EVALUATING THE EFFICIENCY OF MALARIA TREATMENT IN SOUTH EASTERN NIGERIA: THE ROLE OF PHARMACOECONOMICS AND HEALTH OUTCOMES RESEARCH

BY

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SEPTEMBER 2015

DECLARATION

I certify that the work reported in this dissertation was carried out by me under the supervision of Professors Charles Esimone and Mathew Okonta.

The presentation describes the results obtained from my research work except where appropriate references have been made in the text. No part of the dissertation has been presented for any other degree in this or any other university

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CERTIFICATION

We hereby certify that Ezenduka, Charles Chukwuemeka carried out this research work in the Department of Clinical Pharmacy & Pharmacy Management of Nnamdi Azikiwe University Awka.

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DEDICATION

TO GOD ALMIGHTY, TO WHOM ALL GLORY AND HONOUR BELONG

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To GOD, all the glory and honour

LIST OF PUBLICATIONS & PRESENTATIONS FROM THE STUDY

The following papers have been published as elements from this research work

1. ***Ezenduka CC,*** Okonta J.M, Ogbonna B.O (2013) Survey of antimalarial drugs prices and availability in retail outlets in Enugu urban South East Nigeria. *Value in Health* 2013; 16(3):A96. DOI:10.1016/j.jval.2013.03.451**[ONLINE]**

2. ***Ezenduka CC,*** Ogbonna BO, Ekwunife OI, Okonta MJ, Esimone CO. Drugs use pattern for uncomplicated malarial in medicine retail outlets of Enugu urban, southeast Nigeria: implications for malaria treatment policy. **Malar J** 2014, 13:243 **doi:10.1186/1475-2875-13-243 [ONLINE]**.

3. ***Ezenduka CC***, Okonta M J, Esimone C O. Adherence to treatment guidelines for uncomplicated malaria at two public health facilities in Nigeria; Implications for the 'test and treat' policy of malaria case management. Journal of Pharmaceutical Policy and Practice 2014 7:15 **[ONLINE]**

4. ***Ezenduka CC.*** Treatment costs for uncomplicated malaria at a public health facility in Awka, South East Nigeria. *Value in Health* 2015; **18(3): A236.** 2015. DOI: 10.1016/j.jval.2015.03.1371 **[ONLINE].**

Similarly, elements of this dissertation have been presented in conferences as follows;

1. ***Ezenduka C.C,*** Okonta J, Ogbonna B.O. Survey of antimalarial drugs prices and availability in retail outlets in Enugu urban South East Nigeria. Third International Conference for Improving the Use of Medicines (**ICIUM**): **Antalya Turkey: 14 – 18 November 2011**

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ABBREVIATIONS/ACRONYM

AA	Artesunate +amodiaquine	IRS	Indoor residual spray
ACER	Average cost-effectiveness ratio	ITN	Insecticide treated net
ACPR	Adequate clinical and parasitological response	ITT	Intention to treat
ACT	Artemisinin-based combination therapy	LGA	Local Government Area
ADR	Adverse drug reaction	LLIN	Long lasting insecticidal treated net
AL	Artesunate + lumefantrine	LTF	Late treatment failure
AQ	Amodiaquine	MCO	Managed Care Organization
AS	Artesunate	MMV	Medicine for Malaria Venture
ASAQ	Artesunate + amodiaquine	MDG	Millennium development Goals
ASMQ	Artesunate + mefloquine	MNCH	Maternal, newborn and child health
ASSP	Artesunate + sulphadoxine-pyrimethamine	MQ	Mefloquine
BIA	Budget impact analysis	MSH	Management Sciences for Health
CBA	Cost benefit analysis	NAUMC	Nnamdi Azikiwe University Medical Center
CDC	Center for Disease Control	NAUTH	Nnamdi Azikiwe University Teaching Hospital
CEA	Cost effectiveness analysis	NGO	Non-Governmental Organization
CER	Cost effectiveness ratio	NHIS	National Health Insurance Scheme
CIE		NMCP	National Malaria Control Programme
CMA	Cost minimization analysis	OAU	Organization of African Unity
COI	Cost of illness	OOP	Out-of-pocket
CQ	Chloroquine	OTC	Over the counter
CUA	Cost utility analysis	PE	Pharmacoeconomics
DALY	Disability adjusted life years	PE/HE	Pharmacoeconomics/Health Economics
DDT	Dichlorodiphenyltrichloroethane	pLDH	Plasmodial lactacte dehydrogenase
UK-DFID	United Kingdom Department for International Development	PMI	US President's Malaria initiative
		PMV	Patent Medicine Vendors
DG	Director general	PP	Per Protocol
DHAPQ	Dihydro-artemisinin-piperaquine	PSA	Probability sensitivity analysis
DRC	Democratic Republic of Congo	QALY	Quality adjusted life years
ECHO	Economic, clinical and humanistic outcomes	QN	Quinine
ETF	Early Treatment Failure	RBM	Roll Back Malaria

FMCH	Free maternal and child health	RCT	Randomized Controlled Trial
GDP	Gross Domestic Product	RDT	Rapid Diagnostic Test
GFATM	Global Fund for HIV/AIDS, tuberculosis and malaria	ROI	Return on Investment
GOPD	General outpatients department	SA	Sensitivity analysis
HAI	Health Action International	SEA	South East Asia
HIV/AIDS	Human Immunodeficiency Virus/Acquired Immune Deficiency Syndrome	SuNMaP	Support for Nigeria Malaria Programme
		SP	Sulphadoxine –pyrimethamine
HRP	Histidine-rich protein	SSA	sub-Sahara Africa
HRQL	Health related quality of life	SuNMaP	Support for Nigeria's Malaria Programme
ICER	Incremental cost-effectiveness ratio	THE	Total Health Expenditure
ICU	Intensive Care Unit	TTT	Test, Treat and Track
IMCI	Integrated Maternal and Child Illness	UNDP	United Nations Development Programme
IOM	Institute of Medicine (USA)	UNICEF	United Nations International Children Fund
IPD	Inpatient department	UNO	United Nations Organization
IPT	Intermittent preventive therapy	USP	United States Pharmacopoeia
IPTc	Intermittent preventive therapy in children	WB	World Bank
IPTp	Intermittent preventive therapy in pregnancy	WHO	World Health Organization
IQWIG	Institute for Quality and Efficiency in Healthcare	WTP	Willingness to pay

ABSTRACT

Background: Malaria officially remains a leading cause of death and disability in Nigeria, responsible for over 300,000 deaths annually, mostly in children and pregnant women with huge economic burden. Inefficiency in drug treatment leads to widespread resistance and treatment failures, undermining treatment goals and worsening disease burden. Pharmacoeconomics provides the basis for informed choices between treatment options and alternative medications based on a combination of information on their costs and health outcomes, to enhance the efficiency of treatment and improved therapeutic outcomes.

Objective: The study aimed to evaluate the efficiency of malaria treatment in south east Nigeria, using the principles of pharmacoeconomics to generate evidence-based information for improving the efficiency of malaria treatment in Nigeria.

Methods: An eclectic mix of methods were used to analyze the treatment for uncomplicated malaria at both the public and private health facilities in Enugu and Anambra states; ranging from cross-sectional observational studies in Enugu urban city, review of treatment practices at the Nnamdi Azikiwe Teaching Hospital Nnewi and University Health Center Awka, costs study to clinical evaluation of effectiveness at the University Health Center Awka. In the major clinical study, under routine clinical setting, the relative costs and clinical effects of commonly used antimalarial drugs: Artemeter-lumefantrine (AL), Dihydro-artemisinin-piperaquine (DHAPQ), artesunate-amodiaquine (ASAQ) and artesunate-sulphadoxine+pyridoxine (ASSP) were evaluated to determine their relative efficiencies in the treatment of uncomplicated malaria. Cost and effect data were collected from patients who presented at the Health Centre with uncomplicated malaria, and were randomized to a three-day course of treatment and followed-up for 28 days. Effects data were based on efficacy and compliance to treatment. Cost data were based on the direct costs of capital and recurrent expenditures. Results were presented as incremental cost-effectiveness ratio (ICER), in terms of additional cost per successfully treated malaria episode with each drug.

Results: Artemisinin-based combination therapies (ACTs) were the most widely used antimalarial drugs at both the private (72%) and public (93%) health facilities. Monotherapy accounted for up to 27% of drug use in the retail sector, while 48% of presumptive diagnosis of malaria cases was documented in the public health facilities. Treatment was characterized by substantial over-diagnosis of cases, poor and over use of medications and wastages. With a wide range of antimalarial drugs, AL followed by DHAPQ was the most prescribed antimalarial drug at both the public and private healthcare facilities. It cost an average of N4, 944 (US$31.49) to treat an episode of uncomplicated malaria in the health facility, with personnel and antimalarial drugs accounting for 82% and 6.6% of the total, respectively. The ICERs ranged between $4.10 (DHAPQ) and 6.73 (ASSP) per additional malaria case treated. Further results showed that DHAPQ generated the least cost per additional malaria case treated, dominating other ACTs as the most cost-effective agent. Diagnostic accuracy, cost of drugs and compliance to treatment were the key parameters that significantly influenced the cost-effectiveness results, without changing the order of magnitude.

Conclusion: Study suggests significant inefficiency in malaria treatment in the South East, indicating a wide scope for improving efficiency. Dihydro-artemisinin-piperaquine at a given budget, is the most cost-effective regimen for treating uncomplicated malaria, generating the most cost-savings and greatest number of malaria treatments, compared to other agents. This should inform policy on the choice of first line drug for improved efficiency in malaria treatment in Nigeria, to achieve treatment goals and reduced burden of malaria disease. Efficiency is achieved under strict adherence to treatment guidelines.

CHAPTER ONE

INTRODUCTION AND STUDY BACKGROUND

1.1 Introduction

This study offers opportunities at addressing the challenges of effective case management of malaria in Nigeria, to enhance the use of safe, effective and cost-effective antimalarial drugs through the use of pharmacoeconomic tools. The importance of pharmacoeconomics has grown rapidly over the last twenty years across the world, informed by the need for efficiency in the provision of drug therapies for diseases. Given the escalating costs of healthcare, driven mainly by growing pharmaceutical expenditures, policy makers are increasingly adopting rational approach to resource allocation to optimize the use of available scarce resources. The cost of medicaments, as a key determinant of treatment success are now routinely collected and compared to their effectiveness, to determine the ones that offer the best values for money. Consequently, the last fifteen years has witnessed a rapid growth of pharmacoeconomic evaluation as an important policy process used by governments and other stakeholders to inform pharmaceutical interventions in the healthcare system. This process has become more imperative for low income countries such as Nigeria, where scarcity of resources are extreme due to poverty, compounded by high incidence of communicable diseases, such as malaria. This dissertation uses pharmacoeconomic methods to assess malaria treatment in south eastern Nigeria. As a leading cause of death and disability, malaria constitutes a big challenge to health care funding due to high cost of treatment, particularly with regards to policy recommendations on the use of Artemisinin-based Combination Therapy (ACT) and high incidence of attack. Reports suggest that malaria treatment consumes significant proportion of the county's

Total Health Expenditure (THE) with increasing potential, because with greater exposure of the population to malaria attack, more cases are expected. Antimalarial drug sales have continued to skyrocket with a wide range of agents in circulation. There is little or no information regarding their economic efficiency, suggesting wastages in the use of available resources, even as effective treatments have continued to elude significant proportion of the low income population due to high cost of treatment. Hence, economic evaluation of antimalarial treatment becomes imperative to provide relevant information to improve efficiency in malaria treatment in Nigeria.

This chapter presents the general overview of issues related to the efficiency of malaria treatment in relation to antimalarial drugs, to establish the basis for this dissertation. It provided a context of issues related to the global burden of malaria and its consequences especially in sub-Sahara Africa (SSA), the historical perspective of control and contemporary approaches to the control of malaria. Case management of clinical malaria episodes, as a key component of malaria control was reviewed. The chapter also reviewed the burden of malaria in Nigeria with an overview of the Nigerian healthcare system in relation to the provision of malaria treatment. Challenges posed to appropriate case management of malaria at both the public and private health facilities are reviewed. The determinants of efficiency in malaria treatment (effectiveness, costs, accuracy of diagnosis, rational drug use) are presented, in order to identify the relevant research gaps for this study.

1.2 The Burden of Malaria Disease

1.2.1 *Malaria Disease*

Malaria is an infectious disease of humans caused by a protozoan parasite known as *Plasmodium*. The parasite is transmitted through the bite of a mosquito and is

characterized by fever, chills, loss of appetite, body aches and pains. In severe cases the disease can progress to excessive anaemia, convulsions, coma and death (Sinclair *et al.,* 2009). It is a vector borne disease transmitted by the female *Anopheles* mosquito which is injected into the human blood by a bite of the mosquito. The parasite multiplies and attacks the red blood cells causing symptoms that include fever and pains which can become severe and progress to coma and death if untreated. There are five species of the *Plasmodium* parasite that are known to cause infection when transmitted to man. These include *Plasmodium falciparum, P. malariae, P. vivax, P. ovale* and *P. knowlesi*. While *P.vivax* is known to be responsible for the largest number of malaria infections in the world, severe cases of attack is caused by *P. falciparum* (Sing *et al.,* 2004), accounting for about 90% of deaths from the disease (Mendis *et al*., 2001). The other species of *P.ovale* and *P. malariae* are known to generally cause milder forms of malaria, rarely fatal. *P. knowlesi* is zoonotic, prevalent in South East Asia (SEA), causing malaria in macaques but can also cause severe infections in humans.

1.2.2 *Uncomplicated and severe malaria*

1.2.2.1 *Uncomplicated malaria*

Malaria disease is divided into uncomplicated and severe/complicated malaria.

Uncomplicated malaria is characterized by symptoms of fever, headache, muscle pains and vomiting (Grobusch *et al*., 2005). If untreated this may progress to severe malaria with complications that eventually lead to death (Sinclair *et al.,* 2009).

1.2.2.2 *Severe malaria*

Severe malaria is characterized by symptoms of organ dysfunction or high level of parasitaemia, manifesting with lactic acidosis, severe anaemia, hypoglycaemia,

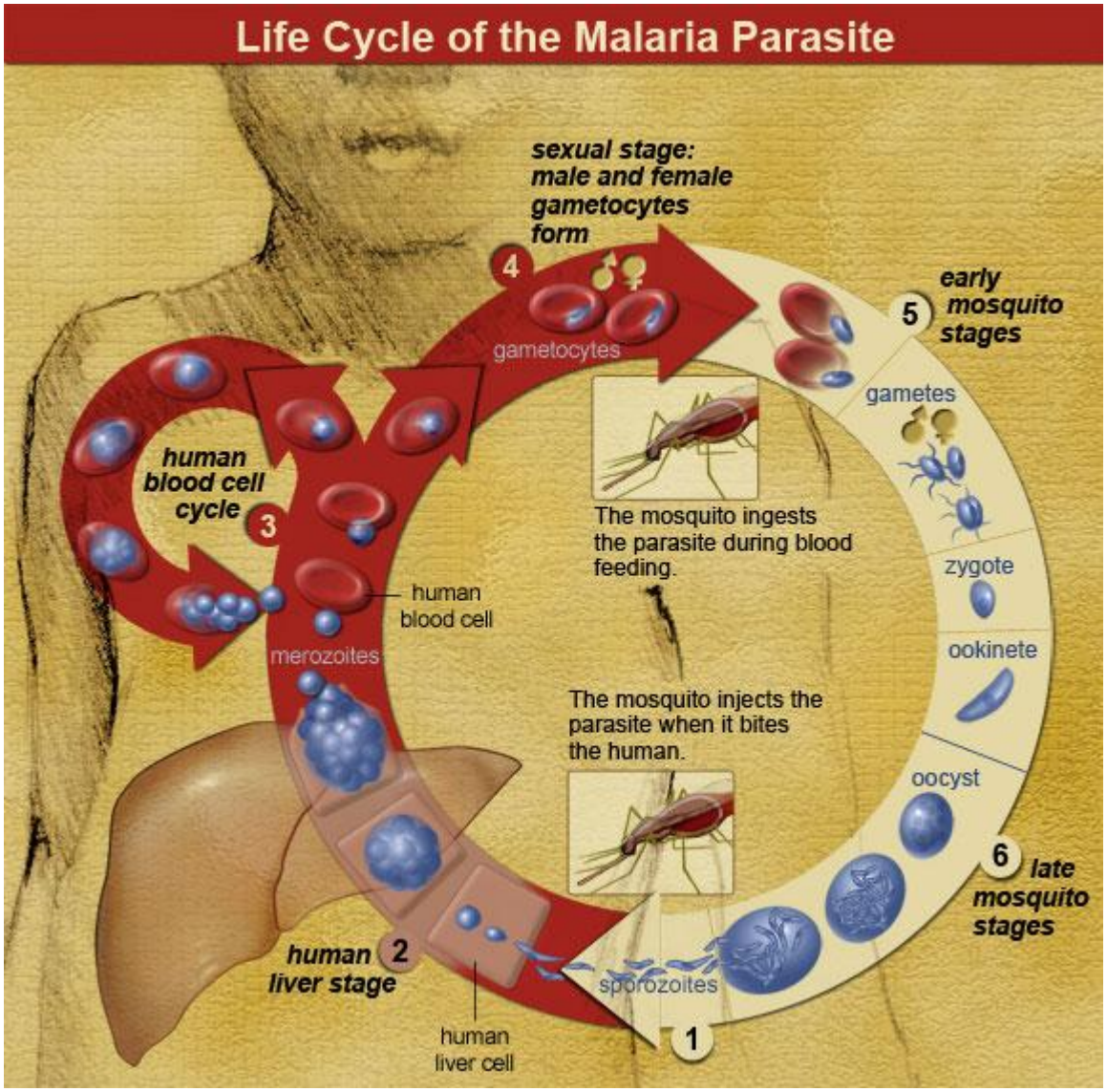
renal failure and coma (characteristics of cerebral malaria). If not quickly and appropriately treated at this stage, the condition would progress to death. Case fatality rates of about 10 - 20% of treated cases have been reported (van Vught *et al.*, 2011). In highly endemic countries, older children and adults usually develop partial immunity which lowers the risk of developing severe malaria (van Vught *et al.*, 2011). *P. falciparum* causes both complicated and uncomplicated malaria attacks.

1.2.3 *Malaria parasite life cycle*

The malaria *Plasmodium* parasite has two broad phases of life cycle, comprising a first phase of sexual replication (sporogony) occurring within the mosquito, and an asexual phase that occurs in the human victim (Gilles, 1993). In the first phase, the mosquito ingests both male and female *gametocytes* (micro- and macro-gametocytes, respectively, while taking a human blood meal. These gametocytes undergo maturation within the mosquito, fertilizing together in the mosquito gut to form a globular zygote. Subsequently the zygote develops, becoming elongated and motile to form an oökinete. The oökinete next invades the midgut wall of the mosquito to further develop into a static oöcyst. As the oöcyst matures, it ruptures to release motile sporozoites which migrate to the salivary glands of the mosquito, to be then injected into humans during the next blood meal (Garnham, 1988; Amin Thesis 2005).

Sporozoites that survive the human body defences invade the liver cells, entering into *the exo-erythrocytic stage* to form the liver schizonts. The resultant schizonts rupture to release thousands of merozoites into the blood stream. In the case of *P.* vivax and

P. ovale, some sporozoites remain in the liver cells to form hypnozoites, which often lead to relapse in malaria attack. The merozoites now circulate in the blood to infect red blood cells as part of erythrocytic stage. Within the erythrocytes, the merozoites multiply, from where they are periodically released into the blood stream to infect more and more red cells. This cycle of massive release and attack of red blood cells corresponds to the clinical symptoms that are recognized as malaria. As the merozoites circulate in the blood some differentiate into gametocytes which are then ingested by the mosquitoes when they bite the human body for a blood meal. In the mosquito another cycle begins as the ingested gametocytes undergo further maturation in the mosquito gut to form sporozoites. The sporozoites then migrate to the mosquito salivary glands from where they are injected into the human hosts in the next blood meal, and the cycle continues (Figure 1.1).



Source: NIAID:

Figure 1.1: Life cycle of *Plasmodium* in man and in the mosquito
(http://www.niaid.nih.gov/topics/malaria/pages/lifecycle.aspx)

1.2.4 *Global burden of malaria disease*

Malaria disease has remained a global leading cause of death and disability in which about 50% of the world population is estimated to be at risk, especially in low and middle income countries (WHO 2005). In 2009, the WHO estimated about 225 million cases of malaria attack the world-over, with over 780,000 deaths (WHO, 2010). Further report indicated that every year about 219 million people are said to develop attack resulting to an average of 660,000 deaths (Ay *et al*., 2010; Murray *et al*., 2012; WHO 2012). Greatest proportion of the burden occurs in sub-Africa alone which accounts for 81% of cases and 91% of deaths, occurring mostly in children (Davis *et al.,* 2011), with sub-Sahara Africa the main theatre of events (Arrow *et al*., 2004). Although 109 countries are currently classified as endemic for malaria, the whole of sub-Sahara Africa and 45% of south east Asian (SEA) population are at risk (Buchanan *et al.,* 2010; van Vught *et al*., 2011). The risk profiles of SEA countries are said to vary between stable, unstable and no risk (Buchanan *et al*., 2010). Nigeria is at the top of the six highest burden countries in the WHO African region (in order of estimated number of cases) which include Democratic Republic of the Congo (DRC), United Republic of Tanzania, Uganda, Mozambique and Cote d'Ivoire. These six countries account for an estimated 103 million (or 47%) of malaria cases (WHO 2012). According to current WHO estimate, Nigeria and DRC together account for about 40% of the global malaria burden (WHO 2013). Two species of the malaria parasites, *P. falciparum* and *P.vivax* are responsible for most attacks with *P. falciparum* accounting for 90% of cases (94% in SSA, 57% in South East Asia (SEA) (Buchanan *et al*., 2010).

Women and children bear the greatest burden of malaria disease, as the most vulnerable groups. The majority of malaria-related deaths (87%) occur in children

under five years in SSA (Davies *et al* 2011; Hay *et al*., 2004). Malaria deaths in children mainly result from cerebral malaria and anaemia. Up to 20% of the children who survive severe malaria are said to experience neurological sequelae including behavioral disorders, and other sequelae (Sachs & Malaney 2002). Evidence suggest that pregnant women with malaria have a higher risk of developing severe anaemia and the percentage of maternal deaths attributed to malaria range from 0.5% to 23% (Desai *et al*., 2007). There is a very high risk of a baby to be born with low birth weight (LBW) from women with placental malaria. Protein calorie deficient nutrition as well as micronutrient deficiencies, in particular zinc and vitamin A have been identified to contribute substantially to malaria burden (Caulfield *et al*., 2004).

In recognition of the heavy burden of malaria disease, the United Nations embedded malaria control in one of the Millennium Development Goals, "to combat HIV/AIDS, malaria and other communicable diseases; Goal number 6 (UNO, 2005). Similarly in 2000 the World Health Organisation (WHO), in conjunction with the governments of malaria-afflicted nations and other development agencies like the World Bank, United Nations International Children and Education Fund (UNICEF) and the United Nations Development Programme (UNDP), initiated the Roll Back Malaria (RBM) programme with the objective of halving the burden of malaria by the year 2010 (OAU, 2000). Preventive intervention involving the use of insecticide-treated bed nets (ITN) is one of the key components of the RBM which also includes intermittent preventive treatment (IPT) during pregnancy as well as the early and effective treatment of clinical cases with artemisinin-based combination therapy (ACT) (Hanson and Goodman, 2004)

Even as several global efforts at control have led to a substantial reduction of the disease burden in the last decade, the malaria disease has continued to pose a major

challenge to global health and healthcare in the current civilisation (Lemma, 2012). Widespread regional and international efforts at controlling malaria began in the 1940s and 1950s, with strategies evolving over time (CDC; Tanner *et al.,* 2008). Elimination of the malaria disease occurred in parts of Americas, Europe and Asia from the early 1950s until 1978 (CDC; Tanner *et al.,* 2008). However, such efforts have not been successful in many of the hardest hit areas, particularly SSA (CDC; Tanner *et al.,* 2008). Nevertheless, recent support and attention given to these regions by the United States, other donor governments, multilateral institutions, and affected countries, has helped to increase access to prevention and treatment to reduce cases and deaths (WHO 2013; RBM 2008; UN, MDGs 2011). Yet, even though access to interventions has increased, gaps and many challenges have continued to complicate the efforts at malaria control in these hard-hit areas. These challenges include poverty, poor sanitation, weak health systems, limited disease surveillance capabilities, drug and insecticide resistance, natural disasters, armed conflict, migration, and climate change (WHO 2003; CDC; Tanner *et al.,* 2008;RBM 2008; Senior 2008).

1.2.4.1 *Economic burden of malaria*

The economic impact of malaria disease provides, in quantitative terms information on the extent of the disease, which forms an important complement of data on the disease burden. Although malaria disease is preventable, it causes tragic human impact with tremendous social and economic consequences. These impacts include the direct costs of treatment and prevention, at the household and health system levels, as well as the indirect costs of human productive time losses, such as absenteeism from work and school attendance, welfare and income losses as well as travel expenses (van Vught *et al.,* 2011). There are also expenditures from the

government through specific national intervention strategies for malaria control as well as through surveillance systems implemented in the country. Economic impact also includes the loss of investment and tourism (Greenwood *et al* 2005). In endemic countries, the disease has been estimated to account for between 25% and 40% of hospital admissions, 20-50% of outpatient visits, and up to 40% of government/public health expenditures (WHO-RBM, 2009).

1.2.5 *Malaria control strategies*

In recognition of the burden of malaria, the global community through the WHO identified the disease as a priority project, announced by the DG in 1998. Initiatives were subsequently introduced to reduce the global burden with particular focus on endemic areas of Africa (Goodman *et al*., 2000). A package of interventions were introduced for effective control of the disease; namely prevention through treated bed-nets, environmental control through indoor residual spray and the use of DDT, and case management of the disease.

Global efforts to combat malaria, aimed at eradication started in the 1940's with regional eradication campaigns. In 1955 the WHO introduced the Global Malaria Eradication Program. The efforts were targeted at vector control, changes in the land use, agricultural practices and quality house construction (Greenwood & Mutabingwa 2002). Highlight of this eradication programme was the use of diclorodiphenyltrichloroethane (DDT) sprays developed 1939. The eradication efforts led to elimination of malaria only in the United States of America and most European countries, but failed in the endemic countries, particularly Africa. This was blamed on logistics, high costs of the programme, resistance of many communities to

continued spraying of their houses and reported resistance of the vector to the spray chemical (Greenwood & Mutabingwa 2002). Consequently, for not clearly eradicating the diseases at global level, the eradication programme was considered a failure (Mutabingwa 2008). More concerted effort at the control was initiated through the WHO with the launching of the Roll Back Malaria (RBM) partnership in Abuja, Nigeria in 1998, aimed at halving malaria deaths by the year 2010 (Yamey 2004)

Malaria control strategies derive from the WHO recommendations and the RBM Initiative, which is incorporated into the National Malaria Control Programme (NMCP) of malaria endemic and non-endemic countries. These include vector control with the ITNs and IRS, case management with effective anti-malaria agents, and intermittent preventive treatment in pregnancy (IPTp). Among these strategies the promotion of the insecticide treated bed nets (ITNs) has become the most prominent because of its estimated greater impact on malaria control, particularly among the most vulnerable groups (Hanson & Goodman 2004). Its action is based on the reduction of the human-vector contact by preventing and even killing the vector mosquito before getting to bite the victim and transmitting the malaria parasite (Yartey, 2006). The effectiveness and cost-effectiveness of ITNs in malaria control has been documented in different settings (D'Alessnndro *et al.*, 1996; Lengeler 2004; Goodman *et al*., 1999; Yukich *et al*., 2006; Hanson *et al*., 2003; Mulligan *et al*., 2008). The other vector control strategy, IRS has similarly had a notable history of success in malaria control, which has been documented in many reviews (Kouznetsov 1977; Mabaso *et al.* 2004). IRS operates as an insecticide by repelling mosquitoes from entering houses as well as by killing female mosquitoes which rest inside the houses after taking blood meals.

1.2.6 *Malaria Case Management*

Case management of malaria consists of early detection and prompt treatment with effective antimalarial drugs. This requires the need for quick approach to malaria diagnosis and treatment, to help prevent progression to severe/complicated malaria which has high fatality case. Malaria is a completely preventable disease with grave consequences when not promptly attended to. Prompt diagnosis is followed by timely administration of safe and effective antimalarial drug, aimed at clearing the *Plasmodium* parasite from the blood. Malaria diagnosis and treatment is one of the core components of malaria control strategies. The principle approach includes the diagnosis and prompt treatment with highly effective antimalarial combination therapy on confirmation of uncomplicated malaria episode. This contributes to complementing the efforts at malaria prevention by reducing the number of malaria cases progressing to severe attack, preventing or at least delaying the development of resistant strains against the combination therapies, and finally contributing to reductions of malaria transmission by reducing the reservoir of parasite stages (FMoH 2008). The general objective of case management is to achieve timely and equitable access to malaria diagnosis and treatment by all sections of the population and as close to the home as possible. Key interventions of the strategy include;

i) The use of microscope or RDT for parasitological confirmation of malaria cases
ii) Treatment of uncomplicated malaria with effective antimalarial drug (ACT) within 24 hours of fever onset through healthcare providers (public and private)
iii) Expansion of access to free ACTs to community level where this is feasible
iv) Early recognition and improved management of severe malaria cases

1.2.6.1 *Malaria diagnosis*

Effectiveness of malaria treatment to achieve the goals of case management relies on proper recognition and identification of the malaria disease before treatment with appropriate drug. This is carried out in clinical practice using presumptive diagnosis or parasitological confirmation with microscopy or rapid diagnostic test (RDT) instrument. Upon presentation of a patient with clinical features of the malaria disease, for which fever is the hallmark, a case of malaria is confirmed using either of the methods. However, given the non-specificity of the clinical/presumptive diagnostic method, which results in misdiagnosis and over-treatment (Rolland *et al*., 2006), microscopy or the RDT is currently recommended for malaria diagnosis in all patients suspected to have malaria before treatment is started (WHO, 2010). In the past, recognizing that in most African settings, many of the health facilities lack microscopic support for malaria diagnosis, it was recommended that malaria (fevers), especially in children in endemic countries be routinely diagnosed on clinical basis (D'Acremont *et al.,* 2009), to boost access to antimalarial drugs in those areas, as part of the Integrated Maternal and Child Illness (IMCI) (WHO 2006). Such treatment based on clinical suspicion should only be considered when a parasitological diagnosis is not accessible.

Given the current focus to enhance the efficiency of malaria treatment and prevent wastages from inaccurate diagnosis and high costs of ACT, emphasis is now on accuracy of diagnosis. This is important because misdiagnosis of non-malarial febrile cases result to over-treatment and hence wasteful use of expensive antimalarial drugs. Consequently, it can be said that malaria is diagnosed using three methods namely; presumptive/clinical diagnosis, microscopy and RDT.

Presumptive diagnosis is based on the clinical presentation of symptoms such as history of fever or temperature of 37.5°C or above (Chanda *et al*., 2005). However, due to non-specificity of the presumptive method and the need to ensure efficiency of treatment, the use of microscopy and RDT remains the current focus. Microscopy is a laboratory based method, involving the use of reagents and analysis of blood samples for malaria parasite. The accuracy and efficiency of the technique relies on the expertise of personnel to analyse the blood sample. Similarly it has cost implications given the cost of acquiring the microscope and expertise and as such not all health centers, especially in rural areas with most malaria cases, can afford it. Hence, the use is limited by affordability. Many health care centers actually lack laboratory facilities. The need for improved prompt delivery of laboratory result led to the introduction of the RDT tool, the third diagnostic technique based on antigen detection principle. The RDT principle is currently operated on two detection methods which make use of two main sensitive antigens present in the malaria parasite; HRP-II for *P. falciparum* and pLDH for all the four human malaria parasites (Ly AB *et al.,* 2010). The use of the two laboratory-based techniques has been variously demonstrated to be very effective and cost-effective in malaria treatment, with microscopy as the gold standard for malaria diagnosis (Bell and Peeling 2006; Hamer *et al*., 2007; Uzochukwu *et al.,* 2009).

1.2.6.2 *Treatment with antimalarial drugs*

Antimalarial drugs are designed to cure or prevent malaria attack. Treatment of malaria is achieved in individuals who are suspected or have confirmed cases of the infection. In prevention, the drugs are used in routine intermittent treatment of some population groups (such as pregnant women and children) in endemic regions,

known to be most vulnerable to attack. Prevention is also intended in individuals who visit malaria-endemic regions and have no immunity. The principle in malaria treatment requires that effective antimalarial drug be administered to the patient to achieve a minimum of clinical cure which involves the resolution of overt clinical signs and symptoms of the acute disease (Phillip and Phillips-Howard 1996). This cure is achieved through the clearing of the symptoms and preventing the reappearance (recrudescence) within 14 days of the treatment. Clearance is achieved when the drug completely eliminates the malaria parasite through parasitological failure (radical cure). Treatment is therefore defined as adequate parasitological and clinical response. In severe or complicated malaria, treatment priority is to administer a rapid acting drug, preferably given parenteral and the drug regimen is expected to attain adequate blood concentration as quickly as possible, without causing serious adverse effects (Phillips and Phillips-Howard 1996). The parenteral drugs are administered at higher dose regimens since the bioavailability is impaired in severe diseased conditions. For uncomplicated cases of malaria disease which is much more common, the drugs need to be more affordable for large scale use. Effective use of antimalarial drugs is critical to achieving the goals of malaria case management. Their effectiveness largely depends on their efficacy, compliance to treatment regimen, appropriate prescription and cost/affordability (Goodman *et al.*, 1999). These factors therefore impact on the efficiency of malaria case management at different levels. High costs of drugs and treatment hinder patients from seeking appropriate care, resorting to the use of ineffective alternatives and other inappropriate practices (Goodman *et al.*, 2000).

Treatment with antimalarial drugs is divided into first, second and third line drugs. First-line drugs are first used and if treatment fails, (possibly due to drug resistance),

second- and third-line drugs may be used. Previously, treatment was divided into two stages, when presumptive treatment was offered, aimed to ameliorate symptoms and reduce the risk of complications and death (Phillips and Phillip-Howard 2005). Subsequently, treatment designed to give a radical cure may be given once after laboratory confirmation is obtained. Based on the current concept of malaria treatment involving the use of ACT which relies on the individual properties of combined components, treatment is aimed at achieving rapid cure and reduced risks of parasite resistance and treatment failure (Chanda *et al*., 2007). This derives from the high efficacy of the artemisinin compounds which are combined with partner drugs to achieve this objective (White *et al*., 1997; Price *et al.,* 1999; Targett *et al*., 2001)

1.2.7 *Drugs used for malaria treatment*

A range of drugs is available for malaria treatment, targeted at clearing the parasite from the system and preventing multiplication in the blood. Generally, antimalarial drugs are classified according to their chemical and biological actions (WHO 1990). Blood schizonticides are the main types of drugs which are used to cure acute cases of attack (curative treatment of acute cases). They act primarily at the asexual blood stages of the parasites. Examples include chloroquine and amodiaquine. Other drugs act on the pre-erythrocitic/tissue stages of the parasite, thereby preventing the disease from relapse, e.g Primaquine. The choice of an effective antimalarial drug treatment requires an understanding of the intrinsic properties of the drug as well as the extent of parasite resistance to the available drugs (Phillip and Phillip-Howard 1996).

Table 1.1 shows the types of selected antimalarial drugs according to their category and activity.

Table 1.1: Types of available antimalarial drugs by category and activity

		Schizonticidal activity	
Class	***Drug***	***Blood***	***Tissue***
4- Aminoquinolines	Chloroquine (CQ)	++	-
	Aminodiaquine (AQ)	++	-
8-Aminoquinolones	Primaquine (PQ)	-	+
Arylaminoalcohols	Quinidine (QD)	++	-
	Quinine (QN)	++	-
	Mefloquine (MQ)	++	-
Phenantrenemethanols	Halofantrene (HF)	++	–
Artemisinin derivatives	Artemsinin (AS)	++	–
	Artemether (AS)	++	–
	Artesunate (AS)	++	–
Antimetabolites	Proguanil (PG)	-	+
	Pyrimethamine (P)	+	-
	Sulphadoxine (S)	+	-
	Sulfalene (S)	+	-
	Dapsone (DS)	+	-
Anti-bacterial	Tetracycline (TCN)	+	-
	Doxycycline (DCN)	+	+
	Minocycline (MCN)	+	+

Symbols: ++ = high activity; + = some activity; - = no activity

Although a wide range of antimalarial drugs exists in Africa, economic reality limits the use of contemporary malaria chemotherapy to only a handful of the drugs (Winstanley *et al*., 2004). For many years until the widespread development of *Plasmodium* resistance, chloroquine (CQ), a 4-aminoquinoline was a popular first-line drug in many countries in SSA and is still used significantly in many parts of the continent. Amodiaquine (AQ), another 4-aminoquinoline share similar property with CQ but its use has been limited by concerns regarding its safety. In particular, agranulocytosis and acute hepatitis have been well-documented with the use of AQ in prophylaxis (Hatton *et al*., 1986; Larrey *et al*., 1986; Neftel *et al*., 1986; Rhodes *et al*., 1986; WHO, 1987; Rouveix *et al*., 1989; Phillips-Howard, 1990; Orrell *et al*., 2001). Safety concerns actually led to the exclusion of AQ from the WHO essential drugs list until a systematic review showed that its toxic effect is similar to and *not* more than that of SP in the treatment of uncomplicated malaria (Olliaro *et al*., 1996).

The antifoliate class of antimalarial drugs, namely the combination of sulphadoxine or sulfalene with pyrimethamine (SP) was found very useful in SSA, becoming the first-line drug in many countries, until the emergence of resistance which developed rapidly. The combinations are blood schizonticides, highly effective against *P. falciparum* but less effective against other *Plasmodium* species. They have no cross-resistance with the 4-aminoquinolines, mefloquine, quinine, halofantrine or the artemisinin derivatives (WHO 2001). With long half-lives of sulfa drugs, the combinations are given as single dose therapy, conferring high compliance rate. SP is given twice in pregnancy for malaria prophylaxis, at the second and third trimesters. Folic acid is said to antagonize the activity of the combination and hence, the supplement is advised to be given one week after treatment with SP (van Hensbroek *et al*., 1995).

Another antifolate combination found to be more efficacious than SP but less prone to drug resistance was chlorproguanil-dapsone (Lapdap®). However, while the safety of the drug (which was available for a very short period) was being evaluated in routine use under the WHO, the use was greatly limited by the global attention and thrust towards ACT. Hence, for a possible consideration of the drug for uncomplicated malaria, its combination with artesunate (chlorproguanil-dapsone-artesunate, CDA) will make it more attractive as a policy option in the fight against malaria.

Quinine remains a useful antimalarial drug for generations throughout the world since its discovery in the 17th century. It has remained especially useful as a reserve drug for complicated malaria in many countries, and therefore often a second- or third-line drug. While some countries adopt oral quinine as a second-line drug therapy for uncomplicated malaria, the use is highly limited by its pronounced side effects and symptomatic toxicity such as tinnitus, in addition to apparent complex dosing regimen (taken in several doses daily for seven days), making it very challenging as an oral drug. Less commonly used antimalarial drugs in Africa include halofantrine, mefloquine, atovaquone-proguanil and the antibiotic antimalarials such as tetracycline, doxycycline and clindamycin (Winstanley *et al.*, 2004).

Artemisinin compounds: The discovery of the artemisinin compounds revolutionized drug treatment for malaria, in view of their high activity against the *Plasmodium* parasites. The artemisinin compound is a potent and rapidly acting blood schizonticide, with faster parasite clearance times than chloroquine or quinine and rapid symptomatic responses (WHO 1994). Evidenced showed the compound to be effective against parasites resistant to all other operationally used antimalarial drugs (WHO 1994, 2001). The use of the artemisinin compound is found more beneficial

when used in combination with another effective blood schizonticide, to reduce the recrudesence rate and the risk of development of resistance, as well as to improve compliance (WHO 2001). This informed WHO recommendation for the use of the combination in first line treatment for uncomplicated malaria. The combination principle has been successfully used in tuberculosis, leprosy, cancer and HIV/AIDS management. Artemisinin monotherapy was limited to specific indications, such as in patients with a history of adverse reactions to the combination drug. As monotherapy, a 7-day course of was recommended to reduce the incidence of recrudescence, and adherence to treatment is emphasized. The rectal formulations of artemisinin monotherapy have been found potentially useful in the treatment of uncomplicated falciparum malaria in children who not able to take oral medication, as well as emergency treatment prior to referral in situations when parenteral antimalarial drugs are not available or cannot be administered.

1.2.8 *Antimalarial drug resistance*

Since preventive vaccination against malaria does not currently exist, malaria control presently relies heavily on antimalarial drugs to kill the parasite in the human body. One of the major draw-backs to the treatment and control of malaria has been the development of resistance of the parasite to treatment with effective drugs. Development of parasite resistance to antimalarial drugs has posed increasing threat to public health in view of the enormous health burden and productivity losses which it causes. Drug resistance leads to increased costs of treatment, associated with either the use of an ineffective drug or the higher costs of the next-line drug. This certainly puts more strain on already lean budgets of low-income countries of sub-Sahara Africa (SSA) responsible for over 90% of the disease burden. Increasing drug

resistance reduces the cost-effectiveness of the malaria treatment even with the appropriate choice of drugs and diagnosis.

Parasite resistance was discovered to arise as a result of spontaneous development or selection of parasite mutations which survive in the presence of the antimalarial drug (Bell & Winstanley 2004). It was further discovered that antimalarial drugs which have long terminal elimination phases are known to favour the mutation selection process. Hence, in the presence of sub-therapeutic concentrations of the drugs, new infectious parasites (recrudescence) which harbour the beneficial mutations are preferentially selected (Watkins *et al*., 1993). This may have therefore contributed to the demise of chloroquine and SP because of their long-halves. Chlororoquine was the most popular antimalarial drug used for many years to save millions of lives for most part of the 20th century, due to its effectiveness at low cost, affordable to majority of low income population in most malaria settings (Arrow *et al.*, 2004). It acts at both the pre-erythrocitic and blood stages of the parasites. However, in a major set-back in the course of global malaria control effort, beginning in the 1970's, malaria parasite developed resistance to the drug. This was first noticed in Asia but it soon became widespread over all malaria settings. This led to considerable treatment failures with increasing deaths and morbidity. The world was thereby challenged to seek for replacement to chloroquine in addition to other more expensive agents such as halofantrine. Subsequently, sulphadoxine-pyrimethamine (SP) was discovered, replacing chloroquine for first-line treatment for uncomplicated malaria. The parasite shortly after, developed further resistance to SP, posing more challenges to the global community for more effective agents. Subsequently, Artemisinin compound from a Chinese plant, Quinghaosu, was discovered with strong promises of rapid clearance of

parasite over a short period of time. In recognition of the need to reduce the risk of parasite resistance to the new agents, the global community through the WHO recommended combination strategy with a partner drug to leverage rapid action of the new agents with longer duration of the partner drugs, to reduce the rate of development of parasite resistance. Consequently, ACT was introduced in 2001 by the WHO to replace SP and chloroquine as first-line treatment for uncomplicated malaria (WHO, 2002).

1.2.9 *Artemisinin-based Combination Therapy (ACT)*

For more than 50 years (since 1960) chloroquine provided the key treatment for malaria disease, silently saving millions of lives and curing billions of malaria episodes (Arrow *et al.*, 2004). However, growing resistance of the P*lasmodium* parasite (pf) to chloroquine was reported by several studies (Trape *et al*., 2003), leading to widespread treatment failures, observed from the late 1980's, and spreading rapidly from then (Chanda *et al.*, 2007). SP was introduced in the 1980's to replace the chloroquine as first line treatment for malaria. Further resistance to SP was reported which at the same time highlighted the increasing risk of using monotherapy as first line treatment due to ease of developing resistance. Recognising the challenge of resistance and global concern about monotherapy, the WHO and RBM partners promoted global campaign for the replacement of chloroquine and SP with Artemisinin-based combination therapy (ACT), as first line treatment for uncomplicated malaria (Chanda *et al.*, 2007). Artemisinin compound from a Chinese plant Quinghaosu was discovered with strong promises of rapid clearance of parasite over a short period of time. The artemisinin-based products were established to possess high efficacy by producing rapid clinical improvement and clearance of the

malaria parasite. They further reduce gametocyte carriage in the blood, thereby decreasing the parasite load (Price et al., 1999; Targett *et al*., 2001). Hence, in combination with other antimalarial agents, efficacy of therapy will be enhanced which will have the advantage of slowing down the rate of resistance in addition to faster and more complete clearance of the parasites from the blood (White *et al.,* 1997). The combination thus, is able to reduce treatment failures and disease recurrence, in consequence reducing probability of progression to severe malaria (Chanda *et al.,* 2007).

ACTs are therefore acclaimed to significantly avert malaria morbidity and mortality. Subsequently, in recognition of the need to reduce the risk of parasite resistance to the new agents, the global community through the WHO recommended combination strategy with a partner drug to leverage rapid action of the new agents with longer duration of partner drugs, to reduce the rate of development of parasite resistance. Advantages of the ACT therefore were to obtain rapid parasite clearance and symptomatic relief as well as slow the development of resistance to the drug (van Vught *et al*., 2011). The combination principle has been used successfully to manage other infectious diseases like tuberculosis and HIV/AIDS (White *et al*., 1999; Nosten & Brasseur, 2002). ACT was formerly introduced in 2002 by the WHO to replace SP and chloroquine as first-line treatment for uncomplicated malaria (WHO, 2002). There was significant decline in malaria burden, in terms of mortality, morbidity and treatment failure after the introduction of ACT (Gilha *et al.,* 2010). Commonly used ACTs are presented in Table 1.2

Table 1.2: Commonly used Artemisinin based Combination Therapy (ACT) recommended by the WHO for first line treatment

S/N	Artemisinin-based combination treatment	Abbreviation	Region
1	Artemether combined with lumefantrine	AL	SSA & SEA
2	Artesunate combined with amodiaquine	ASAQ	SSA
3	Artesunate combined with mefloquine	AS-MQ	South America
4	Artesunate combined with sulphadoxine-pyrimethamine	AS-SP	South America
5	Dihydro-artemisinin combined with piperaquine	DHA-PQ	Southeast Asia (SEA)

Guidelines for malaria treatment with ACT included the need to restrict treatment to people with positive parasitological tests, at least for non-pregnant adults and children over five years (Lubell *et al*., 2007). SP was recommended for prophylaxis in pregnant women and children through Intermittent Preventive Therapy in pregnancy and children respectively (IPTp and IPTc). Artemeter injection and quinine were reserved for severe/complicated malaria. Following recommendations, several countries in malaria settings have since adopted the policy accordingly (Doodoo *et al*., 2009; Davies *et al.*, 2013).

1.2.10 *Economic implication of malaria resistance*

Development of parasite resistance to chloroquine in the 1990's posed the greatest challenge to date on the global efforts of malaria control (a major challenge and draw-back to efforts at malaria control and treatment). The widespread resistance seriously hampered the global efforts at control, leading to increased health and economic burden. Cost implications arise from the huge failures of the previously effective and cheap drugs such as chloroquine which was used to save millions of lives from the disease, as well as the development of new but very expensive agents which cost between 50 and 700% more (Phillips and Phillip-Howard 1996). The huge budget implication created the need to weigh the costs and benefits of the decisions to use expensive but more effective new agents. Antimalarial drug resistance also has implication for the choice of diagnostic tool, between the cheap but less specific clinical/presumptive diagnosis and the more specific but expensive technologies. The introduction of the more effective new agents has made the use of the less specific diagnosis more inefficient, given the wasted treatment of suspected cases that do not actually have malaria (misdiagnosis and over-treatment). This makes the investment on the more efficient technologies more worthwhile (Phillips and Phillip-Howard). Consequently, several studies have found the use of laboratory diagnosis (including RDT) very cost-effective (Rolland et al., 2006; Lubell *et al.,* 2006; Shilcutt *et al.,* 2008; Chanda *et al.,* 2009; Uzochukwu *et al*., 2009).

1.2.11 *The Prices and availability of antimalarial drugs*

The prices of antimalarial drugs are very critical to achieving the goals of malaria treatment due to the implication for affordability and access to effective treatment. Since the introduction of the antimalarial policy, the use of ACT in developing countries have been limited by their high cost, as they typically cost between 20 – 40

times the commonly used but less effective alternatives, such as SP and AQ (WHO, 2008; UNICEF RBM, 2007; Kachur *et al*., 2006; Sabot *et al*., 2009). Even before the introduction of the ACT, reports indicated considerable variation in the prices of antimalarial drugs. A review of listed sources of pharmaceuticals over 20 years ago (Forster, 1991) showed a considerable variation in the prices of antimalarial drugs before the introduction of the currently used ACTs. This indicated the need for careful comparison of prices from different sources, for a more efficient procurement. Subsequently, reliable sources were identified for comprehensive, accurate and up-to-date information of drug prices from international suppliers such as the WHO site (www.who.int/medicines/organisation/par/ipc/druginfo.shtml) and the Management Science for Health in collaboration with WHO for Antimalarial Drug Price Indicator for essential medicines (MSH, 2002, http://erc.msh.org). However, following the introduction of the ACT, the price situation became more complex and significant. True to prediction at the time, given their regimes, the cost of malaria treatment with the ACT rose to several dollars per case, more than the well below the recommended $1 per treatment at the time (WHO, 2003). This created affordability and accessibility problems and hence achievement of the goals of malarial case management. Since introduction, several studies showed that ACTs are expensive, with various brands costing between 10 and 20 times the cost of conventional mono therapies (Njau *et al*., 2008; Goodman *et al.*, 1999; Boland, 1999; Amin & Snow 2005; WHO, 2006; Chuma *et al*., 2010). This posed considerable challenges to achieving the goals of treatment, considering the issue of affordability and access to largely low income population of malaria endemic countries. Consequences include the resort to the use of the cheap but ineffective monotherapies and other drugs, in addition to unhealthy practices which results to increasing risk of parasite resistance to effective antimalarial drugs

and widespread treatment failures. Hence, apart from limited availability at the time and inadequate knowledge on the effectiveness of the ACT, high cost was identified as the major drawback to their uptake and effective use for the treatment of uncomplicated malaria in the low income endemic countries. The introduction therefore posed a major cost challenge to the already resourced-constrained SSA governments (Bloland *et al*., 2000; Snow *et al*., 2003). Drug policy based on the use of the ACT was estimated to impose a budget of between 1.6 and 3.4 billion US dollars on Africa for success in malaria treatment (Snow *et al*., 2003). This called for the funding support of the international donor community, in particular through the Global Fund for AIDS, tuberculosis and malaria (GFATM). Further efforts at significantly reducing the cost burden of the ACTs was envisaged to be achieved through more effective targeting of resources to most at risk populations such as free delivery to children under-five patients, as well as further provision of diagnostic facilities (e.g. RDTs) for malaria (Snow *et al*., 2003). Similar observations on the high costs of malaria therapy in Africa were made by United States Institute of Medicine (IOM) in a seminal report entitled "Saving lives, buying time: economics of malaria drugs in an age of resistance". It called for sustained global subsidy on ACTs "…as the most economically and bio-medically sound means to meet the challenge of malaria" (Arrow *et al*., 2004). Consequently, in recognition of the high procurement cost and limited availability, the Global Fund in collaboration with malaria partners introduced the Affordable Medicine Facility-malaria (AmFm) in 2009, to reduce the cost of supply and improve affordability and access to the utilisation of quality ACTs in low income countries (Davies *et al*., 2013). The initiative was aimed at increasing consumer access to the ACTs, through a subsidy introduced at the top of the distribution. Nigeria was listed as one of participating countries to benefit from the

AMFm Phase 1; aimed to enable public, private not-for-profit and for-profit providers to purchase ACTs at significantly lower prices and "to pass this benefit on to patients'' (AMFm, 2010). Hence the Phase 1 was designed to provide a platform for rapidly increase in access to effective and affordable ACTs.

1.2.12 *The quality of antimalarial drugs*

Widespread distribution and use of poor quality antimalarial drugs, in terms of low dose of recommended and other ineffective antimalarial drugs have been documented in many studies in Africa (Jande *et al.,* 2000; Newton *et al*., 2001; Taylor *et al*., 2001; Onwujekwe *et al*., 2009). Poor treatment practices also impact on the efficiency of treatment as the use of ineffective agents and poor adherence impede the success of treatment. Sub-standard, fake and adulterated antimalarial drugs are continually reported in circulation given the high burden of disease and demand for care in the continent. As one of the most widely used drugs in Africa, antimalarial drugs are major targets for counterfeiting. These have implications on the effectiveness and efficiency of malaria treatment, because as a major problem of malaria treatment, high incidence of treatment failures has been attributed largely to the prevalence of poor quality adulterated and counterfeit drugs (Newton *et al*., 2006; Hall *et al*., 2006; Bate *et al.,* 2008). A counterfeit formulation has been described as the one that is "deliberately and fraudulently mislabeled with respect to identity and/or source. Counterfeiting can apply to both branded and generic products and counterfeits may include products with the correct ingredients or with the wrong ingredients, without active ingredients, with insufficient active ingredient or with fake packaging" (Wondemagegnehu 1999). The intuitive link between quality of drugs and drug resistance makes it important to always pay attention to drug quality issues. The main outcome of the use of sub-standard and counterfeit drugs is the administration of low

therapeutic doses of drugs below the minimum concentration in the blood required to elicit physiological response (for instance lowering blood pressure or glucose), or kill a parasite such as in malaria and other infectious diseases. The implication is increased disease burden and high risk of death. For the infectious disease, low therapeutic doses have been linked to drug resistance which is explained to result from "selection pressure" in which low levels of a drug selectively kill susceptible parasites, leaving the resistant ones to survive. The surviving parasites subsequently become resistant to future exposure to effective drugs even at therapeutic levels. Drugs with long half-lives (e.g. SP) are said to be particularly prone to resistance due to their long presence in the body at usually below minimum inhibitory concentrations required to kill a parasite. Sustained and haphazard use of drugs produces similar effects, due to residual and sub-therapeutic levels of drug in the host which would likely encounter re-infecting parasites, leading to selective kill and hence parasite resistance. This is a common feature in high transmission areas with high rates of re-infection such as in most of SSA (Watkins & Mosobo, 1993; Nzila *et al*., 2000). Counterfeit drugs could also result in administration of higher levels of substances that could precipitate toxic or adverse drug reactions and become injurious to the system.

Distribution of sub-standard and counterfeit drugs has remained a major public health issue in many countries, especially in developing countries (WHO, 1999b; Newton *et al.,* 2001). This is especially so with antimalarial drugs which probably have wider drug quality problems given their greater demand in these countries. Even though advances have been made over the years to check the incidence, with increasing

global standards for quality becoming increasingly rigorous, concerns about quality of medicines in circulation remain (WHO, 1999a).

Several studies in Africa have reported high incidence of counterfeit and adulterated antimalarial drugs distributed across the countries. Taylor *et al* (2001) reported more than 50% quality failure rate for all drug groups investigated (including antimalarials) according to BP specifications. Some of the preparations contained no active ingredients, some had little while others contained too much. Antimalarials drugs investigated included CQ, QN and SP. An antimalarial drug quality study in Anambra state Nigeria, by Onwujekwe *et al* (2009) showed that 37% of the sampled drugs did not meet the United States Pharmacopeia (USP) specifications for active ingredients. The suspect drugs either lacked the active ingredients or contained suboptimal quantities of the active ingredients. Majority (78%) of the suspect drugs were from private facilities, mostly low-level providers, such as patent medicine vendors (PMVs). A drug quality study in Tanzania, reported that of the nine brands of SP investigated, only four passed dissolution test even though all the nine samples fell within the limits for content of the active ingredients (Jande *et al*., 2000).

A similar study in Southeast Asia by Newton *et al* (2001,) which investigated the distribution of counterfeit artesunate tablets, showed that of 104 shop-bought "artesunate" samples from Cambodia, Laos, Myanmar (Burma), Thailand, and Vietnam, 38% did not contain artesunate.

Common features of poor quality drugs reported as failures include too little, too much, or complete absence of the active ingredient. Sometimes the active ingredient is substituted with a closely related substance (for instance sulphamethoxypyrazine

with sulphamethoxypyridazine) or unrelated one (sulphamethoxypyrazine with paracetamol) (Amin 2005). Other problems include poor dissolution profiles, inadequate labeling, and faulty packaging. Most SP drugs tend to fail the dissolution test, especially with regard to the pyrimethamine component. In all, findings across Africa and other developing countries indicate widespread prevalence of poor quality antimalarial drugs, requiring constant policy interventions to improve the supply and distribution of quality drugs for the success and efficiency of malaria treatment. Reinforcement of laws and regulations relating to drug supply and distribution, which is generally weak in these countries, cannot be over-emphasized. The problem of counterfeiting is therefore a major threat to the effectiveness and goal of treatment with the current policy on the use of ACT, given the risk of developing parasite resistance and treatment failure.

1.2.13 *Health seeking pattern for uncomplicated malaria in Africa*

A number of studies have shown that treatment-seeking for malaria treatment in developing countries indicates a high rate of self-treatment (MCcombie, 2002). This has implications for appropriate use of antimalarial drugs and cost of treatment, as self-treatment is characterized by inappropriate use of antimalarial drugs such as under-dosing and the use of monotherapy and other ineffective antimalarial drugs. Time factors, cost and perception of severity have also been identified as the main factors for self-treatment (MCCombie 2002). Patients generally undertake self-treatment to save time, lower cost of treatment (Mugisha *et al*., 2002) and uncomplicated malaria is considered non-severe. Concern is that poor treatment of uncomplicated malaria will result to severe case, with high risk of cost and health consequences. Self-treatment has also been associated with socio-economic status, as

high income individuals are more likely to self-medicate. Similarly, some other studies have linked self-medication in low-income countries to patients who obtain drugs without prescription, which was associated with low education and perception. A study in Nigeria showed that self-medication was more common among males and single people (Brieger *et al.,* 1986). Similarly in Kenya, a study showed that boys between 11 and 17 years are more likely to self-treat and to use Western medicines (Geissler *et al.,* 2000). On socio-demographic factors studies in Africa have shown that younger children are more likely to be taken to health facilities (Kaseje *et al.,* 1987; Slusker *et al*., 1994; Molyneux *et al*., 1999). Education level has been considerably found to be associated with health behaviour, like malaria. Education levels are always higher in urban areas, noted for higher self-treatment. Self-treatment for malaria in the private retail sector is also highly characterized by presumptive treatment based on signs and symptoms, leading to the likelihood of unnecessary and irrational use of antimalarial drugs. This results to misdiagnosis of other disease-causing fevers for malaria (Onwujekwe *et al.,* 2005; Genton *et al*., 1994), thereby underestimating the burden of the malaria disease (Onwujekwe *et al.,* 2009b).

In a review by Chuma *et al* in 2009, treatment-seeking pattern for malaria in Africa is generally similar across settings and ages, though children were more likely than adults to be treated by the formal sector (private and public health providers), who have more professional trainings and mainly because malaria is perceived to be more severe in children (Molyneux *et al.,* 1999). Factors that have been identified to influence treatment-seeking behaviour for malaria include affordability (related to cost of service and ability to pay); acceptability (related to perceptions and acceptance, (perceptions of effectiveness of drugs and/or health worker/provider

competence/attitude); and availability, in terms of physical and geographical availability, often related to stock availability-stock-outs. For instance, ACT stock-outs have been widely reported to significantly compromise the uptake and utilisation and hence the effectiveness of the drugs (Thwing *et al*., 2011). These factors favour consumers' preference for retail outlets due to closeness to homes, availability of drugs, good relation with staff, convenience based on flexibility of timings, no payment of fees etc.

1.2.14 *Treatment practices for uncomplicated malaria in Africa*

Provision of malaria treatment occurs at both the public and private sector facilities in Africa. Adherence to the treatment guidelines is critical to achieving the goals of treatment to reduce the burden of the disease. This requires that suspected malaria episode is promptly diagnosed through appropriate techniques and if confirmed, effective antimalarial drug, currently the ACT is administered to ensure appropriate cure and relief from clinical symptoms. Diagnostic approach used in malaria management depends on cost and availability of diagnostic instrument. Syndrome approach based on clinical signs and symptoms of the disease is the most commonly used. The use of microscopy involving the laboratory examination of patient's blood sample for the presence of plasmodium parasite is the most accurate method and gold standard for malaria diagnosis (Hamer *et al.*, 2007). However, the use of the microscopy is often limited by cost and expertise required for its operation. Hence, many facilities in developing countries lack the instrument, making presumptive management a very popular choice in these environments. However, due to overlap of malaria fever symptoms with other illnesses such as pneumonia, there is often a significant misdiagnosis of malaria based on presumptive management. Consequently, presumptive approach to malaria management is characterized by high inaccuracy as

many cases of non-malaria fevers have been reported (Uzochukwu *et al*., 2010; Onwujekwe *et al.,* 2005). Over 50% of those treated for malaria actually had diseases other than malaria (Bauden *et al.,* 1985; Genton *et al.,* 1994; Onwujekwe *et al.,* 2005). Presumptive treatment of malaria therefore enhances irrational use of antimalarial drugs with the potential to overestimate the burden of malaria disease. In the past, recognising the high burden of malaria disease especially in high risk settings and mostly in children who often die at home, and the need to provide prompt and affordable treatment within 24 hours of onset of illness, home treatment for all childhood fevers which is based on presumptive treatment was part of policy recommendations (Amexco *et al.,* 2004). During this period, treatment of malaria with monotherapy such as chloroquine as drug of choice was inexpensive making presumptive diagnosis cost-effective. However, with the introduction of the ACTs which are more expensive, it can only be more cost-effective to use the more accurate diagnostic methods (Goodman *et al.,* 2001). Continued use of presumptive diagnosis will result to wasteful use of now expensive ACT arising from significant treatment of misdiagnosed cases which do not actually have the malaria disease. Accurate diagnosis will ensure the treatment of only identified or confirmed malaria cases thereby enhancing the efficiency of treatment and preventing wastages of limited resources. Hence, the current use of ACTs which are quite expensive makes presumptive treatment much less efficient and the use of accurate diagnostic approach more imperative, to enhance the efficiency and cost-effective treatment of malaria infection (Goodman *et al.,* 2001). Presumptive malaria treatment increases the risks of over-treatment, masking and prolonging underlying potentially fatal conditions (O'Dempsey *et al*., 1993;) and unnecessary side effects of drugs (Amexco *et al.,* 2004). The need to enhance accuracy of diagnosis for malaria disease led to the

introduction of the RDT method which required limited expertise at lower cost. Hence, emphasis on laboratory diagnosis before patients are treated for malaria with the expensive drugs makes the RDT and ACTs important compliments in malaria treatment, especially in Nigeria. The use of the laboratory diagnosis enhances rational use of antimalarial drugs, preventing unnecessary use of drugs and in turn reducing costs of treatment. Appropriate diagnosis has been found to reduce the total cost of prescription by about 68% in Malawi (Chitaka *et al*., 1998). Introduction of RDT becomes important component of malaria treatment with the ACTs to enhance efficiency and cost-effectiveness of treatment, given the high cost of the ACTs.

1.2.15 *The efficiency and challenges of malaria treatment in Africa*

High cost has continued to constitute the major constraint in the scale-up of implementation of the ACTs in malaria treatment in African countries such as Nigeria (Goodman *et al.*, 1999; Yeung *et al*., 2004, Wiseman *et al*., 2005, Chanda *et al.*, 2007), which in effect is affecting the achievement of the objectives of malaria case management. Governments and stakeholders are therefore faced with difficult challenges of resource allocation decisions across a broad range of disease programmes. In effect, effectiveness of the interventions may no longer be sufficient as the only criteria for selecting new interventions for implementation. Hence, given the high cost of the ACTs, there is a greater need for ensuring efficiency in the use of resources, by relating the cost of the interventions to their effectiveness, to determine alternative that generates the greater value for money. For malaria case management this requires accuracy in the diagnosis and treatment of malaria using the ACTs. Given the state of the healthcare systems and the high costs of the ACTs in low income countries, efficiency and effectiveness of malaria treatment will expectedly be

significantly influenced by the weaknesses in the diagnostic and prescription practices inherent in these healthcare systems (Chanda *et al*., 2007). This dissertation will therefore attempt to generate systematic evidence on the efficiency of malaria treatment given the high cost and effectiveness of the ACTs and treatment practices.

In recognition of these challenges, several interventions have been variously implemented to improve malaria case management. These include the use of more effective antimalarial drugs, improved compliance, strengthening diagnosis and the use of combination drugs (Goodman *et al.,* 1999). To demonstrate the impact of compliance on the cost-effectiveness of malaria case management, Goodman et al (1999) evaluated interventions to improve compliance, including provider training, health education for patients and care-takers and co-packaging of drugs in plastic bags. This was found to be highly cost-effective, with cost-effectiveness ratio (CER) under $25 for a very low income country with high transmission at any level of drug resistance below 77%. Other factors that were found to enhance the cost-effectiveness of malaria case management include the improved availability of second and third line drugs. A clear hierarchy of drugs is recommended to be available for the treatment of uncomplicated malaria so that patients who experience treatment failure with the first line drug are easily prescribed alternative (Goodman *et al.,* 1999). The availability of a wide range of ACTs appears to have addressed this issue, as they provide alternative choices in the event of failed treatment with the first option. Prior to current policy, this was a challenge in real practice given the limited access to alternative drugs for the treatment of uncomplicated malaria at peripheral facilities, such as the choice existing between chloroquine and SP. Analysis of a case management model which included availability of second and third line drugs showed a potentially highly cost-

effective intervention where, for a very low income country, the CER range was below $25 at any level of chloroquine resistance greater than 6% (Goodman *et al.*, 1999)

1.3 The burden of malaria in Nigeria and the challenge of treatment

1.3.1 *The Burden of malaria in Nigeria*

Nigeria is reported to be atop of the six countries in the WHO African Region which have the highest burden (47%) of malaria disease (WHO, 2012), with the country in conjunction with the DRC, estimated to account for up to 40% of the global malaria burden (WHO 2013). About 50% of the over 170 million population is said to be at risk of malaria, with at least one episode of attack per person per year (FMoH 2005). Children under 5 years have at least 2 – 4 attacks per annum. Women and children under five are the greatest victims of malaria attack, leading to about 300,000 child deaths per annum. It is responsible for 25% of infant mortality, 30% of childhood mortality and 15% of maternal mortality (FMoH 2005). Malaria is the commonest cause of hospital attendance in all age groups and one of the commonest causes of childhood mortality in Nigeria, in addition to upper respiratory infections (pneumonia), diarrhoea and measles (FMoH 2005). It causes maternal anaemia, increase miscarriages and low birth weight (LBW) in pregnant women. Assuming that 25% of childhood mortality is due to malaria, it translates to about 49 deaths per 1000 live births annually. According to the federal government, "Malaria impedes human development and is both a cause and consequence of under development. Every year, the nation loses up to 132 billion Naira (over US$1 billion) from the cost of treatment and absenteeism from work, schools and farms" (FMoH 2005). Notwithstanding the limitations in estimating its true prevalence, malaria has been estimated to cause a loss

of between 1-5% of total GNP annually in Nigeria (Leighton *et al.*, 1993). At the household level, it was estimated that malaria could cause a loss of between 3-11% of annual household income from both treatment and control expenditures and lost workdays (Leighton *et al*., 1993). Malaria in Nigeria is stable and perennial in all parts of the country (FMoH 2005). Transmission is higher in rainy season with seasonal differences more striking in the northern part of the country. The burden of malaria in Nigeria is said to be one third of the global incidence

1.3.2 *Nigerian health care system*

The organization and effectiveness of a country's healthcare system is central to meeting the health goals of the system. The health care delivery system in Nigeria is organised into three tiers of care; primary, secondary and tertiary health care, shared between the local, state and federal government levels. To some extent, the three tiers are all involved in the three major functions of stewardship, financing and service provision. The local government is responsible for primary health care whose units of service provision are the several health centers and health posts. These facilities provide mainly ambulatory care and outreach services. The state governments provide secondary health care, managed through general hospitals, used for services such as inpatient, emergency, surgical and outpatient services/care, as well as some level of referral services to the primary care centers. The federal government is responsible for the provision of tertiary healthcare, which include referral hospitals used for the provision of *highly* specialised services, research and training. Generally, the federal government through the Federal Ministry of Health (FMoH), is responsible for policy and technical support to overall health system in addition to service provision at the tertiary level. It is also responsible for international relations on health matters and

national health management information system. The state governments, through the State Ministries of Health (SMoH) also regulate and provide technical support for primary health care services. However, although the organization of the health system may appear coordinated, its practical implementation is not as seamless. Roles and responsibilities are often duplicated among the three tiers, with implications of weaknesses in the coordination and performance tracking and benchmarking. The health care system also comprises of several private for profit and private not-for profit organisations in addition to traditional/complimentary medicine practitioners.

The health care delivery system in Nigeria is community focused, which forms the structure for implementation of the primary healthcare services, as the key focus of the nation's healthcare. Consequently, the national health policy of 1988 created the primary health care (PHC) management and technical committees at the local government level, the ward development committees and community/village development committees at the ward and community levels. However, the functioning of these committees has been well below expectations (Adeniyi *et al.*, 2001). Generally, the Nigerian health care system comprises of the public and private health care. The public sector, which is described above represents the formal sector of health care provision. The private health care, representing the informal sector is made up of private for profit and private not-for profit organisations. Within the private sector are the private retail outlets made up of retail pharmacies and patent medicine vendors (PMVs).

Malaria treatment in Nigeria is provided mainly through the primary health centers and majority of the private health facilities. While the public health facilities include hospitals and health centers, private facilities comprise hospitals, clinics and drug

outlets (pharmacies and patent medicine stores (PMVs). In many states of the federation, malaria treatment is free in children under-five years old in public health facilities, provided through packages such as free maternal and child health care services. There are also the Village Health Teams used in the provision of community malaria services by trained resource persons to conduct health education and provide minor treatment to children under five years old including malaria treatment.

Healthcare finance in Nigeria is largely out-of-pocket (OOP) but generally through multiple sources made up of public (government), private OOP, donors, employers and the non-governmental organizations (NGOs). OOP, as household expenditure accounts for more than 60% (ranging between 60 and 70%, 1998 - 2002) of Total Health Expenditure (THE) (Soyibo 2004). According to current WHO statistics, THE per capita in Nigeria was estimated at US$115 in 2013, comprising 27.6% of government, 69.3% OOP, and 5.2% of external sources. As a percentage of the GDP, this translates to 3.9% (WHO 2013). Hence, OOP is the dominant source of healthcare finance in Nigeria, with massive implication for access to essential healthcare, particularly the MNCH. The burden of healthcare falls on individuals as private expenditures constitutes about 70% of THE out of which OOP accounts for over 90% (Onwujekwe *et al.,* 2010). Malaria treatment policy in Nigeria has not been made to address household OOP. The impact of OOP is generally known to deter early diagnosis and adequate treatment which undermines malaria control efforts in addition to the burden of labour market (Orem *et al*., 2013). It further influences treatment-seeking behaviours of households, subsequently impacting negatively on malaria treatment outcomes (Orem *et al*., 2013). Hence, this paper generates

information for policy to improve malaria treatment outcomes to help achieve the goals of case management.

1.3.3 *Nigerian National Malaria Control Programme (NMCP)/Malaria Control strategies*

Nigeria's malaria control policies are anchored on the Roll Back Malaria (RBM) strategy which seeks multi-stakeholder approach in a partnership and network to implement control interventions. The RBM is a global initiative of the WHO, UNICEF, UNDP and the World Bank to improve malaria control in the context of health sector reform (WHO/RBM 2008). The initiative sets specific deadlines for achieving defined goals. To achieve the goals of malaria control in Nigeria, measures are currently in place facilitated by the federal government of Nigeria namely; massive distribution of long-lasting insecticidal nets (LLIN) with about 46.8 million nets distributed in about 30 states of the federation according to minister for health in 2013 (FMoH 2013); Indoor Residual Spray (IRS) and larviciding; massive distribution of antimalarial drugs; capacity building of health workers at both national and state level and establishment of coordinating structures at national and state levels. Malarial Household Survey conducted in 2010 in 9 states of Kano, Jigawa, Bauchi, Gombe, Kaduna, Anambra, Delta, Akwa-Ibom and Rivers reported increase in percentage of households with at least one insecticide-treated nets (ITN) from 2.2% to 88%. The survey also showed an increase in proportion of children less than five years old who slept under the nets the night preceding the survey from 3% to 44.6%

1.3.4 *National Antimalarial Treatment Policy*

As part of the national malaria control policy and the essential drug policy which conforms with the overall national health policy, Nigeria established a national

malaria treatment policy, comprising a set of recommendations and regulations concerning the availability and rational use of antimalarial drugs for the country. Nigeria's antimalarial treatment policy, updated in 2005 has as its primary goal to cure the patient of the infection and reduce mortality and morbidity (FMoH 2005). Implication is so to select and make access to the population at risk, safe, effective, good quality and affordable antimalarial drugs to ensure that the disease can be promptly, effectively and safely treated. Secondary goal is to encourage rational drug use to prevent or delay development of resistance to the drug. In line with global focus and recommendation following parasite resistance to age-long use of chloroquine and later SP, the policy recommended the use of ACT for the first line treatment of uncomplicated malaria, based on the rapid effect of the Artemisinin compound and long duration of action of the partner drugs (to ensure rapid cure and low level of recrudescence). Artemeter-lumefantrine (AL) was the first ACT recommended, with Artesunate-amodiaquine (AA) and Artesunate-mefloquine (ASMF) as alternate agents. Quinine and artemether injections were recommended for severe or complicated malaria, while SP is reserved for intermittent preventive treatment (IPT) in pregnancy. In malaria treatment guidelines, adjunctive therapy in malaria is recommended for the relief of symptoms and complications (FMoH 2005). Achievement of the goals of malaria treatment policy relies on the availability of appropriate antimalarial drugs which should be used rationally. The drugs should be regularly available at all levels, at costs affordable to the people. The policy emphasises the need for the provision of proper education of providers and consumers on malaria and treatment, with effective monitoring and evaluation of the system to ensure achievement of objectives.

Successful implementation of the antimalarial treatment policy therefore depends on availability, accessibility and affordability of the drugs needed at all levels of the healthcare system. Availability relies on the presence of reliable, well coordinated and regulated antimalarial drugs supply system, beginning from procurement, storage and distribution to the final consumer. In procurement, the policy recommended and emphasises decentralization with significant local content. Packaging of the drugs should be based on single treatment dosage packages, to discourage the use of under-dosing. Children under the age of 5 years are to receive treatment free of charge. Severe malaria is to be treated at tertiary health facilities while lower categories of health facilities may provide pre-referral treatment with artesunate suppository. Second line treatments for severe malaria approved include quinine, artesunate or artemether injection, while oral artemisinin monotherapy was banned.

1.3.5 *The provision of malaria treatment services in Nigeria*

Treatment of malaria in Nigeria is provided by a wide range of sources, classified as public and private sectors. The public sector comprises of formal/government health facilities which include the primary, secondary and tertiary healthcare facilities. The primary and secondary health facilities handle majority of the malaria cases which are mostly uncomplicated malaria, while the secondary and tertiary facilities are handle mostly the referral cases of severe malaria. The private sector is made of the private hospitals and the commercial retail outlets. The retail outlets, which dominate the private sector, are made up of the pharmacies and the patent medicine vendors (PMVs). The public sector facilities are generally noted for poor infrastructure development, poor service delivery, non-motivated staff, frequent stock outs, poor accessibility, among others. These affect the effective delivery of services making the

sector unattractive for majority of patients (Onwujekw *et al.,* 2005; 2009a). However over the years support for the sector has increased with increasing educational interventions on the provision of malaria treatment. The sector gets more attention for many interventions designed to improve service provision particularly malaria treatment. Provision of malaria treatment in the private sector is known to be significantly unsatisfactory in view of the widely reported cases of inappropriate practices (Onwujekwe *et al.,* 2005; 2010; 2011; Mangham *et al*., 2011). This poses the risks of treatment failures and the consequences of increased malaria morbidity and mortality. The use of monotherapy, sub-optimal doses, substandard and ineffective drugs, and inaccurate diagnosis are widely reported (Hanson *et al*., 2004; Onwujekwe *et al*., 2009). Presumptive treatment of malaria based on clinical symptoms is the predominant mode of diagnosis in the private sector, which is highly prone to misdiagnosis and unnecessary/irrational use of antimalarial drugs leading to wastages and risk of developing parasite resistance.

In the past during the use of inexpensive chloroquine as the drug of choice, presumptive treatment was cheap and cost-effective compared to microscopic examination (Boland *et al.,* 2003; Onwujekwe *et al*., 2009). The current use of ACTs which are quite expensive makes presumptive treatment much less efficient and the use of accurate diagnostic approach more imperative, to enhance the efficiency and cost-effective treatment of malaria infection.

1.3.6 ***Private sector provision of malaria treatment***

In Nigeria treatment for malaria is provided through a variety of sources, together classified as public and private sectors. Treatment seeking pattern for the malaria disease shows that the private retail sector, (made up of private hospitals and drug

retail outlets) is the most preferred sector by the patients for malaria fever (Onwujekwe *et al.,* 2005; 2010; Mangham *et al.,* 2011). According to the FMoH of Nigeria 2000, over 50% of malaria treatment is provided through the private sector (FMoH 2000). The retail outlets, especially the patent PMVs are often the first choice of patients for obtaining drugs for the treatment of common ailments as well as for advice on illness and drug therapy from both the rural and urban populations (Malik *et al*., 2013; Okeke *et al*., 2006). Findings show that closeness to peoples' homes, convenience, availability of drugs, low cost of service, quicker services, friendliness of staff, shorter waiting times are some of the main causes of preference (Goodman *et al*., 2004; Onwujekwe *et al.,* 2005). The public health facilities in Nigeria, as in most developing countries are fraught with infrastructural deficiencies, lack of adequate stock, consultation/high cost, non-motivated/unfriendly staff, long waiting times, long distances from people's homes etc (Hanson *et al*., 2004;). This makes the retail sector an important source of malaria treatment in Nigeria, close to the patient. Adults, especially men use the retail outlets for antimalarial drugs more than children who receive treatment mostly from health facilities (Hertz *et al*., 2008; 1 & 2; Onwujekwe *et al*., 2005). People seek formal sectors for care mostly when they become very ill, with severe malaria, for more sophisticated services (Onwujekwe *et al*., 2009a). The use of multiple sources is also common as patient may begin with self-treatment by purchasing drugs from the private commercial sector, and then later seek care from the public sector when the treatment fails and the case becomes severe (Hanson *et al.,* 2004; Onwujekwe *et al*., 2009). Although the private sector is the major source of treatment, it is characterized by poor/ inadequate malaria treatment provision which increases the risk of treatment failures, undermining the goals of malaria treatment (Hanson *et al*., 2004). Many of the outlets (PMVs) are manned by untrained/

unqualified people who dispense medicines at sub-optimal/inadequate dosages with the consequences of resistance development of malaria parasite to effective medicines (Nabyonga Orem *et al*., 2013, 2011). As part of the private sector driven care, self-treatment for malaria is very common in Nigeria, as in most developing countries (Onwujekwe *et al*., 2005; Salako *et al*., 2001; Erhun & Osagie 2004; Reubish *et al*., 2005; MCcombie 2002). It is often the first resort to malaria treatment, obtained through retail outlets and home management. This creates the problems of lack of awareness on the correct use of antimalarial medicines, resulting to sub-optimal dosages and duration of treatment, use of monotherapies and other ineffective antimalarial drugs. Self-treatment for malaria in the private retail sector is also highly characterized by presumptive management, based on signs and symptoms, leading to the likelihood of unnecessary and irrational use of antimalarial drugs, due to misdiagnosis of other disease-causing fevers for malaria (Onwujekwe *et al*., 2005; Genton *et al*., 1994), thereby underestimating the burden of the malaria disease (Onwujekwe *et al*., 2009).

1.3.7 *Health seeking behaviour for malaria treatment in Nigeria*

The behaviour and pattern of patients in seeking care for malaria treatment is critical to the success of malaria case management. It has implications on the treatment outcomes in terms of cost and health outcomes and in consequence, the success of treatment. Poor adherence to treatment guidelines by either the providers or patients negatively impacts on treatment outcomes, contrary to goals of treatment. The cost and quality of service delivery vary between the formal (public) and informal (private) providers. As a result, the significant inappropriate provision of treatment in the private sector has implication for efficiency of malaria treatment in Nigeria.

Documented reports show that treatment seeking pattern for uncomplicated malaria in both endemic and non-endemic areas are wide and varied. Patients with suspected malaria seek treatment from both formal and informal providers using more than one source of care at the same time (Goodman 2003). In many cases, it is often difficult to distinguish between treatment failures and re-infection in such a way that it may be hard to differentiate the end of one episode and the beginning of another. Consistent with health care practices in many countries, patients from low income segment access care more from public health facilities. However, majority of malaria cases are treated at private retail outlets as in most developing countries. Studies in Nigeria indicate that over 50% of malaria cases are treated at the private retail outlets, made of pharmacies and patent medicine vendors (PMVs) (Onwujekwe *et al.,* 2003; Mangham *et al*., 2011). Report by the Nigerian Demographic Health Survey in 2008 estimated that about 65.4% suspected malaria cases sought treatment from the private sector, comprising retail pharmacies (13.8%), Patent Medicine Vendors (28.7%), private clinics (8.3%), shops (8.7%) and other private sector areas (NDHS 2008). The report stated that the PMVs account for about 50% of treatment in the rural areas and about 36% in the urban areas. A study by Oladapo *et al* (2007) in Enugu indicated that about 30.6% of malaria cases were treated at the PMVs alone. Generally, studies in Enugu undertaken around 2005 - 2010 show that between 40 – 60% of uncomplicated malaria cases are treated at the PMVs (Onwujekwe *et al*., 2005; Meremikwu *et al*., 2007; Okeke & Okeibunor 2010). Hence, the predominance of malaria treatment in the retail outlets, characterized by poor treatment practices indicates substantial inefficiency of malarial treatment. Poor adherence to malaria treatment guidelines undermines treatment goals with increase risks of treatment failures and development of parasite resistant. Presumptive treatment is common among health providers at

both the private and public health facilities in Nigeria (Onwujekwe *et al*., 2009; Uzochukwu *et al*., 2010; Mangham et al., 2011). Self-medication is very prevalent among the general populace, with the consequences of irrational use of drugs and attendant risks. Limited knowledge of effective drugs and treatment, particularly among self-medication is a major cause of monotherapy use and inappropriate treatment practices by the patients and some providers. The regulation of practices is very limited or unavailable among the providers. These practices contribute significantly to inefficiency of malaria treatment resulting to wastages and widespread treatment failures and increasing risk of parasite resistance to the current policy drugs. The consequence is increasing malaria disease burden of morbidity and mortality. This dissertation therefore generates information on the relative costs and effectiveness of the ACTs to guide policy and practice on the use of quality, safe, effective, cost-effective and affordable antimalarial drugs for the efficiency of malaria treatment in Nigeria.

1.3.8 *Prices and availability of antimalarial drugs in Nigeria*

Prices and availability of antimalarial drugs are important determinants of access to effective treatment and hence critical to achieving the goals of current treatment policy. Affordability is generally known to imply financial access (Obrist *et al*., 2007; Oliver *et al*., 2004; Thiede *et al.*, 2007) and cost have been identified to constitute a major barrier to effective malaria treatment, affecting the demand for malaria treatment (Chuma *et al*., 2010). Since the change in policy in Nigeria introducing the ACTs for first line treatment of uncomplicated malaria, the prices have remained high and unaffordable to majority of low income population, as in most of developing countries in SSA, limiting access to effective malaria treatment. Nigeria benefited

from the AMFm initiative of GFATM, to provide platform for increasing access to the ACT through the public and private health facilities in the country. The AMFm strategy was to limit the consumer price of ACTs to less than $1.00 per dose. Since the introduction, even though significant success was recorded with the initiative, ACTs remain more expensive compared with monotherapy in Nigeria. Prices remain high even with a wide range of brands in circulation. There are currently five registered ACT regimen for first line treatment of uncomplicated malaria in the country. These agents come in various brands leading to over 100 brands of antimalarial drugs in circulation. In a study to determine the range, prices and availability of antimalarial drugs in 2011 by Ezenduka *et al* (2013) in Enugu state, south east Nigeria, about five years after the introduction of ACT, and barely one year of AMFm Phase 1initiative, the prices of ACTs ranged between N280 ($1.83) and N1250 ($8.17), with a median price of N800 ($5.23) per adult dose. This was about 16 times higher than the median price of monotherapy CQ which cost N55 ($0.36) as the cheapest antimalarial drug, and about seven times higher than the price of monotherapy SP which cost N120 ($0.78) (N50 – N300), as the cheapest most commonly used antimalarial drug regimen during the period (Table 1.3).

Table 1.3: Prices and availability of antimalarial drugs in Enugu, South East Nigeria 2011

Drug	Availability (%) (n=35)	Prices in Naira(US$)		
		Median	*Lowest*	*Highest*
ACTs	97	800 (5.23)	280 (1.83)	1250 (8.17)
SPs	100	120 (0.78)	50 (0.33)	200(1.31)
Artesunate	100	300 (1.96)	250 (1.63)	400 (2.61)
Amodiaquine	100	140 (0.92)	120 (0.78)	200 (11.31)
Chloroquine	62	55 (0.36)	20 (0.13)	150 (0.98)

Exchange rate 2011: US$1 = N153

While prices were used to assess the cost and affordability, and hence access to effective antimalarial drugs, the presence and availability of these agents in circulation is an important determinant of access. This also gives an indication of the demand and use pattern of the antimalarial drugs. The significant presence of these monotherapy agents largely explains the extent of their use in practice. The same study, which adapted the WHO/HAI recommended approaches for surveying the price levels of drugs, showed availability of a wide range of antimalarial drugs which averaged a total of ten brands per outlet (Ezenduka *et al.*, 2011). ACTs had the widest brands of antimalarial agents with over 55 brands identified. At least one brand of monotherapy AS and SP was found in every outlet (100%) surveyed while ACT was found in all but one sampled PMV (97%), (Table 1.3).

Figure 1.2 shows the stocking frequency of selected brands of the antimalarial drugs in the studied outlets. As a measure of availability, the presence or stocking of the

antimalarial brand showed that monotherapy brands of AQ and AS were respectively found in all selected outlets. At least three brands of SPs and one each of monotherapy AS and AQ were found in all sampled outlets. Chloroquine preparations were found in 62% of the outlets, although retail audit indicated not more than 4% of pack sales. Findings suggest that the antimalarial drug market is dominated by the SPs, ACTs and monotherapy AS, in terms of availability and pack sales, together accounting for about 85% of the total antimalarial drug market.

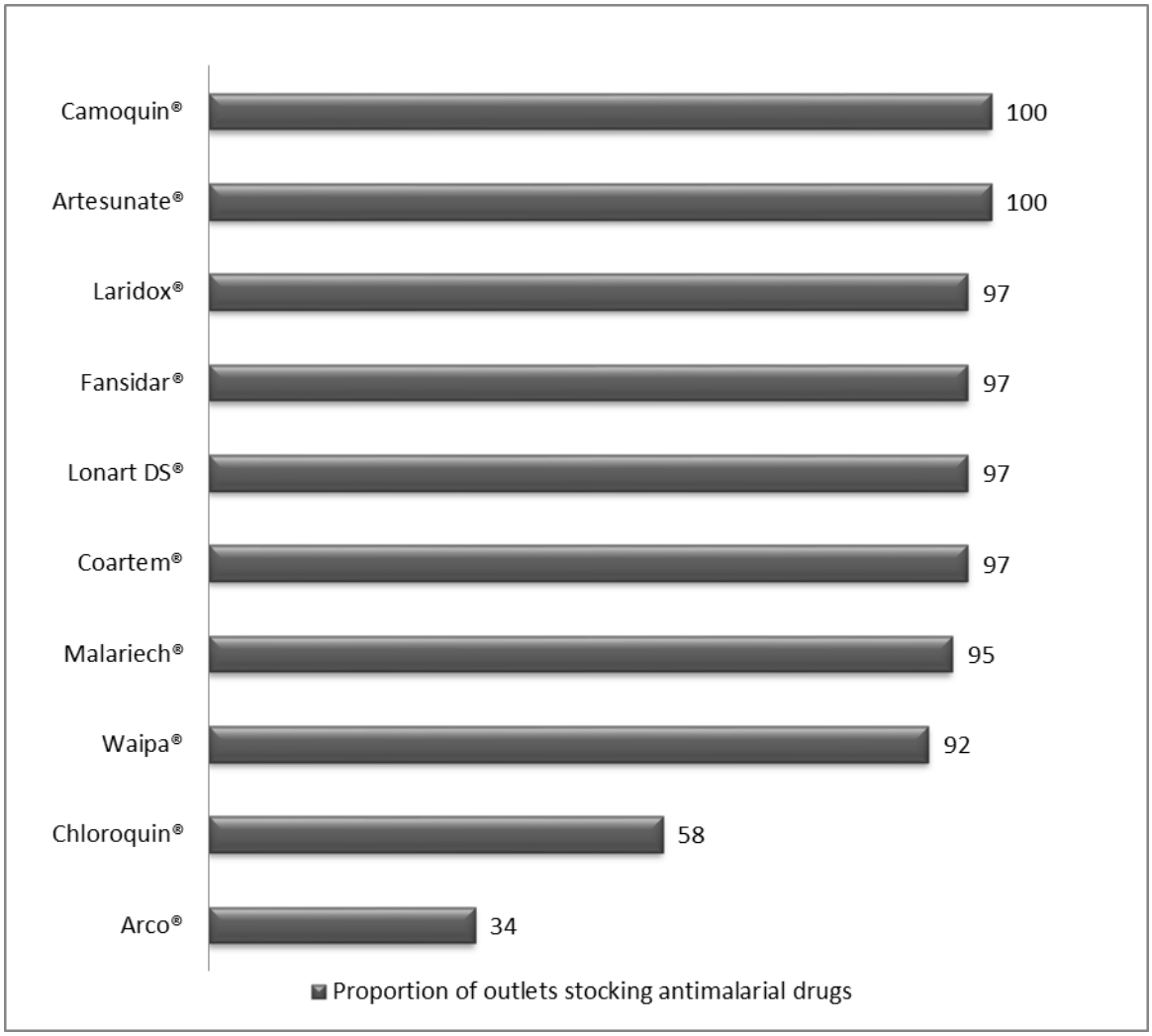


Figure 1.2: Stocking frequencies of antimalarial drugs in retail outlets audited in 2011 (Ezenduka *et al.*, 2013)

Even with a wide range of antimalarial drugs in circulation, prices of the ACTs remain high. In a country in which more than 50% of the population live below the poverty line, affordability becomes a major issue regarding the mean cost of the antimalarial drugs. The implication is that majority of the low income population, which disproportionately bear the greater burden of the malaria disease are unable to afford or access appropriate and effective antimalarial drugs. In consequence, they resort to cheaper but inappropriate sources of treatment including self-treatment and seeking for care from private sector also characterized by inappropriate practices (Onwujekwe *et al*., 2005; 2010; Mangham 2011).

This largely explains the significant use of monotherapy and ineffective drugs mostly available in the retail outlets.

Considering the challenges of high cost ACT as the effective antimalarial drugs and inappropriate practices that accompany malaria treatment which result to wastages and increasing risks of treatment failures and parasite resistance, it is very necessary that this study was carried out to generate evidence-based information to guide the efficiency of malarial treatment in Nigeria to reduce wastages and achieve the goals of reducing the burden of malaria in Nigeria. Hence, it is necessary to provide information on the relative costs and effects of the current policy drugs, ACT, to guide policy and practice on the efficiency of malaria treatment, as this study set out to provider.

1.3.9 *Summary; The challenges and inefficiency of malaria treatment in Nigeria*

Following global response to the widespread resistance of the *Plasmodium falciparum* malaria to chloroquine as well as sulphadoxine-pyrimethamine (SP), Nigeria adopted

the use artemisinin-combination therapy (ACT) as the drug of first-line treatment for uncomplicated malaria in 2005 (FMOH), to enhance the efficiency of malaria treatment.

The policy was informed by the established high efficacy of the ACT in rapidly and completely clearing the *Plasmodium* parasites from the blood and subsequently slowing down the rate of resistance (White 1997; 1998). The combination is thus able to reduce treatment failures and disease recurrence, in consequence reducing probability of progression to severe malaria (Chanda *et al*., 2007). The policy recommended the use of ACTs as the first line treatment for uncomplicated malaria at both the public and private facilities. Artemether-lumefantrine (AL) was the first ACT to be introduced followed by artesunate-amodiaquine (ASAQ) combination. Subsequently, a range of other ACTs is currently widely available in the country, in addition to a variety of other antimalarial agents. However, since the change in antimalarial treatment policy adopting the ACT for first line treatment for uncomplicated malaria, Nigeria continues to face several challenges that affect the efficiency of treatment, due mainly to the high cost of care, the use of ineffective agents and poor treatment practices. The change in policy was not accompanied by a comprehensive economic evaluation, to provide useful information for enhancing efficiency in malaria treatment. The ACTs are significantly more expensive than existing mono-therapies and ineffective agents. Majority of low income Nigerians who live below poverty line and disproportionately bear the burden of malaria disease, are unable to afford them. In spite of the efforts to enhance affordability and access to the drugs through the AMFm initiative, the ACTs have remained expensive with limited access for the low income population. As a consequence, the use of cheaper and less effective monotherapy agents remain high contrary to the malaria

treatment policy. This is compounded by limited knowledge of the general public on the availability of effective antimalarial drugs.

Activities of some providers such as the PMVs who have no formal training on drug dispensing also contribute to poor use of ACTs due to lack of adequate and professional information on their relative benefits. Reported cases of widespread uncontrolled use of antimalarial drugs, which in many cases include substandard drugs as well as sub-optimal treatment have been suggested to contribute to the spread of antimalarial resistant (White 1999, C. Goodman 2004). Poor treatment practices and indiscriminate use of these drugs are reported at both the private and public health facilities, leading to wastages and huge economic consequences. Information on the relative costs and effectiveness of the agents are lacking. Low quality, inadequate knowledge and inefficient healthcare system contribute to widespread use of ineffective antimalarial agents. Regulatory control is similarly very poor in ensuring that providers effectively adhere to policy guidelines on the use and sale of antimalarial drugs in Nigeria (Onwujekwe et al., 2010). These result to increase risk of widespread parasite resistance and treatment failures, with the consequences of increased malaria morbidity and mortality.

In the face of these challenges, it has become necessary that information on the relative costs and effectiveness of available agents be generated to guide the choice and selection of safe, effective, affordable and cost-effective antimalarial drugs to enhance efficiency in the implementation of malaria case management. These challenges informed the goal of this thesis, which was therefore carried out to generate information for enhancing the efficiency of malaria treatment in Nigeria

towards achieving the goals of reducing the burden of malaria in Nigeria. Hence, the study is aimed at generating evidence on the relative health and economic outcomes (clinical effects, costs and cost-effectiveness) of antimalarial drugs in Nigeria, in particular the ACTs, from routine practice to inform policy for efficiency in the implementation of malaria case management

1.4 **Aim and Objectives of the Study**

1.4.1 *Main aim*

The study was designed to assess the efficiency of malaria treatment based on the concept of pharmacoeconomics and generate evidence for planning and policy for effective implementation of malaria case management.

1.4.2 *Specific objectives of the study include;*

a. To assess the treatment and utilization pattern of antimalarial drugs in medicine outlets in Enugu urban
b. To describe the prescription pattern of antimalarial drugs in public health facilities in Anambra state
c. To determine the treatment costs for uncomplicated malaria at a public health facility
d. To evaluate the costs, effectiveness and cost-effectiveness of ACTs in the treatment of uncomplicated malaria
e. To make recommendations for improving the efficiency of malaria treatment in Nigeria

1.5 *Significance of the Study*

Findings of this study will add significantly to the knowledge and understanding of evidence-based approach to decision-making process and policy to enhance access to

effective and cost-effective provision of antimalarial treatment in Nigeria. Specifically, the findings will be relevant in the following areas;

a) Generate information on the cost of malaria treatment, important in research and planning for efficiency in targeting and evaluating the effect of new interventions
b) Provide evidence-based information for planning and implementation of malaria control services; justify investment in malaria research and control
c) Generate evidence to inform resource allocation between different malaria control strategies and other competing programmes
d) Generate evident-based information for effective diagnosis and treatment of malaria based on appropriate use of laboratory confirmation of parasite.

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As the highest contributor to disease burden with consequent high economic burden, findings will contribute to measures that would be deployed to improve the health and economic development in Nigeria and Africa in general.

1.6 **Rational/Justification for the Study**

As a leading cause of disease burden in Nigeria, accounting for greater percentage of drug prescriptions in public and private health facilities, malaria treatment consumes a substantial portion of the nation's health expenditure. Information on the relative costs and effectiveness of antimalarial drugs based on the Nigerian setting is lacking. As a result, the choice of effective antimalarial drugs is limited by the presence of high costs, low quality, cheap and ineffective antimalarial drugs, in addition to poor knowledge of malarial treatment and inefficient healthcare system. The consequences include widespread treatment failures, increase risk of resistance of plasmodium to effective antimalarial agents and general economic wastages. Hence, in view of the high costs of

the ACTs which have replaced SP and chloroquine as first line antimalarial drugs, it becomes crucial that the cost-effective information be generated to inform policy for enhancing efficiency in the implementation of malaria case management in Nigeria.

1.7 *Conceptual Framework of the Study: Efficiency of malaria treatment*

The main focus of this study is on the efficiency of malaria treatment within the limit of available resources. This is based on the concept of pharmacoeconomics conducted within the context of rational use of drugs to enhance the efficiency of malaria treatment. Within the efficiency framework of pharmacoeconomics, information on the cost of pharmacotherapy is related to its effectiveness to determine the efficiency of therapy. For malaria treatment, efficiency is achieved through effective utilization of treatment resources to achieve optimal outcomes. This translates to the cost of resource utilization and outcome measured in terms of clinical effectiveness of pharmacotherapy. Therefore, the main objective of this study is two-pronged; within the limit of scarce resources, to examine the costs of antimalarial drugs commonly used in Nigeria and secondly estimate the relative effectiveness of these drugs. This followed a two-stage approach. First, all the clinical effects (desirable and undesirable clinical outcomes) of the agents used in treating diagnosed malaria attack in routine practice, were identified and measured, based on standard treatment procedures. The net effect/outcome becomes the effectiveness of the antimalarial drugs. Secondly, for each of the products all resources used up in the treatment process (direct and indirect costs of treatment) were identified, measured and valued based on standard accounting procedures. The net costs and effectiveness of the each of the agents were compared to similar values of a known control to determine the comparative incremental effectiveness, costs and cost-effectiveness of each of the agents. Hence the model is based on the combination of

evidence from clinical study in routine practice and observational data (clinical and observational data). Each antimalarial agent will be evaluated against a known control using net incremental cost-effectiveness ratio (ICER).

1.7.1 *Linking objectives, research questions and efficiency framework*

This study is conducted within the context of rational use of antimalarial drugs which emphasizes effectiveness, affordability and appropriateness of drug use to ensure achievement of therapeutic goals and reduced wastages. As an efficiency measure, the study applied resource allocation principles of pharmacoeconomics to assess the efficiency of malaria treatment. Since treatment is provided through the framework of malaria case management, efficiency is achieved through effective implementation of appropriate diagnosis and prompt treatment with recommended antimalarial drugs. Hence, efficiency of treatment goes beyond the use of effective drugs but requires adherence to treatment guidelines to ensure efficiency and achievement of the goals of malaria case management.

In line with the framework of this study, the objective of exploring the treatment and utilization pattern of the antimalarial drugs at the private retail outlets is concerned with ascertaining how and whether the resources are appropriately and efficiently used in line with guidelines to achieve the intended outcome. Hence, the focus is on availability, affordability and resource use dimensions of efficiency of malaria treatment.

The objective of exploring adherence to treatment guidelines at the public health facilities is linked similarly to ascertaining how and whether the resources are available and efficiently utilized by healthcare providers in terms of appropriate

diagnosis and the use of recommended drugs. Focus is therefore on availability, affordability and resource utilization as dimensions of efficiency.

The objective of estimating the facility costs of malaria treatment is concerned with determining the cost of treating malaria as the standard in the provision of malaria treatment, to ascertain the efficiency of resource utilization in the treatment of uncomplicated malaria from a public health facility. Hence, it is concerned with adherence, affordability and resource allocation aspects of efficiency (diagnostic accuracy and compliance with treatment guidelines).

Finally, the cost-effectiveness objective is mainly concerned with effectiveness, affordability and resource allocation dimensions of efficiency and quality of care, by assessing the relative costs and effects of available antimalarial regimens. Table 1.4 details the links between the study objectives, research questions and efficiency focus of the dissertation.

Table 1.4: Linking study objectives, research questions and efficiency framework

SN	*Study objectives*	*Research questions*	*Efficiency focus*
1	Treatment and utilization pattern of antimalarial drugs in medicine retail outlets	What is the relative availability of antimalarial drugs in the retail outlets? Are the recommended drugs appropriately used? What is the extent of use of monotherapy and ineffective agents? To what extent is diagnosis carried out before the use of antimalarial drugs? What are the costs of available antimalarial drugs? What is the relationship between the cost of treatment and the use and availability of the agents?	Availability Affordability Adherence Rational drug use
2	Exploring adherence to treatment guidelines for uncomplicated malaria in public health facilities (prescription pattern/practices for uncomplicated malaria)	What antimalarial drugs are used in the facilities? Is laboratory diagnosis carried out before treatment? To what extent is monotherapy used in the facilities? Are the recommended drugs appropriately used? What proportion of patients are treated for uncomplicated malaria relative to the total number of outpatient pat	Availability Affordability Accessibility Adherence Rational drug use
3	Estimating facility cost of treatment for uncomplicated malaria	What is the average cost of treatment for an episode of uncomplicated malaria from the health facility? What proportion of facility budget is used for the treatment of uncomplicated malaria in a public health facility setting?	Availability Resource allocation Affordability Accessibility
4	Determine the cost-effectiveness of antimalarial drugs (ACT)	What are the relative costs, effectiveness and cost-effectiveness of available antimalarial drugs (ACTs) in Nigeria?	Effectiveness Affordability Resource allocation

1.8 *Scope of the study*

i. Private sector evaluation of antimalarial drug utilization review (DUR) and price survey in urban city of Enugu metropolis, Enugu state

ii. Public sector antimalarial drug utilization review in primary/secondary and tertiary health facilities in Awka and Nnewi cities respectively, in Anambra state

iii. Evaluation of facility cost of treatment for uncomplicated malaria at the \University Medical Center at Awka, Anambra state

iv. Evaluation of the costs, clinical effects and cost-effectiveness of the ACTs at the University Medical Center, Awka Anambra state

1.9 *Outline of the dissertation*

The paper is divided into five chapters. In Chapter One, the general overview of the malaria disease burden and issues related to the efficiency of treatment is presented, to establish the basis for this dissertation. Literature review on the role of pharmacoeconomics and outcome research in health care decision making is presented in Chapter Two, to establish the basis of the concept in guiding the efficiency of malaria treatment in Nigeria. Summary review of previous studies on the cost-effectiveness (pharmacoeconomic evaluation) of ACTs is also presented in this chapter. In Chapter Three, the appropriate mix of methods used in achieving the objectives of the dissertation is presented. Findings and results of the studies are presented in Chapter Four. The discussions of the study findings, conclusions and recommendations to policy on the use of antimalarial drugs for efficiency of malaria treatment in Nigeria are presented in Chapter Five.

CHAPTER TWO

LITERATURE REVIEW ON THE ROLE OF PHARMACOECONOMICS IN HEALTHCARE DECISION MAKING

2.1 *Introduction*

This chapter reviews the concept and principles of pharmacoeconomics as applied in this thesis/dissertation, describing the application of the principles in guiding decision making processes to enhance efficiency in healthcare programmes and interventions. Review was also carried out on studies that evaluated the cost-effectiveness (pharmacoeconomic evaluation) of antimalarial drugs in Africa and other related regions.

2.2 *The Principles of Pharmacoeconomics*

Pharmacoeconomics has been defined as the description and analysis of costs and consequences of pharmaceutical products and services and their impact on individuals, health system and the society (Bootman 1995). As a branch of health economics, it analyses the allocation of healthcare resources among various alternative pharmaceutical products and services, to enhance efficiency. Information generated by pharmacoeconomic analysis provide important tool to decision makers to make informed decisions in choosing between several alternative interventions for enhanced efficiency in the provision and implementation of health care programmes. Hence, pharmacoeconomics aims to provide decision makers the tool to make informed choices in the provision of healthcare programmes and interventions. As a result many

countries, including developing countries are increasingly using PE analysis to generate evidence for decision making in the health care system (Mori *et al*., 2013)

To generate the relevant information for decision making, the process of pharmacoeconomic research or evaluation involves identification, measurement, valuation and comparison of the costs, and consequences (both risks and benefits) of interventions, services, or therapies to determine the alternative that produces the best health outcome for the resource invested (Drummond *et al*., 1988). The process generally translates into assessing the cost of providing a pharmaceutical product or service and comparing with the outcome (benefits) generated by using the product or service so as to determine which alternative produces the best outcome per money spent (Dipiro *et al*., 1998). This information then provides the basis for clinical decision making in selecting the most cost-effective treatment options (Lee *et al*., 1991).

The concept of pharmacoeconomic shares distinct relationship with outcomes research and pharmaceutical care. Broadly, *Outcome research* has been defined as the studies which attempt to identify, measure, and evaluate the results of healthcare services in general (Bootman 1995). The results of the outcome studies are measured in terms of economic, clinical and humanistic outcomes (ECHO). Consequently, Pharmacoeconomics can be considered as a division of outcomes research that can be used to quantify the value of pharmaceutical care products and services (Sanchez 1998). *Pharmaceutical care* on the other hand, has been defined as the responsible provision of drug therapy for the purposes of achieving definite outcomes (Hepler *et al.*,1990). This paradigm or vision for pharmacy makes the profession accept responsibility for managing drug therapy so that positive outcomes are produced (Dipiro *et al*., 1998).

2.3 *Components of pharmacoeconomics*

The concept of PE makes cost and consequences (outcome) the key areas of focus for analysis. While *Cost* is defined as the monetary value of resources used up in the provision or consumption of a pharmaceutical product or service, *Consequence* describes the effects of the programme or therapy in terms of its outputs or outcomes generally. The comparison of costs and consequences/outcomes of pharmaceutical products and services distinguishes most pharmacoeconomic evaluation methods from traditional cost-containment strategies and drug-use evaluations.

Healthcare costs or economic outcome are measured and valued in monetary units, such as naira, dollars etc. Depending on the perspective of study, costs are identified and categorized as direct, indirect and intangible costs. Direct cost is further classified as direct medical and direct non-medical items. Figure 2.1 shows the components of PE. Consequences (effectiveness) are measured in terms of *clinical* and *humanistic* outcomes and the quantification of these consequences determine the pharmacoeconomic methods of analysis, since the measurement of costs is relatively standard (Sanchez 2005). *Clinical outcomes* represent the medical events which result from disease burden or its treatment (such as safety and efficacy end points) (Kozma *et al.,* 1993). *Humanistic outcomes* are used to represent the effects or consequences of disease or its treatment on patient's functional status or quality of life occurring in several dimensions (such as physical/social function, general health and well-being, and life satisfaction) (Kozma *et al*., 1993). The assessment of the economic and health outcomes (ECHO) associated with a treatment alternative provides a complete model for decision making (Sanchez 2005). Using pharmacoeconomic methods, costs and consequences of a product are measured following the choice of a perspective

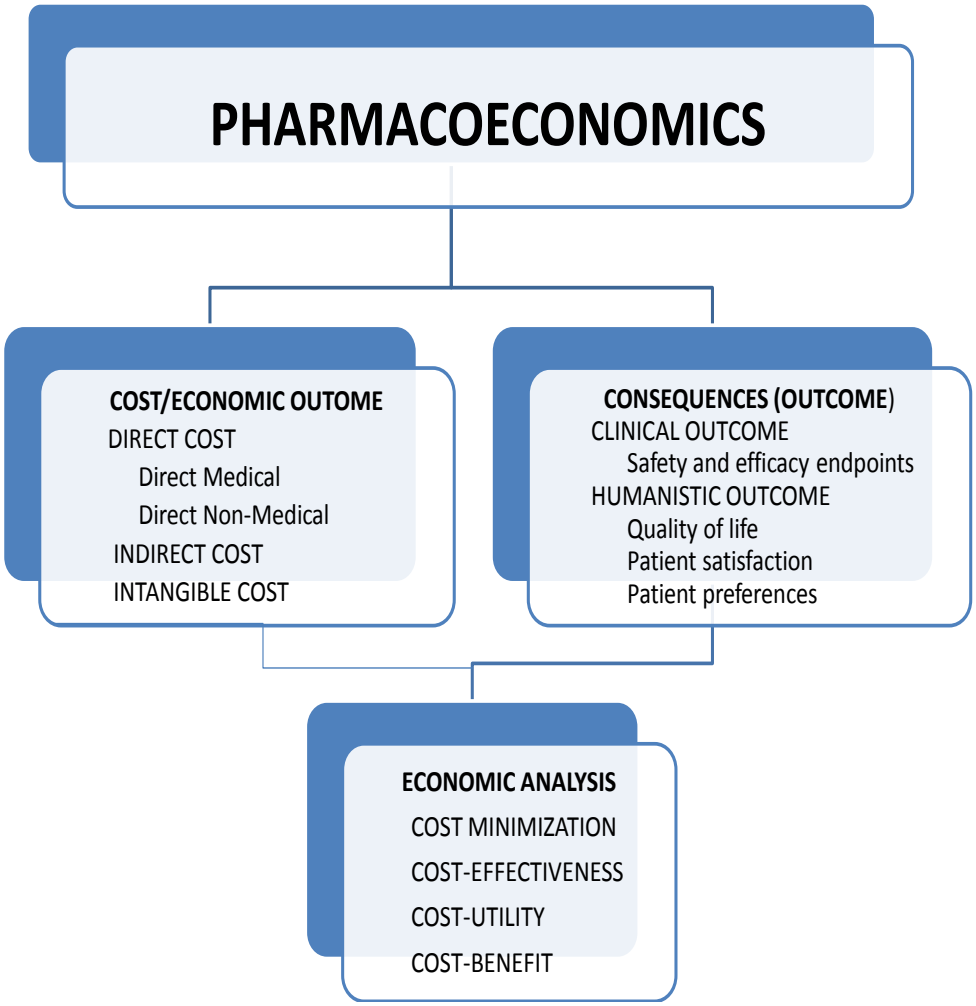


Figure 2.1: Components of pharmacoeconomics

2.4 *Efficiency principles of PE*

Two concepts of efficiency are described in PE; technical and allocative efficiencies.

1. **Technical efficiency**: deals with efficiency within a programme. Measures the extent to which resources are combined to achieve/produce maximum outcome/benefit; i.e.

producing a given level of output at a minimal cost or producing the maximum amount of output for a given cost. Example, in a mutually exclusive situation, making a choice between two or more alternative interventions to determine the one that achieves higher benefits/outcome at a given cost; For example, making a choice between two or more drugs for the treatment of a disease

Allocative efficiency: a broader concept of efficiency which focuses on choosing or selecting the optimal mix of interventions within a given level of expenditure, ie interventions that maximize health gains – "doing the right things". It measures the extent to which resources are allocated to areas, groups or individuals (in a mutually inclusive setting) which achieves the most (maximum) benefits. For example, among a patient group, identify a high risk group for which intervention is provided to achieve higher benefits, compared to low risk patients. In other words, allocative efficiency requires that high-risk patients to be targeted as a priority (primary prevention), resulting in an improved level of health associated with the treatment. Allocative efficiency deals with, 1) comparison across programmes; for instance, how programmes compete for allocation of scarce resources, 2) comparison across programmes such as surgery, ICU, renal services etc. Example is choosing in a programme, among two services to be expanded for improved productivity.

2.5 *Perspectives in pharmacoeconomics*

Perspective in pharmacoeconomics is a very important consideration in pharmacoeconomic evaluation. It determines the extent to which the costs and consequences of a products or intervention are to be collected and analysed for the necessary analysis. The value of a pharmaceutical product or service depends greatly on the perspective of the evaluation. This is because the perspective or viewpoint of the

analysis describes the extent to which resources or costs were expended and the benefits generated. It shows whose resources are used and what benefits were generated. The common perspectives in PE include those of the patient, provider, payer, and society. However, in pharmacoeconomic evaluation, the value of a product or service can be assessed from a single or multiple perspectives, but it is important that clarification of the perspective is provided because the results of the analysis depend heavily on the perspective taken (Sanchez 2005). Clarification of the perspective/s precedes the full evaluation of relevant costs and consequences in a PE study. Furthermore, perspective is critical because it determines the appropriate value of a product or treatment alternative which depends heavily on the viewpoint taken.

2.5.1 *Patient Perspective*

Patients are the ultimate users of healthcare products and services hence, the perspective is paramount. Costs from patient perspectives include those payments or resources used/consumed by him/her in the use of a product or service. The consequences/benefits in this perspective are assessed as the clinical effects of a product or treatment alternative. Examples of costs include the out-of-pocket (OOP) expenses (drug purchases, travel costs e.t.c), as well as indirect costs, such as lost wages. Patient perspective is adopted when evaluating the impact of a drug treatment on quality of life or when a patient is expected to pay out-of-pocket expenses for a healthcare service.

2.5.2 *Provider Perspective*

Providers may include hospitals, private-practice physicians or managed-care organizations (MCOs). In this perspective, costs include the actual expenses incurred

in providing a product or service, irrespective of the charges. Cost of hospitalization, drug costs, laboratory tests, supplies, and salaries of healthcare professionals are examples of direct costs of resources collected and analysed. Indirect costs are not of importance to the provider and hence not often collected. Provider perspective is the relevant viewpoint when making formulary or drug-use policy decisions. The major issue with this perspective is that true economic costs are not always collected in many studies (Sanchez 2005). Often, data on charges which do not reflect the true cost of healthcare may be more freely available. Moreover, translating charges into actual costs can be challenging, resulting to the use of cost-to-charge ratio as a useful alternative. Similarly, average wholesale price (AWP) is often used as a common proxy for costs of medications even though providers do not actually pay AWP for their drugs. Therefore AWP is not an accurate proxy for drug-cost data.

2.5.3 *Payer Perspective*

The payer perspective represents the charges for healthcare products and services or payments made by payers which include employers, government or insurance companies. Direct cost is the primary cost in this perspective but the indirect costs of lost workdays (absenteeism) and other causes of lower productivity can also contribute to the total healthcare cost to the payer. The payer perspective is adopted when employers and insurance companies are choosing healthcare services/benefits for their employees, or have contract with MCOs

2.5.4 *Societal Perspective*

The perspective of society considers and captures the benefits of the society as a whole and therefore the broadest of all perspectives. All the costs/resources that are

consumed from the society in the course of providing care are included in the analysis. This means that all direct and indirect costs associated with therapy or service provision are included in the evaluation. These include patient morbidity and mortality as well as the overall costs of providing and receiving medical care. The perspective also includes all the important benefits or consequences which a patient could experience in the course of receiving care. The societal perspective has been considered by many researchers and academicians as the most appropriate perspective for conducting pharmacoeconomic analysis (Gold *et al.,* 1996). However, conducting studies from this perspective can be very resource-intensive, time consuming and expensive.

As soon as a perspective is selected, the costs and consequences of the product or service being evaluated can be identified, measured and valued using pharmacoeconomic methods.

2.6 Pharmacoeconomic Evaluation Techniques

Pharmacoeconomic evaluation is defined as the process of identifying, measuring, analyzing, summarizing and comparing the costs and consequences of alternative programmes or intervention, to determine the one that produces the more benefits at a given cost. The process uses a set of analytical techniques or principles to systematically analyze and compare the costs and consequences of health care interventions, to identify the alternative/s that achieves the greatest value for money. These tools differ principally on how the consequences or health outcomes are measured and valued (unit of measurement of health benefits or outcome), which have

implications on their application in the health system, while their input/cost measurement is carried out in similar monetary terms/units.

2.6.1 *Cost of illness study (COI)*

COI study is carried out to measure the economic impact of a disease, which measures the total value all the resources used up or lost by the society as a result of the disease. The study involves the extensive identification and measurement and evaluation of the direct, indirect and intangible resources consequent upon the disease occurrence and management. Direct costs are made up of medical and non-medical costs such as cost of medication, consultation, laboratory/diagnostic, admission (direct medical costs); travel cost, waiting time, (direct non-medical). Indirect costs include productivity/wage loss for patients and caregivers, time lost by unpaid caregivers who assist in managing patients relations. Intangible cost is a measured value of pain of suffering and reduced quality of life. However, the extent to which the cost data are collected in COI is highly dependent on the policy perspective of the study. When the perspective of the society as a whole is the choice, the full range of the costs is collected, (in terms of direct, indirect and intangible costs), which has made it the generally adopted ideal viewpoint as recommended by the Committee on the Cost-effectiveness in Health and Medicine (Gold *et al.*, 1996). However, few studies have actually applied this approach. What is important is the specification of reasons and methods behind any approach adopted.

Therefore information from COI studies are used to support health policies which provide guidance for healthcare decision making in such areas as identifying the cost components of a specific disease management (diagnosis and treatment), the burden

of disease on the society, identification of clinical priorities based on economic impact, guide research towards prevention activities, identification of patients' consumption pattern as well as evaluating and comparing the prescription pattern of physicians. COI provide useful information for identifying elements that are indispensable for conducting subsequent economic evaluation studies.

2.6.2 *Cost Minimization Analysis (CMA)*

CMA is a technique undertaken to evaluate interventions which produce equivalent outcomes. Since the outcomes are equivalent, the choice of the intervention will be based on the one that operates at a lower cost. Although this technique involves the analysis of cost to determine intervention that produces a given outcome at a lower cost, it is not regarded same as cost analysis which is carried out without recourse to outcome generation. In CMA cost of alternative intervention with same outcome are identified, measured, valued and compared to determine the one with the lower cost.

2.6.3 *Cost-Effectiveness Analysis (CEA)*

CEA is the method used to evaluate and compare interventions whose outcomes occur in natural or physical units and therefore differ in the size of the effects or outcomes. This requires that the unit of measurement must be the same for the interventions being evaluated or compared. Interventions whose size of outcome is more than the alternative, at a given unit cost is said to be more cost-effective. In CEA, benefits are measured in natural units such as lives saved or life years gained and the role of the economist is to estimate the cost per unit of outcome achieved – the cost per life year or the cost per life saved. This does not allow for a direct comparison of costs and benefits but programs can be ranked in order of their 'desirability' with the caveat that

nothing else is of importance. In malaria treatment for instance, an antimalarial drug which prevents more malaria cases at a given cost (naira or dollars) is said to be more cost-effective. Since malaria cases or death preventions are the major goals of treatment and control, CEA is a popular technique of pharmacoeconomic evaluation of antimalarial drugs. When decisions have been taken on the treatment of a particular disease, CEA is carried out to identify the more efficient one that achieves the higher benefits at a given cost. The technique is frequently used in randomized control trials (RCTs). CEA is routinely carried out alongside RCT at which large scale prospective information on the actual cost of resources used and their variability in RCTs. This approach enhances the possibility of there being adapted to other settings. Of all the tools available, CEA is the most commonly used tool in healthcare (Gold *et al*., 1996).

2.6.4 *Cost Utility Analysis (CUA)*

CUA is considered a part or extension of CEA. Outcomes of interventions are measured in utility values based on quality of life. Some interventions especially pharmaceutical products also produce effects which impact on the quality of life of individual patients expressed in utility measures. To capture the measure of quality in addition to quantity of life savings (survival), a unit of measure was developed to evaluate the interventions. The commonly used units of measure are the Quality Adjusted Life Year (QALY) and Disability Adjusted Life Year (DALY). These units combine quality (utility) and quantity (survival). CUA is particularly useful in evaluating antimalarial drugs. Key advantage of this technique is comparison across interventions which have different outcomes, to determine the differences in both the quality and quantity. Interventions that improve the quality of life can be compared with those that extend life years. CUA is particularly useful in disease conditions

where death/survival is important and frequent outcomes e.g. cancer, cardiac surgery, renal dialysis. QALY has been variously used to compare treatments and programmes which compete for scarce resources.

2.6.5 *Cost benefit Analysis (CBA)*

This technique is based on measuring both the cost and intervention benefits in monetary units. This means that generated outcomes of interventions are converted to monetary units and compared with the cost outcome in monetary unit. The implication is that different interventions can easily be directly compared across programmes including outside the sector, an important tool at top level decision making and investment. Programmes can also be easily compared against itself to determine the return on investment (ROI). CBA can be used to answer question on resource allocation such as, should resources be allocated to road traffic control programmes or malaria prevention programme, or education programme. However, key issue in CBA is that decision making concept about resource allocation to health may not be optimal to the society as a whole, since this may be a 'knock-on' effect on other sectors outside health.

2.7 Pharmacoeconomic Evaluation Process

2.7.1 *Determination of Cost – Measures of cost*

Cost, defined as the monetary value of resources consumed in the provision of goods and services, measures all the resources that are used up in the provision of health/pharmaceutical goods or services such as provision of treatment, and summarizes the measure in monetary terms, e.g. Naira or Dollars. Costs are broadly categorized into direct, indirect and intangible costs;

Direct costs comprise of those resources that are directly associated with the provision of medical care, and they are further classified as d*irect medical and direct non-medical* costs (Eisenberg 1989). The direct medical costs are those medical resources that directly go into the provision of medical service such as surgical fees, drugs, laboratory tests, professional fees, admission fees etc, while the non-medical items that do go directly into clinical services but are directly spent in the course of treatment such as transport fares to facility, home care for patient etc.

Indirect cost of loss of Productivity; this represents the loss of human productivity due to disease morbidity and mortality. It includes the loss of work days, absenteeism from work or education, loss of investment due to disease.

Intangible cost; the cost of pain per se; measure of the discomfort/disability caused by the disease

2.7.2 *Other forms/measures of costs in health economics/pharmacoeconomics*

Opportunity cost: this is the amount a resource would earn in its best alternative use or the cost of the next best alternative forgone. It describes all the benefits that are given up in deciding for a course of action. Hence, it determines the real cost of resource use.

Incremental cost: This is difference in cost between a new intervention and the current or usual care

Marginal cost: the change in total cost due to one unit change in output

Average cost: The cost of producing one unit of output. Total cost divided by total output

Financial cost: This represents the monetary payments or expenditure on all resources (goods and services) consumed or given up in the provision or delivery of care.

Economic cost: This is a measure of the opportunity cost of providing care or service delivery. It includes the financial costs and other use of resources such as time losses. Examples include volunteer time, donated resources. Hence, economic cost reflects a better or true measure of resource use or total cost associated with therapy or service delivery. However, financial costs can be useful in providing some necessary information, as a good or larger proportion of interventions are reported in financial terms (White *et al*., 2011)

2.7.3 *Framework for cost determination*

This describes the steps undertaken in determining costs in pharmacoeconomic evaluation. It follows a five step approach

i. *Identification*; specification and documentation of all input resources used in providing care, in terms direct, indirect and/or intangible costs
ii. *Measurement*; Quantification of each resource item/input to determine the total number used
iii. *Valuation*: Assigning monetary values to quantity measured, by applying unit prices of each item on the total number of resources to obtain the total cost or monetary value of resource use
iv. *Discounting*: Adjusting for time differences in monetary value of resource use where applicable, using an established rate of interest, based on a standard accounting procedure

v. *Sensitivity analysis*: Allow/account for uncertainty due to variability of data and assess the impact or robustness on the findings by varying the values of parameters used, for instance using worst and best case scenarios to recalculate the result.

2.7.4 *Measures of Health Outcomes - Clinical and Humanistic Outcomes*

Health outcomes are used to describe the effectiveness or impact of pharmaceutical products and services on the health of the individual. They are generally referred to as either clinical or humanistic, depending on the type of intervention and desired effect they produce on the human health. These outcomes provide the basis for assessing or measuring the value of the product or intervention.

2.7.4.1 Clinical outcome

Clinical outcomes are effects or consequences of interventions generated in terms of mortality and morbidity/disability measures as well as specific clinical endpoints such as blood pressure, blood glucose, blood cholesterol levels etc. Although mortality and morbidity outcomes such as death prevented, lives saved, cases averted etc. are popular, many pharmacoeconomic studies use clinical indicators or endpoints as proxy surrogates or intermediate outcomes for final outcomes (Kozma *et al.,* 1993). CEA is the often the appropriate method for evaluating interventions/therapies that produce clinical outcomes.

2.7.4.2 Humanistic outcome

Humanistic outcomes represent the psychosocial effects that are produced by drug therapies or medical care/interventions, in terms of patient's health related quality of life (HRQOL), patient preferences, and patient satisfaction, which have all grown in

popularity and application to pharmacotherapy decisions. These outcomes describe the effects of intervention on the physical, social and emotional well-being of the patient. The effects correspond to the WHO definition of health as the complete state of physical, mental/emotional, social and psychological well-being of a patient, and not the mere absence of disease and infirmity (WHO 2000). These describe the ability of the individual to perform routine daily functions, important for productivity. Hence, pharmacoeconomic evaluation methods also focus on these outcomes to evaluate the impact of disease and its treatment in humans. Clinicians also use these methods to quantify the value of pharmaceutical products. HRQOL is defined as the assessment of the functional effects of illness and the resultant treatment as perceived by the patient (Schipper *et al*., 1990). The measurement of HRQOL is achieved using patient-completed questionnaires, available mostly in either disease-specific or generic measures of health status (Spilker 1990; 1992).

2.7.5 *Steps for conducting a cost-effectiveness Study*

Pharmacoeconomic economic evaluation is carried out to answer a study question involving a decision to make a choice between two or more therapeutic alternatives. Conducting pharmacoeconomic research in any setting can be a challenging process. Common limitations include resource constraints, small sample sizes, poor randomization, limited placebo comparison, and the difficulty in generalizing results (DiPiro *et al*., 1995). For example, this can be observed when there is a need to determine and select the most cost-effective drug for hospital formulary decision. The lack of financial and time resources may affect the conduct of a prospective study which can be scientifically rigorous. As a result, this may lead to a decision to conduct retrospective database analysis. Today, many pharmacoeconomic studies are

carried out through such analysis for pharmacy and medical claims databases, covering many therapeutic areas (Johnsrod and Crismon 2002; London *et al*., 2003; Kleinman *et al*., 2006).

Some criteria for quality economic evaluation are recommended to guide effective conduct of pharmacoeconomic evaluations (Drummond *et al*., 1997; Bootman *et al*., 2005). This section briefly describes below, a 14-step process updated from a 10-step guide, which serve as a guide for conducting a local pharmacoeconomic study (Sanchez 1995). The process consists of 14 fundamental steps for conducting a pharmacoeconomic evaluation in any healthcare system which is practically applicable to any therapeutic area or healthcare service.

Step 1: Define the pharmacoeconomic problem

The first important step requires the clear definition of the decision problem. An example might be making a choice between available antimalarial drugs; in terms of, "Which antimalarial drug combination represents the best value for the treatment of uncomplicated malaria?" it is important that the problem is concise and measurable

Step 2: Assemble a cross-functional study team

To reflect the diversity and multidisciplinary nature of pharmacoeconomics, given the variety of outcome, it is important to organize a study team that can provide appropriate resources for a pharmacoeconomic evaluation. Team membership varies depending on the type of analysis but they may include representatives from economics, pharmacy, medicine, nursing, hospital administration, and information systems, etc.

Step 3: Define the appropriate study perspective

As described in the previous section, decision on the most relevant study perspective(s) to the question should be made.

Step 4: Identify treatment alternatives and outcomes

The treatment options are clearly identified and described and these may include pharmacologic and non-pharmacologic alternatives. However, all clinically relevant options should be included. Identified outcomes should also include both positive and negative clinical outcomes.

Step 5: Identify the appropriate pharmacoeconomic method to use

Depending on the nature of outcome, the pharmacoeconomic evaluation method is chosen from the available techniques, namely CMA, CBA, CEA, and CUA. The use of improper method can adversely affect medication decisions influencing both cost and quality of care.

Step 6: Place a monetary value on treatment alternatives and outcomes

This requires the monetary valuation of all the treatment options and outcomes which includes the costs of drug administration, acquisition costs as well as the cost of positive and negative clinical outcomes (e.g., determining the cost of ADRs and treatment failures). This can take the form prospective or retrospective cost assessments or 'estimated using comprehensive databases or expert panels'.

Step 7: Identify resources to conduct study in an efficient manner

Resources needed to conduct the study are clearly identified at this stage, and this will vary depending on the type of study. Resources can include access to medical or computerized records, average medical personnel wages, and specialty medical staff.

Step 8: Identify probabilities that outcomes may occur in the study population

Having identified the outcomes of the study in step 4 above, the probabilities that they are actually occurring in clinical practice are ascertained at this stage. These can be obtained using primary literature and expert opinion, which may manifest as efficacy rates and incidence of ADRs.

Step 9: Employ Decision Analysis

In most cases decision analysis provide the basis conducting various pharmacoeconomic evaluations, although it may not be necessary for some evaluations. They can provide solid backbone or platform for the required decision. Decision tree, for instance can be used to graphically present treatment alternatives, their outcomes and probabilities, which can all be reduced algebraically to a single value/number for comparison (i.e., cost-effectiveness ratio). Having reduced the variables to these numbers or ratios, they become for meaningful comparison. For a CEA study for instance, the treatment alternative which produces a better cost-effectiveness ratio than the others (i.e., lower cost per unit of outcome) becomes the more cost-effective option and would be selected and promoted for use.

Step 10: Discount costs or perform a sensitivity or incremental cost analysis

As a standard in economic evaluation, costs and consequences which occur in the future must be discounted back to their present values, to account for differences in time value of money. Variables identified to be sensitive must be tested over a clinically relevant range and results recalculated in a sensitivity analysis. An incremental analysis of the costs and consequences should be performed if it is appropriate.

Step 11: Present study results

The results of the study should be presented appropriately to the cross-functional team, as well as to appropriate committees of an institution. The style of the presentation and content can vary depending on the audience.

Step 12: Develop a policy or an intervention

Results of the study should be used to develop a policy or an intervention that can improve or maintain quality of care, possibly at a cost savings.

Step 13: Implement policy and educate professionals

Appropriate time and resources should be used to strategically implement the policy or intervention based on the study results. Healthcare professionals who are most likely to be affected by this policy should be appropriately educated using various strategies such as verbal, written, and online communication.

Step 14: Follow-up documentation

Once the intervention or policy developed from the study results has been implemented for a reasonable period of time, follow-up data should be collected. Collected data should provide feedback on the success and quality of the policy or intervention.

(*Adapted from Sanchez LT; Pharmacoeconomics: Principle, Methods and Application. Chapter 1in Pharmacotherapy)*

2.7.6 *Sources of data for pharmacoeconomic evaluation*

There are two main sources of data for pharmacoeconomic evaluation:

- Primary data; collection of original data based on study designs ranging from RCTs to case studies. This involves conducting of primary pharmacoeconomic study
- Secondary/integrative method; collecting data from primary studies/sources, e.g. meta-analysis, literature reviews, modelling

Most pharmacoeconomic studies use secondary sources of data collection

2.7.7 *Primary source: Conducting Pharmacoeconomic Evaluation*

With adequate availability of data, local PE evaluations can be conducted by using original data from practice settings. More often, this involves the use of RCT and other clinical research designs to collect clinical data while cost data are collected alongside. Primary PE evaluation can be conducted when literature is not sufficient, or when published results are not easily extrapolated to clinical practice or the use of model will not be appropriate (Sanchez L 1998). Conducting the study will require adequate knowledge and application of the available pharmacoeconomic techniques or methods, including their similarities and differences. Local PE studies are however resource intensive, time consuming and expensive. This suggests the need to reserve the strategy of primary PE evaluation for pharmacy decisions which may yield significant impact on outcomes such as cost and/or quality of care. Depending on the study question and type of data analysis (prospective or retrospective) required resources and evaluation technique will vary. Highlights of the advantages and disadvantages of the respective analyses are presented in Table 2.1. In the recent

times studies based on retrospective database analysis have become increasingly important sources of outcomes data. In 2003, a check-list of 27 items was published to provide assistance for decision makers in evaluating the quality of published studies (Motheral *et al*., 2003). These items are useful in planning retrospective database analysis. This dissertation used a primary source of data collection to conduct a PE study, based on both retrospective and prospective data collection methods.

Table 2.1: Advantages and Disadvantages of Retrospective and Prospective Analyses

Prospective observational analysis	**Advantages**	**Disadvantages**
	• Flexible • Yields provider-specific data • Reflects "usual care" or effectiveness • Usually offer comparative data • Data from multiple sources can be used • Less expensive than randomized controlled trials • Prospective	• Prospective • Expensive (time and money) • Difficult to control and randomize • Potential for patient selection bias • Small sample size • Difficulty generalizing results to other providers • Longer timeframe
Retrospective database analysis	• Has potential for large sample size • Can provide data quickly • Is customer specific • Reflects 'usual care' or effectiveness • Relatively inexpensive • Shorter timeframe • Data collection is unobtrusive	• Retrospective • Inconsistent coding/upcoding • Variations in database quality among managed care plans • Inconsistent access to pharmacy versus medical claims • Inability to randomize patients to treatment

(*Adapted from Sanchez LT; Pharmacoeconomics: Principle, Methods and Application. Chapter 1in Pharmacotherapy)*

2.7.8 *Secondary source: The use of literature*

The popularity of pharmacoeconomic literature for PE information and decision-making has increased over the years as most studies now use secondary sources of data collection, to quantifying the value of pharmaceuticals (Dipirio *et al*., 1996). Published literature of primary medical and pharmacy studies has therefore become the source of many pharmacoeconomic analyses. Hence, the number of published pharmacoeconomic studies has increased over the past 40 years. The major concern however, is the quality of the pharmacoeconomic evaluations of drugs is far outweighed by the eagerness to publish such studies. Hence, quality variations and indiscriminate use of pharmacoeconomic terminology have been documented in relevant medical and pharmacy literature sources (Mcghan *et al*., 1978; Doubilet *et al*., 1986; MacKeigan and Bootman 1988; Lee and Sanchez 1991; Schumock *et al*., 1995; Bradley *et al*., 1995). This is why it necessary that, to use the literature as aid in clinical decision making, it should certify the conditions such as, it must be (1) critically evaluated for quality and rigor and (2) interpreted correctly (Sanchez 1995). As a priority, the potential limitations of these data should therefore be recognized by decision makers before using pharmacoeconomic data to make clinical and policy decisions.

In recognition of the differences in healthcare settings and countries, the generalizability of the results of PE studies is a major consideration in the evaluation and interpretation of PE study. Generalizability of the published results can be difficult primarily due to vast differences in practice patterns, patient populations and costs between healthcare systems and countries. There are also the issues that bother on the differences in the study perspectives, sources of data, and analytic styles. This may however pose a challenge in trying to extrapolate the cost savings to the local or

their own practice or other settings. Therefore, the following points should be considered in order to enhance the ability to use published pharmacoeconomic results.

1. The technical merit of the study
2. Applicability of the results to local decision making
3. Generalizability of the study results to different jurisdictions with different perspectives (Mason 1997)

Consequently, these considerations led to the publications of various guidelines, criteria, and consensus-based recommendations for evaluating, conducting, and reporting pharmacoeconomic literature (Eisenberg 1989; Langley 1993; Desky 1993; Drummond *et al.*, 1997). These guidelines have been summarized into 11 categories that are most relevant to pharmacotherapy (Sanchez 1995).

The criteria and pertinent questions are summarized in Table 2.2 below.

Table 2.2: Basic Criteria for Evaluation of Pharmacoeconomic Literature (Sanchez, 2005)

Objective What is the question(s) being considered? Is the question clear, defined, and measurable?
Perspective What is/are the perspective(s) of the analysis? Is the perspective appropriate given the scope of the problem?
Pharmacoeconomic method What pharmacoeconomic tool was used? Is it appropriate given the problem? Is it actually what was conducted?
Study design What was the study design? What were the data sources? Is the evaluation suitable if carried out in a clinical trial?
Choice of interventions Were all appropriate alternatives considered and described? Were any appropriate alternatives omitted? Are the alternatives relevant to the perspective and clinical nature of the study? Is there evidence that the alternatives' effectiveness has been established?
Costs and consequences What are the costs and consequences (outcomes) included? Are the costs and outcomes relevant to the perspective chosen? Do they include negative outcomes (failures, ADRs)? How were they valued? Were costs and consequences measured in the appropriate physical units?
Discounting Was the study performed over time? Were costs and consequences that occur in the future discounted to their present value? Was any justification given for the discount rate used?
Results Are the results accurate and practical for medical decision makers? Were the appropriate statistical analyses performed? Was an incremental analysis performed?
Sensitivity analysis Are the cost ranges for significant variables tested for sensitivity? Are the appropriate and relevant variables varied? Do the findings follow the anticipated trend?
Conclusions Are the conclusions of the study justified? Is it possible to extrapolate the conclusions to daily clinical practice?
Sponsorship Was there any bias due to the sponsorship of the study?

ADRs, adverse drug reactions
Source: Pharmacotherapy

2.7.9 *Modeling*

Models are the representation of real-life situations in mathematical forms that enables predictions to be made into the future outcomes of the real-life processes, based on the parameters that define the processes. The functional relationship between the variables that define the real-life processes such as diseases, provide the basis for synthesizing and analyzing data to make predictions into possible outcomes of diseases or interventions designed to prevent the progression. These features have made modeling to become an important technique in economic evaluation, used to synthesize data from different sources (primary and secondary) on the cost and effects of interventions. Modeling is particularly important in pharmacoeconomic evaluation due to the challenges of inadequate data from clinical trials. Comprehensive and adequate information on the long-term health and economic consequences of new technologies/interventions are seldom available from clinical trials necessary for relevant decision making in healthcare systems (Schulpher *et al*., 2006; Lang *et al*., 2003). As a result, modeling has become an important component of economic evaluation for assessing the economic effects of new technologies. As an analytical tool, used to understand world systems, models can be used to estimate outcomes from a given a set of inputs, as well as determine the effects of changes made to the system being modeled (Siebert and Sroczynski 2005). It uses a standard methodology to compare the cost-effectiveness of different interventions which has become very useful to generalize results from country-specific studies, to be able to predict cost-effectiveness in other economic and epidemiological settings, as well as in operational rather than trial situations. In addition, cost-effectiveness could be predicted over time eg as resistant to antimalarial drugs or insecticide increases (Goodman *et al*., 2000). Models have become very useful in economic evaluation; performing important roles

particularly when empirical evidence is limited and uncertainty is high and policy decisions are needed.

Key advantages of modeling include synthesizing data from different sources to inform analysis, making for generalizability of results. However, the process of reducing a set of components of real world system into a model requires significant assumptions, which is subject to uncertainty. In view of the need to ensure accuracy and reliability of model results, it is important that models are as realistic as possible and results made comprehensible to policy makers for whom they are intended (Goodman et al., 2000). It is crucial that models are valid to in a way that truly reflects the system it represents (iQWIG working papers Modeling 2009). Generally, pharmacoeconomic models are often defined to include decision analysis, using Markov models, multivariate regression analysis, and basic spread sheet analyses. Types of models include;

1. Decision tree
2. Markov models
3. Probability sensitivity analysis (PSA) (Monte Carlo simulations)

The modeling process can be based on either modification and adaptation of existing models or decision to develop a distinct model to answer a specific question (Sanchez and Lee 2000).

2.8 Applications of pharmacoeconomics principles and methods

There are two broad applications of pharmacoeconomics occur in clinical practice and healthcare decision making.

2.8.1 *Pharmacy practice*

Applied pharmacoeconomics can be defined as "the application of pharmacoeconomic principles, methods and theories in practice to quantify the *value* of pharmacy products and pharmaceutical care services used in real-world environments" (Chez 2005). These principles and methods can be applied in daily practice by healthcare practitioners, irrespective of the practice setting. In today's practice, due to resource constraints, there is increasing demand on health practitioners to justify the value of the products and services they provide. This has made applied pharmacoeconomics to become very useful in providing the means or tools for this valuation.

Pharmacoeconomics is primarily applied in practice to aid clinical and policy decision making. With appropriate application, decision makers are able to make better and more informed decisions regarding the provision of their products and services. In pharmacotherapy decisions, three basic types of outcome areas are described in PE information; namely economic, clinical, and humanistic outcomes (ECHO). This is unlike in the past where most of drug therapy decisions were based only on the clinical outcomes, such as safety and efficacy of treatment options. However, with the introduction of PE, it has become popular in the past 30 years, to also include an assessment of the economic outcomes associated with a treatment alternative. Currently, there is the trend to incorporate patient preferences or decision-making

component based on the assessment of the humanistic outcomes associated with a treatment option. This ECHO model for medical decision making has therefore become prominent in the current healthcare settings (Kozma *et al.*, 1993). Drug selection decisions based only on acquisition costs is no longer appropriate in today's healthcare environment. Consequently, three critical components are currently being incorporated into clinical decisions through appropriate application of pharmacoeconomic principles and methods.

2.8.2 *Healthcare decision making*

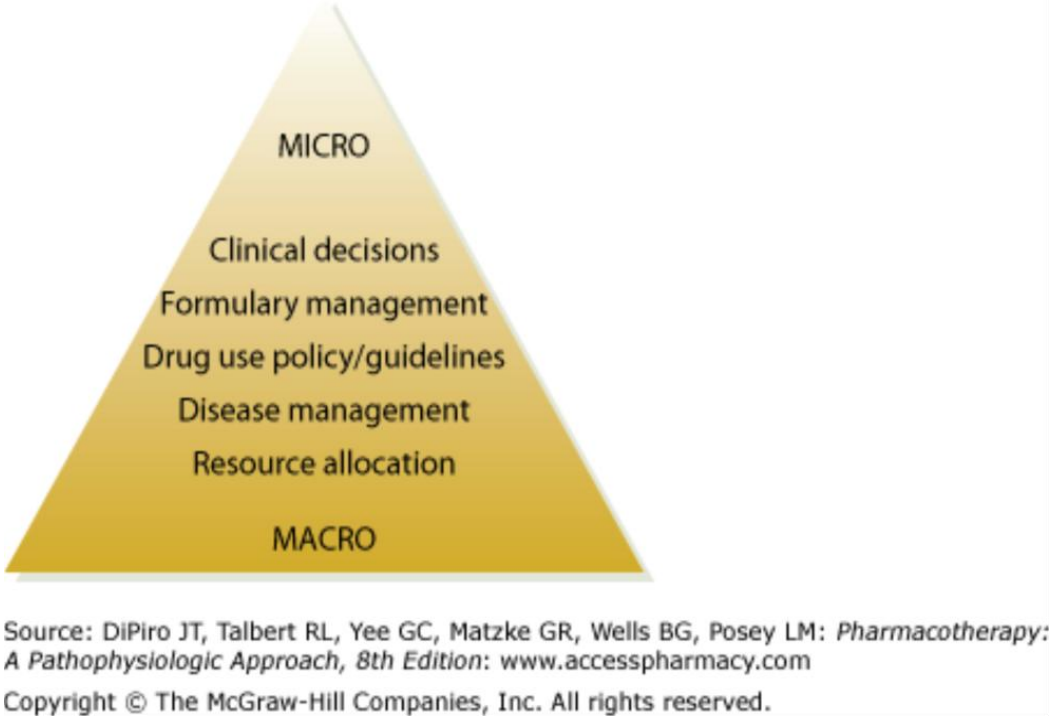
Uses of PE/HE information depend on the context of health care decision making and the uses of the studies. There are three contexts/levels of healthcare system under which PE information are used for decision making. This ranges from the primary (patient) level, secondary (hospital) and the central (entire health system) levels.

a. *Central/health system level decision;* decisions are made about policies and programmes for the populations of particular countries or regions. In some jurisdictions these include centralized procedures for the pricing and reimbursement of pharmaceuticals (eg, Australia, Ontario). In a wider range of jurisdictions there are national programmes for prevention of disease, including screening and immunization

b. *Local level:* many decisions are made at this level, such as in health plan, hospital or practice levels. These may include the adoption of treatment guidelines or the inclusion of drugs on the local or regional formulary of that organization. In some countries, such as the USA, the majority of resource allocation decisions in healthcare system are made at the local level.

c. *Patient/micro level;* health care resource allocation decisions are made in all health care systems at the *patient level*. However, in general the main application and relevance of PE/HE studies is at the central and local levels, although these decisions undoubtedly condition the treatment decisions taken by doctors on behalf of their patients. For example, if a given drug is not on the local formulary, or is at the third tier attracting a high patient co -pay, physicians are less likely to recommend it for their patients if they are aware of the situation.

Figure 2.2 shows various levels of decision making that can be supported using pharmacoeconomics. These include patient level treatment, effective formulary management, drug use policy/guidelines and resource allocation (Sanchez and Lee 1994). The application of PE in decision making is basically divided into, drug therapy and clinical pharmacy service evaluations, to enhance discussion.



Source: DiPiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM: *Pharmacotherapy: A Pathophysiologic Approach, 8th Edition*: www.accesspharmacy.com

Figure 2.2:
Levels of Pharmacoeconomic decision making

2.8.3 *Drug therapy evaluation*

At this level PE principles and methods are applied to support clinicians and practitioners in making more informed and comprehensive drug therapy decisions. For instance, to provide cost-effectiveness information on the decision to either include or remove a drug to or from a hospital formulary. This appears to have become a standard practice in formulary actions in many Drug and Therapeutic Committees. Hence, PE is used by organizations to select the most cost-effective drugs for their formularies. It is however important that appropriate policy guidelines based on sound pharmacoeconomic data is developed and implemented to effectively and positively influence prescribing patterns. Sound guidelines/policies ensure the use of most appropriate and cost-effective drugs in the healthcare system.

Very importantly, pharmacoeconomics at patient's level treatment is useful in selecting the most efficient drug between two or more drugs, by assessing the effect of a drug on a patient's HRQOL. This is considered as one of the most important uses of PE, even though the applications can also be one of the most difficult (Sanchez 1995).

2.8.4 *Clinical Pharmacy Service Evaluation*

Recently, PE principles and methods have become particularly useful in justifying the value of pharmacy services, as in various healthcare services. The ability to provide the necessary information on optimal use of allocated resources by the system administrators makes it useful in choosing between specific services competing for hospital or MCO resources. “Pharmacoeconomics can be useful in determining the value of an existing service, estimating the potential worth of implementing a new service, or capturing the value of a “cognitive” clinical intervention. Practitioners and administrators can then use these data to make more informed resource-allocation decisions” (Sanchez 1998). An example could be a decision to implement a pharmacy-based therapeutic drug monitoring program. An option would be expected to make the service improve the quality of patient care as well as save money for the healthcare system. Expected benefits can include reduced total drug costs and reduced incidence of ADRs.

Cost reduction may come mainly from salary and benefits for a pharmacy personnel and additional diagnostic/laboratory tests to monitor patients.

As an important decision making tool, there is need to ensure that the good research practices of pharmacoeconomics/health economics studies pay attention to the needs of health care decision-makers and to develop a ‘toolbox’ for the health care decision-maker wishing to interpret and use PE/HE studies (ISPOR).

2.8.5 *Strategies for Incorporating Pharmacoeconomics into Pharmacy practice/ pharmacotherapy*

There are various strategies for incorporating PE principles and methods into pharmacy practice. These include the use the results or literature of published pharmacoeconomic studies, developing economic models, and conducting pharmacoeconomic research (Sanchez 1994). Advantages and disadvantages of these strategies are summarized in Table 2.3 below

Table 2.3: Advantages and Disadvantages of Pharmacoeconomic Application Strategies

Strategy	Advantage	Disadvantage
• Use published literature	• Quick • Inexpensive • Subject to peer review • Results can be from RCT • Variety of results can be examined	• Results from RCT • Difficult to generalize results • May not be comparative • Misuse of pharmacoeconomic terms • Variations in rigor/quality
• Build an economic model	• Quick • Relatively inexpensive • Yields organization-specific results • Bridges efficacy and effectiveness • Data collection is unobtrusive	• Results dependent on assumptions • Potential for researcher bias • Controversial • Reluctance of decision makers to accept results
• Conduct a pharmacoeconomic study	• Flexible • Usually comparative • Yields organization-specific data • Reflects "usual care" or effectiveness • Data from multiple sources can be used	• Expensive • Time consuming • Difficult to control and randomize • Potential for patient selection bias • Potential for small sample size

RCT = Randomized Controlled Trial.
Source: Pharmacotherapy

2.8.6 *The relevance of pharmacoeconomic research in developing countries*

Given the features of PE concept and principles, and the extreme scarcity of resources in developing countries, opportunities exist in these settings for improving the efficiency of resource allocations in the provision and utilization of products and services. The following are important roles which PE can play in several areas of the health care system in developing countries;

- Government: as payer, PE can be used as a tool to inform decision on efficiency in pharmaceutical financing/reimbursement, to contain health care budget
- Government/NAFDAC: as a regulator to ensure the approval and registration of economic efficient products and protect the people and the economy from inefficient products.
- Pharmaceutical companies: Provide information early in drug development to identify economic efficient products, to improve regulatory approval and enhance market access/position
- Insurance Companies/NHIS: guides the HMOs in developing drug list to ensure efficiency and contain costs.
- Hospitals: An important tool for clinicians to make informed clinical decisions on the use of drugs and formulation of therapeutic guidelines
- Health agencies. Provides information to guide efficiency in drug procurement and management
- Patients: Pharmacoeconomics can provide information for decision on the best choice of drug to purchase
- **Pharmaceutical industries**

➢ Provides information early in product development for efficiency in resource allocation

➢ Provides foundation for communicating product values to external decision makers

➢ Basis for establishing product price at the time of registration

➢ Used to convince doctors and managers that high priced drugs could result to lower costs and/or better quality of care

- Generally has substantial commercial and market values for the launching and promotion of new products, distinguishing new products from competitors.

2.9 Review of studies on the cost-effectiveness of antimalarial drugs in Africa

A literature review on the cost-effectiveness (pharmacoeconomics) of antimalarial drugs was carried out by conducting bibliographic electronic searches on databases particularly using Pub Med and the UK's National Health Service Economic Evaluation Database (NHS EED), as well as ad-hoc searches to identify cost-effectiveness studies on antimalarial drugs. The review covered the period of between 2000 and 2014, using the keywords, uncomplicated malaria, malaria treatment, antimalarial drugs, cost, effectiveness and economic evaluation. Inclusion criteria used were; a) measurement of cost and effectiveness undertaken together in the form of a full economic evaluation, b) the use of appropriate measures of outcome such as malaria cases treated or disability adjusted life years (DALYs) averted, c) inclusion of major cost items, d) use of standard methods for cost estimation and (e) the study was reported in English. Included studies were analysed to identify the costing methods adopted as well as the cost-effectiveness analysis to make the results of the present study comparable. Review and analysis of the published studies followed the criteria for evaluating cost-effectiveness study namely; country of study, date of study/publication, cohort/target group, perspective adopted, comparators used, study design/analytical technique, outcome measures, the discount rate used, sensitivity analysis and results.

- **Studies analysed**

  Over twenty studies were identified by the initial search out of which nine met the inclusion criteria and were selected for the review. Many studies were excluded because

only costs were measured and some others were published before 2000. The results showed that very limited number of cost-effectiveness studies of antimalarial drugs have been conducted in Africa. Most of the studies focused on ACTs, evaluating mainly AL and other combinations apparently coinciding with the period of introduction of ACT to replace chloroquine and previous monotherapies. Key aspects of the studies included are discussed in the following sections while the summary characteristics are presented in Table 2.9.1.

- **Cohort/target group**

  Majority of the studies were carried out in children under five, in apparent reflection of the disease concentration in the population group. Only two of the studies were conducted in all patient age groups (Muheki *et al.*,2004; Chanda *et al.*,2007).

- **Comparators used**

  Comparators varied between the studies in which monotherapy SP, AQ and CQ or their combinations were used to evaluate the cost-effectiveness of the ACT. In two of the studies (Pfeil *et al*., 2014; and Mori *et al*., 2014), AL was directly compared with DHAPQ. One study (Goodman *et al*., 2000) did not indicate the comparator.

- **Perspective adopted**

  Almost all the studies analysed were conducted from the providers' perspective although two of them (Wiseman *et al*., 2006 and Pfeil *et al*., 2014) reported societal perspective. One study (Davies *et al*., 2011) was conducted from a societal perspective.

- **Outcome measures**

  Two main outcome measures were adopted by the studies; namely cost per malaria case treated/averted and cost per DALYs averted. One study (Muheki *et al*., 2004) was based on measures of cost per malaria visit avoided limiting comparability with other studies.

Costs included

All the studies measured capital and recurrent costs, included as both financial and economic costs. Although there were variations in the items included, major cost inputs included equipment, supplies, personnel, social mobilization, transport and cost of treatment. The antimalarial drugs were treated as recurrent items in all cases, constituting a significant component of the total costs. In all cases, personnel represented the largest component of the recurrent costs. All studies did not include the costs of research. Financial costs were adjusted to obtain economic costs particularly through annualization of capital items and incorporation of other donated resources but methods varied greatly among studies. A 3% discount rate was reported in most studies. One study, (Muheki *et al.,* 2004) reported a discount rate of 8% for capital items. One study (Davies *et al*., 2011) was undiscounted because of its brevity. One study, (Chanda *et al.,* 2007) did not indicate discount rate. All studies presented their findings in US Dollars.

- **Study design**

  Most of the studies were designed around RCTs to determine the clinical effectiveness of antimalarial drugs. One study, (Chanda *et al*., 2007, was based on clinical effectiveness study rather than RCT, carried out in routine practice/outpatient setting. Two studies (Pfeil *et al*., 2014; and Mori *et al*., 2014), used Markov model to evaluate

the effectiveness of the study drugs. Muheki *et al* (2004) was based on a case controlled study.

- **Sources of data**

  Depending on the study design, sources of cost data were mixed and varied between the studies. Sources included primary and secondary sources of trial and non-trial/routine practice settings such as, RCTs, financial records (budget and expenditure), published and unpublished literature, price catalogues and consultations with stakeholders, and researchers and programme managers. Effectiveness data were mainly derived from RCTs and clinical effectiveness studies carried out in the area for non-trial based studies but for trial-based studies (Chanda *et al*., 2007 and Goodman *et al*., 1999), primary data were collected. For one study (Muheki *et al*., 2004) effectiveness data were based on a case-control study.

- **Method of analysis/PE technique**

  All studies used the CEA technique to inform their evaluation given that their effectiveness outcome measures occur in natural units. In most of the studies, incremental analysis informed the cost-effectiveness measurements. Muheki *et al* (2004) used the average cost-effectiveness measure.

- **Sensitivity analysis**

  Most of the studies performed sensitivity analyses (SA) to test the impact of uncertain/variable parameter estimates by way of one-way analyses. Common parameters tested by most studies included accuracy of diagnosis, discount rates, rate of compliance, personnel costs and drug prices. Two studies (Pfeil *et al*., 2014 and Mori *et*

al., 2014) carried out probability sensitivity analysis (PSA) based on the modelling studies. Sensitivity analyses in Muheki *et al* (2004) and Davies *et al* (2011) were not quite specific.

- **CEA results**

  The cost effectiveness results range from $4.10 to $6.97 per case treated and $0.03 to $12.5 per DALY averted. The results fall within the very attractive and attractive range of cost-effective programmes based on the yardstick for measuring efficiency of interventions (Jamison *et al*., 1993) which suggest that ratios under $25 per DALY are among the best possible use of funds and those below $250 are considered efficient. Therefore, although there are variations in the study methods, the CEA results suggest that the ACTs represent efficient use of scarce resources in malaria treatment and control.

Table 2.4: Summary characteristics of reviewed CE studies of antimalarial drugs treatment

Author/ Date	Country	Comparator/s	Perspective	Study Design /PE Technique	Target group	Sensitivity analysis\ Discount rate	Outcome measure/s.
Muheki *et al*., 2004	South Africa	SP/ AL	Provider	Case controlled/ CEA	All ages	Non-specific decision tree modelling/8% rate of discount on capital costs	Sick child visit, deaths averted
Wiseman *et al*., 2006	Tanzania	AQ/ AQ+SP AL, AS+AQ,	Provider, Societal	Randomized effectiveness trial/CEA. (ICER)	Children	Univariate SA / 3%	Malaria cases averted, Cost per case averted
Chanda *et al*., 2007	Zambia	SP/ AL	Provider	Clinical effectiveness study/CEA (ICER)	All ages	Univariate SA	Costs, Case treated, Cost per malaria case treated
Davies *et al*., 2011	Papua new Guinea	CQ+SP/ AL, DHAPQ, ASSP	Provider	Clinical effectiveness study/CEA (ICER)	Children under 5	Non-specific/ Undiscounted	Cost per case, cost per life year saved
Pfeil *et al*., 2014	Africa	AL/ DHAPQ	Tanzania: Provider/ community	Markov modelling/CEA (ICER)	Children under 5	PSA (Monte Carlo simulation)/3% discount rate	DALYs averted, Deaths averted, Cost per DALY averted
Mori *et al*., 2014	Tanzania	AL/ DHAPQ	Provider	Markov modelling/CEA (ICER)	Children under 5	PSA (Monte Carlo simulation)/ 3% rate of discount	DALYs averted, cost per DALY averted.
Lubel *et al*., 2009	Myanmar, India	Quinine/ Artesunate	Provider	Randomized Clinical study/decision tree modelling	Children under 5	One-way SA and PSA	Cost per DALY averted, Cost per death averted
Lubel *et al*., 2011	SSA	Quinine/ Artesunate	Provider	Randomized Clinical study/Decision tree modelling	Children under 5	One-way SA and PSA	Cost per DALY averted, Cost per death averted
Goodman *et al*., 1999	SSA		Provider	Controlled trial	Not stated	3	DALYs averted

PSA; SSA; DALYs;

- **Conclusion**

The results and analysis of this section have shown that cost-effectiveness studies of antimalarial drugs, for the period of the review are generally very limited. Included studies were carried out in only three African countries and one from Papua New Guinea. All the studies evaluated AL followed by DHAPQ. Only one study evaluated almost all the ACT except ASMQ. Findings confirm reported frequent lack of data on the costs and effectiveness of antimalarial drugs which has been identified as a major constraint to the evaluation of antimalarial drugs (Goodman *et al*., 1999). As a result, decision tree models are commonly used to translate changes in intermediate outcomes, such as compliance and drug efficacy, to the final health outcomes. Consequently, two studies used modeling studies to evaluate the cost-effectiveness of DHAPQ and AL in the treatment of uncomplicated malaria in Africa (Pfeil *et al.,* 2014; Mori *et al.,* 2014).

The studies indicate that the ACTs are very cost-effectiveness agents for the treatment of uncomplicated malaria. AL and DHAPQ are shown to be the most cost-effective ACTs, although the most current studies suggest that DHAPQ dominates Al as the most cost-effective antimalarial drug. In severe malaria, the studies suggest that artesunate/artemether is more cost-effective compared with quinine (Lubel *et al*., 2009, 2011), demonstrated the superiority of artesunate over quinine in the treatment of severe malaria in children under five. Cost-effectiveness was found to be dependent on geographical location of health facilities. In patients who live more than 6 hours away from healthcare facilities, pre-referral treatment was more cost-effective compared with no pre-referral intervention (van Vught *et al.,* 2011). IPT in children using SP is cost-effective and safe for reducing malaria burden in children in areas of seasonal malaria transmission.

Although there were variations, standard costing methodology were applied by the studies with most studies frequently quoting three leading texts in the field (Drummond *et al.*, 1996 & 1997; Gold *et al*., 1996 and Creese and Parker, 1994). The findings for both costing methodologies and effectiveness estimates were adequate to make the results of the present study comparable.

CHAPTER THREE

STUDY DESIGN AND METHODS

3.1 Introduction

An eclectic mix of methods was deployed in both the public and private health facilities to answer the study questions and achieve the objectives. In all, a total of four studies were conducted. In the first study, prospective cross-sectional survey was carried out to assess the utilization pattern and cost of antimalarial drugs in private retail sector. In a second study, a retrospective analysis of patients records, complemented with provider questionnaire was carried out in two public health facilities, to assess the treatment practices for uncomplicated malaria and determine adherence to treatment policy in relation to the use of ACT. The third study used the cost of illness approach to estimate the treatment cost for uncomplicated malaria in a healthcare facility. The fourth and major study was conducted to evaluate the clinical effects, costs and cost-effectiveness of selected antimalarial drugs in used in Nigeria.

3.2 Study area

The studies were carried out in three cities, (Awka, Nnewi and Enugu) located in Anambra and Enugu states, all in the south east area of Nigeria. The south east zone is noted to be one of the most important sources of drugs particularly antimalarial drugs in Africa, where the popular 'Bridge-Head' market Onitsha is located, as the center of drug trade (Onwujekwe *et al.,* 2007). Malaria in the area is perennial with marked seasonal variation, and incidence rate of between 10 – 35%. Peak transmission coincides with the rainy season which occurs between June and October. The relevant studies were carried out in three selected sites of the cities.They include the Nnamdi Azikiwe Teaching Hospital (NAUTH) Nnewi, University Health Center Awka,

Anambra state capital, and the Enugu urban, Enugu state capital. The sites represent primary, secondary and tertiary health facilities involved in malaria treatment. They were selected based on the opportunities they present for collecting quality and reliable data from existing records under routine conditions (Chanda *et al*., 2007).

P. falciparum is the dominant malaria specie in the states as in most of Nigerian population and AL is first-line treatment for uncomplicated malaria since 2005. AA was shortly added as alternative first line drug to AL. However, a wide range of ACTs are currently registered in the country for the first line treatment of uncomplicated malaria, such as DHAPQ and ASMQ, and these are widely available in the two states.

3.3 Study I: To assess the costs and utilization pattern of antimalarial drugs for uncomplicated malaria in medicine retail outlets in Enugu urban

3.3.1 *Study area and population*

The study was conducted in Enugu urban city, capital of Enugu State, south-eastern Nigeria. Geographically, the state has a land area of 7,617.82 km2 located in the southern zone of Nigeria between 7°10′N and 7°45′N of the Equator and on longitude of 7.4878°E and latitude of 6.4231°N. It is bordered on the east by Ebonyi state, on the west by Anambra state, on the south by Abia and Imo states and on the north by Kogi and Benue States. *The bioclimatic zone is rainforest in nature with annual rainfall between 152 cm and 203 cm and temperature ranges from 22.2°C to 30.6°C.* The state has a population of 3,289,589 people by 2006 population (National Bureau of Statistics: www.nigerianstat.gov.ng). The people are predominantly Ibos of ethnic group, who are mainly farmers, civil servants and businessmen, with significant number of artisans. Other occupation includes fishing, wine tapping, poultry-keeping and rearing of domestic animals. Administratively the state is divided into 17 LGAs. The study site, Enugu urban (comprising Enugu East, Enugu South and Enugu North LGAs) is the largest predominantly urban area of state with a population of 722,664. However, large proportion of about 30% of Enugu East and South LGAs is rural (Wiseman *et al*., 2012).

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There are two tertiary health institutions, two secondary and about 15 primary health care facilities. Similarly there is several numbers of private health care facilities, comprising private for-profit and private not-for profit organisations. There are about 236 retail outlets; 75 pharmacies and 161 patent medicine vendors (PMVs). Retail pharmacies and PMVs are the two outlets licensed to sell and dispense drugs, including antimalarial drugs. While pharmacies are licensed to dispense both prescription and over-the-counter (OTC) drugs, PMVs, operated by people who have no formal trainings, are licensed to sell only OTC medicines, even though they are known to deal with a wide range of drugs (Okeke *et al.,* 2006). Malaria is a major disease burden in the area with children and pregnant women as the most vulnerable (EMoH, 2007). In Enugu state there is a free maternal and child health (FMCH) programme, introduced by the government in 2008 to provide free medical treatment for children below 5 years and pregnant women at the public health facilities. However, many households still bear a significant burden of malaria treatment despite the programme, in view of frequent drug stock-outs in government facilities (Onwujekwe *et al*., 2013)

Studies in the study area show that the PMVs, (also known as patent medicine dealers) are the major source of treatment for malaria (Onwujekwe *et al*., 2009; Uzochukwu *et al*., 2010). The studies also show that chloroquine, SP, and artesunate monotherapy are still provided and consumed for the treatment of malaria (Wiseman *et al*., 2012; Ezenduka *et al.,* 2013).

3.3.2 *Study design and data collection*

A prospective, descriptive, cross-sectional survey was carried out in medicine retail outlets comprising pharmacies and PMVs, between the months of May and August,

2013. A pretested questionnaire of six key questions was designed to collect data on patients' demographics, drugs demanded, drugs supplied, cost of prescription, co-prescribed medications, and mode of delivery. Data were collected on anti-malarial drugs sold to patients for self-medication (drugs specifically requested by a patient without formal prescription), recommendation by retail outlet, and by prescription from a hospital. In view of the challenges and sensitive nature of data collection from the retail outlets and nature of the study, convenient sampling approach was used to purposively select a representative number of outlets across seven sections of the Enugu urban city; it was not possible to conduct a probability sampling using a sampling frame. However the sampling was designed to include outlet type and utilization levels, such that outlets with extremely low utilization were excluded. Utilization was defined as the rate of sales of anti-malarial drugs. Outlets selling fewer than 20 antimalarial drugs per week were not considered, as they would not be adequate to capture the pattern of drug-use compared to those with higher rates. The outlets were selected to cover all parts of the city and each outlet type (pharmacy and PMV), informed by estimated number of retail outlets in a section and expected sales of anti-malarial drugs. The outlets (20) that agreed to participate and met criteria were initially selected during the selection period but four were dropped due to incomplete and inconsistent client data on age, gender, as well as antimalarial drug and concomitant medications dispensed. Accordingly, at least two outlets (one pharmacy and one PMV) were selected from each area, and a total of 16 outlets were selected.

Initial visits were carried out to the outlets to discuss the study, obtain permission and agree on date of survey. During the period, investigators observed the outlets' routine drug dispensing and documentation processes, examined prescriptions for necessary

information and updated outlet staff on collection of appropriate information from clients or potential patients. Trained research assistants were engaged to participate in data collection by assisting outlet staff in collecting relevant information. Data were collected over ten consecutive days from each outlet over the three-month period.

For the purposes of the study, the drugs dispensed were categorized into three groups: those dispensed by prescriptions from hospitals or health facilities, prescription by the outlets (when treatment is provided by outlet), and for self-treatment by patients (when a patient specifically requests and purchases a particular anti-malarial drug, which is taken to mean treatment that does not involve consulting a health care provider). If a parent requested for and purchased a particular antimalarial drug for his/her child from an outlet, this was considered self-treatment. However, the limitation of this definition of self-treatment is recognized, because some requests may have involved recommendations from friends and associates, which is comparable to consulting health centres (McCombie, 2002). It was necessary to use this definition because the demand pattern was measured by the number and type of drugs actually dispensed. It should be noted that when the same drug was available in different strengths, it was counted as one item. Similarly, if the same drug was available by different routes of administration, it was counted as one item. Combination of drugs was also treated as a single item.

The drugs were identified and categorized as ACT and monotherapy based on current malaria treatment policy. Monotherapy was further divided into artesunate monotherapy and non-artesunate monotherapy. Their use were then analysed by

gender, age categories, mode/source of treatment, and outlet type. The range, prices and cost of treatment were similarly analyzed.

3.3.3 *Data management and Statistical analysis*

The statistical software, Statistical Package for Social Science (SPSS) version 16 (SPSS Inc., Chicago, IL, USA), was used to analyze the data. Quantitative variables were described using appropriate summary statistics (mean, median, standard deviation and range); categorical variables are presented using frequency and proportions. Association between two categorical variables was examined using the Chi-square test of independence. Data was analysed at 5% significant level. Values of $p \leq 0.05$ were considered statistically significant.

3.4 Study II: To assess the prescription pattern of antimalarial drugs for the treatment of uncomplicated malaria at two public health facilities in Anambra state

3.4.1 *Study area*

The study was undertaken in Anambra state, south-east Nigeria, with a total population of 4.18 million inhabitants by 2006 Nigerian census, considered as the second most densely populated states in the country (1,500 – 2000 persons per km^2). Divided into three senatorial zones, the state has 21Local government Areas (LGAs). The people, who are predominantly ethnic Ibos, are mainly involved in farming as the main occupation, while a significant number is into trading and commerce. Malaria transmission in the state is perennial with incidence rate of between 10 – 35% and peak season coinciding with the rainy season running between March and October every year. Children and pregnant women are the most affected by malaria in the state. There are about 382 primary health centres (PHCs), managed by the LGAs, 32 secondary health facilities run by state government and two tertiary health facilities owned by the state and federal governments respectively. The state is noted as one of the most important sources of drugs supply in Africa, particularly antimalarial drugs with the presence of the popular 'Bridge-Head' market, a center of drug trade located in Onitsha, the largest commercial city in the state.

3.4.2 *Study sites*

The study was carried out in two sites of a federal institution in the state, the Nnamdi Azikiwe University (NAU). They are located in two major cities of the state, namely Awka, the state capital and Nnewi. These include the NAU Medical Center

(NAUMC) Awka and NAU Teaching Hospital (NAUTH), Nnewi. The sites represent primary/secondary and tertiary health facilities involved in malaria treatment and were selected based on the opportunities they present for collecting quality and reliable data.

The NAU Medical Center is a health facility which primarily provides outpatient services, in a university community of about 50,000 people as the catchment population. Significant number of the Awka community also accesses care at the facility. It has about 10 medical officers who provide clinical services to patients in addition to nurses, pharmacists, laboratory officers and other health workers. The center has a functional laboratory which provides microscopy and RDT services. There are 10 in-patient beds which are used to provide brief admissions for emergency cases. Over 10,000 outpatient cases are treated annually in the facility. The supply of anti-malarial drugs is carried out through a process that is based on a procurement guideline. Donors also provide support through donations of drugs such as the Affordable Medicine Facility-malaria (AMFm) drugs, though quantities of supply are relatively small. Availability of antimalarial drugs in the facility is said to be regular although, in many occasions there a limited range of the products at any one point in time, due to purchasing procedure. Payments are made by all patients including staff, students and community members who access services at the center. Payment by the students is deducted from fees paid in advance.

NAUTH is a 500-bed tertiary healthcare facility providing a variety of specialized clinical and teaching services. It is the main referral public health facility in the state run by the federal government. As at 2010 the hospital had total staff strength of about

2400 workers, spread across the various clinical and non- clinical departments; comprising over 300 doctors, 400 nurses and 62 pharmacists including intern pharmacists. There are 15 wards with estimated 80% bed occupancy. The general outpatient department (GOPD) attends to over 12,000 out-patient visits annually. Patients pay for services and their drugs at the point of delivery.

3.4.3 *Study design and data collection*

A descriptive cross-sectional study was conducted, based on retrospective cohort event monitoring of patients treated for uncomplicated malaria in the course of medical practice. Facilities were selected to ensure availability of adequate patient load and coverage, and the need to recruit large enough patients in a short period. Hospital records of patients diagnosed or treated for uncomplicated malaria within a six-month period of between January and June 2013 were collected and audited. Cases of severe/complicated malaria and pregnant women were excluded. Two pharmacy graduates were trained to extract and record the data from the patients' records into a pre- designed Excel data form. Individual patient-level records and prescription were collected for each outpatient treated at the facilities. Collected data included demographics, diagnosis, laboratory tests results, drugs prescribed, number of drugs, cost of drug prescription and co-prescribed medications, over the study period. Medication doses and route of administration were not documented. Semi-structured questionnaires of 15 questions were distributed to the prescribing physicians in selected facilities, to assess the intent of the prescribers on the treatment of uncomplicated malaria, in terms of the use of laboratory services, antimalarial drug-use and prescription pattern.

3.4.4 *Data management and analysis*

Data was double entered, cleaned and managed with Excel spread sheet. Analysis was carried out for diagnostic approaches, (use of microscopy and/or RDT), use of ACT, monotherapy, concomitant medication and cost of medication. Prescriptions were categorized into ACT and mono therapy. Analysis was carried out at whole facility level (facilities are located in the same state) and then separately for individual facility, to assess the differences in treatment pattern between the facilities in conforming to malaria treatment guidelines. Conformity to treatment guidelines was on the basis of laboratory diagnosis, use of ACTs and rational use of drugs.

Data was collected using Excel spread sheet designed to collect relevant information. Statistical analysis was performed using SPSS version 16 (SPSS Inc., Chicago, IL, USA) and GraphPad Prism 5 for Windows, (GraphPad Software, San Diego California USA). Association between variables of interest and the prescription of antimalarial drugs were estimated using logistic regression. Chi squared test of independence was used to determine association between categorical variables, independent student's t-test for continuous variables, and univariate analysis to predict the prescription of ACT and concomitant medications. Results were considered statistically significant at $p \leq 0.05$.

3.5 Study III. To estimate the treatment costs for uncomplicated malaria at a public/secondary health care facility.

3.5.1 *Study site*

The study was carried out at the Nnamdi Azikiwe University medical center (NAUMC), Awka which provides primary and limited secondary health care services to the university community of over 50,000 people, made up of staff and students. The facility has a capacity of 10 – 15 beds, with 15 doctors, 3 pharmacists, 32 nurses and several other health workers. The health workers are appropriately trained to provide relevant services. There are both microscopy and RDT options for laboratory diagnosis and confirmation of malaria parasite. The center attends to adequate number of patient flow, with over 10,000 outpatient visits per annum. The health workers are adequately informed on malaria treatment guidelines and logistics management. Pre-package ACTs are available in the form of AL, DHAPQ, ASSP, ASMQ, ASAQ, for the treatment of uncomplicated malaria. Other drugs available in the facility include SP tablets, Quinine and artemether injections for severe malaria and IPTp in women and children. HRP-II RDTs are also available. Patient flow and treatment practices are in line with treatment guidelines as described in previous study above.

3.5.2 *Framework and study design*

Cross-sectional cost of illness approach, based on a standard costing procedure was used in this study to estimate the facility cost of malaria treatment. The costs are broadly divided into financial and economic costs. Financial costs represent direct expenditures on resource procurement, while economic costs are the financial costs in addition to the opportunity costs of resource utilization such as the costs of donated

items, volunteer services and the adjustment of financial costs through annualization of capital items, as well as quantification and valuation of all resource inputs (including donated items) utilized in the intervention. The costs were then categorized into recurrent and capital expenditures. Capital costs include those items whose useful life is considered to be longer than one year. Recurrent costs are those costs that lasted for less than one year or if payments for them were made more than once a year, such as the cost of training. The framework is illustrated graphically in Figure 3.1. Since the medical center operates mainly as a primary healthcare facility, (services are basically outpatient) costing approach involved a full costing activity for estimating outpatient costs. The approach uses a detailed cost and healthcare utilization data, so the costs of all the activities in the facility were estimated, divided into capital and recurrent items.

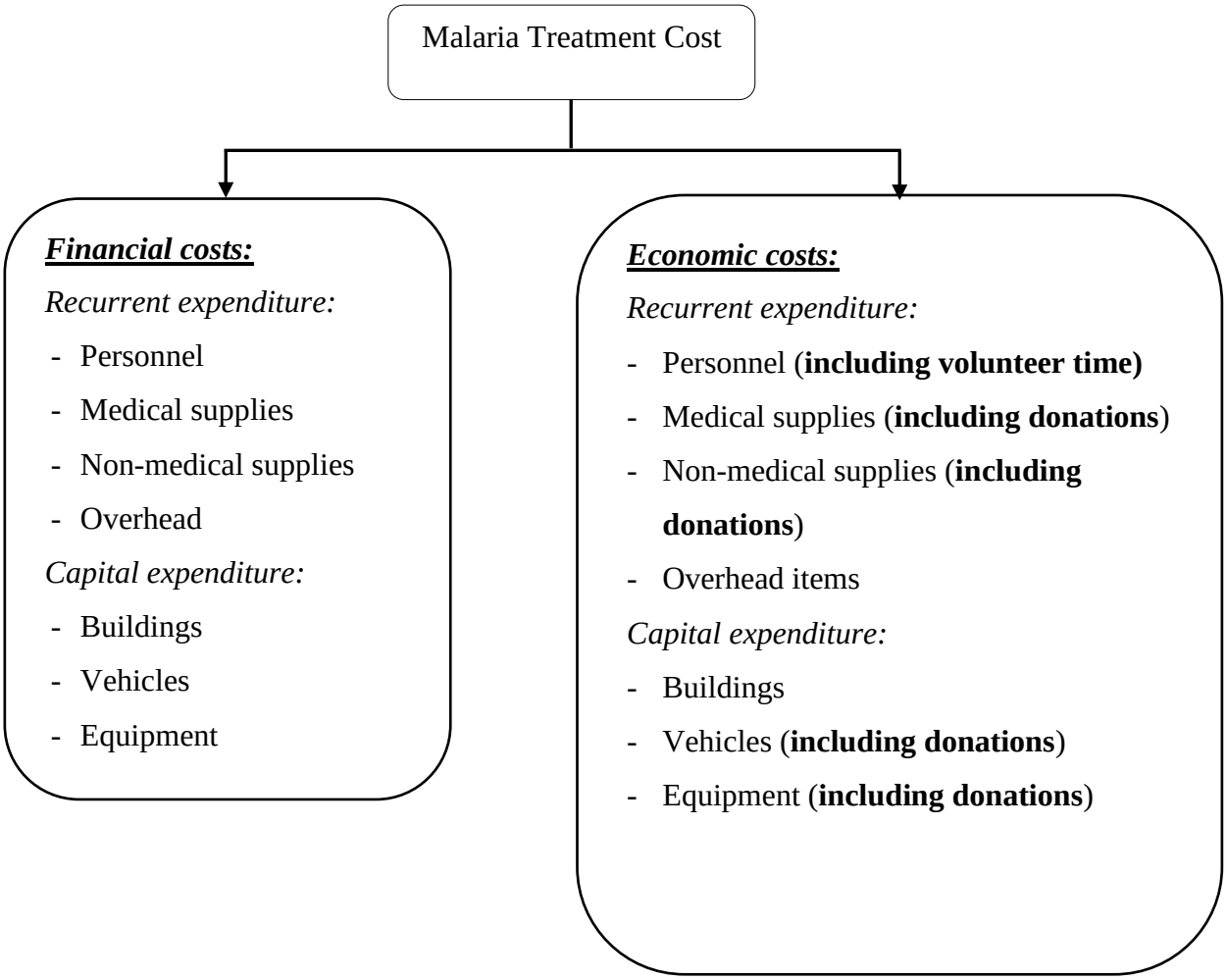

Figure 3.1: Components of health facility cost of malaria treatment

3.5.3 *Cost data identification and collection*

Cost resources were collected and analyzed from the perspective of the health care provider, which includes the cost of personnel and overhead, building, equipment, transport, etc. Hence, only the direct medical and non-medical costs of malaria treatment were collected, and do not include indirect cost of loss of productivity. The ingredient approach was used to identify and collect all resources used up in the delivery of malaria treatment, collecting actual line item expenditure and activity data wherever possible. Top-down calculations were performed to allocate capital resources where detailed information was not possible or available. The baseline data on hospital resource use for malaria treatment were collected from records of patients treated for uncomplicated malaria between the months of January and June 2013, from the medical records and pharmacy departments. A pharmacy research assistance was engaged and trained to collect and document all patient related encounters at the facility's dispensing units using a prepared notebook for collecting and documenting relevant variables per patient such as date, age, sex, diagnosis for malaria and co-morbidity and the costs of all medications and supplies dispensed. The records were comprehensively reviewed to obtain information on the level of resource use per patient. Resource use data included the direct medical costs of medication (including the type, frequency, amount, duration and route of administration of medications), supplies and laboratory tests. Others included the costs of staff/personnel, building, equipment, utilities and other sundry expenses. Utilities and overheads include administrative costs, office maintenance, water and electricity bills, telephone, fax and postage. Supplies comprised office stationery and other consumables. Vehicle maintenance and transport were included in the fuel/maintenance costs. A detailed list of items collected and measured, and their source is shown in Table 3.1. The

expenditure data were collected from the bursary/accounts and stores/maintenance departments responsible for salary payments and expenditures. Budget data were also used to estimate expenditure in some instances. In-depth interviews were held with the chief medical director, chief-nursing officer, pharmacist and other heads of departments in the facility to identify the type and number of staff and equipment that are used in malaria treatment. Non-hospital costs, such as patients' costs/contributions, in terms of payment for drugs, travel and time costs were not collected.

Collected data were then double entered into a Microsoft Excel spread sheet and checked for consistency. Discrepancies were identified and resolved while referencing the original data forms. The costs data were analyzed at 2013 price level.

Table 3.1: Cost items and sources of collection

	Item	**Source**
A	***Capital Items***	
	Building/space	Maintenance
	Vehicles	Stores
	Furniture/Equipment	Stores
	Medical devices (e.g. stethoscopes, surgical instruments)	Departments
	Non-medical devices (e.g. furniture, televisions, air conditioners etc.)	Departments/ stores
B	***Recurrent costs***	
	Drugs procurement costs	Pharmacy
	Personnel	Administration
	Training/capacity building	Administration
	Utilities/ overhead	Administration
	Fuel/maintenance	Maintenance
	Supplies/office costs	Stores

3.5.4 *Cost calculations*

All costs were measured at their current market values in local Nigerian currency (Naira) and converted to the US dollar at the 2013 exchange rate (157 Naira = 1 US$). Capital costs were measured and valued by first annuitizing the initial market price of the capital items over their expected useful life and then adding them to the annual recurrent estimates. This reflects the value-in-use of the capital assets. Vehicles and equipment costs were annualized over a ten year period and discounted at 3% (Wiseman *et al.,* 2003). The effect of variation of discount rate was examined in the sensitivity analysis. Building cost was estimated from office floor spaces, measured and valued on the basis of a standard cost per square meter land valuation measurement, and annualized over a useful 30 year period at 3% discount rate (Chanda *et al*., 2007). Allocation of shared costs in joint offices was based on the proportion of malaria treatment.

Personnel costs were valued according to existing annual staff gross salary scales, including benefits and allowances. Time spent by each staff category in malaria treatment or suspected malaria case is multiplied by the pro rata earnings for each category. Given the variation of staff time per patient which presents with challenges when estimated on patient-specific basis, the time cost item was included in the outpatient visit cost. The direct medical and non-medical costs of supplies and consumables were obtained by summing their used quantities within the period, multiplied by their individual or replacement costs. Actual purchase prices for resources were used for estimating the unit costs. For items whose prices were not available, replacement costs were used to obtain their values. The costs of shared supplies and utilities were valued using a step-down approach and allocated on the

basis of facility utilization of malaria patients (Chanda *et al.*, 2007). However, for resources unique to malaria treatment such as laboratory diagnosis, full allocations were made based on the actual malaria service utilization. Medication cost per patient was estimated by multiplying the quantities of drugs prescribed/dispensed by the prices obtained from the pharmacy department.

Generally and for simplicity, while drugs and laboratory examination were treated as recurrent, other costs were regarded as overheads, such that the costs related to malaria treatment were obtained by direct attribution based on proportion of treated malaria cases. This was done by multiplying the cost of the overhead with the proportion of malaria cases to the total outpatient visits in the facility within the study period. Finally, the total recurrent and capital costs were then summed up to estimate the total annual cost of malaria treatment. Malaria treatment cost per patient was obtained by dividing the facility's total annual cost of malaria treatment by the total number of malaria cases during the period.

The study estimated both the costs of outpatient treatment for uncomplicated malaria without co-morbidity and with co-morbidities, where 'uncomplicated malaria' is defined to include all malaria cases where no hospitalization was required.

Examples of administrative costs include the cost of communication, cleaning materials, fuel, stationery and other utilities

3.5.5 *Assumptions*

The following assumptions in Table 3.2 informed the cost calculations for both the financial and economic analyses.

Table 3.2: Assumptions used in the cost calculations

Parameter	***Assumption***	***Source***
Discount rate	3%	CBN interest rate
Personnel costs	Staff Gross earnings	Finance/Audit department
Drug costs AL ASAQ DHAPQ ASMQ SP AS	Pharmacy purchase prices N430 N350 N400 N850 N80 N200	Pharmacy purchase prices
Exchange rate	N157 = USD 1	Nigerian foreign exchange rate
Malaria prevalence	0.47 (Sensitivity anal. 0.27)	Hospital records (University-wide data)

3.5.6 *Sensitivity analysis*

The study tested the robustness of the estimated costs by conducting a sensitivity analysis by varying the following parameters;

a. Discount rate (3 -5%)

b. Staff salaries; reduced by 50%

c. Malaria prevalence; 0.47 to 0.27

d. Change in drug cost

3.5.7 *Data analysis*

The data were analyzed for financial and economic costs. Unit cost per case was obtained by dividing the total cost by the total number of outpatient malaria cases during the period. Further analysis was carried out for costs without co-medication (using only antimalarial drugs) and with co-medication. Data were managed and analysed using Microsoft Excel (Microsoft, version 2007) as well as Statistical Package for Social Sciences (SPSS) version 16 and GraphPad Prism 5. The costs data were calculated and presented as means and medians. Since the distribution of the data was heavily skewed, non-parametric testing as described by Hahn and Meeker was used to compute 95% confidence intervals for medians. Wilcoxon rank and Kruskal-Wallis tests were used to assess for difference across two and three categories, respectively (Keitel *et al*., 2014).

3.6 Study IV: To evaluate the costs, effectiveness and cost-effectiveness of Artemisinin-based Combination Therapy (ACT) for the treatment of uncomplicated malaria

3.6.1 *Study site*

The study was conducted at the Nnamdi Azikiwe University Medical Center, as described in section 3.5.2

3.6.2 *Conceptual Framework*

The cost-effectiveness study was based on identification and analysis of costs and effects of all the antimalarial drugs evaluated, consistent with standard treatment for uncomplicated malaria. All the costs and effects data were measured from the provider perspective. Effectiveness was measured as number of successfully treated malaria cases and outcome expressed as cost per successfully treated case. Incremental approach, using SP as the comparator drug was used to estimate the costs and effects by comparing each alternative ACT against SP monotherapy as the previous policy drug, to measure the additional cost per malaria case successfully treated, as incremental cost-effectiveness ratio (ICER), Figure 3.6.1.

3.6.3 *Drug combinations compared*

As the latest class of antimalarial drugs, the artemisinin compounds are known to have very short half-life (less than 8 hours), rapidly reducing the parasite load, and in combination with other agents, the chances of *Plasmodium* resistance is reduced (White *et al*., 2004; Agarwal *et al*., 2013). Hence, the ACTs are highly effective with the potential for preventing drug resistance. However, cases of artemisinin resistance, especially along the Thai-Cambodian border have been reported, which is being

attributed to the likelihood of sub-therapeutic doses, and as monotherapy (Dondorp *et al.,* 2009). Generally, the safety and tolerability of the artemisinin derivatives have been documented in many studies (Nosten *et al*., 2007). Recently, a report of dose-dependent risk of neutropenia was documented with a seven-day artesunate monotherapy in adult malaria cases at doses higher than usual (6 mg/kg/day) (Bethell *et al*., 2010). Delayed haemolytic anaemia has also been reported in a recent reviews following treatment of severe malaria with artemisinin derivatives (Schramm *et al.,* 2013).

By 2005 majority of malaria endemic countries, including Nigeria, have adopted the policy (Srivastava *et al.,* 2013; Nosten *et al*., 2002). Although a wide range of ACTs is currently in use in Nigeria, the study has selected four combinations of artemisinin derivatives with different types of other antimalarial agents, for the evaluation.

1. *Artemether-lumefantrine (AL)*

AL, a highly effective and safe combination, is about the most commonly used ACT in many African countries as first-line treatment for uncomplicated malaria (Amin *et al.,* 2007; Dorsey *et al*., 2007; Makanga *et al*., 2011). It was the first drug of choice in Nigeria in 2005 before ASAQ was added as alternate first line drug. The combination is the most widely available in Nigeria with about the widest range of brands, especially in the south east (Ezenduka *et al*., 2013). Safety and efficacy of AL in Nigeria have been demonstrated in many studies in Nigeria and other African countries (Meremikwu et al., 2006, 2013; Falade *et* al., 2008; Bello *et al.,* 2010; Gbotosho *et al.,* 2011; Ojurongbe *et al.,* 2013). Many observational studies have reported high cure rates for AL (Meremikwu *et al*., 2006). The fact that the drug

components are co-formulated in the same tablet gives it an advantage, since it is less likely to be misused as monotherapy. However, the drug is expensive even when discounted in addition to the relatively complex multi-dose schedule of six dose regimen, compared to other ACTs (Meremikwu *et al.*, 2006, 2013). This raises a concern for its effects under unsupervised settings, considering the degree of compliance to the recommended dose schedules. Poor adherence is expected to reduce the effectiveness of the drug, exposing the parasite to sub-therapeutic drug levels that would then favour the development of resistance to the drug (White and Oliaro 1996)

2. Artesunate-Amodiaquine (ASAQ)

ASAQ is the alternative ACT to AL for the first line treatment of malaria in Nigeria. It is one of the most widely used ACTs in endemic countries and has been the drug of first choice for uncomplicated malaria attack in Liberia in 2003 (Schramm *et al.*, 2013) and Ghana since 2004 (Doodoo *et al.*, 2009). The safety and efficacy of the combination has been documented (Brasseur *et al.*, 2007; Sirima *et al.*, 2009). However, Amodiaquine (AQ) administered alone at high doses for treatment or prophylaxis of malaria has been noted for serious safety issues in the past, with case reports of severe adverse events (AEs) of agranulocytosis, hepatitis *(*Neftel 1986*;* Hatton *et al.*, 1986*;* Markham *et al.*, 2007*;* Schramm *et al.*, 2013) or severe neurotoxicities (involuntary movements/dystonia) *(*Akpalu *et al.*, 2011). In Nigeria ASAQ was the alternate first-line ACT adopted for uncomplicated malaria in 2005. The drug may be less expensive than other ACTs, it is mostly non co-formulated which would likely lead to being misused as monotherapy. It is believed that because of parasite resistance to amodiaquine, cure rates of the combination regimen may be lower than with artemether-lumefantrine (Meremikwu 2006).

3. *Dihydroartemisinin-piperaquine (DHAPQ),*

DHAPQ is an ACT regimen which has been studied in East Africa as an alternative to AL (Agarwal *et al.,* 2013; Anonymous 2011; Arinaitwe *et al*., 2009; Bassat *et al.,* 2009). It has a once daily dosing regimen as well as longer half-life of the partner drug which may prevent re-infection in areas of intense malaria transmission (Agarwal *et al*., 2013). These represent important advantages over the AL combination. Equivalent safety and efficacy profiles for DHAPQ and AL have been demonstrated by many studies (Bassat *et al*., 2009; Yavo *et al*., 2011; Nambozi *et al*., 2011). It was registered as one of the first-line treatment for uncomplicated malaria in Nigeria. Dihydroartemisinin is the active metabolite of all artemisinin compounds (artemisinin, artesunate, artemether, etc.) and is also available as a drug in itself. It is a semi-synthetic derivative of artemisinin and is widely used as an intermediate in the preparation of other artemisinin-derived antimalarial drugs (Woo *et al*., 1998). Piperaquine is a 4-aminoquinoline derivative known to be highly lipophilic. It interferes with physiological function of the trophozoites membranes, leading to auto phagocytosis of the parasites. Similar to the lumefantrine, its side effects include dizziness, headache, nausea, vomiting, anorexia, myalgia, cough, asthenia, arthralgia, abdominal distress, pyrexia, eosinophilia, QT prolongation.

4. *Artesunate+ sulphadoxine-pyrimethamine (AS+SP)*

Efficacy of ASSP as an ACT has been demonstrated in several studies (Srivastava *et al.*, 2013) making it the drug of first-line treatment recommended throughout India for uncomplicated falciparum malaria. In the combination AS inhibits the P. falciparum enzyme, DHFR, a folate biosynthetic pathway, rapidly clearing the parasite in the

blood, while SP, an inhibitor of the enzyme DHPS (Brown *et al.,* 1962) with a long half-life kills the remaining parasite. Hence based on the clinical and parasitological treatment outcomes, early treatment failure (ETF) may be associated with AS failure while late treatment failure (LTF) may with SP failure parasites (Srivastava et al., 2013). Thus, given the pre-existence resistance of the malaria parasite to SP it would be necessary to evaluate the effectiveness of the ASSP combination as well as the treatment failure and malaria parasite clearance.

5. *Artesunate-mefloquine(ASMQ)*

ASMQ is one of the five ACTs that were recommended by the WHO for the first-line treatment of uncomplicated malaria, having been found effective, safe and rapid (WHO, 2010). A fixed dose combination (FDC) of the drug is also recommended to be used whenever necessary to increase the compliance to treatment (Santelli et al., 2012). The combination was considered for use as a strategy in Asia to mitigate resurgence of malaria and the spread of antimalarial drug resistance even before the WHO recommendation for the use of ACT (Santanelli et al., 2012). Consequently, the combination has been used successfully in the last 20 years in reducing the transmission of multidrug resistant malaria in the low transmission areas of the Thai Burnese border, as well as reversing the trend of increasing MQ resistance (Nosten et al., 1997, 2007; Santanelli et al., 2012; van den Broek et al., 2005). Though similar in efficacy with DHAPQ, ASMQ probably causes more nausea, vomiting, dizziness, sleeplessness, and palpitations than dihydroartemisinin-piperaquine (moderate quality evidence) (Zani *et al.,* 2006)

3.6.4 *Study method and approach*

The study was based on the use of data generated from routine clinical practice, rather than randomized clinical trial approach. This is because the introduction of the ACTs as the current choice of malaria treatment is not expected to interfere with the treatment protocol (Chanda e*t al*., 2007). However, it is expected that in Nigeria, where malaria treatment is highly characterized by presumptive diagnosis (Onwujekwe *et al.,* 2009), treatment practices is expected to affect the effectiveness and cost-effectiveness of the new policy drugs, ACTs. It was therefore necessary to test the cost-effectiveness of the policy drugs from actual/routine practice setting to reflect the true context of the study. It is also assumed that given the context of the study, the underlying malaria incidence is not expected to change significantly (Chanda *et al*., 2007).

Unlike efficacy, which describes the effect of a drug in a controlled situation, the effectiveness of a drug describes the ability of the drug to achieve the desired effect when it is used in an uncontrolled or unsupervised environment (Meremikwu *et al.,* 2013), and this depends on compliance with the recommended treatment regimen (White *et al*., 1996). With poor compliance, treatment effectiveness will most likely decrease, exposing the parasite to sub-therapeutic levels which in turn favours the development of resistance to the drug (White *et al*., 1996). In clinical trials carried out under supervised setting, the efficacy of the drugs is assessed. Cure rates of drugs obtained in these clinical trials are not often the same as those obtained under routine settings, represented by outpatients' situation. Given the routine nature under which the antimalarial drugs are used to treat uncomplicated malaria in Nigeria, it is only

necessary that effectiveness and cost-effectiveness of the drugs are assessed under routine setting.

3.6.5 *Study design and population*

The study was designed to evaluate the operational cost-effectiveness of four ACT regimens commonly used in Nigeria for the treatment of uncomplicated malaria. This involved building a database to capture the costs and short term clinical effects of treating patients with new antimalarial drugs, in view of the current policy on the use of ACT as first line drugs, namely AL, DHAPQ, ASSP and ASAQ, from a routine clinical setting. The study took place between September 2013 and August 2014, in a university medical center. It was conducted in line with the WHO standard protocol for evaluating the efficacy of antimalarial drugs as well as compliance surveys (WHO 2009). The study population consisted of patients with uncomplicated *P. falciparum* malaria who attended the health facility and met inclusion criteria specified below. They were followed up for up to 28 days, consisting of a fixed schedule of check-up visits to carry out relevant clinical and laboratory examinations. Based on the results of the_assessments, the patients were classified as either having early or late therapeutic failure or an adequate response. During the follow-up period, the proportion of patients experiencing adequate clinical and parasitological response (therapeutic response was used to estimate the efficacy of the study drugs. All adult patients signed informed consent forms for participation in the study. Parents or guardians signed the informed consent forms on behalf of their children. Children over 12 years of age signed the consent form.

3.6.5.1 Inclusion criteria

- Age between 1 – 75 years
- Presence of fever/axillary temperature $\geq 37^{\circ}C$
- Mono-infection with *Plasmodium falciparum*
- Absence of general danger signs or signs of severe and complicated malaria
- Absence of febrile condition caused by diseases other than malaria
- Informed consent by patient or parent/guardian of children

3.6.5.2 Exclusion criteria

- Presence of severe malaria
- Malaria in pregnancy
- History of allergy to the drugs
- Presence of severe malnutrition

For a child who met the inclusion criteria, the parent/guardian was asked to sign the consent form to participate in the study.

3.6.6 *Sample size determination*

The study sample size derived from the WHO guidelines for assessing antimalarial drugs (WHO 2003). To determine the clinical effects of the drugs, the study analysed categorical data, comparing parasitological failure rates between the alternative ACT treatments. To obtain the appropriate sample size for the study, acceptable level of error was set at 5% with 80% power. An alpha level was set at 0.05. 50% of malaria prevalence was used (conservative OPD data) while 35% incidence reduction was

expected from the interventions. Hence using Cochran's sample size formula for a study population of greater than 10, 000 populations;

n =

$$\frac{(a+b)^2\ (p_1\ \ q_1) + (\ p_2\ q_2\ \ )}{x^2}$$

Where

n = sample size required for each group/arm

t = (a+b) = value for alpha level (Confidence interval of 95%, equivalent to coefficient of 1.96, Z) and depends on the power, 80%

p_1 = prevalent rate, 50%

q_1 = estimate of variance (1-p_1)

p_2 = incidence/prevalence reduction

q_2 = variance of reduction (1 – p_2)

x = desired level of precision (acceptable margin of error for proportion being estimated) = 50% – 35% = 0.15, representing size of difference of clinical importance

$$n = \frac{[1.96 + 0.80]^2\ [(0.50*0.50) + (0.35*0.65)]}{[0.15]^2} = 95$$

To provide for loss to follow-up where 80% response rate was assumed, the minimum sample size was adjusted up as follows

$$n_2 = \frac{\text{min sample size (95)}}{0.80}$$

= 118

This gives the number required in each of the trial's four groups. Therefore the total sample size is 5*118 or 590.

Therefore, the study used a total sample size of 590 patients (118) in each of the treatment and comparator groups) to sufficiently detect a clinically important difference of 15% between groups in the rate at 28 days, using a two-sided Z-test of the difference between proportions with 80% power and a 5% significance level. The 15% difference represents the difference between a 50% parasitological failure rate in the comparator group and a 35% rate in the ACT/treatment group.

3.6.7 *Data collection*

Data on costs and effects of the interventions were collected through the field clinical study, complemented with information obtained through reviews of published and unpublished literature (Mori *et al.,* 2014; Chanda *et al.,* 2007), such as data on compliance and comparator efficacy data obtained from Nigeria antimalarial efficacy study for SP (FMoH 2002). Given the unacceptably high level of treatment failure/resistance of malaria parasite to SP (in excess of 80%, for which it was replaced as first-line drug), the study was constrained by ethical issues to use previously reported efficacy and compliance data of SP, rather than conducting a direct study (Meremikwu *et al.,* 2006). Treatment failure of more than 80% with SP (less than 20% efficacy) in Nigeria was documented (MoH 2005; Meremikwu *et al.,* 2002; 2006). Hence, approximately 20% efficacy data was used for SP in this study. Extensive consultation with experts in both research and programme implementation was also used to reinforce data. Effectiveness estimates were based on operational effectiveness obtained through operational or routine clinical trials and adjusted by behavioral variables, such as compliance (Goodman *et al* 1999; Mori *et al.,* 2014)

Due to the high degree of uncertainty and variability around key parameters of the study, one-way and two-way sensitivity analyses were carried out to assess their impact on the CER of baseline results, using best and worst case scenarios of the input parameters (Wiseman *et al*., 2005; Chanda *et al*., 2007). All data were collected through the months of September 2013 and august 2014.

3.6.8 *Clinical procedures*

This study was a five-arm prospective evaluation of clinical and parasitological responses to directly observed treatment for uncomplicated malaria (WHO 2009). Once a clinical diagnosis of malaria was made by the study staff, samples of blood were obtained from a finger prick to prepare thick and thin smears for malaria microscopy and haemoglobin level determination. People with uncomplicated malaria who met the study inclusion criteria were enrolled, treated on site with AL, DHAPQ, ASSP and ASAQ, and monitored for 14/28_days. The inclusion criteria were age between 1 to 65 years; infection with *P. falciparum* detected by microscopy; presence of axillary temperature of ≥ 37.5 °C or oral or rectal temperature of ≥ 38 °C or history of fever during the past 24 hour; ability and willingness to comply with the study protocol for the duration of the study and to comply with the study visit schedule; and signed informed consent form by the patient or from a parent or guardian in the case of children. Patients were excluded if they had severe malaria or general danger signs in children aged under 5 years; malnutrition; had other febrile conditions due to diseases other than malaria (e.g. measles, acute lower respiratory tract infection, severe diarrhoea with dehydration) or other known underlying chronic or severe diseases; regular medication, which may interfere with antimalarial pharmacokinetics;

had history of hypersensitivity reactions or contraindications to any of the medicines being tested or used as alternative treatment.

Through simple random sampling technique, patients were randomized in blocks to receive AL, DHAPQ, ASSP or ASAQ. Treatment was started on the day of randomization (Day 0) and completed on day 2, while follow-up continued up to day 28 (Meremikwu *et al.*, 2006). Clinical examinations were carried out on day 0 to measure axillary temperature and body weights, while follow-up visits were undertaken on days 1,2, 3, 14 and 28. Each follow-up visit was used to conduct clinical examination on axillary temperature, screen thick blood film specimen for the presence of malaria parasites and density by light microscopy. Haemoglobin was estimated on day zero and repeated on days 14 and 28.

3.6.9 *Laboratory examination*

Following each visit, blood samples were collected from each patient. Thick and thin blood smears were prepared and stained in 3% Giemsa solution for 30 minutes. In line with recommended standard, the thick smear was used to quantify the *P. falciparum* asexual parasites, read to 100 fields per µL and gametocytes (number per 1000 white cell count). Calculation of parasite density was on the assumption of a normal leucocyte level of 8,000/µl. The thin film was used to speciate the parasites. (Meremikwu 2013). Heamoglobin (Hb) levels were determined on days 0, 14 and 28.

$$\text{Parasite Density (parasites } \mu L - 1) = \frac{\text{Number of parasite x WBC count (8000)}}{\text{Number of leucocytes counted x (200)}}$$

3.6.10 *Treatment and follow-up*

Drug regimen: Treatment in each study arm was carried out on days 0, 1 and 2. All the treatments were three-day oral regimens dosed by body weight or age, according to the manufacturer's instructions:

AL (Coartem®; Novartis, Basel, Switzerland) was administered according to body weight: patients weighing 5–14 kg were given one tablet, those weighing 14–24 kg received two tablets, those weighing 25–34 kg received three tablets, and those weighing more than 34 kg were given four tablets at presentation (0 hours), 8 hours later, and 24, 36, 48, and 60 hours after the first dose. Each tablet of AL contained 20 mg artemether and 120 mg lumefantrine. The initial dose was administered with fat cooky and patients were counselled to take remaining doses with fat meals

ASAQ co-formulated (*ASAQ Winthrop®, Sanofi-Aventis*/Coarsucam; Sanofi Aventis, Casablanca, Morocco) was given according to age or body weight as follows : children weighing 9 –18 kg or aged 1–5 years received 0.5 tablets, those weighing ≥18–36 kg or aged 6–13 years received one tablet, and those weighing ≥36 kg and above or aged 14 years and above received two tablets. Each tablet of ASAQ co-formulated contains 270 mg amodiaquine base and 100 mg artesunate co-formulated in a bilayer.

DHAPQ (Solartep) were administered as tablets, consisting of 40 mg dihydroartemisinin and 320 mg of piperaquine phosphate. They were administered once daily according to patient age or body weight: patients who aged 1 - 5 years received one tablet daily; those 6 – 11 years received one and half tablets daily; those

between 11 and 16 years were given two tablets daily on days 0 and 2; those over 16 years and above received 3 tablets on days 0 and 1 and two tablets on day 2. Standard DHAPQ dosage of 2.5 mg/kg and 20 mg/kg per dose of dihydro-artemisinin and piperaquine, respectively, was used, rounded up to the nearest half tablet.

ASSP was administered as AS (Sanofi-Aventis, Paris, France), 4 mg per kg daily for 3 days, plus sulphadoxine 25mg plus Pyrimethamine1.25mg per kg with the first dose of AS. As was necessary, patients were provided with antipyretics (paracetamol tablets and syrups) every 8 hours for 24 hours).

Children's weight was rounded to the nearest kg for dosing of the study drug.

Administration of the first dose during this period (day 0) was based on directly observed therapy for all the drugs. All treatments were administered with a glass of water and each was observed for 30 minutes. If a patient or child vomited or rejected the medication during this period or within the monitoring period, the same dose (full dose) was re-administered. If vomiting occurred again within 30 minutes, the patient was withdrawn from the study and rescue treatment given. Participants that did not return on schedule for follow-up were visited at home on the appropriate days.

3.6.11 *Safety assessment*

Safety of the drugs was based on the assessment of adverse events (AEs), defined as signs, symptoms or abnormal laboratory findings not present at enrolment, but occurring during follow-up, or being present at day 0 and becoming worse during follow-up despite clearance of parasitaemia. Patients were monitored for AEs which were recorded, assessed using laboratory evaluation, physical examination and by

asking the patient about the progress of presenting symptoms and new symptoms noticed during follow-up.

3.6.12 *Outcome measures*

Efficacy outcomes were assessed by clinical and parasitological outcomes using WHO definitions (WHO 2009). Patients were classified as early treatment failure (ETF) if any of the following criteria was observed: development of severe malaria by day 3, if day 2 parasitaemia was greater than day 0 parasitaemia, if there was parasites presence on day 3 with axillary temperature ≥37.5°C, or if day 3 parasitaemia was greater than 25% of day 0 parasitaemia. Patient who did not meet ETF criteria but had *P. falciparum* parasitaemia occurring between days 14 and 28 without fever were classified as late parasitological failure (LPF). Those who had fever occurring between days 14 and 28 with parasitaemia were classified as late clinical failure (LCF). If no failure was recorded by day 14 or 28, the outcome was classified as adequate clinical and parasitological response (ACPR).

All treatment failures with uncomplicated malaria were treated with alternative ACTs while treatment failures with severe malaria were treated with parenteral artemether or quinine, in line with standard procedure (FMoH 2005). Follow-up ended once a study subject met one of the four classification criteria: ETF, LPF, LCF or ACPR. Primary efficacy outcomes included day 28 ACPR, which was PCR-uncorrected for each ACT regimen. Secondary outcomes included haematologic response, rates of fever clearance and parasite clearance by day 3, rates of ETF, LPF and LCF. All efficacy outcomes were measured using proportions.

3.6.13 *Effectiveness estimates*

Effectiveness is determined by the clinical impact of the drugs which was based on the combination of efficacy and rate of compliance to treatment with each drug. Patient compliance to treatment in routine practice is considered a key factor to the effectiveness of antimalarial drugs (Chanda *et al.,* 2007; Mori *et al*., 2014; Goodman *et al.,* 2000). Hence, in this study effectiveness of each drug was estimated from the following formula;

$$E_{ff} = E_1 C + E_{nc}(1 - C)$$

Where E_{ff} is effectiveness (measured in terms of malaria cases successfully treated), E_1 is the efficacy, C is compliance rate and E_{nc} is effective cases among non-compliers, assumed to be 10 – 30% as in many cost-effectiveness studies (Mori *et al*., 2014; Coleman *et al*., 2004; Goodman *et al.,* 2000; Arroe *et al.,* 2004).

Indicators of efficacy in the field (as described earlier) were based on ACPR which was determined by the ability of the drugs to clear the malaria parasite and improve clinical symptoms, preventing progression to severe malaria.

The effectiveness measures define the clinical impact of the drugs (ACTs) being evaluated, measured in terms of malaria cases successfully treated. Successful treatment was obtained as patients who showed negative parasitaemia after day 28 of treatment with the antimalarial drug. Day 28 of treatment was recommended by the WHO and accordingly used in most efficacy studies. In efficacy studies of malaria treatment, days 28 and 43 are considered important end points of parasite clearance because they are believed to produce more realistic estimates of disease free periods

after treatment. Similarly, the use of polymerase chain reaction (PCR) correction is considered to give a true estimate of efficacy of treatment, because it is able to adequately separate re-infection from recrudescence (Whitty and Staedke, 2005). However, it has been argued that PCR corrected results are not helpful as aids to decisions at points of treatment, unlike the PCR uncorrected results which provide the basis for clinical decisions on treatment success.

This study used a 28-day PCR non-corrected cure rates to evaluate the relative effectiveness of the ACTs, because in the form of simple microscopy of blood smears, uncorrected results represents important clinical tool for declaring cure, clinical resistance and/or switch (Whitty and Steadke, 2005). In actual sense, uncorrected parasitaemia assesses the efficacy of treatment against pre-treatment parasitaemia and post-treatment prophylaxis. Moreover, parasitaemia constitutes on-going risk of clinical disease irrespective of whether it is due to re-infection or recrudescence. Hence, it would be necessary to compare the ACTs using the uncorrected parasitaemia at days 28 to measure the probability of declaring clinical cure or otherwise and 'any ACT that performs better in this regard may claim clinically important superiority'(Bello *et al.,* 2010)

Efficacy data of the evaluated ACTs were collected from the field survey. However, due to ethical issues regarding the use of previous policy drug based on treatment failures, efficacy data of comparator SP was based on data at policy replacement. This was approximated to 20% based on more than 80% treatment failure rates reported from previous studies in Nigeria (MoH 2005; Meremikwu *et al.,* 2002 and 2006; Ezedinachi *et al.*,2007), for both chloroquine and SP.

There is limited evidence on the rate of compliance to the ACTs but available information indicates varied rate of compliance, ranging from 38 – 90% (Chanda *et al.,* 2007; Bauxvoort *et al*., 2014; Banek *et al*., 2014; Mori *et al.,* 2014). Compliance studies of AL show a range of 38 - 75% (Chanda *et al.,* 2007; Buxvoort *et al*., 2014); ASAQ indicates a range of 65 – 90% (Beer *et al*., 2009; Ratsimbasoa *et al*., 2012). Information on the compliance rate for DHAPQ and ASMQ are limited. Since they have once daily dosage regimen, compliance rates close to those of ASAQ, 60 – 90% is assumed in the base case (Mori *et* al., 2014).

3.6.14 *Cost measurement*

The details of cost data collection and measurement are presented in section 3.5.4 above. Costing was done from a provider's perspective which involved the collection of only the costs borne by the health facility in the treatment of uncomplicated malaria. Patients related costs (costs and time borne by patients to access malaria treatment) were not collected. All the costs of capital and recurrent items such as personnel, drugs, laboratory examination (recurrent items), building spaces, vehicles and other hospital equipments (capital items) were identified, collected and measured, using standard procedures (Drummond 1997). Capital costs were measured by first annualizing the market price of the capital items over their expected useful life, discounting at 3% and then adding them to the annual recurrent estimates.

Apart from personnel, the costs of recurrent items were calculated based on the actual use of resources for malaria treatment. Personnel and other cost items were treated as overheads, such that the costs related to malaria treatment were obtained by direct attribution based on proportion of treated malaria cases. This was done by multiplying the cost of the overhead with the proportion of malaria cases to the total outpatient

visits during the study period. Personnel costs were valued according to existing annual staff gross salary scales, including benefits and allowances. Time spent by each staff category in malaria treatment or suspected malaria case is multiplied by the pro rata earnings for each category. The total recurrent and capital costs were then added up to obtain the total annual cost of malaria treatment. To obtain the average treatment cost per patient for uncomplicated malaria, the annual cost of treatment was divided by the total number of malaria cases during the period. The costs represent expenditures incurred over a one year period, for the treatment of uncomplicated malaria, to determine additional cost of treatment using alternative ACTs compared to SP. The cost of individual drug was based on the mean treatment costs with each regimen. In line with the study focus, to reflect routine practice setting, price of individual drug was based on the median price of available brands obtained in a survey of antimalarial drugs prices in a previous study in Chapter one. All costs were collected in local currency (Naira) and converted to the US Dollar at the 2013 exchange rate of 1USDollar to N157.00

3.6.15 *Cost Effectiveness evaluation framework*

Criteria for evaluating the cost-effectiveness ratios (CERs), to determine the cost-effectiveness of alternative use of resources often depends on the context of decision making. The most cost-effective alternative achieves the greatest outcome/benefit at a given cost. This could be determined either by Average Cost Effectiveness Ratio (ACER) or Incremental Cost-Effectiveness Ratio (ICER). ACERs measures the total costs of treatment divided by the total number of cases treated, to obtain cost per case treated. This is defined by the following formula;

$$ACER(A) = \frac{\text{Estimated Cost of treatment (A)}}{\text{Effectiveness (Total number of cases treated)(A)}}$$

Where 'A' stands for alternative ACT (AL, DHAPQ, ASSP, ASAQ)

The use of average measure is relevant when there is no existing practice and comparison between alternatives will be based on the ACER (Ezenduka *et al*., 2012). Hence the alternative which generates the greatest benefits at a given cost would be the chosen as the most cost-effective option.

However when policy seeks to replace an existing option/drug, as in malaria treatment, where ACT replaced SP, or monotherapy AQ, an incremental measure is used to determine additional cost required to achieve superior benefits with more effective strategy compared to baseline (Chanda *et al*., 2009). ICER seeks to identify the alternative that would replace an existing practice in the form of mutually exclusive option (Ezenduka *et al.,* 2012). This is defined as additional costs divided by additional benefits. It measures the differences in treatment costs between each alternative antimalarial drug and the existing drug divided/compared with differences in their respective health effects, depicted in the formula as follows;

$$ICER = \frac{\text{Expected total treatment cost } (ACT) - \text{ Expected total treatment cost } (SP)}{\text{Expected effectiveness/malaria cases } (ACT) - \text{Expected effectiveness } (SP)} = \frac{\Delta\text{Cost}}{\Delta\text{Effectiveness}}$$

Where 'ACT' could either be AL, DHAPQ, ASSP or ASAQ

ICER is used to determine at what cost the new alternative drug is used to compensate for the inferior benefits of the existing drug/SP, which comes at extra cost, making the new drug more expensive. The next question then will be whether the extra cost will

be worth paying for or not, which is determined by the capacity and willingness to pay of the relevant organ or system. This analysis (based on ICER) addresses the question of whether the extra cost per additional benefit generated is worth paying for. This is a common question in economic evaluation, where the results are used to compare with those of similar studies in similar settings, as well as refer to the ICER thresholds that are often applied in cost-effectiveness studies (Chanda *et al.,* 2007). As a reference, the study uses common baseline conservative estimates of US$25 and US$150 per case averted, recommended by the WHO and the World Bank for developing countries (WHO 1996; WB 1993). An intervention is considered "highly attractive" if the range for the cost per case averted fell below $50, and "attractive" if it fell below $150. To give an indication of affordability, estimates were made for the total cost of implementing each intervention in a 'typical' low income country (Goodman *et al.,* 2000). In this study, the drug that yielded the lowest ICER value was considered the most cost-effective, which is to be put forward to policy for consideration. Comparison based on ACER would also mean that the method that produces the lowest ACER value would be considered the most-effective.

Using the ICER criteria, when an intervention produces more health benefits at a lower cost than the comparator, it is said to be 'strongly dominant and more cost-effective. However, if the intervention is more costly and also more effective, it is considered to be more cost-effective, this depends on the willingness to pay (wtp) threshold (Mori *et al.,* 2014). When the ICER of the intervention is higher than that of the most effective option, 'extended dominance occurs. Willingness to pay of $150 per DALY averted has been recommended as a cut-off point (Mori *et al.,* 2014)

3.6.16 *Sensitivity analysis*

Univariate and bivariate sensitivity analyses were performed by varying the values of uncertain parameters such as diagnostic accuracy, compliance rate, discount rate, drug cost and personnel cost, to determine the effect on the cost-effectiveness results. The impact on the results will determine the robustness of the study findings.

3.6.17 *Budget impact analysis (BIA)*

The budget implication of the use of ACT was estimated based on the annual costs of treating all cases of uncomplicated malaria with each ACT in place of SP over the period. This was calculated from the cost per outpatient care with each product multiplied by the annual number of uncomplicated malaria cases, assumed for each of the antimalarial drug (ACT). Costs were also calculated with the exclusion of capital costs (overheads and labour), which are those cost items that are common to all drugs and therefore not immediately affected by the choice of antimalarial drug treatment. The hospital records for total annual number of uncomplicated malaria treated during the period January to December 2013 was used for the calculation.

3.6.18 *Data presentation and analysis*

Efficacy analysis of this study was on both intention to treat (ITT) and per protocol (PP) basis. Patients were enrolled with the intention to treat (ITT) but those who completed the study without violating the protocol were considered as PP population (Falade *et al.,* 2008). As stated previously, cost-effectiveness evaluation of the drug regimens was on the basis of incremental estimates, to determine the additional costs of using each intervention for achieving superior health effect compared to the previous policy drug. Average costs of intervention were also presented for

comparative purposes. The cost-effectiveness model as previously described, reported both ACER and ICER to determine the most cost-effective antimalarial drug. ICER was used to determine the additional cost required for achieving superior health benefit/more treatment effect compared to previous policy antimalarial drug)

3.6.19 *Statistical Analysis*

Data were recorded in record forms and entered and analyzed with Excel 2007 spreadsheet as well as SPSS version 16 and GraphPad Prism 5 for further analysis. For the main outcomes, the treatment effect was measured as proportions (effect size). Means and standard deviations (±SD) were used to analyze normally distributed/ numerical data, and compared using Student's t-test. Proportions were compared using Chi-square and Fisher's exact tests. Haematological responses were assessed using mean haemoglobin levels on day-14 and day-28. Differences were considered significant at $p < 0.05$.

3.6.20 *Ethical considerations*

The study was carried out to conform to Good Clinical Practice and the Helsinki declaration. Ethical approval to conduct the study was obtained from the Nnamdi Azikiwe University Teaching Hospital (NAUTH), Ethical Review Board. Informed consent forms to participate in the study were signed by the patients before the commencement of the study. Parents or guardians signed for their children or wards. To ensure confidentiality all information on patients remained confidential and was shared only by the study team. Unique identifiers were used for computer-based data entry and blood samples. In all cases, the principal investigator ensured that screening forms, the case report forms and the completed identification code list were kept in locked files.

CHAPTER FOUR

STUDY RESULTS

4.1 Study I: Antimalarial drugs utilization pattern for uncomplicated malaria in medicine retail outlets in Enugu urban

4.1.1 *Demographic characteristics and summary findings*

A total of 1321 prescriptions were analyzed. Table 4.1 shows that there were more male cases (55.9%) than females (44.1%). Majority of the cases were adult prescriptions (85.2%), while children below the age of 5 years accounted for the least number of cases (6.4%). ACTs were received by 961 (72.7%) patients, while monotherapy was dispensed to 27.3%. AMFm drugs accounted for 23.5% (326) of antimalarial drugs, representing 33.9% of ACTs. Within monotherapy category, artemisinin monotherapy was used in 17.8% of cases while sulphadoxine-pyrimethamine (SP) accounted for the highest number of non-artemisinin monotherapy dispensed to 68.9% of the group. Self-medication was responsible for the highest number of drug treatment (46.1%), while prescription from health facilities accounted for 18.2% of sample study.

Table 4.1: Demographic characteristics and summary findings

SN	Variable	Number	Percentage (%)
1	**Gender**		
	Male	738	55.9
	Female	583	44.1
2	**Age (years)**		
	Below 5	74	6.4
	5 to 12	113	8.4
	13 and above	1134	85.2
3	**Drug category**		
	ACT	961	72.7
	Monotherapy	360	27.3
	Artemisinin monotherapy	64	17.8
	Non-artemisinin monotherapy	296	82.2
	AMFm	326	23. 5
4	**Treatment Mode**		
	Self-treatment	614	46.1
	Outlet treatment	473	35.7
	Prescriptions	234	18.2
5	**Average no of brands per outlet (stdev)**	18 (±4.47)	

ACT = Artemisinin Combination Therapy; PMV = Patent Medicine Vendor; AMFm = Affordable Medicine Facility for malaria;

4.1.2 *Range of antimalarial drugs treatment*

A wide range of antimalarial drugs were identified in a total of 13 different regimens, comprising over 75 brands of products, including tablets, suspensions and injections. Each outlet stocked an average of 18 (±4.47) brands. The number and frequency of use of the different types and combinations of antimalarial drugs regimen are shown in Figure 4.1 AL brand was the single most used regimen at 50.6% (668), followed by SP and DHAPQ at 18.8% and 12.9% respectively. Chloroquine (CHLQ), proguanil (PL) and mepacrine (MEP) were the least used agents as shown in Figure 4.1. ACTs were available in six different combinations or regimens, accounting for the widest range of antimalarial drugs dispensed. AL brands make up the highest number of brands within the entire antimalarial regimes. AMFm drugs were found in every outlet surveyed

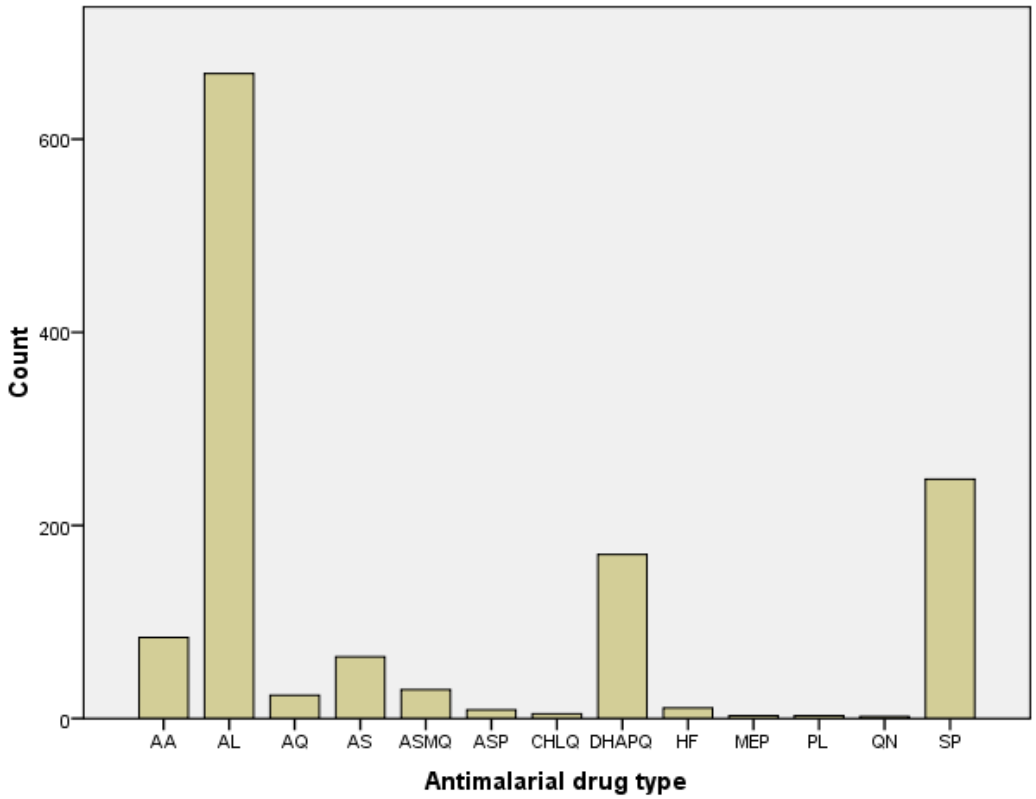

Figure 4.1: Utilization pattern of antimalarial drugs by types. AA = artesunate-amodiaquine; AL = artemether-lumefantrine; AQ = amodiaquine; AS = artesunate; ASMF = artesunate-mefloquine; ASSP = artesunate-sulphadoxine + pyrimethamine; CHLQ = chloroquine; DHAPQ = dihydroartemisin-piperaquine; HF = halofantrine; MEP = mepacrine; PL = proguanil; QN = quinine; SP = sulphadoxine + pyrimethamine.

4.1.3 *Drug utilization pattern*

Table 4.2 shows the distribution of antimalarial drugs by category, their mode of treatment and the pattern of use across age, gender, mode of treatment and outlet type. Females are more likely to use ACTs (74.3%) than males (71.3%), though this was not statistically significant ($p > 0.05$). Across the age groups, ACTs were used more in children than in adults. Use of ACTs under the treatment modes shows that highest proportion of use occurred among hospitals and outlet prescriptions at 91% and 90% respectively, while monotherapy was used most under self-medication by patients (47.4%). In retail outlets, compared to monotherapy, the use of ACTs was higher in pharmacies (74%) than in PMVS (70.7%). As shown in Table 4.1.2 the highest proportion AMFm drugs (54/102) as ACT, was used in children 5 to 12 years old. In adults over 12 years old, AMFm represents only 31% of ACTs.

Table 4.2 also shows that hospital prescription was the highest source of antimalarial drug treatment for children under 5 years old, at 40% compared to other modes, followed by outlet prescription. Only 16% of adult doses were dispensed from hospital prescriptions.

Table 4.2: Distribution of antimalarial drugs and mode of treatment across demographic groups and sources of treatment

	Gender		Age group			Mode of treatment			Outlet type	
	Male n (%)	Female n (%)	< 5 years n (%)	5-12 years n (%)	≥13 years n (%)	Self-treatment n (%)	Outlet treatment n (%)	Prescription n (%)	Pharmacy n (%)	PMV n (%)
Drug category										
ACT	527 (71.4)	434 (74.3)	74 (87.1)	102 (91.9)	785 (70.0)	318 (52.2)	425 (90.)	218 (90.8)	594 (74.1)	367 (70.7)
Monotherapy	211 (28.6)	149 (25.6)	11 (12.9)	9 (8.1)	340 (30)	291 (48.8)	47 (10.0)	22 (9.2)	208 (25.9)	152 (29.5)
Total	**738**	**583**	**85**	**111**	**1125**	**609**	**472**	**240**	**802**	**519**
Treatment mode										
Prescription	132 (17.9)	108 (18.5)	34 (40.0)	25 (22.5)	181 (16.1)	-	-	-	138 (17.2)	102 (19.6)
Recommendation	263 (35.6)	209 (35.9)	31 (36.5)	44 (39.6)	397 (35.3)	-	-	-	262 (32.7)	210 (40.5)
Self-treatment	343 (46.5)	266 (45.6)	20 (23.5)	42 (37.9)	547 (48.6)	-	-	-	402 (50.1)	207 (39.9)
Total	**738**	**583**	**85**	**111**	**1125**				**802**	**519**
AMFm	170 (32.2)	156 (36.0)	30 (40.5)	54 (53)	242 (31)	100 (32)	165 (39)	61 (28)	164 (27.6)	162 (44)

ACT = Artemisinin Combination Therapy; PMV = Patent Medicine Vendor; AMFm = Affordable Medicine facility Malaria

Analysis of the use pattern of the ACTs (Figure 4.1.2) which has five different combinations/regimens shows that the AL brand was the most used ACT given to about (961) 70% of the group. This was followed by the DHAPQ (17.7%) and the AA (8.7%) regimens respectively.

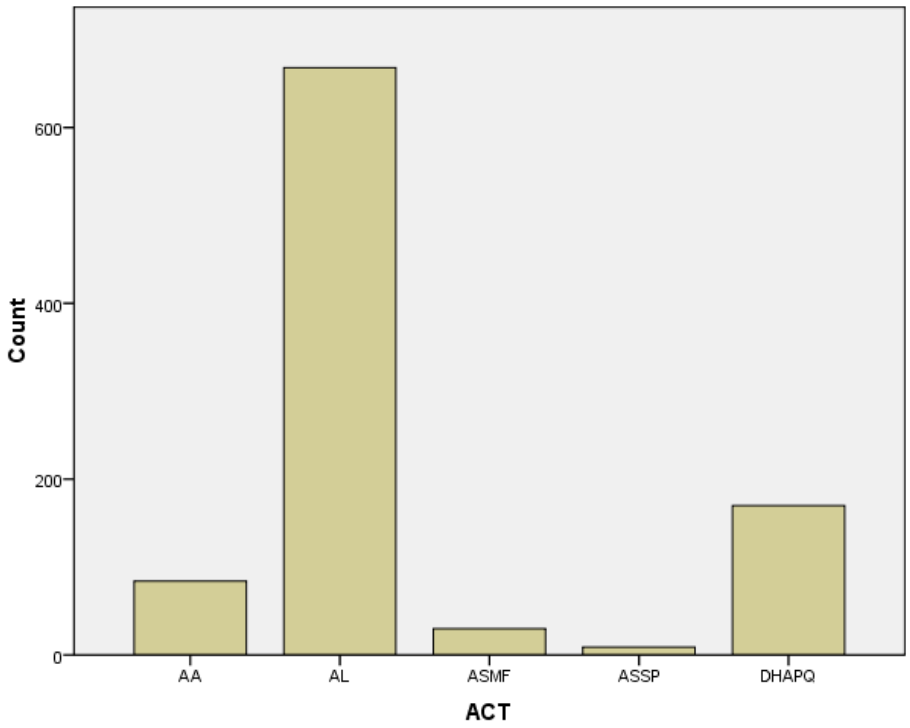

Figure 4.2: Utilization pattern of the ACTs: AA = artesunate-amodiaquine; AL = artemether-lumefantrine; ASMF = artesunate-mefloquine; ASSP = artesunate-sulphadoxine + pyrimethamine; DHAPQ = Dihydro-artemisinin-piperaquine.

The AMFm drugs were used most through outlet prescription where they accounted for about 39% (165) of ACTs dispensed under this mode. They represented 44% (162) of ACTs dispensed through PMVs while in pharmacies they constituted only 27.6%.

4.1.4 *Co-prescribed medication*

Seventy per cent (919) of dispensed drugs contained at least one concomitant medication. Approximately 52% (671/1321) of the patients received analgesics as the most commonly used concomitant medication, followed by antibiotics given to 18% (248/1321) of the patients. Vitamin preparations were contained in 16.5% (218) of co-prescribed medications. Up to 5 drugs were used per patient at a median of 1 drug per patient. Majority of hospital prescription 85% (195/240), contained concomitant medications while the least co-medications was observed with children between 5 and 12 years old, 54% (60/111).

4.1.5 *Drug prices and costs of medication*

Table 4.3 presents the median prices of the antimalarial drugs as well as the mean/median cost of treatment including co-medication. Altogether, antimalarial drugs prices ranged from $0.19 - $13.55, at a median cost of $2.26 per dose. ACTs were the most expensive with a median cost of $2.9 per dose ($0.65 - $7.42). This translates to three times the median cost of monotherapy at $0.97($0.19 - $13.55). AMFm drugs cost between $0.65 and $2.58 at a median price $1.94 per dose. The median prices and costs of treatment are reflected across the various groups and categories. While the lowest median price of $1.61 per antimalarial drug and lowest treatment cost of $2.06 was recorded for children between 5 and 12 years, the highest price and cost of treatment was estimated for the hospital prescription mode at $3.16 and $3.61 respectively.

Table 4.3: The median prices and drugs treatment costs of antimalarial drugs in the surveyed retail outlets, across categories

	Drug price (Naira)		Treatment cost (Naira)			
Variable	**Median**	**Range**	**Median**	**Range**	**Mean**	**95%CI**
Antimalarial drugs	350	30 – 2100	420	50 – 4800	496.77	478.03 – 515.51
ACT	450	100 – 1150	500	100 - 2600	575.78	557.48 - 594.08
Monotherapy	150	30 – 2100	175	50 - 4800	285.86	244.60 - 327.12
AMFm	300	100 – 450	345	100 – 1700	349.82	335.82 – 363.81
Gender						
Male	350	50/1550	420	60 - 2670	500.49	476.56 - 524.42
Female	350	30/2100	410	50 - 4800	492.07	462.23 - 521.91
Age group						
Under 5	300	100/1250	450	100 - 2250	556.24	470.49 - 641.98
5 - 12 yrs	250	70/900	320	70 - 1400	397.39	351.83- 442.95
over 12	350	30/2100	420	50 - 4800	502.08	481.59 - 522.58
Treatment Mode						
Prescription	490	70/2100	560	90 - 4800	678.25	619.73 - 736.77
Outlet treatment	350	60/1900	450	70 - 1900	508.99	485.86 - 532.14
Self-medication	300	30/1550	320	50 - 2670	415.78	389.62 - 532.14
Outlet type						
Pharmacy	350	30/2100	450	50 - 4800	548.61	521.61- 575.61
Patent Medicine Vendor	300	70/1500	380	70 - 1650	416.67	395.20 - 438.14

ACT = Artemisinin-based combination Therapy. AMFm = Affordable Medicine Facility for malaria.

The total cost of medication, including co-medications with ACTs averaged $3.64(95% CI; $3.53 - $3.75), which is about twice the average cost with monotherapy, $1.83(95%CI; $1.57 - $2.1). The average medication cost differed remarkably across age categories. While it was highest for children under five years at $3.32 (95%CI; $2.76 - $3.86) the lowest was observed for children between 5 – 12 years at $2.44 (95%CI; $2.16 - $2.72). Total medication cost also showed significant differences across treatment modes, with hospital prescription having the highest cost at $4.18(95%CI; $3.81 - $4.55). Self-treatment had the least medication cost at $2.66(95%CI; $2.50 - $2.83) per case.

4.2 Study II. Prescription pattern for uncomplicated malaria in two public health facilities in Anambra state

4.2.1 *Study characteristics and malaria diagnosis*

A total of 7949 outpatient visits were identified, of which 2171(27.3 %) cases were treated for uncomplicated malaria. Ninety-four (4%) records were excluded due to either severe malaria, 76% (71/94) or incomplete/missing information on variables of interest. Fifty-two per cent (52.6%) of those treated for malaria was sent for laboratory examination or confirmation while the rest, 47.4% was based on presumptive diagnosis. About 52% of laboratory diagnosis tested slide positive while 48% tested negative. Only the tertiary health facility reported the use of RDT tool. Figure 4.3 shows the schematic presentation of selection process. The proportion of uncomplicated malaria cases was higher at the medical center, 47% (1261/2674) compared to the teaching hospital, 17% (910/5252).

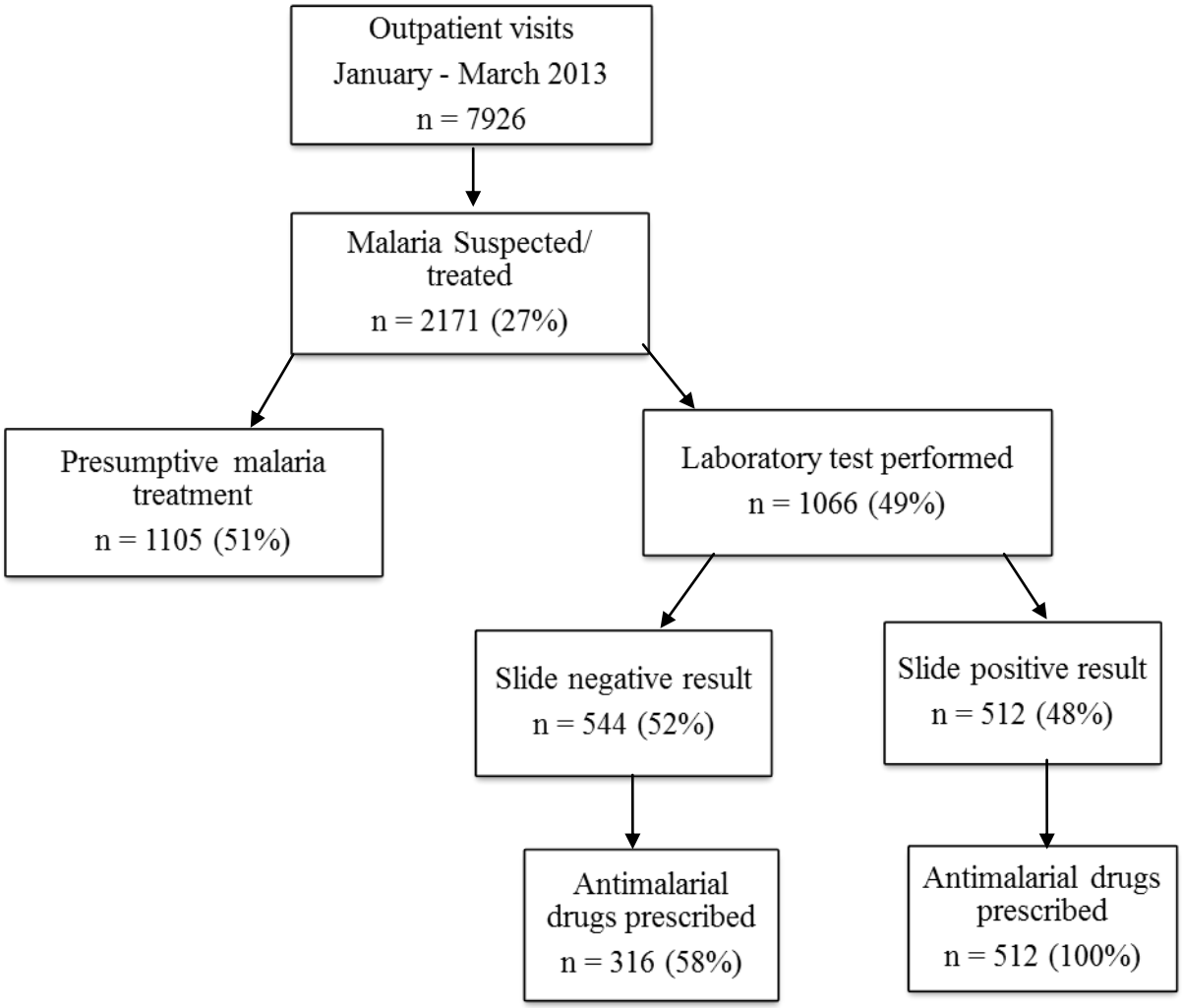

Figure 4.3: Schematic of selected malaria cases included in the study

Characteristics of cases finally analyzed (Table 4.4) shows that overall, females 56% outnumbered males (43%). Gender disparity was higher at the teaching hospital than the medical center where females, 65% outnumbered males, 35%, ($p < 0.0001$). Most cases (62%) fall between 19 years and above, at a median age of 23 years, ranging from one month to 98 years. Children below 5 years accounted for 10% of total cases. The proportion of children under five years was higher at the teaching hospital, 20% (181/910) than at the medical center, 2.6% (33/1261). The proportion of ACT prescribed at the medical center (95%) was significantly higher than at the teaching hospital, (91%, $p<0.003$).

Table 4.4: Characteristics of study population by facility

Variable	Total facility n (%)	NAUMC Awka n (%)	NAUTH Nnewi n (%)	Chi square difference	p-value
Total number of outpatient visits	7926	2674	5252	-	-
Proportion of malaria cases	2171 (27)	1261 (47)	910 (17)	729.8	0.0001***
Mode of diagnosis					
Microscopy	989 (46)	652 (52)	337 (37)	9.95	0.0016**
RDT	152 (7)	-	152 (17)	-	-
Presumptive	1030 (47)	609 (48)	421 (46)	0.875	0.3497
Gender					
Female	1207 (56)	635 (50.4)	573 (63.0)	42.09	0.0001***
Male	942 (43)	626 (49.6)	316 (34.7)	-	-
Unknown	22 (1.0)	-	21 (2.3)	-	-
Age category (years)				20.29	0.0001***
Under 5	214 (10)	33 (2.6)	181 (20)	-	-
5 – 12	52 (2)	22 (1.7)	30 (3)	-	-
13 – 18	104 (5)	78 (6.2)	36 (3)	-	-
19 and above	1354 (62)	1026 (81.4)	330 (36)	-	-
Unknown	447 (21)	102 (8.0)	343 (38)	-	-
Median age of cohort (range)	23 (0.1 – 98)	23 (1 – 82)	24 (0.1 – 98)		
Antimalarial drugs					
ACT	2027 (93)	1198 (95)	828 (91)	13.02	0.0003***
Monotherapy	144 (7)	63 (5)	81 (9)	-	-

= significant: *= very significant: ****= highly significant. NAUMC = Nnamdi Azikiwe University Medical Center; NAUTH = Nnamdi Azikiwe University Teaching Hospital; RDT = Rapid Diagnostic Test; ACT = Artemisinin Combination Therapy.

4.2.2 *Antimalarial drugs prescription pattern*

Table 4.5 shows the distribution of antimalarial drugs (including co-medication) prescribed by facility. A total of 2171 drug encounters were analysed. 93% (2027) contained an ACT, while 7% (144/2171) of the cohort was prescribed monotherapy. There were some variations in prescription pattern between the facilities. The proportion of patients who received ACT compared to monotherapy at the medical center, 95% (1198/1262) was significantly higher than the proportion prescribed at the teaching hospital at 91% (828/910), p = 0.003. Overall, the pattern of prescription shows that AL, at 51% (1024/2027) was the most prescribed ACT at both health facilities, followed by dihydro-artemisinin-piperaquine (DHAPQ), 17% (339/2027) and ASAQ 12%. While this pattern was similar at the medical center, it differed from the teaching hospital where artesunate-mefloquine, (ASMF) and artesunate-sulphadoxine+pyrimethamine (ASSP) were the second and third most prescribed ACT respectively, after AL. Highest proportion of monotherapy was prescribed as sulphadoxine+pyrimethamine (SP), 47 % (67/144), followed by artesunate monotherapy (AS), 29.2%. SP, 46.5% (67/144) and monotherapy AS, 29.2% (42/144) were the first and second most prescribed monotherapy respectively. The pattern however reversed at the teaching hospital where AS, 43% (35/81) was the most prescribed monotherapy followed by SP, 22% (18/81). More monotherapy (9%) was prescribed at the teaching hospital than the medical center (5%). Prescription pattern also varied by age and by gender. Higher proportion of SP, 49% compared to other monotherapy agents was prescribed to females than males, 44%. Similarly more females, 29% received monotherapy AS than males, 27%

Table 4.5: Distribution of antimalarial drugs and co-medication prescribed by facility

Antimalarial drugs	**Total Facility n (%)**	**NAUMC Awka n (%)**	**NAUTH Nnewi n (%)**	**Chi square difference**	**P = value**
Artemisinin-based combinations (ACTs)	2027 (93)	1198 (95)	829 (91)	13.02	0.0003***
Artemether-lumefantrine	1024 (50.5)	647 (54)	377 (45.5)	-	-
Artesunate-amodiaquine	244 (12)	206 (17.2)	38 (4.5)	-	-
Artesunate-mefloquine	232 (11.5)	-	232 (28)	-	-
Artesunate-pyridoxine+pyrimethamine	188 (9.3)	56 (4.7)	132 (16)	-	-
Dihydroartemisinin-piperaquine	339 (16.7)	289 (24.1)	50 (6)	-	-
Mono-therapy	144 (7)	63 (5)	81 (9)	13.02	0.0003***
Artesunate	42 (29.2)	7 (11.1)	35 (43.2)	-	-
Amodiaquine	14 (9.7)	-	14 (17.3)	-	-
Proguanil	15 (10.4)	1 (1.6)	14 (17.3)	-	-
Quinine	6 (4.2)	6 (9.5)	-	-	-
Sulphadoxine+pyrimethamine	67 (46.5)	49 (77.8)	18 (22.2)	-	-
Proportion of co-medication n (%)	1722 (97)	1248 (99)	864 (95)	32.37	0.0001***
Analgesics	1722 (79)	1124 (89)	598 (66)	176.8	0.0001***
Vitamin preparations	1364 (63)	993 (79)	371 (41)	324.8	0.0001***
Antibiotics	1084 (50)	721 (57)	363 (40)	63.18	0.0001***

***= very significant: NAUMC = Nnamdi Azikiwe University Medical Center; NAUTH = Nnamdi Azikiwe University Teaching Hospital; RDT = Rapid Diagnostic Test; ACT = Artemisinin Combination Therapy.

4.2.3 *Co-prescribed medication*

At least one co-prescribed medication was received in 97% of the patients at an average of 4 (±1.5) drugs per prescription. Analgesics were the most commonly prescribed co-medication given to 79% (1722/2171) of the cohort, followed by vitamin preparations (63%) and antibiotics (50%). Overall analysis shows an average of 4 (±1.5) drugs per prescription. The pattern varied significantly between the facilities and across categories (Tables 4.5 and 4.6). Proportion of co-prescribed medications was higher at the medical center, 99% than at the teaching hospital, (95%, $p< 0.0001$) (Table 4.5). This was similar for all the most commonly co-prescribed medications at the facilities. Majority, 57% of children under 5 years were more likely to be prescribed antibiotics than children between 5 and 12 years (37%, $p < 0.001$) and adults, (53% ; $p< 0.05$) (Table 4.2.3).

Table 4.6: Utilization of antimalarial drugs across demographic categories

	Gender		**Age category (years)**			
Antimalarial drugs	**Female n (%)**	**Male n (%)**	**Under 5 n (%)**	**5 – 12 n (%)**	**13 – 18 n (%)**	**19 and above n (%)**
Artemisinin-based combination therapy (ACT)	1127 (93)	881(94) 446 (51)	182(85) 128 (70)	45 (87) 31 (69)	101(97) 50 (50)	1286 (95) 624 (49)
Artemether-lumefantrin (AL)	568 (50)	125 (14)	29 (16)	3 (7)	15 (15)	184 (14)
Artesunate-amodiaquine (ASAQ)	113 (10)	64 (7)	-	-	5 (5)	113 (9)
Artesunate-mefloquine (ASMF)	168 (15)	72 (8)	18 (10)	11 (24)	9 (9)	82 (6)
Artesunate-sulphadoxine+pyrimethamine (ASSP)	115 (10) 163 (14)	174 (20)	7 (4)	-	22 (22)	283 (22)
Dihydroartemisinin-piperaquine (DHAPQ)						
Monotherapy	80(7)	61(6)	32(15)	7 (13)	3 (3)	70 (5)
Sulphadoxine+pyrimethamine (SP)	39 (49)	28 (44)	4 (13)	2 (29)	2 (67)	44 (63)
Artesunate (AS)	23 (29)	17 (27)	11 (34)	1 (14)	1 (33)	19 (27)
Amodiaquine (AQ)	7 (9)	6 (9)	12 (38)	1 (14)	-	-
Quinine (QN)	2 (3)	4 (6)	-	1(14)	-	5 (7)
Proguanil (PG)	9(11)	6(14)	5 (16)	2 (29)	-	2 (3)
Co-medication						
Analgesics	920 (76)	783 (83)	119 (59)	34 (54)	87 (84)	1148 (85)
Vitamin preparations	701 (56)	646 (69)	106 (52)	35 (56)	69 (66)	951 (70)
Antibiotics	569 (47)	502 (53)	115 (57)	23 (37)	59 (57)	720 (53)

4.2.4 *Prescription pattern in children under 5 years*

Of the 214 children less than five years identified in this study, 85% (182) received ACT. The AL, at 70% (128/182) was the most preferred antimalarial drug of choice in this age category, followed by ASAQ, 16% and ASSP, 10%. The use of monotherapy occurred most in this group compared to other age categories, and amodiaquine, 38% (12/32) was the most commonly prescribed monotherapy, followed by monotherapy artesunate (AS), 34%. Majority, 57% of children less than 5 years are more likely to be prescribed antibiotics than children between 5 and 12 years (37%, $p < 0.001$) and adults, (53% ; $p< 0.05$) (Table 3). In many cases the antibiotics were prescribed in combination with cough medications. Co-prescription with analgesics and vitamin preparations was also common in children.

4.2.5 *Costs of medication*

Table 4.7 shows that the overall median cost of medication (including co-medication) per patient at the two facilities was US$7.48 (N1160). The medication cost of treatment per patient at the tertiary hospital, N1378 (US$8.89) is about 1.3 times higher than at medical center N1083 (US$6.99)

Table 4.7: Medication cost of treatment

	Treatment cost (Naira)			
Variable	***Median***	***Range***	***Mean***	***95%CI***
Antimalarial drugs				
ACT	1176	45 – 41520	1587	1511 – 1663
Mono-therapy	750	30 – 8485	1158	927 – 1389
Gender				
Male	1158	72 – 41520	1340	1220 – 1460
Female	1110	30 -16010	1499	1403 – 1594
Age group				
Under 5	1062	45 – 7760	1151	1024 – 1277
5 - 12 yrs	776	30 – 3734	914	741- 1087.2
13 – 18	1118	150 – 7900	1243	1067 – 1418
19 and above	1160	85 41520	1503	1412 – 2595
Facility	1160	30 – 41520	1559	1486 – 1632
NAUMC	1085	85 – 8000	1171	1135 – 1207
NAUTH	1378	30 – 41520	2101	1940 – 2262

NAUMC = Nnamdi Azikiwe University Medical Center; NAUTH = Nnamdi Azikiwe University Teaching Hospital; ACT = Artemisinin Combination Therapy.

Between the groups median cost of mediation was lowest in children 5 – 12 years (N776) compared to adults 19 years and above (N1160). The cost of treatment with ACT (N1176) is about 1.6 times higher than the median cost of treatment with monotherapy, N750. It was not possible separating the cost of malaria component of treatment from that of co-morbidity due to inadequate documentation on diagnosis. Hence medication cost includes the cost of co-morbidity.

Questionnaire distribution recorded 100% response rate. While every respondent would often request for laboratory test for malaria before treatment, all (100%) would sometimes treat by clinical diagnosis alone. Some of the reasons for presumptive diagnosis given include confidence in their ability to diagnose malaria without laboratory test (100%), severity of symptom (80%), patient loads and lack of waiting time (20%) and previous experience with particular symptom/s (60%). All prescribers (100%) would sometimes prescribe antimalarial drugs in slide-negative results for a variety of reasons; need to prevent malaria infection (40%), unreliable result (40%), and unaware of result (40%). All respondents were aware of availability of malaria treatment guidelines and all would use AL as the preferred ACT of choice for its efficacy and minimum side effects. All doctors use ACT based on recommended guidelines.

4.3 Study III: Treatment costs for uncomplicated malaria at a public/secondary health facility in Nigeria

4.3.1 *Financial and economic cost estimates*

Distribution of the financial and economic costs of malaria treatment at the facility during the study period is shown in Table 4.8. It shows a total annual financial cost of N33, 533,217.86 (US$213,587.37), comprising capital and recurrent components. The costs are presented in local currency (Naira) converted to the United States Dollars (US$) at the 2013 exchange rate of 157 naira to the US dollar. The total annual economic cost was estimated at N28, 723,723.15 (US$182,953.65), comprising 98.2% recurrent and 1.8% capital items. Major cost drivers include personnel cost, at 82.5% constituted the greatest component of the annual cost, distantly followed by antimalarial drugs, at 6.6%. Laboratory services contributed 1.4% to the total. Based on the number of malaria cases treated during the study period, the cost translated to an average of N4, 943.84 (US$31.49) per OP episode of uncomplicated malaria, without co-medication. The estimates reflect the cost of treating outpatient uncomplicated malaria without co-morbidity. However, with co-medication the unit cost showed an average of N5, 522.29 (US$35.63) per uncomplicated malaria episode. Overall, overhead cost (represented by the costs of administration and utilities) contributed a total of N1, 040,357 representing 3.6% of the total cost of malaria treatment. Figure 4.4 shows the relative composition of the annual economic costs of treatment for uncomplicated malaria in the facility, showing personnel as the largest component of the total cost.

Table 4.8: Annual financial and economic costs of malaria treatment (2013 prices)

Items	Type of resource	Financial cost (in Naira)	Cost profile (%)	Economic cost (in Naira)	Unit cost (Naira)	Unit costs (US$)	Cost profile (%)
Capital items	Buildings/space	2,113,277	6.3	137,475.76	23.66	0.15	0.5
	Vehicle	3,209,894	9.6	376,200.56	64.75	0.41	1.3
	Medical devices	0.00	0.0	0.00	0.00	0.00	0.0
	Non-medical devices	0.00	0.0	0.00	0.00	0.00	0.0
	Subtotal	*5,323,171.04*	*15.9*	*513,676.32*	*88.41*	*0.56*	*1.8*
Recurrent items	Personnel	23,684,380	70.6	23,684,380	4,076.49	25.96	82.5
	Utilities	1,040,357	3.1	1,040,357	179.06	1.14	3.6
	Drugs	1,906,197	5.7	1,906,197	328.09	2.09	6.6
	Medical supplies & consumables	1,188,980	3.5	1,188,980	204.64	1.30	4.1
	Laboratory	390,134	1.2	390,134	67.15	0.43	1.4
	Subtotal	*28,210,047*	84.1	*28,210,047*	*4,855.43*	*30.93*	***98.2***
	Total cost	33,533,218	100	28,723,723	**4,943.84**	**31.49**	100

Currency conversion rate: US$1.00 = Nigerian Naira(N) 157

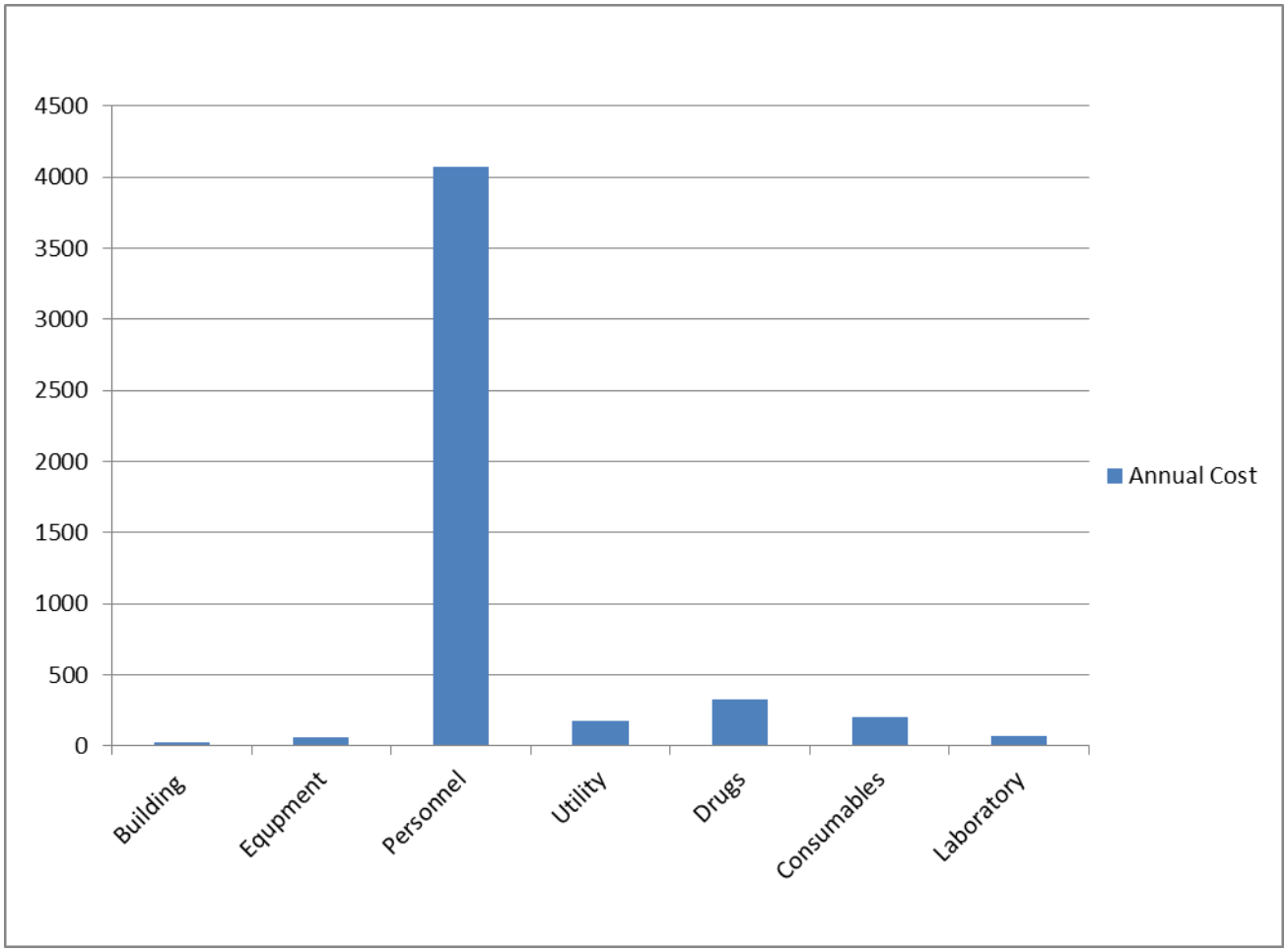

Figure 4.4: Composition of annual economic costs of the facility

4.3.2 *Drugs treatment costs*

Antimalarial drugs treatment amounted to a total economic cost of N1, 906,197 (US$12,141.38) per annum at N328 (US$2.08) per case, representing 6.6% of the total cost. When the cost of co-medication is included, it increased to N5, 266,968 per annum at N906 (US$5.77) per case, and representing 16.4% of the total cost.

4.3.3 *Sensitivity analysis*

Results of sensitivity analyses are presented in Table 4.9. The unit cost of treatment changed by 37% when malaria prevalence rate of 0.27 was used in place of the hospital rate of 0.47. This reflects the measure of accuracy assuming that 43% of the treated cases do not actually have malaria. Reducing personnel cost by 25% and 50% respectively (to compare with other non-university health facilities), showed significant drop in the total and unit values by 21% and 41% respectively. Changes in the discount rate and drug prices did not significantly impact on the treatment costs.

Table 4.9: Sensitivity Analysis of uncertain parameters on the study results

Parameter	***Percent change in parameter***	***Effect on treatment costs***	***Comments/Justification***
Malaria prevalence	43% reduction in rate used from 0.47 to 0.27	Total and average costs significantly reduced by 37%	Indicates the significant impact of accuracy of diagnosis on the cost of treatment. Change in rate based on findings of previous study to reflect malaria prevalence in a hospital wide findings
Personnel salary	25% reduction in personnel cost	Treatment costs (total and average) reduced by 21%	High cost of personnel indicated significant contribution to the high of treatment
	50% reduction in personnel cost	Treatment costs reduced by 41%	
Discount rate	3% to 5%	No significant change in treatment costs	Discount rate shows no impact on treatment costs. Reflects standard practice in economic evaluation (Drummond et al., 1997)
	3% to 10%	No significant change in treatment costs	
Drug costs	Increased by 25%	Total and average cost per case increased minimally at 2%	Drug prices do not significantly impact on the total cost of treatment
	Decreased by 25%	Total and cost per case reduced minimally at 3.3%	

4.4 Study IV: Effectiveness and Cost-effectiveness of antimalarial drugs in south east Nigeria

4.4.1 *Baseline characteristics of study participants*

A total of 590 patients were recruited for the study after eligibility screening, out of which only 480 completed the protocol. Figure 4.5 summarizes the selection and randomization to drug treatment groups. In Table 4.10, the demographics and baseline parasitological and clinical parameters are presented which appear similar between the treatment arms. It also shows the distribution of patients' weight and age, by drug dosage group and study arm. All randomized patients were exposed to at least one dose of each study drug, and the number of patients completing the study according to schedule in each arm is indicated in the table. Treatment was completed on day 2, for a three-day period. Incomplete treatment or loss to follow-up occurred in 18% (21/19) of AL patients; 19 (22/118) of DHAPQ patients; 17% (19/114) of ASAQ patients and 20% (24/120) of ASSP patients. Reasons for non-completion included premature study-discontinuation, repeated vomiting of dose (ASAQ), and missed/incorrect dose-intake.

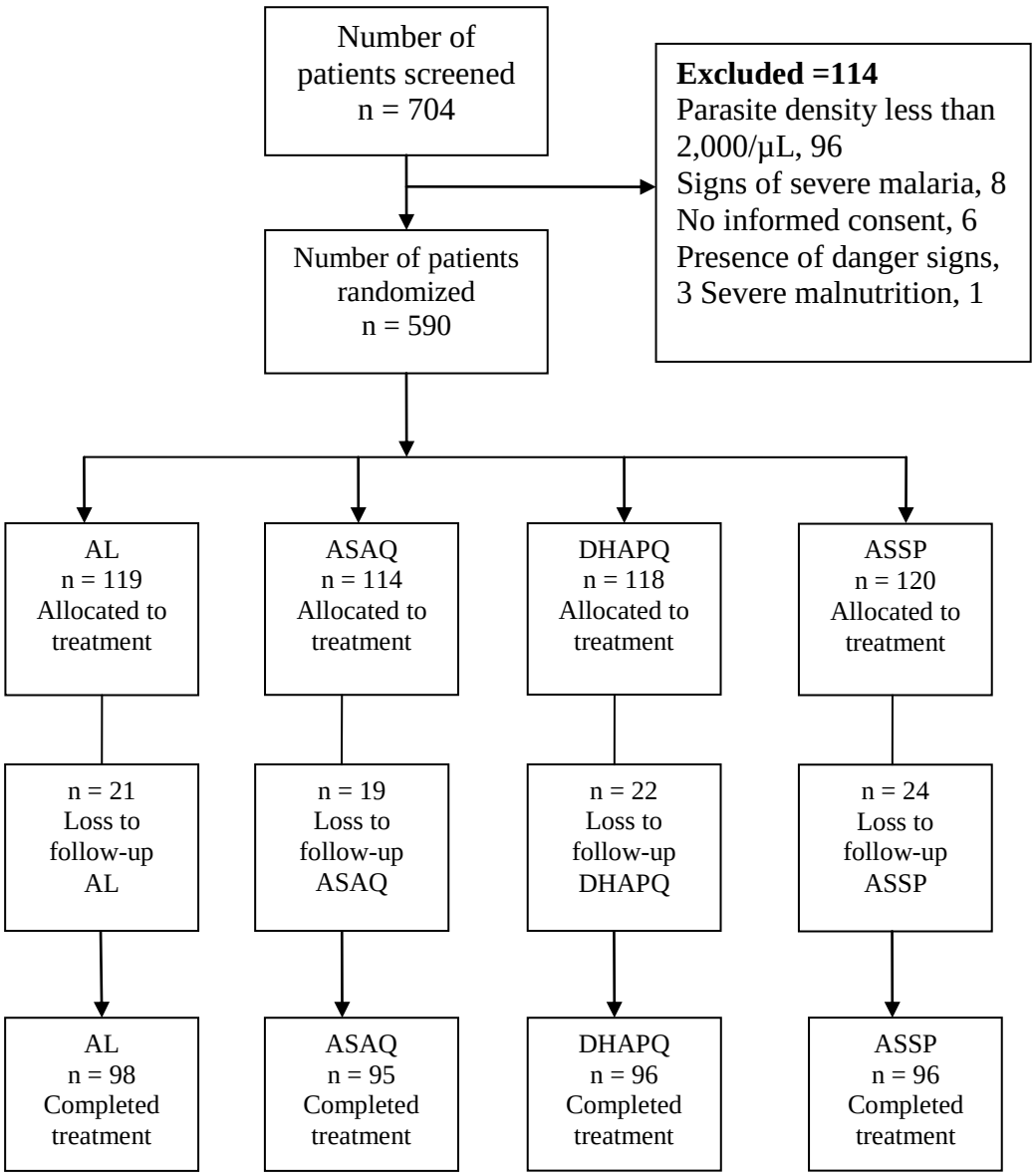

Figure 4.5: Schematic of cases selected and randomized to study groups

Table 4.10: Baseline characteristics of participants according to treatment group

Characteristics	AL (n = 120)	ASAQ (n = 118)	ASSP (n = 118)	DHAPQ (n = 116)
Sex: Male: Female (%)	45 : 55	43 : 57	45 : 55	44:56
Age (Years)				
Mean	27.7 ± 11.8	28.0 ±11.8	26.8 ± 10.9	28.9 ± 12.6
Median	24.0	24.0	24.0	24.0
Range	3 – 82	3 - 75	3 – 82	2 – 32
Weight (Kg)				
Mean ± SD	69.2 ± 11.8	69.5 ± 11.1	69.1 ± 10.6	69.5 ± 11.4
Median	70.0	71.0	71.2	67.8
Range	15.2 – 100	15 – 96	24 – 96	18 – 70
Temperature ^{o}C				
Mean ± SD	37.8 ± 0.94	38.3 ± 0.94	38.1 ± 0.97	37.7.0 ± 0.84
Heamoglobin (Hb) g/dL				
Mean ± SD	11.4 ± 1.9	11.1 ± 2.0	12.8 ± 14.1	11.5 ±2.1
Parasite density (μL^{-1})				
Mean ± SD	19,797 ± 33,397.3	27,010 ± 35,704	20541.3 ± 42091.4	35,431.3± 37615.2
Range	2000 - 220,000	2018 - 124,342	2024 - 221,000	2108 – 21334

AL= Artemether-lumefantrine; ASAQ = Artesunate-amodiaquine; DHAPQ = Dihydro-artemisinin-piperaquine; ASSP = Artesunate - sulphadoxine+pyrimethamine

4.4.2 *Programme costs/Unit costs of treatment*

Table 4.11 shows the summary of the average cost of treating uncomplicated malaria with each ACT regimen compared with comparator drug SP, as used in the cost-effectiveness study. The key cost items, as described in the previous section were personnel and drugs. Among the alternatives evaluated, DHAPQ was the least costly followed by ASAQ and ASSP. AL was the most expensive option. Personnel and the other components of the drug treatment costs, which were used to derive the treatment cost from provider's perspective were treated as fixed costs and therefore were the same for all the study arms or patient groups.

Treatment cost was highest for AL while the comparator drug SP has the least cost per case of treatment. However, if patient's costs and time are included, comparator cost of SP is expected to be higher considering the need for retreatment of failed cases. Retreatment costs will be incurred mainly from the times spent in seeking care from different sources, time spent at the hospital and care givers' time (Wiseman *et al.*, 2006).

Table 4.11: The mean treatment cost per uncomplicated malaria episode by drug item (Naira)

Category	Item	Facility	%	SP	AL	DHAPQ	ASAQ	ASSP
Recurrent	**Drug**	328.1	6.6	50	430	350	400	400
	Personnel	4,076.1	81.4	4,076.1	4,076.1	4,076.1	4,076.1	4,076.1
	Laboratory	67.1	1.8	67.1	67.1	67.1	67.1	67.1
	Utilities	179.1	4.1	179.1	179.1	179.1	179.1	179.1
	Consumable	204.64	4.2	204.64	204.64	204.64	204.64	204.64
Capital	**Building**	23.7	0.5	23.66	23.66	23.66	23.66	23.66
	Equipments	64.8	1.3	64.75	64.75	64.75	64.75	64.75
Average Total cost per case (N)		**4,943.84**	100.0	**4,665.75**	**5,045.75**	**4,965.75**	**5,015.75**	**5,015.75**
Average Total cost per case ($)		**31.49**	-	29.72	32.14	31.63	31.95	31.95

AL= Artemether-lumefantrine; ASAQ = Artesunate-amodiaquine; DHAPQ = Dihydro-artemisinin-piperaquine; ASSP = Artesunate - sulphadoxine+pyrimethamine

4.4.3 *Outcome /Effectiveness estimates*

Results of the clinical outcomes measured in terms of ACPR are presented in Table 4.4.3. The results show that in the per protocol analysis, of the 475 cases with *P. falciparum* malaria who completed the trial, 394 (83%) had an adequate parasitological and clinical response. The AL and DHAPQ groups have relatively the highest rates of success at 85.4% and 84.2% respectively. ASAQ and ASSP groups had 80% and 79% respectively. The table also shows that the DHPQ arm demonstrated the highest rate of compliance of 79% and consequently the greatest proportion of treatment success with 63 cases, followed by AL. AL is given in a 12 hourly dose format, after the initial 8 hour dose following the first dosing. This made it a little cumbersome for the patients compared to 24 hourly doses of the alternatives. However, efficacy among the non-compliant cases was highest among the AL group. The incremental number of successes and costs, as well as the incremental cost–effectiveness ratios, compared with SP are also presented in Table 4.4.3.

4.4.4 *Effectiveness and Cost-effective ratios (CERs) per case of uncomplicated malaria*

Using the cost-effectiveness framework described in the previous sections, ACER and ICER were estimated for the selected drugs using the costs and effects data estimated above. The results are presented in Table 4.5.3. Each result represents average cost per case and incremental cost per case of uncomplicated malaria episode successfully treated. Effects data were derived from the model which uses input data on efficacy and compliance to determine treatment success. The input data on costs and effects were obtained from the field study. Data on compliance were complemented with information from previous studies. 71% compliance rate was estimated for AL, while

60% of the patients who did not comply with treatment regimen were assumed to be cured (Chanda *et al.,* 2007; Coleman *et al.,* 2004).

Table 4.12 shows that the ACER was lowest for DHAPQ at N7, 454.63 (US$47.48) per case treated, as the most cost-effective ACT, followed by AL which showed an average cost of N8, 306.29 (US$52.91) per malaria case treated. ASSP generated the highest ACER at N9, 193.90 (US$58.56), suggesting the least cost-effective option based on the average measure.

The study primary measure of cost–effectiveness was the incremental cost–effectiveness ratio (ICER), in which the cost and effect of the options are measured relative to the comparator. SP, which has the lowest efficacy was used as the comparator, serving as the baseline for the determination of the ICER. Hence, cost-effectiveness ratio was calculated incrementally as all the options were referenced to the common baseline, starting with DHAPQ. The result of ICER shows that DHAPQ similarly has the lowest ICER of N643.6 (US$4.10) or cost per additional case of uncomplicated malaria successfully treated, followed by AL with N932.6 (US$5.94), compared to other ACTs. ASSP and ASAQ have the highest and second highest ICERs at N1, 012.87 and N969.84 respectively. Going by the 'Rule of Thumb' as suggested by the WHO, on the range of cost-effective interventions, and especially in low income countries, the ICER values of the ACTs fall within the range of very cost-effective options, suggesting that altogether, the ACTs under study are very cost-effective, with DHAPQ as the most cost-effective option. Both ACER and ICER results show that DHAPQ is the most cost-effective ACT in Nigeria. The details of the ACER and ICER results are shown in Table 4.12.

Table 4.12: Costs, effects and cost-effectiveness of evaluated ACTs

Effectiveness measures/Item	*SP*	*AL*	*DHAPQ*	*ASAQ*	*ASSP*
Number starting treatment	95	95	95	95	95
Efficacy, E (ACPR) %	20	85.3	84.2	80	79
Compliance C, (%)	100	71	79	70	69
Efficacy despite non-compliance (%)	0	60	43	28	35
Effectiveness (Cases successfully treated)	19	58	63	53	52
Cost of malaria treatment per arm	443,247	479,347	471,747	476,497	476,497
Average cost per case (ACER)	23,328.77	8,306.29	7,454.63	8,942.58	9,193.90
Incremental cost per case (ICER)	-	932.60	643.60	969.84	1012.87
ACER $	148.59	52.91	47.48	56.96	58.56
ICER $	-	5.94	4.10	6.18	6.45

AL= Artemether-lumefantrine; ASAQ = Artesunate-amodiaquine; DHAPQ = Dihydro-artemisinin-piperaquine; ASSP = Artesunate- sulphadoxine+pyrimethamine;. ACPR = Adequate clinical and parasitological response; ACER= Average cost-effectiveness ratio; ICER = Incremental cost-effectiveness ratio

However, even though they are all very cost-effective in line with standard criteria, AL, ASSP and ASAQ are dominated and extendedly dominated by DHAPQ, by being lower in cost and more effective than any of the other options. This indicates that DHAPQ is cost-saving when compared to the other options. It generated higher effect and lower cost than ASSP, ASAQ or AL. Consequently, they were removed from the cost-effectiveness frontier and analysis. The results suggest that from a provider's perspective, DHAPQ is the most cost-effective ACT for the treatment of uncomplicated malaria in Nigeria.

Table 4.13 shows the details of the average and incremental CE ratios distributed across the alternative therapies, showing the dominance of DHAPQ over the alternative regimens. Using the criteria for determining the most cost-effective

therapy, analysis indicates that DHAPQ demonstrated primary and secondary domination over the other ACTs, by virtue of being both cheaper and more effective by treating more malaria cases. Arranged in order of increasing costs, the table shows that at a lower cost, DHAPQ generated higher effects/benefits than ASAQ which is the next but more expensive option, effectively eliminating it from the analysis in the form of primary dominance. Similar dominance occurred in sequence with both ASSP and AL which also generated lower effects at higher costs compared to DHAPQ, consequently making DHAPQ the dominant cost-effective ACT for the first line treatment of uncomplicated malaria in Nigeria. This implies that the use of DHAPQ is cost saving while treating more cases of uncomplicated malaria when compared with the other agents.

This precluded these agents from further cost-effectiveness analysis since the results imply that DHAPQ is cost saving when compared with the other alternatives.

Table 4.13: Average and incremental cost-effectiveness ratios of ACTs showing the dominance of DHAPQ over the other regimens

Drug	COST (N)	EFFECT	ΔCOST (N)	ΔEFFECT	ACER	ICER (N)	ICER (US$)	ACER (US$)
SP	443,246.56	19	-	-	23,328.77	#VALUE!	0.00	0.00
DHAPQ	471,746.56	63.2824	28,500.00	44.28	7,454.63	643.60	4.10	47.48
ASAQ	476,496.56	53.284	33,250.00	34.28	8,942.58	969.84	6.18	56.96
ASSP	476,496.56	51.82745	33,250.00	32.83	9,193.90	1,012.87	6.45	58.56
AL	479,346.56	57.70885	36,100.00	38.71	8,306.29	932.60	5.94	52.91

ACT = artemisinin combination therapy; AL= Artemether-lumefantrine; ASAQ = Artesunate-amodiaquine; DHAPQ = Dihydro-artemisinin-piperaquine; ASSP = Artesunate- sulphadoxine+pyrimethamine; ACER= Average cost-effectiveness ratio; ICER = Incremental cost-effectiveness ratio

Data was not collected from the societal perspective to determine the impact on patient and family costs, and the indirect cost of loss of productivity due to malaria illness on the cost-effectiveness of the ACT. It is expected that given the greater reduction in malaria episodes by the ACTs, there would be resource savings generated in terms of gains from fewer re-treatments of failed cases, some of which may have progressed to severe malaria (Wiseman *et al.*, 2006).

4.4.5 *Sensitivity analysis*

One-way and two-way sensitivity analyses were carried out to test the impact of varying parameters known to be very variable, on the cost-effectiveness results. Parameters tested included accuracy of diagnosis, personnel cost, the discount rate for valuing the capital items, drug costs and compliance rates. Findings are presented in Table 4.14. Accuracy of diagnosis, drug prices and compliance rates showed the most notable impacts on the CER results. Changes in the discount rate did not produce any

significant change in the CER results. Accuracy of diagnosis demonstrated the most notable effects on the results, as it strongly influenced the effectiveness and cost-effectiveness of all the drug treatments. For instance, assuming that 25% of the cases were wrongly diagnosed/misdiagnosed and do not actually have malaria, the number of cases successfully treated by the respective drugs reduced significantly by about 25% across the treatment groups. The ACER of the individual drug groups increased significantly by 33.3% while the ICER increased most significantly by between 55% and 65% across the drug groups, reducing the cost-effectiveness of the drugs. However, even as the cost-effectiveness falls, the ACTs remain better value for money compared to monotherapy, with DHAPQ remaining the most cost-effective alternative; saving most resources and treating most malaria cases. Changes in the cost of drug treatment led to significant changes in the incremental costs across all treatment options but did not affect the order of the CER results which shows DHAPQ as the most cost-effective option. Increasing the drug costs by 25% across the groups increased the ICERs by up to 29%, while ACER increased minimally at 2%. While the change in personnel salary led to notable change in the average cost of treatment, it did not affect the cost-effectiveness results. Assuming 100% compliance rate for all the regimens significantly increased their cost-effectiveness (reduced ICER) by between 27% and 41%, but DHAPQ remained the most cost-effective. Considering the variability of the rate of compliance and prices of AL, a two-way sensitivity analysis was also performed to determine how the various combinations of compliance rates of AL and DHAPQ will affect the CER results. 25% increase in compliance and 25% reduction in the price of AL significantly increased its ICER, making it more cost-effective than DHAPQ.

Table 4.14 (a): Results of sensitivity analysis on the cost-effectiveness results

Parameter / variable	Percent change in parameter/ variable	Effect on CER results				Comments
		AL	DHAPQ	ASAQ	ASSP	
Accuracy of diagnosis	Assuming 25% of cases are misdiagnosed for malaria (reduced efficacy of drugs by 25%)	Total cost remains the same. ACER increased by 33.2%. ICER increased by 59.1% to $9.45 (reduced cost-effectiveness) Number of cases treated reduced by 24.9% to 43.	Total cost remains same. ACER increased by 33.3%. ICER increased by 55.4% to $6.37 (reduced cost-effectiveness). Number of cases treated reduced by 25.1 to 47.	Total cost remains the same. ACER and ICER Increased by 33.3% and 63.3% respectively. Number of cases successfully treated reduced by 25% to 40. Reduced cost-effectiveness	Total cost remains the same. ACER and ICER increased by 33.1% and 64.6 respectively. Number of cases successfully treated reduced by 24.91% to 39.	Accuracy of diagnosis significantly impacts on the cost-effectiveness (efficiency) of antimalarial drugs, as misdiagnosis reduces the cost-effectiveness of malaria treatment.
Personnel salary	25% reduction in wage	ACER reduced by 20% to $43.98. No change in ICER result	ACER reduced by 21% to $38.03. No change in ICER result	ACER reduced by 20% to $48.27. No change in ICER	ACER reduced by 20% to $48.84. No change in ICER	High cost of personnel indicated significant contribution to the high of treatment
	50% reduction	ACER reduced by 40.4% to $32.84. No change in ICER result	ACER reduced by 41% to $28.21. No change in ICER result	ACER reduced by 40.6% to $35.96. No change in ICER	ACER reduced by 40.6% to $356.38. No change in ICER	
Discount rate	3% to 5%	Non-significant (0.3%) increase in ACER). No change in ICER	Non-significant (0.3%) increase in ACER). No change in ICER	Non-significant (0.3%) increase in ACER). No change in ICER	Non-significant (0.3%) increase in ACER). No change in ICER	Discount rate shows no impact on the cost-effectiveness result.
	3% to 10%	ACER increased by 1%. ICER remained unchanged	ACER increased by 1%. ICER remained unchanged	ACER increased by 1%. ICER remained unchanged	ACER increased by 1%. ICER remained unchanged	Reflects standard practice in economic evaluation (Drummond et al., 1997)
Drug costs	Increased by 25%	ICER increased by 28.3% to $7.62 while change in ACER was minimal at 2.1%	ICER increased by 29.1% to $5.29 while change in ACER was minimal at 1.8%	ICER increased by 28.5% to $7.94 while change in ACER was minimal at 2%	ICER increased by 28.6% to $8.29 change in ACER minimal at 2%	There is significant change/reduction in cost-effectiveness result
	Decreased by 25%	ICER reduced by 28.3% to $4.26. ACER change minimal at -2.1%	ICER reduced by 29.2% to $2.9. ACER change minimal at -1.8%	ICER reduced by 28.6% to $4.4. ACER change minimal at -2%	ICER reduced by 28.6% to $4.61. Change in ACER minimal at -2%	Drug costs significantly impact on the cost-effectiveness result

Table 4.14 (b): Results of sensitivity analysis on the cost-effectiveness results

Parameter/ variable	Percent change in parameter/ variable	Effect on CER results				Comments
		AL	DHAPQ	ASAQ	ASSP	
Compliance rate	AL compliance rate increased by 25%	Both ACER and ICER reduce by 19.8% and 26.9% respectively. Cases treated increased by 19.8% to 72 cases	Not applicable/Remain the same	Not applicable/Remain the same	Not applicable/Remain the same	Cost effectiveness of AL increased but still dominated by DHAPQ
	Compliance rate assumed same for all evaluated drugs at 100%	ACER and ICER reduced by 28.8% and 37.6% respectively. Cases treated increased by 40.4%. (58 – 81).	ACER and ICER reduced by 20.9% and 27.4% respectively. Cases treated increased by 26.4% to 80	ACER and ICER reduce by 29.9% and 39.9% respectively. Cases treated increased by 42.6% to 76	ACER and ICER reduced by 30.9% and 41.3% respectively. Cases treated increased by 44.6% to 75 cases	DHAPQ remains the most cost-effective even though AL becomes slightly most effective
Drug cost and compliance rate	Reduce AL price by 25% and increase compliance by 25%	ACER and ICER reduce by 21.5% and 47.6% to the lowest values, $41.51 and $3.11 respectively	Not applicable/Remain the same	Not applicable/Remain the same	Not applicable/Remain the same	AL becomes the most cost-effective

CER = Cost-effectiveness ratio; AL= Artemether-lumefantrine; ASAQ = Artesunate-amodiaquine; DHAPQ = Dihydro-artemisinin-piperaquine; ASSP = Artesunate- sulphadoxine+pyrimethamine; ACER= Average cost-effectiveness ratio; ICER = Incremental cost-effectiveness ratio

4.4.6 *Budget impact*

The study estimated the budget impact on the hospital annual budgets, of switching from the previous policy drug SP, to the alternative antimalarial drugs based on the current policy on the use of ACTs. Using the hospital's annual patient's load for uncomplicated malaria, Table 4.15 indicates minimal impact of switching to the ACTs. It indicates an average 9.34% increase in annual budget for the treatment of uncomplicated malaria. This reflects the high cost of treatment with ACTs. However, when the cost of retreatment of failed cases with SP is factored in, the impact would become minimal or cost saving. The benefits of the ACTs include treatment of failed cases and the prevention of progression to severe malaria. Hence, the cost of treating severe episodes will be averted leading to cost savings. These benefits were not captured in this study because they were beyond the scope for uncomplicated malaria. The budget accounted for mostly the cost of direct expenditure on drugs and other medical equipment. The impact ranged from an annual cost of approximately N1.8m (US$11,454) with DHAPQ to about N2.28m (US$14,508) with AL. Exclusion of the overhead costs for capital expenditures reduces the cost by 20% to an annual average cost of US$9,766. Assessment from the societal perspective will lead to cost-savings, by capturing savings from travel costs, treatment of severe malaria and absenteeism from work.

Table 4.15: Number of outpatient visits for uncomplicated malaria and impact on hospital budgets of switching from SP to ACT for the treatment of uncomplicated malaria.

SN	Parameter	AL	DHAPQ	ASAQ	ASSP
1	Annual outpatient visits for uncomplicated malaria	5994	5994	5994	5994
2	Cost per case of treatment with each antimalarial drug	5,045.75 ($32.14)	4,965.75 ($31.63)	5,015.75 ($31.95)	5,015.75 ($31.95)
3	Annual cost of treatment with antimalarial drug	30,244,245 ($192,639)	29,764,725 ($189,584)	30,064,425 ($191,493)	30,064,425 ($191,493)
4	Annual cost of switching from SP to ACT including capital costs in Naira and (US$)[a]	2,277,720 ($14,507.77)	1,798,200 ($11,453.5)	2,097,900 ($13,362.42)	2,097,900 ($13,362.42)
5	Annual cost of switching to ACT excluding capital costs in Naira and (US$) [b]	1,747,776 ($11,132.33)	1,268,256 ($8,078.06)	1,567,956 ($9,986.98)	1,567,956 ($9,986.98)

AL= Artemether-lumefantrine; ASAQ = Artesunate-amodiaquine; DHAPQ = Dihydro-artemisinin-piperaquine; ASSP = Artesunate - sulphadoxine+pyrimethamine;.

The budget analysis was based on individual estimates for each ACT studied. However, in real practice the ACTs are used together to complement each other, to provide alternative therapy in cases of treatment failures or side effects/adverse drug reactions with specific regimen, depending on individual patient response. The hospital record showed different levels of use of the antimalarial drugs, informed by preferences, availability and cost of each drug. Hence, the weighted average of the estimates will provide the realistic estimate for the budget implication. Consequently, using the hospital record that showed substantial preference for AL, the budget estimates calculated from weighted averages of the drugs treatment was similar to the estimates obtained from the previous section above.

CHAPTER FIVE

DISCUSSIONS, CONCLUSIONS AND RECOMMENDATIONS

5.1 Assessment of antimalarial drugs utilization pattern in medicine retail outlets in Enugu urban

This study unlike previous ones relied on actual drug utilization data to assess implementation of malaria treatment policy in the retail sector. Compared to previous studies (Mangham *et al.,* 2011), the findings suggest vastly improved use of ACT in the sector, some eight years after their introduction as the first-line treatment for uncomplicated malaria in Nigeria. The study by Mangham *et al* in 2009, about five years after policy change in the same area suggested utilization rate of 24.2% for ACT in medicine outlets, using patients' exit questionnaire (Mangham *et al.,* 2011). Findings corroborate the results of previous studies in the same area, in terms of availability and utilization of anti-malarial drugs (Onwujekwe *et al*., 2009; Uzochukwu *et al*., 2010; Mangham *et al*., 2011; Ezenduka *et al.,* 2013). Prescriptions were mostly adults, while child cases were limited, comprising prescriptions from hospitals. Predominance of adult prescriptions agrees with previous findings that adults make more use of retail outlets than children (Abuya *et al.,* 2007; Hetzel *et al*., 2008). The study shows that AL, as the policy first-line drug in Nigeria, is the most commonly used ACT followed by DHAPQ, corroborating the studies in 2009 by Mangham *et al*. and in 2010 by Uzochukwu *et al.* which documented similar findings for both public and private health facilities in the same area. Studies in Uganda and Zambia have also shown preference for AL regimen over other ACT in health facilities (Sears *et al*., 2013). The use of AA brands in this study appears quite limited at 8.7% of ACT, even though it was the alternative first-line drug in Nigeria. Safety concerns associated with the use of AA is

the possible reason for this, in addition to availability of a wide range of other ACT. AA has been associated with varying degrees of side-effects, which have limited its use, especially in adult patients (Dodoo *et al*., 2009; Faye *et al*., 2010; Schramm *et al.*, 2013). The preference for AL may reflect expectation of efficacy and/or safety in the study environment. Other likely factors include availability of formulations and promotional activities of pharmaceutical companies operating in the country. In consequence, the AL regimen had the widest range of brands in the study as well as the most available. The high proportion of dispensed ACT therefore indicates a positive development on the part of retail outlets in the provision of malaria treatment. This can be attributed to several interventions that have been implemented in the sector to enhance appropriate use of anti-malarial drugs. These include the introduction of AMFm drugs accompanied by public campaigns and targeted provider trainings to enhance uptake of effective antimalarial drugs, as well as community-based interventions (Mangham *et al*., 2011; Davies *et al*., 2013). The appreciable presence of AMFm drugs, which accounted for up to 23% of dispensed anti-malarial drugs, reinforced the use of ACT based on affordable prices. Consequently, their use impacted positively on prices and costs of treatment.

The study indicates that monotherapy, either as artemisinin- or non-artemisinin-based monotherapy is used significantly at 27% in the retail sector. The use of artemisinin-based monotherapy is contrary to policy recommendation in view of the potential risk of parasite resistance as a result of its short half-life (WHO 2006). The extent of monotherapy in this study suggests substantial inappropriate use of anti-malarial drugs, which undermines treatment goals by promoting development of drug resistance and treatment failures, and should be a cause for concern. Analysis suggests that

monotherapy was used more in adults and in PMVs, and obtained mostly through self-medication. These point to the need for more public education for appropriate use of anti-malarial drugs and better-targeted strategy to improve the use of ACT through PMVs and pharmacy sales staff, since they are known to command a significant population seeking malaria treatment in Nigeria (Onwujekwe *et al*., 2005; Meremikwu *et al*., 2007). Reason for use may be attributed to the higher costs of ACT, availability of monotherapy agents and lack of adequate information on appropriate use of effective anti-malarial drugs. This situation is likely to be worse in rural areas where the level of awareness is lower and choice may be more limited (Dodoo *et al*., 2009).

The extent of monotherapy is reinforced by the prevalence of self-medication as the highest source of drug utilization in this study. This was not surprising because previous studies have documented widespread self-medication among patients with anti-malarial drugs obtained from retail outlets, in most developing countries (McCombie *et al.*, 2002; Erhun & Osagie 2004; Onwujekwe *et al*., 2005). It was therefore expected that self-medication was the highest source of monotherapy, due to lack of adequate knowledge of effective anti-malarial drugs on the part of consumers, leading to inappropriate use of drugs. Self-treatment may be attributed to previous experience with a particular drug, such as having used the same drug for similar symptoms, or neighbour, friend, or relative previously taking the same drug for similar symptoms (Watsierah *et al.,* 2011). Self-medication, which is mostly based on presumptive diagnosis, will similarly be faced with consequences of misdiagnosis, over-treatment of malaria, masking of underlying, potentially fatal conditions and unnecessary side-effects (O'Dempsy *et* al., 1993; Amexco *et al.,* 2004). This reinforces the increasing

calls for interventions to improve treatments from these outlets through regular education programmes (Hanson *et al*., 2004; Marsh e*t al.,* 2004; Okeke *et al*., 2006).

Outlet prescriptions reflect malaria treatment practices in medicine outlets, in terms of the use of ACT and findings suggest significant use of ACT, especially in pharmacies. This indicates positive impact of educational programmes on effective malaria treatment implemented in the past, as part of intervention strategies to educate private providers. It is expected that regular training of these providers translates to appropriate use of anti-malarial drugs. However the extent of monotherapy use in this study, especially through the PMVs, suggests the need for reinforced and regular training and education for these providers on effective use of anti-malarial drugs. The little difference in the use of ACT between the pharmacies and the PMVs is notable and can be explained by the significant presence of sales staff who do not have formal training, and which is expected to impact on service delivery through pharmacies. The successes achieved so far with the training programmes point to the usefulness of targeted interventions. Evidence of improved performance of the providers through targeted training has been demonstrated in studies carried out in Kenya and Tanzania (Tavrow *et al.,* 2003; Marsh *et al*., 2004; Mbwasi 2005). Prescriptions from hospitals which consists almost entirely of ACT is consistent with findings that the public sector conforms more to policy on the use of ACT and that prescribing pattern is not influenced by patient demand, compared to the private retail sector (Okeke *et al*., 2006; Onwujekwe *et al*., 2009; Uzochukwu *et al*., 2010). Fewer cases of monotherapy prescription through this mode may be explained by the use of SP for prophylaxis in pregnancy. This may have contributed to making SP the highest used monotherapy in this study.

A major issue of concern in malaria treatment through the retail sector is presumptive treatment. Studies have shown that treatment through the medicine outlets is mostly based on clinical symptoms and this has been shown to result to over 50% being non-malaria cases (Onwujekwe *et al.*, 2005; Uzochukwu *et al*., 2010), leading to wastage and inappropriate management of fevers and other complications. Although data was not comprehensively collected on laboratory diagnosis in this study, evidence showed that the majority of malaria treatment was not supported by laboratory diagnosis. This is reinforced by the fact that anti-malarial drugs are treated as OTC medicines and the use is not regulated as prescription, even though regulation of drug sales in Nigeria, as in most developing countries, is not enforced. Some patients undertake diagnostic tests for malaria in private laboratories before visiting the outlets for treatment, sometimes with prescriptions from laboratory attendants (Onwujekwe *et al*., 2011). This study suggests a high level of presumptive malaria treatment, which encourages the use of wrong drugs, limiting the use of effective anti-malarial drugs. Patient demand for diagnostic testing was limited, in addition to limited accessibility of laboratory services. Policy should, as a matter of urgency, consider the introduction of RDT in retail outlets to enhance accuracy and efficiency of malaria treatment in the sector. The WHO current approach to effective malaria treatment emphasizes the TTT strategy, which translates to malaria diagnosis, early treatment with effective anti-malarial drugs and follow-up monitoring to ensure effective implementation.

Even though this study may not have adequately captured the extent of co-medication in the study, analysis indicates a substantial degree of concomitant treatment with other drugs. Understandably, analgesics were the most frequently used, followed by

antibiotics with implications for increased cost of treatment. Vitamin preparations were the third most used co-medication. Analgesics are often required to relieve accompanying fevers and pains in malaria infection even though many cases actually resolve with effective anti-malarial drugs. The use of vitamin preparations, especially those containing minerals and trace elements (such as zinc, iron (Fe2+), copper, etc) with anti-oxidant properties has implications for the effectiveness of ACT. Anti-oxidants, vitamin C and vitamin E have been found to interfere with artemisinin compounds, thereby reducing their efficacy (Meshnick *et al*., 1989; Oreagba and Ashorobi 2007); the advice is they may be used after the completion of ACT dose, if needed (Ganiyu *et al*., 2012). The extent of concomitant medication in this study indicates substantial wastage when viewed against the prevalence of presumptive treatment of malaria which, in addition increases inefficiency in malaria treatment. Co-medication with antibiotics was apparently based on presumptive co-morbidity with mostly typhoid fever, which is often informed by previous laboratory findings and experiences, while a few are informed by laboratory tests accompanying malaria treatment requests. Widespread co-medication with antibiotics has implications for safety in view of the potential for drug-drug interactions and other safety concerns. Antibiotics are known to have high incidence of adverse events, such as rashes and pruritus, which might even be attributed to the new anti-malarial drugs (Dodoo *et al.,*2009). This study suggests that children aged below five years are more likely to be prescribed co-medication. The study in Ghana reported similar findings where children below five received more co-prescribed antibiotics than other age categories (Dodoo *et al*., 2009). Co-morbidity with pneumonia and related conditions is commonly associated with childhood malaria, which informed earlier recommendation for symptomatic treatment of childhood fevers with a combination of antimalarials and

antibiotics (O'Dempsey *et al*., 1993). The lower proportion of co-medication in this study compared to the Ghana study may be explained by the fact that the retail sector is characterized by self-medication, where the choice and number of drugs may be limited by cost of treatment. It is also very likely that this study did not capture all co-medications used among the cohorts, for many reasons. Many patients may still have other medications such as analgesics and multivitamins which routinely used mostly in children. This is particularly so for prescriptions dispensed through self-medication. The use of antibiotic co-prescription would suggest less confidence of actual diagnosis of malaria, hence prescribing antimalarials would be a 'cover' for potential infection or to prevent subclinical infection becoming manifest (Dodoo *et al*., 2009). Similar findings were reported from a study in Tanzania for patients with a history of cough for which antimalarials were prescribed (Reyburn *et al.*, 2006). The issue of concomitant medication also contributes to irrational use of anti-malarial drugs due to polypharmacy and increased cost of care. Just as in many other studies, over-use of medication in malaria treatment results in polypharmacy, encouraging poor adherence in addition to the risks of drug interactions, adverse drug reactions and in consequence, treatment failures.

Study findings suggest significant reductions in prices and costs of treatment based on previous studies. The study by Mangham *et al.* (2011) on the treatment of uncomplicated malaria (five years after introduction of ACT) showed the median cost of adult dose of ACT in the retail outlets to be N600 (US$3.87). A previous study in 2010 showed a median price of the ACT at N700 (US$4.52) per adult dose (Ezenduka *et al*., 2013). The current price of N400 (US$2.67) per adult dose therefore suggests a significant reduction from previous prices. This can easily be attributable to the

penetration of AMFm drugs which showed wide utilization across age and gender categories. However, at a median cost of $1.94 per adult dose, the current prices of AMFm drugs are still well above intended targets of US$0.42-1.00 to achieve expected goals (Davis *et al.*, 2013). Available information suggests limited availability of AMFm products below their market demand and as a result, they are sold at costs higher than recommended prices, in response to market forces. The median cost of ACT at US$2.67 per adult dose remains high and unaffordable for many low-income patients who therefore resort to cheaper monotherapy, thus contributing to the incidence of monotherapy.

5.1.1 *Limitations of the study*

Although significant information was obtained from the study, there were limitations that need to be highlighted to better interpret and use the information. Although sampling may suggest bias towards outlets with high patient turnover, the pattern of utilization which cuts across different parts of the city reflects health-seeking behaviour of patients using retail outlets and therefore likely represents sample population with malaria in the city (Dodoo *et al.*, 2009). The study did not collect further information to accurately analyze the use of monotherapy and determine those that were used appropriately for prophylaxis in pregnancy and children, as well as those purchased to complete a dose in single-dose combination. Similarly, information on laboratory diagnosis following antimalarial drug treatment was not adequately collected due to inconsistency and this would have helped inform a more comprehensive analysis of the drug use pattern in the retail sector. Due to the challenges of data collection in the retail sector and their unwillingness to volunteer information, data may be incomplete and potentially unreliable; hence, the use of

large data to enhance the validity of findings, in addition to the use of trained field staff to assist in data collection from many of the premises. In spite of these limitations study findings largely reflect the pattern of anti-malarial drug utilization in the retail sector.

5.1.2 *Conclusion*

This study suggests a vastly improved and substantial uptake of ACT as the antimalarial drug of choice for the first line treatment of uncomplicated malaria in medicine retail outlets in Nigeria, eight years after policy change. This portends positive development towards achieving the goals of malaria treatment, considering the challenges of the sector. Evidence suggests positive contributions from the AMFm drugs, which was accompanied by targeted education programmes to improve the use of effective anti-malarial drugs, as well as the availability of a wide range of ACT. However the use of monotherapy and ineffective drugs remain significantly high due mainly to the prevalence of self-medication as the predominant mode of malaria treatment in the sector, in addition to poor treatment practices of the providers. This would certainly lead to increasing risk of development of parasite resistance to effective antimalarial drugs and treatment failures, thereby undermining the goals of malaria treatment policy. In view of the challenges of the sector, characterized by self-medication and the presence of poorly informed providers, there is need for improved targeting of the general public and the retail providers for enhanced and sustained education on effective use of antimalarial drugs. This is crucial if the goals of malaria treatment policy are to be achieved, considering the role of the sector in the provision of malaria treatment in Nigeria.

5.2 The prescription pattern of antimalarial drugs for the treatment of uncomplicated malaria in two public health facilities in Anambra state

This study illustrates practical realities in the treatment of uncomplicated malaria in public health facilities in Nigeria, which has implications for the implementation of malaria treatment guidelines. Findings reflect practices as they relate to the test and treat policy of malaria control. The predominance of the female gender is consistent with many studies (Meremikwu *et al*., 2007; Mangham *et al*., 2011; Thwing *et al*., 2011; Sears *et al*., 2013;), where females outnumbered males in health facilities compared to the retail sector. This observation agrees with the suggestion that females make more use of public health facilities than males, who tend to prefer medicine outlets (Ezenduka *et al*., 2013). The finding also implies that women suffer more from malaria attack than males in the study area. The higher proportion of malaria cases at the medical center, (a primary/secondary health facility) is easily explained by the fact that primary health facilities are the main sources of treatment for uncomplicated malaria (Chuma *et al*., 2009). The 27% malaria incidence in this study would suggest a declining incidence compared to previous reports of 60% incidence for outpatients consultations in Nigeria (FMoH 2000).

The use of laboratory diagnosis for malaria treatment in the two facilities was limited to 49%, relying substantially on presumptive diagnosis, contrary to the test and treat recommendations of current guidelines. This indicates high incidence of over-diagnosis and over-use of antimalarial drugs, in view of the degree of inaccuracy associated with presumptive malaria treatment (Chitaka *et al*., 1998; Reyburn *et al.,* 2006; Uzochukwu *et al.,* 2010). The finding corroborates previous studies in Nigeria and other African countries which have reported widespread limited use of laboratory diagnosis in malaria

treatment, even with the presence of diagnostic tools (Reyburn *et al*., 2006; Meremikwu *et al*., 2007; Uzochukwu *et al.*, 2010; Zurovac *et al*., 2014). It reflects the level of confidence and popularity to which prescribers attach to presumptive malaria treatment, as was confirmed by doctors' responses. This is consistent with the findings by Onwujekwe *et al*. in 2009 and Uzochukwu *et al*., in 2010, in which over 80% of providers at both hospital and non-hospital alike, are confident in clinical diagnosis of malaria. The study by Meremikwu *et al*. in 2007, reported laboratory test rate of 45%, while Uzochukwu *et al*. reported a rate of 51.1% in Enugu, suggesting no significant improvement since 2010. The level of confidence in clinical diagnosis should be considered unrealistic in view of the evidence to the contrary and the high incidence of inaccuracy and wastages associated with presumptive malaria treatment (Chitaka *et al*., 1998). Consequences include missed diagnosis of other illnesses and increased risk of morbidity (Reyburn *et al*., 2004). This underscores the need for intensified efforts at promoting the use of diagnostic approach to malaria treatment at the facilities, through regular education programmes for health workers (Zurovac *et al*., 2014). In addition, findings also suggest that low utilizations of diagnostic test was due to high patient load and hence, lack of waiting time for receiving the result of the test, which should be noted for improvement. The benefit of RDT in terms of rapid delivery of results addresses this problem. Patients were treated presumptively even with the availability of laboratory tools in the facilities. The proportion of patients who received antimalarial drugs with slide negative results was quite substantial, considering the enormous wastages that accompany this. This was justified by the prescribers for a number of reasons; (1) unreliability of laboratory results due to poor laboratory reagents, (2) RDT insensitivity (further studies may be required to explore this), and 3) unaware of laboratory results. Previous studies in the area have similarly reported unreliability of

laboratory results as a major cause of treatment of slide negative results, especially with RDT (Onwujekwe *et al*., 2009; Uzochukwu *et al*., 2010). Hence the study showed limited use of RDT compared to microscopy, even when it was available in both facilities, confirming the lack of trust of providers on RDT test results. This should worry policy considering the international focus on the use of RDT and implication for the goal of TTT policy (WHO 2010; Zurovac *et al*., 2014). Further investigation on the supply of quality RDT products for intervention is required, to ensure reliability of its results and the success of the test and treat policy. There is clear need for improved laboratory standards for malaria diagnosis, which can be achieved through a simple system of quality control. Continuous education of providers through regular seminars and workshops, on the benefits of confirmatory diagnosis cannot be over-emphasized. The extent of treatment of slide negative results and doctors responses to the issue calls for strategies to enhance their respect for negative results. There is need to enforce quality control to enhance reliability of diagnostic results. Benefits of confirmatory diagnosis and consequences of poor laboratory practices should be part of the regular updates to boost the confidence of prescribers in adhering to laboratory diagnosis.

Pattern of prescription in the study shows a clear preference for ACT, as the drug of choice for uncomplicated malaria at the two health facilities. This indicates high conformity to policy recommendation. The preference for AL, the policy first line drug at both facilities indicates providers' confidence in the efficiency of the regimen, as was confirmed by the questionnaire responses. The pattern appears similar to what obtained in the retail sector in the area, where DHAPQ was also found to be the second most prescribed antimalarial drug /ACT (Ezenduka *et al*., 2013). However, the greater dominance of ACT in this study, 95% compared to the retail sector 73%, is consistent with findings that public health facilities conform more to policy guidelines than the

retail sector (Ezenduka *et al.,* 2013). The retail sector is dominated by self-medication, which is characterized by high incidence of monotherapy use. The fact that the medical center uses more ACT than the tertiary health facility can be explained by the predominance of children and female cases at the later in which monotherapy was most prescribed for prophylaxis. Preference for AL is consistent with many study findings in both Nigeria and other African countries (Sears *et al*., 2013; Ezenduka *et al.,* 2013; Zurovac *et al.,* 2014). Similar to the retail sector, the use of AA which was the policy's alternative policy drug, was limited in this study. This was also explained by the reported safety concerns associated with the use of AA, especially in adults known to present with varying degrees of side effects (Ezenduka *et al*., 2013). The prescription of SP, mostly for prophylaxis in the study conforms to guidelines for its use in Intermittent Preventive Treatment in pregnancy and children (IPTp and IPTc). However, the use of AS and quinine is not in line with policy and therefore should be of concern.

The use of an average of four drugs per prescription in this study suggests high incidence of co-medication, going by the WHO recommendation of two to three drugs for developing countries. This gives an indication of poly-pharmacy in the studied facilities, increasing the risks of drug interactions, adverse drug reactions and high cost of treatment for the patients. Co-medication was higher at the medical center with five drugs per prescription. While poly-pharmacy may be justified in some cases by the significant number of co-morbidity, proportion of co-medication with vitamin preparations and antibiotics has implications for the safety and efficacy of antimalarial drugs. The fact that many of the prescriptions were on the basis of presumptive diagnosis, made this situation more critical, contributing to further wastages. There are concerns with co-administration of vitamin preparations with ACT in view of the antioxidant effects of vitamin compounds such as zinc, iron, vitamins C and E, on

artemisinin compounds (Oreagba and Ashorobi 2007; Ganiyu *et al*., 2012). This may lead to reduced availability and hence reduced efficacy of the agents, and in consequence, contribute to treatment failures and increasing resistance of the *Plasmodium*. It has been advised that if needed, vitamins preparations could be used after completing the ACT dose. The use of antibiotics in absence of co-morbidity also has implications for safety, in view of their known side effects, which may be wrongly attributed to the antimalarial drugs. Co-prescription with antibiotics occurs usually as 'a cover' for potential co-infection which would suggest that the prescriber is less confident of actual diagnosis, or to prevent subclinical infection becoming manifest (Dodoo *et al*., 2009). Hence, many prescriptions were secondary to diagnosed infections. Similar findings were reported from a study in Tanzania, for patients with a history of cough in the last 48 hours, for which antimalarials were prescribed even with negative results (Reyburn *et al*., 2006).

Although this study did not assess the appropriateness of antibiotics use, the likelihood of overtreatment with antibiotics, similarly reported in many other studies (Dodoo *et al*., 2009; Mtove *et al*., 2011) had led to the call for better diagnostic approach to non-malarial fevers and development of guidelines for management of such illnesses, which should be incorporated into malaria case-management trainings for health workers (Zurovac *et al*., 2014). This recommendation should be treated as priority to enhance the rational use of both antimalarial drugs and antibiotics.

The total cost of medication per prescription (including co-medication) in this study, which showed a median of US$7.48, is about 2.6 times higher than similar cost obtained for retail outlets, (US$2.90) in a study undertaken at about the same period in a neighbouring city (Ezenduka *et al*., 2013). This is consistent with reported higher cost

of care in public health facilities, due to the cost of more professional services (Chuma *et al*., 2009). This relatively higher cost of medication in public health facilities has remained as one of the major factors that inform the preference for the retail sector by a significant proportion of patients' population for malaria treatment (Chuma *et al*., 2009)]. The higher cost of medication at the tertiary health facility may be explained by the higher cost of expert care at a tertiary/ referral center.

Treatment practices varied notably between the two facilities, in terms of patients' characteristics. The p-value shows significance in many of the variables, indicating differences in prescribing practices of doctors between the facilities. These differences highlight the variation in prescribing cultures between similar facilities across the country, suggesting differences in dissemination of anti-malaria training information. The differences may also point to the levels of exposure to malaria treatment practices. Regular updates therefore provide opportunity for promoting appropriate malaria treatment practices in these health facilities (Sears *et al*., 2013). Indicators suggest better performances at the teaching hospital compared to the medical center, which is consistent with reports that prescribers in tertiary institutions tend to adhere more to national treatment guidelines (Gbotosho *et al*., 2009). The presence of more specialized doctors at the tertiary center, who are probably better exposed to information than those at the medical center, may explain this.

5.2.1 *Limitations of the study*

A few limitations are reported in this study. The selected sample facilities may reflect a potential bias towards public health facilities with high patient load. However, considering the health-seeking pattern for malaria treatment in Nigeria, where majority of cases are treated in the public sector compared to the private sector

(Onwujekwe *et al.,* 2005), selected facilities may be a likely representative of study population. Comprehensive diagnostic information was not collected due to inadequate documentation of patient diagnosis, to better inform the use of antibiotics and other concomitant medications. The study did not assess the appropriateness of prescription dosages and weights. However, most of the ACTs were administered according to age-related dose packages and hence most likely to conform to patients' ages and weights. While the study may be limited in scope in terms of the number of facilities studied, findings reflect, to a greater extent the practice pattern in the sector, considering the similarity in many ways, of the findings of previous studies carried out in the area (Meremikwu *et al*., 2007; Onwujekwe *et al.*, 2009; Mangham *et al*., 2011; Uzochukwu *et al.*, 2010) and other settings (Doodoo *et al*., 2009). However, the study needs to be scaled-up to strengthen the findings for enhanced policy interventions for improved malaria case management.

5.2.2 *Conclusion*

Eight years after the change in antimalarial drug policy, there is substantial compliance to policy on the use of ACT, as the first line treatment for uncomplicated malaria at the two health facilities. However, treatment practices are substantially characterized by limited use of laboratory diagnosis, relying mostly on presumptive treatment which leads to over-diagnosis, over-treatment, co-medication and lack of routine information on malaria treatment. These create the risk of developing parasite resistance and treatment failures, undermining the goals of malaria treatment policy. There is therefore a wide scope for improved diagnostic and treatment practices at the two health facilities, to enhance the efficiency of malaria case management. Targeted intervention through promotion and regular education of providers on appropriate

malaria treatment practices is imperative, based on recommended guidelines and the test and treat policy. This would surely improve confirmatory diagnosis and rational drug prescribing, to achieve the goals of malaria case management. There is also the need to ensure adequate supply of quality and sensitive diagnostic equipments, which is critical to the success of the 'test and treat' policy of malaria case management.

5.3 Treatment costs for uncomplicated malaria at a public/secondary health facility

Findings of this study suggest that the medical center generated a total annual economic cost of N28, 723, 723.15 (US$182, 954) for the treatment of uncomplicated malaria, during the study period, comprising both recurrent and capital expenditures. Personnel accounted for an overwhelming proportion of the total cost at 82.5%, followed by antimalarial drugs which contributed 6.6%. This translates to an average provider cost of N4, 943 (US$31.49) for treating one episode of uncomplicated malaria from the OPD. This amount however, represents the cost of treatment with antimalarial drugs alone. When the cost of co-medication is included, the average value increased to N5, 522.29 (US$35.23) per case. This cost represents about 20% of total hospital expenditure, indicating a significant proportion of the facility's annual budget.

The unit cost estimates falls within a range of similar studies documented in a systematic review by White *et al* (2011), for both financial and economic costs of treating uncomplicated malaria from a provider perspective. The economic cost range between $9.14- $37.99 per episode of uncomplicated malaria at a median cost $22.48. A study in Nigeria by Onwujekwe *et al* (2013) carried out in selected public primary health facilities in a rural setting, estimated a provider cost of US$30 per outpatient malaria treatment. However, this estimate represented only the recurrent component and

did not include the cost of capital items, reported to be US$133 per case. The unit cost estimates of this study are comparable with those of a study by Muheka *et al* (2004) in South Africa, which estimated a hospital cost of outpatient malaria treatment at between US$28.55 (baseline) and US$37.99 (post-intervention with ACT) per case. Similarly, a study in India by Gotgay *et al* (1998), estimated a hospital treatment cost of between US$15.64 and US31.87 per outpatient malaria. Like this study, these were hospital level cost studies.

Similar provider cost estimates in other African countries suggest a range of 3 – 6 US$ per case of uncomplicated malaria (Sicuri *et al*., 2013), indicating enormous differences compared with the result of this study. However, these studies did not report comprehensive analysis of the provider cost of malaria treatment, to enhance comparability. The analysis represented a 'snap short' analysis of provider cost data (Kone *et al*., 2004). Hence, when compared to other studies, the result of this study suggests a remarkable high unit cost of uncomplicated malaria treatment in the medical center. The differences can be attributed to various factors; ranging from methodological differences, composition of health personnel and the high rate of malaria prevalence in this study compared to previous studies. Differences in methodological approach (to cost analysis) has been reported in previous reviews (Chima *et al*., 2003; Goodman *et al*., 2003), affecting comparability of the study results. Most importantly, the studies were conducted in health centers which are lower level health facilities and therefore command less expensive services compared with hospital level facilities where health workers are paid higher salaries. Hence, hospital services cost more than twice those of health centers, mainly due to higher personnel and capital unit costs (Muheki *et al*., 2004). As a university health care center, with highly

subsidized services, there is a disproportionately high number of health personnel with higher salary scales compared with other public health care facilities in Nigeria which have fewer staff and lower salary scale. In this study, personnel cost averaged US$26 per case of uncomplicated malaria. This is considerably higher than the unit cost of US$3.98 reported by Wiseman *et al* (2006) in Tanzania, but close to the value of US$24.00 documented in the study by Onwujekwe *et al* (2013) in health centers.

In this study, a baseline malaria prevalence rate of 0.47 was used for the analysis, based on the proportion of malaria treatment in the facility. This is significantly higher than the values used in previous studies, which ranged between 0.15 and 0. 23 (Chanda *et al*., 2008). These studies assumed malaria prevalence rates in the study settings rather than the facility rate as used in this study. The high proportion of malaria treatment in this study may reflect malaria prevalence and high transmission rate in the area. However, the high incidence of presumptive malaria treatment reported earlier in the center (section 4. 2), increases the incidence of malaria treatment, thereby overstating malaria prevalence. As a result, there is overtreatment and wastages which significantly contributes to increasing cost of care. Thus, when the prevalence rate was reduced to 0.27 in sensitivity analysis, the unit cost estimate significantly dropped by 37% per case. To reduce cost and prevent wastages, there is a clear need to improve accuracy of treatment through effective laboratory confirmation of malaria cases, using microscopy or RDT. Laboratory diagnosis has been demonstrated severally to be cost-effective (Shilcut *et al.,* 2008; Uzochukwu *et al.,* 2009). The limited use laboratory diagnosis is reflected in the low proportion of laboratory costs to the total cost of treatment.

Furthermore, the high unit cost of this study may also suggest low-capacity or under-utilization of the hospital resources, based on the number of patient visits, or alternatively due to disproportionate use of personnel resources, either way indicating inefficiency of resource utilization. Strengthening the healthcare system through efficient utilization of resources will make it function more effectively and reduce overall cost to the provider and consumer (Onwujekwe *et al.,* 2013)

Drugs were other significant contributors to treatment cost, in addition to materials and supplies. Current use of ACT, which is many times more expensive than monotherapy would have contributed to increased cost of care. The high cost of treatment can therefore be reduced through more efficient approach to malaria treatment, by reducing the incidence of presumptive diagnoses to increase accuracy of treatment and reduce wastages.

This provider cost of treatment has implication on the burden of malaria treatment to the patient or households through cost transfers as professional fees. When viewed against the need to recover costs, especially from the private health facilities, this cost is transferred to the patient in the form of hospital/professional charges/fees, thereby increasing patients' out-of-pocket (OOP) expenses in addition to indirect costs of productivity losses. Added to the indirect cost of productivity loss, the cost would increase beyond the capacity of many low income patients, considering that majority of the population live below the poverty line (Ezenduka *et al.,* 2012). Onwujekwe *et al* (2013) reported household expenditures/cost of US$12.57 and US$23.20 for OP and IPD respectively. High facility cost of treatment contributes to making patients seek alternative sources of care for malaria treatment (Goodman *et al.,* 2000;), with

implications for quality. When viewed against similar costs and economic status of the population, this cost represents a significant proportion of GDP in low income settings. However, unlike in the private health facilities where cost recovery is expected to be full, health services are highly subsidized in public health facilities in Nigeria, leading to limited cost recovery measures (Ezenduka *et al*., 2012).

Further recognition of the burden of malaria in low income settings such as Nigeria has made many states to operate free maternal and child health (FMCH) services for a package of services including malaria treatments (Ezenduka *et al*., 2013; Onwujekwe *et al.*, 2013). This implies that the provider bears a significant proportion of malaria treatment (Onwujekwe *et al*., 2013). This high cost of malaria treatment therefore underscores the need for more donor support in the provision of malaria treatment services. Assistance has been provided by international donors such as the Global Fund, PMI, AMFm, PMI, DFID (SuNMaP) etc. Information like this present opportunity for the provision of relevant support in implementing malaria intervention programmes.

Generally, cost of malaria treatment (comprising household or health system costs) has been shown to be high in Nigeria (Onwujekwe 2000; 2013) and other low income settings of SSA where malaria is most predominant. The proportion of who pays for the treatment varies between the health system and the household, depending on the context. Previous studies in Nigeria have shown that cost of malaria treatment in health facilities is high but due to high level of indirect costs, and lack of financial risk protection, households bear greater proportions of malaria treatment costs (Onwujekwe 2013). This becomes catastrophic to some households in view of the low income status of the population. However, this is not the case in health systems where financial risk

protection is operated, as the provider bears most of the cost of treatment at the point of care (Onwujekwe 2013). Hence, some kind of financial mechanisms become imperative to protect the households from the catastrophic health expenditure and achieve the goals of malaria treatment and control. Even though Nigeria has since launched the national health insurance to provide the necessary buffer to health expenditure, the effect is yet to be felt as majority of the citizens still pay out of pocket. The provision of free maternal and child health (MCH) services in many states of the federation, for population groups mostly affected by malaria is commendable but the effectiveness and sustainability need substantial improvement. On the whole, improved efficiency in the utilization of resources will enhance the effectiveness of the health care system and reduced overall cost to the provider and consumer.

5.3.1 *Study Limitations*

The limited scope of this study may affect generalizability of the estimates in view of varying degree of hospital resources and treatment practices. This informed variation in key parameters of the study in the sensitivity analysis in order to reflect the variability of parameters in different settings and facilities, and assess the impact on the final/unit cost estimates. However, as reported in previous studies, the facility shares many characteristics with university health centers in particular, and other primary and secondary health care centers in Nigeria. Scaling-up the study would however strengthen the findings for enhanced relevance for policy. Although data on patients and household costs were not included, findings provide useful baseline information for designing future scale-up measures. Finally this study used a costing method that evaluated the cost of treating episodes on uncomplicated malaria through an outpatient clinic. Hence, there is need to exercise care when comparing the

estimates from other studies due to differences in costing objectives and methodologies. As a result direct comparison would not be straightforward. (Sicuri *et al*., 2013). *Economic costs* may not have captured all the donated items and volunteer staff due to lack of data. This explained why economic cost component in the study is close to the financial cost. Hence, recurrent items constitute a considerable proportion of the total cost, compared to capital cost. *Study site;* The study was conducted in a hospital setting such that the findings may not be true representation of the general population in the area, considering that health facilities in the general population is dominated by lower level facilities where most malaria cases are treated. This explained the cost findings which are much higher than those estimated in primary health facilities.

5.3.2 *Conclusion*

The study shows that the health system bears a significant proportion of malaria treatment costs. The health system cost of malaria treatment in the facility is very significant, constituting a considerable proportion of the healthcare expenditure, with opportunity costs in other service delivery areas. This has implications for effective malaria treatment in view of the transferred cost to the patients, already burdened by high indirect cost of productivity loss and OOP expenses. This emphasizes the huge economic burden of the malaria infection in the country, underscoring the need for continued government and donor agency support for malaria treatment and control in the country. To enhance efficiency in malaria treatment and control, there is need to strengthen the health care system to make it function more effectively and reduce the overall economic_burden of care to the provider and consumer. Results of this study

may help provide information to guide further studies as well as solicit appropriate funding allocation for malaria control.

5.4 Costs, effectiveness and cost-effectiveness of ACTs for the treatment of uncomplicated malaria

This study represents about the first comprehensive cost-effectiveness analysis of commonly used antimalarial drugs in Nigeria, since the introduction of current policy in 2005, on the use ACT for the first line treatment of uncomplicated malaria. Data were collected from routine practice setting to reflect real practice situation in determining the cost-effectiveness or economic justification of the use of ACTs, in view of their high cost of procurement compared to monotherapy. This was necessary to reflect the influence of real practice situation on the efficiency of malaria treatment using the drugs under evaluation. For instance, it was necessary to capture the actual costs and effects of the drugs under real practice situation given the influence of behavioral factors such as compliance and treatment practices. The cost and effect data were measured at 28-day treatment follow-up to adjust for a combination of re-infection and recrudescence of malaria. The efficacy data (cure rates), measured in terms of adequate clinical and parasitological response (ACPR) showed an average cure rate of between 79% and 85.5%, with AL and DHAPQ showing relatively the highest cure rates of 85.3% and 84.2% respectively. These efficacy findings are consistent with those of similar studies carried out in Nigeria that were not PCR-corrected. The cure rates of identified studies range between 81% and 87% for AL and ASAQ respectively (Meremikwu *et al.,* 2006; Bello *et al*., 2013), which were however carried out in children under 5. Analysis in children under 5 in this study could not be carried out due to limited data on children attendance, given the university setting of the study. However, there are no reasons to believe that the findings will differ, given the findings of previous studies (Wiseman *et*

al., 2006; Chanda *et al*., 2007, Davies *et al*., 2011). Hence, the randomized clinical trial results showed that the regimens are efficacious in clearing malaria parasites from the blood with little differences between them, in addition to being well tolerated in the course of treatment. Even though there were some little differences in their efficacies, measured in terms of ACPR, DHAPQ demonstrated highest effectiveness in terms of successfully treated cases, followed by AL. This was apparently due to the higher compliance rate of DHAPQ compared to AL which demonstrated a little higher efficacy. While DHAPQ was given in a once daily dose, AL dosing was more complex, impacting on patients' compliance and consequently effectiveness. Lower cure rates were obtained from ASAQ and ASSP. The findings were similar to those reported previously for Nigeria (Meremikwu *et al*., 2006; Bello *et al*., 2013). Efficacy of ASAQ is similarly affected by reduced compliance due to higher incidence of side effects which has also been reported in previous studies (Dodoo *et al*., 2009) and corroborated in earlier sections of this dissertation.

Results of the cost-effectiveness analysis showed the ICERs ranging between $4.10 and $6.45 per additional case of successfully treated malaria, for all the drugs evaluated. The ratios fall well below the threshold of $25 set for very cost-effective interventions for low income countries or three times their GDP by the WHO (WHO 2000). This demonstrates the cost-effectiveness of the ACTs in case management of uncomplicated malaria, even though they are more expensive than monotherapy. With enhanced accuracy of diagnosis, the cost-effectiveness of these agents increase in addition to enhanced savings. The study further shows that clinically and economically, DHAPQ with the lowest ICER of $4.10 per case treated compared with the other ACTs, is the most cost-effective option for the treatment of uncomplicated malaria. It is followed by

AL and ASAQ at $5.94 and $6.18 per successfully treated malaria case respectively. ASSP generated the least ratio close to ASAQ. However, further to the principles of cost-effectiveness analysis as described earlier, DHAPQ demonstrated primary and secondary dominance over AL, ASAQ and ASSP, by being cheaper and at the same time more effective by curing more malaria cases, effectively precluding them from further analysis. The results implied that DHAPQ will achieve more benefits, curing more malaria cases at a lower cost compared with any other agent (which means more than achieving more cases at the same cost). Hence, when compared with any other ACT at a given budget, DHAPQ will successfully treat more malaria cases while saving more money. Currently, the Nigerian antimalarial treatment guideline designated AL as the first line antimalarial drug of choice, with ASAQ as the alternative choice.

The cost-effectiveness results compare well with the results of similar studies in Africa. Wiseman *et al* in 2006 reported cost-effectiveness ratios of $5.26 and $6.66 for AL and ASAQ respectively, from a provider perspective in Tanzania. Similarly, from a provider perspective in Zambia, Chanda *et al*, 2007 documented a cost-effectiveness ratio of $4.10 for AL, compared to SP (Chanda *et al*., 2007). A study in Papua New Guinea (Davies *et al.*, 2011) in children under 5 reported cost-effectiveness ratios of $2.95 and $6.97 per additional treatment success for DHAPQ and AL respectively. A current study in Tanzania by Mori *et al* in 2014 showed that at $12.40 per DALY averted, DHAPQ was more cost-effective than AL which was dominated. Hence, this study reinforces the cost-effectiveness of ACTs in the case management of uncomplicated malaria, their high cost of procurement notwithstanding, and the fact that DHAPQ is the most cost-effective regimen. The implication of the adoption of ACT is the increased budget for malaria treatment as shown by the BIA. However, adopting DHAPQ as the

first line drug would mean that at a given budget, there will be more resource savings and greater number of malaria cases successfully treated. Resource savings will come from the prevention of further management of treatment failures with previous monotherapy, or reduced progression to severe malaria (Chanda *et al*., 2007).

As stated earlier, AL and ASAQ until now were the most widely used ACTs in Africa (Chanda *et al*., 2007), and AL has been found to be about the most effective and cost-effective brand by many studies (Muheki *et al*., 2004; Wiseman *et al.,* 2006; Chanda *et al*., 2007; Davies *et al*., 2011). They were however the earliest ACT regimen officially registered for first line treatment of uncomplicated malaria in Nigeria (MoH 2005). This study suggests that before now, policy may have been justified from economic viewpoint on the adoption of AL as the first-line drug compared to ASAQ, reserved as the alternative ACT, at least before the registration of the other alternatives, DHAPQ, ASSP and even ASMQ which is not part of this study. However, the study has demonstrated that given baseline data, DHAPQ is the most cost-effective ACT, dominating AL and the other agents. Findings suggest that even though the clinical effects of the drugs are similar in terms of their efficacies in curing malaria disease, the use of DHAPQ will cost lower, yielding greater resource savings when it is compared with AL and other regimens evaluated. In other words, at a given amount of resources, the use of DHAPQ will cure a greater number of people with uncomplicated malaria than AL and other ACTs.

The advantages of DHAPQ as the most cost-effective drug derive from the combination of two factors; compliance and cost. It is given once a day, with bioavailability that does not depend on fatty meals (Tarning *et al*., 2014). This is expected to enhance

adherence/compliance to treatment regimen which will in turn minimize wastages and improve treatment outcomes. In addition, the drug has a long elimination half-life which may prolong its prophylactic effect and in consequence reduce its future cost from recurrent infections (Pfeil *et al.,* 2014). The difference in ICER value between DHAPQ and AL, the closest and the other agents appear very large. DHAPQ is the cheapest of the ACTs. Comparatively, compliance with the AL regimen is relatively lower, apparently due to its relatively more complex dosing frequency, taken 12 hourly after the first day of first dose administration at the study site, and 8 hours later. At about the same compliance, DHAPQ advantage was highly reduced as the cost-effectiveness of AL was highly increased, because of the similarity in their efficacies. In addition AL requires fatty meals to enhance its absorption and hence efficacy. This is another major draw-back that may have limited the efficacy of AL. The fact that in many cases malaria episodes may be characterized by anorexia or loss of appetite, discourages the patients from eating, thereby limiting the absorption and hence effectiveness of the drug. Therefore, in situations where the drug is poorly absorbed the efficacy is compromised. Given the complex dosing of AL, requiring the need to take meals before administration of the drug, the regimen would benefit from supervised environment

The findings of this study seem to reflect the pattern of use of the antimalarial drugs in real practice, judging by the earlier findings of this dissertation (section 4.1 and 4.2) and previous studies in the area which have reported AL and DHAPQ as the most commonly used antimalarial drug regimens at both the public and private sectors (Onwujekwe *et al.,* 2009; Ezenduka *et al.,* 2013) and other African settings (Davis *et al.,* 2013; Sears *et al.,* 2013).

The study showed significant differences in the cost-effectiveness results, even though the efficacy measure was similar between the drugs. Sensitivity analyses demonstrated the robustness of the study findings, reinforcing the cost-effectiveness of the ACTs, and in particular DHAPQ as the most cost-effective regimen. Various permutations in the one-way SA of varied parameters did not alter the order of magnitude of the cost-effectiveness results, even though variations in some parameters such as accuracy of diagnosis, compliance and drug prices significantly influenced the CERs.

The results further support the superiority of the DHAPQ over other ACTs as the most cost-effective antimalarial drug. However, the effect of varying these parameters on the CER results was indicative. Of particular note is the effect of reducing diagnostic accuracy by 25% which considerably reduced the cost-effectiveness results (increased CERs) by up to 65%, indicating the implications of presumptive diagnosis which is highly associated with inaccurate diagnosis. Several studies, including the findings in section 4.2 of this study, have reported high incidence of presumptive diagnosis associated with significant inaccurate and inefficient malarial treatment and wastages in Africa (Reyburn *et al.,* 2006; Meremikwu *et al*., 2007; Uzochukwu *et al.,* 2010; Zurovac *et al*., 2014). Similarly, studies have since demonstrated the cost-effectiveness of laboratory diagnosis in malaria treatment (Goodman *et al.,* 1999; Shilcutt *et al.,* 2008; Lubell *et al.,* 2008; Uzochukwu *et al*., 2010). Significant savings are made as inaccurate diagnosis and over-treatment is avoided, improving the rational use of antimalarial drugs. This study has previously in section 4.3 documented substantial over-diagnosis of malaria in the study facility which impacted significantly on the high unit costs of treatment in the facility. This finding should provide evidence for improve malaria diagnosis and treatment. The findings reinforce the need to enhance adherence

to treatment guidelines which emphasizes accurate diagnosis and prompt treatment with effective antimalarial drugs.

The effects of drug costs and compliance also demonstrated the influence of drug prices and adherence to drug regimen on the cost-effectiveness of the antimalarial drugs. In a two-way SA, varying the price and compliance rate of AL made it more cost-effective compared with DHAPQ. This suggests that any policy measure to reduce the cost of drugs, such as the inclusion in donor programme, would make the product more cost-effective, similar to DHAPQ. This would apparently explain the popularity of AL as the most commonly used ACT in Africa (Reyburn *et al.*, 2006; Ezenduka *et al*., 2013), especially following the introduction of the AMFm initiative to reduce the costs of the ACTs and make them more affordable and accessible to the majority of the low income population in Africa. Extending this facility to DHAPQ as the most cost-effective option will therefore boost the advantage, especially with recent development in the market. To make DHAPQ more affordable and accessible, the European Medicine Agency (EMA) has recently given an approval to use the donor fund (Ubben and Poll 2013) to reduce the procurement cost of the drug to affordable maximum price of US$1or below per dose (Global Fund, 2013). Similarly, a new water-dispersible formulation of the drug (Eurartesim®) for children under 5 is being developed by the manufacturer, Sigma Tau in collaboration with Malaria for Medicine Venture (MMV).

5.4.1 *Policy implications of findings*

This study has demonstrated that case management of uncomplicated malaria using the ACTs represents extremely good value for money, in low income country such as Nigeria with high malaria transmission. Although current policy adopted AL as the

first line drugs, current CE information (which may have justified policy decision prior to the introduction of more ACTs), will require making DHAPQ, which has shown a superior result in this study, the policy first line drug. The finding implies that, given a fixed amount of money in the treatment of uncomplicated malaria DHAPQ will produce greater resource savings while curing more number of people than any other antimalarial drug currently registered for the treatment of uncomplicated malaria in Nigeria. This suggests that making DHAPQ the policy first line drug would make more economic or investment sense. This calls for the review of the current policy that adopted AL as the first line drug since introduction of the ACT (MoH 2005). The significant difference in the cost-effectiveness result between the two most cost-effective regimens makes the finding robust, justifying the review in policy, in order to save more resources for health providers while successfully treating more malaria cases. However, considering the determinants of cost-effectiveness, as shown in this study, choices will depend on factors such as compliance to treatment, prices of drugs and availability. Policy measures to modify these factors would apparently improve the cost-effectiveness of AL, making it the preferred choice. Changes in compliance to treatment and prices of the drugs were particularly indicative. Measures to improve compliance to AL treatment will enhance its cost-effectiveness; such as in improving the dosing frequency through development of once daily regimen, and possibly enhance the pharmacokinetic properties to improve absorption, without the need to be taken with fatty food. Technological techniques are now available that improve pharmacokinetic properties of drugs, although this may come at increased cost which may further increase the already high cost of procurement of the regimen. The current AMFm facility to reduce the cost of AL at affordable maximum price of $1 or below (Global fund), is

surely one measure that makes AL very cost-effectiveness. Although this facility has not been available to DHAPQ, recent approval to extend the facility to the regimen will be boost its cost-effectiveness.

5.4.2 *Limitations of the study*

There were some limitations of the study that need to be reported to better understand the findings and place them in true context.

Study site/Financial constraint: This study was limited to a single center study in a university setting, affecting the generalizability of the findings to the general population. The broadening of the study to more representative sample of health facilities would have improved the reliability of the results, but this was highly limited by lack of funding considering the nature of the study and the heavy financial burden and logistics required to finance quite a number of the activities, such as cost of reagents, transports, communication, supervision, monitoring and other contingent expenses

Study perspective: Due to lack of funds, data was not collected from the societal perspective to determine the impact of patient and family costs, and the indirect cost of loss of productivity due to malaria illness on the cost-effectiveness of the ACT. It is expected that given the greater reduction in malaria episodes by the ACTs, there would be resource savings generated in terms of gains from fewer re-treatments of failed cases, some of which may have progressed to severe malaria. However, this may not have affected the relative cost-effectiveness of the ACTs, based on the findings of previous studies, apart from determining the extent of resource savings (Wiseman *et al*., 2006).

Unit of outcome measure: Like in similar studies the cost-effectiveness outcome was measured in terms of cost per malaria case treated. However, evaluation of CERs using cost per disability adjusted life years (DALY) enhances comparison with the cost-effectiveness of alternative uses of resources, depending on specific context. DALY is a composite measure of health outcome which incorporates both premature death (quantitative) and morbidity/disability (qualitative), and this facilitates comparison with other interventions that improve the quality of life, as well as with those that save lives (Goodman *et al*., 1999).

Adherence to treatment assessment: Adherence to treatment was assessed by the use of pill count method which involved the use of number of tablets left unused in the sachet. The success of this method depends on what the participant is able to show to the investigators. The use of biological marker, based on the assessment of plasma concentration of drug after administration usually provides a more objective and accurate option. Under the method, information on the recent drug administration is readily obtained, which also takes into consideration factors such as mal-absorption, drug interaction and individual metabolic differences which may cause low concentration of the drug. This approach is however expensive and therefore limited by high cost. Hence, observational method was used in this study. Considering the importance of adherence in the efficacy of antimalarial drugs, it is important that adequate measures are designed to improve the use and efficiency of the drugs

Loss to follow-up, was a major draw-back to the clinical trial, considering the involvement of human subject in our environment which is highly characterized by poor cooperation and loss to follow-up. The study experienced a lot of loss to follow-up as a result of change of mind, loss of interest etc. This was however anticipated

during the sampling period in making provision made for over 30% provision for loss to follow-up during sampling.

CERs across groups: Given the likelihood of variability of efficacy/effectiveness and costs of drugs across different groups, such as age groups, men and women or between patients in different centers, the cost-effectiveness of the alternative ACTs would likely vary, which would provide necessary information to guide the choice of ACT across the respective category. Analysis of this study across age categories would have provided useful information to guide efficient use of ACT across the groups. However, data was very inadequate for the investigation and some of these analyses are possible in multi-center study, hence the analysis was limited to general assessment. Moreover, evidence from previous studies carried out in under 5 children in many African countries suggest similarity of cost-effectiveness results across the age groups (Davies *et al*.,2011; Mori *et al.*, 2014).

Reliability of study data: Poor documentation practices in the health center, such as in the Records, Stores and Accounts may have affected the reliability of some data. The results however reflect significantly, the true state of activities in the health care facility.

5.4.3 *Conclusion*

This study has demonstrated the cost-effectiveness of ACTs in the case management of uncomplicated malaria in areas of failed monotherapy due to resistance, even though they are more expensive than monotherapy. The study shows that the ACTs can be very cost-effective provided that they prescribed only to those who actually have malaria (accurate diagnosis). The study findings further justify the adoption of the ACT as a replacement for chloroquine and SP for the first line treatment of

uncomplicated malaria in Nigeria, following the change in antimalarial treatment policy in 2005. The study further shows that among the commonly used ACTs registered in Nigeria since policy change, DHAPQ is the most cost-effective regimens finding imply that, at a given budget, the use of DHAPQ will generate more savings and treat more malaria cases than AL and other ACTs in the treatment of uncomplicated malaria in Nigeria. This information provides evidence to policy for efficiency in the case management of malaria, to achieve the goals of reducing the burden of malaria disease in Nigeria. As cost effective drugs, these regimens may be more expensive compared to commonly used mono-therapy but are more effective, producing additional benefit, in terms of the potential to reduce the need for further treatment. The findings suggest that serious consideration be given to the review of the current ACT policy in Nigeria, to make DHAPQ the first-line antimalarial drug for the treatment of uncomplicated malaria, considering its superiority over AL, (the current first line drug) from the pharmacoeconomic perspective (from both clinical and economic point of view).

5.5 General Conclusion

This study has used pharmacoeconomic principles to analyze malaria treatment in south east Nigeria, to generate evidence for improved efficiency of malaria case management. Given the significant inefficiency in malaria treatment in the region, reflected in inappropriate practices and the use of monotherapies and ineffective antimalarial agents and subsequent wastages, this study has demonstrated the role of pharmacoeconomics in guiding the efficiency of malaria treatment in Nigeria. The study has shown that, ten years after the change in policy on the use of antimalarial drugs in Nigeria, the ACTs have become the dominant antimalarial drugs in use. However, availability and use of monotherapies and other ineffective agents remain significant at both the private and

public health facilities. Monotherapies and other ineffective agents are freely available and used mostly in the private health facilities. Treatment practices are highly characterized by significant inappropriate and irrational use of antimalarial drugs, including presumptive diagnosis and treatment which leads to significant wastages and high risks of parasite resistance to effective drugs and treatment failures. These practices occur with little or no regulation to ensure adherence to policy on the use and provision of malaria treatment. Consequently, treatment goals are undermined with increasing risks of development of parasite resistance to the new agents and widespread treatment failures.

Although several education and awareness programmes have been implemented at both the public and private sectors, targeting providers and the general public on the effective use of antimalarial drugs in line with policy guidelines, substantial inappropriate practices contrary to guidelines suggest a scope for further and continued education to ensure adherence to treatment guidelines for uncomplicated malaria with effective agents.

Using pharmacoeconomic principles and analysis, which combined information on the relative costs and effects of interventions, the study has demonstrated the cost-effectiveness of ACTs in the treatment of uncomplicated malaria, justifying their adoption to replace SP as the previous policy drug, as good investment. The study further demonstrated DHAPQ as the single most cost-effective agent for treatment of uncomplicated malaria, by successfully treating more patients and at the same time saving more costs, compared with other ACTs. The study showed that even though AL is by far the most widely and frequently used antimalarial drugs in the country, followed distantly by DHAPQ; the DHAPQ is the most cost-effective agent, treating more cases even at a lower cost compared to AL. The effectiveness and cost-effectiveness of the

ACT is however enhanced by accurate diagnosis of malaria parasite, adherence to treatment regimen and enhanced availability and affordability of the agent/s. The robustness of the study findings suggest that the adoption of DHAPQ as the policy first line drug for treatment of uncomplicated malaria will prevent wastages while treating more malaria cases, compared with other agents. To enhance malaria control and achieve the goals of reduced mortality and morbidity and eventual elimination, success of improved access through affordable/comparable pricing of antimalarial drugs need to be complemented with strengthened health care systems, better patient education on the use of ACTs, and further innovations in antimalarial drug therapy and accessibility. To improve the efficiency of malaria treatment in Nigeria and prevent wastages while treating more malaria cases, recommendations are made in the following sub-section.

5.6 Recommendations for the efficiency of malaria treatment in Nigeria

This study has generated important information that would require the attention of policy and health managers to inform the provision and utilization of antimalarial drugs to enhance the efficiency of malaria case management in Nigeria. The findings derive from factors and practice that impact on the efficiency of malaria treatment, such as the factors of efficacy (monotherapy, inappropriate practices, poor quality drugs), compliance/adherence and high cost of antimalarial drugs and treatment. Efforts at addressing these issues will therefore enhance the efficiency of malaria treatment. Consequently, the following recommendations are made for policy consideration to improve the efficiency of malaria treatment in Nigeria.

1. *Dihydro-artemisinin-piperaquine as policy drug*: Given the findings of this study and the robustness of the results, policy should consider the adoption of dihydro-artemisinin piperaquine (DHAPQ) to replace artemether-lumefantrine (AL) as first

line drug for the treatment of uncomplicated malaria in Nigeria. This would definitely result to enhanced efficiency of malaria treatment in Nigeria, through resource savings and increased success rates in malaria treatment

2. *Alternative ACTs*: Although DHAPQ is the most cost-effective agent, dominating other ACTs, it does not preclude the use of the alternatives. The fact that the product still produces some extent of failures indicates the need for the alternative regimens to possibly treat the failed cases. Hence, allocation criteria which would rely on the proportion of clinical success rates of the individual drugs can be used to determine availability of the drugs to complement DHAPQ as the preferred choice.
3. *Regular and up-to-date provider education*: Enhanced education of the providers on the use of ACT as the preferred drugs for treating uncomplicated malaria. The study has shown that many staff and workers in retail outlets lack adequate knowledge and incentive to provide appropriate malaria treatment services in line with guidelines. Even with the education packages provided in the past to accompany the AMFm roll-out, significant inappropriate practices still persist in the sector. Regular and up-to-date education of the providers is required to enhance the provision of appropriate malaria treatment in the country.
4. *Public education and campaign*; Evidence from the study show that the provision of malaria treatment in the private sector is mostly obtained through self-medication and demand for ineffective antimalarial drugs. The study also corroborated previous findings that most cases of self-medication are undertaken without diagnosis. There is need for continued and regular education of the general public on the use of ACT and emphasise the importance of diagnosis through continued education and campaign to promote the use of RDT to ensure accuracy in malaria treatment and reduced wastages

5. *Promotion of RDT use in retail pharmacies.* As part of the private retail sector which is the primary source of antimalarial drugs for uncomplicated malaria, retail pharmacies are responsible for majority of malaria treatment characterized by presumptive diagnosis and inefficiencies. This situation and the role of retail pharmacy in reaching a significant proportion of malarial patients (most people use pharmacies as their main source of malaria treatment) underscores the need to promote the use of RDT in these facilities as part of the efforts at reinforcing and enhancing laboratory diagnosis and confirmation of malaria parasite before treatment.
6. *Enhanced subsidy of ACTs*: High cost of effective antimalarial drugs (ACT) is clearly a major determinant of cost-effectiveness and efficiency in the treatment of uncomplicated malaria; in terms of affordability and compliance to treatment. Evidence from the study has shown high cost of the ACTs significantly reduced the cost-effectiveness and efficiency of treatment, in addition to the issue of equity of access. Although at current prices, the ACTs are very cost-effective compared with monotherapy, the prices remain expensive and unavailable to majority of low income population, who resort to the use of ineffective monotherapy for care, undermining the goals of the treatment. Hence, reduction of the prices through subsidies like the AMFm initiative will not only enhance the efficiency of the drugs but make them more affordable to the low income population. Although the AMFm initiative has achieved significant success in this area, more still needs to be done to reach greater number of the population, in view of current challenges ( )
7. *Improved regulation*: Regulation to enhance adherence to malaria treatment guidelines is key to achieving the goals of malaria treatment. Enhanced regulation is recommended at different levels

a. *Health facility level*: Health facility managers (hospitals, health centers etc.) should be encouraged to keep in place the process of ensuring that providers adhere to treatment guidelines, including making sure diagnostic tools for malaria treatment are available and regular workshops or updates carried out to encourage the use of test results and adherence to guidelines for treatment.

b. *Maintenance of quality of drugs*: There is also the need for regular monitoring of drug storage facilities (in particular medicine retail outlets) to ensure the maintenance of appropriate storage facilities for optimum drug quality. Poor storage condition will likely reduce the quality and hence efficacy of a drug which was of good quality at the time of manufacture.

8. *Drug Utilization Research/Studies:* The importance of drug utilization research cannot be under-estimated in monitoring the use of drugs in the public and private health sectors, to ensure the rational use of drugs. Hence, it is important to emphasise research in antimalarial drug utilisation in health facilities, to identify the possible challenges that militate against adherence to malaria treatment guidelines and identify opportunities for interventions to address the challenges. This is also part of the recommendations of Nigeria's Antimalarial Drug Policy (FMoH 2005).

9. *Recommendations for Further Research:* Enlarged scope or scale-up of the study beyond one facility/site and geographical area will be necessary to broaden the findings and make them more generalizable and useful for policy implementation. There is need for more comprehensive pharmacoeconomic analysis across population groups to truly reflect demographic differences and obtain comprehensive evidence to inform more effective policy for efficiency in malaria treatment.

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APPENDICES

APPENDIX I

NNAMDI AZIKIWE UNIVERSITY TEACHING HOSPITAL

P.M.B. 5025, NNEWI, ANAMBRA STATE, NIGERIA

Prof. S. N. Nnatu
MB, BCH, FWACS, FICS, FMCOG, FRCOG London
Chairman
Board of Management

B.O. Chukwuma
B.Sc., MA, MHA, AHA
Director of Administration/
Secretary to the Board

Prof. R. O. Ofiaeli
MBBS (IB), FMCS, FICS, FWACS,
Chief Medical Director/
Chief Executive

Dr. A. O. Igwegbe
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Our Ref: NAUTH/CS/66/VOL.4/62

Your Ref:

Date: 21st March, 2013

Ezenduka Charles Chukwuemeka,
Department of Clinical Pharmacy and Pharmacy Management,
Faculty of Pharmaceutical Sciences,
Nnamdi Azikiwe University,
Agulu Campus.

ETHICAL COMMITTEE APPROVAL

RE: PHARMACOECONOMIC EVALUATION OF MALARIA TREATMENT IN NIGERIA

I write to inform you that after due consideration of your revised research proposal, approval is hereby conveyed for you to commence the study.

The principal investigator is required to send a progress report to the Ethical Committee at the expiration of three (3) months after ethical clearance to enable the Committee carry out its oversight function.

.....
Prof. P.U Ele
Chairman, NAUTH Ethical Committee

.....
J.U. Ugochukwu (Mrs)
Sec., NAUTH Ethical Committee

APPENDIX II

Informed Consent Form

My name is Charles Ezenduka, a PhD student of the Dept. of Clinical Pharmacy, Fac. of Pharma. Sciences Unizik, Awka. I am conducting a study to evaluate the costs-effectiveness of antimalarial drugs in Nigeria, focusing on the south east of Enugu and Anambra states.
Malaria is reputed to be a major killer particularly in Nigeria where a child is reported to die of malaria every 45 seconds, making children the most vulnerable to attack. Huge funds are expended on treatment on daily basis due to wide range of available drugs at various prices, many of which are unaffordable to the majority of low income Nigerians. Information on the relative effectiveness of these drugs is lacking to justify their high costs of treatment, leading to wastages and increase risks of attacks. This study is being conducted to determine how effective the antimalarial drugs are in relation to their high cost to generate information to improve the use of quality and more effective antimalarial drugs without wasting money
You or your child is being recruited in this study because you satisfy the condition for eligibility which include having malaria, appropriate age, no contraindication to the use of any of the drugs being used in the study, you are not pregnant or breastfeeding. The study will require a finger prick of blood, data collection. You will be assigned to one of the antimalarial drugs. You are not required to make any payment as to the study. You are assured of strict confidentiality. Your participation is completely voluntary and you or your child is free to withdraw from the study at any point without penalty.
Once you are enrolled in the study, you will be required to follow the instructions on how to take the drugs as instructed and detailed on the envelope / avoid alcohol / smoking / any other precautions. You will be told about your visit schedules and you will have to report to the hospital. You are not allowed to take any medications other than the ones prescribed by your investigator. At each visit, the study physician will examine you. Blood tests will be carried out at each visit. 2ml of blood will be collected at each visit. Blood collection involves prick with a needle and syringe. The potential risks of providing blood may occasionally include pain, bruising, fainting or a small infection at the puncture site. These tests are essential to monitor your condition, and to assess the safety and efficacy

I have obtained permission for this study from the NAUTH Ethics Committee
Do you have any questions about the study? Do you agree to participate in this interview?

Yes ------- No ----------

---------- ----------

Signature of participant Date

Please Note: Participants will not be paid remuneration for participating in the study

APPENDIX III

ANTIMALRIAL DRUG TREATMENT SURVEY QUESTIONNAIRE

Dear Dr.,

As part of the PhD study on the cost-effectiveness of antimalarial drug treatment at both the NAUMC and NAUTH at Awka and Nnewi respectively, we are collecting data on the treatment pattern of the providers to enable comprehensive evaluation of the drug treatment. Your kind and sincere responses on your treatment approaches is highly appreciated. Your names are not needed, but try to help fill the questionnaire accordingly. Every information will be taken in confidence, in strict compliance to the study ethics and approved protocol

Thank you for participating

1. Facility ☐
2. Gender: Male ☐ Female ☐
3. Qualification: MBBS ☐ Consultant ☐ PhD ☐ Prof ☐ Others
4. Years of practice as a clinician ☐

MALARIA TREATMENT PRACTICES

1. What informs your use of antimalarial drug in your practise? Tick as many
    a. Laboratory confirmation of malaria parasite
    b. Symptoms of malaria parasite
    c. Based on experience with malaria infection
    d. Age of patient and symptom
    e. Need to preclude malaria infection
    f. All of the above
2. How frequently do you treat malaria cases without laboratory results?
    Always ☐, Sometimes ☐, Rarely ☐, Not at all ☐
3. Reasons for treatment of suspected malaria without laboratory test? Tick as many
    a. Confidence in ability to diagnose malaria clinically
    b. Intensity/severity of symptoms
    c. High patient load and lack of time for the result
    d. Previous experience with particular symptom/s
    e. All of the above
    f. None of the above
4. Do you request for laboratory test for malaria before treatment? Always ☐ sometimes ☐, Neutral ☐

5. Reasons for laboratory request for malaria confirmation. Tick as many
    a. Based on treatment guideline
    b. Symptoms not clear
    c. Availability of laboratory tools
    d. Resistant malaria
    e. Ease of access to lab services
    f. Basically routine

6. Reasons for antimalarial treatment of slide negative laboratory result
    a. Unaware of result before treatment
    b. Need to prevent malaria infection
    c. Unreliable laboratory test result
    d. Reliability of diagnostic tool used (Microscopy or RDT)
    e. Symptoms severe and classical
    f. Other, please indicate
    g. Does not treat without result

7. Which of the antimalarial drugs do you use most for uncomplicated malaria? **ACT**☐, Quinine ☐ Artemeter inj☐, Monotherapy ☐, Other ☐
8. Which of the antimalarial drugs do you use most for severe/complicated malaria? ACT☐, Quinine ☐ Artemeter inj☐, Monotherapy ☐, Other ☐

9. Please indicate, in order of preference the type of antimalarial drug you prescribe for uncomplicated malaria
    a. Artemether-lumefantrine (AL)
    b. Dihydroartemisinin-piperaquine (DHAPQ)
    c. Artesunate-sulphadoxine+pyrimethamine (ASSP)
    d. Artesunate-mefloquine (ASMF)
    e. Sulphadoxine+pyrimethamine (SP)
    f. Artesunate
    g. Artemether
    h. Quinine preparation
    i. Proguanil
    j. Amodiaquine

10. What factor/s inform your choice of antimalarial drugs prescription
    a. Laboratory confirmation
    b. Availability of the drug
    c. Cost of the drug
    d. Age of patient
    e. Side e

11. When do you normally prescribe the following antimalarial drugs; Sulphadoxine+Pyrimethamine (SP), Artesunate (AS) as monotherapy, Proguanil (Paludrine), chloroquine, etc
    a. Prophylaxis/prevention of malaria
    b. Resistant malaria
    c. Severe malaria
    d. In combination with ACT
    e. Known efficacy of the montherapy
    f. Malaria in children
    g. Not at all/doesn't use any

12. Please indicate your preferred choice of drug for prophylaxis (please order your preference, ie 1,2,3 etc)
    a. SP
    b. Artesunate
    c. Amodiaquine
    d. Quinine
    e. Proguanil
    f. ACT
    g. None

13. Are you conversant with any malaria treatment guideline? Yes☐, No☐ Name one
14. Does the hospital operate a malaria treatment guideline? Yes☐ No☐
15. Does the hospital undertake periodic updates/seminar on clinical/disease management programmes and guidelines? Yes☐, No☐

THANKS FOR YOUR RESPONSES

APPENDIX IV

MALARIA CASE REPORT FORM								Contact/Home Address: Telephone:								
Study site:		Full name:				Study Number:		Guardian's Name:								
Date of Birth/Age (Yrs):		Sex:	Weight (kg):	Hb/Ht: (Day 0)	Hb/Ht (Day 14):			Drug Name/Code				Total dose (mg base)				
	Day 0	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**	**Day 8**	**Day 9**	**Day 10**	**Day 11**	**Day 12**	**Day 13**	**Day 14**	**Day 28**
Date																
Danger signs																
History of fever																
Previous medication																
Temperature (Axillary)																
Parasite count																
Treatment (No. of tabs)																
Concomitant medication																
Reasons for exclusion or loss to follow up																
Observations																
Overall assessment		**ETF**		**LTF**		**Exclude**			**Loss to follow-up**							

Transport cost

APPENDIX V

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MALARIA JOURNAL

RESEARCH Open Access

Drugs use pattern for uncomplicated malaria in medicine retail outlets in Enugu urban, southeast Nigeria: implications for malaria treatment policy

Charles C Ezenduka[1*], Brian O Ogbonna[1], Obinna I Ekwunife[1], Mathew J Okonta[2] and Charles O Esimone[3]

Abstract

Background: Malaria treatment policy recommends regular monitoring of drug utilization to generate information for ensuring effective use of anti-malarial drugs in Nigeria. This information is currently limited in the retail sector which constitutes a major source of malaria treatment in Nigeria, but are characterized by significant inappropriate use of drugs. This study analyzed the use pattern of anti-malarial drugs in medicine outlets to assess the current state of compliance to policy on the use of artemisinin-based combination therapy (ACT).

Methods: A prospective cross-sectional survey of randomly selected medicine outlets in Enugu urban, southeast Nigeria, was conducted between May and August 2013, to determine the types, range, prices, and use pattern of anti-malarial drugs dispensed from pharmacies and patent medicine vendors (PMVs). Data were collected and analyzed for anti-malarial drugs dispensed for self-medication to patients, treatment by retail outlets and prescription from hospitals.

Results: A total of 1,321 anti-malarial drugs prescriptions were analyzed. ACT accounted for 72.7%, while monotherapy was 27.3%. Affordable Medicines Facility-malaria (AMFm) drugs contributed 33.9% (326/961) of ACT. Artemether-lumefantrine (AL), 668 (50.6%) was the most used anti-malarial drug, followed by monotherapy sulphadoxine-pyrimethamine (SP), 248 (18.8%). Median cost of ACT at $2.91 ($0.65-7.42) per dose, is about three times the median cost of monotherapy, $0.97 ($0.19-13.55). Total cost of medication (including co-medications) with ACT averaged $3.64 (95% CI; $3.53-3.75) per prescription, about twice the mean cost of treatment with monotherapy, $1.83 (95% CI; $1.57-2.1). Highest proportion 46.5% (614), of the anti-malarial drugs was dispensed to patients for self-treatment. Treatment by retail outlets accounted for 35.8% while 17.7% of the drugs were dispensed from hospital prescriptions. Self-medication, 82%, accounted for the highest source of monotherapy and a majority of prescriptions, 85.6%, was adults.

Conclusion: Findings suggest vastly improved use of ACT in the retail sector after eight years of policy change, with significant contributions from AMFm drugs. However the use of monotherapy, particularly through self-medication remains significant with increasing risk of undermining treatment policy, suggesting additional measures to directly target consumers and providers in the sector for improved use of anti-malarial drugs in Nigeria.

Keywords: Anti-malarial drugs, Utilization pattern, Artemisinin-based combination therapy, Private retail sector, Affordable Medicines Facility-malaria

Background

Although malaria treatment policies are well established, with countries in Africa adopting artemisinin-based combination therapy (ACT) as first-line treatment for uncomplicated malaria, problems on implementation in many settings still persist, undermining the goals of malaria treatment policy [1,2]. Understanding the extent of these problems is essential for generating evidence for policy interventions to improve implementation. In Nigeria, although ACT has been adopted for first-line treatment of uncomplicated malaria since 2005, evidence abounds on the improper use of anti-malarial drugs, such as the use of monotherapy and other less effective anti-malarial drugs, as well as inappropriate use of ACT [2]. This is especially so in the retail sector where studies have reported significant inappropriate use of anti-malarial drugs [3-6]. Since the introduction of ACT in many countries, reports have shown that while public sector malaria treatment has largely conformed to policy recommendations, the private sector is significantly characterized by inappropriate use of anti-malarial drugs [3-7]. The use of monotherapy, inadequate use of ACT, fake and adulterated drugs is widely reported, increasing the risk of treatment failures and development of drug resistance. Reports indicated limited access to the new agents in spite of a wide range of anti-malarial drugs in circulation. Since introduction, ACT remains the most expensive anti-malarial agent compared to commonly used monotherapy, with a median cost of between US$5 and $11per adult dose [8,9]. In recognition of the role played by the private sector and the drug supply chain on the high cost of anti-malarial drugs, the Global Fund for HIV/AIDS, Tuberculosis and Malaria (GFATM), in collaboration with malaria partners, introduced the Affordable Medicine Facility-malaria (AMFm) in 2009, to reduce the cost of supply and improve access to the utilization of quality ACT in low-income countries [10]. This was complemented with public campaigns and targeted provider-training to increase uptake of effective anti-malarial drugs. Furthermore, the use of artemisinin monotherapy poses concern about the development of resistance of malaria parasites to artemisinin derivatives when not used in combination with partner drugs in line with recommendations [2,11]. With a variety of anti-malarial drugs in circulation in retail outlets, there are issues with drug quality and accuracy of dosing as a result of wide variations in brand formulations and composition of active ingredients [2]. Irrational provision and use of anti-malarial drugs constitutes a major risk of increasing *Plasmodium* resistance to effective products and treatment, undermining the goals of malaria control. Factors that contribute to inappropriate use of anti-malarial drugs are influenced by demand for drugs by consumers, such as costs, lack of information about appropriate treatment and difficulties in assessing quality treatment by patients [12]. Similarly, providers in the retail sector are often influenced by their knowledge, financial incentives, competition, perceptions of patients' attitudes, and regulatory sanctions [12]. Okeke *et al.* went further to suggest that prescribing patterns are more likely to follow patient demands and expectations as well as profit motive rather than professional principles [3,5]. Adherence to anti-malarial treatment policy by providers and patients alike is essential to achieve the goals of the policy [4,13], and the retail sector as a major provider of malaria treatment is key in achieving the objectives. Since the greater number of malaria treatment services are provided through the private retail sector in Nigeria [14,15], as is the case in most other developing countries, the sector represents a greater risk of policy failure in view of significant inappropriate use of medicines. Appropriate attention to this sector is therefore critical to achieve the goals of malaria case management. Regular monitoring of drug utilization, as recommended by policy [16] becomes important when identifying opportunities for enhancing effective implementation of the ACT policy. This study aimed to analyse the current demand and utilization pattern of anti-malarial drugs in medicine retail outlets in Enugu urban, in relation to ACT policy in order to generate information for improving effective implementation of malaria treatment policy.

Methods

Study area and population

The study was conducted in the urban city of Enugu, capital of Enugu State, southeast Nigeria. The city is populated by 722,664 inhabitants according to the 2006 census. The population is predominantly Ibo ethnic group, who are mainly civil servants and businessmen, with a significant number of artisans. Of the 17 local government areas (LGAs) of the state, three make up the Enugu urban: Enugu East, Enugu South and Enugu North [2]. There are two tertiary health institutions, two secondary and about 15 primary health care facilities, as well as several private health care facilities, comprising private for-profit and private not-for-profit organizations. There are 236 medicine retail outlets, 75 pharmacies and 161 patent medicine vendors (PMVs). Retail pharmacies and PMVs are the two outlets licensed to sell and dispense drugs, including anti-malarial drugs. While pharmacies are licensed to dispense both prescription and over-the-counter (OTC) drugs, PMVs, operated by people who have no formal training, are licensed to sell only OTC medicines, even though they are known to deal with a wide range of drugs [3]. Similarly many pharmacies are either owned and/or manned by employees who received no formal/professional training. The study was undertaken in these two categories of retail outlets. Malaria is a major disease burden in the area with children and pregnant women the most vulnerable [17].

APPENDIX VI

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JOURNAL OF PHARMACEUTICAL POLICY AND PRACTICE

RESEARCH Open Access

Adherence to treatment guidelines for uncomplicated malaria at two public health facilities in Nigeria; Implications for the 'test and treat' policy of malaria case management

Charles C Ezenduka[1]*, Mathew J Okonta[2] and Charles O Esimone[3]

Abstract

Objectives: Adherence to treatment guidelines for uncomplicated malaria is critical to the success of malaria case management. Poor adherence has implications for increased malaria burden, in view of the risk of widespread parasite resistance and treatment failures. This study analyzed the diagnostic and prescription pattern for uncomplicated malaria at two public health facilities, south east Nigeria, to assess the current state of compliance to policy guidelines on the use of artemisinin-based combination therapy (ACT).

Methods: Retrospective audit of patients' records, treated for uncomplicated malaria, between the months of January and March 2013, was undertaken at two public health facilities. Demographics, diagnostic information, medication and cost data were extracted. Questionnaires were distributed to providers to assess their malaria treatment intent. Data from the facilities were analyzed and compared for similarities and systematic differences, and conformity to malaria treatment policy, in terms of laboratory diagnosis, use of ACT, co-medication and cost of medication.

Results: A total of 2,171 records of patients who had been treated for uncomplicated malaria were analyzed. Of these, 1066 (49%) were sent for laboratory confirmation of malaria using mostly microscopy, out of which 480 (45%) tested positive. 51% (1105) of the prescriptions was on the basis of presumptive treatment. 58% of slide negative results received antimalarial drugs. 93% of patients received ACT, with artemether-lumefantrin, AL (50.5%) as the most prescribed antimalarial drug. Monotherapy accounted for 7% of prescriptions, comprising mostly sulphadoxine + pyrimethamine, SP (46.5%) and monotherapy artemisinin, AS (29.2%). 97% of the prescriptions received at least one co-medication. Antibiotics were prescribed to 50% of patients. Overall, median cost of medication was N1160.00 (US$7.48 (US$0.19 - 267.87) per case, higher in tertiary than the secondary facility. There were significant variations in treatment practices between the two facilities.

Conclusion: Evidence suggests good compliance to policy on the use of ACT as first line treatment for uncomplicated malaria. However, there exists significant scope for improved diagnosis and rational drug use, to enhance accuracy of treatment, reduced wastages and risks of adverse drug reactions, in line with the goals of 'test and treat' policy of malaria case management.

Keywords: Uncomplicated malaria, Treatment guidelines, Policy adherence, Antimalarial drugs, Prescription practices, Health facility, Nigeria

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Introduction

Case management remains a major strategy for effective control of malaria, comprising diagnosis and prompt treatment with effective antimalarial drugs. In recognition of its high efficacy and potential for preventing development of parasite, ACT was recommended for the first line treatment for uncomplicated malaria in 2001 [1]. However, in view of the need to achieve efficiency in malaria treatment and enhance the goals of case management, the World Health Organization (WHO) recommended the test, treat and track (TTT) policy, which emphasizes improved diagnosis of malaria infection, prompt treatment with effective antimalarial drugs and regular monitoring through routine information system to ensure effective implementation [2,3]. Subsequently many malaria endemic countries in Africa adopted the policy, highlighting the importance of parasitological diagnosis using either microscopy or rapid diagnostic tests (RDTs) for malaria treatment, in all age groups and in all epidemiological settings [3,4]. This led to an increased supply of RDT. However, major challenge to implementation of policy guidelines has remained that change in policy recommendations does not always translate to immediate and effective change at health care provider levels and hence, inadequate quality case management at the point of care [5]. Consequently, inappropriate practices in the provision of malaria treatment have been reported among healthcare providers, from facilities in many malaria settings [5-8]. This constitutes non-adherence to treatment guidelines, contributing to undermining the goals of malaria treatment policy.

Adherence to policy guidelines by healthcare providers and patients is essential for achieving the success of this policy [3,9]. Studies in developing countries suggest that many years after the introduction of ACT, inappropriate prescription and use of antimalarial drugs persist, at both public and private health facilities [6-9]. With better exposure to information, it is expected that health workers in public facilities would have better access to malaria treatment guidelines, and be more likely to adhere to recommended strategy for uncomplicated malaria [7]. Although the public health facilities, more than the private sector, are known to largely conform to policy on the use of antimalarial drugs [10,11], reports indicate substantial inappropriate treatment practices, such as presumptive treatment, treatment of slide -negative results, co-medication (poly-pharmacy), use of low quality and expensive ACT and monotherapy [7-9]. These lead to wastages and inefficiency in the implementation of malaria case management, thereby increasing the risk of widespread resistance and treatment failures.

A study in Kenya [12] demonstrated how lack of adherence to treatment guidelines was associated with inappropriate prescription practices. The use of sub-therapeutic doses of drugs contributes to the risk of developing parasite resistance [13]. Drug regimens with long duration of treatment, such as monotherapy artesunate also contribute to poor adherence [8,14]. Concomitant medications further contribute to inappropriate prescription through polypharmacy, which increases risks of drug interactions, adverse drug reactions, non-adherence and treatment failures, in addition to high cost of care [11]. Presumptive treatment in health facilities have been shown to be widespread even with the availability of diagnostic instruments. Evidence also suggests frequent use of antimalarial drugs by health workers on slide-negative results [3,5,7,15]. Given the substantial misdiagnosis of febrile patients for malaria cases, using presumptive diagnosis, the use of antimalarial drugs under the current policy involving the use of more expensive ACT, represents substantial economic losses.

Several factors have been identified to be responsible for the non-adherence of prescribers to recommended guidelines. Inadequate supply of recommended drugs, unnecessary use of more expensive recommended drugs, continuous availability of monotherapy, staff shortages and high work load, as well as contradicting training messages that confuse workers [9,16], have been reported. These represent supply-side factors which limit effective implementation of malaria treatment policy. In Nigeria, although change in policy to the use of ACT was introduced in 2005 [17], inappropriate practices have been reported by many studies [7,10]. Understanding these issues is essential for generating information for implementing strategies to improve effective malaria treatment. This study was aimed to describe and assess the diagnostic and treatment patterns for uncomplicated malaria at two public health facilities in Nigeria, and determine current conformity to policy guidelines.

Methods

Study population

The study was undertaken in Anambra state, south-east Nigeria, with a total population of 4.18 million inhabitants by 2006 Nigerian census, considered as the second most densely populated state in the country (1,500 – 2000 persons per km^2). Divided into three senatorial zones, the state has 21Local government Areas (LGAs). The people, who are predominantly ethnic Ibos, are involved in farming as the main occupation, while a significant number is into trading and commerce. Malaria transmission in the state is perennial with incidence rate of between 10 – 35% and peak season coinciding with the rainy season, running between March and October every year. Children and pregnant women are the most affected by malaria. There are about 382 primary health centres (PHCs), managed by the LGAs, 22 secondary health facilities run by state government and two tertiary health facilities owned by the