TREATMENT OF UNCOMPLICATED MALARIA IN ADULTS AT DORMAA PRESBYTERIAN HOSPITAL, DORMAA AHENKRO

by

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DECLARATION

I hereby declare that this submission is my own work towards the award of MSc clinical pharmacy and that, to the best of my knowledge, it contains no material previously published by another person nor material which has been accepted for the award of any other degree of the University, except where due acknowledgement has been made in the text.

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DEDICATION

I dedicate this work to my loving mother Majoros Katalin who always believed in me and gave me encouragement with strong support.

To my family, especially my understanding husband Dr. Kofi Amo-Kodieh and my children, who patiently and continuously prayed for me throughout this course.

May God Almighty richly bless you all with perfect health and everlasting love.

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ABSTRACT

In 2005, due to the development of resistance to Chloroquine, Ghana implemented the Artemisinin-based Combination Therapy Policy (Artesunate plus Amodiaquine) with reports of associated adverse drug reactions. This was a cross-sectional descriptive study to assess the management of uncomplicated malaria in adults at Dormaa Presbyterian Hospital in the year 2008. Two types of quantitative data collection methods were employed. 1537 cases were selected by stratified sampling method from patient folders and six (6) clinicians were selected by purposive sampling to complete a questionnaire. The results showed that 12 different anti-malarial regimens were prescribed for the general population (1447 cases), compared to 9 recorded for pregnant patients (90 cases). In adherence to the policy, the Artesunate-Amodiaquine combination was the drug most frequently prescribed (66%), however contrary to the policy 35% of prescribed anti-malaria drugs for pregnant women in the 2nd trimester was an artemisinin derivative as mono therapy. The prescriptions had no correct dosages in 552 (36%) cases. Only in 65 (4.5%) cases for the general population, in 2 (6%) cases for pregnant women in the 2nd and in 5 (9%) cases in the 3rd trimester was the diagnosis based on laboratory evidence. Majority of prescribers will not prescribe Artesunate-Amodiaquine against the patient's wishes but rather will prescribe Artemether/Lumefantrine, because the clinicians perceive Artemether/Lumefantrine to have less severe side-effects, easy to administer and effective.

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LIST OF ABBREVIATIONS

ACT	Artemisinin-based Combination Therapy
AL	Artemether-Lumefantrine
AM	Artemether
AS	Artesunate
AQ	Amodiaquine
CD	Chlorproguanil-Dapsone
CPA	Commonwealth Pharmacists Association
CQ	Chloroquine
GHS	Ghana Health Service
GNDP	Ghana National Drugs Programme
IPT	Intermittent Preventive Treatment
ITNs	Insecticide Treated Nets
KNUST	Kwame Nkrumah University of Science and Technology
L	Lumefantrine
MHMT	Municipal Health Management Team
MOH	Ministry of Health
MPD	Malaria Parasite Detection
MPS	Malaria Parasite Seen
NMCP	National Malaria Control Programme
NSTG	National Standard Treatment Guidelines
OPD	Out-Patients Department
PSGH	Pharmaceutical Society of Ghana
RBM	Roll Back Malaria
RDTs	Rapid Diagnostic Tests
SP	Sulphadoxine-Pyrimethamine
USAID	United States Agency for International Development
WHO	World Health Organization

CHAPTER ONE

1.1 INTRODUCTION

1.1.1 Definition and Epidemiology of Malaria

Malaria is an infection caused by a protozoon (plural: protozoa) of the genus Plasmodium. It is transmitted through the bite of an infected female Anopheles mosquito.[1,2] Plasmodium falciparum is the commonest specie of the Plasmodium parasite in virtually all parts of Africa accounting for 90-98% of malaria cases and is associated with significant morbidity and mortality. Other species which include P. malariae and P. ovale, form up to 2 – 10% of the cases. P. vivax is very rare in Africa.[3] Human beings can be infected with these microbes repeatedly, or carry them for any length of time, without developing a full resistance to them. The pattern of endemicity of malaria in Ghana is stable malaria.[3]

1.1.2 Malaria Burden

Global malaria burden: Malaria is a serious problem in over half of the world's countries. Malaria kills over one million people each year, and three hundred million people are infected.[2] Eighty percent of global malaria cases and ninety percent of global deaths are recorded in Africa. Death may occur because of lack of access to health care, life-saving drugs and insecticide-treated bed nets. Malaria accounts for ten percent of Africa's disease burden.[3]

Burden of Malaria in Ghana: Annually 3.5 million cases of malaria and 40,000 deaths due to malaria are recorded. This as an avoidable tragedy because:

- ✓ Malaria deaths can be reduced with the affordable solutions currently available, such as existing medicines, tools and strategies.
- ✓ When health care is strengthened, malaria can be rolled back.[3]

1.1.3 Roll Back Malaria

Roll Back Malaria (RBM) as a global movement was established on the 31st July, 1998.[2,3] Rolling back malaria is one of the World Health Organization's highest priorities. The RBM targets in the African Region by 2010 are:

- Reduction of malaria morbidity and mortality by 50% of the 2000 levels.

In 2000, Ghana adopted the RBM Strategy with the promise of working towards achieving these goals. Targets were set, aiming to have 60% of children under five and pregnant women sleeping under insecticide treated nets, 60% of pregnant women taking intermittent preventive treatment, and 60% of children under five and pregnant women having access to prompt, affordable and appropriate treatment for uncomplicated malaria using effective anti-malaria medication within 24 hours of the onset of symptoms of the disease.[4]

Rolling back malaria helps roll out under development caused by the negative impact of malaria on human and economic development.[3]

1.1.4 Ghana`s Current Anti-Malaria Drug Policy

Based on the research findings which showed that there is resistance of Plasmodium falciparum to chloroquine (CQ), the anti-malaria drug policy was revised and Ghana adopted a new anti-malaria drug policy in November 2004.[5]

The policy statement specifies that Artesunate-Amodiaquine shall be the drug combination of choice for treating uncomplicated malaria, except for pregnant women in the first trimester.[1, 5, 6] The dose for the combination shall be Artesunate (AS) 4mg/kg body weight and Amodiaquine (AQ) 10mg/kg body weight administered concurrently for three consecutive days,[5] e.g. the recommended dosage regime for the body weight more than

50 Kg and more than 14 years of age is 200mg of AS and 600mg of AQ administered concurrently orally daily for three consecutive days.[6]

The use of AS and AQ as mono therapies for the treatment of any type of malaria outside the provisions of the new treatment policy shall be discontinued in all health institutions. Also Sulphadoxine-Pyrimethamine (SP) shall be reserved only for use in the prevention of malaria during pregnancy under observation (IPT).The use of SP as mono therapy for uncomplicated malaria shall be discontinued.[5]

Oral Quinine shall be used to treat pregnant women with uncomplicated malaria only in the first trimester. However, oral Quinine or the combination of Artesunate-Amodiaquine shall be used in the 2nd and 3rd trimesters.[5]

1.1.5 The Challenging Process of Drug Policy Change

Since the implementation of this policy in January, 2005 the process of drug policy change for malaria has been slow and challenging.[3] There has been noncompliance to the Policy as a result of the side-effects of Amodiaquine.[7,8] Poor prescribing habits by health providers, inappropriate use and misuse by the general population could cause the newer more effective but expensive antimalarial drugs to suffer the same fate as chloroquine did. Chloroquine was a cheap and effective anti-malaria drug which had to be deleted from NSTG due to increasing resistance to it.[3]

Public education and capacity building of stakeholders and prescribers is crucial to the successful implementation of this policy and it has to be followed by monitoring and evaluation.[5]

1.1.6 World Health Organization Approved Strategies and Tools

The progress gained by Ghana in achieving the 2010 RBM targets resulted from significant steps taken to apply the WHO approved strategies and tools, which included:

1. Prevention strategies- Public health facilities distribute subsidized ITNs to target vulnerable groups.

2. Achieving universal coverage- This requires development of proper storage facilities in all districts, so that the products can reach every person at risk.

3. Intermittent Preventive Treatment (IPT) of malaria in pregnancy-This specifies that all pregnant women receive at least two or three full doses of SP under directly observed therapy by 2015.This is a key objective of the National Malaria Control Program directed at saving the lives of pregnant women and their unborn babies.

4. Malaria case management-This requires ensuring access to prompt, and accurate diagnosis and effective treatment of malaria. Also conducting operational research, monitoring drug quality and efficacy and pharmacovigilance as well, are very important.[4]

1.2 LITERATURE REVIEW OF UNCOMPLICATED MALARIA TREATMENT AND CLINICAL TRIALS

The World Health Organization recommends that uncomplicated P. falciparum malaria is treated using artemisinin-based combination therapy (ACT). A systematic review conducted by the International Health Group, Liverpool aims to assist the decision making of malaria control programmes by providing an overview of the relative benefits and harms of the available options. The objectives were to compare the effects of ACTs with other available ACT and non-ACT combinations for treating uncomplicated P. falciparum malaria. It was concluded that Dihydroartemisinin-piperaquine is another effective first-

line treatment for P. falciparum malaria. The performance of the non-ACT (AQ plus SP) falls below World Health Organization recommendations for first-line therapy in parts of Africa.[9]

In the last five years, countries have been faced with changing their malaria treatment policy to an ACT, many with no national data on which to base their decision. This is particularly true for a number of West African countries, including Guinea. Two studies were conducted in 2004/2005 in programmes supported by Medecins Sans Frontieres, when chloroquine was still national policy, but AS/SP had been used in refugee camps for two years. The conclusion was that both AS/AQ and AS/SP are highly efficacious in Dabola, whereas there is molecular evidence of established SP resistance in Laine. This supports the choice of the national programme of Guinea to adopt AS/AQ as first line antimalarial treatment.[10]

Artemisinin and its derivatives (artesunate, artemether, dihydroartemisinin, artemotil) produce rapid clearance of parasitaemia and rapid resolution of symptoms. They reduce parasite numbers by a factor of approximately 10 000 in each asexual cycle, which is more than other current antimalarials (which reduce parasite numbers 100- to 1000-fold per cycle). Artemisinin and its derivatives are eliminated rapidly. When an artemisinin compound is given in combination with a rapidly eliminated compound (tetracyclines or clindamycin), a 7-day course is required; but when given in combination with a slowly eliminated antimalarial (amodiaquine, lumefantrine or piperaquine), a 3-day course is effective.[11]

To test the hypothesis that AS/AQ is as effective as artemether-lumefantrine (AL) in the treatment of acute uncomplicated malaria in Nigerian children, a study was

conducted. AS/AQ was found to be as effective as AL and both combinations were efficacious and safe.[12]

Numerous trials have demonstrated high efficacy and safety of ACT under supervised treatment. In contrast effectiveness studies comparing different types of ACT applied unsupervised are scarce. A randomized open-label trial was conducted at two district hospitals in the Ashanti region, Ghana, an area of intense malaria transmission. The aim of this study was to compare effectiveness, tolerability and acceptance of AS/AQ to AL in Ghanaian children with uncomplicated Plasmodium falciparum malaria. They evaluated the clinical and parasitological outcomes, adverse events and haematological recovery. The acceptance of treatment with AS/AQ was higher than that with AL. Researchers concluded that unsupervised AL and AS/AQ treatment showed high adequate clinical and parasitological responses, though AL was inferior in preventing late clinical failures.[13]

At least 15 African countries have adopted AS/AQ as treatment policy. As no pharmacokinetic data on this combination have been published before, a group of researchers investigated its pharmacokinetic interactions and tolerability in healthy volunteers in Africa. In a randomized, three-phase, cross-over study, AQ (10 mg/kg) and AS (4 mg/kg) were given as single oral doses to 15 healthy volunteers. The pharmacokinetics of AS and AQ and their main active metabolites were compared following mono therapy and combination therapy using analysis of variance. It was concluded that the total drug exposure to both drugs was reduced significantly when they were given in combination. The clinical significance of these interactions is unclear and must be studied in malaria patients.[14]

Artesunate plus amodiaquine is often given as a coblistered tablet in a single daily dose. It has been suggested that, in view of the number of tablets to be taken (particularly in adults), it may be possible to improve compliance by allowing patients to divide the daily dose. A randomized, comparative, open-label, multicentre study was conducted in Senegal and in Cameroon in 2005 to demonstrate the non-inferiority and to compare the safety of AS/AQ, as a single daily intake versus two daily intakes. The responses to treatment were similar for the two treatment regimens. The statistical analyses demonstrated the non-inferiority of administering AS/AQ as two intakes. The drug was well tolerated. The main adverse events were gastrointestinal disorders and pruritus; safety profiles were similar in the two groups. This study showed the efficacy and good tolerability of AS/AQ, administered either in one or in two daily intakes.[15]

In order to improve the monitoring of the anti-malarial drug resistance in Madagascar, a new national network based on eight sentinel sites was set up. In 2006/ 2007, a multi-site randomized clinical trial was designed to assess the therapeutic efficacy of CQ, SP, AQ and AS/AQ, the anti-malarial therapies recommended by the National Malaria Control Programme (NMCP) of Madagascar. The research findings (i) constitute an updated baseline data on the efficacy of anti-malarial drugs recommended by the NMCP, (ii) show that anti-malarial drug resistance remains low in Madagascar, except for CQ, and (iii) support the current policy of AS/AQ as the first-line treatment in uncomplicated falciparum malaria.[16]

An open label, randomized trial was conducted by the Kintampo Health Research Centre in 2008. AS+AQ and AL are the most frequently recommended first line treatments for uncomplicated malaria in Africa. Artesunate plus chlorproguanil-dapsone (AS+CD) was a potential alternative for treatment of uncomplicated malaria. A comparison of the

efficacy and safety of these three drug combinations was necessary to make evidence based drug treatment policies. In the per-protocol analysis, the parasitological and clinical failure rate at day 28 post treatment was lower in the AS+AQ group compared to the AL or AS+CD groups. The incidence of adverse events was comparable between the groups. The conclusion of the research was that AS+AQ is an appropriate first line treatment for uncomplicated malaria in Ghana and possibly in the neighbouring countries in West Africa. The effectiveness of AL in routine programme conditions needs to be studied further in West Africa.[17]

Lumefantrine bioavailability is enhanced by food, particularly fat. As the fat content of sub-Saharan African meals is approximately a third that of Western countries, it raised the question of whether fat consumption by African patients is sufficient for good efficacy.[18] Co-administration of AL with a relatively small amount of fat (as soya milk) was required to ensure maximum absorption of lumefantrine in healthy adult volunteers.[19] In conclusion, it appears that only a very small amount of dietary fat is necessary to ensure optimal efficacy with AL and that the fat content of standard meals or breast milk in sub-Saharan Africa is adequate.[18]

There is little information on the efficacy of AS/AQ and AL regimens on subsequent episodes beyond 28 days, or on the safety of repeated treatments. There was a high incidence of potentially AQ-resistant parasites in the study area in Ghana. The incidence of adverse events, such as pruritus, fatigue and neutropaenia were similar in the two treatment groups of children. No patient showed signs of hearing impairment, and no abnormal neurological signs were observed during one year of follow-up. Other adverse events were mild in intensity and overlapped with known malaria symptomatology. No adverse event exacerbation was observed in any of the subjects who received multiple

treatment courses with these ACT regimens during one year follow-up. It was concluded that AS/AQ and AL were efficacious for treatment of children with uncomplicated malaria in Ghana and drug-related adverse events were rare in treated subjects during one year of follow-up.[20]

Four antimalarial drug combinations, AS plus AQ (Arsucam), AS plus mefloquine (Artequin), AL (Coartem; four doses and six doses), and AQ plus SP, were studied in five health districts in Senegal, in a descriptive, analytical, open, randomized study to evaluate the efficacy and tolerability of these four antimalarial combinations in the treatment of uncomplicated falciparum malaria using the 2002 WHO protocol. On day 28, all combinations resulted in an excellent clinical and parasitological response rate, except for the four-dose AL regimen. The combinations were well tolerated clinically and biologically. No unexpected side-effect was observed and all side-effects disappeared at the end of treatment. No serious side-effect requiring premature termination of treatment was observed. It was concluded that with the exception of the four-dose AL regimen, the four combinations are effective and well tolerated.[21]

In another systematic review researchers sought evidence of the superiority of the six-dose regimen of AL over existing treatment regimens as well as its effectiveness in clinical situations.[22]

A randomised trial to compare the efficacy, safety and pharmacokinetics of AL when given in a supervised or unsupervised setting to patients of all ages (weight >10 kg) with acute, uncomplicated falciparum malaria in Mbarara, Uganda was conducted. AL was found to have a high cure rate irrespective of whether given under supervision with food or under conditions of routine clinic practice. If used as first-line treatment, AL could make a substantial contribution to malaria control in Africa, though cost is an issue.[23]

Irreversible ototoxicity associated with AL has been reported recently and suggested to be a serious limitation in the use of this ACT. A study was conducted in south-west Ethiopia to compare ototoxicity, tolerability and efficacy of AL with that of quinine and atovaquone/proguanil in the treatment of uncomplicated falciparum malaria. A standard oral regimen of AL was found to have no detrimental effect on peripheral hearing or brainstem auditory pathways in patients with uncomplicated falciparum malaria. In contrast, transient hearing loss is common after quinine therapy.[24]

A system for monitoring adverse events in anti-malarial trials conducted in Uganda was developed. The reporting system was reviewed, and the difficulties faced in analysing and interpreting the safety results were illustrated, using data from the trials. It was observed that although the World Health Organization has supported the development of pharmacovigilance systems in African countries deploying ACTs, additional guidance on adverse events monitoring in anti-malarial clinical trials is needed, similar to the standardized recommendations available for assessment of drug efficacy.[25]

There is an urgent need to assess the drug safety in pregnant women who may be inadvertently exposed to or actively treated with ACTs. Fourteen relevant studies on ACT use in pregnancy were identified by the Department of Infectious and Tropical Diseases, London School of Hygiene & Tropical Medicine via searches of databases, to examine existing published evidence with regard to the safety of artemisinin compounds when administered during pregnancy and on the relationship between these compounds and adverse pregnancy outcomes. The limited data available suggest that artemisinins are effective and unlikely to cause foetal loss or abnormalities, when used in late pregnancy. However, none of these studies had adequate power to rule out rare serious adverse events, even in 2nd and 3rd trimesters and there is not enough evidence to effectively assess the

risk-benefit profile of artemisinin compounds for pregnant women particularly for 1st trimester exposure. Methodologically rigorous, larger studies and post-marketing pharmacovigilance are urgently required.(26)

A study to determine the efficacy and safety of AS+AQ, SP+AQ, CD and SP in pregnant women with uncomplicated malaria was set out by the London School of Hygiene & Tropical Medicine in 2009 in Tanzania. Failure rates with mono therapy (CD, SP) were unacceptably high. The two combinations tested (AS+AQ, SP+AQ) were efficacious and appeared safe. It should not be assumed that efficacy in pregnancy is the same as in children.(27)

An open-label randomised controlled trial comparing directly observed treatment with AL 3 days or artesunate mono therapy 7 days (AS7) was conducted in Karen women in the border area of northwestern Thailand who had uncomplicated P. falciparum malaria in the second and third trimesters of pregnancy. The researchers concluded that the current standard six-dose AL regimen was well tolerated and safe in pregnant Karen women with uncomplicated falciparum malaria, but efficacy was inferior to AS7 mono therapy and was unsatisfactory for general deployment in this geographic area. Reduced efficacy probably resulted from low drug concentrations in later pregnancy. A longer or more frequent AL dose regimen may be needed to treat pregnant women effectively.(28)

Analytical approaches for the interpretation of anti-malarial clinical trials vary considerably. The aim of a study conducted by Centre for Clinical Vaccinology and Tropical Medicine, Churchill Hospital, Oxford in 2009 was to quantify the magnitude of the differences between efficacy estimates derived from these approaches and identify the factors underlying these differences. It was observed that estimates of anti-malarial clinical efficacy vary significantly depending on the analytical methodology from which they are

derived. In order to monitor anti-malarial efficacy, standardized analytical tools need to be applied in a transparent and systematic manner. [29]

The introduction of ACT in sub-Saharan Africa has prompted calls for increased use of parasitologic diagnosis for malaria.[30] Although there are newer techniques, manual microscopy for the examination of blood smears (invented in the late 19th century), is the gold standard for malaria diagnosis and it requires special training and considerable expertise. It has been shown in several field studies that manual microscopy is not a reliable screening method when performed by non-experts due to lack of training.[31]

The use of a confirmatory diagnosis with either microscopy or rapid diagnostic tests (RDTs) is expected to reduce the overuse of anti-malarials by ensuring that treatment is targeted on patients with confirmed malaria infections as opposed to treating all patients with fever. There is, however, little documented evidence that this is so. The main problem is that providers of care, although may be willing to perform diagnostic tests, do not always comply with the results, especially when they are negative. Being aware that delay in providing effective treatment can be fatal for a malaria patient, they are often reluctant to withhold treatment on the basis of a negative result.[11]

A study to evaluate the relative cost-effectiveness in different sub-Saharan African settings of presumptive treatment, field-standard microscopy and RDTs to diagnose malaria was conducted. RDTs were more than 50% likely to be cost-saving. RDTs have the potential to be cost-effective in most parts of sub-Saharan Africa. Appropriate management of malaria and non-malarial febrile illnesses is required to reap the full benefits of these tests.[32]

1.3 ERADICATION OF MALARIA

Since the perceived failure of the Global Programme for Malaria Eradication in 1969, the eradication of malaria has not been considered a feasible goal. However, in October 2007 the goal of malaria eradication was resurrected by Melinda and Bill Gates, and this aspiration has subsequently been endorsed by the WHO and by the Roll Back Malaria Partnership. This change in direction of malaria control has provoked a vigorous debate within the malaria research and control communities as to whether resurrection of the goal of eradication at this point in time is helpful or likely to be counterproductive. The consensus that has emerged is that eradication of malaria, although theoretically possible, is not likely to be feasible within the medium term using existing control tools. However, malaria elimination (cessation of local transmission) is a realistic short- to medium-term goal for an increasing number of countries that are already bringing malaria under control.[33]

Malaria case management is an important tool in the process of bringing malaria under control and as such should be monitored and evaluated regularly, e.g. through operational research studies such as this study conducted at Dormaa Presbyterian Hospital.

1.4 JUSTIFICATION FOR STUDY

Medical records in the Dormaa District of Brong Ahafo Region, Ghana indicate that the annual incidence of malaria was on the increase from the year 2005 – 2007. In the year 2005, there were 51,163 OPD cases diagnosed as malaria. In 2006, there were 66,833 cases, indicating 30.63% increase. In 2007, there were 93,216 cases representing an increase of 39.48%. With the increase in malaria cases, it is increasingly important to treat cases promptly and effectively to avoid progression to severe disease, limit the duration of

disease and minimize the risk of spread of drug resistant parasites.[1] In the following year 2008, there were 88,381 cases representing a decrease of 5.19%.

1.5 AIM

To assess the management of uncomplicated malaria in adults at Dormaa Presbyterian Hospital.

1.6 OBJECTIVES

1. To find out which anti-malaria drugs are used in the treatment of uncomplicated malaria in adults and the reasons for choice.
2. To evaluate prescribers' compliance with the Anti- Malaria Drug Policy for Ghana, in the treatment of uncomplicated malaria in adults.
3. To determine whether patients' compliance and acceptance as perceived by the prescriber, influence prescriber prescribing habits.
4. To assess the importance given to laboratory evidence obtained with microscopy for malaria parasite detection in making the diagnosis of malaria.

CHAPTER TWO

2.1 MATERIALS AND METHODS

2.1.1 STUDY DESIGN

This was a retrospective cross-sectional descriptive study of treatment of uncomplicated malaria in adults.

2.1.2 STUDY POPULATION

The study population consisted of the folders of adult patients treated for uncomplicated malaria in the year 2008 at the Out-Patient Department (OPD) of Dormaa Presbyterian Hospital and prescribers.

2.1.3 INCLUSION CRITERIA

- Folders of OPD cases of uncomplicated malaria aged 15 years and above.
- All clinicians who treat patients for malaria.

2.1.4 EXCLUSION CRITERIA

- Women in the first trimester of pregnancy.

2.1.5 DATA COLLECTION

a) Ethical consideration

The concept of the research was discussed with the Municipal Director of Health Services and the MHMT and it was accepted. The study protocol was followed and permission was sought from the management of Dormaa Presbyterian Hospital. The staff of the Records Department voluntarily assisted in the picking of the patient folders and confidentiality is

part of their every day work. Participation in the answering of the questionnaire by the clinicians was voluntary and confidentiality was maintained.

b) Data collection methods

Based on the objectives of the study set out above two types of quantitative data collection methods were employed:

1. Data collection from patient folders

Patients visit the Dormaa Presbyterian Hospital OPD from Monday to Friday (except on holidays). The following is recorded in the consulting room record books:

- The date of the visit.
- The patient folder number.
- The name of the patient.
- The address of the patient.
- The age and sex of the patient.
- New or old case.
- The diagnosis made.

This was used by the Records Department (Health information service) to generate computerized data on cases diagnosed as malaria. From Jan. to Dec. 2008 there were 7,684 new OPD cases of uncomplicated malaria in all ages of 15 years and above.

Sampling

Out of these 7,684 cases 20% was selected by Stratified sampling method with uniform random sampling fraction, to enhance representativeness and increase the precision of results. The sampling was stratified by month. If a case already picked did not correspond

with the inclusion criteria, it was excluded and the case with the next folder number was picked. Since a patient can be diagnosed with malaria more than once during the year, the same folder number can appear with more than one malaria case but with a different date.

Pre-testing and review of the data collection tool

The first twenty (20) folder numbers which were selected were used to pre-test the framework for data collection and based on the feedback it was adjusted. A sample of the Framework for data collection is set out in Appendix I.

A retrospective review of records was then carried out for the cases selected from the period January-December 2008. For better quality data were double checked for completeness and accuracy by the researcher.

2. Data collection from clinicians

A self-administered questionnaire to know the acceptance of the use of artemisinin- based combination therapies in the treatment of uncomplicated malaria in adult patients was given to clinicians.

Piloting of the data collection tool

The questionnaire was piloted with six (6) clinicians selected by purposive sampling based on the inclusion criteria, to obtain their views concerning:

- The understanding of the questionnaire,
- The content of the questionnaire.

The questionnaire was then analysed and modified based on the feedback to obtain the final questionnaire (Appendix II).

Sampling and administration of the questionnaire

The six (6) clinicians selected by purposive sampling method based on the inclusion criteria were issued with the final questionnaire.

c) Data processing and analysis

For easy analysis the data recorded on the framework for data collection was coded using a coding frame and entered into SPSS 16.0 for Windows software. The coded and punched data for computer analysis was double checked for completeness and accuracy. The data was analyzed by combining the 12 strata together to obtain overall results and also by stratum to show how prescribing was changing during the year 2008 and then presented in tables and charts using Microsoft Office Excel 2007 software.

The answers from the self-administered questionnaire were listed for each question and analyzed by hand because of the small samples size. Statements and ideas expressed by clinicians were reported verbatim to support the findings and discussions.

2.2 RESULTS

2.2.1 RESULTS FROM PATIENT FOLDERS

2.2.1.1 Demographic characteristics

Data was collected on 1537 cases, which are 20% of all uncomplicated malaria cases from Jan. to Dec. 2008 (Table 2.1). The data collection took about six (6) weeks. Males were 404 (26%) and females 1133 (74%), of which 177 were aged 15-18 years and the remaining 1360 cases were over 18 years.

Table 2.1: Number of cases selected by month

Month (Stratum)	Total no. of cases	Number of cases in each 1 in 5 random sample
January	604	121
February	527	105
March	452	91
April	589	118
May	774	155
June	755	151
July	766	153
August	556	111
September	646	129
October	879	176
November	550	110
December	586	117
Total	7,684	1,537

Out of the 1133 female patients, 90 (8%) were pregnant. The age of these patients was 15-18 years in 9 cases (10% teenage pregnancy) and more than 18 years in 81 cases. Majority of them were in the third trimester (62%), see Figure 2.1 and Figure 2.2. Patients in the first trimester were not part of this study.

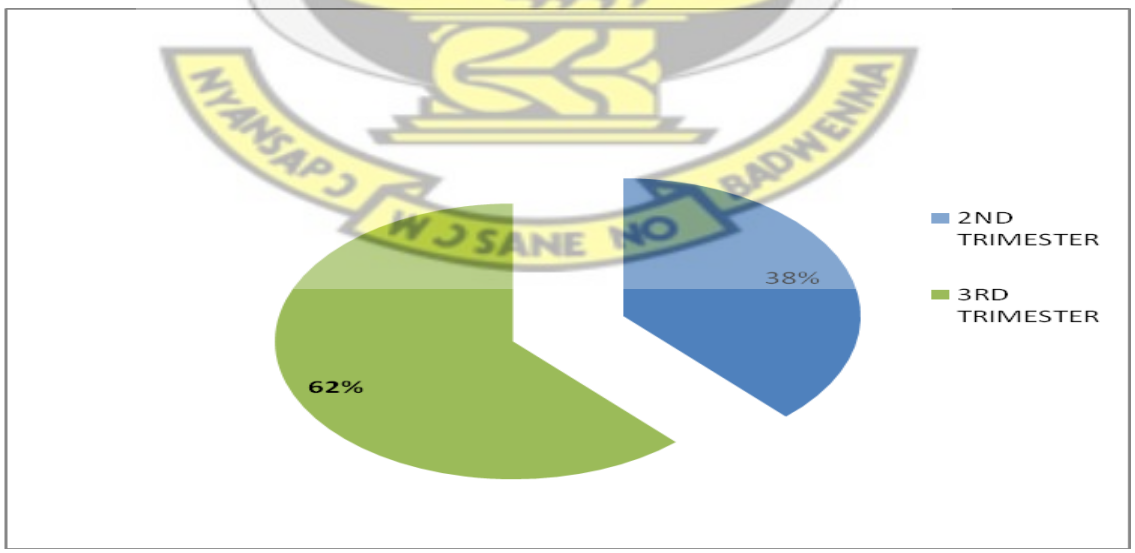

Figure 2.1: Percentages of trimester of pregnancy

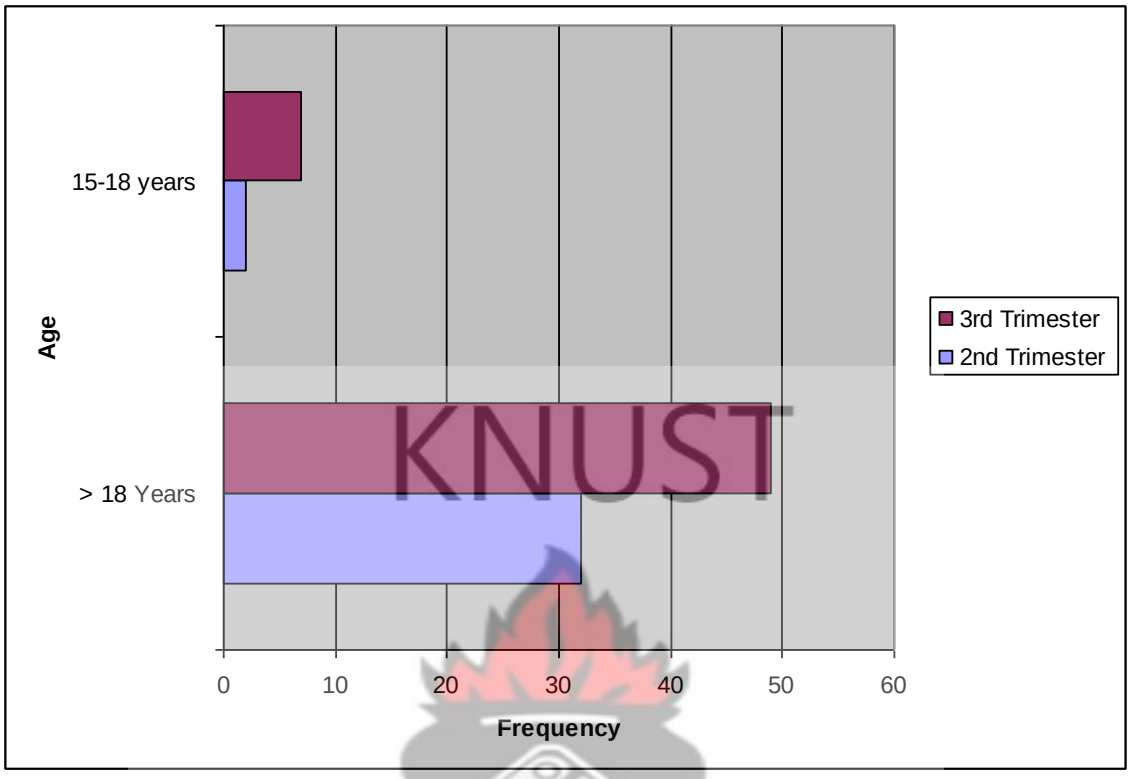

Figure 2.2: Frequency distribution of trimester of pregnancy by age of patient

The body weight of 51-70 Kg was the most frequent, see Table 2.2.

Table 2.2: Frequency distribution of body weight

Count

		Pregnant patients		General population
	Body weight	Number in 2nd trimester	Number in 3rd trimester	
	Not measured	8	12	145
	50kg and less	8	1	375
	51 -70kg	13	36	795
	More than 70kg	5	7	132
Total		34	56	1447

2.2.1.2 Types of Anti-Malaria Drugs-prescribed and dispensed

Results on types of anti-malaria drugs-prescribed and dispensed to 1447 patients from the general population (Table 2.3) and to 90 pregnant patients (Table 2.4).

Table 2.3: Frequency and percentages of types of anti-malaria drugs-prescribed and dispensed to the general population

Drug(s)	Prescribed		Dispensed	
	freq.	%	freq.	%
Tab AS +AQ	951	65.7	965	66.7
Tab AL	201	13.9	185	12.8
Tab Artemisinin derivative	116	8.0	119	8.2
Inj AM + (Tab AS + AQ)	86	5.9	86	6.0
Inj AM + Tab AL	39	2.7	35	2.4
Inj AM + Tab Artemisinin derivative	14	1.0	14	1.0
Tab AS + Metakelfin	13	0.9	9	0.6
Tab SP	12	0.8	12	0.8
Tab AS + SP	8	0.6	10	0.7
Tab Metakelfin	5	0.3	5	0.3
Inj AM + Tab Metakelfin	1	0.1	1	0.1
Supp AM + (Tab AS + AQ)	1	0.1	0	0
Inj AM + (Tab AS + SP)	0	0	0	0
Inj Quinine + (Tab AS + AQ)	0	0	0	0
Tab Quinine	0	0	0	0
None dispensed	-	-	6	0.4
Total	1447	100	1447	100

The number of different anti-malarial regimens prescribed for the general population is 12. Drugs were dispensed in 99.6% of these cases.

Table 2.4: Types of anti-malaria drugs-prescribed and dispensed to pregnant women

% of **Types of Anti-Malaria Drugs-prescribed and dispensed** within Trimester of pregnancy	**Trimester of pregnancy**	
	2nd trimester (%)	3rd trimester (%)
Tab AS +AQ	26.5	46.4
Tab Artemisinin derivative	35.3	25.0
Tab Quinine	29.4	8.9
Inj AM + (Tab AS + AQ)	5.9	5.4
Tab AL	2.9	5.4
Inj AM + Tab Artemisinin derivative	0	3.6
Tab AS + Metakelfin	0	1.8
Inj AM + (Tab AS + SP)	0	1.8
Inj Quinine + (Tab AS + AQ)	0	1.8
Total	100	100

The number of different anti-malarial regimens prescribed for pregnant patients is 9.

All prescribed anti-malarial drugs were dispensed to pregnant women.

2.2.1.3 Duration of treatment

The ACT of 3 days duration was 89% for patients from the general population (Figure 2.3) and only 35% in the 2nd trimester of pregnancy (Table 2.5).

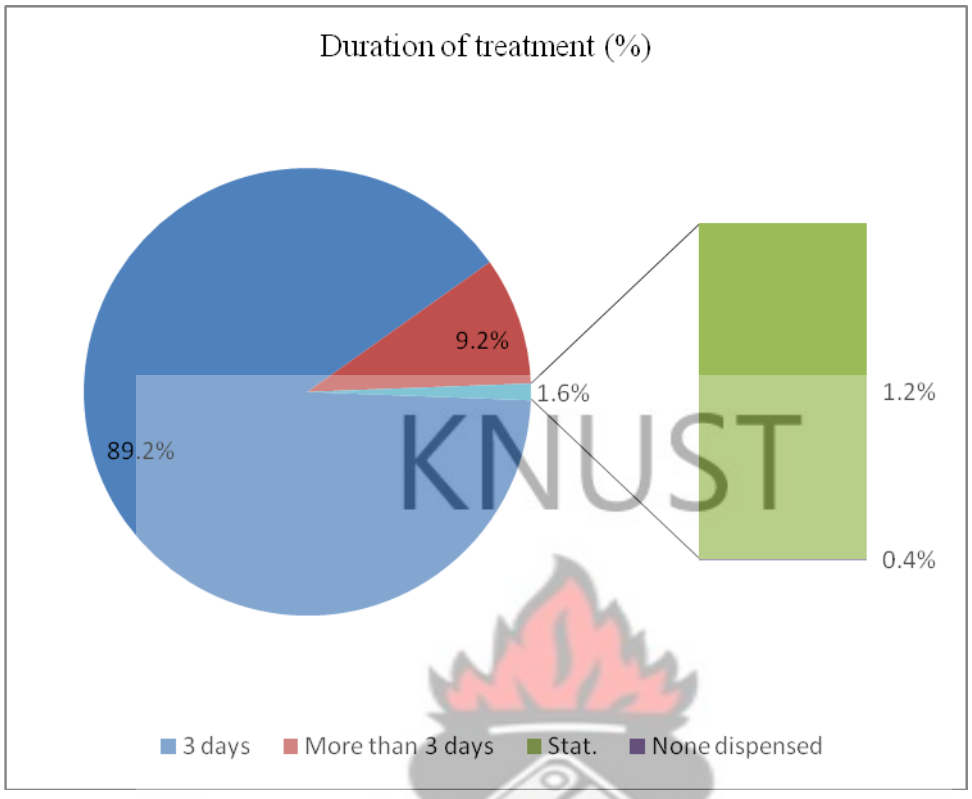

Figure 2.3: Duration of treatment for patients from the general population

Table 2.5: Duration of treatment for pregnant patients

Count and percent

		Duration of treatment			
	Trimester of pregnancy	3 days		More than 3 days	
		freq.	%	freq.	%
	2nd trimester	12	35	22	65
	3rd trimester	35	63	21	37

2.2.1.4. Results of microscopy for Malaria Parasite Detection

Microscopy for Malaria Parasite Detection (MPD) was not performed for majority of patients; see Figure 2.4 for patients from the general population and Table 2.6. to compare it with the results for pregnant women. In 65 (4.5%) cases for the general population, in 2

(6%) cases for pregnant women in the 2nd and in 5 (9%) cases in the 3rd trimester was the diagnosis based on laboratory evidence.

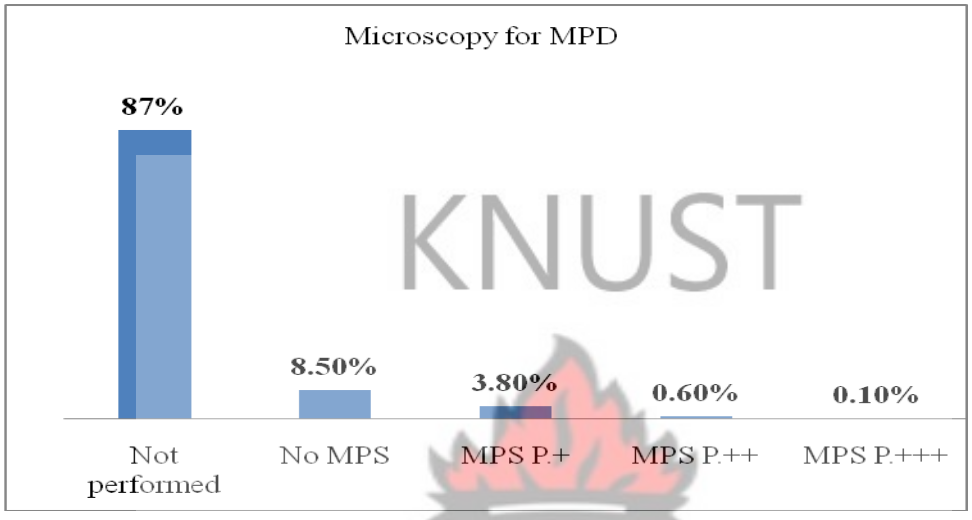

Figure 2.4: Results of microscopy for MPD for patients from the general population

Table 2.6: Results of microscopy for Malaria Parasite Detection

Diagnosis of malaria	**Result of microscopy for MPD**	**Trimester of pregnancy**				**General population**	
		2nd trimester		3rd trimester			
		Freq.	(%)	Freq.	(%)	Freq.	(%)
Diagnosis not based on laboratory evidence	Not performed	30	88.2	47	83.9	1259	87.0
	No MPS	2	5.9	4	7.2	123	8.5
Diagnosis based on laboratory evidence	MPS P.+	0	0	4	7.2	55	3.8
	MPS P.++	2	5.9	1	1.7	9	0.6
	MPS P.+++	0	0	0	0	1	0.1
Total		34	100	56	100	1447	100

2.2.1.5 Some results on all the 1537 cases

Table 2.7: Types of Anti-Malaria Drugs-prescribed by Result of microscopy for MPD

% of **Types of Anti-Malaria Drugs-prescribed** within Result of microscopy for MPD	**Result of microscopy for MPD**				
	Not performed (%)	No MPS (%)	MPS P.+ (%)	MPS P.++ (%)	MPS P.+++ (%)
Tab AS +AQ	62.9	69.8	81.4	58.3	
Tab AL	14.4	5.4	5.1	8.3	100
Tab Artemisinin derivative	9.2	14.0	1.7		
Inj AM + (Tab AS + AQ)	6.1	1.6	8.5	25.0	
Tab Quinine	0.7	2.3	3.4		
Inj AM +Tab Artemisinin der.	1.1			8.3	
Inj AM + Tab AL	2.8	1.6			
Tab AS + Metakelfin	0.9	1.6			
Tab SP	0.7	2.3			
Tab Metakelfin	0.2	1.6			
Tab AS+SP	0.6				
Inj AM + (Tab AS + SP)	0.1				
Inj Quinine + (Tab AS + AQ)	0.1				
Inj AM + Tab Metakelfin	0.1				
Supp AM +(Tab AS+AQ)	0.1				
Total	100	100	100	100	100

There is an 18.5% increment in the prescribing of Tab AS+AQ with the MPS P.+ microscopy result compared to the microscopy not performed result.

Tab AL was prescribed for the patient with the MPS P.+++ microscopy result.

Table 2.8: Result of microscopy for MPD by Body temperature

% of **Result of microscopy for MPD** within Body temperature	Body temperature		
	Not taken (%)	< or = 37.5 ˚C (%)	> 37.5 ˚C (%)
Not performed	94.2	88.8	59.6
No MPS	2.9	8.1	14.9
MPS P.+	2.9	2.8	16.7
MPS P.++	0	0.2	7.9
MPS P.+++	0	0	0.9
Total	100	100	100

There is a 13.8 % increment of the MPS P.+ results with the body temperature higher than 37.5 ˚C compared to the body temperature not taken category.

Table 2.9: Dose of Tab AS+AQ dispensed by the Body weight of the patient

Frequency of **Dose of AS+AQ dispensed** within Body weight of the patient	**Body weight of the patient**				Total
	Not measured	50kg and less	51-70kg	More than 70kg	
Tab AS200mg +AQ600mg daily for 3 days	98	190	534	102	924
Tab AS200mg +AQ400mg daily for 3 days	11	86	60	1	158
Tab AS150mg +AQ400mg daily for 3 days	1	2	1	0	4
Tab AS100mg +AQ200mg daily for 3 days	0	4	0	0	4
Tab AS200mg +AQ800mg daily for 3 days	0	0	0	2	2

Tab Artesunate-Amodiaqine combination therapy (Tab AS+AQ) was dispensed in five different doses to patients. All the other drugs were dispensed in one dosage regimen to all patients.

Table 2.10: Types of anti-malaria drugs-prescribed by the Month of treatment

% of **Anti-malaria drugs-prescribed** within month of treatment	**Month of treatment**											
	JAN. (%)	FEB. (%)	MAR. (%)	APR. (%)	MAY (%)	JUNE (%)	JULY (%)	AUG. (%)	SEPT. (%)	OCT. (%)	NOV. (%)	DEC. (%)
Tab AS + AQ	86.0	75.2	51.6	72.9	69.7	82.8	67.3	55.0	67.4	46.6	54.5	37.6
Inj AM + Tab Artemisinin derivative			3.3	0.8	5.8	1.3	0.7					
Inj AM + Tab AL				1.7	1.3		1.3		0.8	6.8	3.6	13.7
Inj AM +Tab Metakelfin						0.7						
Supp AM+ (Tab AS+AQ)					0.6							
Inj AM + (Tab AS + SP)					0.6							
Inj Quinine+(Tab AS+AQ)												0.9
Tab Artemisinin derivative	8.3	21.0	24.2	19.5	9.0	6.0	8.5	6.3	5.4	5.1	4.5	0.9
Tab AS + SP	0.8			1.7	2.6			0.9				
Tab AS + Metakelfin		1.0	14.3									
Tab SP			1.1	0.8		0.7	0.7			2.3	3.6	
Tab AL				0.8			8.5	28.8	17.8	29.0	29.1	45.3
Inj AM + (Tab AS + AQ)		1.9	3.3	0.8	7.7	8.6	13.1	8.1	8.5	8.0	4.5	0.9
Tab Metakelfin	1.7		2.2		0.6							
Tab Quinine	3.3	1.0		0.8	1.9			0.9		2.3		0.9
Total	100	100	100	100	100	100	100	100	100	100	100	100

Table 2.10 shows how the anti-malaria drugs-prescribed changed during the year 2008.

2.2.2 RESPONSE TO THE QUESTIONNAIRE FROM CLINICIANS

Six clinicians were selected by purposive sampling.

2.2.2.1 Socio demographic characteristics of clinicians

Two of the prescribers were medical assistants and four were medical officers. Five of them have been in clinical practice for 1-5 years and one medical assistant above 20 years.

2.2.2.2 Antimalarials prescribed for the management of uncomplicated malaria

Table 2.11: List of clinicians' drug choices

Drug / Combination drug	Order of choice	Number of Clinicians	Reasons for choice
Tab AS +AQ	1st	5	Following the Anti-malaria Drug Policy for Ghana
Tab AS +AQ	2nd	1	Following the Anti-malaria Drug Policy for Ghana
Tab AL	1st	1	National guideline and less side-effects than Artesunate + Amodiaquine
Tab AL	2nd	1	National guideline and less side-effects than Artesunate + Amodiaquine
Tab AL	2nd	1	National guideline
Tab AL	2nd	1	Easy to administer and effective
Tab AL	2nd	1	Less side-effects than Artesunate+Amodiaquine and well tolerated by majority
Tab AL	3rd	1	For those who are not comfortable with Artesunate+ Amodiaquine

CONT. previous Table 2.11

Drug / Combination drug	Order of choice	Number of Clinicians	Reasons for choice
Tab AS + SP	4th	1	For those allergic to Amodiaquine and/or Lumefantrine
Tab AM + SP	2nd	1	For resistant malaria
Tab SP	4th	1	Patient's choice
Tab AM	3rd	1	For those who react to Amodiaquine and/or Lumefantrine
Tab Quinine	3rd	1	For pregnant women and those who cannot tolerate the drug combinations with AQ and L
Tab Quinine	3rd	1	For pregnant women
Tab Quinine	4th	1	For pregnant women

2.2.2.3 Anti-malaria drugs in injection form

Two of the clinicians prescribe anti-malaria drugs in injection form for the treatment of uncomplicated malaria in adult patients and four of them not.

Reasons for Yes are:

1) If patient is presenting with nausea some are given start dose in injection form to continue with oral medication.

2) If there is excessive vomiting.

Reasons for No are:

1) There is no need for injection if the malaria is uncomplicated.

2) Oral drugs easily absorb and work fast, no pain and do not need a technical person to administer.

3) Oral anti-malaria drugs are relatively safe in the treatment of uncomplicated malaria.

4) Uncomplicated malaria responds well to anti-malaria drugs administered by oral or rectal route.

2.2.2.4 Side-effects of Artesunate+Amodiaquine observed and graded

The grades of side-effects with the number of clinicians respectively were Mild (2), Mild to Moderate (1), Moderate (2) and Moderate to Severe (1).

Figure 2.5: Percentages of clinicians giving the grades of side-effects observed

2.2.2.5 Side-effects of Artesunate+Amodiaquine observed and listed

Table 2.12: List of the side-effects of Artesunate+Amodiaquine observed with the number of clinicians

Side-effects of Tab AS + AQ observed	Number of Clinicians
Acute dystonic reactions	4
Dizziness	2
Weakness	2
Loss of appetite	1
Drowsiness	1
Hypersensitivity reaction	1
Lethargy	3
Vomiting	2
Gastrointestinal upset	1
Uneasiness	1
Nausea	1
Palpitations	1

2.2.2.6 Side-effects of Artesunate+Amodiaquine before stopping the therapy

Table 2.13: List of the side-effects which could compel the clinician to stop the Artesunate-Amodiaquine combination therapy

Side-effect	Number of Clinicians
Acute dystonia	4
Severe vomiting	2
Severe itching of the body	1
Hypersensitivity reaction	1
Palpitations	1
None	1

2.2.2.7 Clinicians' impression on patients who complete the Artesunate-Amodiaquine combination therapy and on percentage of patients who return with treatment failure

All six clinicians interviewed had an impression that majority of patients complete the 3 days course of Artesunate-Amodiaquine combination therapy.

Table 2.14: The percentage of patients who return with treatment failure after the 3 days course of Artesunate-Amodiaquine combination therapy

Number of Clinicians	Percentage
2	Less than 1%
1	Less than 5 %
2	5 %
1	5 – 10 %

2.2.2.8 A patient's preferred choice for the kind of malaria treatment

If a patient with a new episode of uncomplicated malaria does not wish to take Artesunate-Amodiaquine combination again, two of the clinicians will still prescribe Artesunate-Amodiaquine combination and four of them will not.

Reasons for Yes are:

1. In most cases the side-effects wear away after the first or second day of treatment.
2. Patient is advised to complete the course.

Reasons for No are:

1. Patient's wishes must be respected, especially if it is because of an adverse drug reaction.
2. The clinician will rather prescribe another Artemisinin-based combination therapy because the patient may not be compliant.
3. Patient will not comply with the next prescription of Artesunate-Amodiaquine combination and the malaria can become worse or complicated.
4. Patient has a right to drug education and choice.

2.2.2.9 Side-effects of Artemether/Lumefantrine observed and listed

The grades of side-effects with the number of clinicians respectively were Not observed so far (2), Mild (2), Mild to Moderate (1) and Moderate (1).

Table 2.15: List of the side-effects of Artemether/Lumefantrine observed with the number of clinicians

Side-effects of Tab AL observed	Number of Clinicians
Dizziness	2
Weakness	3
Mild nausea	1
Mild palpitations	1
Excessive vomiting	1
Vomiting	1
Nausea	2
None	1

2.2.2.10 Side-effect of Artemether/Lumefantrine before stopping the therapy

Table 2.16: List of the side-effects which could compel the clinician to stop the Artemether/Lumefantrine combination therapy

Side-effect	Number of Clinicians
Excessive vomiting	1
Hypersensitivity reaction	2
None	4

2.2.2.11 Clinicians' impression on patients who complete the Artemether/ Lumefantrine combination therapy and on percentage of patients who return with treatment failure

All six clinicians interviewed had an impression that majority of patients complete the 3 days course of Artemether/Lumefantrine combination therapy.

Table 2.17: The percentage of patients who return with treatment failure after the 3 days course of Artemether/Lumefantrine combination therapy

Number of Clinicians	Percentage
1	2 %
1	3 %
2	5 %
2	None

2.2.2.12 Microscopy for malaria parasite detection

None of the prescribers ask for microscopy for malaria parasite detection every time before they diagnose malaria.

Reasons for this are:

1. Practically impossible because of high patient load (by 2 clinicians).

2. Some cases of uncomplicated malaria are diagnosed only clinically, what reduces the burden on the few laboratory staff.

3. In most cases the results are always negative. When the signs and symptoms are clear, the clinician goes ahead and treats.

4. The clinician uses the clinical signs and proper history taking most of the time.

5. Because the sensitivity and specificity of this test is not encouraging, also many patients take anti-malaria drugs before seeing a clinician.

2.2.2.13 The type of cases sent for microscopy for Malaria Parasite Detection

Table 2.18: Type of cases sent for microscopy for MPD

Type of cases	Number of Clinicians
In complicated malaria cases	4
In cases where a 1st line anti-malaria drug has been given and there are still symptoms of malaria	3
When diagnosis is not certain, there is fever without any other sign or symptom	2
In early pregnancy	1
In some uncomplicated malaria cases	1

CHAPTER THREE

3. 1 DISCUSSION

3.1.1 Types of Anti-Malaria Drugs-Prescribed for General Population

The number of different anti-malarial regimens prescribed were 12, compared to 23 recorded in a study in Urban Ghana.[34]

In adherence to the Policy, the Artesunate-Amodiaquine combination (Tab AS+AQ) was the drug most frequently prescribed (66%) compared to the 24% observed in a study at the KNUST Hospital[35], 43% in a study in Urban Ghana[34] and 83% in a study in the Assin North District.[36] Contrary to the Policy, Artemisinin derivatives as mono therapies and Sulphadoxine-Pyrimethamine as mono and combination therapies were prescribed, despite the fact that the evidence of ACTs' superiority in comparison to mono therapies has been clearly documented.[11] Most clinicians followed the Anti-malaria Drug Policy for Ghana. Those who deviated from it did so because of reactions to AS+AQ.

Almost 10% of cases had an injection of an anti-malaria drug as start dose followed with oral treatment. This was low compared to 21% observed at the Korle-Bu Polyclinic[37], meanwhile the preferred route of administration in uncomplicated malaria is the oral route.[1] In compliance to the Guidelines, four clinicians (67%) answered that there is no need for injection if the malaria is uncomplicated, because oral anti-malaria drugs are relatively safe in the treatment of uncomplicated malaria, easily absorb and work fast. The uncomplicated malaria responds well to anti-malaria drugs administered by oral or rectal route. Also there is no pain and do not need a technical person to administer. Contrary to the Guidelines, two clinicians (33%) prescribe an injection of an

anti-malaria drug as start dose followed with oral treatment of uncomplicated malaria, if the patient presents with nausea or vomiting.

The World Health Organization and Ghana Government/Ministry of Health recommend Tab AS+AQ as the first line drug and Artemether/ Lumefantrine (AL) as the second line drug for the treatment of uncomplicated malaria.[4] With 14% of total prescriptions AL was the second most frequently prescribed drug. That was better than the 65.3% at the Korle-Bu Polyclinic[37], but worse than the 4% at the KNUST Hospital.[35] Most clinicians followed the recommendation stated above, because AL is for those who are not comfortable with AS+AQ and it is easy to administer and effective.

Clinicians expressed a more favourable opinion about the treatment with AL. They observed fewer and less severe side-effects of AL compared to AS+AQ. They had a view that lower percentage of patients return with treatment failure after the 3 days course of combination therapy with AL. Also fewer side-effects are viewed as severe enough to compel the clinician to stop the therapy with AL than with AS+AQ. This can influence the clinicians to prescribe AL more frequently than AS+AQ, with its negative economic and public health implications on malaria treatment in the hospital.

The side-effects of AS+AQ mentioned by the clinicians correspond with the side-effects documented[11], meanwhile some of the side-effects documented were not observed yet by the clinicians, these are: tinnitus, reticulocytopenia, neutropenia, elevated liver enzyme values and electrocardiographic abnormalities as side-effects of Artesunate, and leucopenia and agranulocytosis after repeated use of Amodiaquine. The frequency and nature of adverse events among the healthy volunteers were of concern, and suggest laboratory monitoring would be needed in malaria patients treated with

AS+AQ.[14] The side-effects of AL mentioned by the clinicians also correspond with the side-effects documented[38], meanwhile some of the side-effects documented were not observed yet by the clinicians, these are: abdominal pain, sleep disturbances, anorexia, diarrhoea, cough, headache, asthenia, arthralgia and myalgia. Inj AM+Tab AL, Tab AS+Metakelfin, Tab Metakelfin and Inj AM+Tab Metakelfin were also prescribed contrary to the recommendation. Supp AM + Tab AS+AQ combination-prescribed was minimal, even though based on research findings Artemisinin suppositories rapidly eliminate parasites and appear to be safe.[39]

3.1.2 Types of Anti-Malaria Drugs-Dispensed to General Population

According to the Policy, monitoring of the Policy implementation will focus on the availability and the quality of Artesunate-Amodiaquine and Quinine.[5] Out of 1447 cases for the general population in 1441 drugs were dispensed to the patients, showing a high anti-malarial drug availability of 99.6% in the year 2008.

Comparing the types of anti-malaria drugs-prescribed with the types of anti-malaria drugs-dispensed, AS+AQ-dispensing was increased by 1.0% and AL-dispensing was reduced by 1.1%. The Artemisinin-based mono therapies-dispensed were increased by 0.2% and the drugs with Tab SP-dispensed were also increased by 0.1%. Inj AM+Tab AL-dispensing was reduced by 0.3% and Tab AS+Metakelfin-dispensing was also reduced by 0.3%. The percentage of all therapies with injection form of anti-malaria drugs-dispensed was reduced by 0.2%. Supp AM+Tab AS+AQ combination was not dispensed, meanwhile it is an alternative for cases with persistent vomiting to use rectal Artesunate.[1] Although these percentages of increase and decrease were not significantly high, I can conclude that the availability of Tab AS+AQ was better than that of Tab AL.

The reasons for this could have been various like; the Policy was more strictly followed by the drug procurement committee than by the prescribers and/or AS+AQ was more affordable and available at the supplier.

3.1.3 Duration of Treatment for General Population

The percentage of patients that received combination therapies was 89% since the duration of treatment of 3 days represents the Artemisinin-based combination therapies and the duration of treatment of more than 3 days and statim represents the mono therapies with 11%. This was worse than at the KNUST Hospital where 95% of the total anti-malarials prescribed were combination therapies whiles 5% were mono therapies.[35] The use of mono therapies does not correspond with the Policy and has negative public health implications, e.g. the use of the Artemisinin derivatives as mono therapy may increase the development of malaria parasites resistant to ACTs.

The Malaria Control Programmes faced difficulties in implementing ACTs, but cannot predict how long their therapeutic life will be, especially in countries which have chosen drugs also available as mono therapies.[10] The high prevalence of potentially AQ resistant parasites raises questions about the utility of AQ as a partner drug for ACT in Ghana. The efficacy of AS+AQ in Ghana requires, therefore, continuous monitoring and evaluation.[20]

3.1.4 Treatment of Uncomplicated Malaria in Pregnant Patients

Malaria in pregnancy is serious, and drug resistance in Africa is spreading.[26] Adding to this, 10% of pregnancies were teenage pregnancies making the sickness even more dangerous. Nine different anti-malarial regimens were prescribed for pregnant patients. This was better than the 12 recorded for the general population.

Following the Policy, Tab AS+AQ was the most frequently prescribed drug with 46% in the 3rd trimester. Tab Quinine was also prescribed in the recommended dosage regime of 600mg 8 hourly for 7 days(6) in the 2nd and 3rd trimester.

Contrary to the Policy, an Artemisinin derivative as mono therapy was most frequently prescribed with 35% in the 2nd trimester. Some drug combinations were specially prescribed in the 3rd trimester of pregnancy, they are Inj AM + (Tab AS + SP) and Inj Quinine + (Tab AS +AQ). Also the rest of the drugs prescribed in pregnancy do not correspond with the Policy. The reasons for the high level of Artemisinin mono therapy prescribing in pregnancy could have been that prescribers found it being more effective(28) and/or without the side-effects of Amodiaquine(11).

Although the prescribed drugs are considered to be safe in the 2nd and 3rd trimester of pregnancy and were always dispensed, the fact that high number of different anti-malarials were used including mono therapies, underlines its negative effect on the anti-malaria drug policy implementation and on public health.

3.1.5 Dosage for the Combination in the Treatment of Uncomplicated Malaria

Tab Artesunate-Amodiaqine combination therapy was dispensed in five different doses to patients. All the other anti-malarials were dispensed in one dosage regimen to all patients.

The Artesunate-Amodiaquine combination therapy was dispensed in the following dosages based on the NMCP treatment charts:

1. Tab Artesunate 100mg + Tab Amodiaquine 200mg base to be administered daily concurrently for three consecutive days and it was a correctly body weight

adjusted dose dispensed to 4 patients in the 50 kg and less body weight category, in accordance with the Policy recommendation.

2. Tab Artesunate 150mg + Tab Amodiaquine 400mg base to be administered the same way as stated above and it was dispensed as a correctly body weight adjusted dose to 2 patients in the 50 kg and less body weight category. In 1 case of 51-70 kg body weight the dosage was reduced contrary to the Policy recommendation.
3. Tab Artesunate 200mg + Tab Amodiaquine 400mg base to be administered the same way as stated above and it was dispensed to 86 patients in the body weight category of 50 kg and less where the dosage of Amodiaquine was weight-adjusted but the dosage of the Artesunate was not. In the 51-70 kg category the dosage of Amodiaquine was reduced in 60 cases and also in the More than 70 kg body weight the dosage was reduced in 1 case, contrary to the policy recommendation.
4. Tab Artesunate 200mg + Tab Amodiaquine 600mg base to be administered the same way as stated above and it was dispensed in the recommended dosage to 534 patients in the body weight category of 51-70 kg. In the 50 kg and less the dosage is appropriate for the age of more than 14 years but it could have been reduced to be weight-adjusted in 190 cases. In the More than 70 kg the dosage could have been increased to be weight adjusted in 102 cases.
5. Tab Artesunate 200mg + Tab Amodiaquine 800mg base to be administered the same way as stated above and it was dispensed to 2 patients in the More than 70 kg category but the dose of Artesunate was not body weight-adjusted.

Adding to these not correctly body weight-adjusted doses (442), in 110 cases the body weight was not measured at all and AS+AQ therapy was given, meaning that 35.9% of all (1537) prescriptions had no correct dosages. This was better than in Assin North District (68.2%)[36] and at Korle-Bu Polyclinic (77.9%).[37]

Though providers are prescribing AS+AQ, the dosages prescribed according to the NMCP charts are not right because the charts have too wide weight ranges and this leads to systematic under dosing and overdosing of some patients.[36] This, in addition to the incorrect dosages stated above, could have contributed to the treatment failures and side-effects mentioned by the clinicians. It is important to ensure that the right drug and right dosage are being prescribed, since this would help to minimize the development of resistant strains and to improve patient's care and save cost.[35] So it is important to measure the body weight for every patient so that the right dose could be calculated.

3.1.6 Discussion on whether Patients' Compliance and Acceptance as Perceived by Prescriber, Influence Prescriber Prescribing Habits

There have been significant changes in prescriber prescribing habits at Dormaa Presbyterian Hospital between January and December 2008.

Types of anti-malaria drugs-prescribed changed during the year, e.g. there were wide variations in the prescribing patterns as a high rate of AS+AQ prescribing in January and low in December. The rate of AL prescribing increased and the Artemisinin derivative prescribing reduced over the year. The prescribing of other mono and combination therapies has been also very much reduced by the end of the year 2008 (Table 2.10). So while in Jan. 2008 Tab AS+AQ was prescribed as 1st choice drug with 86.0%, by Dec. 2008 Tab AL has become the 1st choice drug with 45.3% and Tab AS+AQ the 2nd choice

with 37.6%. Artemether-Lumefantrine is the most prescribed antimalarial at Korle-Bu Polyclinic also.[37]

Two Medical Assistants and four Medical Officers took part in the study, five of them being in clinical practice for 1-5 years and one above 20 years. As the questionnaire to the clinicians was administered in April 2009, it could not influence prescriber prescribing habits during the year 2008 which was the period covered by the retrospective study. On the other hand the results of retrospective study guided the questions put to the clinicians so that the objectives of the study could be fully achieved. The clinicians observed that majority of patients complete the 3days course of AS+AQ and AL therapies. Two clinicians also think that if a patient with a new episode of uncomplicated malaria does not wish to take AS+AQ again they will still prescribe AS+AQ for him or her, because in most cases the side-effects wear away after the first or second day of treatment and they will advise the patient to complete the course. Meanwhile four clinicians think that they will not prescribe AS+AQ if a patient does not wish to take AS+AQ again, because patient's wishes must be respected, especially if it is because of an adverse drug reaction. The patient will not comply with the next prescription of AS+AQ and the malaria can become worse or complicated. Also the patient has a right to drug education and choice and the clinician will rather prescribe another ACT (Artemether-Lumefantrine) because the patient may not be compliant. So it can be concluded, that the prescribing habit of 67% of the prescribers was influenced by their perception of the patients' compliance and acceptance of the therapy and that led them to prescribe contrary to the Policy.

A study in Urban Ghana (24 participating healthcare facilities) shows that nearly 2 years after the change in the national anti-malarial policy, the recommended first-line

therapy was adhered to in less than 50% of cases.[34] Reasons for this may be attributed to the initial safety concern raised over the AS+AQ combination therapy.[34] A study at the KNUST Hospital indicates that prescribers are aware of the combination therapy for uncomplicated malaria but are not using the recommended medicines. Further studies should be conducted to find reasons for this, as good prescribing habit is an important component of rational use of medicines.[35]

The results of this study at Dormaa Presbyterian Hospital underline the importance of constant dialogue with prescribers and their education, so that prescriber prescribing habits could be developed to correspond to the Drug Policies of the country, so that they can have a positive impact on population health.

3.1.7 Assessment of the Importance Given to Laboratory Evidence Obtained with Microscopy for Malaria Parasite Detection in Making the Diagnosis of Malaria

In most of the cases (87%) no laboratory evidence was obtained before making the diagnosis of malaria. In addition to this in 8.5% of cases no malaria parasites were seen. So in summary only in 4.5% of cases for the general population the diagnosis was based on laboratory evidence and in 95.5% was not, compared to Korle-Bu Polyclinic, Accra were 92.9% of prescriptions had no diagnosis of malaria stated, showing a very high level of presumptive diagnosis of malaria.[37]

For pregnant women there was an increment in the percentage of cases diagnosed based on laboratory evidence from 5.9% in the 2nd trimester to 8.9% in the 3rd trimester and also compared to the general population (4.5%).

Also in cases with increased body temperature (> 37.5 ˚C) the result improved, since in 40.4% of cases the microscopy for MPD was performed, compared to cases with body

temperature < or = 37.5 ˚C with 11.2% and the body temperature not taken category with 5.8%.

The percentages of malaria parasites seen one (1) plus (MPS P.+) and malaria parasites seen two (2) plus (MPS P.++) results of microscopy for MPD are higher in pregnant patients than in the general population. Also they are much higher in increased body temperature (> 37.5 ˚C) (where the malaria parasites seen three (3) plus (MPS P.+++) is also to be found) than in cases with body temperature < or = 37.5 ˚C and in the body temperature not taken category, e.g. there is a 13.8 % increment of the MPS P.+ results with the body temperature higher than 37.5 ˚C compared to the body temperature not taken category.

The percentages of types of anti-malaria drugs-prescribed within the results of microscopy for Malaria Parasite Detection show that the percentage of Tab AS+AQ is the highest under the MPS P.+ with 81.4% and under the MPS P.++ its combination with injection (Inj AM+Tab AS+AQ) is increased. The percentage of Tab AL is also increased and the drug prescribed for MPS P.+++ is Tab AL with 100%.

A study in Urban Ghana suggests an important role of confirmatory diagnosis in rational prescribing, because patients with parasitologically confirmed diagnosis were 9 times more likely to be prescribed AS+AQ than those with presumptive diagnosis, indicating that confidence of healthcare professionals in the first-line therapy is enhanced by having access to confirmatory test.[34] In Dormaa Presbyterian Hospital there was an 18.5% increment of Tab AS+AQ prescribing between not performed tests of microscopy for MPD and tests with MPS P.+ results.

None of the clinicians asked for microscopy for malaria parasite detection every time before they diagnose malaria. They are saying that it is practically impossible

because of high patient load on the few laboratory staff. They also think that many patients take anti-malaria drugs before seeing a clinician and the sensitivity and specificity of this test is not encouraging. So when the signs and symptoms are clear, they diagnose clinically and go ahead and treat.

They mostly ask for microscopy for malaria parasite detection in complicated malaria cases, when diagnosis is not certain and there is fever without any other sign or symptom of malaria, in early pregnancy, in cases where 1st line Anti- malaria drug has been given and there are still symptoms of malaria and only in some uncomplicated malaria cases. Meanwhile, in 2008, the MOH with the support of USAID, WHO and other stakeholders published the National Guidelines for Laboratory Diagnosis of Malaria. The application of this valuable document will ensure that prescribers know what they are treating -Malaria and treat it effectively.[4]

3.1.8 Limitations

It might have been interesting and useful to ask the patients also about their experiences, views and possible complaints about the anti-malaria drugs used before. However due to foreseen constraints it was not part of this study.

3.2 CONCLUSION

- Majority of prescribers adhered to the Anti-Malaria Drug Policy for Ghana.
- The dosage for the Artesunate-Amodiaquine combination in the treatment of uncomplicated malaria was not always adjusted correctly for body weight.
- Contrary to the Policy, Artemisinin derivatives were given as mono therapies and Sulphadoxine-Pyrimethamine and combinations were prescribed.
- Furthermore the clinicians perceive Artemether/Lumefantrine to have less severe side-effects, easy to administer and effective, lower percentage of patients return with treatment failure and it is for those who are not comfortable with Artesunate-Amodiaquine.
- Prescribers perceive that majority of patients comply and complete the 3 days course of the combination therapy, but majority of prescribers will not prescribe Artesunate-Amodiaquine against the patient's wishes but rather will prescribe Artemether/Lumefantrine.
- The laboratory diagnosis of malaria is seldom in Dormaa Presbyterian Hospital. In pregnancy there was an increment in the percentage of cases diagnosed based on laboratory evidence compared to the general population. Also the percentage of performed microscopy for malaria parasite detection was higher in the case of increased body temperature.

3.3 RECOMMENDATIONS

1. Health officials and agencies could further initiate the revision of the Policy to state that: An Artemisinin-based Combination Therapy shall be the combination drug of choice for treating uncomplicated malaria, and to list the approved combinations, e.g. Artemether-Lumefantrine, Artesunate-Amodiaquine, etc.
2. The Policy regulations must be enforced by the Ministry of Health, and the misuse of Artesunate, Sulphadoxine-Pyrimethamine and any mono therapy should be stopped.
3. Correctly body weight-adjusted dosage regimes of ACTs should be prescribed and dispensed in all healthcare institutions and it should be monitored regularly by the rational use of medicines monitoring teams.
4. The availability of the ACTs at all times has to be enforced by the Hospital Management. Periodic audits should be conducted to monitor which anti-malaria drugs are stocked, prescribed and dispensed in the Hospital. This could be supported by the Government of Ghana and the private sector.
5. To improve the clinicians and patients' compliance and acceptance, public education is needed to totally remove the negative attitude towards Artesunate-Amodiaquine and the other ACTs has to be made equally available, so that clinicians can select the most appropriate drug for a particular patient.
6. Since prompt and accurate diagnosis of malaria is key to effective management of malaria cases, the laboratory diagnosis of malaria has to be strengthened. The infrastructure, equipment, supplies and the number of adequately trained personnel has to be adjusted to the increased patient load and to gain the confidence of the prescribers.

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APPENDIX I

FRAMEWORK FOR DATA COLLECTION

NO	PATIENT FOLDER NO.	INITIALS	SEX	AGE (YEARS)	DATE OF TREATMENT PRESCRIBED	BODY TEMP (^{o}C)	BODY WEIGHT (KG)	TRIMESTER OF PREGNANCY (2^{nd} / 3^{rd})	TYPES OF ANTI-MALARIA DRUG(S)		DOSE	DURATION OF TREATMENT	RESULT OF MICROSCOPY FOR M. P. D.
									PRESCRIBED	DISPENSED			

APPENDIX II

QUESTIONNAIRE TO DETERMINE THE USE OF ARTEMISININ-BASED COMBINATION THERAPIES IN THE TREATMENT OF UNCOMPLICATED MALARIA IN ADULT PATIENTS AMONG CLINICIANS

FORM №.: ….

1. Professional Background.

☐ Medical Assistant ☐ Senior Medical Officer

☐ Medical Officer ☐ Specialist

2. How long have You been in Clinical Practice?

☐ Less than 1 year ☐ 1 – 5 years

☐ 6 -10 years ☐ 11 – 20 years

☐ Above 20years

3. Which Anti-malaria drug(s) do you prescribe for the treatment of uncomplicated malaria in adult patients and why? Please, write the drug you prescribe the most often as the first and the drug you prescribe the least often as the last.

DRUG / COMBINATION DRUG	**REASONS FOR CHOICE**
1.	
2.	
3.	
4.	
5.	
6.	

4. Do you prescribe Anti-malaria drug(s) in injection form for the treatment of uncomplicated malaria in adult patients?

☐ Yes ☐ No

5. If Yes to (4), what are your reasons?

……

……

6. If No to (4), what are your reasons?

……

……

7. How would you grade any side-effect(s) that you have observed with the use of Artesunate-Amodiaquine combination in patients?

☐ Not observed so far ☐ Severe

☐ Mild ☐ Fatal

☐ Moderate

8. List the side-effects that you have observed so far with the use of Artesunate-Amodiaquine combination therapy:

……

……

9. List the side-effects which could compel you to stop the Artesunate-Amodiaquine combination therapy:

……

……

10. What is your impression of your patients who completed the 3days course of Artesunate-Amodiaquine combination therapy?

☐ They are in minority. ☐ They are in majority.

11. In your view what percentage of patients comes back with treatment failure after the 3 days course of Artesunate-Amodiaquine combination therapy?

……

……

12. A patient with a new episode of uncomplicated malaria does not wish to take Artesunate-Amodiaquine combination again. Will you prescribe Artesunate-Amodiaquine combination for him/her?

☐ Yes ☐ No

13. If Yes to (12), what are your reasons?

……

……

14. If No to (12), what are your reasons?

……

……

15. How would you grade any side-effect(s) that you have observed with the use of Artemether-Lumefantrine combination therapy in patients?

☐ Not observed so far ☐ Severe

☐ Mild ☐ Fatal

☐ Moderate

16. List the side-effects that you have observed so far with the use of Artemether-Lumefantrine combination therapy:

……

……

17. List the side-effects which could compel You to stop the Artemether-Lumefantrine combination therapy:

……

……

18. What is your impression of your patients who completed the 3days course of Artemether-Lumefantrine combination therapy?

☐ They are in minority. ☐ They are in majority.

19. In your view what percentage of patients comes back with treatment failure after the 3 days course of Artemether-Lumefantrine combination therapy?

……

.....

20. Do you ask for microscopy for malaria parasite detection every time before you diagnose malaria?

☐ Yes ☐ No

21. If Yes to (20), why?

……

……

22. If No to (20), why?

……

……

23. If No to (20), in which type of cases do you ask for microscopy for malaria parasite detection?

……

……

……

.....