course of the treatment as prescribed.
2. To identify the reasons for non-adherence among malaria patients in the Berekum District put on artesunate –amodiaquine combination treatment.
3. To identify the health system related factors that influence patient's adherence to artesunate –amodiaquine treatment in the Berekum District.

CHAPTER TWO

LITERATURE REVIEW

2.1 Etiology and Pathogenesis of Malaria.

Malaria is a parasitic infection caused by a protozoan of the genus *Plasmodium*. In humans, the species causing diseases are *Plasmodium falciparum, Plasmodium malariae* (Gilles, 1993). The most common species is *Plasmodium falciparum* and is responsible for up to 80% of all malaria cases and 90% of malaria related deaths (Marsh, 1996). *Plasmodium vivax* is rare in Africa, particularly in West Africa because the Duffy blood antigen (the erythrocyte molecule to which its merozoites bind) being rare in the African population (Gilles, 1993). Transmission of the *Plasmodium* parasite is mainly from person to person through the bite of a female *Anopheles* mosquito (Mendis *et al.*, 2001). Occasionally transmission can occur through blood transfusion, inoculation of infected blood from one person to another, or transplacentally from an infected mother to her unborn child. The malaria parasite has a unique life-cycle adapted to man. The life cycles of all *Plasmodium* species transmitted to humans are the same with three reproductive phases.

The species differ in the time taken to complete each phase, which is also dependent on the ambient temperature. There is an initial phase consisting of a single cycle of sexual reproduction which occurs in the female mosquito and is

known as sporogony. During this process, sporozoites that infect man are produced. At 24°C sporogony takes 9 and 21 days in *Plasmodium falciparum* and in *Plasmodium malariae* respectively. When the infected mosquito bites man it injects the sporozoites into the blood. The sporozoites then travel to the liver where the next phase, a single cycle of asexual reproduction takes place in the human liver cell called. This stage is called pre-erythrocytic phase producing merozoites. The merozoites enter the blood when the liver cells burst and invade the red blood cells. The third or final phase known as erythrocytic cycle consists of several cycles of asexual reproduction and takes place in red blood cells. This phase produces new merozoites during each cycle which invade new red blood cells and start the erythrocytic cycle again. However, some of these merozoites differentiate into male and female gametocytes, which are taken up by the blood-sucking female *anopheles* to start the next sporogonic cycle in the mosquito.

The disease is characterized by fever, chills, headache and anorexia. However these symptoms are non-specific and are common to many diseases and conditions (Marsh, 1996). Malaria is a common cause of fever and illness in endemic areas, *but* it is not possible to apply any one set of clinical criteria to the diagnosis of all types of malaria in all patient populations (Marsh, 1996). The appropriateness of particular clinical diagnostic criteria varies from area to area according to the intensity of transmission, the species of malaria parasite, other prevailing causes of fever, and the health service infrastructure (WHO, 2000). The advent of HIV/AIDS

has changed the clinical epidemiology of malaria. HIV can increase the risk of malaria or the progression to severe malaria. It can also lead to an increase in the incidence of febrile disease that is not malaria (Nwanyanwu, 1997).

The transmission intensity varies from place to place depending on the proximity to breeding sites, rainfall pattern and the species of mosquitoes. In West Africa, the most effective vectors are *Anopheles gambiae* (WHO, 2007).

2.2 The Epidemiology of Malaria

A host of factors influence malaria epidemiology. These include host, environmental, socio-economic factors and climatic factors.The transmission intensity varies from place to place depending on the proximity to breeding sites, rainfall pattern and the species of mosquitoes (WHO, 2007).

The female *Anopheles* mosquito is the definitive host. There are about 400 different species of *anopheles,* but there are only about 60 that are vectors of malaria and of these, about 40 are important. The most important vectors in Africa are the *Anopheles gambiae* (most efficient vector) complex and *Anopheles funestus* (Service, 1996). Malaria epidemiology is influenced by vector type and density. Because of seasonality in climate, especially rainfall, mosquito abundance and malaria transmission tends to be seasonal. During the wet season, breeding sites are created in stagnant water leading to high mosquito populations and hence increased malaria transmission.

In highly endemic areas, newborn infants are relatively protected against mild clinical malaria and severe malaria, compared to older children (Brabin 1990). Most of the estimated over one million malaria deaths every year are in children up to 5 years old who live in areas of intense transmission of *P. falciparum*, especially in sub-Saharan Africa (WHO, 1996).

Malaria contributes to as much as half of all mortality in children aged between 1 month and 5 years living in endemic areas (Alonso *et al*. 1993).

Many studies have shown that malaria is not a common cause of death among children under the age of 6 months and that in malaria endemic areas; very young infants rarely contract malaria (Akum *et al*. 1996). This protection has mainly been attributed to transplacentally acquired malaria antibodies, as well as to other biological factors. However, after six months of age, unprotected infants suffer repeated and severe attacks that become milder as they grow older.

Differences in malaria parameters have been found in ethnic groups living in the same area. In the central region of Burkina Faso, the parasitologic data from five cross-sectional surveys in a rural area showed a lower *P. falciparum* prevalence in the Fulani ethnic group for all age groups and lower parasite densities in the Fulani children under 10 years of age. Moreover, the clinical episodes of malaria were markedly fewer among the Fulani than in the Mossi and Rimaibé Modiano *et al*. 1996). This was explained by genetic differences between groups.

However, it is also likely that cultural and socio-economic differences between ethnic groups contribute to marked differences in malaria risk, e.g. through differences in exposure or through differences in health seeking behaviors (Brinkmann, 1991).

Malaria is governed by a large number of environmental factors, which affect its distribution, seasonality and transmission intensity (Snow *et al*. 1999).

The peak in morbidity and mortality is generally obtained in the rainy season, the time when malaria transmission is at its peak, and the number of deaths during this period has been shown to be over threefold higher than in the rest of the year (Jaffar *et al.* 1997). In a 3-year prospective study of paediatric admissions to the Royal Victoria Hospital in Banjul, The Gambia, 83% of the 1525 children with cerebral malaria were admitted during the extended rainy season from July to December (Greenwood 1993).

High levels of parasiteamia are also found much more frequently in the rainy season than in the dry season, and the mean packed cell volumes are lower in the rainy season than in the dry season (Greenwood, 1993).

The relationship between malaria vector density and the distance of a settlement from a river is an important indicator of malaria transmission. In The Gambia ITN study, there was an inverse relationship between the numbers of mosquitoes in a village and the distance of settlement from the river (Lindsay *et al*., 1993).

In a comparative study of the presentation of severe malaria in urban and rural areas of Burkina Faso characterised by different levels of transmission, Modiano and others found that the prevalence of cerebral malaria was higher in the urban sample (53,6% versus 28,9%) while that of severe anaemia was higher in the rural patients (47,4% versus 14,8%). The urban area is characterised by relatively low transmission (1 to 10 infective bites per person per year), while the EIR in rural zones is 50 to 200 infective bites per person per year (Modiano *et al*.,1998).

The level of household income has been found to directly influence the purchase and prolonged use of bed nets. In their studies on use of malaria preventive measures in Malawian households, (Ziba *et al.* 1994), found respondents with moderate or high incomes compared to respondents from low-income households to be five times more likely to have ever purchased malaria preventive products. One of the most important determinants of human behaviour and knowledge is the formal educational level. It is considered as an indicator for people's socio-economic status and thus systematically explored in social studies.

It has been shown that knowledge of mosquitoes as the cause of malaria increased with education level and that men were more knowledgeable about the correct cause of malaria than women (Aikins *et al*., 1993).

2.3 The Global Burden of Malaria.

Malaria is a global public health problem, responsible for up to 500 million febrile illnesses and approximately 1 million deaths each year (Breman, *2001*). The burden of disease is primarily in sub-Saharan Africa, where approximately 90% of all malaria-related deaths occur in children younger than 5 years of age ((Greenwood *et al*., 2005)).Annually, malaria in pregnancy accounts for about 200,000 infant deaths (Gamble *et al*., 2007). Approximately 50 million women living in malaria endemic areas become pregnant every year. Fifty percent of these live in areas of intense *Plasmodium falciparum* transmission and are at rsik of the health impact of malaria (Menendez, 2006).

It is estimated that malaria cost Africa 12 billion US dollars in lost gross domestic product every year (WHO, 2001). Up to 40% of outpatient visits and between 10 and 15 percent of hospital admissions in Africa are attributed to malaria (WHO, 1999*)*. It is estimated that malaria alone accounts for an average of 3% of the total global disease burden (World Bank, 1993) and 36 million disability-adjusted life years (WHO, 1999). In the year 2000, malaria was responsible for 2.05% of the total global deaths and 9.0% of all deaths in Africa (WHO, 2002). About 2% of children who recover from cerebral malaria suffer brain damage (WHO/UNICEF, 2003) resulting in various degrees of learning disabilities.

2.4 The Impact of Malaria on Economic Growth

Africa spends about US$ 2 billion annually in managing malaria (WHO, 1997). Countries with substantial level of malaria grew 1.3% less per person per year in their national income for the period 1965 – 1990 and a 10% reduction in malaria was associated with 0.3% higher growth in the economy for the same period (Gallup *et al.,* 2001).

In various studies to explore the impact of macro policy on malaria morbidity across countries and the role of indirect effects of malaria on total productivity, it was found that a negative association exists between higher malaria morbidity and GDP per capita growth rate (McCarthy *et al.,* 2000). Most of the Sub-Saharan African countries studied incurred an average annual growth reduction of 0.55% (McCarthy *et al.,* 2000) and where malaria prospers most, human society have prospered least (Sachs *et al.,* 2002).

2.5 The Malaria Situation in Ghana

In Ghana, malaria accounts for about 45% of all outpatient visits, 25% of mortality in children under five years and 10% of maternal mortality (Ghana Health Service, 2005). It is a leading cause of mortality among children under five years old in the country (UNDP, 2000). The prevalence of malaria in Ghana is estimated at 15,344 per 100,000 and the malaria death rate for all ages is estimated at 70 per 100,000 (United Nations, 2003*).* Malaria is the leading cause of workdays and potential

income lost due to illness in Ghana, accounting for an average of 3 work days lost per fever episode by the patient and 2 work days by the caretaker (Asenso - Okyere *et al*., 1997*).*

2.6 Mode of Actions and Side Effects of Anti-malarial Drugs

2.6.1Chloroquine

Chloroquine is a 4-aminoquinoline that has been used extensively for the treatment and prevention of malaria for many years *(*Krugliak *et al*., 1991*)*. As is the case with other 4-aminoquinolines, it does not produce radical cure. Chloroquine interferes with parasite haem detoxification *(*Bray *et al*., 1998).

The principal limiting adverse effects in practice are the unpleasant taste, which may upset children, and pruritus, which may be severe in dark-skinned patients (Mnyika *et al.*, 1991). Other less common side effects include headache, various skin eruptions and gastrointestinal disturbances, such as nausea, vomiting and diarrhoea. More rarely central nervous system toxicity including, convulsions and mental changes may occur. Chronic use (>5 years continuous use as prophylaxis) may lead to eye disorders, including keratopathy and retinopathy. Other uncommon effects include myopathy, reduced hearing, photosensitivity and loss of hair. Blood disorders, such as aplastic anaemia, are extremely uncommon (Taylor *et al.*, 2004). Acute over dosage is extremely dangerous and death can occur within a few hours.

The patient may progress from feeling dizzy and drowsy with headache and gastrointestinal upset, to developing sudden visual disturbance, convulsions, hypokalaemia, hypotension and cardiac arrhythmias (Riou, 1998).

2.6.2 Amodiaquine

It is also a 4-aminoquinoline with a mode of action similar to that of chloroquine. It is effective against some chloroquine-resistant strains of *Plasmodium falciparum,* although there is cross-resistance *(*Bray *et al.,* 1998). The adverse effects of amodiaquine are similar to those of chloroquine. Amodiaquine is associated with less pruritus and is more palatable than chloroquine, but is associated with a much higher risk of agranulocytosis and, to a lesser degree, of hepatitis when used for prophylaxis *(*Hatton *et al.,* 1986*).*

2.6.3 Sulfadoxine

Sulfadoxine is a slowly eliminated sulfonamide. It is very slightly soluble in water. Sulfonamides are structural analogues and competitive antagonists of *p*-aminobenzoic acid. They work by competitively inhibiting dihydropteroate synthase, the bacterial enzyme responsible for the incorporation of *p*-aminobenzoic acid in the synthesis of folic acid. Side effects such as nausea, vomiting, anorexia and diarrhea may occur. Crystalluria causing lumbar pain, haematuria and oliguria may occur though rare. Hypersensitivity reactions may affect different organ

system. Cutaneous manifestations can be severe and include pruritus, photosensitivity reactions, exfoliative dermatitis, erythema nodosum, toxic epidermal necrolysis and Stevens-Johnson syndrome (Miller, 1986). Treatment with sulfadoxine should be stopped in any patient developing a rash because of the risk of severe allergic reactions *(*Bjorkman *et al.,* 1991*)*

2.6.4 Artemisinin

Artemisin also known as qinghaosu, is a sesquiterpene lactone extracted from the leaves of *Artemisia annua* (sweet wormwood). It has been used in China for the treatment of fever for over a thousand years. It is a potent and rapidly acting blood schizontocide and is active against all *Plasmodium* species *(*Price *et al.,* 2001).

It has an unusually broad activity against asexual parasites, killing all stages from young rings to schizonts. In *P. falciparum* malaria, artemisinin also kills the gametocytes – including the stage 4 gametocytes, which are otherwise sensitive only to primaquine. Artemisinin and its derivatives inhibit an essential calcium adenosine triphosphatase, PfATPase *(*Eckstein-Ludwig et al., 2003).

Artemisinin and its derivatives are safe and remarkably well tolerated (Price *et al.,* 2001). There have been reports of mild gastrointestinal disturbances, dizziness, tinnitus, reticulocytopenia, neutropenia, elevated liver enzyme values, and electrocardiographic abnormalities, including bradycardia and prolongation of the QT interval, although most studies have not found any electrocardiographic

abnormalities. The only potentially serious adverse effect reported with this class of drugs is type 1 hypersensitivity reactions in approximately 1 in 3000 patients (Leonardi *et al.,* 2003) Neurotoxicity has been reported in animal studies, particularly with very high doses of intramuscular artemotil and artemether, but has not been substantiated in humans (Hien *et al*., 2003*).* Similarly, evidence of death of embryos and morphological abnormalities in early pregnancy have been demonstrated in animal studies (Hien *et al.,* 2003).

2.6.5 Quinine

This is an alkaloid derived from the bark of the *Cinchona* tree. Four antimalarial alkaloids can be derived from the bark: quinine (the main alkaloid),quinidine, cinchonine and inchonidine. Quinine is the L-stereoisomer of quinidine. Quinine acts principally on the mature trophozoite stage of parasite development and does not prevent sequestration or further development of circulating ring stages of *P. falciparum*. Like other structurally similar antimalarials, quinine also kills the sexual stages of *Plasmodium vivax, Plasmodium malariae* and *Plasmodium ovale*, but not mature gametocytes of *Plasmodium falciparum*. It does not kill the pre-erythrocytic stages of malaria parasites. The mechanisms of its antimalarial actions are thought to involve inhibition of parasite haem detoxification in the food vacuole, but are not well understood *(*Bruce-Chwatt *et al.,* 1987).Administration of quinine or its salts regularly causes a complex of symptoms known as cinchonism,

which is characterized in its mild form by tinnitus, impaired high tone hearing, headache, nausea, dizziness and dysphoria, and sometimes disturbed vision (Taylor *et al.*, 2004).

More severe manifestations include vomiting, abdominal pain, diarrhoea and severe vertigo. Hypersensitivity reactions to quinine range from urticaria, bronchospasm, flushing of the skin and fever, through antibody-mediated thrombocytopenia and haemolytic anaemia, to life threatening haemolytic-uraemic syndrome. Massive haemolysis with renal failure ("black water fever") has been linked epidemiologically and historically to quinine, but its etiology remains uncertain (Bruce-Chwatt *et al.,* 1987). The most important adverse effect in the treatment of severe malaria with quinine is hyperinsulinaemic hypoglycemia (White *et al.*, 1983). This is particularly common in pregnancy (50% of quinine-treated women with severe malaria in late pregnancy). Intramuscular injections of quinine dihydrochloride cause pain, focal necrosis and in some cases abscess formation, and in endemic areas are a common cause of sciatic nerve palsy. Hypotension and cardiac arrest may result from rapid intravenous injection (Bruce-Chwatt *et al.*, 1987).

Quinine causes an approximately 10% prolongation of the electrocardiograph QT interval – mainly as a result of slight QRS widening (White et al., 1983). The effect on ventricular repolarization is much less than that with quinidine. Quinine has been used as an abortifacient, but there is no evidence that it causes abortion,

premature labour or fetal abnormalities in therapeutic use. Overdosage of quinine may cause oculotoxicity, including blindness from direct retinal toxicity, and cardiotoxicity, and can be fatal (Boland *et al.,* 1985). Cardiotoxic effects are less frequent than those of quinidine and include conduction disturbances, arrhythmias, angina, hypotension leading to cardiac arrest and circulatory failure (White *et al.,* 1983).

2.7 Resistance to Anti-malarial Drugs

The development of resistance can be considered in two parts: the initial genetic event, which produces the resistant mutant; and the subsequent selection process in which the survival advantage in the presence of the drug leads to preferential transmission of resistant mutants and thus the spread of resistance (Lipsitch *et al.,* 1997). In the absence of the antimalarial, resistant mutants may have a survival disadvantage. This resistance mechanism may result in a decline in the prevalence of resistance once drug pressure is removed (Lipsitch *et al*., 1997). Resistance to one drug may select for resistance to another where the mechanisms of resistance are similar (Bonhoeffer *et al*., 1997). This is called cross-resistance. There are many similarities between resistance to antimalarials and antibiotic. In particular resistance to antimalarials and resistance to antituberculosis drugs are similar, in the sense that in both situations transferable resistance genes are not involved in the emergence of resistance (Austin *et al.*, 1999).

Various factors determine the propensity for antimalarial drug resistance to develop *(*White *et al.,* 1999). These include the intrinsic frequency with which the genetic changes occur, the degree of resistance (the shift in the concentration-effect relationship, conferred by the genetic change), the fitness cost of the resistance mechanism, the proportion of all transmissible infections that are exposed to the drug (the selection pressure), the number of parasites exposed to the drug, the concentrations of drug to which these parasites are exposed , the pharmacokinetic and pharmacodynamic properties of the antimalarial, individual (dosing, duration, adherence) and community (quality, availability, distribution) patterns of drug use, the immunity profile of the community and the individual, the simultaneous presence of other antimalarials or substances in the blood to which the parasite is not resistant (White *et al*., 1999).

2.7.1Chloroquine Resistance

The first reports of chloroquine resistance occurred in Thailand and Colombia in the late 1950s , around 12 years after the drug's introduction. By 1980, all endemic areas in South America were affected, and by 1989, most of Asia and Oceania (Vieira, 2004). In Africa, chloroquine resistance emerged in 1978 in the east, and gradually spread westwards through the 1980s ((*(*Wellems, 2001). Resistance has now been documented in all falciparum-endemic areas except Central America and the Caribbean (Wongsrichanalai *et al.,* 2002) Recent molecular studies favour

importation of chloroquine resistance to Africa from East Asia Chloroquine resistance has emerged independently less than ten times in the past 50 years *(*Wellems, 2001).

2.7.2 Sulfadoxine-pyrimethamine Resistance

Resistance to pyrimethamine emerged rapidly after its deployment for treatment, prophylaxis and, in some areas, mass treatment in the 1950 s. Resistance to both components of sulfadoxine-pyrimethamine was noted shortly after this drug was introduced over a decade later(Hurwitz et al., 1981). In South-East Asia this occurred on the Thai-Cambodian border in the mid-1960s. Resistance became an operational problem in the same area within the few years of the introduction of sulfadoxine-pyrimethamine to the malaria control programme in 1975 (Hurwitz et al., 1981). High-level resistance is found in many parts of South-East Asia, southern China and the Amazon basin, and lower levels of resistance are seen on the coast of South America and in southern Asia and Oceania (Plowe et al., 2004). In eastern Africa, sulfadoxine-pyrimethamine sensitivity was observed to be declining in the 1980s and resistance has progressed westwards across Africa over the last decade. Clinical failure rates of more than 25% have already been reported in Liberia (Checchi *et al.*, 2002), Guinea Bissau (Kofoed *et al.*, 2002) and Malawi (Plowe, 2004) now have high-level resistance with high-treatment failure rates n

children. Recent molecular evidence suggests a common South-East Asian origin of the resistant *P. falciparum* parasites (Hurwitz *et al*., 1981).

2.7.3 Quinine Resistance

The first reports of possible quinine resistance occurred in Brazil almost 100 years ago. Even today, however, clinical resistance to quinine monotherapy is reported only sporadically in South-East Asia and western Oceania, and resistance in Africa and South America is much less frequent (Wernsdorfer,1994).Widespread use of quinine in Thailand in the 1980s led to significant reduction in its sensitivity (Wernsdorfer,1994). Mutations associated with chloroquine resistance are believed to be associated with reduced susceptibility to quinine, (Zalis, 1998).

2.7.4 Artemisinin Resistance

Except in an animal model, there have been no confirmed reports of artemisinin resistance in malaria parasites that infect humans (WHO, 2004). The characteristics of the drug, namely short elimination half-life, rapidity of action and ability to reduce gametocyte carriage, should delay the onset of significant resistance. Artemisinin derivatives are associated with high recrudescence rates (~10%) after monotherapy, so are usually combined with longer-acting antimalarials for clinical treatment. These recrudescence, however, are not a result of resistance (Anderson, 2004).

2.8 The Issue of Adherence

2.8.1 The Need for Adherence

Adherence is defined as the extent to which a patient fulfills the intention of the prescriber in taking medication (McGavock, 1996). In sub-Saharan Africa, there are several problems associated with the treatment of malaria. These include effectiveness, financial and physical access, safety, tolerability, and adherence (Kokwaro, 2005). Even in an ideal situation in which the first three factors are not a problem, adherence would still be problematic, especially when dealing with rural populations in developing countries, where relief of symptoms of malaria is often interpreted as cure and where there is, therefore, great reluctance to continue taking the rest of the medication as prescribed (Kokwaro,2005). It must however be stated that adherence is a critical component of the overall effectiveness of a drug (Amin *et al.,* 2004). There is growing consensus that artemisinin based combination therapies (ACTs) are the best treatment for uncomplicated falciparum malaria (WHO, 2001). They have proved to be highly efficacious, rapidly effective, and have few side effects in extensive clinical trials (Nosten *et al.,* 2000; *von* Seidlein *et al.,* 2000*;* Dorsey *et al.,* 2003). There have been more clinical trials on artemisinin and its derivatives, either alone or in combination, than with any other antimalarial drugs (Myint *et al*., 2004). Artemisinin-based combination therapies also delay the emergence and spread of resistance and reduce the transmission of falciparum

malaria in low transmission settings (Price *et al*., 1996; Brockman *et al.,* 2000). Indeed many countries have introduced new, effective, but more expensive antimalarials. There is however concern that the high levels of efficacy observed in clinical trials may not be translated into effectiveness in the normal context of use because of non-adherence (Yeung *et al*., 2005). With the acceptance of combination therapy, especially that which contains artemisinin derivatives, as the way forward in confronting the serious problem of drug-resistant *Plasmodium falciparum* malaria (White *et al.*, 1999), the issue of adherence must be addressed if we are to succeed in reducing the burden of malaria and in delaying resistance to these combination therapies.

Patient adherence is a major determinant of the therapeutic response to antimalarial drugs, as most treatments are taken at home without medical supervision (Yeung *et al.,* 2005). Non-adherence may result in patients taking sub-optimal doses; a situation that may favour the development of resistance and non-recovery from the illness. With the limited efficacious drugs available for the treatment of malaria, we cannot afford these grave consequences of non-adherence.

2.8.2 Factors Affecting Adherence

Patient, provider and drug related factors influence adherence. Providing the drug through trained community health workers (Pagnoni *et al.,* 1997, Kaduna *et al.,* 2000), training shopkeepers (Marsh *et al.,* 1999), and wholesalers (Tavrow *et al.,*

2003) all improve adherence. Several drug-associated factors may affect adherence (McGavock, 1996). These include appropriateness of the prescription, side effects, lose regimen, drug presentation and formulation, number of drugs prescribed concurrently, and duration of treatment (Kokwaro, 2005). Adherence to antimalarial drugs has been shown to be better with effective treatments, increased knowledge by the health care professional, better medication packaging, and provision of correct dosages (Yueng *et al*., 2005). Artemisinin-based combination therapy need to be given for at least 3 days to maximize the number of parasites killed (Kokwaro, 2005). Adherence is a critical component of the overall effectiveness of a drug (Amin *et al*., 2004). Complicated dose regimens may compromise effectiveness through reduced adherence (Kokwaro, 2005). Dispensing prepacked unit doses (Yeboah-Antwi *et al.*, 2001*)* with improved labeling (Agyepong

et al., 2002) have both been shown to enhance the proportion of patients who receive and complete the recommended dose.

In Nigeria, adherence to chloroquine reached 73.3% after introducing a combination of illustrated dosing instructions and health worker counseling (Okwonko *et al*., 2001). In Ghana, adherence reached 91% through an intervention promoting prepackaged tablets (Ansah *et al.*, 2001).

CHAPTER THREE

MATERIALS AND METHODS

3.1Study Area

The study area is Berekum District in the Brong-Ahafo Region of Ghana. This district wa purposefully selected for reasons of proximity and also because it was among the first districts in the country to introduce the new policy using artesunate-amodiaguine combination for the treatment of malaria. Berekum District is one of the nineteen administrative districts in the Brong Ahafo Region of Ghana. It has a total surface area of 1094.2 sq.km. The estimated population based on the 2000 census with a growth rate of 2.5% is approximately 110,827 for the year 2007. Male to female ratio in the district is 1:1.1. The inhabitants are mainly Brongs with other ethnic groups from all over the country. Over 55% of the population live in the rural area.

It is bounded on the north, by Jaman district, Wenchi and Tain districts to the northeast, Dormaa district to the southwest, Sunyani to the southeast and Asunafo to the south. Geographically, Berekum is located on latitude 07.29N and longitude 02.34W.

The District has been divided into three sub-districts; Berekum North, Berekum South and Jinijini Sub-districts. The district capital, Berekum is located approximately 30 kilometres west of the regional capital, Sunyani.

The district is about 800-900m above sea level and lies in the equatorial double rainfall region with an average rainfall of 203cm. The raining seasons are March to July and September through November. These are also the peak malaria transmission months.

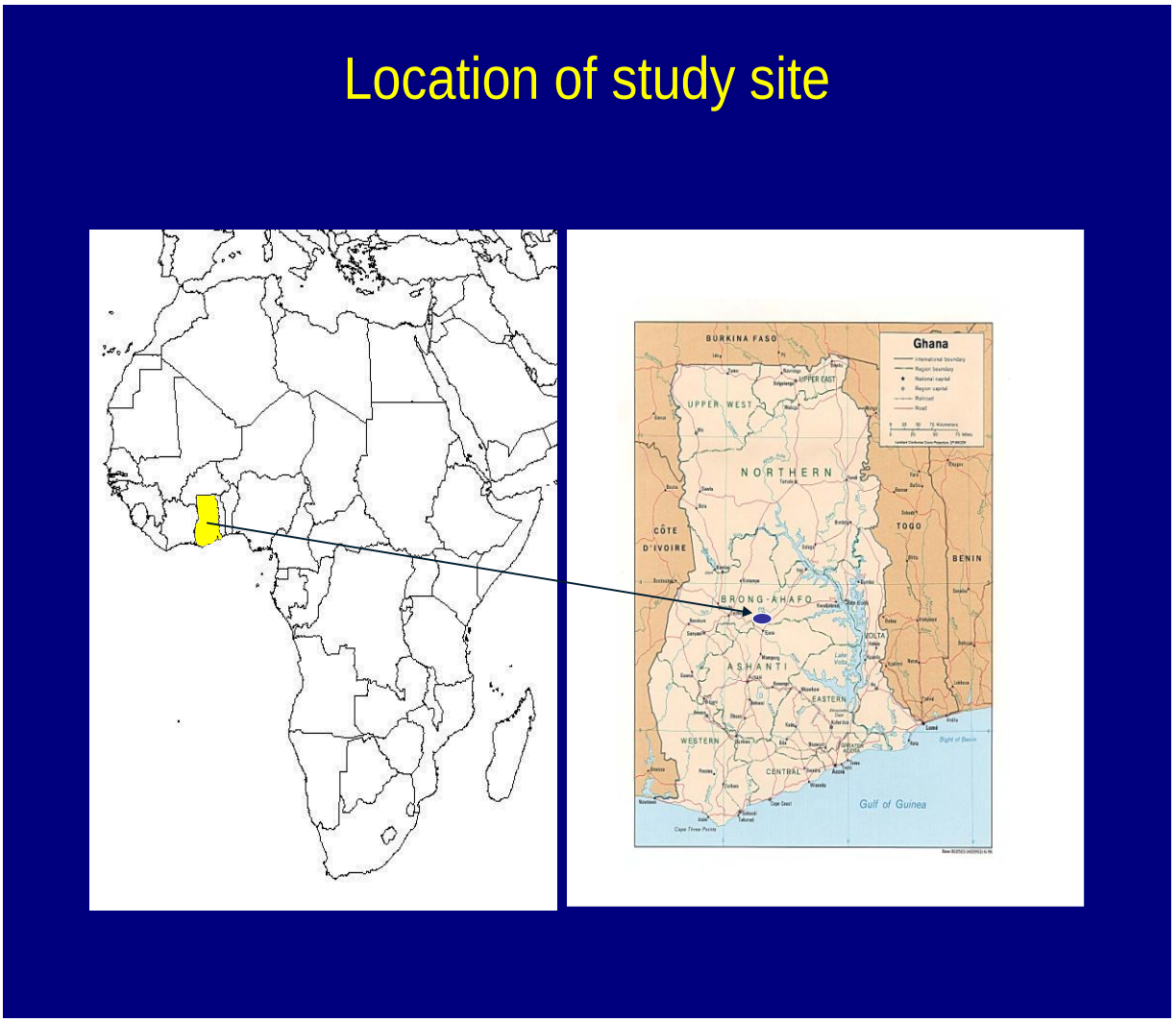


Fig. 3.1 Map Of Africa Showing The Location Of Ghana And On The Left Is The Map Of Ghana With The Arrow Pointing To Berekum, The District In Which The Study Was Conducted.

3.2 Study Design

The study was a cross sectional study in adults. Data collection was done between 22nd August, 2007 and 18th November, 2007

3.3 Study Population

The study population included adults ages 18 years and above living in Berekum District and had health insurance.

3.4 Study Unit

The study unit is an individual age 18 years and above living in Berekum District, who had health insurance and who attended clinic at any of the district health facilities from 22nd August, 2007 to 18th November, 2007 and was diagnosed as having malaria and was put on artesunate-amodiaquine combination therapy.

3.5 Sample Size and Sampling Procedure

The occurrence of side effects of the combination therapy is used to power the study. Given a power of 80%, at 95% confidence interval and a non-adherence of 35% among those who did not develop side effects (non-exposed) and a minimum odds ratio of 2, an initial sample size of 292 was calculated for the study (Epi info version 3.3.2). Adding 10% to the initial sample size to take care of non response, the final sample size that ought to have been used for the study is 321. However, a total of 326 eligible patients consisting of 235 females and 91 males were

interviewed. Patients who reported to any of the district health facilities and were diagnosed as having malaria and put on artesunate-amodiaquine combination therapy were selected by convenience sampling. Their addresses were obtained from their medical records. Using these addresses we traced them to their houses after the fourth day of treatment. We counted the number of remaining tablets and administered semi-structured questionnaires to collect data on various demographic and socio-economic variables, adherence, and reasons for non-adherence, side effects experienced, and the information given to patients by health care providers. The data was coded, entered into the computer and analyzed using *E*pi-*Info version 3.3.2;* 2005. Descriptive statistical analysis was done for the socio-demographic variables by calculating simple proportions. Odds ratios were calculated and Chi square analysis was done for p-values and 95% Confidence intervals.

Adherence was measured by patients self report together with tablet count at the time of interview. Patients would be deemed to have adhered to the treatment if as per the questionnaire they report that they have taken the medications as prescribed and there is neither artesunate nor amodiaquine tablets among the drugs prescribed still in their possession. The combination therapy is supposed to be taken as a divided dose taken 12 hourly for duration of three days.

3.6 Variables under Study

The variables under study were age, sex, educational level, tribe, religion, occupation, marital status, side effects and health system factors which are the dependent variables and treatment adherence, reasons for non – adherence which are the independent variables.

3.7 Operational Definitions of Study Variables

Age:	number of completed years of the respondent at the time of the study
Sex:	gender of the respondent.
Occupation:	the work or job of the respondent.
Marital status:	whether or not the respondent is married, single or divorced
Religion:	the religious group to which the respondent belongs.
Educational level:	the highest educa 13 attainment of the respondent.
Tribe:	the ethnic group to which the respondent belongs.
Adherence:	the extent to which the patient takes the drugs as prescribed.
Reasons for non-adherence:	what made the patient not to take the drugs as prescribed.

Side effects:	any adverse event following the ingestion of the drugs and thought to be due to the drugs
Health system factors:	the information given by the prescriber and dispenser to the patient
Tablet count	Number of artesunate and amodiaquine tablets available at the time of the interview.

3.8 Data Collection Methods

Ten people were trained to sample eligible patients from the health facilities and to collect data in the field. Semi-structured questionnaires were administered to study participants to collect data on various demographic and socio-economic status of the study participants, adherence, and reasons for non-adherence, side effects experienced, number of tablets of the combination therapy still in the possession of study subjects and the information given to patients by health care providers.

3.9 Data Management and Analysis

Quality checks were done by assessing the completeness and consistency of completed questionnaires. The data was coded and entered into the computer. Data analysis was done using Epi-*Info version 3.3.2;* 2005 after data cleansing. Descriptive statistical analysis was done for the demographic variables by calculating simple proportions. For dichotomous variables such as the health

system related factors influencing adherence, odds ratios with their 95% confidence intervals and p-values were calculated.

3.10 Ethical Issues

Various ethical issues were addressed. The study was well explained to the participants and written informed concern was obtained from each of them. We emphasized the fact that no one was under any obligation to participate in the study.

3.11 Limitation

The best way to assess adherence is by measuring bio-availability of the drugs. However, this was not done because of resource constraints.

CHAPTER FOUR

RESULTS

In all, 326 people who were put on artesunate-amodiaquine combination therapy were interviewed. They consisted of 235 females and 91 males. Their ages were between 18 years and 73 years. The socio-demographic characteristics assessed were age, educational levels marital status, occupation, and religion.

One hundred and fifty four subjects representing, 47.2% of the study participants adhered to the combination therapy whiles 52.8% did not adhere as shown in Table 4.1 below.

Table 4.1: Adherence of Malaria Patients to Artesunate-amodiaquine Combination Therapy in the Berekum District of Ghana, 2007

Adherence	Number	Percentage
Yes	154	47.2
No	172	52.8
Total	**326**	**100.0**

There was no statistically significant difference in adherence between males and females as shown in Table 4.2 below.

Table 4.2: Sex Distribution of Malaria Patients their Adherence levels to Artesunate-amodiaquine Combination Therapy in the Berekum District of Ghana, 2007

Factor	Adherent	Non-Adherent	OR (95% CI)	P-value
Male	49	42	1.44 (0.86-2.42)	0.14
Female	105	130		

There was no statistically significant association between age and adherence.

Table 4. 3: Age Distribution of Malaria Patients and their Adherence levels to Artesunate –amodiaquine Combination Therapy in the Berekum District of Ghana

Age group	Adherent	Non-Adherent	OR (95% CI)	P-value
18-22	26	20	1.54 (0.79-3.030	0.17
23-27	25	18	1.66(0.83-3.34)	0.12
28-32	8	20	0.42(0.16-1.05)	0.07
33-37	10	12	0.93(0.36-2.38)	0.86
38-42	14	10	1.62 (0.65-4.07)	0.26
43-47	10	10	1.13 (0.42-3.02)	0.80
48-52	17	17	1.13 (0.53-2.43)	0.73
$\geq$ 53	44	65	0.66 (0.40-1.08)	0.08

Table 4.4: Levels of Education of Malaria Patients and their Adherence levels to Artesunate-amodiaquine Combination Therapy in the Berekum District of Ghana, 2007

Level of education	Adherent	Non-Adherent	OR (95% CI)	P-Value
None	47	72	0.61 (0.38-0.99)	0.04
Primary School	28	24	1.37 (0.73-2.59)	0.37
Junior High School	47	41	1.40 (0.83-2.36)	0.23
Senior High School	24	19	1.47 (0.74-2.36)	0.30
Tertiary Education	8	16	0.53 (0.20-1.37)	0.23

Those who had no formal education were less likely to adhere to the treatment and this finding was statistically significant ($P<0.05$). Again those had tertiary education were less likely to adhere to the treatment. However, this finding was not statistically significant ($P>0.05$). Those who had primary education, Junior High School education or Senior High School education were more likely to adhere to the treatment. Again these findings were not statistically significant as shown by the respective p-values in table 4.4

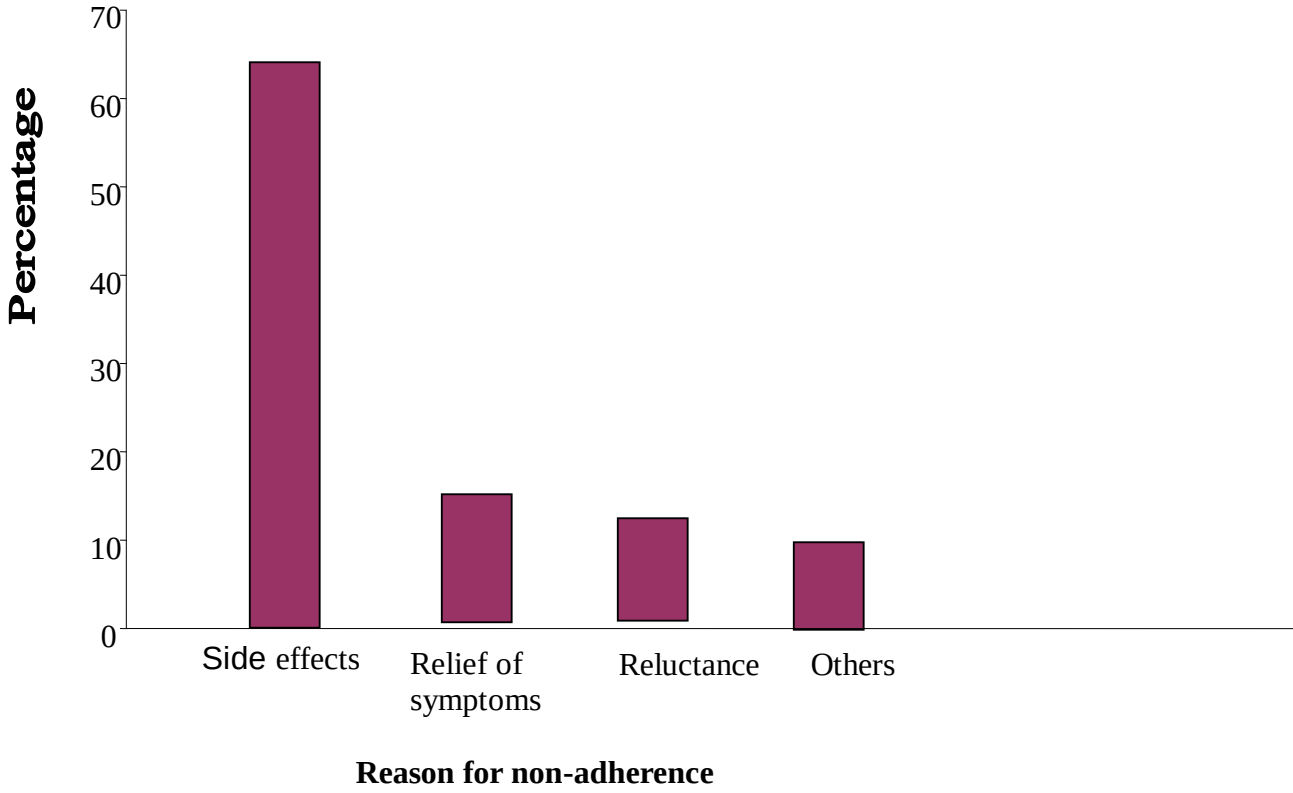
Table 4.5: Occupations of Malaria Patients and their levels of Adherence to Artesunate-amodiaquine Combination Therapy in the Berekum District of Ghana, 2007

Occupation	Adherent	Non-adherent	OR (95% CI)	P-Value
Farmer	70	78	1.00 (0.63-1.59)	0.93
Teacher	4	12	0.36 (0.09-1.59)	0.06
Apprentice	8	11	0.80 (0.29-2.22)	0.82
Trader	24	24	1.14 (0.59-2.19)	0.80
Seamstress	5	1	5.74 (0.64-131.27)	0.08
Artisan	4	16	0.26 (0.07-0.85)	0.02

Artisans were less likely to adhere to the treatment compared to those with other occupations and this finding was statistically significant (P<0.02). Also, teachers and apprentices were less likely to adhere to treatment but these findings were not statistically significant. Traders and seamstresses were more likely to adhere to the treatment compared to those with other professions. Again these findings were not statistically significant as shown by the odds ratios and the P-values in the table above.

Side effects were the main reason for non-adherence. Over 60% of those who did not adhere did so because of side effects. Early relief of symptoms and mere reluctance to complete treatment were also reasons for non-adherence.

Figure 4.1: Reason for non-adherence to Artesunate -amodiaquine Combination Therapy for Malaria in the Berekum District, Ghana



The main side effects of the drugs experienced were weakness and dizziness as shown in the table below. In all 54.3% of all study subjects experienced side effects.

Table 4.5: Types of side effects experienced by malaria patients who were put on artesunate- amodiaquine combination therapy in the Berekum District of Ghana, 2007

Type of side effects experienced	Number	Percentage (%) N=326
Weakness	108	33.1
Dizziness	43	13.2
Insomnia	11	3.4
Itching	9	2.8
Itching	6	1.8
Total	**177**	**54.3**

Table 4.6: Side Effects and Adherence among Patients put on Artesunate-Amodiaquine Combination Therapy for Malaria in the Berekum District of Ghana, 2007

Had side effects	Non-Adherent	Adherent	OR (95% CI)	P-value
Yes	110	67	2.3 (1.44-3.69)	0.00
No	62	87		

Those who experienced side effects were 2.3 times less likely to adhere to the therapy as those who did not experience side effects and this association was statistically significant ($P<0.05$)

Majority of the study participants were not educated on the various issues regarding the combination therapy as shown in the table below.

Table 4.7: Proportion of Patients put on Artesunate-Amodiaquine Combination Therapy Counseled by Health care Providers in the Berekum District of Ghana

What they were told	Number (%) =326
Told to take drugs after meals	318 (97.5)
Told about possible side effects	75 (23.0)
Advised to sleep under insecticide treated bed nets	162 (49.6)
Told the names of the drugs	153 (46.9)
Advised to return if the condition worsened	100 (33.1)
Had opportunity to ask questions about treatment	40 (12.3)
Told what to do if they vomited after a dose of treatment	20 (6.1)
Told to take drugs alone and not share it with others	185 (56.7)
Told to take drugs with water	280 (85.9)
Told to take two daily doses of the drug	306 (93.9)
Received treatment for other conditions in addition to the combination treatment for malaria	134 (41.1)

Less than fifty percent of the patients are being told about possible side effects, the names of the drugs, to return if their conditions worsened, and what to do if they vomited. Only a small proportion of patients had the opportunity to ask questions and more than a third of the patients received treatment for other conditions in addition to the combination treatment for malaria.

Table 4.8: Instruction to Patients by Healthcare Providers and Adherence in the Berekum district of Ghana, 2007.

Instruction	Non-Adherent	Adherent	OR (95% CI)	P-value
Advised to sleep under insecticide treated bed nets				
Yes	31	131	0.04 (0.02-0.07)	0.000001
No	142	23		
Told the names of the drugs				
Yes	18	135	0.02 (0.01-0.07)	0.000001
No	154	19		
Received treatment for other conditions in addition to malaria			2.74 (1.69-4.47)	0.00001
Yes	90	44		
No	82	110		

Patients who were advised to sleep under insecticide treated nets or told the names of the drugs were more likely to adhere to the treatment. These findings were statistically significant. Those who received treatment for other diseases in addition to other diseases were less likely to adhere to the artesunate–amodiaquine combination treatment compared to those who had only the combination therapy and this finding was statistically significant ($P<0.05$).

Table 4.9: Instructions to Patients by Healthcare Providers and Adherence in the Berekum district of Ghana, 2007

Factor	Non-Adherent	Adherent	OR (95% CI)	P-value
Told to take drugs after meals				
Yes	165	153	0.15(0.01-1.26)	0.05
No	7	1		
Told about possible side effects				
Yes	39	36	0.96(0.56-1.66)	0.88
No	133	118		
Told not to share the drugs with others				
Yes				
No	89	96	0.65 (0.41-1.03)	0.05
	83	58		
Told to take two daily doses of the drug				
Yes	157	149	0.35(0.11-1.07)	0.07
No	15	5		
Told what to do if they vomited after a dose of treatment				
Yes	9	11	0.72 (0.26-1.93)	0.47
No	163	143		
Told drugs were intended to treat malaria				
Yes	62	63	0.81(0.51-1.31)	0.37
No	110	91		
Had opportunity to ask questions about the treatment				
Yes	23	17	1.24(0.61-2.56)	0.52
No	149	137		

Patients who were told to take drugs after meals, about the possible side effects, not to share the drugs with any one, to take two daily doses of the drugs, what to do if they vomited after treatment or told that the drugs were intended to treat malaria were more likely to adhere to the treatment even though these findings are not

statistically significant. However, those had the opportunity to ask questions were less likely to adhere to the treatment. Again this finding was not statistically significant ($P>0.05$).

CHAPTER FIVE

DISCUSSIONS, CONCLUSIONS AND RECOMMENDATIONS

5.1 Discussions

Adherence is an important aspect of the effectiveness of a drug. In our current study, 47.2% of study participants adhered to the artesunate-amodiaquine combination therapy. This compares favorably with the findings from a study on adherence to sulphadoxine pyremethamine-artesunate combination therapy in Zambia in which only 39% of the patients were adherent (Depoortere *et al.,* 2004). However, the study in Zambia was conducted among refugees which cannot easily be compared to our study which was done in a stable population. In another study in Tanzania where the patients were followed up after 24 hours, adherence to sulphadoxine pyremethamine artesunate combination therapy was 75% (Kachur *et al.,* 2004). Findings from several cross-sectional studies have demonstrated that only a small fraction of children received adequate doses of chloroquine. The proportion of children who received complete treatment with chloroquine ranged from 30% in Togo (Deming *et al.,* 1989) to 12% in western Kenya (Ruebush *et al.,* 1995) and 7% in Malawi (Slutsker *et al.,* 1994). Again these findings cannot easily be compared with the findings in our study because of differences in the study designs. Patients' adherence is a major determinant of the therapeutic response to

antimalarial drugs (Yeung *et al.*, 2005). Indeed, adherence is a critical component of the overall effectiveness of a drug (Amin *et al.,* 2004). However, with the current level of adherence, clinical and parasitological cure may not be achieved in most adult patients. Non-adherent patients who do not recover may blame their situation on the drug. They may think that the drug is not effective and this may influence their adherence to future treatment. Also of concern is the fact that, the low level of adherence if not addressed could compromise the ability of the combination therapy to delay the development of resistance. Sub-optimal doses of the drug provide a conducive environment both for the development of resistance and its spread. The low level of adherence to artesunate-amodiaquine combination therapy may also be reflected in other combination therapies in the country. It is possible that, adherence to combination therapies for tuberculosis and HIV is also low. If the level of adherence is equally low with the treatment to these two diseases then we are in a public health emergency. With tuberculosis, such a situation will lead to the development of multi-drug resistance and worse still extreme drug resistance. With HIV, the development of resistance to antiretroviral drugs would make it difficult to treat the millions of HIV positive individuals in the world.

Although a greater proportion of males adhered to treatment compared to females, the findings were not statistically significant. Also, age was not statistically associated with adherence. The statistically significant finding that study participants who had no formal education were less likely to adhere to the treatment

could be due to their limited knowledge about the drug and the need for adherence. It is possible that these people are less informed about these medications and the various issues regarding adherence. Being an artisan was also significantly associated with non-adherence. Most of these artisans have very low education and usually work under someone. With limited understanding of how these drugs work, they are likely to stop taking the drugs as soon as the start feeling better.

Side effects were the major reasons for non-adherence among study participants. This finding was statistically significant. This is consistent with the findings in a review of the literature on antimalarial drug adherence. In this review, side effects were identified as important drug related factors affecting the level of adherence (McGavock, 1996). The occurrence of side effects may be interpreted by the patient as worsening of the condition and non-effectiveness of the drug –a recipe for non-adherence. Patient counseling about possible side effects is important in preparing them as to what to expect. If patients are appropriately counseled on what side effects to expect they will be in a better position to handle the situation. However, less than a quarter of study participants were told what side effects to expect. The rest took the drugs without any clue of the possible side effects and what to do under such circumstances. This may explain the high level of non-adherence among those who experienced side effects. Indeed non-adherence was less among those who were told about the possible side effects even though this finding was not

statistically significant. The issue of side effects ought to be addressed if we are to improve on the adherence.

The commonest side effect was weakness. Independent of any drug, malaria may present with weakness. Any drug induced weakness would aggravate the situation and this may discourage the patient from continuing with the medication. Also, malaria patients may not eat well because of nausea and this can make them weak. Advising patients to take the drugs with food may be useful in reducing the level of weakness experienced.

Over a third of the study participants did not adhere to the treatment for reasons such as relief of symptoms, reluctance to continue treatment among others. This is similar to findings from other studies on adherence to antimalarial drugs. In one such study in Kenya, it was found that among rural populations relief of symptoms of malaria is often interpreted as cure and therefore, great reluctance to continue taking the rest of the medications as prescribed (Kokwaro, 2005). This may be a reflection of the level of education provided by the prescriber to the patient. It is important to educate patients on the need to complete treatment even if they are relieved of the symptoms. Adhering to the treatment is important for clinical but more so parasitological cure. The exposure of parasites to sub-optimal doses provides an opportunity for the development of resistance.

Most patients put on the combination therapy are not adequately counseled or provided with adequate information by the health system to help them to adhere. This coupled with the fact that only a small fraction of them (6.2%) had the opportunity to ask questions on issues they did not understand may explain the low levels of adherence. Patients who do not understand what is expected of them may take the medication in a non-adherent manner. The importance of ensuring that patients understand what is expected of them in achieving adherence cannot be overstated. Patients who were counseled to take drugs with meals, told about possible side effects, told what to do if they vomited, told to take drugs alone and not share it with anyone, told to take drug with water or told to take two daily dose were more likely to adhere to the treatment than their counterparts who were not told same even though these associations were not statistically significant. Statistically significant positive association was found between advising patients to sleep under insecticide treated bed nets, telling patients the names of the drugs and adherence. Health care providers who advised patients to sleep under insecticide treated bed nets or told them the names of the drugs may also counsel the same patients on the other issues such as side effects. Such providers in an attempt to get patients to understand are likely to offer an opportunity to patients to ask questions. All these would go a long way to improve adherence and this may explain the significantly positive statistical association.

Sleeping under insecticide treated bed nets is a very effective strategy in preventing malaria. However only about 50% of the study participants were advised to sleep under insecticide treated bed nets. The other 50% were not told anything about bed nets. This constitutes a missed opportunity in the effort to increase bed net use to prevent malaria. Prescribing artesunate-amodiaquine with other medications was significantly associated with non-adherence. The issue of polypharmacy may have to do with the prescriber not being sure whether he or she is dealing

with malaria or any other disease. In an attempt to treat all the possible diseases under consideration, they may prescribe many drugs. The patient then has to deal with many drugs and this situation favors non-adherence. The patient may get fed up with the many drugs that must taken daily or may make mistakes in taking the medications.

5.2 Conclusions

The proportion of patients who adhered to the combination therapy is lower than expected. At the current adherence level of 47.2%, clinical and parasitological cure may not be achieved for most adult patients. Also, the ability of the combination therapy to delay the development of drug resistant malarial parasites may be compromised if the low level of adherence is not addressed. Similarly low adherence levels may also be associated with combination therapies for tuberculosis and HIV.

The main reasons for non-adherence were side effects, early relief of symptoms and mere reluctance to complete treatment were the major reasons for non-adherence. The main side effect was weakness.

Finally, health service provider factors such as inadequate counseling of patients plays an important role in bringing about the high level of non-adherence. Patients are not given adequate information that will help them to adhere. Health workers are also missing the opportunity to educate patients on the use of insecticide treated bed nets.

5.3 Recommendations

1. Health professionals in the district who are involved in managing malaria should be retrained to provide adequate and appropriate counseling to patients. They should be trained to provide effective counseling on side effects and what to do to minimize these side effects. This training should also emphasize the need to educate patients on the use of insecticide treated bed nets.
2. Since side effects are very common, there is the need to intensify routine monitoring of adverse drug reactions resulting from the combination therapy in the district so as to provide information for intervention. Adverse drug reactions that are not addressed may discourage people from further taking the drugs. However, if these are identified and addressed, it may help in building patients confidence in the medication.

3. The district health directorate should use every communication channel available to intensify public education on the combination therapy in general and on the absolute need for adherence to treatment in particular.
4. It is recommended that the regional health directorate creates a forum for the findings of this study to be shared with other districts in the region.
5. Support districts to conduct studies into determining the situation in their districts so as to give a regional view of the adherence situation.
6. Conduct studies in other district to determine the national situation as far as adherence to the combination treatment is concerned. This would provide information for national intervention. It would also provide information on policy considerations.
7. Explore better alternative combination therapies that patients are more likely to adhere to.

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APPENDICES

APPENDIX (i): Questionnaire

Questionnaire on Patients Adherence to Artesunate-Amodiaquine Combination Therapy for Malaria in the Berekum District of Ghana, 2007

I am ……working with the Ghana Health Service. I am carrying out a study on patients' adherence to artesunate –amodiaquine combination therapy for malaria in the Berekum District. The findings of the results will be used to make recommendations for the successful implementation of the new anti-malaria drug policy. No names will be taken. All data will be handled confidentially.

Questionnaire no……Date……Name of health facility:……...

Participant ID no…….

SOCIO-DEMOGRAPHIC AND ADHERENCE DATA

1. Age (in years) ☐

2. Sex? Male ☐

Female ☐

3. Educational Level None ☐ Primary ☐ JSS ☐

SSS ☐ Tertiary ☐

4. Tribe Akan ☐ Brong ☐ Ewes ☐

Northerners ☐ Fantes ☐ Others (specify);

……

5. Religious affiliation a) Christian ☐ b) Moslem ☐ c)

Traditionalist ☐ d) others (specify); ……

6. Occupation a) Farmer ☐ b) Teacher ☐ c) Apprentice ☐

d) Trader ☐ e) Hairdresser ☐ f) Seamstress ☐ g)

Artisan ☐

h) Others (specify) ……..

7. Marital status a) Single ☐ b) Married ☐ c)

Divorced ☐….

d) Living with a Partner ☐ e) widowed ☐

ADHERENCE DATA

8. Were you weighed when you went to the hospital? Yes ☐ No ☐

9. Show me the medicines that were given to you a week ago when you attended clinic?

(Interviewer *should* i*dentify the artesunate and amodiaquine tablets still available and take count of them*)

9a Number of artesunate tablets counted ☐

9b Number of amodiaquine tablets counted No ☐

10. You were given a combination of artesunate – amodiaquine. (Please show the respondent the sample drug) For how long did you take the drugs?

1 day ☐ 2 days ☐ 3 days ☐

others (specify); ……..…

12. Reasons for not completing the full course of treatment? a) Relief of symptoms ☐

b) Side effects ☐ c) Reluctant to complete the course of treatment ☐

d) Symptoms worsen ☐ e) others (specify); ……

13. If the answer to question 12 above includes (b), go to question 14, otherwise skip to question

14. What side effects did you experienced? (Tick as many)

a) Rash ☐ b) Weakness ☐ c) dizziness ☐ d) Joint pain ☐

e) Insomnia ☐ f) Vomiting ☐ g) body itching ☐ others (Specify)……

15. When do you take your drugs?

Morning and evening ☐

Morning and afternoon ☐

Only in the morning ☐

Only in the afternoon ☐

Afternoon and bed time ☐

Others (specify)……..

16. How did you take your drugs in relation to meals?

Usually after meals in the morning and evening ☐

Usually before meal in the morning and evening ☐

Usually before or after meal afternoon ☐

Others (Specify) ……

(C) HEALTH SYSTEM FACTORS

17. Were you told about the following at the hospital either by the prescriber or the dispensing health worker?

a) That the drugs were intended to treat malaria? Yes ☐ No ☐

b) About possible side effects? Yes ☐ No ☐

c) Advised to sleep under an insecticide-treated net? Yes ☐ No ☐

d) The names of the drugs? Yes ☐ No ☐

e) Advised to return if the condition worsened? Yes ☐ No ☐

f) Given a chance to ask questions? Yes ☐ No ☐

g) What to do if you vomit after a dose? Yes ☐ No ☐

h) That the drugs were for you only? Yes ☐ No ☐

i) To take the medicines with food or water? Yes ☐ No ☐

j) To take 2 daily doses of artesunate - amodiaquine at home? Yes ☐ No ☐

18. Did you receive medication for any other condition in addition to the malaria treatment? Yes ☐ No ☐

APPENDIX (ii): Work plan

Activity	Aug 07	Sep 07	Oct 07	Nov 07	Dec 07	Jan 08	Feb 08	Mar 08
Finalize proposal								
Ethical Clearance								
Data collection								
Data analysis								
Submit 1st draft								
submit Thesis								

APPENDIX (iii): Patient Consent form

Name of Principal investigator: Dr. Simon Nyovuura Antara

Name of Organisations: Ghana Health Service/ FELTP-Kenya

Study title: Patients' Adherence to Artesunate-Amodiaquine Combination Therapy for Malaria in the Berekum District of Ghana, 2007

Dear Participant,

I am doing a study on patients, adherence to artesunate-amodiaquine combination therapy. This is a study done in collaboration with the Ghana Health Service.

Purpose of the study

Adherence is an important component of the overall effectiveness of a drug. However, following the introduction of the combination therapy, there has been several complaints about non-adherence to the drugs. This study seeks to describe the level of adherence and the various factors influencing it.

Study Procedures

If you agree to participate, you will be asked questions regarding how you took the drug and what happened to you when you took it. In addition, you would be asked what you were told at the hospital when the drug was given to you.

Risks and discomfort

There are hardly any risks associated with your participation in this study.

Benefit

The benefit of taking part in this study is that if you have any questions concerning the combination therapy, we will try to answer them. You would also be contributing to knowledge that is useful for the successful implementation of the new malaria drug policy.

Incentives

You will not be given any incentives to take part in the study.

Confidentiality

Any information about you that will be collected during the study will be confidential and will be stored in a file which will have only a number assigned to it and not your name.

Right to refuse or withdraw

Your participation in this study is purely voluntary and you are free to withdraw at any point in the study. You would not suffer any penalty for refusing to participate or for withdrawing from the study at any point

Who to contact

This proposal has been reviewed and approved by the Medical Research Review Committee of the Ghana Health Service, whose responsibility it is to make sure that research participants are protected from harm. If you wish to find more about the Review Committee, please contact the chairman of the committee at the Ghana Health Service Headquarters, Accra.

CONSENT FOR STUDY PARTICIPATION

I have read the foregoing information, or it has been read to me. I understand that the purpose of the study is to assess adherence to artesunate –amodiaquine combination therapy for malaria with the view to providing knowledge that would be useful for the successful implementation of the new malaria drug policy in Ghana.

I have had the opportunity to ask questions. I consent voluntarily to participate in this study and understand that I have the right to withdraw with no consequent penalties.

Participant Name	Signature/thumb print
……..……..	…….
……..……..	…….
……..	……
Date	Place

For further information on the study please contact;

Dr Simon Nyovuura Antara

Ghana Health Service

Post Office Box 282, Berekum

Tel: 0642-22230, 0244-966-937

Email: antarason@yahoo.com