Evaluation of Antimalarial Chemotherapeutic Practices and Outcomes in the Southwest region of Nigeria.

OLUWAFEMI O AKINSOLA

School of Environment and Life Sciences.

University of Salford, Manchester, UK

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DECLARATION

I certify that this thesis, which I submit to the University of Salford as partial fulfilment of the requirements of Doctor of Philosophy, is a presentation of my own research work. Wherever contributions of others are involved, every effort is made to indicate this clearly with due reference to the literature and acknowledgement of collaborative research and discussions. The content of this thesis has not been submitted for a higher degree at this or any other university.

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To my parents; Mr, and Mrs, Akinsola

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ABBREVIATIONS

ACT - Artemisinin Combination Therapy

AL – Artemether- Lumefantrine

AMFm - Affordable Medicine Facility for Malaria

API - Active Pharmaceuticals Ingredients

ATR - Attenuated Total Reflection

BCC - Behaviour Change Communication

BP - British Pharmacopoeia

CD - Chlorproguanil-Dapsone

COI - Cost Of Illness

DALY - Disability Adjusted Life Years

DDT - Dichlorodiphenyltrichloroethane

DHFR - Dihydrofolate reductase

ECBS - Expert Committee on Biological Standardization

ECM - Effective Case Management

ESR - Electron Spin Resonance

FDA - Food and Drug Administration

FMOH - Federal Ministry of Health

FTIR - Fourier Transform Infrared;

GFATM - Global Fund to fight AIDS, Tuberculosis and malaria

GRA - Government Reserved Areas

HIV – Human Immunodeficiency Virus

IR – Infrared Radiation

IRS - Indoor Residual Sprays

ITN - Insecticide Treated Nets

IVC - Integrated Vector Control

LCD – Least Significance Difference

LGAs - Local Government Areas

LLIN - Long Lasting Insecticide Nets

NAFDAC - National Agency for Food and Drug Administration and Control

NIMR - Nigeria Institute of Medical Research

NMCC - National Malaria Control Committee

NMCP - National Malaria Control Programme

NMR - Nuclear Magnetic Resonance (NMR)

NTG - National antimalarial Treatment Guideline

NTP - National antimalarial Treatment Policy

PBS - Phosphate Buffered Saline

PDB - Protein Data Bank

PF - Production Function Approach

PMVs – Patient Medicine Vendors

PP - Personal Protection

PPMVs - Patent Proprietary Medicine Vendors

RBM - Roll Back Malaria

RDT – Rapid Diagnostic Test

SEA - Southeast Asia

SES - Social Economic Status

SMOH - State Ministry of Health

SP - Sulphadoxine Pyrimethamine

SPSS - Statistical Package for Social Science

UNICEF - United Nations International Children's Emergency Fund**.**

WHO - World Health Organisation

WM - Wash Media

WTP - Willingness To Pay

ABSTRACT

With over 100 million cases of morbidity annually worldwide; control, elimination and eradication of malaria still remains a major challenge, particularly in sub-Saharan Africa. In some endemic countries, aggressive malaria control has reduced the malaria burden to a point where malaria elimination is becoming feasible. Nevertheless, sustained malaria control is crucial to prolong this downward trend for endemic countries. A major factor that affects the effective treatment of malaria is the lack of awareness of the recommended treatment guidelines and standardised protocols to routinely decipher the quality of the available drugs in the regions. Nigeria bears more than a quarter of the global burden of malaria, with 97% of the population at risk of the disease. The high rate of counterfeit and substandard drugs in Nigeria is therefore a barrier to effective case management of malaria. Therefore, this project proposes to qualitatively and quantitatively analyse chemotherapeutic practices and outcomes at an individual and community level in two selected states (Lagos and Osun) in the South West Region of Nigeria, in a bid to define barriers to effective case management.

A quantitative approach, involving the use of questionnaires was used to explore the current pattern of malaria treatment and antimalarial drug use in Osun and Lagos State communities, pharmacies and hospitals. The study also investigated the different socio-economic factors affecting treatment behaviours in the communities. Commonly used antimalarial drugs, including Artemether combination drugs (ACTs) were also randomly sampled from the communities to check for substandard and counterfeits using i*n-vitro* culture and FT-IR techniques.

In Lagos and Osun urban regions of the study, ACTs contributed to primary treatment choice (60% and 59% respectively), although this was often a result of self-medication (50% and 46% respectively). The majority of the people in the rural regions (74% in Lagos and 57% in Osun) preferred non-ACTs, with a high level of self-medication. A strong significant association was found between employment, salary earned, hospital treatment and adherence to recognised malaria treatment recommendations ($P < 0.001$) in both urban regions. However, in the rural regions, only hospital treatment showed a significant association to recognised malaria treatment recommendations ($P < 0.001$). Also, there was also a strong association ($P < 0.001$) for self-medication and place where antimalarial was purchased in the Lagos rural region which was not observed in the Osun rural region. The gender of client also had a significant association ($P < 0.001$) with the type of store where treatment was received in Osun rural area but not in Lagos rural area. Hospital data further shows that the rural

regions are the most challenging places to experience malaria infection. With already poor treatment practices in place, 81% of the suspected cases of malaria in Osun State rural area were confirmed positive. When compared to Lagos urban and Osun urban areas, where 65 % and 53% were confirmed to be positive, this shows the urgent need for improved intervention programmes to promote better treatment practices in the rural regions. However, low confirmation of malaria cases in the urban regions also illustrates the danger of self-medication that occurs when patients visit pharmacy stores and drug vendors since often no form of diagnosis is offered at these establishments prior to treatment.

While all of the ACT samples tested with Fourier Transformed–Infrared spectroscopy showed consistency with ACT reference drugs, some chloroquine (22%) and sulphadoxine-pyrimethamine (20%), did not show consistency with reference samples; particularly if acquired from the rural regions. Moreover, some ACTs, primarily if acquired from the rural regions (65%), showed low efficacy against *Plasmodium falciparum in vitro* cultured parasites compared to reference samples.

In addition to the ongoing intervention programmes creating awareness about effective malaria control and management of malaria, it is important to intensify efforts, especially in the rural regions, since this thesis work highlights that adherence to treatment practice is low and there is a high risk of treating malaria with either a counterfeit drug or a substandard antimalarial. Creating a platform for effective case management of malaria infections will require collaboration across international and national boundaries, bringing together intervention programs and influencing health policy.

CHAPTER 1: INTRODUCTION

1.1 Malaria: a historical perspective

Malaria's history extends to antiquity (Balint, 2001; Krungkrai *et al.*, 2010; Cox, 2002). Malaria or a disease similar to malaria has been around for more than 4,000 years. The name malaria was invented because the disease was thought to be associated with marshy areas giving rise to the misguided belief that it was caused by miasmas; the Italian '*mal aria*', or 'bad air' in English. Despite decades of effort to effectively eradicate or at the very least manage and control malaria, it remains one of the most devastating diseases to scourge the earth. Harrison (1978) postulates that human primate ancestors showed some symptoms of malaria even before they were recognised as humans. The symptoms of malaria were described in ancient Chinese medical writings and later found in clay tablets from Mesopotamia (2000 BC) and Egyptian papyri from 1570 BC (Cox, 2010). However, more trusted data and historical records of malaria started from Hippocrates in ancient Greece (400 BC), writings described the periodicity of malaria and the association between an enlarged spleen and people living in poor, marshy areas (Power, 2001). It was then widely identified in Greece by the 4th century BC, where it was responsible for the reduction of many of the city-state populations (CDC, 2010), It is described in the writings of Assyrian, Indian, Arabic, and European physicians (Carter and Mendis 2003; Cox, 2002). In addition to ancient symptomatic descriptions, recent empirical evidence has shown the existence of *Plasmodium falciparum* malaria in Egyptian mummies from the Fayum depression in 800 BC (Lalremruata *et al.,* 2013) and in amber preserved mosquitoes in the Dominican Republic from the mid-Tertiary period, 25-400 million years ago (Poinar, 2005). Extending through Darwinian descent, malaria has therefore had a huge impact on human exploration, colonisation and development of the world as we know it today (Harrison, 1978). More recently, malaria along with other diseases has had a huge impact on the world wars, where it is said that for every man lost in battle, another was lost to malaria. Frequently, the conditions of war encouraged the spread and resurgence of the disease (Cox, 2002; Harrison, 1978). The discovery of microorganisms by Antoni Van Leeuwenhoek in 1676 and Louis Pasteur and Roberk Koch in 1878-1879, incriminating microbes as the cause of infectious disease, triggered an intensified search for the actual cause of malaria (Cox, 2010). A French army surgeon named Charles Louis Alphose Laveran, in 1880, was the first person to observe the

presence of parasites in the blood of a soldier suffering from malaria (Cox, 2010); he later received a Nobel Prize in 1907. Laveran in his findings had concluded that there was only one *Plasmodium* species which he named *Oscillaria malariae*, however, William H. Welch in 1897 named the malignant tertian malaria *Plasmodium falciparum.* Italian investigators Giovanni Batista and Raimondo Filetti introduced the names *Plasmodium vivax* and *Plasmodium malariae* for two of the malaria parasite species, and in 1922 John William Watson Stephens named a fourth species *Plasmodium ovale.* Sachs and Melaney (2002) defined malaria as "*a protozoan infestation caused by the presence of the protozoa; Plasmodium in human or other vertebrate red blood cells, usually transmitted by the bite of infected female Anopheles mosquitoes that previously sucked the blood from a person with malaria"*. Researchers suggest that malaria probably spread to the world from Africa in the fifteenth century during slave trade and European voyages of exploration (Cox, 2010; Power, 2001; Olowe, 2015). Another hypothesis suggests that humans and apes both inherited *P. falciparum* infection from their ancestors and that the parasites co-evolved with their respective host for millions of years (Escalante&Ayala, 1994). However, this hypothesis has been refuted after the discovery of a large number of *Plasmodium* parasites from African apes; which clearly shows that *P. falciparum* infection is new for humans and infection must have occurred from a gorilla within the past 10,000 years (Sundararaman *et al.*, 2016; Loy *et al.*, 2017).

Although the disease is usually transmitted by the bite of a blood sucking female *Anopheles* mosquito, transmission can also rarely occur through blood transfusion, trans-placental routes or by sharing contaminated needles. Environmental and geographical factors closely regulate the prevalence of malaria with low incidence reported in temperatures below 16°C or above 30°C and altitudes higher than 2000m above sea level (Roberts & Matthews, 2016). There are four well-established species of the protozoa infecting humans; *Plasmodium malariae*, *Plasmodium vivax*, *Plasmodium ovale* and *Plasmodium falciparum* (the commonest and most deadly species). However, a non-human primate malaria known as *Plasmodium knowlesi* can also infect humans (Su, 2010). Almost all deaths are caused by *Plasmodium falciparum*, as it is the only species that can induce the aggregation of infected erythrocytes to other erythrocytes and to the vascular endothelium. *Plasmodium ovale* was identified as a species and named in 1922 after an oval-shaped malaria parasite was discovered in an infected erythrocyte in the blood of a patient (Collins & Jeffery, 2005) but not much is usually said about it because it has a relatively low infection rate (Su, 2010). Malaria is entirely

preventable if diagnosed early and treated in accordance with WHO recommendations, however, over the years, there has been a major increase in resistance acquisition to commonly used antimalarial drugs. Affum *et al.*, (2013) reports that a significant contributing factor to resistance acquisition is attributed to malpractices in prescription of the current antimalarial and the effects of a rapidly proliferating counterfeit drug industry in endemic areas.

1.2 The global impact of malaria

Malaria continues to be a dominant public health issue even in this millennium; globally, the disease is believed to be responsible for approximately a fifth of all causes of mortality due to infectious disease. This translates to over 100 million cases of morbidity, annually, worldwide and at least one death every 45 seconds, most of which (70%) are recorded in Sub-Saharan Africa (Jombo *et al.,* 2011; WHO, 2017). An estimated number of 3.3 billion people, about half of the world's population living in 109 countries, was mentioned by Hall *et al.*,(2009) to be at risk of contracting the deadly disease at a point in their lifetime. The WHO recorded 216 million cases of malaria worldwide (WHO, 2017), killing approximately 445,000 people every year (WHO, 2018); mostly children under 5 years of age residing in Sub-tropical African countries. In a similar context, it had previously been reported by Trampuz *et al.,* (2003) and Ishola *et al*., (2014) that *Plasmodium falciparum* is responsible for an estimated 300-500 million reported clinical episodes of malaria in Africa each year; with a significant proportion of people having poor access to public health facilities and thus resorting to self-medication and other unsafe methods of treatment. The extent of harm therefore caused by *Plasmodium falciparum* cannot be over-emphasised. However, the intense control measures implemented in collaboration with regional governments in endemic regions are beginning to bear fruit. The distribution of malaria vector species and their dominant global distribution can be seen in Figure 1.1 below.

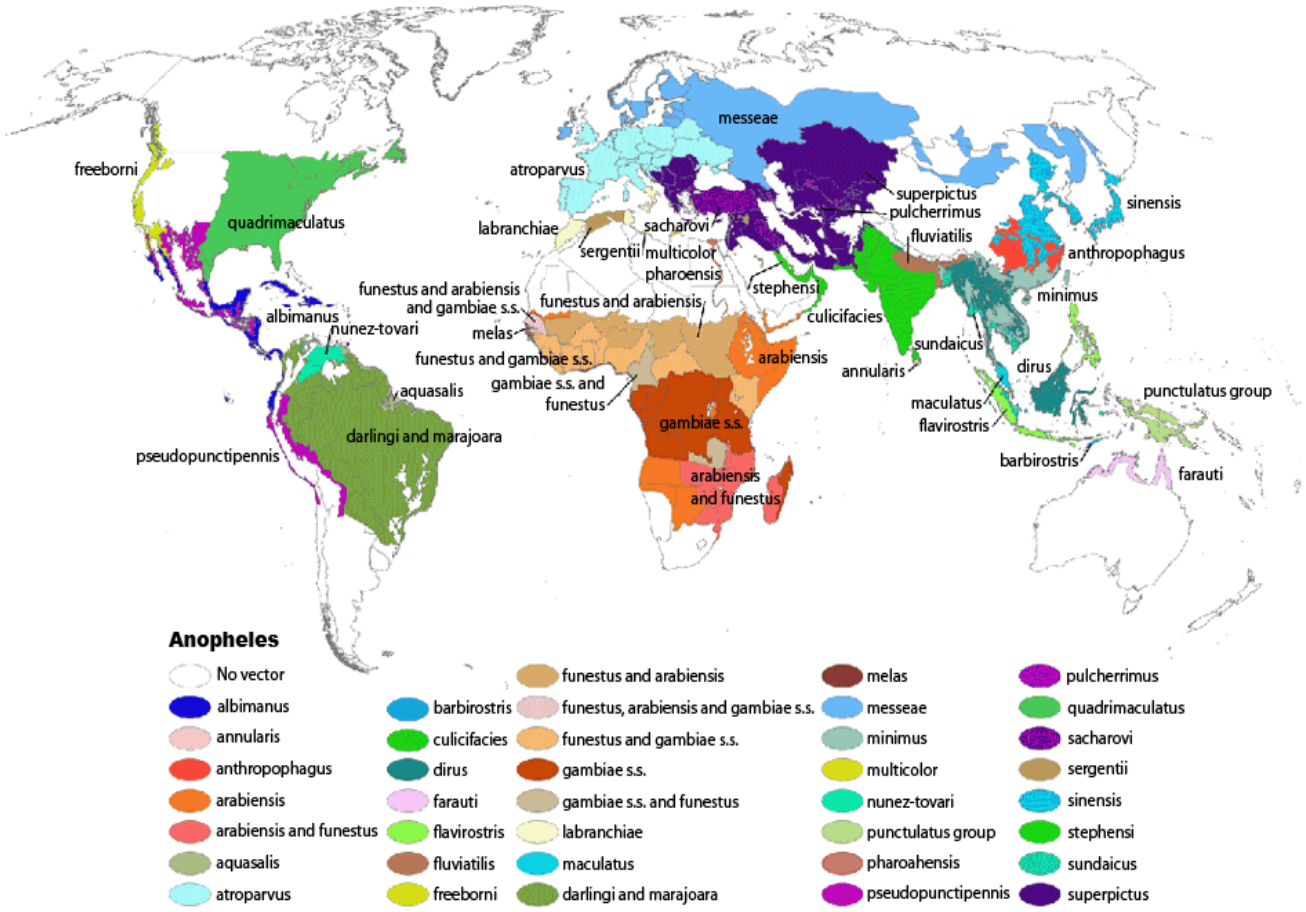


Figure 1.1: A map showing the regional distribution of malaria vector species and their dominant global distributions (CDC, 2015).

A recent estimation by WHO (2016), shows an estimated 37% decrease in the incidence of malaria between 2000 and 2015; bearing in mind that sustenance of the gains made in recent control initiatives will prove a challenge if the pace of resistance acquisition is left unchecked. In a more recent estimation in the WHO Report (2018), it was reported that the global success in malaria control has paused, after an estimated 5 million more cases of malaria was recorded in 2016 than 2015, and deaths caused by malaria stood at around 445,000. Also, Snow *et al*, (2005) found that about 515 million cases (range 300-660 million) of malaria were recorded in 2002; 50% higher than WHO's assessment in the same year and 200% higher for areas outside Africa. This may bring into question the accuracy of data and statistics reported by WHO from these countries. It should, however, be noted that African countries have very poor or sometimes non-existing methods of reporting cases of infectious diseases (including malaria), so differences in general statistics can be expected.

As already established, malaria is a complex disease that varies widely in epidemiology and clinical manifestations in different parts of the world (Chiyaka *et al.*, 2009); there are number of factors that are responsible for this variability, including regional chemotherapeutic practices, the type of *Plasmodium* responsible for the disease, climatic and environmental conditions of the location and the behaviour and level of acquired immunity of exposed populations. Most cases of malaria in 2015 are estimated to have occurred in the African region (88%), South-East Asia region (10%), and the Eastern Mediterranean region (2%). Similarly, it is estimated that in 2015 most deaths (90%) were in the African region, followed by the South-East Asia region (7%) and the Eastern Mediterranean region (2%) (WHO, 2015). 85% of the malaria deaths in Africa occurred in young children under 5-years of age. The disease also poses a significant risk to immunocompromised individuals and naïve travelers to malaria-endemic regions (Andrews *et al.*, 2014; Cohee & Laufer, 2017). Generally, the prevalence of malaria is associated with certain factors relating to suitable breeding habitats for the Anopheline vector including weather patterns, temperature, humidity (Kulkarni *et al.*, 2010). Although freshwater habitats are preferred by the mosquito vector, several species of mosquitos have adapted to brackish water habitats (Ramasamy & Surendran, 2016; Skiff & Yee, 2014). The predominant global distribution of the disease maps to sub-Saharan Africa, South East Asia, and Latin America. Figure 1.2 describes the incidence and mortality rate of malaria globally, over 15 years.

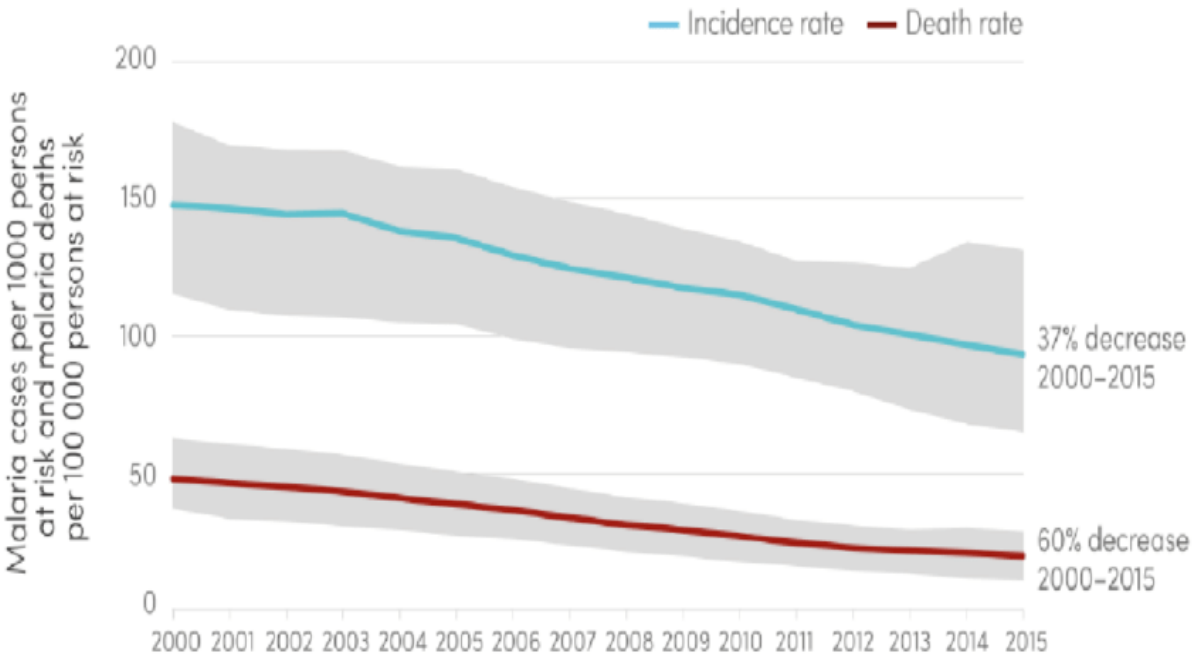


Figure 1.2: Global estimation of malaria case incidence and death rate (WHO, 2015). Showing a 37% decrease in incidence rate and 60% decrease in mortality rate between 2000 and 2015.

1.3 Aetiology of malaria

Malaria is a life-threatening parasitic disease that is transmitted by the bites of female *Anopheles* mosquitoes already infected with *Plasmodium* species. Balaji *et al.,* (2014) aptly describes malaria as an ancient, seasonal, periodic fever. The natural life cycle of malaria involves the *Plasmodium* parasite infecting two hosts; human and female *Anophel*es mosquitoes. Playfair (2004) describes the *Plasmodium* life cycle as complex and beyond imagination; adding that the successive morphologically unique stages in the mosquito gut, salivary glands, human blood, liver and repeating asexual cycles through the red cell makes it difficult to develop a vaccine against it. The *Plasmodium* life cycle (Figure 1.3) starts when an infected female *Anopheles* mosquito injects the parasites in the form of sporozoites into the bloodstream while feeding on a human. The sporozoites remain in the blood briefly (30 minutes) until they invade the liver where the hepatic stage of the parasite's life cycle is initiated by invading hepatocytes. Within the hepatocytes, they undergo a phase of asexual multiplication and differentiate into schizonts containing thousands of merozoites which rupture and target the red blood cells, initiating the cyclic asexual reproduction phase in red blood cells (it takes between 5-15 days before the release of merozoites into the bloodstream). The merozoites in the erythrocytes produce rings and trophozoites, which further divide to produce schizonts with more merozoites. It then takes about 48-72 hours for the red cells to rupture and release the merozoites which in turn attack other red blood cells and begin another asexual cycle. This process continues and at a point, some asexual merozoites develop into male and female gametocytes. Female *Anopheles* mosquitoes then pick these infective sexual forms of blood stage parasites (male and female gametocytes) during a blood meal. Within the mosquito, the gametocytes develop into male and female gametes, fertilization later occurs and a motile zygote (ookinete) is formed within the mosquito's gut; the beginning of a process called sporogony. The ookinete transforms into an oocyst and burst to release sporozoites into the celeriac cavity of the mosquito. Sporozoites move to the mosquito's salivary glands; and when the female *Anopheles* mosquito takes a blood meal from another human, the sporozoites are injected and the cycle re-establishes. Table 1.1 shows the different *Plasmodium* species in man, and disease features.

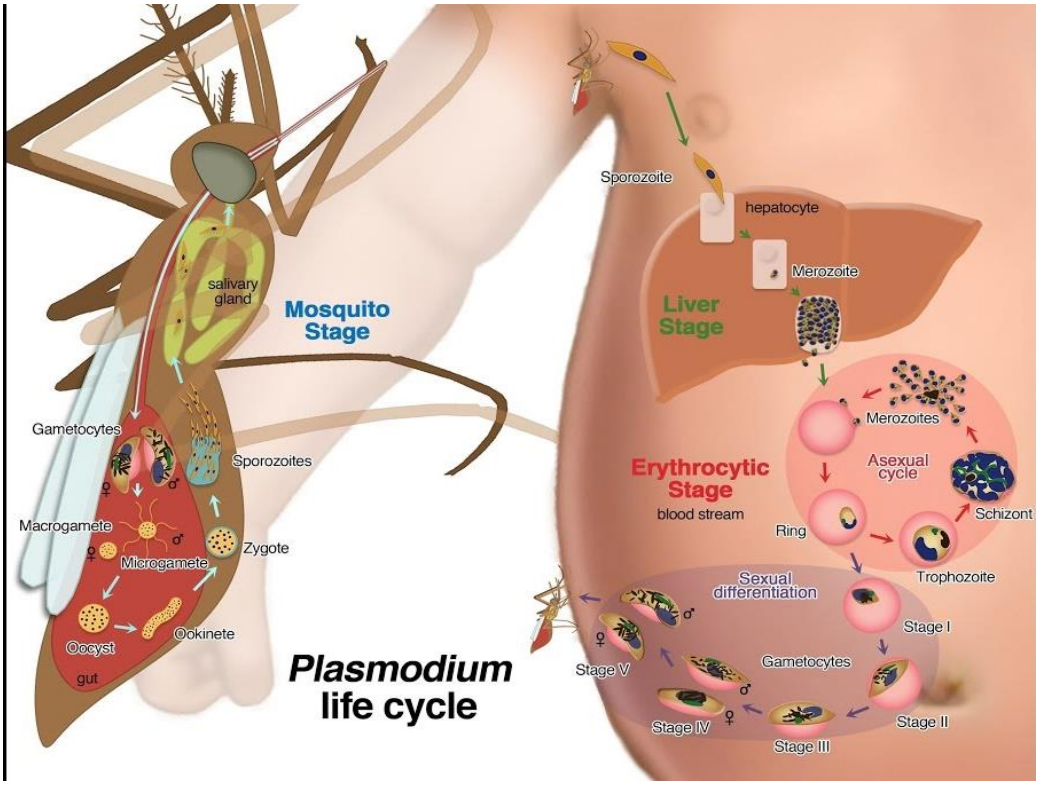


Figure 1.3: Malaria parasite life cycle showing the parasite development in the hepatic erythrocytic and mosquitoes stages (Biamonte *et al.*, 2013).

Table 1. 1: Malaria parasites of man (Playfair and Bancroft, 2004).

Species	Liver stage	Blood cycle and fever peaks	Disease features
P. falciparum	6-14 days	48hr (‘tertian’)	Major complications; may be fatal (Cerebral malaria)
P. vivax	12-17 days	48hr	Seldom fatal
P. malariae	13-40days	72hr (‘quartan’)	Nephrotic syndrome
P. ovale	9-18days	50hr	Rarely severe/fatal

1.4 Clinical signs and symptoms of malaria

Malaria parasite infection may result in different forms of symptoms, from absent or very mild symptoms to severe disease and even death (Bartoloni & Zammarchi, 2012). Therefore, malaria has been categorised as severe (complicated) and uncomplicated. The good news is that malaria is curable if the disease is diagnosed early and appropriately and treated with a recommended antimalarial. As mentioned by Mackintosh *et al.*, (2004), the majority of malaria cases present as generic febrile illnesses can be easily controlled by either antimalarial treatment or, eventually, by host responses. All the clinical symptoms associated with malaria are caused by the asexual erythrocytic or blood stage parasites (Autino *et al.*,

2012; Mackintosh *et al.,* 2004). When the parasite develops in the erythrocyte, a lot of known and unknown waste substances such as hemozoin pigment and other toxic factors accumulate in the infected red blood cell. These are dumped into the bloodstream when the infected cells lyse and release invasive merozoites. The hemozoin and other toxic factors such as glucose phosphate isomerase (GPI) stimulate macrophages and other cells to produce cytokines and other soluble factors which act to produce fever and rigors and probably influence other severe pathophysiology associated with malaria (Lamikanra *et al.,* 2009). Macrophages and endothelial cells are then stimulated by these products to produce cytokines and inflammatory mediators such as tumour necrosis factor (TNF), interferon-γ, interleukin-1 (IL-1), IL-6, IL-8, macrophage colony-stimulating factor, and lymphotoxin, as well as superoxide and nitric oxide (NO) (Chakravorty *et al.,* 2008; Mackintosh *et al.,* 2004). The systemic manifestations of malaria such as headache, fever, rigors and other severe pathophysiology complications have been largely attributed to the various cytokines released in response to these parasites and red blood cell membrane products (Clark *et al.,* 2006). In addition to these factors, the plasmodial DNA is also highly pro-inflammatory leading to the production of cytokines and fever (Mackintosh *et al.,* 2004).

1.4.1 Uncomplicated Malaria

The period between the time of infection and when the parasite becomes detectable in the blood is called the prepatent period, while the period from the time of infection until the onset of malaria symptoms is termed the incubation period. The incubation period can be affected by a number of factors including parasite species, transmission type, degree of previous immune status of the host, the chemoprophylactic use of antimalarial drugs, and probably the density of parasite inocula. The shorter incubation periods (9-14 days) are observed most frequently with *P. falciparum* and *P. vivax*, and the longer ones (18-30 days) with *P. malariae* (Bartoloni & Zammarchi, 2012) with incubation period ranging from 9 to 30 days in all species. The most common symptoms that is observed in all the different malaria species are nonspecific and mimic a flu-like syndrome. Indeed, hallmark of malaria is fever. Up to two days before the onset of fever, prodromal symptoms such as headache, anorexia, nausea, vomiting, lassitude, dizziness, aching joints and muscles, backache in the lumbar and sacroiliac region and a sense of chillness may be experienced. Fever is usually irregular at first and the temperature rises with shivering and mild chills. Then after a few days, fever tends to become periodic. The classical malaria paroxysm presents three stages: a cold stage, followed by a hot stage with a terminal sweating stage. At the physical examination,

splenomegaly may be present during the acute attack but is more commonly observed after the second week. The liver may also be enlarged and palpable (Bartoloni & Zammarchi, 2012). In case of *P. falciparum* infection, if uncomplicated malaria is not promptly treated, the disease can quickly progress to severe malaria (Bartoloni & Zammarchi, 2012).

1.4.2 Complicated Malaria

Severe malaria has been recognized as essentially two major disorders with relatively simple underlying pathogenesis for many years. Severe anaemia caused by destruction of red blood cells and cerebral malaria as a result of the destruction of small vessels of the brain by sequestered parasite (Mackintosh *et al.,* 2004). In recent years, severe malaria has been re-recognized as a complex multi-system disorder that presents with wide ranges of clinical features (Bartoloni & Zammarchi, 2012; Mackintosh *et al.*, 2004). According to the most recent definition by WHO, in a patient with *P. falciparum* infection and no other clear symptoms, the presence of one or more of the clinical or laboratory features indicated in Table 1.2, categorizes the patient as suffering from severe malaria (Bartoloni & Zammarchi, 2012; Farrar *et al.,* (2014). This definition has been proposed to assist clinical and epidemiological descriptions as progression to these complications can be rapid and fatal. Accordingly, a malaria patient must be assessed and treated urgently and rapidly (Bartoloni & Zammarchi, 2012; Farrar *et al.*, 2014; Mackintosh *et al.*, 2004).

Table 1. 2: Clinical features of malaria and possible mechanisms for the disease (Bartoloni & Zammarchi, 2012).

Syndromes	Clinical features	Disease mechanisms
Severe anaemia	Shock; impaired consciousness; respiratory distress	Reduced RBC production (reduced erythropoietin activity, pro-inflammatory cytokines); increased RBC destruction (parasite-mediated, eythrophagocytosis, antibody and complement-mediated lysis)
Cerebral complications (Cerebral malaria)	Impaired consciousness; convulsions; long-term neurological deficits	Microvascular obstruction (parasites, platelets, rosettes, microparticles); pro-inflammatory cytokines; parasite toxins (e.g. GPI)
Metabolic acidosis	Respiratory distress, hypoxia, tachypnea; acidaemia; reduced central venous pressure	Reduced tissue perfusion (hypovolaemia, reduced cardiac output, anaemia); parasite products; proinflammatory cytokines; pulmonary pathology (airway obstruction, reduced diffusion)
Other	Hypoglycaemia; disseminated intravascular coagulation	Parasite products and/or toxins; pro-inflammatory cytokines; cyto-adherence
Malaria in pregnancy	Placental infection; low birth weight and foetal loss; maternal anaemia	Premature delivery and foetal growth restriction; placental mononuclear cell infiltrates and inflammation; pro-inflammatory cytokines

1.5 Malaria chemotherapy

One of the most important and popular methods of controlling malaria is by chemotherapy. Most malaria control strategies today depend on the use of safe and effective drugs, as they have done for decades (Winstanley, 2006). Although, Mugatroyd (1952) described malaria chemotherapy as complicated, being that no antimalarial then was regarded as therapeutically effective against all stages of human malaria; studies have shown that there has been a great improvement to malaria chemotherapy all over the world (Na-Bangchang & Karbwang, 2009; Nigussie *et al.,* 2015). To date, malaria treatment/chemotherapy has relied majorly on chemically related drugs that belong to five classes of compounds:

- 4-Aminoquinolines: for example, Chloroquine, Quinine, Mefloquine, Amodiaquine and Halofantrine,
- 8-Aminoquinolines: for example, Primaquine
- Antifolate compounds: for example, Pyrimethamine, Proguanil, Dapsone, and Sulphadoxine.
- Artemisisnin and derivatives: for example, Artemisinin, Artemether, and Dihydroartemisinin.
- Hydroxynaphthoquinone: for example, Atovaquone (Schuck, 2013).

Most of these drugs used to treat malaria target the erythrocytic stage of the parasite; however, some also target the hepatic stage as well (Santos &Torress, 2013). Drugs from these three groups were/are used as monotherapy and can also be combined with each other depending on patterns of resistance already observed in particular regions. It is very important to understand that the success of malaria chemotherapy depends on the successful interaction of the three parties involved in transmission, i.e. the malaria parasite, the human host, and antimalarial drug. An effective malaria treatment using antimalarial drugs depends on the interaction between the human host and antimalarial drug, i.e., 'pharmacokinetics' and 'pharmacodynamics' and also the interaction between the antimalarial drug and the parasite i.e., 'drug resistance' and 'selective toxicity'. The main control of malaria in Nigeria is through chemotherapy, which leads to the importance of treating every case of malaria appropriately; including accurate diagnosis and effective treatment. For this reason, the use of counterfeit drugs also needs to be checked, having in mind that the use of these substandard drugs does not only affect the health of clients, it also increases the resistance of the malaria parasite (Bassat *et al.*, 2016; Nayyar *et al.*, 2012).

1.5.1 4-Aminoquinolines

The aminoquinoline drugs are among the most important antimalarial drugs. Most drugs from this group target the blood stage of the parasite's life cycle (Nigussie *et al.*, 2015) although some drugs also target the hepatic stage of the parasite's life cycle. Quinolones are able to form a complex with haem in the parasite's food vacuole, thereby preventing its polymerization into non-toxic haemazoin (Schlitzer, 2008). The haem which is then released builds up to poisonous levels so that it kills the parasite with its own toxic waste. The discovery of quinine is considered the most remarkable medical discovery of the 17th century (Achan, 2011) and the use of quinine to treat malaria was the first time a chemical compound was used to treat an infectious disease (David *et al.*, 2005). Quinine is an extract from the

bark of cinchona tree native to South America and it has been used to treat malaria since the 1600s. The cinchona tree is a rich source of medicinal alkaloids (Renslo, 2013). Quinine is used in malaria-endemic countries as a treatment for severe life-threatening malaria and also as a therapy to malaria parasites that have shown resistance to other available antimalarial drugs (Kone *et al.,* 2012). Its use as a monotherapy has shown significant resistance (Renslo, 2013). Other alkaloids apart from quinine include quinidine, cinchonidine and chichonine; all these alkaloids are effective against malaria. Between 1968 and 1986, the efficacies of these four alkaloids were tested and compared in 3600 patients, and results show that these four alkaloids had comparable efficacy rate of about 98% (Achan, 2011). For a very long time, quinine was the mainstay of treatment until other synthetic antimalarials became available. Chloroquine was discovered in 1934 by Hans Andersag and his group at Bayer AG (Thomé *et al.,* 2013; Mushtaque and Shahjahan, 2015). However, chloroquine use did not start until the 1940s and because it showed great efficacies it was extensively used across all endemic countries (Abdi *et al.,* 1995). From 1947 onwards chloroquine became the treatment of choice until recently (Saxena *et al.,* 2003), in fact it was the only drug used for long periods of time in some areas in Africa (Mushtaque and Shahjahan, 2015) due to it being cheap and effective, with acceptable side effects (Thomé *et al.,* 2013). After the second world war, chloroquine was the first-line of treatment against *P. falciparum* malaria and a lot of investment went into a mass drug administration in the Global Eradication Campaign launched by the WHO in 1955 (Severini *et al.,* 2015).

There was a blow to the hope of effective treatment when resistance to chloroquine was observed. In the late 1980s, chloroquine resistant *P. falciparum* was noted on the Thai-Cambodian border and in Colombia (Pickard *et al.,* 2002; Wernsdofer *et al.,* 1991). The widespread use of quinine in Thailand in the early 1950s is a suspected reason for the development of chloroquine resistance (Wernsdofer *et al.,* 1994). In Africa, the first chloroquine resistance episode was documented in 1978 at the eastern part of the continent. However, the resistance spread to the central and southern part and by 1983 it was documented in West Africa (Wongsrichanalai *et al.,* 2002). Chloroquine remains the treatment of choice for *P. vivax, P. malariae, P. ovale* and uncomplicated *P. falciparum* malaria in some geographical areas where this drug can still be trusted. High resistance of *P. falciparum* to chloroquine treatment was the main reason a whole lot of countries in Africa switch from chloroquine to SP as first-line treatment or even sometimes a combination of chloroquine and SP. However, most people in African countries still make use of chloroquine

as monotherapy against the WHO's recommendations of ACTs. This is usually due to chloroquine being cheap and well tolerated (Na-Bangchang *et al.,* 2009), and also a higher cost of quinine in combination with other drugs or ACTs (WHO, 2010). Achan *et al.,* (2011) claim that by 2009, 38 African countries had made quinine-drugs, especially chloroquine, their first-line treatment for uncomplicated malaria, and 31 countries made quinine-drugs a second-line treatment for uncomplicated malaria. Further 32 countries made quinine-drugs a first-line treatment of malaria in the first trimester of pregnancy.

1.*5.2* Antifolates

After the long use of chloroquine to treat malaria, the rampant resurgence of the disease was stalled by the discovery of another class of antimalarial drugs, the antifolates. This drug group was originally developed for the treatment of tumours; however, due to the success recorded antifolates were soon applied to other systems of rapidly dividing cells, such as bacteria and parasites. Proguanil was the first antifolate shown to be effective against *Plasmodium,* in 1945 during the Second World War (Nzila, 2006). Antifolate drugs are one of the first synthetic drugs used as antibiotics or antimicrobials, and antifolate combination such as sulphadoxine-pyrimethamine (SP) has been used to treat malaria (*falciparum*) for more than half a century (Venkatesan *et al.,* 2013). Since the early 1960s where significant evidence of resistance to chloroquine was observed, rate of morbidity and mortality has also increased (Winstanley, 2001). Antifolate drugs are useful antimalarial because of their inhibition to folate metabolism of the parasite, both in the synthesis and use of folate cofactors (Yuthavong, 2013). Antifolate combination therapy uses a combination of dihydrofolate-reductase inhibitors (pyrimethamine, trimethoprim, proguanil) and sulfa drugs (dapsone, sulfalene sulphadoxine etc.). Popular antifolate combinations include sulfalene-pyrimethamine (metakelfin) and sulphadoxine-pyrimethamine (SP or Fansidar). Proguanil and pyrimethamine have been used in monotherapy, but they had poor efficacy as antimalarial until the class I antifolates (dihydropteroate synthase inhibitors) and class II antifolates (dihydrofolate reductase inhibitors) were combined. Although SP is a combination of two drugs (sulphadoxine and pyrimethamine), it is not regarded as a combination therapy, as both drugs act on the folate pathway. However, the combination was found to have synergistic activity and was more effective than either drug used alone (Gregson and Plowe, 2005). The most extensively used sulphadoxine-pyrimethamine combination is Fansidar (SP), at fixed-doses approved by the FDA in 1983 (Gesase *et al*., 2009). Fansidar was largely employed to target chloroquine-resistant parasite populations in the late 1980s and for some

years it effectively replaced chloroquine as a first line treatment for *P. falciparum* malaria (Miller and Su, 2011)

In the 1970s, resistance to SP was first discovered in South Asia and South America which later spread to West Africa in the 1980s (Venkatesan *et al.*, 2013; Farooq and Mahajan, 2004). As a result of very low efficacy of SP as a treatment drug in many endemic countries, it was abandoned as first-line treatment (Bell and Winstanley, 2004) and the use of artemisinin combination therapies (ACTs) was adopted. However, compared to artemisinin, SP's low cost and prolonged prophylactic effects are major factors that make its use as a preventive therapy on the rise in some endemic populations. A review carried out by Kulie (2007) provided evidence to show that intermittent preventive therapy of two SP doses reduced placental malaria. This evidence however led to the World Health Organization (WHO) recommendation of at least two doses of SP beginning in the second trimester of pregnancy (WHO, 2004). This has led to a recent increase (Fig 1.4) in the use of SP among pregnant women in Nigeria.

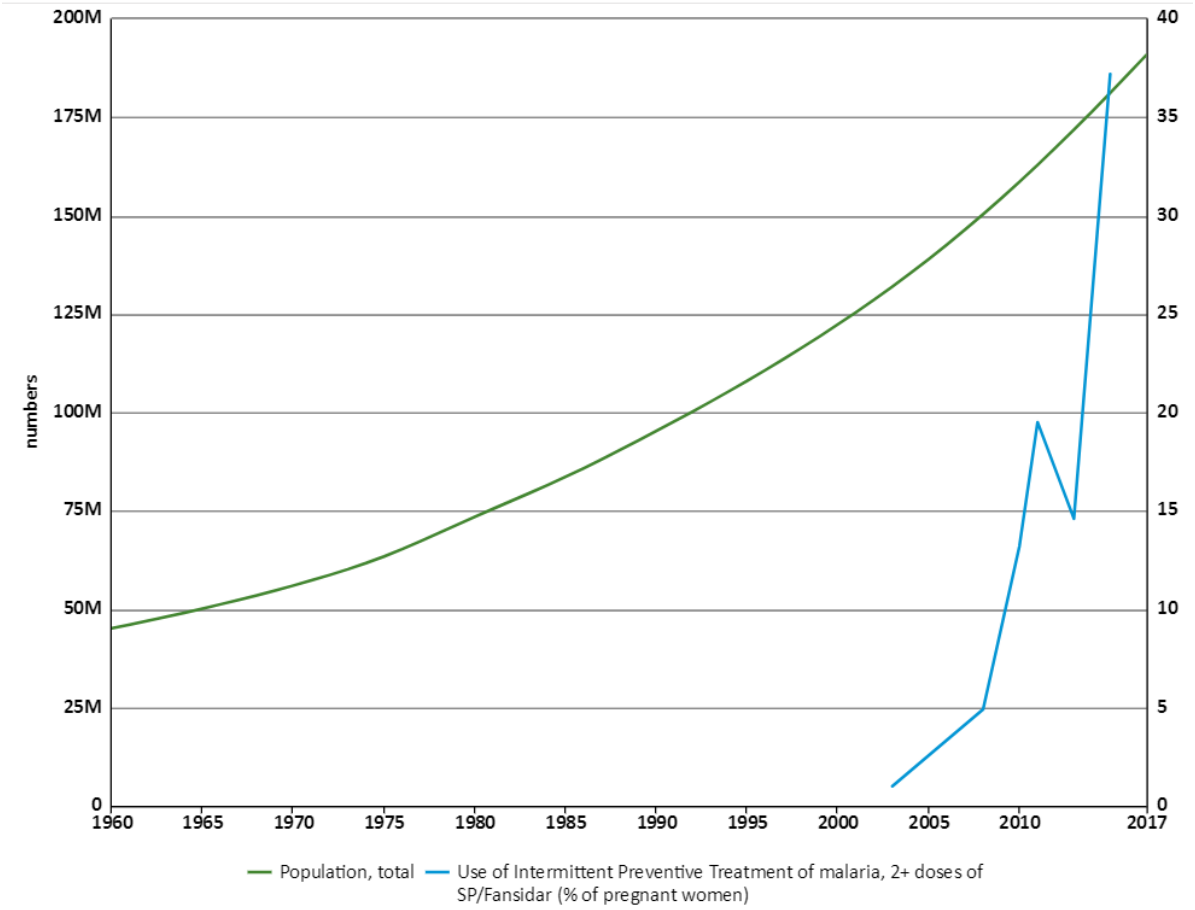


Figure 1.4: Diagram showing the % use of SP/Fansidar by pregnant women in Nigeria between 1960 and 2017. (Source: World Bank: Health Nutrition and Population Statistics, 2018)

1.5.3 Artemisinin and Artemisinin-Combination Therapy (ACTs)

Artemisinin and its derivatives are the latest and most effective antimalarial drugs in current use. Artemisinin is derived from a Chinese sweet wormwood plant called *Artemisia annua* (Travassos and Laufer, 2009. Krungkrai *et al.,* 2010). Artemisinin is thought to have been used as a therapeutic to treat high fevers as far back as 2000 years ago (Ploypradith, 2004). It enhances efficacy and has the potential of lowering the rate at which resistance emerges and spread (Mutabingwa, 2005); artemisinin drugs affect protein synthesis of the parasite. Fairhurst (2016) explained that artemisinins are pro-drugs that are 'activated by haem iron-mediated cleavage of their endoperoxide moiety within the parasite and this forms reactive oxygen that targets the nucleophilic groups in parasite proteins and lipids. The artemisinin derivatives are perceived to be the most promising antimalarial medicines because they offer the following pharmacological properties:

- Rapid and sustained reduction of the parasite biomass (White *et al.*, 1999)

- Rapid resolution of clinical symptoms (White *et al.,* 1999)
- Effective against chloroquine-resistant parasites (White *et al.,* 1999)
- Reduction of gametocyte carriage (White *et al.,* 1999; Travassos and Laufer, 2009)
- Broad stage specificity (Yeung *et al.,* 2005; White *et al.,* 1999)
- 7-day treatment in monotherapy (Travassos and Laufer, 2009; Yeung *et al.,* 2005)

Research has confirmed that artemisinin derivatives effectively and quickly clear *Plasmodium* parasites throughout the asexual blood stages and can also be combined with another antimalarial from a different group (Tilley *et al.,* 2016; Wilson *et al.,*2013; Kulie *et al.,* 1993). The reason why artemisinin needs to be combined with another drug is that the duration of therapy of artemisinin is between 5-7days. Therefore, parasites can sometimes evade the very short duration of action (Ittarat *et al.,* 2003). However, when artemisinin is combined with another longer-acting drug it can effectively be administered over 3 days. The benefit of the combination is that the artemisinin derivatives quickly reduce the parasitaemia while the other long-acting drug clears the parasite (White *et al.,* 1999). However, a problem with this is that if there are new infections with mixed susceptible resistant parasites emerging after the Artemisinin residue has cleared the other drug might not be able to fight the infection effectively and this will lead to treatment failure (Hastings *et al.,* 2000). This rationale is also established and effective in the treatment of cancer, tuberculosis, or infection with human immunodeficiency virus (Yeung *et al.,* 2004). As defined by White (1999), the probability of a parasite developing resistance to a combination of two drugs is the product of the probability of the parasite developing resistance to the first drug and the second drug. This means that if the probability of a parasite developing resistance to drug A is 1 in 10^9 and drug B 1 in 10^9, the probability of developing resistance to drugs AB will be 1in 10^{18}; therefore, representing a billion-fold reduction in probability. Moreover, adherence to seven-day regimen is hard and extremely-low in endemic regions; so a three-day regimen makes adherence more possible because most people stop treatment when symptoms are cured and they feel better; which can also lead to recrudescence and drug resistance (Nosten *et al.,* 1994). According to WHO (cited in Balaji *et al.,* 2014), combination drugs can be used as first-line treatment for children and people who have shown resistance towards chloroquine as an antimalarial drug. Since April 2001, WHO has recommended the use of artemisinin-based combination therapies (ACTs) in countries where *P. falciparum* malaria has shown resistance to amodiaquine, chloroquine and sulphadoxine-pyrimethamine. However, the

WHO believes that the continuous consumption of artemisinin monotherapies in the private sector, if unabated, will promote resistance to artemisinin and compromise the effectiveness of ACTs.

In a study by Rwagacondo *et al.,* (2003) an artemisinin compound was partnered with SP and tested in an area with high SP resistance, treatment efficacy observed was very low compared to efficacy observed when artemisinin compound was combined with another drug of good efficacy and without resistance. This shows that even for ACT to be effective, artemisinin derivatives must be partnered with another effective drug so as to avoid treatment failure and further risk of drug resistance. However, this study did not mention about completion of dosage in people that participated in this test and also knowledge and perception of malaria treatment wasn't recorded as these could have affected the result. Since resistance has been recorded with nearly all available antimalarials used as monotherapy, the use of artemisinin-based combination therapy has been accepted in most malaria-endemic countries. SP is considered a single agent because the mode of action between sulphadoxine and pyrimethamine are similar (Talisuna, 2004).

The use of ACT as first-line treatment of malaria is seen as a breakthrough in this regard. The WHO (2015) claims that in 2013, up to 392 million ACT treatment courses were procured by endemic countries – a rise from the 11 million that was recorded in 2005. However, there are a couple of concerns about the redeployment of ACTs, the most important one being cost (Boland *et al*, 2000). ACTs in Nigeria are very expensive (between $2.5 and $7.5 equivalent of ₦1125 to ₦3375), compared to SP and chloroquine that could be bought for as low as 10 cents. So for these drugs to be generally accepted as the first-line treatment of malaria in Nigeria, there should be a decrease in the amount people pay for them, especially those in rural areas who cannot afford to buy them. As a result, people are easily deceived to buy substandard/fake ACTs of less quality for a cheaper price, leading to treatment failure, drug resistance and death. As Yeung (2003) states, another concern is that by deploying artemisinin derivatives and exposing everyone to it, there is a strong chance of the parasite developing resistance due to self-medication, wrong dosage etc. In Nigeria, where the use of ACTs was officially adopted in 2005, there are still signs of improper use of antimalarial drugs such as inappropriate dosage, use of counterfeit or substandard drugs and the use of other ineffective drugs. The correct use of antimalarial drug is imperative not just to successfully treat malaria but also to avoid the spread of drug resistant malaria. Artemether/lumefantrine was the first fixed dose artemisinin-based combination therapy that

was recommended by the WHO to treat *P. falciparum* and it has shown a great level of efficacy across sub-Saharan Africa, Asia, and other areas with multi-drug resistance *P. falciparum*. Artemether works by blocking the conversion of haem to haemozoin in the food vacuole, as a result destroying existing haemozoin and releasing haem and a cluster of free radicals into the parasite. In Nigeria, the most commonly used ACTs are artemether-lumefantrine, mefloquine-artesunate, and amodiaquine-artesunate. The Federal Ministry of Health (2007) explains that although the use of artemisinin-based combination therapy for the treatment of uncomplicated malaria has been introduced and advised in Nigeria for some years now, its utilization is still below expected levels. The reasons they identified for this includes; Low coverage of public sector health facilities where ACTs are free of charge or insufficient supply management and low awareness of ACT treatment by health workers and patients, Poor availability and high cost of ACT in the private sector. As found in China and Vietnam, (Meng *et al.,* 2010; Witkowski *et al.,* 2013) the progressive reduction of *in vitro* susceptibility to artemisinin of *P. falciparum* has confirmed the risk of resistance.

If *P. falciparum* develops resistance to the artemisinin derivatives currently used to treat malaria, there will be no alternative effective compounds to treat malaria over the next ten years. This is a major reason why quality antimalarial drugs must be used for every case of malaria, at a proper dosage and these must be presented after a proper diagnosis. Although policies that govern the use of antimalarial drugs are well established in countries that have adopted the use of ACTs as first line treatment for uncomplicated *P. falciparum* malaria, Ezenduka *et al.,* (2014) explains that problems in implementation still persist, undermining the goals of malaria treatment policy. To successfully control malaria, treatment with efficacious antimalarial drugs is one of the most important factors to consider. Every country has a National Malaria Treatment Policy that approves the drugs for treatment of both uncomplicated and severe malaria and what to do if first line treatment fails. It must however be noted that artemisinin-resistant strains of *Plasmodium falciparum* have recently been discovered in Southeast Asia and it is a major risk to efforts to control malaria worldwide (Laurent *et al.,* 2015).

1.5.4 Current chemotherapy recommendations

Table 1. 3: Artemisinin and non-artemisinin containing drug combinations for malaria treatment.

Artemisinin-based combinations	Safety	PK mismatch	Evidence of resistance
Artemether-lumefantrine	+/-	-	no/no
Artesunate +mefloquine	+	-	no/yes
Artesunate + SP	+/-	-	no/yes
Artesunate + amodiaquine	+/-	-	no/yes
Artesunate +pyronacridine	+/-	-	no/no
Dihydroartemisinin + piperaquine	+/-	-	no/no
artensuate+Chloroprogunil-dapsone	+/-	-	no/likely
Non-Artemisinin combinations			
Sulfadoxine/Pyramethamine (SP)	+/-	+/-	yes/yes
Chloroquine + SP	+/-	-	yes/yes
Amodiaquine + SP	+/-	-	yes/yes
Quinine + SP	+/-	-	some/yes
Mefloquine +SP	+/-	-	some/some
Quinine + tetracycline	-	+/+	some/no
Quinine + Clindamycin	+	+	some/no
Atovaquone-proguanil	+	+/-	no/no
Chloroprogunil-dapsone	-	++	Possible

(Abbreviations are as follows -= poor, +/-= unclear, += acceptable, ++= desirable. Drugs with – in the title are approved whilst drugs with + are not (Matthews, 2015).

Table 1.3 above describes various examples of artemisinin-based combinations of antimalarial drugs and non-Artemisinin combinations, including their safety for consumption and evidence of resistance.

1.6 Drug resistance mechanisms

Antimalarial drug resistance which is caused by the reduced susceptibility of parasites to commonly used antimalarial drugs is now generally believed to be a major threat to the ability to "roll back malaria" and other malaria eradication programs. Drug resistance is one of the factors responsible for the spread of malaria to a new area and the re-occurrence of malaria in areas where it had once been eradicated. WHO Technical Report Series (1973) defined antimalarial drug resistance as "the ability of a parasite strain to survive and/or multiply despite the administration and use of a drug given in doses equal to or higher than those usually recommended but within a tolerance of the subject". However, Bruce-Chwatt *et al*., (1986) subsequently modified this definition to add that "the drug must gain access to the parasite or the infected red blood cell for the duration of the time necessary for the normal action of the drug".

Howard *et al.,* (2003) rightly says that measuring the impact of drug resistance is vital to understanding the scope of the problem, which gives a greater insight into formulating policies to limit the emergence and spread of resistant organisms. Babalola *et al.,* (2007) in a study reported that the incidence of *P. falciparum* resistance to chloroquine was observed all over the country (Nigeria). The same study also reported that combined antimalarial of pyrimethamine-sulphadoxine has shown a considerable amount of clinical failure when used to treat malaria; which invariably means that *P. falciparum* has developed resistance to this combination. The sample size of this study might not be big enough to generalise the result to the whole country, however, other studies done in different regions support this claim. There are direct and indirect effects of drug resistance to malaria effective case management. Apart from drug resistance resulting to treatment failure, it also increases the number of people that serve as host to *P. falciparum* or any other species hereby leading to a more dangerous form of malaria (e.g. cerebral malaria) and in such a way increasing morbidity and mortality. The global spread of *P. falciparum* drug resistance to antimalarial drugs such as sulphadoxine/pyrimethamine and chloroquine has been recognised as a serious public health problem in countries intensely affected by the disease (Mita *et al.,* 2009; Weinsdorfer 1994; Talisuna *et al.,* 2004). After a breakthrough in the development of antimalarials to fight malaria diseases since the 1940s, there has been a great blow to their effectiveness due to parasites ability to develop resistance to these drugs. Over the years, *P. falciparum* has grown resistant to different antimalarial drugs; for example, chloroquine used to be a very effective antimalarial drug until the late 1950s, when resistance was reported in South-America and Southeast-Asia which eventually spread throughout the world (Ishola *et al.,* 2014). For a disease responsible for over 475,000 deaths worldwide every year with 70% recorded in sub-Saharan Africa (Jombo *et al.,* 2011), the development of resistant species has a huge significant influence on the control of malaria.

After resistance to chloroquine was recorded, it was essential to produce alternative antimalarial drugs such as sulphadoxine-pyrimethamine (SP) to combat the disease. However, considering the WHO's recommendation of combination therapy, SP is not considered to be one because even though it is a co-formulation of two drugs, the mechanism of action of both drugs are closely linked (Travassos and Laufer, 2009). Also, by the late 1980s, resistance to mefloquine and SP was also widespread on the Thai-Cambodian and Thai-Myanmar border areas which later spread to Africa (Wongsrichanalai *et al.,* 2004). *P. falciparum* is the most common species of malaria parasite and it is responsible for the

majority of malaria deaths globally and in Nigeria. It is therefore expected, as *P. falciparum* has been around for many years that it is now highly resistant to most of the available antimalarial drugs. Oshikoya and Senbanjo (2010) explain that this problem has been aggravated by self-medication, use of counterfeit drugs and empiric treatment of malaria. However, amidst all claims of Chloroquine (CQ) and SP resistance, recent studies have shown that there may be an evidence of increased efficacy in these drugs as more people are beginning to use them with reports of an effective result. Adebayo & Krettli, (2011) explains that in Nigeria, a nationwide surveillance data on drug efficacy showed that chloroquine and sulphadoxine-pyrimethamine are no longer effective therapeutic options for the viable treatment of human malaria. Other antimalarial drugs such as mefloquine followed within a few years of introduction (Mockenhaupt, 1995). Wongsrichanalai *et al.,* (2002) shows in a table (Table 1.4) that resistance to drugs commonly develops within 10-15 years after the introduction of a new antimalarial.

Table 1. 4: Dates of introduction and first reports of antimalarial drug resistance (Wongsrichanalai *et al.*, 2002).

ANTIMALARIAL DRUG	INTRODUCED	FIRST REPORTED RESISTANCE	DIFFERENCE (YEARS)
Quinine	1632	1910	278
Chloroquine	1945	1957	12
Proguanil	1948	1949	1
Sulphadoxine-Pyrimethamine	1967	1967	0
Mefloquine	1977	1982	5
Alovaquine	1996	1996	0

The development of this resistance is usually caused by;

- Drug pharmacokinetics (Hastings *et al.,* 2002)
- Drug over use (Simpson *et al.,* 2000)
- Cross-resistance between drugs (Iyer *et al.,* 2001).

Inadequate treatment through inappropriate prescription or administration, non-compliance or poor absorption (Simpson *et al.,* 2000).

The continuous spread of *P. falciparum* resistance to antimalarial drugs presents a serious threat to any form of malaria intervention or control programmes. As effective case

management (ECM) is the main strategy employed to control malaria, it is therefore imperative that every case of malaria is treated not only with the most effective drugs but also with the right dosage. Recently, it is believed that the main drive of malaria control in every malaria endemic country is early diagnosis and the effective treatment of every case found. One of the problems that affect this is that a large proportion of Nigerians (60-80%) treat malaria cases outside the official healthcare system and mostly at home using drugs at incorrect dosages. Hamel *et al.,* (2001) defined home treatment of malaria as "any treatment for presumed malaria with antimalarial drugs that are not given during or after a visit to a health facility such as a health centre, a dispensary, a maternity centre, a private or public hospital". The rapid spread of drug-resistant malaria parasites accompanied by adulterated drugs for case management in the market has made the treatment and control of malaria very challenging (Anyawu and Onyesome, 2007).

1.6.1 Artemisinin-resistant *Plasmodium falciparum* malaria

Artemisinins are the most rapidly acting of currently available antimalarial drugs. However, there is a fast and growing threat to its use as Southeast Asia (SEA) has been fertile ground for the emergence of drug-resistant *P. falciparum* malaria (Figure 1.6). Similar to a trend that has been recorded in chloroquine, sulfadoxine, pyrimethamine, quinine, and mefloquine, this region has now spawned parasites resistant to artemisinin, the world's most potent antimalarial drug (Woodrow and White, 2017). Partial resistance to ACT, defined as delayed parasite clearance in malaria patients treated with an ART derivative or an ACT, has been associated with mutations in the *P. falciparum K13* gene (Straimer *et al.,* 2017). As a result, areas where ACT is the first-line treatment of the disease are at risk of a failed drug due to the prevalence of artemisinin resistance. This worrisome development threatens to make malaria practically untreatable in South East Asia and threatens to compromise global endeavours to eliminate this disease. A recent series of clinical, *in vitro*, genomic and transcriptomic studies in South East Asia have defined *in vivo* and *in vitro* phenotypes of artemisinin resistance, identified its causal genetic determinant, explored its molecular mechanism, and assessed its clinical impact (Fairhurst *et al.,* 2016). Specifically, these studies have established that artemisinin resistance manifests as slow parasite clearance in patients and increased survival of early-ring-stage parasites *in vitro*; it is caused by single nucleotide polymorphisms in the parasite K13 gene, which is associated with an upregulated "unfolded protein response" pathway that may antagonize the pro-oxidant activity of artemisinins, and selects for partner drug resistance that rapidly leads to ACT failures. In South East Asia, clinical studies are

urgently needed to monitor ACT efficacy where K13 mutations are prevalent, test whether new combinations of currently available drugs cure ACT failures, and advance new antimalarial compounds through preclinical pipelines and into clinical trials. Intensifying these efforts should help to forestall the spread of artemisinin and partner drug resistance from South East Asia to sub-Saharan Africa, where the world's malaria transmission, morbidity, and mortality rates are highest. Prolonged courses of artemisinin-based combination therapies are currently efficacious in areas where standard 3-day treatments are failing.

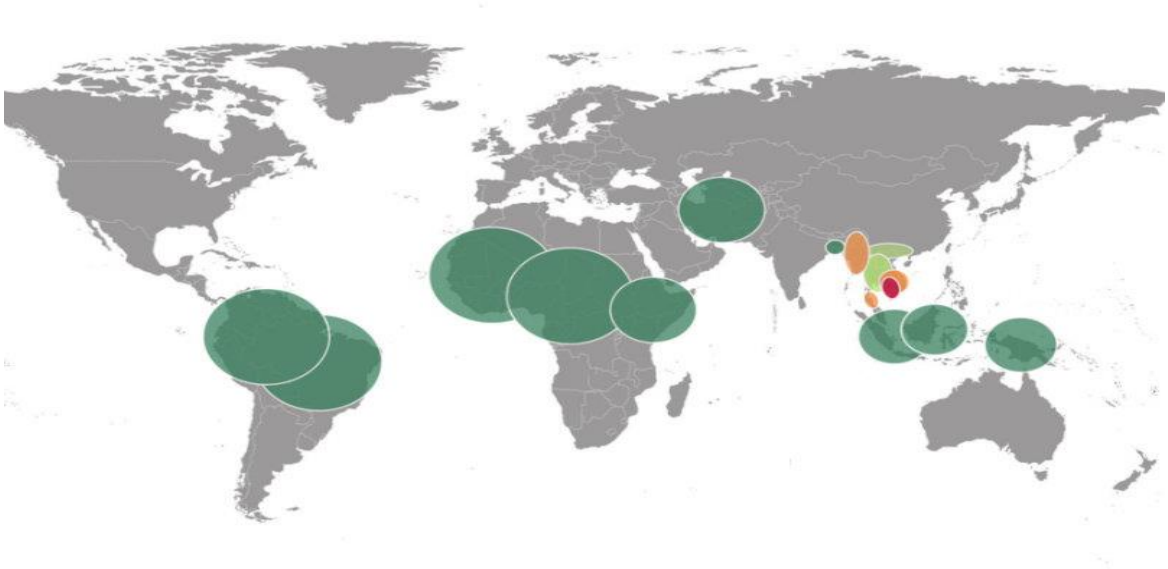


Figure 1.5: The distribution of artemisinin resistance throughout the world. Dark Green regions are places where all parasites are not resistant to artemisinin, Red regions (primarily in South-East Asia) are places where a very high percentage carry a mutation (so-called K13 polymorphism), which is associated with artemisinin resistance.

1.6.2 Chloroquine-resistant *Plasmodium falciparum* malaria

As the malaria parasite digests haemoglobin, large amounts of toxic by-product are formed. The parasite polymerizes this by-product in its food vacuole, producing non-toxic haemozoin (malaria pigment). It is believed that resistance of *P. falciparum* to chloroquine is related to an increased capacity for the parasite to expel chloroquine at a rate that does not allow chloroquine to reach levels required for inhibition of haem polymerization (Foley & Tilley, 1997). This chloroquine efflux occurs at a rate 40 to 50 times faster among resistant parasites than sensitive ones (WHO, 2001). This situation is remarkable considering the major toxicity that occurs through the formation of the haem-chloroquine complex that inhibits haem

degradation by reduced glutathione (GSH). It is possible that higher levels of GSH in some parasites may help protect them from the toxic effects of chloroquine and thus contribute to resistance. In fact, both in *P. falciparum* and in the rodent malaria parasite *Plasmodium berghei*, it has been demonstrated that CQ-resistant lines contained higher levels of GSH than their sensitive counterparts (Meierjohann *et al.,* 2002) and that this was related to increased expression of glutathione-S-transferase (Cravo *et al.,* 2006) as well as γ-glutamylcysteine synthetase (Perez-Rosado *et al.,* 2002).

Further evidence supporting this mechanism is provided by the fact that chloroquine resistance can be reversed by drugs which interfere with this efflux system (WHO, 2001). It is unclear whether parasite resistance to other quinolone antimalarials (amodiaquine, mefloquine, halofantrine, and quinine) occurs via similar mechanisms.

1.6.3 Antifolate-resistant *Plasmodium falciparum* malaria

In combination, antifolate drugs act as synergistic inhibitors of folate biosynthesis, which in malaria parasites, is an obligatory requirement for the production of nucleotides and hence DNA synthesis. Antifolate combination drugs, such as sulfadoxine and pyrimethamine, act through sequential and synergistic blockade of 2 key enzymes involved with folate synthesis. Pyrimethamine and related compounds inhibit the step mediated by dihydrofolate reductase (DHFR) while sulfones and sulfonamides inhibit the step mediated by dihydropteroate synthase (DHPS) (WHO, 2001). Specific gene mutations encoding for resistance to both DHPS and DHFR have been identified. Specific combinations of these mutations have been associated with varying degrees of resistance to antifolate combination drugs (WHO, 2001).

There are 4 single nucleotide mutations causing amino acid replacements associated with pyrimethamine resistance in the wild; a change from serine to asparagine at amino acid position 108 (S108N), from asparagine to isoleucine at position 51 (N51I), from cysteine to arginine at position 59 (C59R), and from isoleucine to leucine at position 164 (I164L). It is thought that these mutations arise sequentially, starting with S108N, as this mutation confers a 10-fold increase in the *K*i value for pyrimethamine (the dissociation constant of the enzyme-inhibitor complex) while maintaining similar kinetic parameters to the wild type enzyme (Sirawaraporn *et al.,* 1997). This is the only single mutation seen in the field (Sirawaraporn *et al.,* 1997). Each sequential mutation adds further increases in *K*i values, with the quadruple mutant exhibiting the highest value. DHPS mutations were found in five

positions 436, 437, 540, 581 and 623 (Brooks *et al.,* 1994) and all gene mutations currently identified, cause diminished affinity of the binding of the drugs to their enzyme targets.

1.6.4 Atovaquone-resistant *Plasmodium falciparum* malaria

Atovaquone acts through inhibition of electron transport at the cytochrome *bc1* complex (Ittarat *et al.,* 1994). Although resistance to atovaquone develops very rapidly when used alone, when combined with a second drug, such as proguanil (the combination used in Malarone™) or tetracycline, resistance develops more slowly (Looareesuwan *et al.,* 1996). Resistance is conferred by single-point mutations in the cytochrome-b gene.

The cytochrome bc_1 complex catalyzes the transfer of electrons from ubiquinol to cytochrome *c*, which is coupled to the translocation of protons across the inner mitochondrial membrane, thereby maintaining the membrane potential of mitochondria used to produce ATP by ATP synthase (Barton *et al.,* 2010). The antimalarial drug atovaquone can inhibit the parasitic cytochrome bc_1 complex by causing a collapse in the mitochondrial membrane potential, which is lethal for the parasite (Barton *et al.,* 2010). Several mutations within the cytochrome b gene can lead to atovaquone resistance, with most mutations altering the ubiquinol binding site of the protein (Gil *et al.,* 2003). This site is highly conserved across phyla. Studies with yeast and transgenic parasites support the theory that atovaquone binds to the ubiquinol binding site, thereby disrupting the electron transfer chain (Peters *et al.,* 2002). It has been hypothesized that in the absence of atovaquone drug pressure the mutations in the ubiquinol binding sites might confer a fitness cost to the parasite (Barton *et al.,* 2010). Indeed, a double mutation in this conserved protein (M133I and G280D) results in 5–9% fitness cost according to cell culture investigations (Peters *et al.,* 2002).

1.7 Disease control strategies

The present approach to controlling malaria vectors is quite different from the approach that was in place in the early-mid 20th century. In the early years, more concentration was placed on just the breeding sites of mosquitoes. Efforts were made to drain swamplands and stagnant water of their content and potholes were covered or layered, with oil to disrupt egg laying and larval development.

1.7.1 Vector control

The first breakthrough of mosquito controls came in 1939 when dichlorodiphenyltrichloroethane (DDT) was discovered. This later became the major control

of mosquito for many years (Oliva *et al.*, 2014). The use of DDT was later banned in some countries because of its toxicity; it was also claimed to be harmful to the food chain and fresh water. However, Curtis *et al*., (2000) explain that the extent of the harm that DDT in indoor spray for mosquitoes create is not clear and a link between DDT and morbidity has not been properly demonstrated. The ban of DDT led to it being replaced by pyretheroids which mosquitoes later developed resistance to (Van Dyk *et al.*, 2010).

Nets have been in use since very early times as a protection against different insects including the mosquito. In recent times, different types of nets have been developed; nets that are made of cotton, nylon, polyester, polyethylene and synthetic with cotton mixtures (Department Ministry of Health, 2002). Insecticide-treated nets which are the recommended type of nets for protection against mosquitoes either kill or irritate mosquitoes in addition to being a physical barrier (Roozendal, 1997), which is the main advantage an insecticide-treated net has over an ordinary untreated net. Curtis *et al.*, 2000, describes an insecticide-treated net that they serve as human baited traps when somebody is sleeping inside by attracting and killing mosquitoes and other biting insects. As the name implies, insecticide-treated nets need to be treated regularly with chemicals for maximal benefit. The commonest chemicals used are second and third generation synthetic pyrethroids (Roozendaal, 1997; Clarke, 2001). Large-scale trials of insecticide-treated nets conducted over two years period in different epidemiological settings across Africa show a reduction of between 15-33% in all cases of child mortality (Diallo *et al.*, 2004). If ITNs are properly used, it can cut malaria transmission by at least 50% (UNICEF 2004). ITNs also provide significant protection for pregnant women against maternal anaemia and low birth weight, which are major contributors for neonatal morbidity (UNICEF, 2004). ITNs are seen to be expensive and some people even find their use to be too complex, however, it was argued that ITNS are cost-effective (Wiseman *et al.*, 2003. Onwujekwe *et al.*, 2003).

It should be added, that even though IRS (Indoor residual sprays) and ITNs show effectiveness in controlling malaria, this on its own cannot eradicate the disease and more should also be done with effective management of every malaria case. In the early weeks of January 2018, the price of Baygon (one of the most trusted and used IRS in Nigeria) had gone up ₦2000 ($5.56) for a 500ml Can. Also, the price of Coartem, one of the most trusted ACTs was ₦1200 ($3.34). This is very worrying and against the belief ‘prevention is better than cure’; at least not in the case of IRSs financially. UNICEF’s statistics in 2007 showed that over 70% of Nigerians live on less than $1 a day, and 92% live on less than $2. It is even

more devastating when you compare the naira-dollar exchange rate now in 2018. Due to the harsh economy in Nigeria, the country is heading to a place where if nothing is done soon, it would not be sensible to advocate prevention over treatment in this area; this is because if people cannot afford to treat using recommended ACTs then how can they afford to use IRSs.

1.7.2 Vaccine development

Vaccine development (as seen in Figure 1.5), has historically contributed to the reduction in the spread and burden of infectious diseases. However, despite extensive efforts, there is currently no licenced vaccine available for the effective management of malaria. Following repeated exposure to infection, people living in malaria-endemic areas develop acquired immunity to limit the inflammatory response to the parasite (Artavanis-Tsakonas *et al.*, 2003), but this immunity seems to be specific for the parasite strain that resides in a specific area. Acquired immunity is therefore lost once the individual moves to an area with a different strain (Wang *et al.*, 2009). An urgent need to develop an effective malaria vaccine cannot be over-emphasised; however, the production of a malaria vaccine has since proved difficult because of the hurdle in pinpointing the immune responses that protect against malaria (Holder, 2009). The WHO Expert Committee on Biological Standardization (ECBS) in 2012 provided a guideline to support quality, safety, and efficacy of new malaria vaccines; these vaccines are to target pre-erythrocytic and blood stages of *Plasmodium falciparum* cycle (WHO, 2015). In 2013, the Malaria Vaccine Technology Roadmap was revised by the WHO and was updated to focus more on research, vaccine development, important capacities, policy and commercialization (WHO, 2013). The malaria vaccine roadmap's major goal was to produce a vaccine by 2015 with a protective efficacy of more than 50% against malaria disease and the vaccine must last longer than a year (WHO, 2013). The second goal is to produce a vaccine with 80% efficacy by the year 2025 (Claudia, 2014). There are three main types of malaria vaccines that could be developed. The pre-erythrocytic vaccines are the one that would target the liver-stage sporozoite and this would in turn decrease or eliminate blood stage infection.

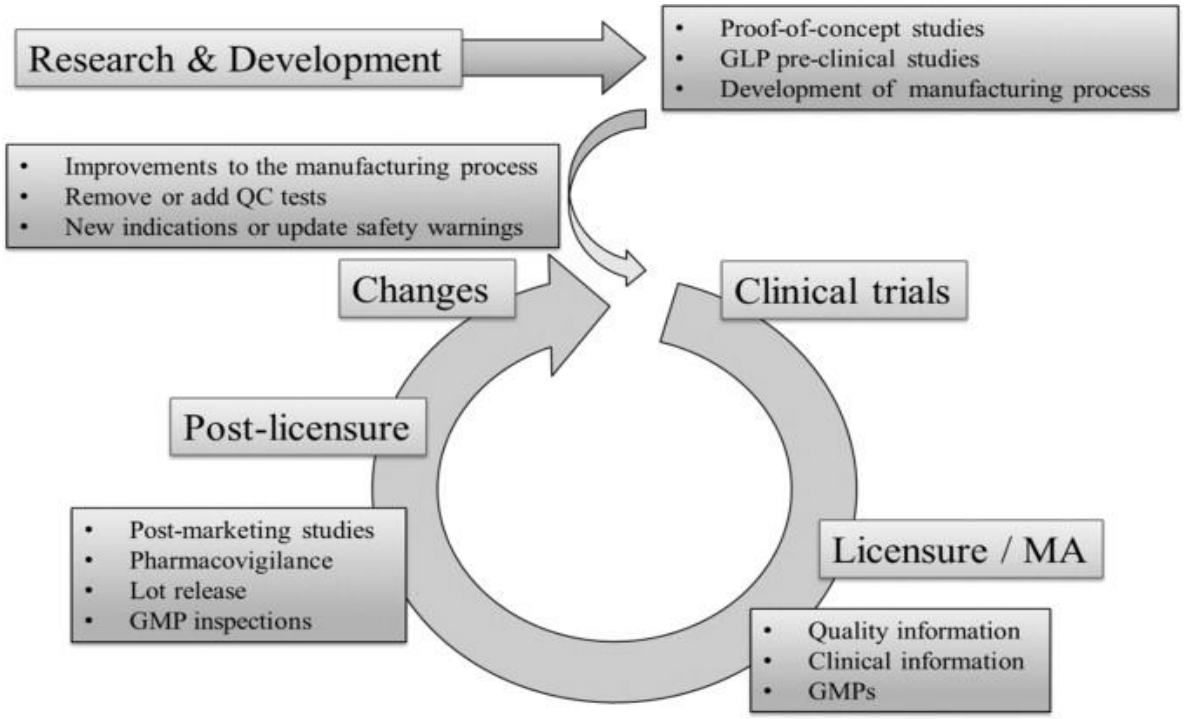


Figure 1.6: Vaccine development cycle; an illustration of a vaccine product life-cycle from research and development through to post-licensure, and the key information requirement during the cycle (Ho *et al.*, 2015)

1.7.2.1 Pre-erythrocytic vaccines

A pre-erythrocytic vaccine targets the sporozoites and hepatic stages of the parasite aiming either to prevent the sporozoites from getting into the liver cells or destroying infected liver cells and hence preventing the emergence of merozoites into the bloodstream (Duffy *et al.*, 2012). The most significant challenge for a pre-erythrocytic vaccine is the time frame. Sporozoites reach the liver in less than two hours after being injected by the mosquito (Mac-Daniel *et al.*, 2014). As a result, the immune system has a limited amount of time to eliminate the parasite. Although most of the potential pre-erythrocytic vaccines are still in Phase I or Phase II trials, one vaccine (RTS, S) has entered the Phase III trial and is showing promise (SCTP, 2015). RTS, S, RTS, S/SBAS2, developed by SmithKline Beecham Biologicals with the Walter Reed Army Institute of Research in 1987, conferred partial protection against malaria in phase II clinical trials (Minsoko *et al.*, 2014). Targeting the pre-erythrocytic phases of *P. falciparum*, RTS, S is a fusion protein consisting of a malaria antigen (circumsporozoite protein) with hepatitis B surface antigen, and includes a new potent adjuvant (AS01) (Minsoko *et al.*, 2014; Stoute *et al.*, 1997; Takashima *et al.*, 2016). RTS, S/ AS01 was the subject of a large multicentre Phase III trial involving more than 15,000 children over 11 sites in sub-Saharan Africa with the aim of licensure and deployment in 2015 (Barry & Arnott, 2014). These trials have had some successes. The earliest results, released in October 2011,

showed that in children aged 5-17 months, vaccination with RTS, S reduced the risk of the clinical malaria episode and severe malaria by 56% and 47%, respectively (Barry & Arnott, 2014). However, the results released in November 2012 indicated that the vaccine was less effective in infants aged 6-12 weeks at first vaccination. In that category, vaccination with RTS, S decreased both clinical malaria and severe malaria by 30%. Final results from the trial, that involved young children up to three years of age, showed a reduction in clinical malaria cases by 26% for the youngest children and 36% for children up to 17 months of age at first vaccination (Barry & Arnott, 2014; Tinto *et al.,* 2015). Considering that the number of malaria cases averted was substantial, this represents an encouraging progress towards licensing of a first-generation malaria vaccine (Barry & Arnott, 2014). In July 2015, the European Medicines Agency recommended that the vaccine should be licensed for use in young children in Africa; WHO is considering the recommendation. Concurrently, a WHO advisory group has recommended pilot 17 implementations of the vaccine in 3-5 sub-Saharan African countries (Takashima *et al.,* 2016).

1.7.2.2 Erythrocytic vaccines or blood-stage vaccines

The blood stage vaccines identify antigens on infected blood cells and fight against infected cells while the antibody-producing vaccines target the sexual stages of the parasite (Moorthy *et al.,* 2007). The aim of the erythrocytic vaccines is to stop the rapid invasion and asexual reproduction of the parasite in RBCs. Recall that the blood stage parasites are responsible for the clinical symptoms of malaria (Richards & Beeson, 2009). Due to the significant number of merozoites produced, erythrocytic vaccines are designed to target merozoite antigens and hence prevent RBCs invasion; thus, reducing the parasite density. In addition to preventing the clinical symptoms, this will also reduce the density of gametocytes contributing to the reduction in malaria transmission (Barry & Arnott, 2014). Other approaches target a surface protein on infected red blood cells known as *P. falciparum* erythrocyte membrane protein (PfEMP1). PfEMP1 mediates adhesion to host cells, a mechanism that is associated with severe malaria (Hviid, 2010); however, there are no blood-stage vaccines that have had the comparable success of the RTS, S vaccine and most are still undergoing Phase I or II trials (Takashima *et al.*, 2016).

At the moment there are currently no licensed malaria vaccines although the RTS/S/AS01 (Mosquirix^{TM}, GSK) is the most advanced candidate in clinical studies (Ho *et al.,* 2015). RTS/S/AS01 is an example of a vaccine that targets the pre-erythrocytic sporozoites of *P. falciparum*. Moreno and Joyner (2015) however claim that the immunity of the vaccine diminishes over time, therefore another dose should be taken after 18 months. RTS/S/AS01 is

a very encouraging starting point for the development of vaccines. Nigeria is one of the Sub-Saharan African countries where RTS/S/AS01 vaccine phase III or IV studies are ongoing or planned (Ho *et al.,* 2015). However, Dunachie *et al* (2015) claim that RTS/S/AS01 vaccine has completed stage III clinical trials and has an efficacy of only 46% in children and 27% in infants. The efficacy rate recorded seems too low at the moment, but it can be improvised and probably there is still hope for a vaccine with 80% efficacy by 2025.

1.7.2.3 Transmission-blocking vaccine (TBV)

The transmission blocking vaccines aim to target antigens expressed during parasite stages in the mosquito host (Barry & Arnott, 2014). Although these altruistic vaccines would not directly protect an individual, they would prevent the onward transmission (Birkett *et al.,* 2013). During a blood meal, the mosquito takes up vaccine-induced antibodies along with Plasmodium gametes, enabling interference with parasites development and preventing transmission of the parasite to the next individuals (Jones *et al.,* 2015; Shimp *et al.,* 2013). The Pfs25 protein expressed on the surface of zygotes and ookinetes during the sexual stages of Plasmodium is a promising target for TBV development (Jones *et al.,* 2015). Phase I human trial results using a recombinant Pfs25H/Montanide ISA51 formulation indicated that human Pfs25 specific antibodies block parasite infectivity to mosquitoes; however, the extent of blocking was likely to be insufficient for an effective TBV (Jones *et al.,* 2015; Shimp *et al.,* 2013). To overcome the poor immunogenicity, processes to produce and characterize recombinant Pfs25H conjugated to a detoxified 18 form of *Pseudomonas aeruginosa* exo-protein A (EPA) have been developed. This new Pfs25-EPA conjugated nano-particle vaccine significantly enhanced the Pfs25 specific antibody responses in mice when adsorbed on Alhydrogel® (Shimp *et al.,* 2013). However, the safety and immunogenicity of the Pfs25-EPA vaccine in humans are currently under evaluation (Shimp *et al.,* 2013). Ultimately, many scientists think that the next logical step is to combine multiple approaches to develop a malaria vaccine, but these individual stage vaccines must show efficacy on their own. Moreover, the major challenge is there are no known correlates for immunity, meaning there is no method other than costly clinical trials in humans to demonstrate a vaccine's efficacy; thus, although great progress has been made, malaria vaccine development will continue to be a costly and multidimensional effort.

1.8 Roll back malaria

There have been some global responses to the outrageous effects of malaria in Nigeria; this includes the establishment of the Roll Back Malaria partnership by the WHO and the Global Fund to fight AIDS, Tuberculosis and Malaria (GFATM) (Jimoh *et al*, 2008). Roll Back Malaria (RBM) was an initiative intended to half the suffering caused by malaria disease by 2010; in the medium-term to reduce the number of malaria deaths to near zero by 2015; through substantial coverage of new tools and in the long term, to maintain near-zero deaths worldwide. However, it has obviously not achieved its goal as at 2015, forcing the WHO to set a further target of 90% reduction by 2030; Binka (2002) believes one of the reasons for this is that the RBM is being grossly underfunded. The World Health Organization, The United Nations Children's Fund, the United Nations' Development Programme and World Bank in 1998 joined forces to fight malaria in malaria-endemic countries. The creation of Roll Back Malaria Campaign and the greater focus on malaria in both local and international levels have increased demand for evidence on the economic impact of malaria. Chima *et al* (2003) explained that such information is needed to justify investment in research and control, and also to target control efforts both efficiently and equitably. So as to achieve the target of reducing malaria morbidity and mortality, Roll Back Malaria (RBM) has recognised access to prompt diagnosis and treatment of malaria incidence by the year 2015, as an outline in Millennium Development Goal (WHO, 2003). Chilaka (2005) explains that the main objective of the RBM initiative is to tackle the political efforts and help develop necessary economic and social conditions for the right tools to be used by all communities and countries that are affected by malaria.

In addition, the goals of the RBM movement include meeting the malaria-related United Nations Millennium Development Goals (MDGs), Abuja Declaration; and the RBM Partnership Global Strategic Plan. RBM Partnership Global Strategic Plan is expected to coordinate all efforts at malaria control; it will promote the development and better utilization of all tools for malaria control – old, new and future - as and where appropriate, and it will help strengthen the health sector. The RBM thrust, however, conforms with the on-going health sector reform (HSR) initiative in Nigeria where first-phase implementation covered 2004-2007 and sought to ensure the health of citizens in the country are guaranteed (FMoH, 2005).

1.9 Malaria in Nigeria: a historical perspective

Also known as the giant of Africa, Nigeria is by far the most populous country in Africa (over 182 million people) with a calculated growth rate of 3.2% annually. Nigeria is divided into six geopolitical zones, namely the North West, North East, North Central, South West, South East, and South South regions. It is also made up of 36 states and 774 LGAs (Local Government Areas). Malaria is endemic in Nigeria and creates a major public health issue despite the preventable/curable nature of the disease. Since malaria is associated with tropical and sub-tropical areas, the disease probably originated from Africa and was transferred to other parts of the world through human migration; especially during the slave trade era. There is no established information about the first occurrence of malaria in Nigeria; however, it is believed that during British colonization, colonialists created Government Reserved Areas (GRA) so as to build their homes far away from Nigerian citizens, because they believed flying long distances from breeding sites was a limiting factor for mosquitoes. Nigeria's quest for effective control of malaria began well before the WHO global malaria eradication period between 1955 and 1968. It started by creating parastatals that monitored the spread of malaria, including the Ministry of Health that dealt with mosquitoes and malaria issues. Also, the National Malaria Control Committee (NMCC) was set up in 1975 with the sole aim of reducing malaria burden by 25%. The NMCC only recorded a small amount of success and it wasn't till after 9 years (1988) that a major health reform was carried out. Within this new policy, malaria was planned to be eradicated using primary health care. However, in spite of these new policies, the malaria situation steadily worsened and is currently estimated at 65% of all ailments reported in Nigerian hospitals (Akanbi, *et al.*, 2009). Currently, Nigeria bears up to 25% of the total cases of malaria recorded in Africa. An estimated number of 350,000 lives are expected to be lost every year in Nigeria as a result of malaria infection; most of which are pregnant women and children under 5 years (WHO, 2018). Efforts to reduce the spread of malaria in Nigeria was boosted in 2003 when over 182 million LLINs were distributed over a couple of years. The Nigeria Institute of Medical Research (NIMR), in 2018 raised an alarm over the continuous increase in the incidence of mosquitoes resistance to LLIN in 18 States out of a total of 36 States. These States includes; Lagos, Niger, Ogun, Nassarawa, Jigawa, Katina, Kebbi, Sokoto, Zamfara, Benue, Kwara, Anambra, Enugu, Rivers, Ondo, Oyo, Osun, (two of these States are represented in this study).

Malaria over burdens an already weak health system in Nigeria with more than 110 million recorded diagnosis of malaria recorded every year; 60% of all outpatient visits and 30% of all hospital admission cases (UNICEF, 2010). Considering the WHO (2005) estimation of 1 million deaths globally, the rate of death recorded in Nigeria alone is staggering and needs urgent attention (Olowe *et al.*, 2015, Afolabi *et al.*, 2007, Jimoh *et al.*, 2007). The huge social and economic burden on Nigeria and its citizens causes an estimated amount of ₦132billion (£278 million; $363 million) loss yearly in payments of prevention, treatment, and also work-hours missed. A summary of a lot of studies from Nigeria has established that the most prevalent species of malaria parasite in Nigeria is *P. falciparum*; which is responsible for over 95% of all malaria infections. *P. ovale, P. malariae* and *P. vivax* are other parasites that can be found in Nigeria, even though they play a very minor or inconsequential role.

With regard to the economic impact of malaria, it can either affect a population directly or indirectly. The effect of malaria is not solely limited to human health, mortality and morbidity; it also has a detrimental effect on the economy, productivity, national growth and development of the areas that are seriously affected by the disease. A high percentage of government funds that could have been used to improve lives are spent on dealing with morbidity and mortality from the prevalence of malaria. Malaria is a major influence on socialisation and the economic wellbeing of people who reside in affected areas. It affects the productivity of a society and nation as a whole; draining human resources, resulting in major interference to educational activities and causing persistent economic depletion (WHO, 2008). Frequently, the effect of the disease on the social aspects of life is often ignored (Jones and Williams, 2004; Ovadje and Nriagu, 2011; Hong, 2013). Malaria is commonly associated with poverty and it is also associated with tropical and subtropical regions because of the climatic conditions. Tropical areas such as Nigeria have the optimal environmental combination of adequate temperature, humidity, and rainfall facilitating for the aggressive reproduction and survival of *Anopheles* mosquitoes. Malaria burden is not evenly distributed. The pattern of malaria transmission is such that the disease is centred in the tropics, but with a reach into subtropical regions in five continents (Sachs & Melaney, 2002).

Nigeria has one of the largest populations at risk of malaria in Africa and in the world (Adetola *et al.*, 2014) and as a consequence, the direct effect of cost related to malaria treatment and control is enormous, given the resource-poor circumstances in the country (Sachs and Melaney, 2002). The research further showed a direct significant correlation

between the rate of economic growth and the burden of malaria, even after adjusting for confounding factors (Sachs and Melaney, 2002).

1.10 The Nigerian health system and delivery structure

The health care system or health system is designed to deliver healthcare services (as seen in Table 1.5). It is a combination of people, institutions and resources that deliver healthcare services to meet the needs of a target population. The effectiveness of any country's health care delivery largely depends on the system under which it operates. The National health system is decentralized into a three-tier structure and constitutionally charges each tier with a specific level of responsibility in the health sector including stewardship, service provision and financing. There are three levels of government in Nigeria; Federal, State, and Local Government Area (LGAs). The federal level which is the highest level and also known as the Federal Ministry of Health (FMOH) is more concerned with the technical support for the whole system and also making policies. It also provides health services through the tertiary and apex referral institutions such as hospitals and National laboratories. The State governments are concerned with secondary health care system. It is also known as the State Ministries of Health (SMOH). They are also responsible for the support and regulation of primary health care services. The Local government tier (known as districts in other countries) is responsible for the primary healthcare where health services are organized through the ward. They are in charge of local dispensaries, routine immunization, environment sanitation/protection etc. There are about 774 LGAs in total and they are expected to target more people and provide easy access to health care by community members. It is, however, the weakest arm of health care system and effective access and treatment is non-existent which in turn forces most community members to seek health services from private providers (usually much more expensive) or at the State of Federal level. Even though the local government in Nigeria can be compared to Councils or Districts in more developed countries, these districts usually have a population of about 145,000 to 200,000 people compared to the LGAs with a population that can be more than 3 million people. To consider that the majority of these people depend on primary healthcare, especially people from rural areas, it is very disappointing how little effort and finance is invested to make sure people have access to good health from these centres. Apart from this, most times, confusion of roles and responsibilities occur among the three tiers of government, leading to weakness in coordinating and performance. Nigeria has a total of 34,173 health facilities: 30,098 primary, 3992 secondary, and 83 tertiary health care units (Agboghoroma *et*

al., 2013). The private sector constitutes 33% of all health facilities in Nigeria (Agboghoroma *et al.*, 2013). Private health facilities include private not-for-profit, private for-profit, pharmacies, proprietary patent medicine vendors (PPMVs), and mobile clinics.

Table 1. 5: Organization pyramid of the Nigeria Health Services

ADMINISTRATIVE LEVEL	SERVICE STRUCTURE	RESPONSIBILITY
Federal Governement	Tertiary Services	Federal Ministry of Health
State Government	Secondary Health Services	State Ministry of Health
Local Government	Primary Health Services	Council
Private Sector	Private Services	Private Health Providers

1.10.1 Nigeria

Nigeria has the second-largest economy in Africa. It is classified as an emerging market owing to rich reserves of natural resources and well-developed financial and communications sectors. The transportation sector and stock exchange of the country add to the finances.

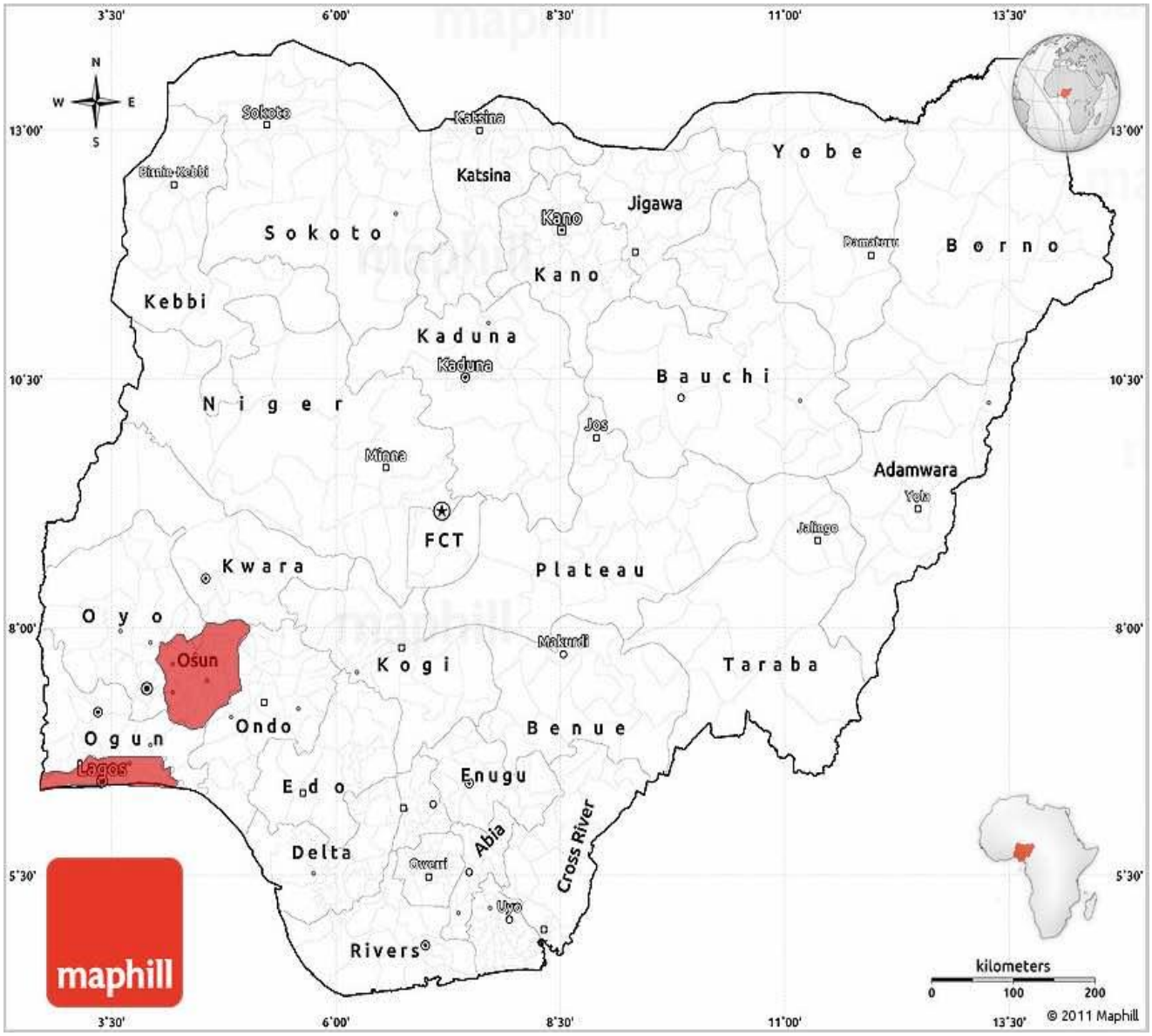


Figure 1.7: Map of Nigeria showing Lagos State and Osun State regions where the study was conducted between 2015 and 2017.

Nigeria (as seen in Figure 1.6 above) is a country comprising of thirty-six states and one Federal Capital Territory. The states are further divided into 774 Local Government Areas (LGAs). Malaria remains one of the most serious health problems worldwide (Narain, 2008) and it is a major public health problem in Nigeria (Federal Ministry of Health, 2005). The geographical location of Nigeria makes the climate suitable for malaria transmission throughout the country (see Figure 1.7). It is estimated that up to 97% of the country's population of 186 million people are at risk of getting the disease. The remaining 3% of the population live in the mountains in southern Jos (Plateau State) and at these altitudes of 1,200 to 1,400m they are at relatively low risk of malaria.

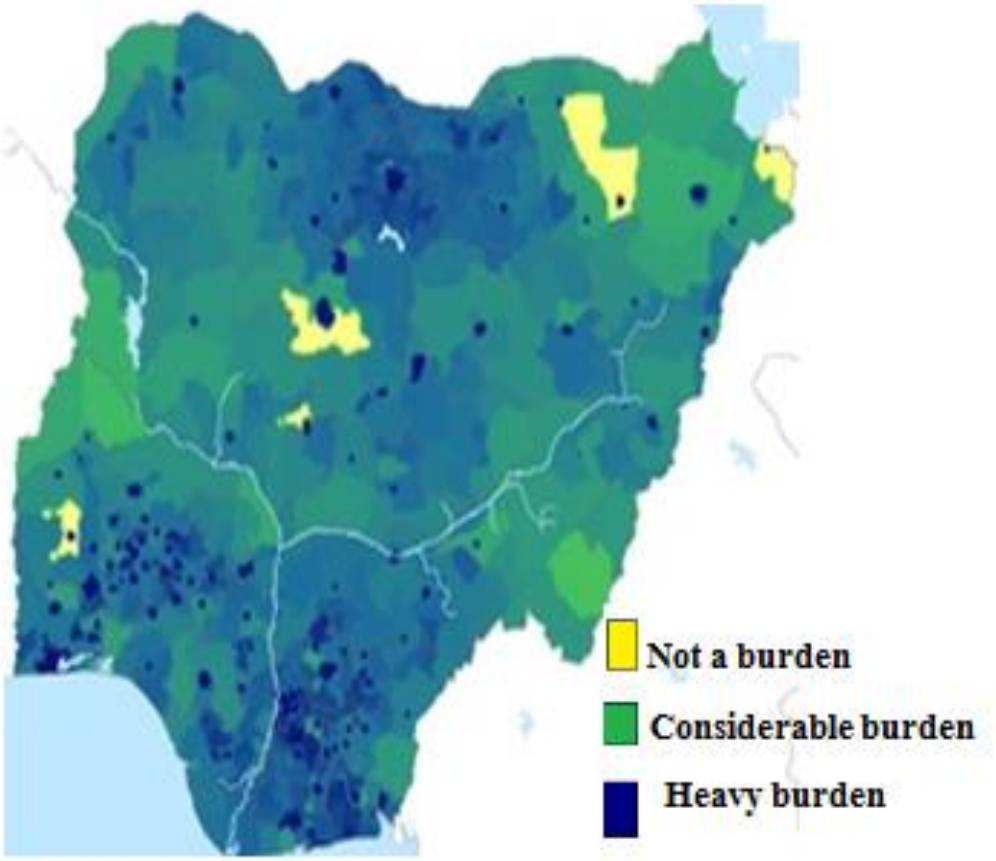


Figure 1.8: Showing the clinical burden of P. falciparum and prevalence by region in Nigeria (Gething *et al.*, 2011).

Malaria accounts for about 60% of all outpatient attendance and 30% of all hospital admissions in Nigeria (Ladi-Akinyemi *et al.,* 2018). Malaria increases the morbidity and mortality rates as well as health problems of developing countries, including Nigeria (Carrington, 2001). For instance in Nigeria, the National Malaria Control Programme (NMCP, 2007) reported that a child is sick due to malaria between 2 and 4 times a year and it

was estimated that malaria was responsible for nearly 110 million clinical cases and an estimated 300,000 deaths per year, including up to 11% of all maternal mortality. Monetary loss due to malaria in Nigeria is estimated to be about ₦132 billion (£2 million; $2.7 million) very year in terms of treatment cost, prevention and loss of man-hours ((Ladi-Akinyemi *et al.,* 2018). In order to reduce malaria epidemics, the Nigerian government and international bodies have developed a series of control measures, dating back to over 60 years (Shiff, 2002) thus, it is a desirable time point to investigate the extent of malaria burden and the effectiveness of various malaria control measures in Nigeria. The findings of the study are expected to generate awareness, which could lead to improvement in the level of government participation in the effective prevention and control of malaria in Nigeria. About half of Nigerian adults have at least one episode of malaria each year and 7 out of every 10 patients seen in Nigerian hospitals are ill of malaria (FMOH, 2005). Furthermore, malaria is one of the principal reasons for poor school attendance in many settings and is thought to account for 13 to 15 percent of medical reasons for absenteeism from school (Holding & Kitsao, 2004). In addition, pregnant women are in the high-risk groups. The Roll Back Malaria program (RBM, 2005) reported that malaria was responsible for one death out of every ten women who died around childbirth, and three out of every ten deaths in children under 5 years of age.

Lagos is a huge city that attracts different professionals from Nigeria and abroad. Its internally generated revenue was estimated to be over ₦503.7bn (£1 billion; $1.3 billion) in 2007 and it received a Federal government (FG) allocation of ₦178bn (£380 million; $490 million). In contrast, Osun state, with more farmers and civil servants, manages to generate internal revenues of approximately ₦700million and it receives a FG allocation of ₦66bn (£142 million; $182 million). The wealth index of each State in Nigeria is shown more clearly in Figure 1.8 below.

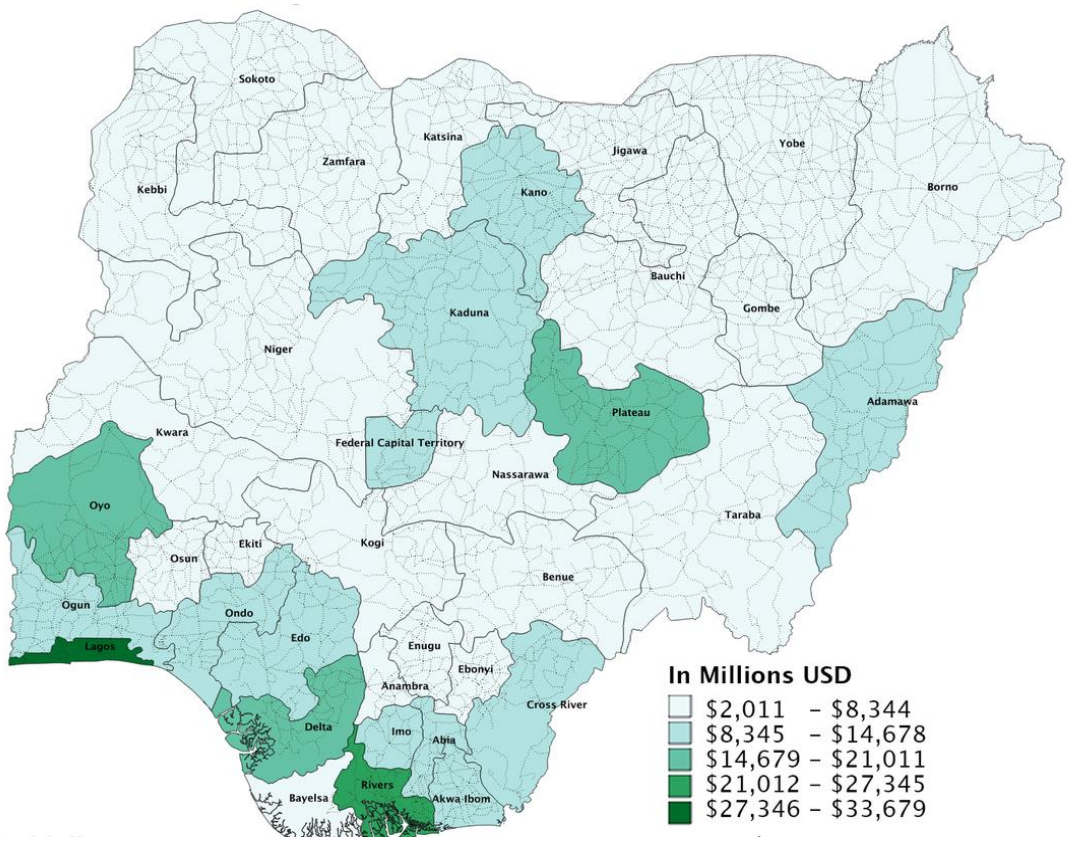


Figure 1.9: Map showing Nigerian States by GDP in 2010. This information provided on this map illustrates the huge difference in wealth of people leaving in Osun State as compared to those living in Lagos State. (Source: http://services.gov.ng/states).

1.10.2 Osun State

Osun state was created in 1991 (Figure 1.9); carved out of Oyo State, it shares borders with Kwara State to the North, Ondo State to the east, Oyo state to the west and Ogun state to the south. The people of Osun State are mostly traders, farmers and civil servants by profession. Osun has a population of about 3,423,535 inhabitants, which is a representation of 2.5% of Nigeria's total population. It covers an area of about 9,251 km^2. There are no extensive records to predict the trend and pattern of malaria in Osun State, but over the years numerous research studies have been carried out on malaria; including epidemiology, prevalence, awareness, control, treatment, morbidity and mortality. A study conducted by Bamidele *et al.*, (2012) on the community participation in malaria control in the Olorunda Local Government Area (Osun state) explains that the awareness of people about malaria infection is high and also, result shows more than 50% rate of community participation in malaria control among participants. However, the same study reports a very low usage of insecticide treated nets (ITNs).

Figure 1.10: Maps of Osun State, South-West Nigeria; showing the urban (Osogbo (A)) and rural (Iwo (B)) regions where the current study was carried out (Source: VON, 2018).

A similar result was observed by Isola *et al.*, (2015) in a study to define perceptions and practice of malaria prevention within Osun State students. Students were shown to have a reasonable knowledge about malaria control and prevention; an impressive 86.5% of the total number interviewed reported malaria to be a mosquito-borne infectious disease. In a further study by Adegun *et al.,* (2011) 75% of farmers interviewed reported that mosquitoes are the cause of malaria. Also, a study among tertiary students in Osun State by Adetola *et al.,* (2014) to define perception and treatment practices among tertiary institution students in Oyo state and Osun state, showed that a high proportion of responders (67.5%) would take prescription advice from medical personnel before treating malaria; 60.8% however did not go for malaria diagnostic tests before taking an antimalarial drug. It should be noted that before you can provide an acceptable prescription from a doctor or medical personnel you must have been diagnosed at a medical centre and the presence of the malaria parasite must have been confirmed. Therefore, in this case, it is either medical personnel in the region that are not following the protocol or just 6.7% of the respondents were actually tested in the hospital and acquired a prescription while others received medical advice outside the hospital recommendations.

Malaria prevention and control strategy is still a challenge in Osun State. Malaria is responsible for the high rate of maternal and childhood mortality. Only 1.9% of households have at least one insecticide treated net. As described by SMOH (Osun State Ministry of

Health), the incidence rate of malaria in Osun state is constantly on the rise among vulnerable groups. The prevalence of malaria in children under 5 was 158,937 in 2006 and then 230,579 in 2007. Among pregnant women, malaria incidence was recorded to be 619 in 2006 and then 9731 in 2007; a massive increase from the previous year. More recent data on the general prevalence of malaria in this region is however not available. With regard to treatment, only 10% of children under 5 were appropriately treated with ACTs in 2007. As recorded by SMOH, barriers to intervention by RBM programme in the State include low level of awareness on malaria, substandard ACTs or high cost of ACTs, low technical capacity of health workers, and unavailability of diagnostic equipment (RDT). The most recent intervention was supported by WHO in 2017, where over two million insecticide treated nets were distributed for malaria control (WHO, 2017).

1.10.3 Lagos State

Lagos state is located in the South-Western geopolitical zone. Although it is the state with the smallest land area in Nigeria, it is the most populous and arguably the most economically important state in the country (map in Figure 1.10). Lagos State contains Lagos city which is the most populous city in Africa with a population of over 21 million people many Nigerians relocate to the city from other regions and there is also many international visitors. Lagos is divided into the island and the mainland regions. The mainland harbours most of the inhabitants of Lagos and most industries are located there. Malaria is endemic in Lagos State and one of the most important reasons for this is people's behaviour and the availability of stagnant water for breeding Anopheles mosquitoes.

Figure 1.11: Maps of Lagos State, South-West Nigeria; showing the urban (Lagos Island (Lekki)) and rural (Lagos mainland (Ikorodu)) regions where the study was carried out. (Source: VON, 2018)

As seen in Figure 1.11, “The road to 2020; Mobilising the Private Sector in Nigeria’s Fight against Malaria” showed an increasing trend of malaria cases in Lagos state between 2004 and 2014.

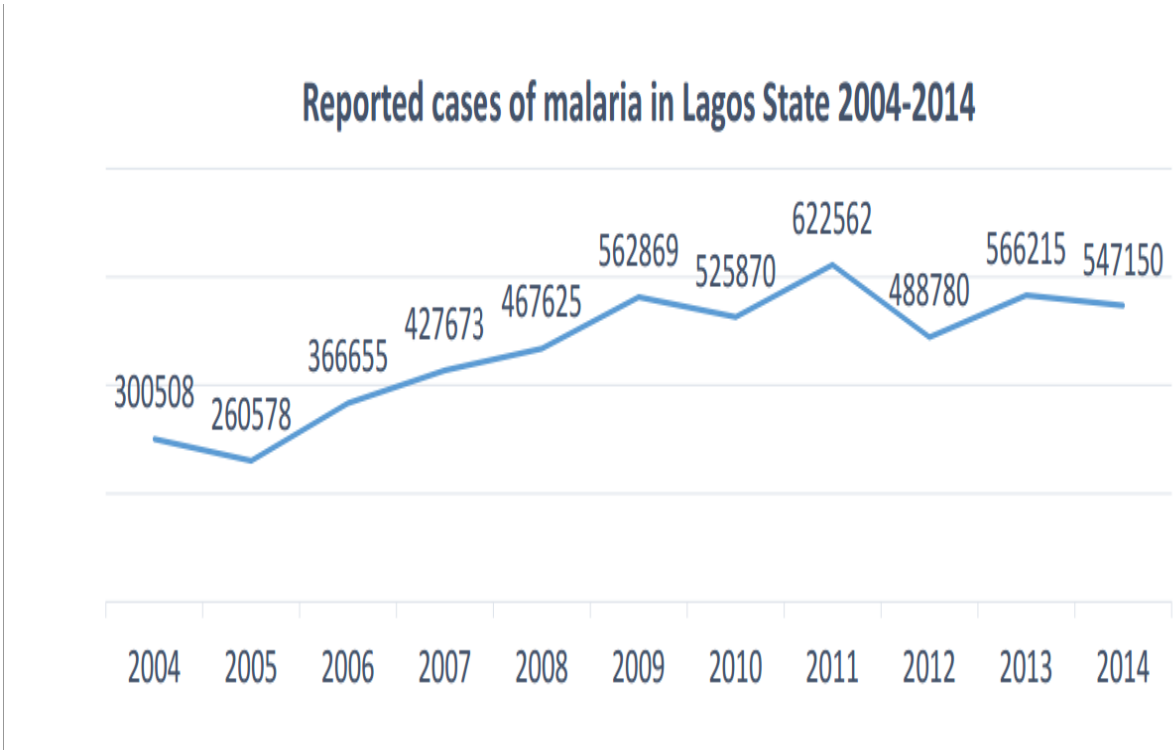


Figure 1.12: Trend of reported cases of Malaria in Lagos from 2004-2014. The number of malaria cases increased by 58% from 260,578 in 2005 to 622,562 in 2011. There was a reduction to 488,780 in 2012 and it increased to 547,150 in 2014. (Osunkiyesi, 2015)

The Lagos State Commissioner for Health, Dr Jide Idris, at the 5th “Doctors Discuss Malaria’’ Programme, in Lagos, said the state recorded 1,199,002 cases in 2016. This shows that just like most States in the country, malaria incidence has been on the increase even though there have been numerous intervention programs to curb this. However, a study by Agomo & Oyibo (2013) showed a low malaria prevalence in a community in Lagos State and the reason was attributed to the scaling up of malaria intervention programs, and mainly because the study was carried out in an urban region. One of the strategies of intervention to control malaria in Lagos included free treatment of all malaria cases in all age groups; however, the state failed to meet set targets to end the trend of morbidity and mortality because of the sudden spread of chloroquine resistant strains of *Plasmodium.*

1.11 Malaria control and treatment

In an attempt to eradicate malaria, the United Nations declared the years 2000-2010 as the malaria decade with the constitution of the Roll Back Malaria (RBM) Initiative. Since then, continuous efforts have been made not only by other international organisations but also in collaboration with malaria-endemic nations, with the sole aim of bringing the disease under control (Folande *et al.,* 2005). In light of this, the World Health Organisation (WHO) in its effort to eradicate/control malaria infection in malaria endemic countries advocates three different strategies;

- Effective Case Management (ECM) – the use of antimalarial drugs to get rid of malaria parasites from already infected individuals.
- Integrated Vector Control (IVC) – the various methods of killing mosquitoes, such as mosquito coils and indoor residual sprays.
- Personal Protection (PP) –the measures that prevent contact between mosquitoes and humans, such as insecticide-treated nets (ITNs).

These three strategies are believed to be the driving force of all parastatals and organizations to create malaria-free nations. However, for the purpose of this study, more emphasis will be placed on malaria Effective Case Management and how it affects malaria control as a whole. One of the challenges of effective malaria control in Nigeria is research-based data on cases of treatment failure to drug-resistant *P. falciparum,* however, as explained by Aribodor *et al.,* (2016), there is a difference between drug resistance and treatment failure. Inadequate clinical response or failure to clear malaria parasites after the use of a drug does not necessarily mean treatment failure and could be as a result of non-patency (inability of the drug to pass through). In an effort to reduce treatment failure, the WHO developed a protocol for assessment and monitoring drug efficacy. Patients are expected to be followed up for 14-28days, depending on the drugs used and the intensity of transmission (WHO, 2002). However, these requirements are not in place in the Nigerian Health System (NHS) unless the patient is on hospital admission before they can be closely monitored.

In Nigeria, it costs about $0.50 (₦200) to treat malaria using self-medication and about $7 (₦3000) to seek treatment from an authorized health care provider. This is because, with self-medication, some processes such has hospital registration (which costs money) can be skipped. The difference in price explains why there is a huge incidence of inappropriate

treatment methods in the country which in turn affects the effective control of the disease. Another way through which poverty affects malaria transmission is that poor individuals cannot live in houses that can protect them from mosquito bites, and they cannot afford the other preventive measures such as ITNs and IRS. On a larger scale, poor communities cannot invest in available preventive measures, governmental controls or development programs (Teklehaimanot and Mejia 2008). In most developed and undeveloped countries the rate of poverty directly affects malaria control; this could be the inability to afford common preventive measures such as mosquito coils, IRS etc. Housing conditions in these countries are also major factors that encourage the spread of malaria. Teklehaimanot and Mejia (2008), explain that the relationship between poverty and malaria has long been recognised but its paths are multiple and complex. Studies show a cycle between malaria and poverty meaning both leads to each other at some point in less developed countries.

The complexity of the life-cycle of malaria parasite is a major challenge to malaria control efforts. The process of sexual reproduction in mosquitoes and asexual reproduction in humans makes it difficult to develop a vaccine which can target the parasite. This makes effective malaria treatment the best option available to effectively control and eradicate the disease.

1.12 Treatment behaviour and perception

Common symptoms of malaria include; fever, headache, back pain, chest pain, nausea, body weakness, vomiting, (Che *et al.,* 2015). In severe cases, complicated malaria can lead to coma and sometimes death of person infected (Bell & Winstanley, 2004; Eugene-Ezebilo & Ezebilo, 2014). Malaria can easily be cured if diagnosed early and treated properly as recommended by the WHO. However, in recent years, there has been a major increase in the resistance of parasite to the commonly (recommended) used antimalarial (Affum *et al,* 2013). One of the challenges of effective case management of malaria is the fact that the symptoms are easily presumed by patients and most times wrong. In epidemic areas like Nigeria, feelings of a headache and nausea can easily be attributed to the presence of the disease and hence, treatment is sorted and most times without prior confirmation through recommended methods as advised by the Ministry of Health. Treatment of malaria without the confirmation of the parasite is a major barrier to effective case management and eventually leads to resistance of the parasite to drugs that would have been effective if used appropriately.

As rightly pointed out by Rumun and Terungwa (2015), the symptoms that are attributed to malaria vary and range from 'feeling unwell' to a rise in body temperature, especially in children. In most endemic areas malaria is over-diagnosed on the basis of symptoms alone because of its non-specificity of symptomatology. In this case, treatment is either delayed or an ineffective treatment is given and this can progress to severe malaria manifesting as coma, severe anaemia, renal failure, hypoglycaemia or acute pulmonary oedema.

In Nigeria, Okeke & Okafor (2008), carried out a study to determine the perception and treatment seeking behaviour for malaria in rural Nigeria amongst 300 caregivers; the results showed that over 60% of respondents believe that malaria is just a common illness and 50% believe that heat from the sun caused malaria. Only 19.8% correctly said mosquito bites caused malaria.

Treatment-seeking behaviour is determined by a number of factors; access to treatment source, attitude towards provider, perceived severity of illness, costs of services, educational status, and cultural belief (Okeke & Okeibunor, 2010). It is believed that rural and urban communities seek treatment differently. A study by Dida *et al.,* (2015) on the treatment seeking behaviour and associated factors among malaria-suspected patients in Ethiopia showed that over 87% of respondents did not seek treatment within the recommended first 24hours from the onset of illness. Also, 15.2% sought treatment from a non-medical centre before visiting the health institution. This data shows the extent of poor treatment seeking approaches by people living in rural areas in developing African countries. Treatment seeking behaviour is an underlying problem that affects the effective treatment of malaria. Similar results were also observed from a different study by Romay-Barja *et al.,* (2015) while trying to understand the rural-urban differences in household treatment-seeking behaviour for suspected malaria in children. Results from this study showed that fever was the main symptom associated with malaria in both rural and urban areas, and most people first treated malaria at home before visiting private clinics and hospitals (for urban households) and hospital and health centre (for rural households). It should be put into consideration that most studies on treatment seeking might only show people's approach to malaria treatment but they do not necessarily show the number of people who had malaria but treated it inappropriately or people who did not have the disease but got treated for it. Also, McCombie (2002) suggests that before examining evidence related to malaria treatment behaviour, it is necessary to consider the difficulties in defining malaria. This is because 'every attempt to develop a clinical definition of malaria that has a predictive value higher than fever alone has been mostly unsuccessful.

A recent study by Singh *et al.*, (2014) in the northern part of Nigeria showed that 12% of respondents had knowledge of the role mosquitoes play in malaria transmission and 10% know that it actually causes malaria. However, this same study showed that 90% of the respondents have a comprehensive knowledge about prevention. This proves that misconceptions about malaria transmission and its cause still exist and knowledge about prevention does not necessarily mean it affects the approach to treatment.

1.13 Self-medication

WHO (2000) agrees that self-medication is an important part of Public Health which plays a key role in healthcare systems. Evidence of self-medication can be traced back to the 1960s (Bhuyan, 2014). As quick treatment using an effective antimalarial drug is the most crucial technique in preventing mortality and morbidity from malaria, it is very important that when treatment is done it is in line with the recommendations of WHO and country's health policies. However, in many malaria-endemic countries, health care structures are poor and most people find it difficult to access health care services (McCombie, 2002). Despite the growing research interest in self-medication, little information has been available about its major determinants especially in developing countries (Afolabi, 2008).

There are various definitions of self-medication or self-care. Metta (2014) defined it as "*a process in which individuals undertake disease prevention, detection, and treatment on their own without consultation to health care providers; it entails self-diagnosis and use of remedies previously prescribed for similar illness and/or the purchase of medications without personal advice*". McCombie (2002) defined self-treatment as "any treatment that does not involve consulting a health care provider or traditional healer". However, for this thesis, self-treatment is defined as any treatment that does not involve consulting health care providers prior to an attempt to buy antimalarial drugs to treat a suspected case of malaria. The reason for this is that some people actually visit health care providers such as in pharmacy stores to discuss their symptoms and buy any antimalarial drug the pharmacists prescribe. The WHO (2002) recommends that before any case of malaria is treated, there must have been a confirmation of the *Plasmodium* parasite in the client's body. Research done in this area shows that people self-medicate because of three important factors; time, cost, and severity of symptoms (Vukovic, 1999). Self-medication can be because of the beliefs that patients spend too much time waiting to be diagnosed or treated for malaria at hospitals and clinics. They prefer a drug vendor or a pharmacy store where they can walk in and finish the whole malaria treatment process quickly. In addition to this, because people in malaria-endemic countries

treat malaria many times in short periods, they believe to have mastered the disease and are 'fit' to prescribe the best treatment. They believe they know which one works better, how fast it works, and how your body reacts to it. Self-medication is so bad in Nigeria that people practise what is called 'counting'; which literally means counting different kinds of antimalarial together to make it effective and fast too. Some people, because of the poor access and state of health facilities prefer to receive initial treatment for illnesses at home using antimalarial drugs purchased from local shops without prescription (Chipwaza *et al.,* 2014) than to go to the hospital; where the efficacy of drugs and its safety cannot be trusted, Mugisha *et al.,* (2002) explains that self-treatment saves time and also reduces cost for treating sickness because people have the power to decide what to buy. It is generally believed that self-medication is prevalent among poor people, however, evidence shows that other socio-demographic factors such as age and educational level can also affect people's attitude towards treatment. Luckvic *et al.,* (2014) described more in details the numerous factors that influence self-medication to include; family attitudes, advertising of drug manufacturers, previous experiences with a disease or symptoms, and also, legislation regulating dispensing and sales of drugs. The risk associated with this is the lack of clinical evaluation by the care provider which could result in misdiagnosis and wrong choice of drugs (including the wrong dosage) (Hughes *et al.,* 2001). It could also lead to treatment failure and other adverse drug reactions.

Poor diagnostic ability in addition to limited knowledge of appropriate management of malaria results in the increase of self-medication and low rate of health care utilization (Afolabi, 2008). The availability of antimalarial drugs over the counter is also a factor that encourages self-medication. People can easily store these drugs at home to treat symptoms of malaria at any time they want. A hospital-based study in Tanzania showed that over 72% of respondents actually have already used home kept antimalarials for fever symptoms (Mnyika *et al.,* 1995).

It should be noted that self-medication is not without its advantages; it can help patients take care of minor ailments, reduce pressure on health care providers especially in developing countries where insufficient health care providers are prevalent. It can reduce the cost of treatment and pressure on medical services, but only when done appropriately and not in malaria suspicious cases.

1.14 Counterfeit drugs

Counterfeit drugs are fast becoming a major public health issue, affecting not only developing countries but also developed countries with effective regulatory systems and market controls. The production of counterfeit drugs is a broad and under-reported problem that is affecting poorer countries (Akinyandenu, 2013). The WHO (2003) defined counterfeit medicine as "any medicine which is deliberately and fraudulently mislabelled with respect to its identity and/or source" and this may include medicines containing the wrong amount of active ingredients, wrong active ingredient, or no active ingredient. The detrimental effect of counterfeit drugs includes unexpected side effects, treatment failure or even death (Lawson *et al.,* 2014). The WHO (2012) states that globally, more than 10% of drugs that are traded are counterfeits. Counterfeiting in general is a huge problem in Nigeria; ranging from entertainment, currency, electronics, among others. None of these, however, can harm citizens as much as drug proliferating can. Counterfeit drugs are produced to look exactly like original drugs that it might only take a laboratory test to differentiate. As Taylor *et al.,* (2001) rightly points out the quality of medicine produced in the majority of the less developed countries have incorrect active ingredients. For example, Newton (2014), described a case of a huge shipment from China of about 1.4million packets of antimalarial was seized in June 2012. One of the groups seized was labelled to be produced by 'Novartis Pharmaceutical Corporation' one of the biggest antimalarial drug producers in Africa. It was labelled as a vital artemether-lumefantrine drug in the Country. It was however after the tablets were analysed using different analytical methods, that it was found that no artemether, lumefantrine, or any active pharmaceutical ingredients were in the tablets.

Unlike counterfeit drugs, substandard drugs are most times genuine but for some reason or the other may not meet the drug quality requirement intended by the manufacturer. As Affum *et al.,* (2013) explains it, substandard drugs most times either do not have up to the appropriate amounts of Active Pharmaceuticals Ingredients (API) or have more than the API required. However, it should be noted that the percentage of API in genuine or authentic drugs may be affected by extreme temperature or humidity (Taylor *et al.,* 2001). There are numerous detrimental effects of the use of counterfeit or substandard drugs; from adverse side effects to treatment failure. One very important after effect of using a counterfeit drug for malaria case management is the development of drug-resistant parasites; the major contributor to the increasing rate of drug-resistant *P. falciparum* is the use of substandard anti-malarial drugs (Affum *et al.,* 2013). This is because these substandard drugs being used

do not have accurate API to clear the parasites from the infected body. Substandard medicines and medical products and counterfeit drugs cause avoidable, mortality, morbidity, drug resistance and loss of faith in health systems, which is one of the biggest problems of health seeking Nigerians. Over time, cases of treatment failure or death recorded in hospitals in Nigeria has made it hard to convince patients to trust and receive treatment for serious ailments (in this case, malaria) in hospitals. The WHO's recommendation of ACTs as the first-line treatment of malaria is emphasised in Nigeria and this has made ACTs a major target for counterfeit production. WHO (2013) estimates that 60% of the counterfeit drugs purchased in developing countries does not have the Active Pharmaceutical Ingredients (API); 17% contained too much or too little while 16% contained the wrong ingredients

A survey was carried out by Newton *et al.*, (2006), on the proliferation of fake drugs between 1999 and 2002, and results showed that 38% to 53% of the artesunate antimalarial drugs produced by Chinese and Indian companies were counterfeited. However, although there is not enough data to support this, some people actually buy these counterfeit drugs on purpose because of their price compared to the authentic drugs and also, because they think the substandard drugs are equally effective (Chiwendu, 2008). Akinyadenu (2013) says that counterfeit drugs are a cause of morbidity, mortality and loss of confidence in health and medicine structures especially in areas where they are endemic. The United Nation Office on Drugs and Crime implies that China and India are major exporters of counterfeit drugs Nigeria (UN, 2010). Therefore all ACTs that are imported into Nigeria from these countries should be properly monitored and evaluated from time to time. A report from Pfizer shows that the profit from counterfeiting even surpasses profits from heroin and cocaine (PGS, 2007). The rate of fake drugs has continuously increased in the past decade that Osibo, (1998) suggested that there may be more fake drugs in circulation than genuine drugs; a statement later supported by WHO in 2013 (WHO, 2013). Nigeria is one of the countries at the centre of the massive counterfeit drug production/usage and this is largely due to inadequate infrastructure and the political will to properly introduce and enforce legislation. The Nigerian government in its effort to reduce substandard and counterfeit drugs in 1998 introduced decree NO 21, which makes it illegal to sell or distribute banned and adulterated drugs (Akinyandenu, 2013). National Agency for Food and Drug Administration Control (NAFDAC), which was created in 1993 was introduced to help curb the distribution of fake drugs and was able to reduce drug failure rate by 16% in 2006 from the total number in 2002 and circulation of counterfeit drugs fell by 80% between 2001 and 2006 (Akinyandenu,

2013). Poverty in developing countries, poor regulatory systems and the rising cost of original therapeutic agents are the main reasons behind the increase in the production of fake drugs because of the huge profit margin (Karunamoorthi, 2014).

Little research has been done in Nigeria to determine the quality of antimalarial drugs including Taylor *et al.,* (2001); *"pharmacopoeial quality of drugs supplied by Nigerian pharmacies".* This study aimed to determine the API of different medicinal drugs being sold at pharmacy stores in two different urban areas using HPLC as a method of analysis. This study, however. did not necessarily check if these drugs were counterfeit or authenticate the source of the drugs. Using the British Pharmacopoeia limits, results showed that out of a total of 581 samples, 279 (48%) contained the amount of active ingredients outside the appropriate limit and for all the group of drugs checked, including antimalarial, antibacterial, and anti-tuberculosis; more than 50% failed to meet the BP specifications. To improve on this research, the test of efficacy and authenticity of antimalarial drugs using FTIR and *in-vitro* cultures to determine two things; the prevalence of counterfeit drugs in the communities where this research is being done and also the efficacy of the antimalarial drugs in *Plasmodium* parasites across urban and rural areas of two different States will be done.

Nigeria is one of the major selling sites for counterfeit product manufacturers (Figure 1.12). The porous control system of the Nigerian economy has enhanced the manufacturing and distribution of fake and substandard drugs in the country (Akinyadenu, 2013). Although there are various laws and policies that are in place to regulate and control the manufacture and distribution of drugs, Erhun *et al.,* (2001) describes the situation as far from adequate.

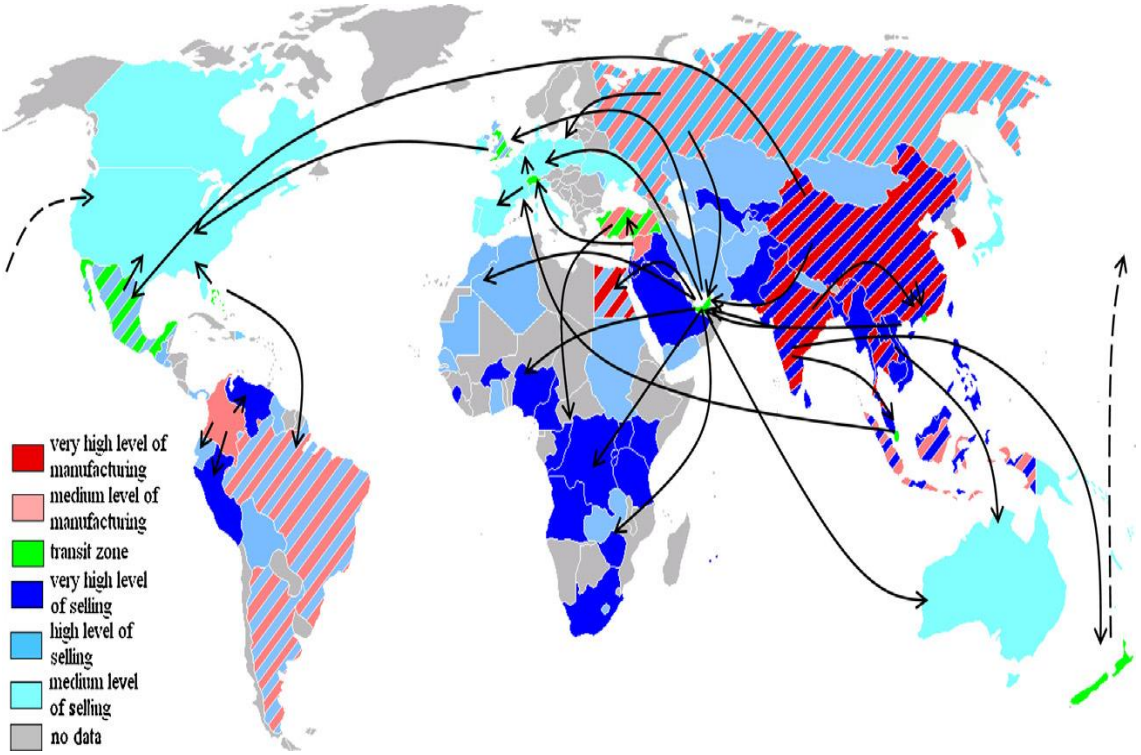


Figure 1.13: Global repartition of medicine counterfeiting in the world – from level of production to selling (Dégardin *et al.*, 2014).

1.14.1 Quality assurance/control

1.14.1.1 FT-IR

FT-IR is a technique that is used to collect an infrared spectrum of absorption, emission, photoconductivity, or Raman scattering of a solid, liquid, or gas. FT-IR stands for Fourier Transform Infrared; it is the desired method of infrared spectroscopy. The process of infrared spectroscopy involves infrared radiation being passed through a sample; some of the radiation is absorbed by the sample being tested while some passes through it. It then provides a spectrum that represents the molecule's absorption and transmission, providing a molecular fingerprint of the sample. Karzarian *et al.*, (2013) defined FT-IR as a highly versatile, label-free, and a non-destructive chemical imaging method that can be used to study a wide range of samples and systems. The information that FT-IR provides includes identifying unknown materials, determining the quality or consistency of a sample and it can also determine the amount of components in a mixture. Since every material is composed of unique combinations of atoms, no two compounds will therefore produce the exact same infrared spectrum. Generally, FT-IR spectrometers are widely used in petrochemical engineering, food analysis, organic synthesis, polymer science and pharmaceutical industry. In order to satisfy a safe and effective therapy, especially drug-related, it is imperative to identify and quantify the impurities present in raw materials, therefore, control of impurities is a key

component of the quality of pharmaceutical substances and their products and it also represents one of the biggest challenges for analysis in the industry.

FT-IR spectroscopy is very often used in the pharmaceutical industry for the identification of drug products (Higgins *et al.,* 2008) and like other optical spectroscopic techniques, FT-IR can also provide quantitative information and can be used to predict the concentration of pharmaceuticals in both solid and liquid states.

1.14.1.2 NMR Spectroscopy

Nuclear Magnetic Resonance spectroscopy is a powerful and theoretically complex analytical tool. NMR spectroscopy is an important technique that can be used to determine the physical and chemical properties of atoms and molecules. The NMR spectroscopy is an important technique for determining physical and chemical properties of atoms and molecules. It is the only spectroscopy method that provides complete information and interpretations of the entire spectrum such as information about the structure, reaction state, dynamics, and chemical environment of molecules. The technique relies on the fact that the atom's intramolecular magnetic field changes its resonance frequency, giving access to the electronic structure of the molecule. The NMR spectroscopy is commonly used to analyse the properties of organic molecules, although it is applicable to any kind of sample that contains nuclei possessing spin.

NMR spectroscopy plays a very important role in the continuous expansion of the pharmaceutical industry and most importantly since high-throughput screening the discovery process for new therapeutics (Powers, 2008). In the pharmaceutical line, there are three important stages that run every pharmaceutical company or industry; lead discovery, drug optimization, and clinical evaluation. NMR provides a valuable contribution to these three stages (Stockman *et al.,* 2009). Fukushi (2006) believes NMR is the analytical tool used to determine the composition and chemical structure of both synthetic and natural product chemical leads. The mode of action of NMR is its use as a powerful, universal and fast-screening technique to detect intermolecular interactions with unparalleled sensitivity and also its ability to provide information about structure-based design. NMR is well known for its ability to identify and quantify small molecules in a complex mixture (Lewis et al, 2007). Nyadong *et al.,* (2009) and Holzgrabe *et al.,* (2011) have also used NMR to identify counterfeit drugs from field samples. The three sub-discipline of NMR are solid-state NMR, NMR imaging (MRI) and solution- state NMR.

1.14.3 High Performance Liquid Chromatography (HPLC)

HPLC is the premier analytical technique used in many pharmaceutical applications including potency/purity/performance assays, pharmacokinetics/bioanalytical testing, purification, high-throughput screening, In-Process control (IPC), monitoring and Quality Control (QC) testing. HPLC can provide information about the composition and quality of drug-related samples. HPLC play an important and critical role in the field of pharmaceutical industries and analysis since it is used to test the products and to detect the raw ingredient used to make them i.e., qualitative and quantitative analysis. Moreover, the importance of HPLC uses in these fields falls under the stringent regulations established by the U.S. Food and Drug Administration (FDA). This obligate all pharmaceutical companies to detect the quality of their products by using the HPLC before allowing them to sell it in the global market. It may also be used to further our understanding of the normal and disease process in the human body through biomedical and therapeutically research during investigation before the drugs registration.

Other methods to determine the quality of a drug includes; the Near Infra-red Spectroscopy (NIR), which produces spectra that carry the information not only regarding chemical but also physical phenomena (Sauzier *et al.,* 2016; Rodionova *et al.,* 2018).

1.15 Summary

Effective malaria case management is pivotal to the complete removal of malaria disease in Nigeria and other countries. To rapidly promote this, the Federal Government has officially prohibited the use of inefficacious medicines such as chloroquine, SP and other monotherapies and has increased its effort to build the system to detect fake and substandard medicines while also monitoring pharmacovigilance in collaboration with NAFDAC. The only drug which has shown high efficacy against the malaria parasite is the Artemisinin-based Combination Treatments (ACTs), and has been adopted by Nigeria for the treatment of uncomplicated cases.

1.16 The aims and objectives

The project proposes to qualitatively and quantitatively analyse chemotherapeutic practices and outcomes at an individual and community level in two selected States (Lagos and Osun) in the South West Region of Nigeria; in a bid to explore the relationship between socio-economic backgrounds, self-medication practices, and treatment practices, as barriers for malaria case effective management. These two locations, with a close proximity, have similar

geographical properties but different wealth status. I am local to these areas as I have lived in both States; which is my main motivation to make a difference in these regions. This level of comparison (between a group of high socio-economic class and lower socio-economic class) provides an opportunity to identify and provide solutions to a group of people with the same malaria endemic rate but with different Socio-economic status (SES), exposure, and employment rate. Other project objectives to assist understanding these barriers are:

- To compare malaria treatment data records from hospitals and regional pharmacies, in a bid to identify barriers to malaria effective case management as a result of a health provider's non-adherence to recommendations and policy.
- To qualitatively analyse randomly sampled antimalarial drugs from the region using FT-IR spectroscopy and in vitro culture methods to evaluate the spread of counterfeit drugs.

Overall, the thesis work aims to contribute to strategies currently in use by international health organizations (such as WHO, UNICEF, etc.), governments and non-governmental organizations to improve malaria intervention programmes; the focus is upon Nigeria but findings could also be applicable to other malaria endemic countries.

Research questions

RQ1: Are the socio-demographics of residents in these regions (as defined by age, educational level, residence, and stated willingness to pay) associated with barriers to malaria effective case management and their malaria treatment-seeking behaviour (as defined by percentage of people who self-medicate or/and are treated with drugs outside the adopted recommendations)?

RQ2: Is the type of medicine store (defined as pharmacy stores and PPMVs) where treatment is sought associated with adherence to recommended malaria treatment practices?

RQ3: Are hospital care-givers adhering to the recommended treatment policies?

CHAPTER 2: MATERIALS AND METHODS

2.1 Field sampling: Study 1 (Hospital)

A retrospective evaluation of quality and types of malaria management was carried out in 25 hospitals; including public and private owned Clinics in Osun State and 19 in Lagos State (Figure 2.1) as part of a larger study to investigate barriers to effective malaria case management in two Southwest States in Nigeria. It is commonly used in Social Sciences, for example information collected by the government for census etc. In this case, data already collected by doctors and nurses for hospital records are used as secondary data for this research.

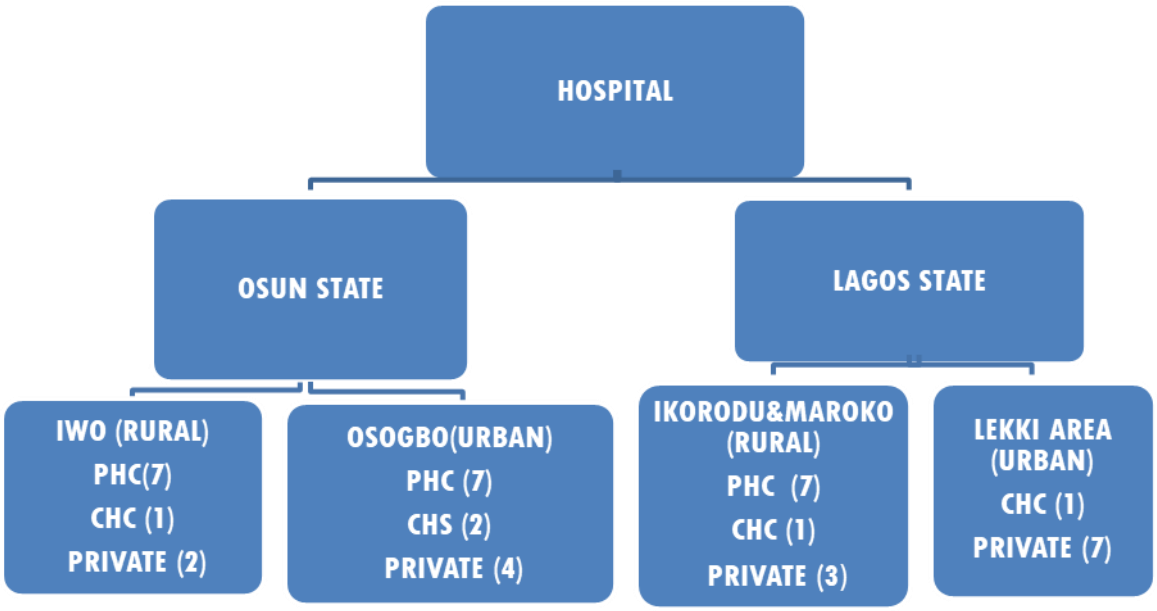


Figure 2.1: Sampling areas for current study: PHC = Primary Health Centre. CHC = Comprehensive Health Centre (General Hospitals, State Hospitals, Dental Centres and Staff Clinics).

2.1.1 Hospital questionnaire

Number of patients suspected to have malaria…….

Suspected malaria patients in whom any test was carried out…….

Suspected malaria patients assessed clinically only…….

Suspected malaria patients tested by microscopy……

Suspected malaria patients tested by RDT……...

Cases appropriately tested using (RDT + Microscopy)……...

Suspected malaria patients found to be negative……..

Confirmed negative cases treated with antimalarial…….

Negative cases not given antimalarial……..

Cases found to be malaria positive……...

Positive cases appropriately treated with ACT……

Positive cases treated with Quinine……..

Positive cases treated with SP……..

Positive cases not treated with antimalarial…….

The questionnaire was designed after a selective literature review on malaria treatment practices in Nigerian hospitals with particular emphasis upon adherence to diagnosis and treatment guidelines (Bamiselu *et al.,* 2016; Onwujekwe *et al.,* 2009; Bello *et al.,* 2013). A purposive sampling method was adopted; hospitals with higher patient loads were targeted in a bid to cover as many patients as possible.

2.2 Field sampling: Study 2 (Pharmacy and Patent and Proprietary Medicine Vendors (PPMVs)

For data collected in regards to drugs purchased by clients, a prospective, descriptive, cross sectional survey was carried out in the two States at medicine retail outlets comprising of pharmacies and PMVs between the month of April and September 2015 and also repeated between September and November 2016 during the second year data collection phase. Cross-sectional studies are simple in design and very useful at finding out the prevalence of a problem or attitude by taking a snap-shot or cross-section of the population. This makes the method appropriate for this part of the research; the attitude or behaviour of a group of people towards malaria treatment can be analysed over a period of time. However, a disadvantage of cross-sectional study is that it is not longitudinal by design, where each participant is observed at multiple time points, thereby allowing trends in an outcome to be monitored over time (Sedwick, 2014).

With the use of a questionnaire which is made up of 8 questions (refer to section 2.4.1), data such as the education level of the pharmacist, patient demographics, drug prescription

method, drugs requested and drugs purchased were obtained. Data were also collected to ask questions about pre-diagnosis, self-medication, and if pharmacist had influenced the clients' decision on which drugs to buy. For the purpose of this research, self-medication was defined as drugs specifically requested by clients without a proof of prescription. However, it should be noted that people sometimes speak with relatives or friends that are qualified health providers and do not necessarily have a form of written prescription.

The way Nigeria's health system is set up makes it unrealistic or impossible to conduct a probability sampling for this study. To accurately capture the pattern of drug use and treatment in all Pharmacy Stores and PPMVs, a convenient sampling was used to purposely select a representative number of medicine retail outlets across urban and rural areas in the three States. This sampling was purposely designed to include pharmacy stores and PMVs with high rate of utilization or patient load, and retail stores with extremely low utilization levels were dropped. For example, outlets with very few clients and number of malarial cases attendance would not produce accurate data to effectively determine an association between variables, compared to data from other stores with high patient load, or test a hypothesis. So, pharmacy stores and PMVs with high utilization level (at least 20 antimalarial per week) were selected. The medicine retail outlets were strategically selected to cover all parts of the urban regions and also the rural regions of each State selected for this study, with 20 people targeted at 10 outlets in each region.

Figure 2.2: Area of Pharmacy and PPMV data collection site (Lagos rural)

Figure 2.3: Area of Pharmacy and PPMV data collection site (Lagos urban)

Figure 2.4: Area of Pharmacy and PPMV data collection site (Osun urban)

Figure 2.5: Area of Pharmacy and PPMV data collection site (Osun rural)

2.2.1 Pharmacy and PPMVs questionnaire

1. Educational level of pharmacist/drug vendor: Primary □ Secondary □ Tertiary □ none □

2. Which Antimalarial drug do you mostly prescribe to clients?

Amatem □ Coartem □ Leonart □ Combiart □ Choloquine □ Fansidar □

Others *(please provide with the name)* ……..

3. Sex of client: Male □ Female □

4. Has the client shown any proof of diagnosis? Yes □ No □

5. Is the client self-medicating? Yes □ No □

6. Which Antimalarial drug was purchased by client?

Amatem □ Coartem □ Leonart □ Combiart □ Choloquine □ Fansidar □

Others *(please provide with the name)* ……..

7. Did the pharmacist influence the decision in which drug to buy?

Yes □ No □

8. Price of Antimalarial drug purchased by client? ₦……..

This questionnaire was designed after a selective literature review on malaria treatment practices in medicine retail outlets. The previous studies (Beyeler *et al.*, 2015; Ezenduka *et al.*, 2014; Isiguzo *et al.*, 2014; Liu *et al.*, 2015; Mamodesan, 2015) have included questions such as education level of the drug seller, antimalarials sold (ACTs or non-ACTs) and price of drug. However, the current research also added questions on the influence of the drug seller on the type of antimalarial sold to the client since a preliminary interview showed that a lot of clients depended on the expertise or knowledge of the seller in prescribing an antimalarial. Also, a purposive sampling method was adopted; pharmacy stores and PPMVs with a high client visitation were targeted in a bid to cover as many patients as possible.

2.3 Field sampling: Study 3 (Community data)

This descriptive cross-sectional study was done between April and September 2015 in the community survey and was repeated between September and November 2016 using cluster sampling methods. Volunteers were recruited from CELSUM (Centre for Life Support Mission) and were properly trained by prior lectures to distribute and assist those unable to complete the questionnaires. Information was collected on the demographic characteristics of the respondents in each selected household, and also participant's malaria treatment method, willingness to pay for antimalarial and malaria dosage completion episodes were recorded. The economic status of responder was also recorded to be able to compare social economic status with willingness to pay for drug.

In selecting the households for questionnaire administration, the state was first divided into two groups (urban centre and rural centre). From each centre, with a random sampling technique, participants were randomly picked to complete the questionnaire with everyone having an equal chance of being picked. The target of respondents was different for both States, with more participants recruited from Lagos compared to Osun State. This was done to accommodate possible errors in questionnaire filling or people not returning the completed questionnaires. Participants were interviewed using the questionnaire and their responses were recorded by them or the interviewer if need be. The Office for National Statistics (2010) explains that the main objectives of a questionnaire are to obtain accurate information from respondents, provide a logical structure to the interview so that it flows smoothly and facilitate data entry and processing through the use of coding. Cotetzee (2005) explains that not only is the use of questionnaires cheap, it also saves time as a lot of information can be collected within a short period of time. In contrast, Welman and Kruger (1999) argue that the possibility of response to a questionnaire is low and researchers have low control over the condition under which the questionnaire is being filled. Trained interviewers/enumerators were used in all centres to help in the gathering of data during the interview session with each participant. The interviewed participants within each centre were selected systematically such that after the first household, every 10 is selected until the target for the village is covered. A preliminary survey was done to find out the prices of the available antimalarials in the market and a mean of the sum was calculated to determine an ideal amount a client would be willing to pay for treatment. However, other questions such as gender, age, employment status and last case of malaria treated has been used in previous studies (Adetola *et al.*, 2014;

Onwujekwe *et al.,* 2013; Klein *et al.,* 2012; Jimoh *et al.,* 2007). Children under the age of 16 were excluded from this study.

2.3.1 Community questionnaire

1**. Sex**: Male □ Female □

2. **Age group**: 16-20 □ 20-25 □ 26-30 □ 30 and above □

3. **Marital status:** Single □ Married □ Divorced/Widowed □

4. **Educational level:** Primary □ Secondary □ Tertiary □ none □

5. **Socio-economic status:** *(Please tick which of the following you possess)*

Car □ Television □ Generator □ Computer □ Owned apartment □

Employed □ Unemployed □

Salary earned per Month: ₦0 - ₦10,000 □ ₦10,000 - ₦50,000 □ ₦50,000 and above □

6. **How much are you willing to pay for treatment?**

Less than ₦500 □ More than ₦500 □

7. **When was the last time you had malaria?**

Within the past 1 month □ within the past 6 months □ within the last 1 year□ can't remember □.

8. **How often do you have malaria in a year?**

Less than 5 times in a year □ Between 5 and 10 times a year □ More than 10 times in a year □

9. **Treatment sorted**: Amatem □ Coartem □ Leonart □ Combiart □

Choloroquine □ Fansidar □ Herbal (*please name*)……. others *(please name*……..

10**. Were you diagnosed before treatment? (Microscopic and others)**

Yes □ No □ I don't know □

11. Where did you get treatment from?

Hospital □ Drug vendors □ Pharmacy store □ did not get treated □ others □

12. How often do you complete your antimalarial dosage?

Always □ Most times □ I stop when I feel better □

2.4 Selection of drugs

After field sampling and information about prescription and treatment method was gathered, the researcher went across pharmacy stores and PPMVs in the community where the field work was done to buy popular samples of antimalarial drugs mostly used by responders. This was done with the aim of checking for the level of substandard and counterfeit drugs usually used to treat malaria in these locations as a barrier to effective malaria case management. Sample drugs kept at room temperature just the way they are kept at Pharmacy Stores and were analysed within a short period of time.

2.5 Data analysis

The initial set of quantitative data obtained was analysed using Statistical Package for Social Science (SPSS). Quantitative variables were described using various statistical approaches as appropriate e.g. mean and median. Categorical variables are analysed using frequency and proportions. Pearson's Chi-square test and Fisher's LSD (Least Significance Difference) test was done to find an association between two variables using a p value of <0.05 as statistically significant. In case of borderline significance, a Fisher's exact test or likelihood ratio was calculated. Data collection for this study was done over two years (2015-2016). The first year of data collection was done in Lagos (Lekki to represent urban region and Ikorodu to represent a rural region) and in Osun State (Osogbo to represent an urban region and Iwo to represent a rural region). The same process was repeated during the second batch of data collection; however, it also included Makoko village (rural) in Lagos. Socio-demographic data and data on treatment choice were collected in the communities with the use of a questionnaire, and this was related to data on treatment practices collected in hospitals, pharmacy stores and PPMVs that are co-located in the community where the research was being done. For every community where data collection was carried out in the first year, 100 responders were targeted and 120 questionnaires were distributed each time. In the second batch of data collection, 60 participants were targeted and 100 questionnaires were distributed.

2.6 Ethical considerations

Ethical approval for this study was obtained separately in each State where the research was carried out. In addition to the ethical approval obtained from the University of Salford (CST 15/32), ethical approval was also obtained from the panel of the ethics board, Ministry of

Education, Osun State (OSHREC/PRS/569T/48) and the panel of the ethics board, at Lagos State University (LREC/10/15/418).

2.7 Consent

Informed Consent was also obtained from hospitals, medicine retail outlets and community individuals that participated in the study prior to obtaining any information. Confidentiality of data was assured and it was cleared that any participant could withdraw their data from this research if they decided not to participate in the research anymore. Copies of all the consent forms are available in the Appendix section.

2.8 Willingness to pay (WTP)

The literature (Asante & Okyere, 2003; Onwujekwe *et al.,* 2007) describes three approaches to measure the economic burden of malaria: Production Function Approach (PF), Willingness To Pay Approach (WTP), Cost Of Illness Approach (COI). The WTP was adopted for the purpose of this research; this is because there are different factors that can affect people's willingness to pay for an antimalarial drug; the most important factor as stated by Onwujekwe *et al.,* (2007) is income and social economic status. Considering the higher amount that a customer has to pay for an ACT compared to the amount you pay for other non-ACT drugs such as chloroquine (Quinine) and Fansidar (SP), it is therefore important to consider people's willingness to pay for ACT as an important factor that can be a barrier to effective case management. The idea behind WTP approach is that it includes asking responders through the use of a questionnaire, how much they would be willing to pay to receive a health-related service or prevent an undesirable health outcome (Jimoh *et al.,* 2007). In this study, a stated WTP was included to identify motivation behind treatment practices.

2.9 Evaluating drug efficacy

2.9.1 FT-IR spectral measurements

For the acquisition of infrared spectra of standard drugs as well as field sample drugs in tablet form, a Thermo Nicolet 5700 FTIR spectrometer equipped with removable KBr optics and deuterated triglycine sulphate (DTGS) detector was used. The Thermo Nicolet 5700 FTIR spectrometer is controlled by OMNIC (Thermo Nicolet Analytical Instrument, Madison. WI), an IR spectra analysis software package. All spectra were recorded averaging 32 scans in the range of 4000-400 cm^{-1} at a resolution of 400 $cm^{-1.}$ Before taking the spectrum of each standard and sample drug, a fresh background was first recorded from a KBr pellet. This was

done so that data from the sample drug is not contaminated with other chemicals Also, the carbon dioxide and other chemicals in the air vibrate when hit with IR radiation and show up in the spectrum if a background spectrum has not been collected. The spectral patterns for the drugs were compared to reference standards obtained from assigned distributors.

2.9.2 FT-IR Sample preparation procedure

The only preparation required for the sample drugs for FTIR analysis is grinding. The tablet samples were weighed accordingly and ground to a fine powder in a mortar to reduce the particle size. The weight of each sample was calculated using the ratio of artemether and lumefantrine present in the drug (some ACTs may have a ratio of 20/120 or 40/480 artemether and lumefantrine respectively). The pellets were scanned from 4000 to 400 cm^{-1} on the Thermo Nicolet 5700-FT-IR spectrometer.

2.10 *In vitro* culture of *Plasmodium falciparum*

All procedures were carried out in the pathogen laboratory (University of Salford) in a sterile hood (ESCO class II Biological safety cabinet), using aseptic techniques and pre-sterilised equipment. Virkon (Antec International, UK) was used to disinfect waste material before autoclaving and disposal. All routine culture methods were consistent with those employed by Read & Hyde (1993).

2.10.1 Preparation of complete media

RPMI 1640, 1x (+) L-Glutamine (+) and 25mM Hepes (Gibco, Life Technologies, UK) was used as the basis of the culture media. Four additives; 2.5 g bovine serum albumin fraction V (Sigma, UK), 2.5 ml 1 mg/ml hypoxanthine (Sigma, UK) in phosphate buffered saline (PBS) (Fisher Chemical, UK), 2.5 ml 40% glucose (dextrose anhydrous, Fisher Scientific, UK) in sterile water and 0.5 ml 50 mg/ml gentamycin (Sigma, UK) in PBS were transferred to a 50 ml falcon tube along with approximately 20 ml RPMI 1640 from a newly opened bottle. The contents of the falcon tube were allowed to dissolve and were subsequently passed through a 0.22 μm filter directly into the 500 ml bottle of RPMI 1640 medium using a 20 ml syringe. Following gentle mixing, the complete media was stored at 2-8°C.

2.10.2 Washing Media

A 500 ml bottle of pre-sterilised RPMI 1640, 1x (+) L-Glutamine (+) and 25mM Hepes (Gibco, Life Technologies, UK) without additives was used as washing media throughout the study and stored at 2-8^{o}C for up to 2 weeks.

2.10.3 Preparation of human blood for culture of *Plasmodium falciparum*

To remove leukocytes, O+ whole blood (obtained from the Manchester Blood Bank) was washed immediately before use. An equal volume of whole blood was added to two 50 ml falcon tubes and centrifuged for 5 mins and 3,400 rpm (1000 g). Following centrifugation, blood plasma and the pale layer (the buffy coat-containing white blood cells) that forms on top of the red blood cells was removed. Blood was then re-suspended in an equal volume of washing media for following centrifugation. The washing process was repeated 3x to ensure that all leukocytes were removed from the blood. For the latter of the three washes, complete media (not washing media) was used. Finally, full blood (100% haematocrit) was re-suspended in an equal volume of complete media to give a final haematocrit of 50% and stored at 2-8^{o}C until further use.

2.10.4 *In vitro Plasmodium falciparum* culture

To begin a new culture, 10 ml of complete media and 0.5ml of washed blood were added to a 50ml culture flask and warmed to 37°C prior to the addition of the parasites. Approximately 0.5ml of parasitized blood (retrieved from liquid nitrogen, refer to section 2.14.8) was then added to the warmed culture media to give a final haematocrit of 5%. Following inoculation, the parasite culture was gassed with a 5% CO_2, 5% O_2 and 90% N_2 gas mixture (BOC Limited, UK) and placed in the incubator (Leec culture safe touch 190 CO_2, Leec Limited, UK) at 37°C.

2.10.5 Routine maintenance of a *Plasmodium falciparum* culture

Parasites were routinely cultured at a final volume of either 10 ml or 30 ml in 25 cm^3 or 75 cm^3 flasks respectively. For experimental set up, smaller flasks (12.5 cm^3) with a final culture volume of 5 ml were used. For each of the varying flask volumes, the culture was maintained at approximately 5% final haematocrit (for every 10 ml of complete media 1 ml of 50% haematocrit blood was added). The media was changed at either 48 or 72 hour intervals. In brief, spent media was removed and discarded without dislodging the parasitized blood layer that formed at the bottom of the flask. Subsequent to the estimation of parasitaemia (see section 2.1.4), the continuous culture was diluted to 0.5-1% parasitaemia with washed blood (50% haematocrit). New complete media was added to give a final haematocrit of 5%. Both washed blood and complete media had been warmed (37^{0}C) prior to the dilution and re-suspension procedure. The culture was then gassed (5% CO_2, 5% O_2 and 90% N_2) and placed in the incubator under conditions described previously.

2.10.6 Estimation of parasitaemia

One drop of concentrated parasitized blood (from the bottom of a culture flask) was transferred to the outer margin of a microscope slide. The blood was thinly smeared across the slide using a second slide and a single swift smooth action to obtain a monolayer of cells. The slide was then air dried at room temperature and fixed by rinsing in 100% methanol. After an additional air drying step, the slide was immersed in Giemsa stain at room temperature for ~20 minutes. The Giemsa staining solution was prepared by diluting Gurr's Giemsa stain solution (BDH/VWR international limited, UK) 1:10 with Giemsa buffer. To prepare the buffer solution one tablet of pH 6.4 (BDH laboratory supplies, England) was added to 1 litre of freshly distilled water. Following staining, the slides were rinsed with a gentle stream of tap water, dabbed dry and viewed under oil immersion (x 100) using a Leica DM 500 compound microscope. Parasitaemia was estimated by counting the total number of red blood cells per field of view (approx 100-200) and noting those containing parasites. Multiple infections were counted as one (as only one parasite is expected to reach full development). For each slide, at least 3 fields of view were counted from which the average percentage of infected cells was calculated.

2.10.7 Preservation in liquid nitrogen

A predominantly ring stage culture at approximately 15-20% parasitaemia was selected for preservation in liquid nitrogen. In brief, the culture was centrifuged at 3,400 rpm (1000 g) for 5 min, the supernatant removed and the culture reconstituted to a 50% haematocrit by adding an equal volume of warm (37^0C) complete media. Aliquots (0.5 ml) of the suspension were transferred into 2 ml cryotubes and 0.5 ml 20% dimethyl sulphoxide (sterile filtered DMSO, Sigma, UK) in Ringer's solution (9 g NaCl, 0.42 g KCl and 0.25 g $CaCl_2$/ Litre) was added. The tubes were immediately snap-frozen in liquid nitrogen for preservation and storage.

2.10.8 Retrieval from liquid nitrogen

Following an initial thawing period at 37°C the contents of the cryotube were transferred to a microcentrifuge tube and centrifuged at 14,000 rpm for ~1 min using the minispin (Eppendorf, UK) centrifuge. Once the supernatant had been discarded the parasitised blood was gently re-suspended in 1 ml of 10% (w/v) sorbitol (Fisher Scientific, UK) solution (in PBS) with continuous mixing. This was then centrifuged and the process repeated twice more with subsequent re-suspensions in 5 % (w/v) sorbitol (in PBS) and finally, complete media. Following the latter washing step in complete media, the culture was re-suspended in

complete media and inoculated into a culture flask containing 0.5 ml of newly washed blood (50 % haematocrit) and 10 ml of complete media.

2.10.9 Sorbitol synchronisation

During continuous culture *P. falciparum* parasites rapidly loose synchronisation. If synchronisation was required prior to experimental set-up, sorbitol synchronisation was used to obtain a predominantly ring stage parasite culture. Sorbitol (5% w/v) was prepared in distilled water and filtered through a 0.22 μm filter. The sorbitol solution was then added directly to pelleted parasite culture (9 ml to 1 ml of culture pellet) and incubated for 5 mins at room temperature. Following this, the culture was centrifuged at 3,400 rpm (1000 g) for 5 mins and the supernatant was discarded. The parasite pellet was then subjected to three washing steps in complete media, before re-suspension in complete media at 50% haematocrit. The synchronised parasite culture was used to set up a new culture as described previously.

2.10.10 Preparation of existing antimalarial primary stock solutions

The four selected existing antimalarials used in the current study were obtained from Sigma Aldrich, UK. Primary stock solutions were prepared in accordance with manufacturer instructions. In brief, atovaquone (Mw = 366.84) was dissolved at 5 mg/ml (13.63 nM) in DMSO. For dihydroartemisinin (Mw = 284.35), 1.4 mg of the powder stock was dissolved in 1 ml of DMSO to obtain a primary stock concentration of 5 mM. Proguanil was dissolved at 1 mg/ml in acetonitrile:water (60/40). All primary stock solutions were passed through a 0.22 μm porosity filter, aliquoted and stored at -20°C until further use. Chloroquine (Mw = 515.86) was prepared freshly on the day of use. An initial stock solution was prepared at 5 mM (10.32 mg/ 4 ml) and sterile filtered. For experimental set up, the primary stock solutions were further diluted with complete medium to give working solutions. Various amounts of the working solution were then transferred as required to achieve final test concentrations.

2.10.11 Calculation of IC_{50} values

For all dose response data sets, values were transferred from respective software programmes into Microsoft excel. The infected blood controls were set at 100% and percentage parasitaemia for drug treated samples was calculated relative to the infected control. For IC_{50} and IC_{90} calculations, data was further processed using Gaphpad prism 5.0. Data was normalised so that the largest value in the data set corresponded to 100% and the smallest value corresponded 0%. Log-transformed drug concentrations were then plotted against the

dose response and the IC_{50} and IC_{90} values were determined using nonlinear regression (Graphpad prism 5.0). The log (inhibitor) vs. Normalised response-Variable slope option was selected for IC_{50} calculation whilst the log (agonist) vs. Response-find EC anything with the F values set at 10 was used for the IC_{90} calculations.

CHAPTER 3: ROLE OF SOCIO-ECONOMIC FACTORS IN THE TREATMENT OF MALARIA

3.1 Introduction

Despite the continuous effort in fighting malaria worldwide, the parasitic disease still kills close to 445,000 people annually (WHO, 2017). Children less than five years of age living in sub-Saharan Africa are mainly the affected groups. In sub-Saharan countries, different factors act as barriers for patients to receiving the appropriate treatment needed. For example, Yakasai *et al.,* (2014) describes the relationship between poverty and treatment, reporting that up to 10% of monthly incomes could be spent on procuring a complete dose of ACT for a child in some countries of Sub-Saharan Africa (SSA). In some African cultures, gender is a huge determinant factor in decision making. Women are perceived to take care of the house and can be trusted to suggest what treatment to be used for what disease; even though in most cases the men pay for them (Lampietti *et al.,* 1999). As rightly explained by the WHO (2007), a gender approach contributes to both understanding and fighting malaria because there are gender norms and values that influence many aspects of family life which could affect disease patterns and access to treatment and care. Furthermore, though men may be more vulnerable than women to exposure, women are known to be more vulnerable to the consequences of malaria (Bates, *et al.,* 2004). Therefore, gender and malaria issues are increasingly being incorporated into malaria control strategies in order to improve their coverage and effectiveness in different contexts.

The level of education is also one of the significant determinant factors when it comes to people's attitude to treatment. In the case of malaria and Nigeria, it is not known if the reason why educated people buy appropriate drugs is because of the knowledge they have on the disease itself or the fact that they can afford it because they have a financial advantage. As mentioned by Dike *et al.,* (2006), most interventions for reducing the burden of malaria and other diseases depend on improved consumers' knowledge about the disease and its control; however, exposure to malaria prevention and treatment might not mean high degree attainment. An in-depth understanding of how different socio-demographic factors, knowledge gaps, and attitudes relate to malaria treatment is very important when developing guidelines and recommendations for effective case management and prevention in many malaria endemic areas of the world including Nigeria. The purpose of this study was to

address this gap by conducting surveys of the knowledge, attitudes and practices of people, from variable socio-demographic backgrounds, residing in selected rural and urban malaria endemic areas in Nigeria.

3.2 Objective

This study aims to characterize the practice of presumptive treatment of malaria in Nigeria and determine where interventions for malaria treatment delivery should be targeted.

3.2.1 Research question 1 and hypothesis:

Does the socio-demographics of residents in these regions (as defined by age, educational level, residence, and stated willingness to pay) associate with barriers to effective malaria case management and their malaria treatment-seeking behaviour (as defined by percentage of people who self-medicate or/and are treated with drugs outside the adopted recommendations)?

H_0: there is no association between participants' socio-demographics in these regions and their malaria treatment-seeking behaviour

H_1: there is an association between participants' socio-demographics in these regions and their malaria treatment-seeking behaviour

3.3 Results

3.3.1 Lagos Urban Community

A total of 178 people responded and returned questionnaires which were correctly filled (Table 3.1). 73 (41%) of the responders were female while 105 (59%) were male. People aged 30 and above treated malaria the most (32%) out of all the age groups recorded. 95 responders had a formal education to a tertiary level (53%), 31 (17.4%) participants had primary education while 42 (23.6%) had secondary and only 9 (5%) lacked a formal education. With regard to the last case of malaria participants had experienced, 31 respondents (17%) received malaria treatment from PPMVs while 53 people (30%) visited the hospital, 82 participants (46%) received treatment from pharmacy stores and 6 people (3%) claimed they did not treat the disease at all. 88 people (50%) admitted that they weren't diagnosed before treatment while 63 (35%) were diagnosed; the rest were not sure. The use of ACTs was 107 (60%) while 71 (40%) of the participants treated malaria with non-ACTs.

89 participants (50%) said they are willing to pay more than ₦500 for treatment while only 89 (50%) also said they are not willing to.

3.3.2 Lagos Rural Community

A total of 121 people responded and returned the questionnaires which were correctly filled (Table 3.1). 68 (56%) of the responders were female while 53 (44%) were male. Only 28 (23.1%) responders had a formal education to a tertiary level; 31 (25.6%) participants had primary education, 31(25.6%) had secondary education and 31 (25.6%) lacked a formal education. With regard to the last case of malaria participants had experienced, 47 respondents (39%) received malaria treatment from PPMVs while 32 people (26%) visited the hospital, 17 participants (14%) received treatment from pharmacy stores and 12 people (9.9%) claimed they did not treat the disease at all. Only 27 people (22%) could confirm that they were diagnosed before receiving treatment, 60 (50%) were not diagnosed and 34 people (28%) were not sure if they were diagnosed. The use of ACTs was poor, with 32(26%) only using the recommended drug while 89 (74%) responders claimed to have treated malaria with non-ACTs. 36 participants (30%) said they are willing to pay more than ₦500 for treatment while as many as 85 (70%) people said they are not willing to.

3.3.3 Osun Urban Community

A total of 142 people responded and returned the questionnaires which were correctly filled (Table 3.1). 63 (44%) of the responders were female while 79 (56%) were male. People aged 30 and above treated malaria the most (35%) out of all the age groups recorded. 82 (23%) responders had a formal education to a tertiary level, 16 (11%) participants had primary education, 39 (28%) had secondary education and 5 (4%) lacked a formal education. With regard to the last case of malaria participants had experienced, 28 respondents (20%) received malaria treatment from PPMVs while 63 people (44%) visited the hospital and 41 participants (30%) received treatment from pharmacy stores. All participants were treated for malaria although 10 people sought other methods of treatment. More people (54%) confirmed that they were diagnosed before treatment in this region, while the remaining participants were either not diagnosed or not sure. The use of ACTs was more than non-ACTs with 83 (59%) using the recommended drug while 59 (41%) responders claimed to have treated malaria with non-ACTs. 68 participants (48%) said they are willing to pay more than ₦500 for treatment while 74 (52%) people said they are not willing to.

3.3.4 Osun Rural Community

A total of 90 people responded and returned the questionnaires which were correctly filled (Table 3.1). 50 (56%) of the responders were female while 40 (44%) were male. People between ages 26 and 30 treated malaria the most (32%) out of all the age groups recorded. 23 (25%) responders had a formal education to a tertiary level, 31 (34%) participants had primary education, 12 (14%) had secondary education and 24 (27%) lacked a formal education. With regard to the last case of malaria participants had experienced, 50 people (56%) in this region preferred visiting the hospital for treatment, 22 respondents (24%) received malaria treatment from PPMVs and 15 people (17%) visited pharmacy stores. 35 people (39%) admitted that they weren't diagnosed before treatment while 20 (22%) were diagnosed; the rest were not sure. The use of ACTs was recorded in 39 (43%) participants while 51(57%) of the participants treated malaria with non-ACTs. 11 participants (12%) said they are willing to pay more than ₦500 for treatment while as many as 79 (88%) said they are not willing to.

Table 3.1: Socio-demographic characteristics of respondents (% given to the nearest figure)

Variable	Lagos urban		Lagos rural		Osun urban		Osun rural	
	n	%	N	%	N	%	N	%
Total	178	100	121	100	142	100	90	100
Age 16-20	22	12	21	17	21	15	12	13
21-25	54	30	41	34	39	28	27	30
26-30	45	25	30	25	33	23	29	32
30+	57	32	29	24	49	35	22	24
Sex M	105	59	53	44	79	56	40	44
F	73	41	68	56	63	44	50	56
Education none	9	5	31	26	5	3	24	27
Primary	31	17	31	26	16	11	31	34
Secondary	42	24	31	26	39	28	12	13
Tertiary	95	54	28	23	82	58	23	26
Marital status Single	115	65	64	53	72	51	32	36
Married	63	35	55	46	70	49	58	64
Employment Yes	109	61	50	41	49	35	38	42
No	69	39	71	59	93	65	52	58
Salary <₦50,000	79	44	86	71	77	54	75	83
>₦50,000	99	56	35	29	65	46	15	16
WTP >₦500 No	89	50	85	70	74	52	79	88
Yes	89	50	36	30	68	48	11	12
Self-medication No	63	35	27	22	76	53	20	22
Yes	88	49	60	50	49	35	35	39

Not sure	27	15	34	28	17	12	35	39
ACT use No	72	40	89	74	59	42	51	57
Yes	106	60	32	26	83	58	39	43
Treated Hospital	53	30	32	26	63	44	50	56
Pharmacy	83	47	17	14	41	30	15	17
PPMV	31	17	47	39	28	20	22	24
Dose completion Always	66	37	50	41	32	23	13	14
Most times	37	21	24	20	30	21	40	44
I stop when I feel better	72	40	47	39	80	56	37	41

1

To create a more representative size from each area, 400 participants were recruited in Lagos State with a total of 300 completing and returning the questionnaires (75% respondent success rate). Being the State with a lower population density, 300 people were targeted in Osun State with 234 people completing the questionnaires (78% respondent success rate).

3.3.5 Relationship between education status and willingness to pay for ACT across the four regions

The relationship between education status and willingness to pay for ACTs across all regions was explored. As depicted in the Figure 3.1 below, education status was defined as four categories; None (those without any formal education), Primary (those with only basic education), Secondary (those with post-basic education) and Tertiary (this includes universities, polytechnics, and colleges of education).

Figure 3.1 below gives information about how the level of education among participants might influence their willingness to pay more than ₦500 (average price for an ACT) for malaria treatment. It can be seen that only people with tertiary education that live in the urban region of Lagos State are willing to spend more than ₦500 to pay for ACTs; those without any education, primary education and secondary education are not willing to spend as much on ACTs for malaria treatment. In other regions, more people across all education levels are willing to pay less than ₦500 except for the Osun urban region where there are equal numbers of people willing to pay more than ₦500 and less than ₦500. The difference between willingness to pay between the urban and the rural regions is very large and is of concern. Even though willingness to pay does not necessarily translate to action, it is seen to be a strong motivational force behind paying for treatment. As observed willingness to pay is

[1] As of April 2015 when this data was collected the exchange rate of the local currency equates £1 = ₦500

worst in Osun rural region, although it can be argued that this region is the least economically viable region of the four study regions.

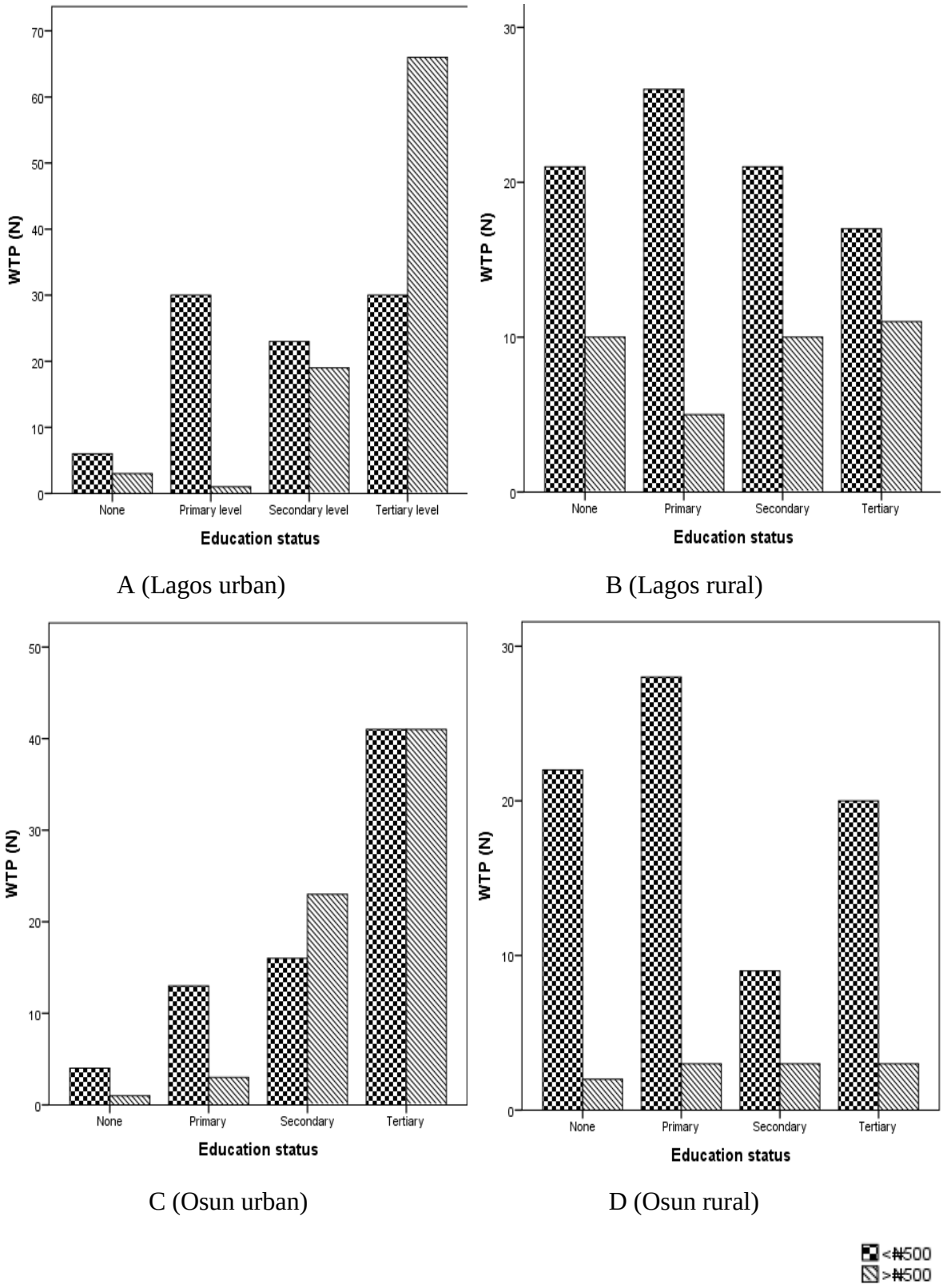


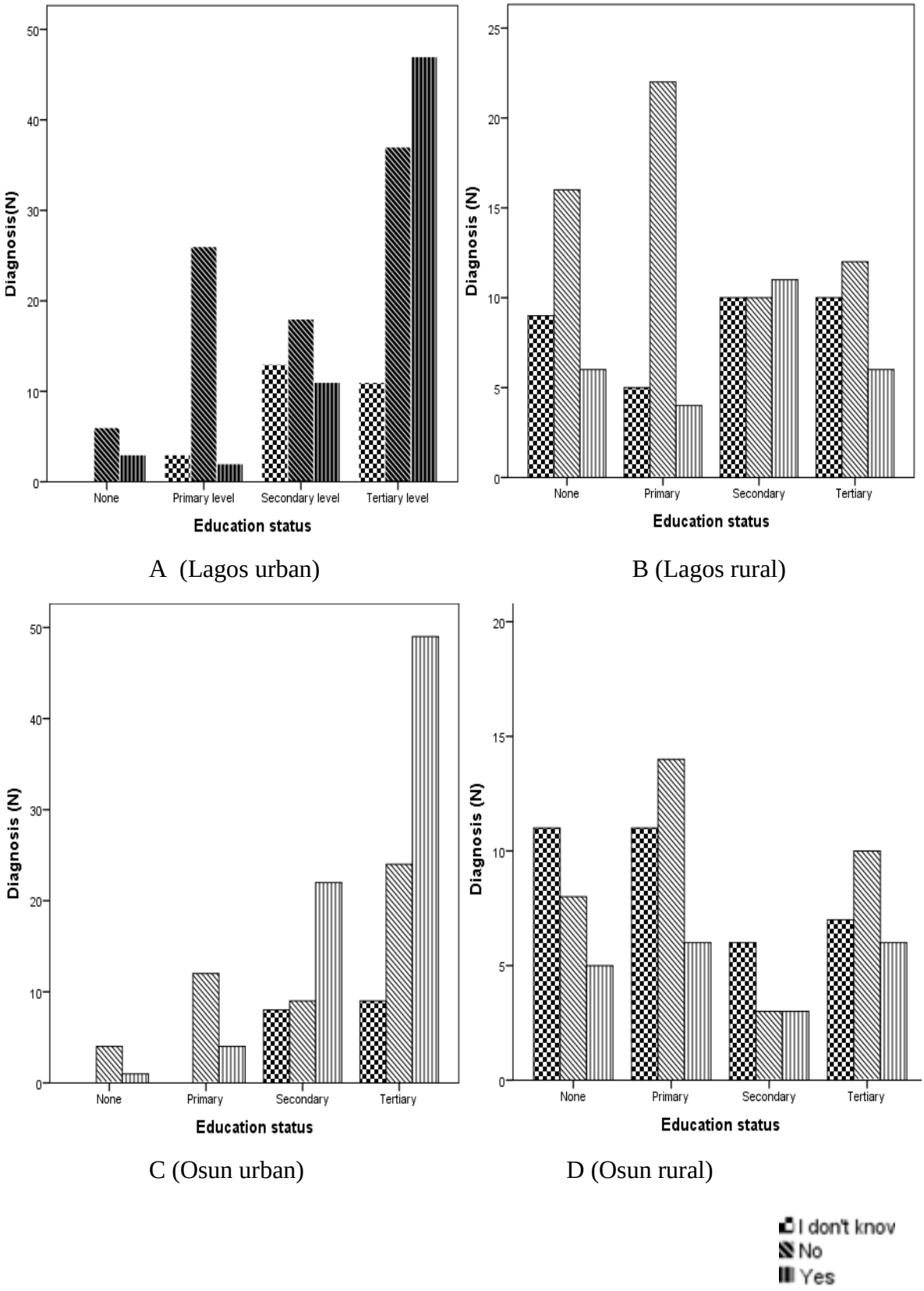
Figure 3.1: Graphs showing the relationship between the education status of

participants and their willingness to pay </> ₦500 (=£1 as at April 2015) for ACTs across all the regions of the study; A (Lagos urban), B (Lagos rural), C (Osun urban) and D (Osun rural).

3.3.6 Relationship between education status and self-medication practices across the four regions

Another comparison was made to explore the relationship between educational status and self-medication practices in these regions. As defined earlier, for this study, self-medication is defined as receiving or buying an antimalarial drug without a prior diagnosis or prescription. Patient groups were clustered according to definitive diagnostic status prior to treatment either by RDTs or through microscopic method. The 3 categories of responses include: 'Yes' (those who were diagnosed before treatment), 'No' (those who were not diagnosed before treatment) and 'I don't know' (responder was unsure if they had been diagnosed).

Figure 3.2 below illustrates how the level of education among participants might influence self-medication. In this case self-medication is simply defined as any participant that has not been tested to confirm presence of malaria parasites prior to treatment. In Lagos urban region, self-medication is seen to be higher across all groups except for those with tertiary education. Lagos State rural region shows a high level of self-medication across all groups regardless of their educational status. More people were diagnosed (53.5%) before treatment in Osun urban region; with a higher percentage among participants with tertiary education. 80% of participants in Osun rural region either self-medicated or did not remember being diagnosed before treatment. Similar to the relationship between education level and WTP (section 3.4.5), there appears to be a correlation between participants with tertiary education living in the urban region and confirmation of diagnosis.



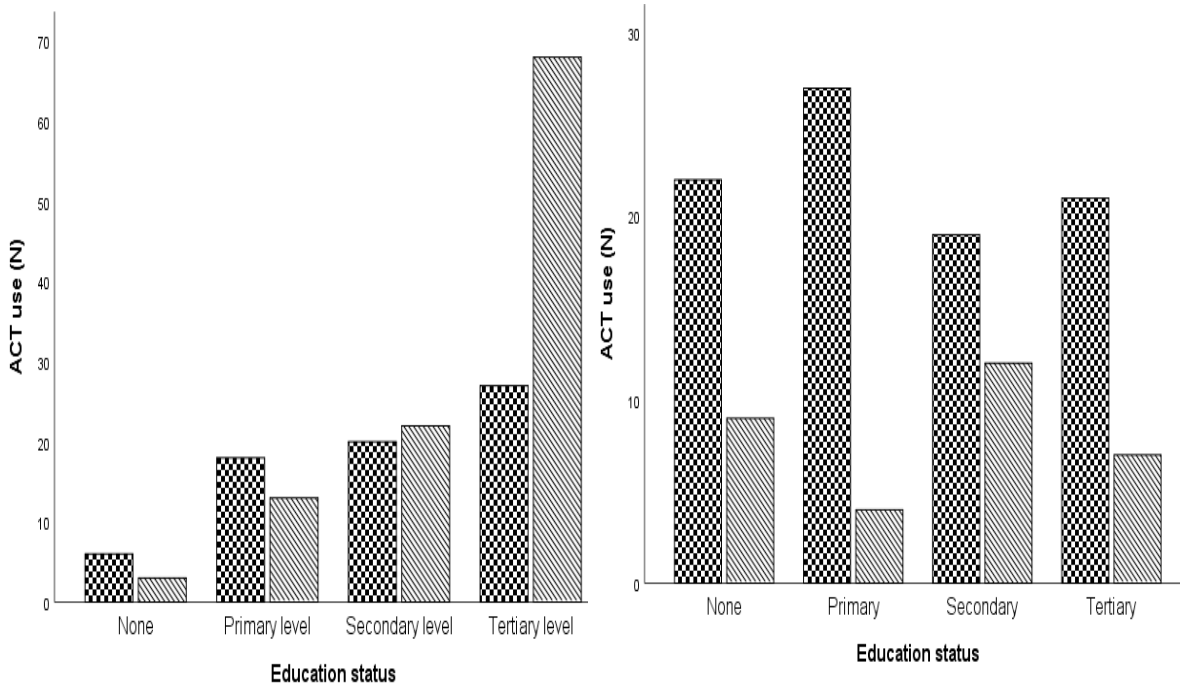
A (Lagos urban) B (Lagos rural)

C (Osun urban) D (Osun rural)

Figure 3.2: Graphs showing the relationship between education status (None, Primary, Secondary and Tertiary) and self-medication practices (including those who said 'Yes' to diagnosis, 'No' and 'I don't know') across the four regions of the study; A (Lagos urban), B (Lagos rural), C (Osun urban) and D (Osun rural).

3.3.7 Relationship between education status and ACT use across the four regions.

Education and awareness is known to influence treatment practices. In compliance to the WHO recommendations, the FMOH has recommended the use of ACT drugs as first line treatment of malaria in these regions, making it an important factor to consider as barrier for effective case management. The common ACT in Nigeria is a combination of artemether-lumefantrine, and other options of treatment includes SP and chloroquine, both of which have been banned for malaria treatment except for special cases. Figure 3.3 below illustrates how the level of education among participants might influence the drug used for malaria treatment. Participants were also asked about the drug they use to treat malaria and it can be seen that most participants in Lagos urban region seek ACT drugs for treatment, also among the secondary school group, more people went for ACTs than any other group of antimalarial. However, this result is not the same in the rural region as more participants across all education levels preferred non-ACT compared to ACTs drugs for treatment. In Osun urban region, there was better use of ACTs between tertiary and secondary school groups (similar to Lagos urban). Also, tertiary group and primary school group in Osun rural area showed better use of ACTs compared to other education status. Excluding the Lagos rural region, this data shows a relationship between educational level and the use of ACTs since people with a tertiary level of education are more likely to use an ACT to treat malaria.



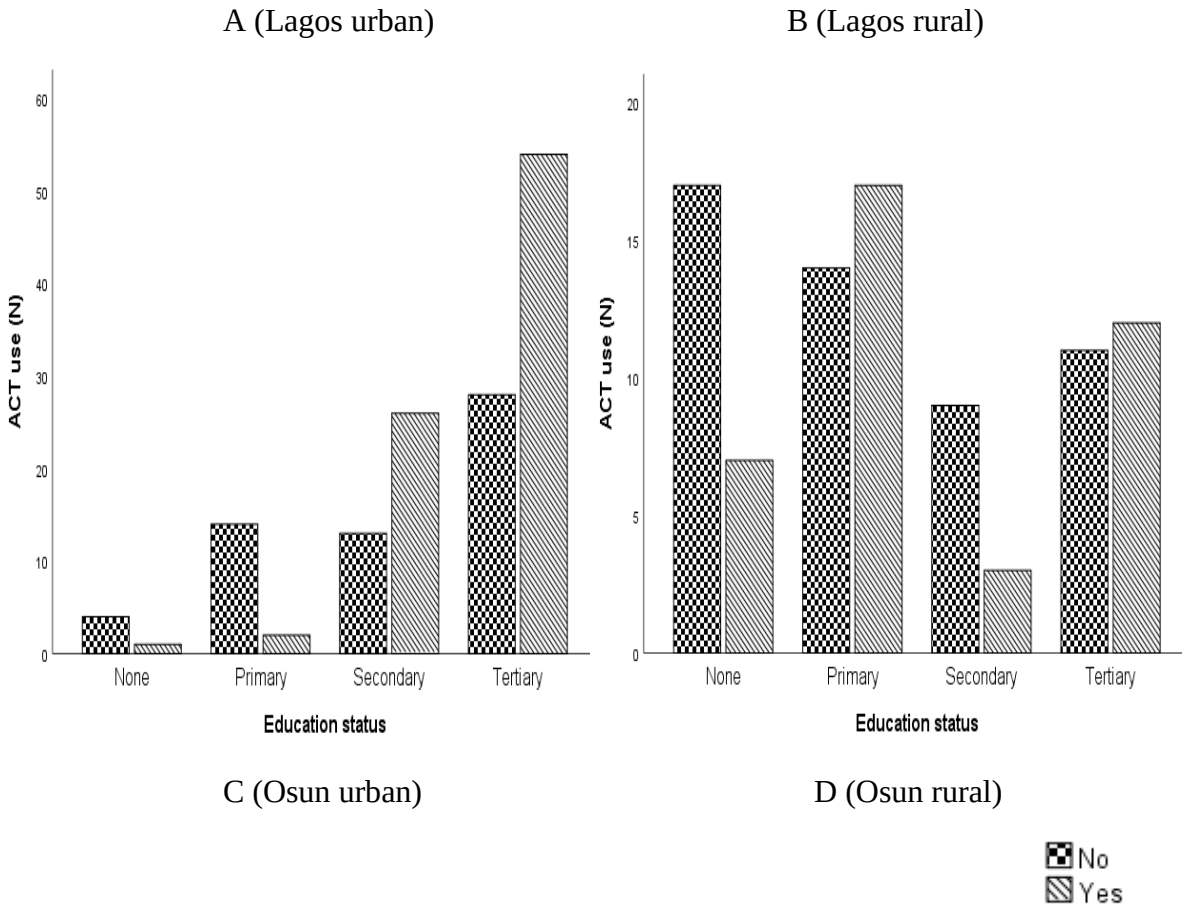


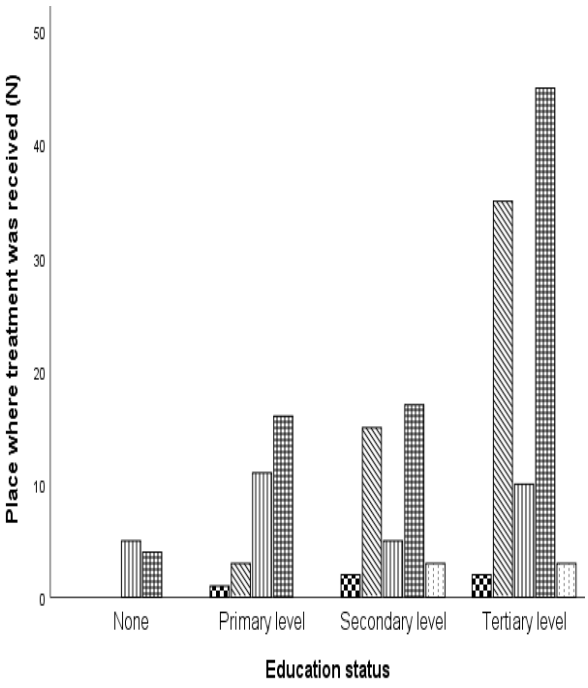
Figure 3.3: Graphs showing education status and ACT use across the four regions. Participants responses in this case are categorised into 'Yes' (the use of ACT for treatment) and 'No' (using other antimalarial or no treatment at all)**;** A (Lagos urban), B (Lagos rural), C (Osun urban) and D (Osun rural).

3.3.8 Relationship between education status and place of treatment

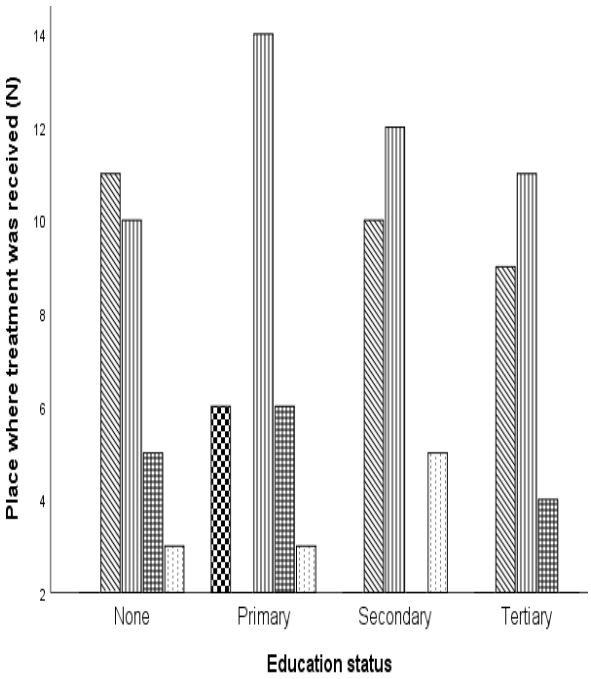
Treatment attitude and practices by care givers vary depending on what type of health provider has been visited. Hospital care givers are perceived to be better exposed to trainings and also, their practices are recorded and monitored. This is in contrast to practices at drug vendors, who are not necessarily trained to dispense drugs and are mostly in the business for profit. In this case, place where treatment was sought was categorised into 'No treatment' (those that were not treated), 'Hospital', 'Drug vendors', 'Pharmacy stores' and 'Others' (including traditional and spiritual).

Figure 3.4 below illustrates how the level of education among participants might influence where they go for malaria treatment. In Lagos urban region, most people visited a pharmacy for malaria treatment regardless of their education level except for those who had no education (could have been affected by the total number of participants). Drug vendors were more patronised amongst people living in the Lagos rural region (39%) followed by a

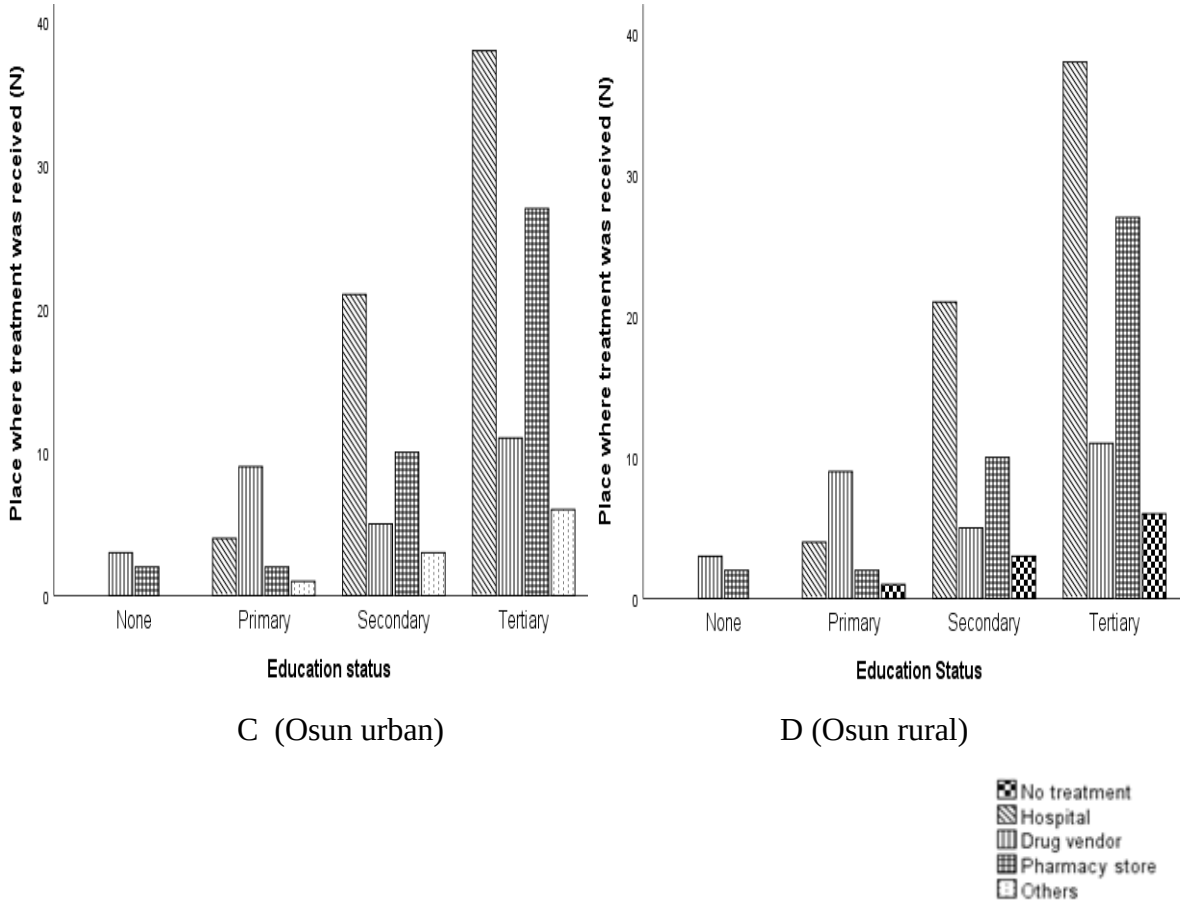
hospital visit (26%), which is recorded across all education level. In Osun urban and rural regions, hospital visits are more common. Waiting times at the hospital is a huge factor that can easily affect this result. Lagos Sate has the most populous city in Africa and one can expect a huge patient load at the hospitals. With a population of just over 3 million (compared to Lagos with about 24 million), the patient load in the hospitals of Osun State can be relatively more easily accessible with less queues and hassle. The only question is affordability and quality of treatment. This result does not show that education level affects where treatment is sought and instead, suggests that community trust in effective and easy treatment providers is most important.



A (Lagos urban)



B (Lagos rural)



C (Osun urban) D (Osun rural)

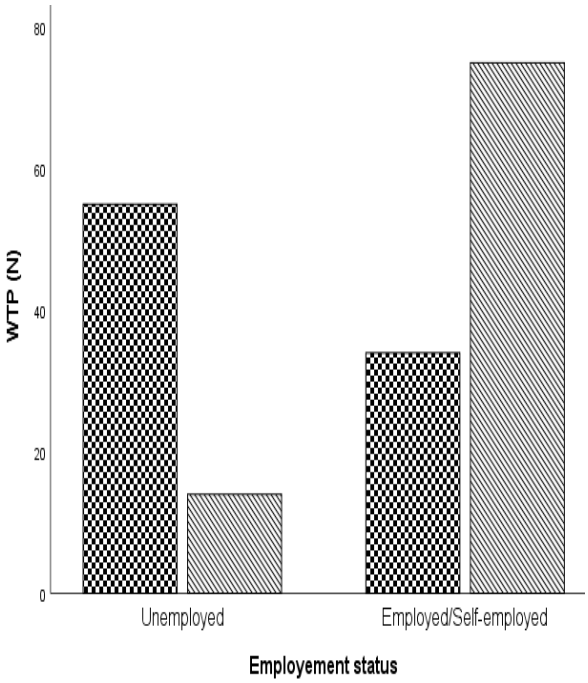
Figure 3.4: Graphs showing the relationship between education status and place where treatment was received across the four regions; A (Lagos urban), B (Lagos rural), C (Osun urban) and D (Osun rural). Categorised into 'No treatment' (those that were not treated), 'Hospital', 'Drug vendors', 'Pharmacy stores' and 'Others' (including traditional and spiritual).

3.3.9 Relationship between employment status and WTP across the four regions.

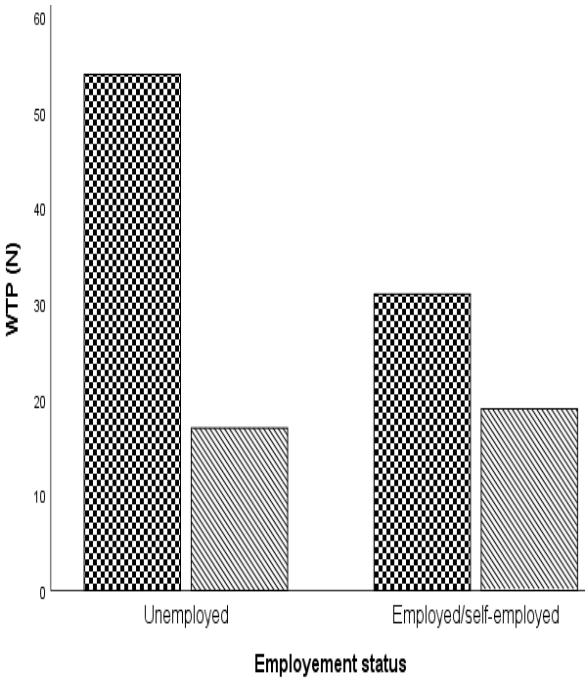
This section explores relationship between those in employment (including self-employment and part-time) and those that are unemployed and their willingness to pay at least ₦500 for malaria treatment.

Figure 3.5 below illustrates how participant's employment status might influence their willingness to pay more than ₦500 for malaria treatment. The graph shows more employed participants willing to pay more than ₦500 compared to people that are not employed. Up to 80% of the respondents that are willing to pay in the urban region have a tertiary level of education. This is however not so in the rural region, as it is observed that both groups have more respondents that are not willing to pay up to ₦500 for malaria treatment. In Osun urban, little difference can be observed between employed participants that are willing to pay up to, or over ₦500 for malaria treatment. This is quite understandable because Osun State is a

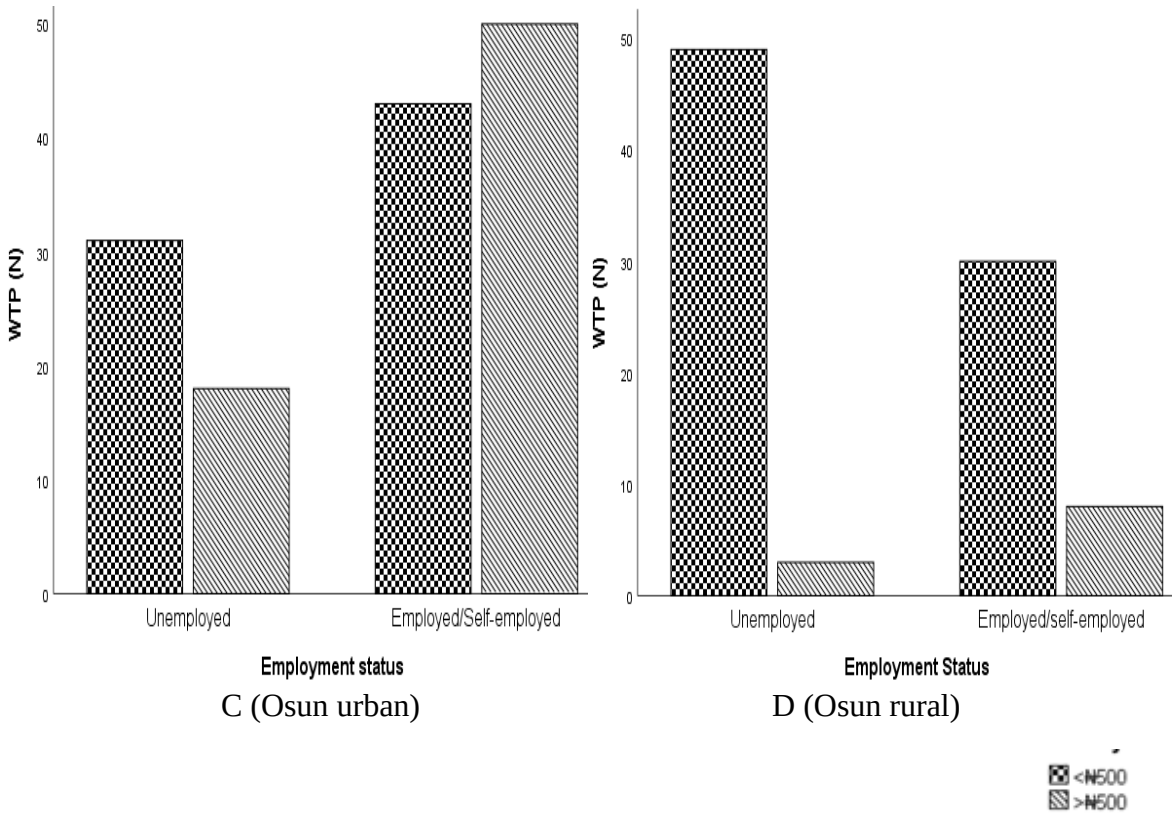
poorer state than Lagos State and being employed in Osun State isn't necessarily the economic advantage associated with being employed in Lagos State. Participants in some sort of employment in the urban area of both States show more willingness to pay more than ₦500 for malaria treatment as opposed to rural areas where both employed and unemployed participants are not willing to pay that much.



A (Lagos urban)



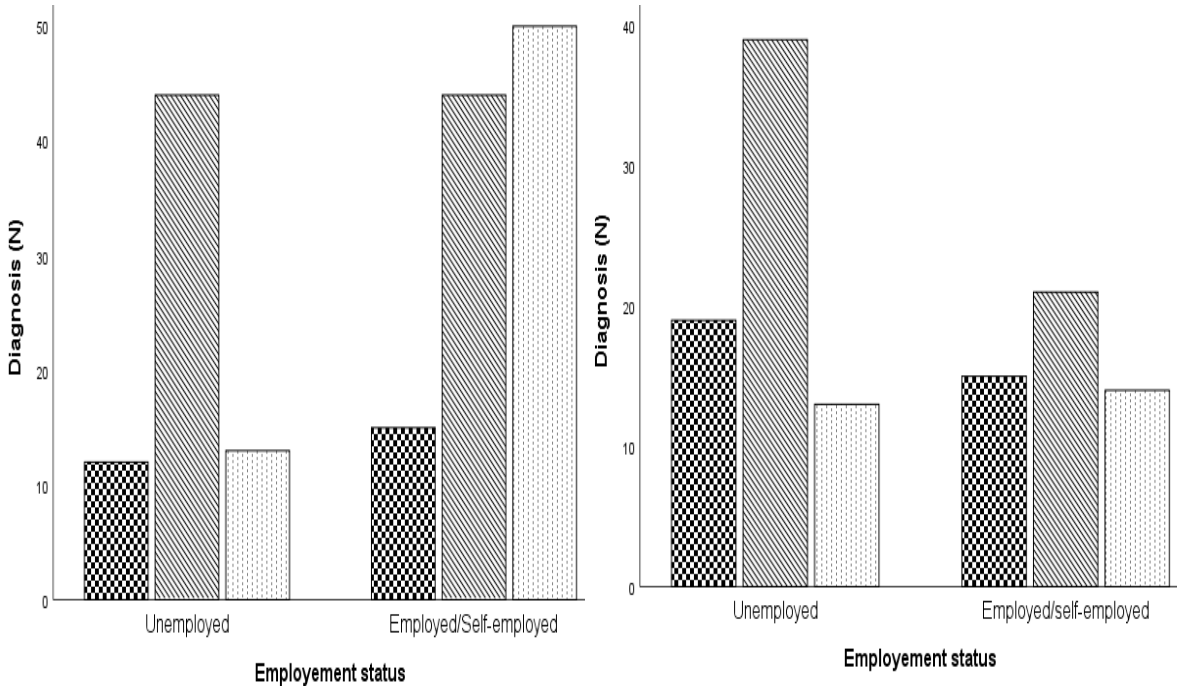
B (Lagos rural)



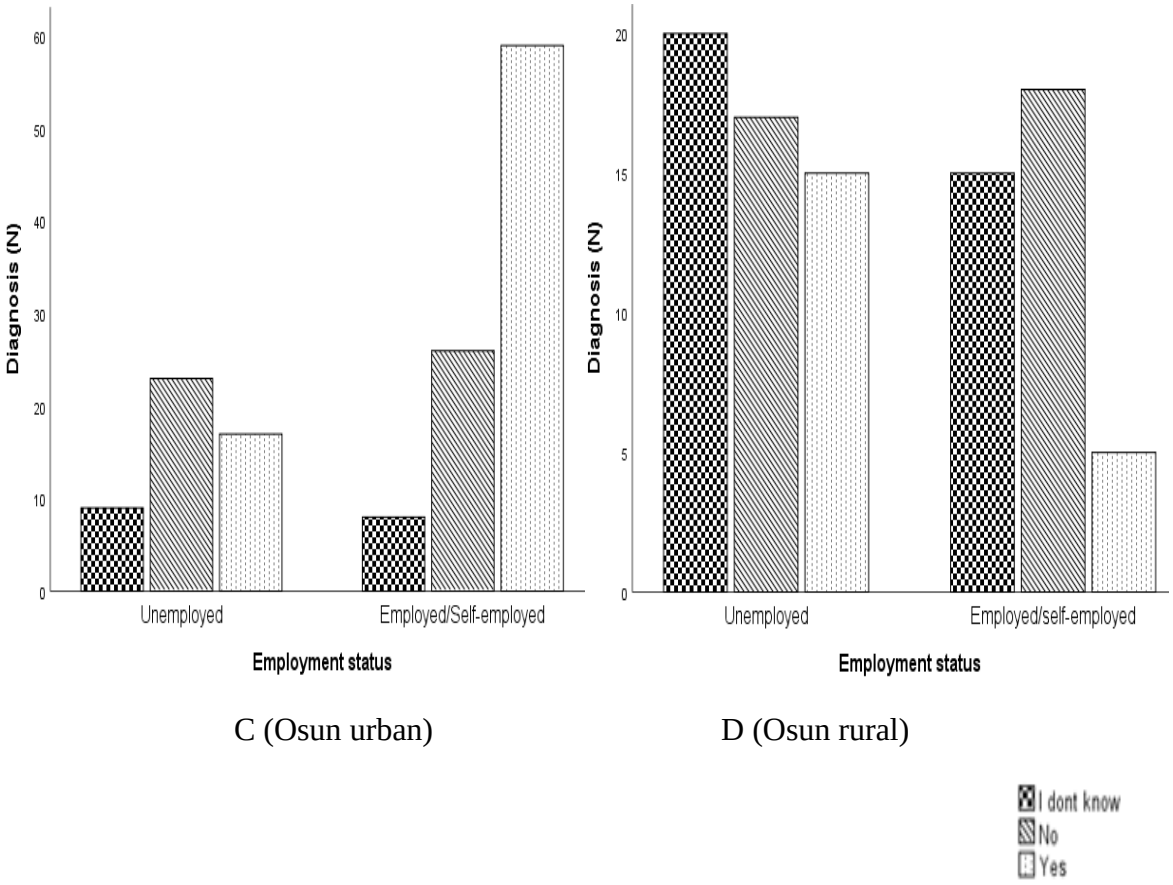
C (Osun urban) D (Osun rural)

Figure 3.5: Graphs showing employment status (including self-employment and part-time employment) and WTP at least ₦500 for treatment across the four regions; A (Lagos urban), B (Lagos rural), C (Osun urban) and D (Osun rural).

3.3.10 Relationship between employment status and self-medication across the four regions.



A (Lagos urban) B (Lagos rural)



C (Osun urban) D (Osun rural)

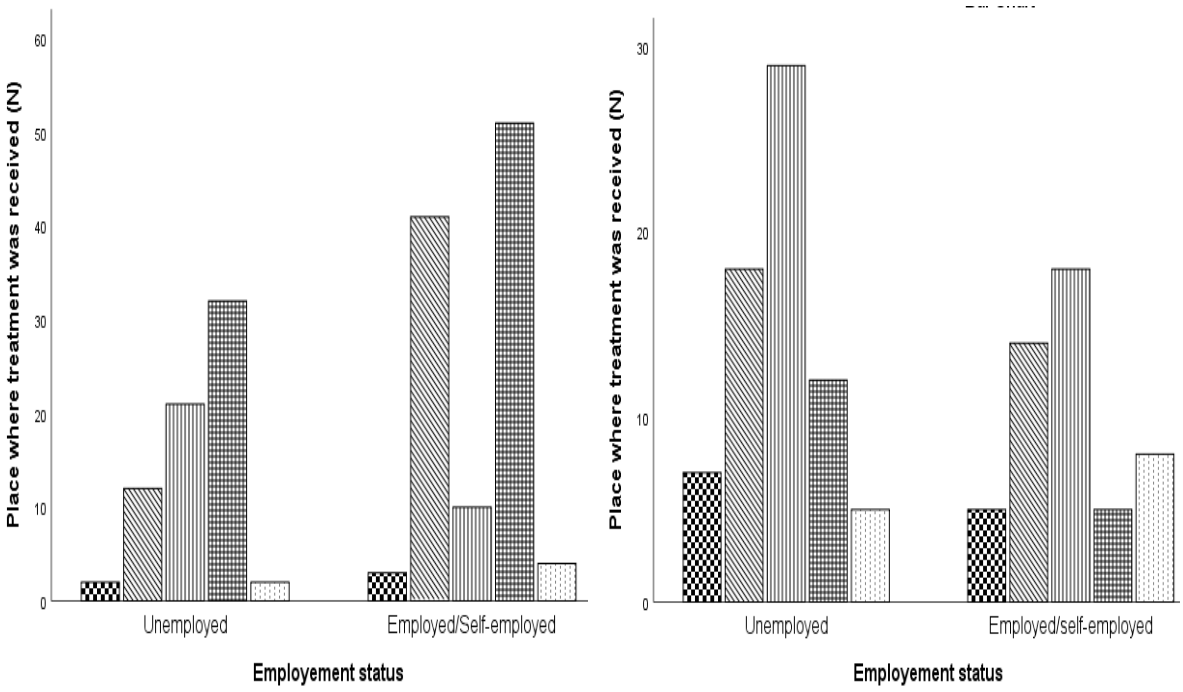
Figure 3.6: Graphs showing employment status and self-medication across the four regions; A (Lagos urban), B (Lagos rural), C (Osun urban) and D (Osun rural). "Yes" = diagnosed, "No" = not diagnosed, "I don't know" = unsure.

This section illustrates how the level of participant's employment status might influence self-medication. As seen in Figure 3.6 above, in both urban regions, the number of employed people that were diagnosed before treatment was more than those that were not diagnosed. The difference in Lagos urban however is so little and a cause for concern. It can be suggested that self-medication is common across all the groups but employed people in Osun urban region are more likely to seek diagnosis. The chart does not distinctively show better treatment approach in people that are employed in this case, as the level of self-medication is high between both unemployed and employed groups. In some cases, malaria patients, depending on the symptoms they have, may not be sure if they have been diagnosed or not. For example, if a patient is unconscious on arrival in the hospital, there is a possibility of

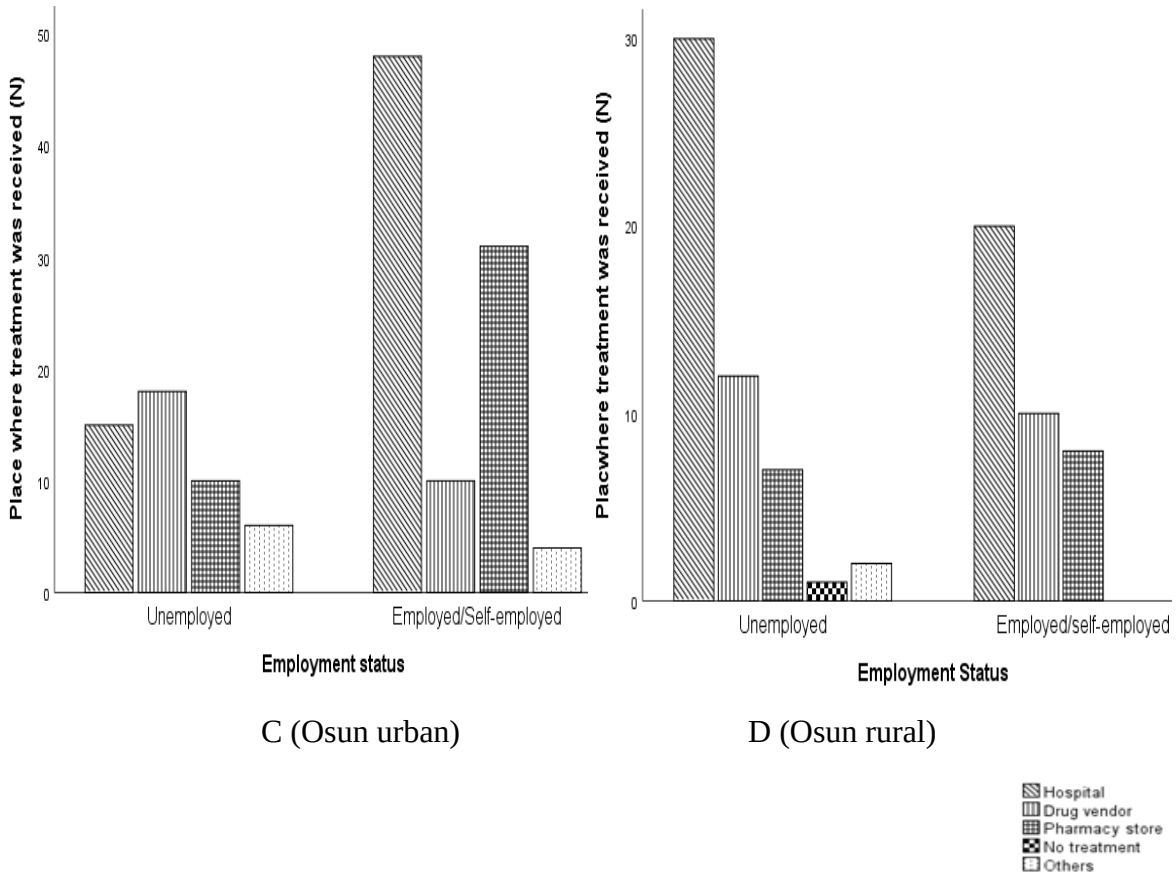
being diagnosed and they are not aware, as treatment practice in most hospitals does not really require doctors to make it clear what process will be/has been done to treat a patient. This means that a number of the patients who are not sure could have been diagnosed before treatment, however, the chart still shows that a lot of improvement is required to check self-medication.

3.3.11 Relationship between employment status and place where treatment was received across the four regions.

Figure 3.7 below illustrates how participant's employment status might influence place where they were treated for malaria. As previously observed more participants visited the pharmacy stores in Lagos urban region, PPMVs in Lagos rural and hospitals in both Osun urban and Osun rural regions. Employment status did not change where participants are more likely to be treated. As hospitals and registered pharmacy stores are more likely to follow the WHO recommendation for malaria treatment, the group at greater risk of wrong treatment are those in the Lagos rural region where most participants, either employed or unemployed, visited PPMVs.



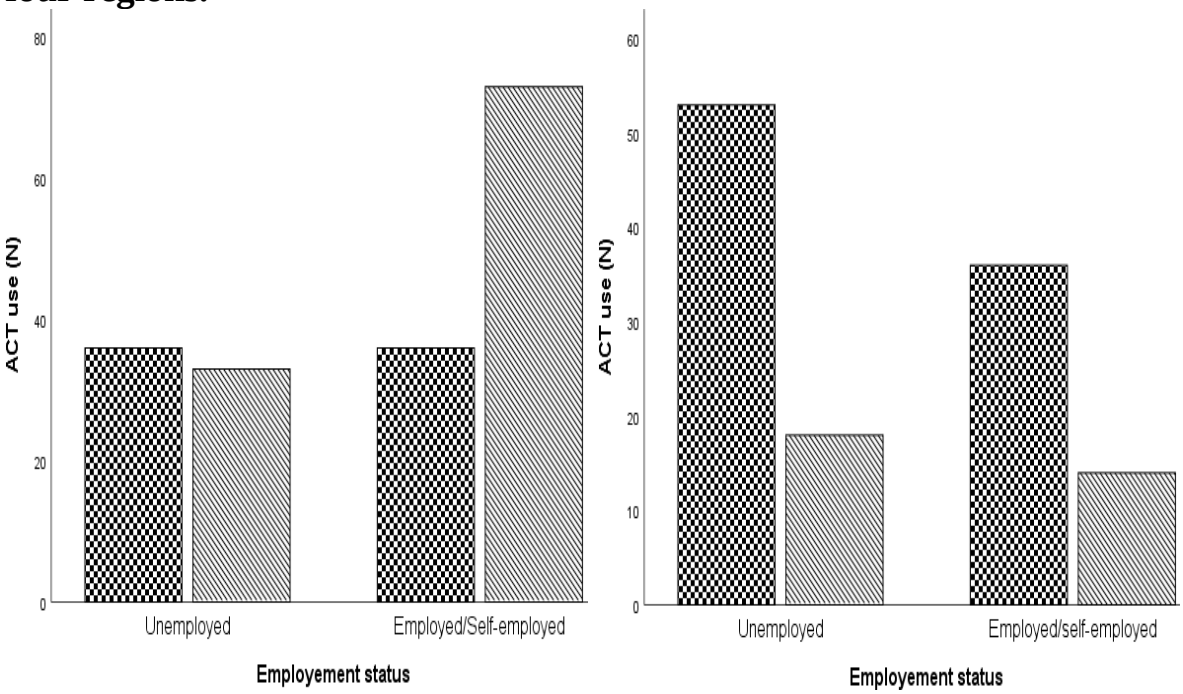
A (Lagos urban) B (Lagos rural)



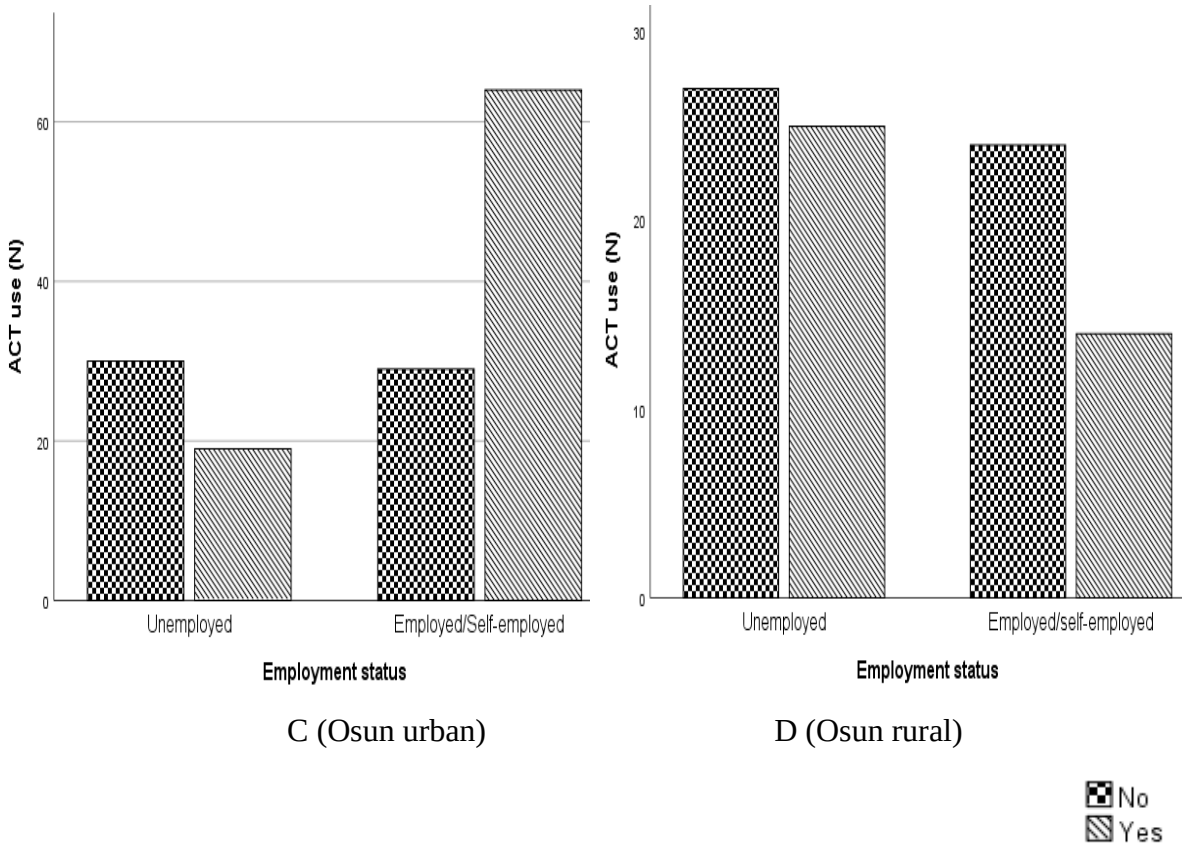
C (Osun urban) D (Osun rural)

Figure 3.7: Graphs showing relationship between employment status and place where treatment was received across the four regions; A (Lagos urban), B (Lagos rural), C (Osun urban) and D (Osun rural).

3.3.12 Relationship between employment status and ACT use across the four regions.



A (Lagos urban) B (Lagos rural)



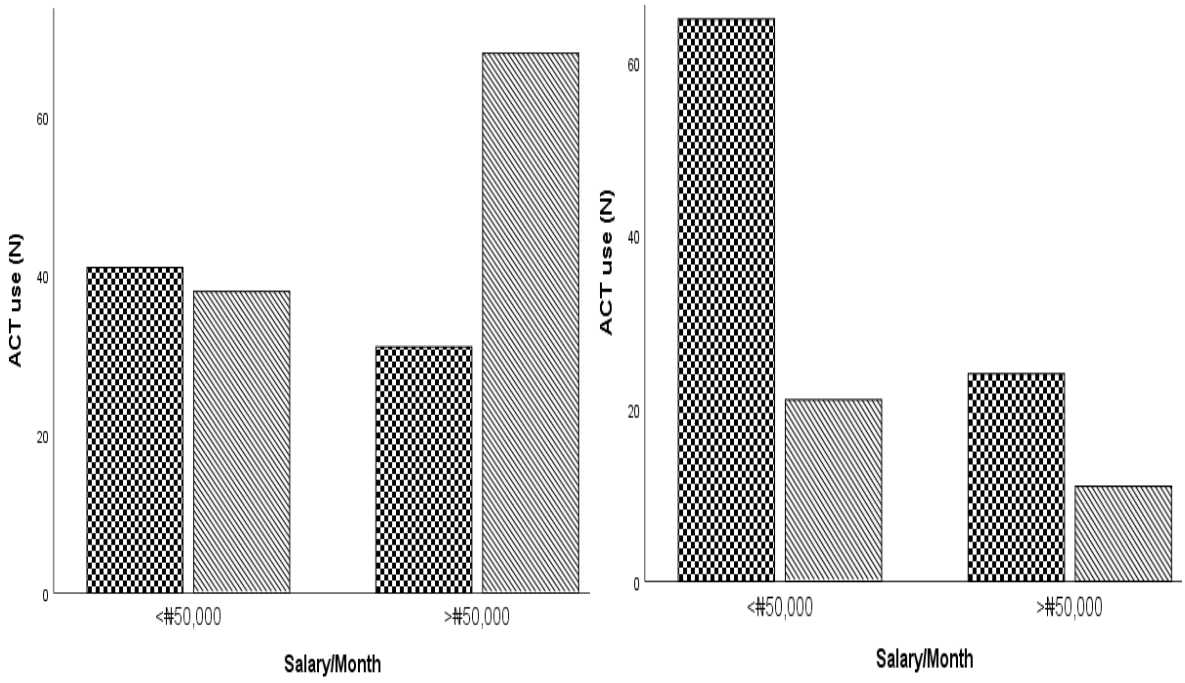
C (Osun urban) D (Osun rural)

Figure 3.8: Graphs showing employment status and ACT use across the four regions; A (Lagos urban), B (Lagos rural), C (Osun urban) and D (Osun rural).

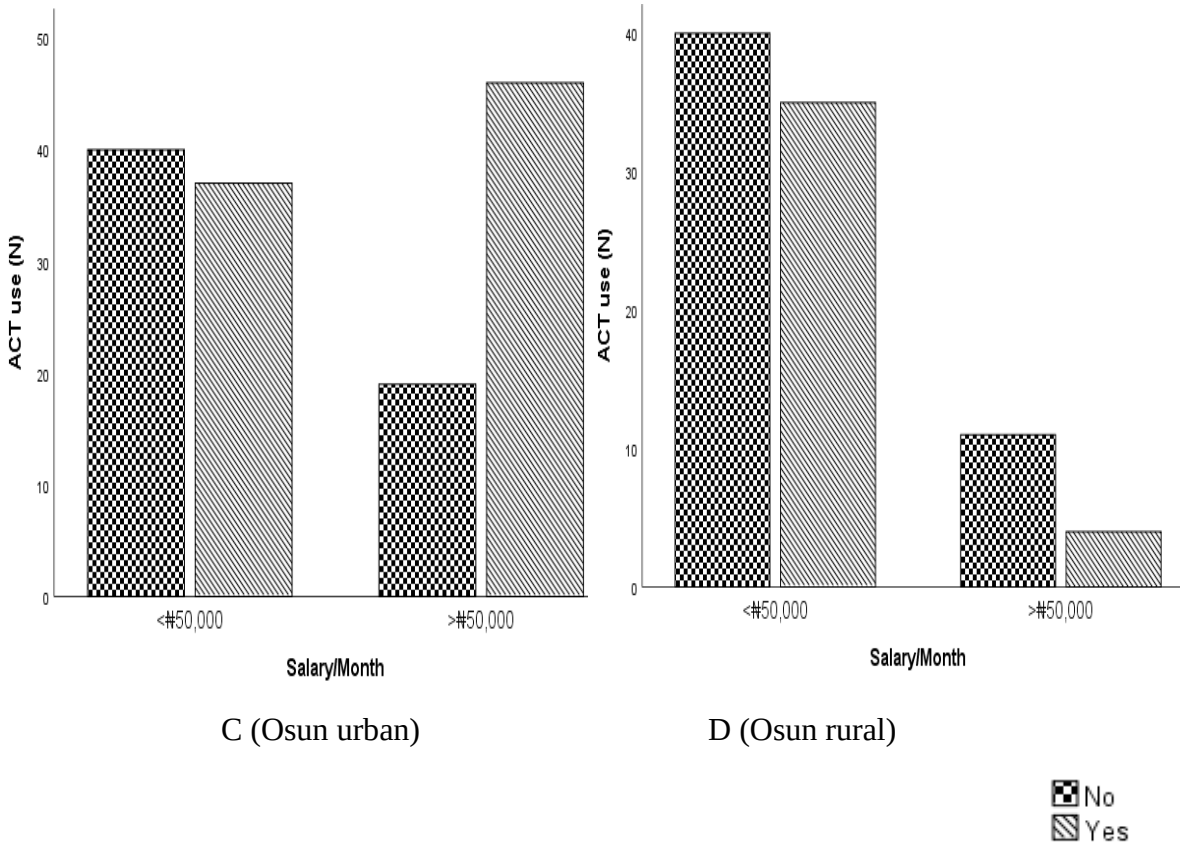
The Figure 3.8 above illustrates how a participant's employment status might influence the use of ACTs as a treatment option for malaria. As price of drug is a very important factor to consider in this study, one can observe that more people in employment chose ACT drugs to treat malaria. Out of a total of 107 participants that used ACT in the Lagos urban region, 74 (70%) were employed while 33 (30%) were unemployed. This is a significant difference that points to the effect employment status has on the use of ACTs in this region. In Lagos rural region, both groups opted more for non-ACT drugs with only 28% of the employed using ACTs. This probably reflects the difference in the standard of living in these regions even though they are within the same State. Use of ACTs was more observed in the employed group in Osun urban as well; 77% (64) of the 83 people that used ACTs in this region were employed. Similar to what is observed in the Lagos rural region, participants in the Osun rural region used more non-ACTs regardless of their employment status.

3.3.13 Relationship between monthly salary and ACT use across the four regions.

Figure 3.9 above illustrates how participant's monthly salary might influence their treatment practice with regard to antimalarial drug type used. It can be observed that people who earn up to, or more than ₦50,000 (£100), are more likely to use an ACT in the urban areas in both states. This was not the case in the rural regions, as it can be seen that even a larger percentage of those who earn more than ₦50,000 preferred non-ACTs for treatment. The difference in this practice between regions points to the fact that in some cases, employment or financial buoyancy, might not be enough to follow recommended procedure with regard to malaria treatment. In places were awareness of recommended treatment isn't absent, other responsibilities would play a role in affecting the type of antimalarial used for treatment.



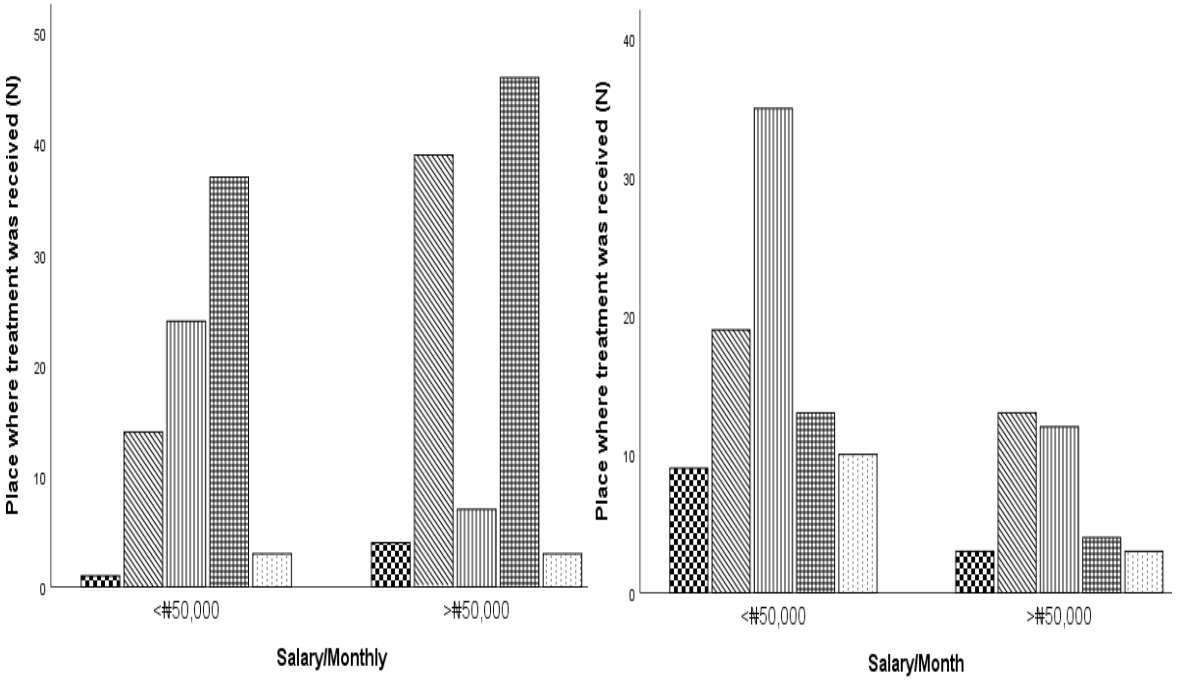
A (Lagos urban) B (Lagos rural)



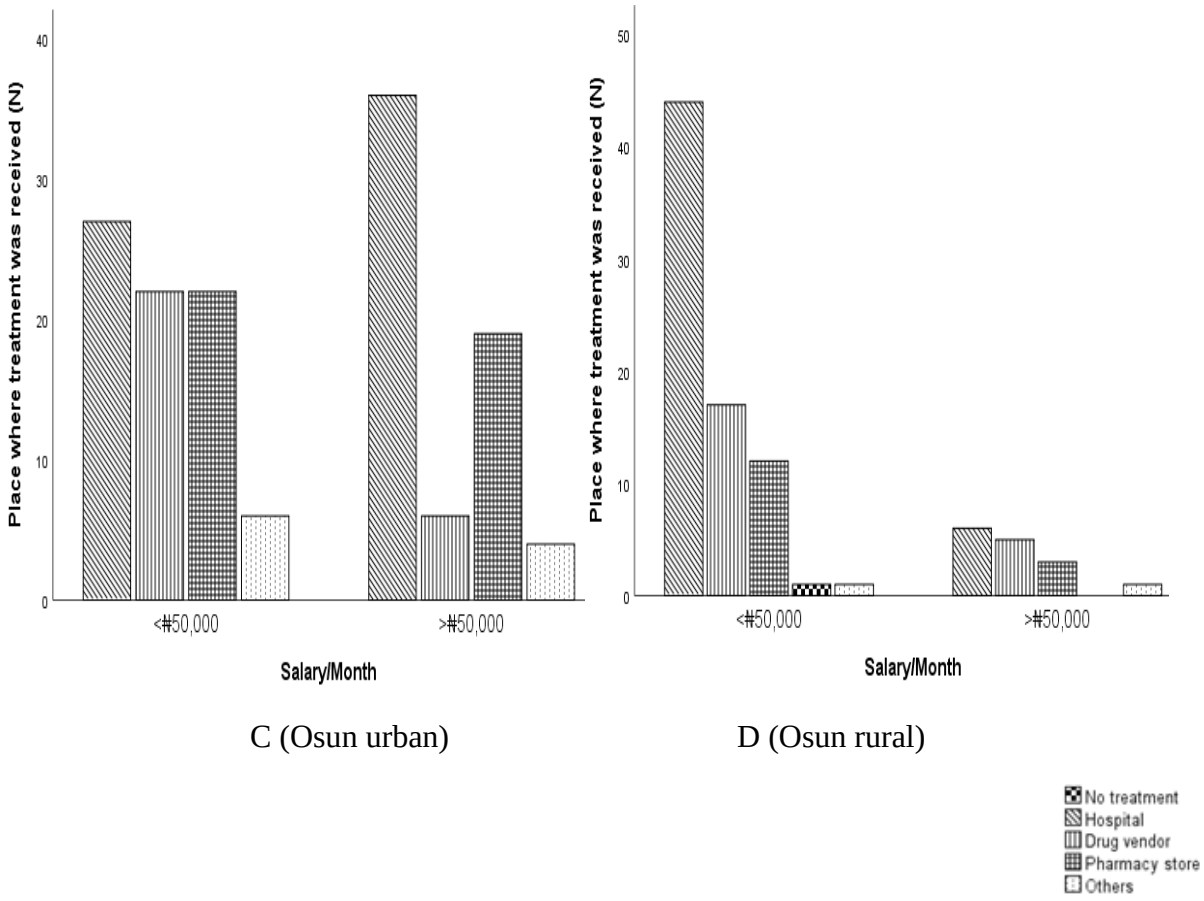
C (Osun urban) D (Osun rural)

Figure 3.9: Graph showing monthly salary (</> 50,000) and ACT use across the four regions; A (Lagos urban), B (Lagos rural), C (Osun urban) and D (Osun rural).

3.3.14 Relationship between monthly salary and place where treatment was received across the four regions.



A (Lagos urban) B (Lagos rural)



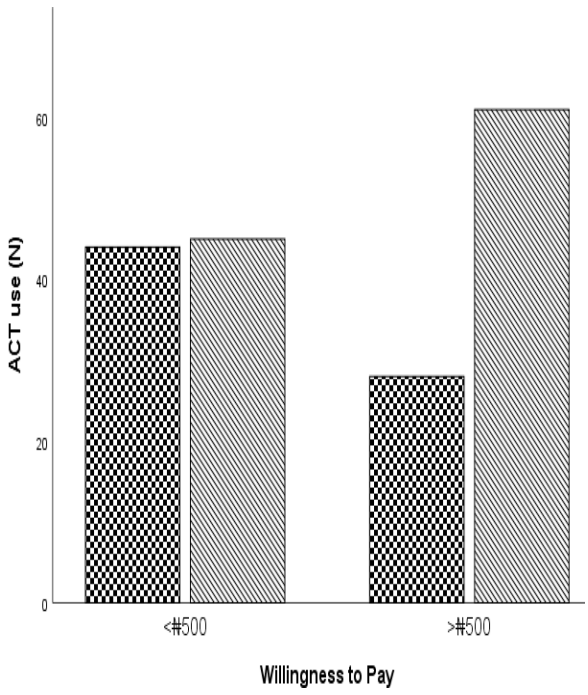
C (Osun urban) D (Osun rural)

Figure 3.10: Graphs showing monthly salary and place where treatment was received across the four regions; A (Lagos urban), B (Lagos rural), C (Osun urban) and D (Osun rural).

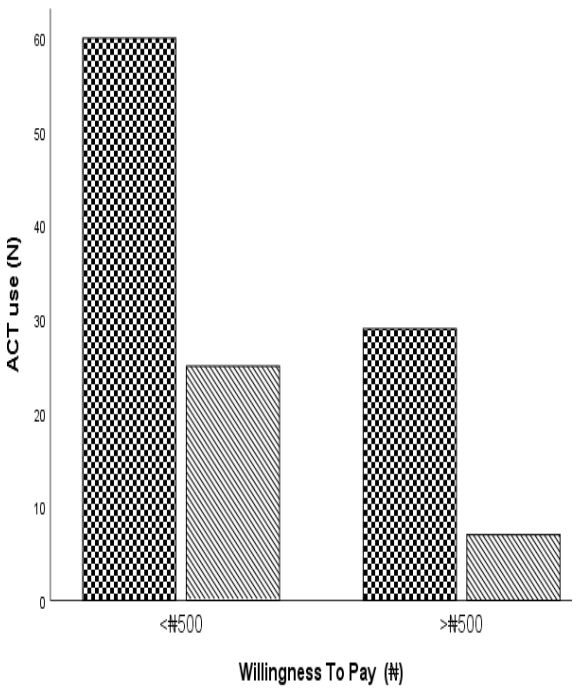
The Figure 3.10 above illustrates how participant's monthly salary might influence the place where malaria treatment is received. Regardless of monthly income, 46% of participants in Lagos urban region visited pharmacy stores; followed by hospital among those earning over ₦50,000 and drug vendors among those earning less than ₦50,000. In Lagos rural, there is almost an equal likelihood of visiting the hospital or drug vendors among those earning more than ₦50,000 whereas a higher percentage (41%) of those earning less than ₦50,000 visited patent medicine vendors. Regardless of monthly income, more participants in Osun urban and rural regions visited hospitals more than any other place, followed by pharmacy stores among those earning more than ₦50,000 in Osun urban and pharmacy store/drug vendor among those earning less than ₦50,000. In Osun rural, most participants visited the hospital for treatment. Interestingly, people that earned less than ₦50,000 were almost twice as likely to visit the hospital (59%) than a PPMVs (23%) or pharmacy stores (16%) whereas for those earning more than ₦50,000, there was little difference in hospital or PPMV visits.

3.3.15 Relationship between WTP and ACT use across the four regions.

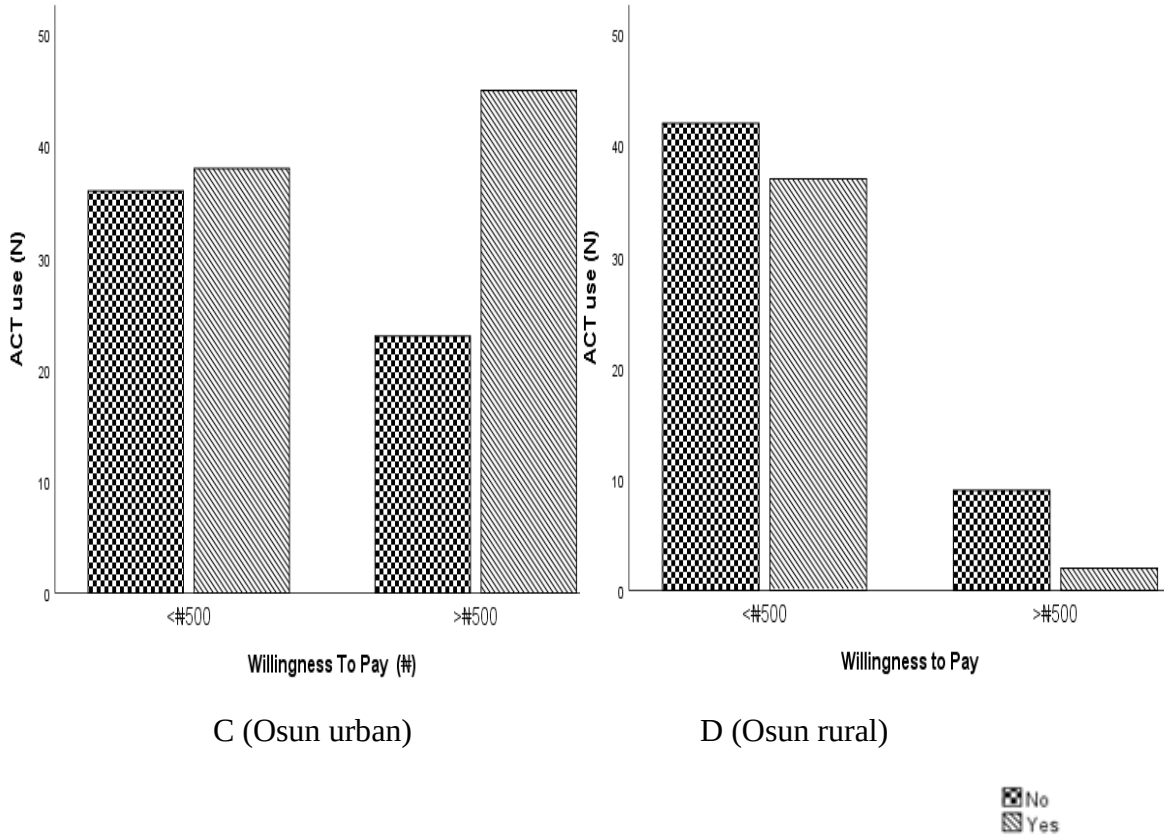
Figure 3.11 below illustrates how willingness to pay more than ₦500 might influence ACT use for malaria treatment. Does willingness to pay a particular price for treatment actually translate to practice? Out of a total of 178 participants in Lagos urban, 50% were willing to pay over ₦500 for malaria treatment and 50 said they were not willing to. Out of the participants willing to pay, 70% actually used an ACT for treatment. Also, among those not willing, 50% used an ACT for treatment. A similar result was observed in other regions since not all those who claim to be willing to pay up to ₦500 actually treated malaria with ACTs and some who are not willing eventually paid over ₦500 for ACT treatment. This shows that WTP does not necessarily translate to practice. Different factors might affect a patient's willingness to pay for antimalarials such as affordability at that point, other responsibilities, combination with other drugs which increases total price, and accessibility. Also, people that are not willing to pay could be advised of proper treatment method at the point of purchase and this might change their attitude towards treatment.



A (Lagos urban)



B (Lagos rural)



C (Osun urban) D (Osun rural)

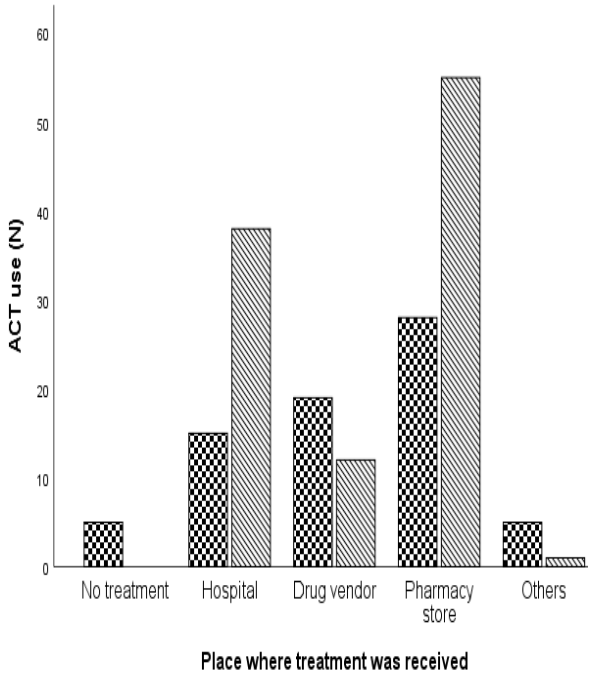
Figure 3.11: Graphs showing WTP and ACT use across the four regions; A (Lagos urban), B (Lagos rural), C (Osun urban) and D (Osun rural).

3.3.16 Relationship between place where treatment was received and ACT use across the four regions.

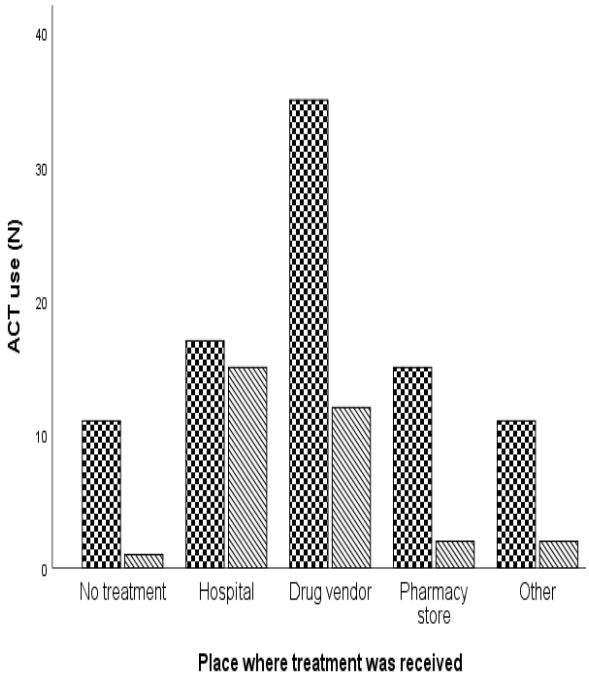
This section will help explore the type of treatment participants received from different health providers. Adherence to recommendations is very crucial to successfully removing barriers to effective malaria case management. This is further explored and discussed in Chapter 4. All providers are expected to adhere to the use of ACT for malaria treatment (except for special cases like 3rd trimester of pregnancy) but this is not always the case.

Figure 3.12 below illustrates how the place where participants visited for treatment might influence the appropriate treatment of malaria. As observed in Lagos urban region, 47% of the total number of participant visited the pharmacy store, 30% visited the hospital and 17% visited a drug vendor and the remainder either used other methods or did not get treated. Out of the total visits to the hospital (53), 72% (38) were treated with the recommended ACT drug. 66% (55) of visits to the pharmacy store resulted in being treated with ACTs whereas only 38% (12) were treated with ACTs at a PPMV store. Non-ACT drugs were the preferred

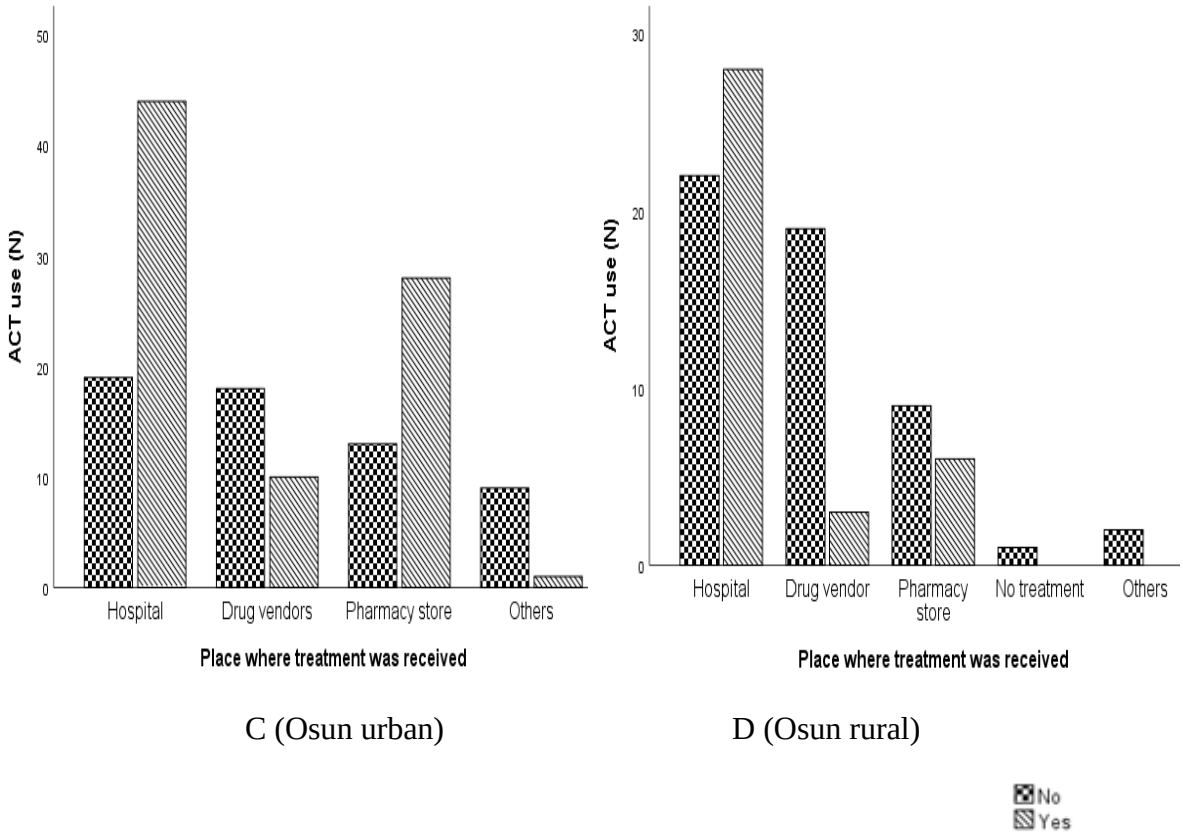
in the rural region of Lagos State; in the hospital, treatment with ACTs is almost equal to treatment with non-ACTs but other outlets sold more non-ACTs and the use of ACTs is low. Similar to Lagos urban, a better treatment practice is seen in the hospital and pharmacy stores compared to other groups in Osun urban; however, the use of non-ACTs for treatment is high in the Osun rural region except in the hospital where more cases were treated with ACTs. This result shows that place of treatment has an influence on the type of drug purchased; as hospitals and pharmacy stores are recommended to treat malaria, one can see that a level of adherence to the FMOH and WHO recommendation is being followed in these venues, although not completely. It should also be noted that some hospital-diagnosed malaria cases are treated with chloroquine injections; this would have increased the data for non-ACTs at the hospital, though by an unknown amount.



A (Lagos urban)



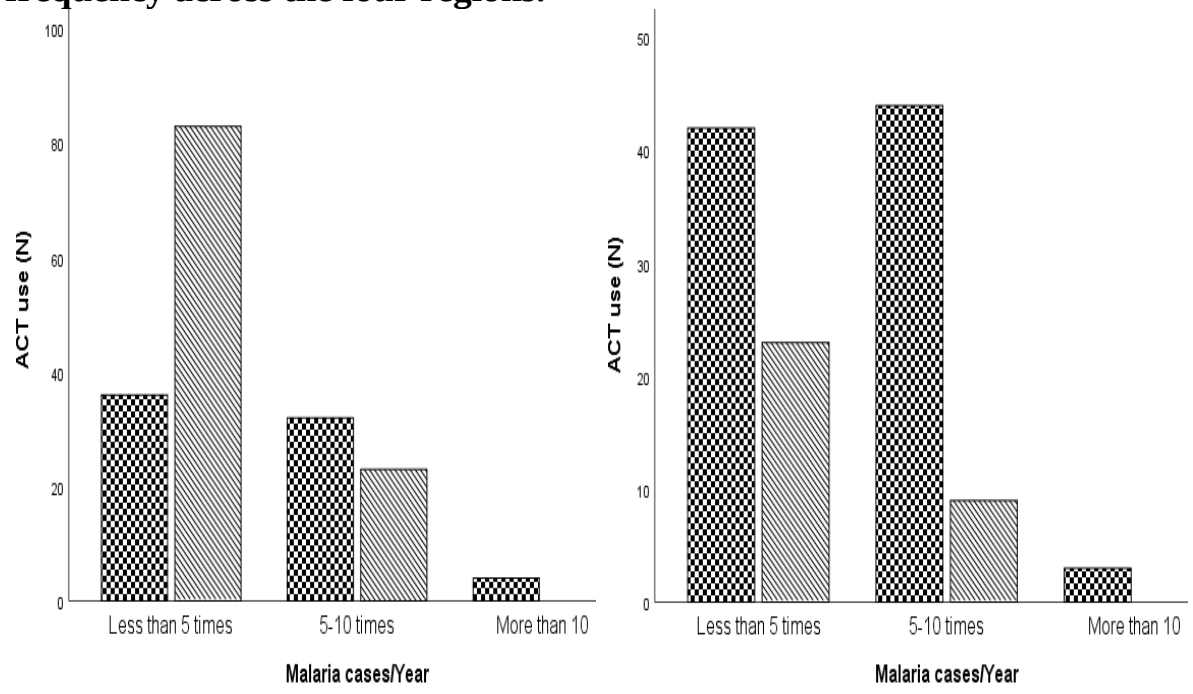
B (Lagos rural)



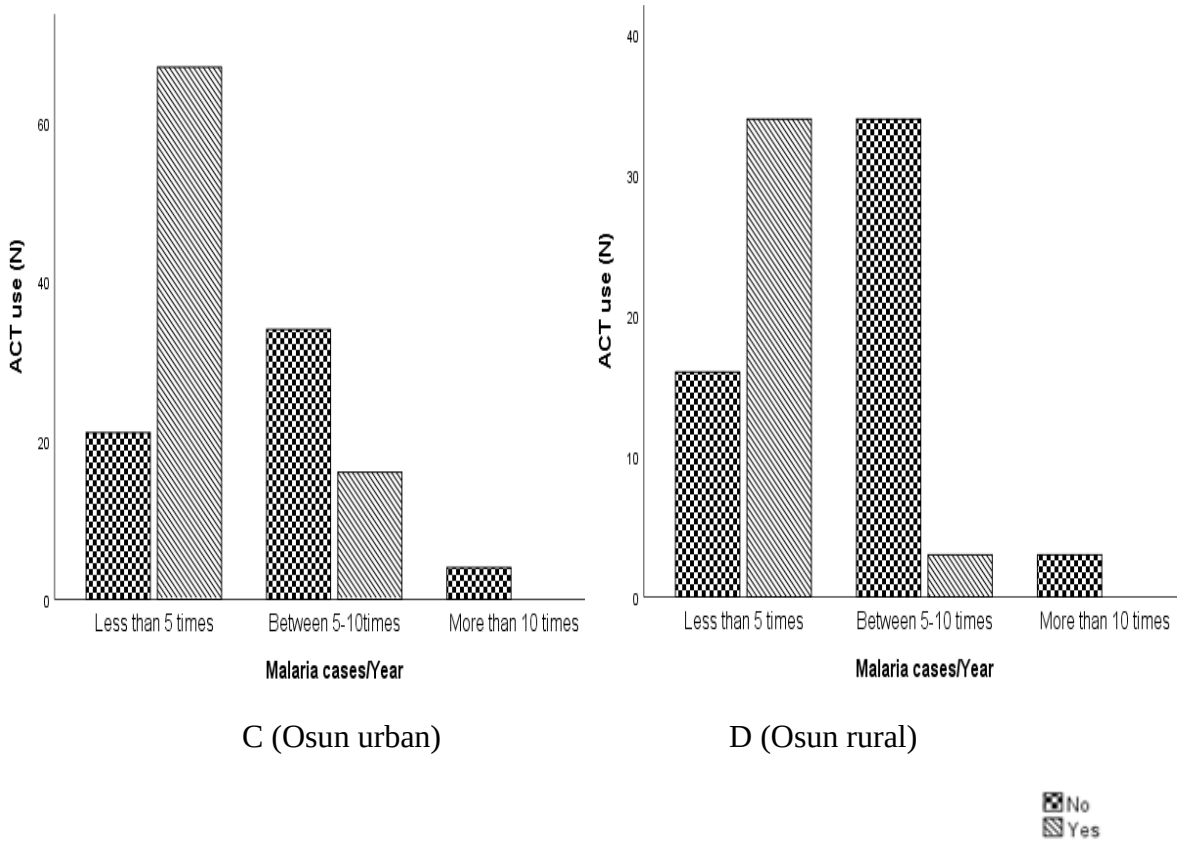
C (Osun urban) D (Osun rural)

Figure 3.12: Graphs showing place where treatment was received and ACT use across the four regions; A (Lagos urban), B (Lagos rural), C (Osun urban) and D (Osun rural).

3.3.17 Relationship between antimalarial drug use and malaria case frequency across the four regions.



A (Lagos urban) B (Lagos rural)



C (Osun urban) D (Osun rural)

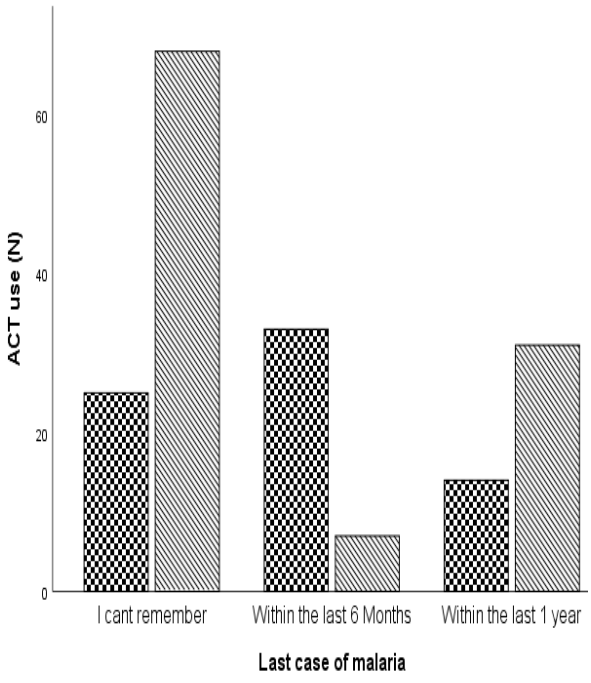
Figure 3.13: Graphs showing place where treatment was received and ACT use across the four regions; A (Lagos urban), B (Lagos rural), C (Osun urban) and D (Osun rural).

Figure 3.13 above illustrates how the use of ACT for malaria treatment might affect the number of malaria cases that participants suffer in a year. As observed across all regions, malaria occurrences are fewer with ACT users. None of the ACT users have cases running over 10 times a year. Out of a total of 106 people that use ACTs in Lagos urban, 78% (83) have less than five cases of malaria in a year while 23% have between 5-10 occurrences. 50% of those who used non-ACTs had more than 5 cases of malaria in a year. In Lagos rural region where a total of 89 people (74%) treated malaria with non-ACTs, 50% of these people had malaria occurrence over 5 times in a year. Osun urban also showed that the majority of ACT users have less than 5 occurrences of malaria in a year while most non-ACT users have more than 5 cases a year. This result confirms the efficacy of ACTs as antimalarials; producing a long-lasting effect in the body of the infected. Non-ACTs are not as effective as ACTs, which means the malaria parasite can easily re-infect, or recrudescence is more rampant when ACTs are not used.

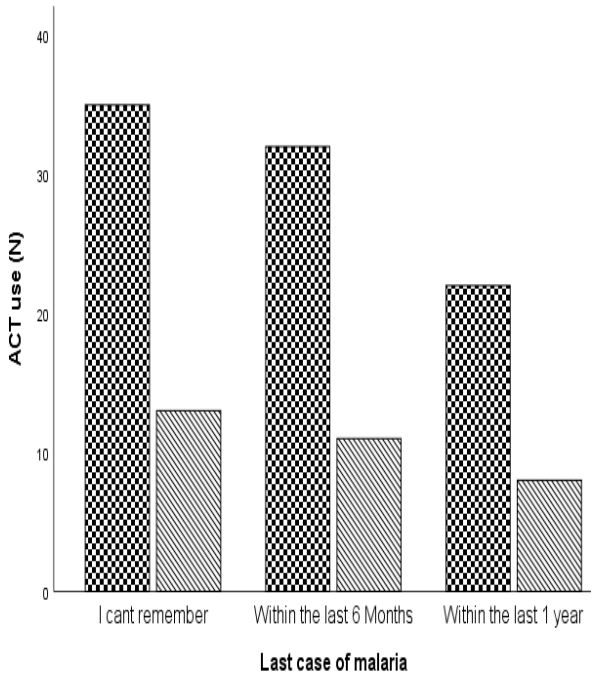
3.3.18 Relationship between history of malaria and ACT use across the four regions.

An effective ACT has the ability to clear more parasitaemia from the blood of an infected person than other antimalarials. Due to the resistance that has been recorded in other antimalarials (for e.g. chloroquine and SP), malaria recrudescence is very common. This section aims to explore how often those who appropriately treat malaria with ACTs have malaria compared to those who use other antimalarial groups.

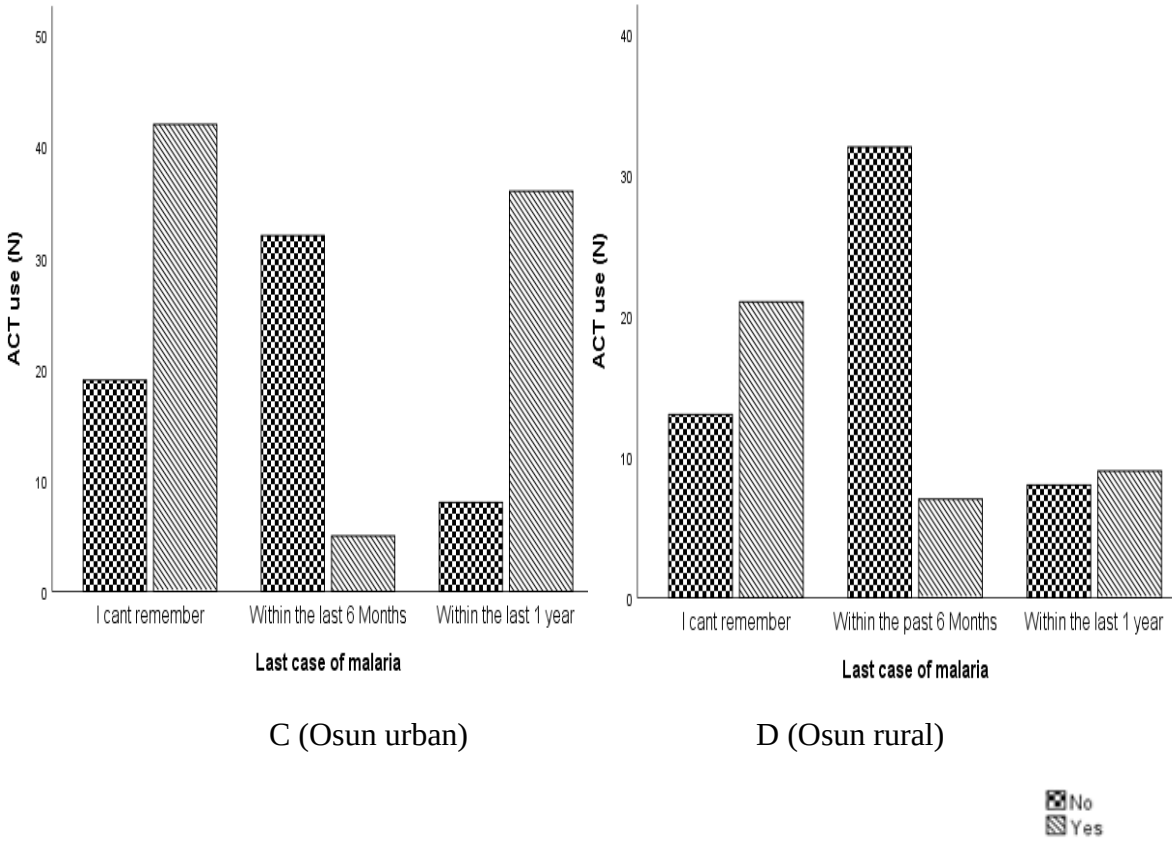
Figure 3.14 below further illustrates what was observed on how ACT treatment might affect the number of malaria cases and history of malaria. In both Lagos and Osun urban regions, it can be seen that most people that treat malaria with ACTs either had a last occurrence of malaria as far back as 6 months, or they cannot remember. In this context, we expect that the reason why participants can't remember the last occurrence is because it is not recent and could have occurred a very long time before this study was done. This means in Lagos urban, 93% of the total participants that treated malaria with an ACT, have at least 6 months interval in infection. Also, in Osun urban, 94% of participants that treated malaria with ACTs, have at least a 6 month interval between malaria infections.



A (Lagos urban)



B (Lagos rural)



C (Osun urban) D (Osun rural)

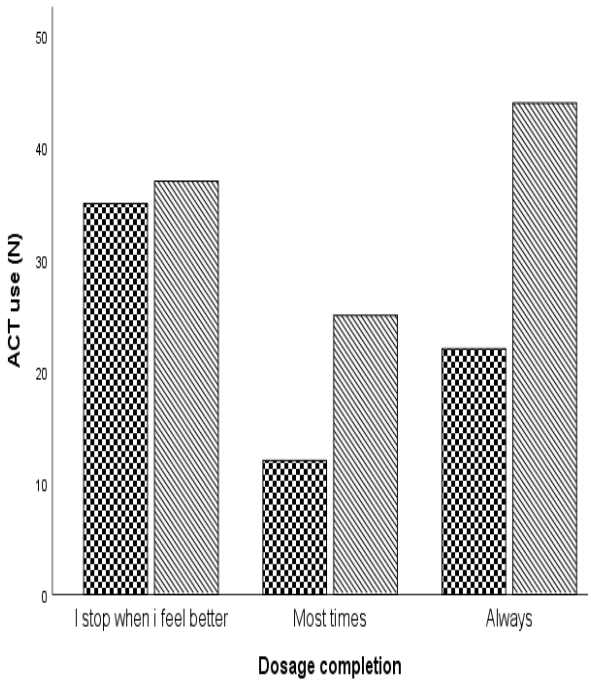
Figure 3.14: Graphs showing history of malaria and ACT use across the four regions; A (Lagos urban), B (Lagos rural), C (Osun urban) and D (Osun rural).

3.3.19 Antimalarial dosage completion across the four regions.

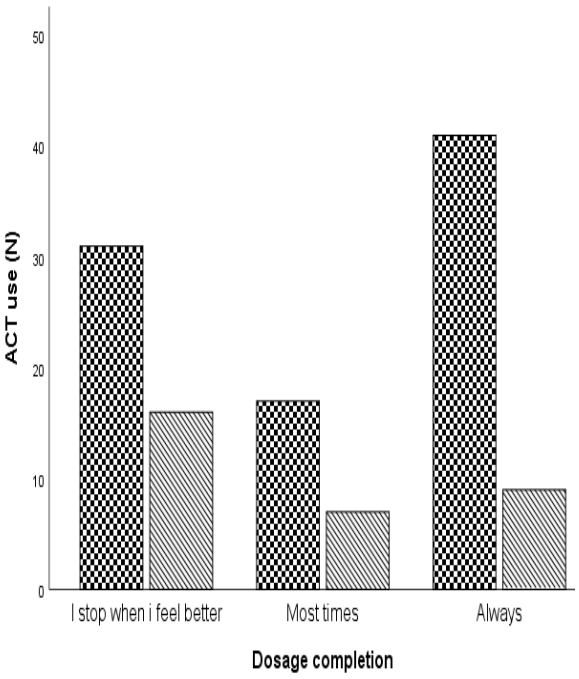
Dosage completion is an integral part of effective treatment of malaria and also prevents treatment failure and development of parasite resistance to the drug used. It is a common practice that health seekers usually stop taking their medication once symptoms have reduced or disappeared. This is a threat to the long term use of the artemether-lumefantrine combination and ACTs in general. Participants were asked if they completed their dosage the last time they had malaria and responses was categorised into 'Always', 'Most times' and 'I stop when I feel better'.

Figure 3.15 below illustrates the relationship between the use of ACTs and completion of dosage as required. In the Lagos urban region, out of a total of 175 participants, 106 (60%) treated malaria with ACTs out of which only 42% (44) completed the recommended dosage. A totally different outcome is noticeable in Lagos rural region, with only 9 participant (28%) ACT users claiming to complete their dosage. In this region, not only is the use of ACT as malaria treatment incredibly low, the ability to stick to the recommended dosage is even

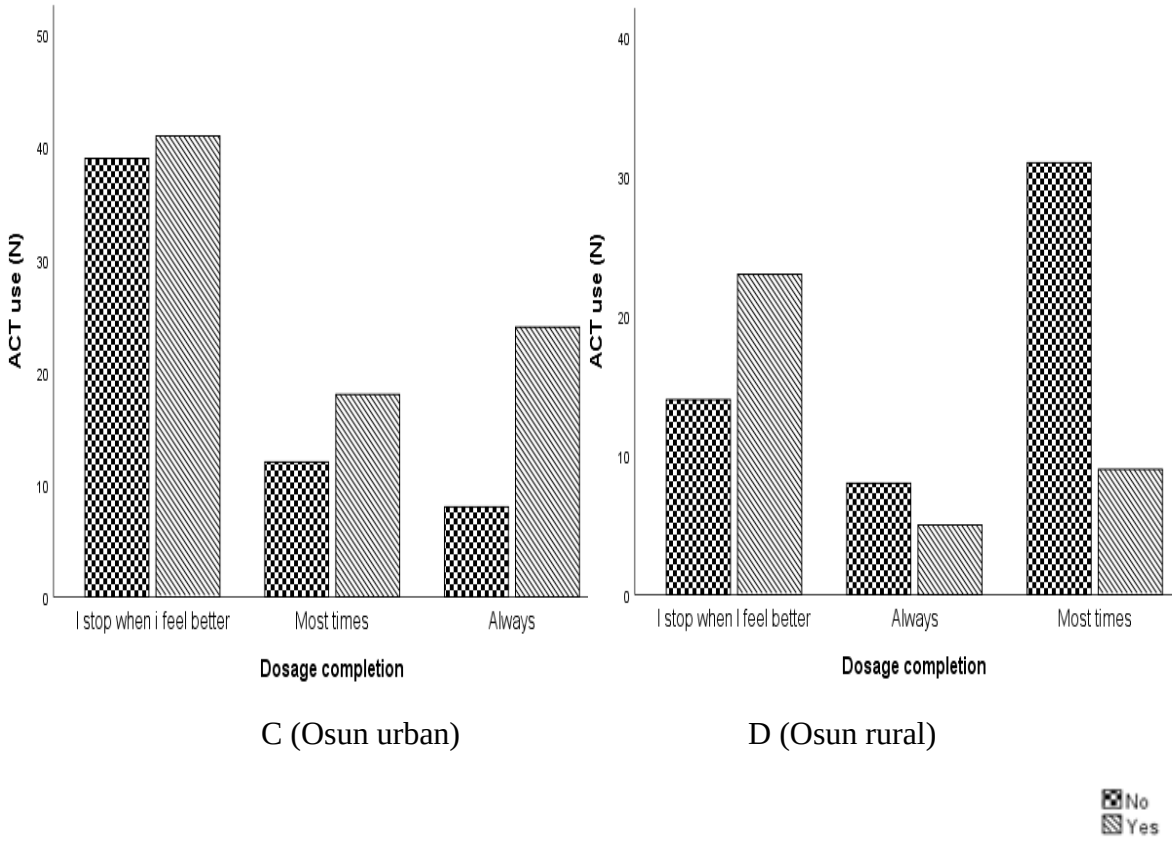
worse. In Osun urban, even though there is a better use of ACTs, only 24 (29%) participants of a total of 83 ACT users claim to complete their dosage; with most people stopping when they don't have the symptoms anymore. In the rural area of Osun state, 11 (28%) participants that use ACTs to treat malaria confirm that they completed the recommended dosage. Although it should be noted that some participants that did not treat with ACTs could have appropriately treated with chloroquine injections, but with emphasis on ACT drugs, this result shows a terrible compliance rate with respect to the recommended treatment method. If dosage completion isn't taken seriously, the malaria parasite will soon develop resistance to the commonly used ACTs as has been recorded for all non-ACT drugs.



A (Lagos urban)



B (Lagos rural)



C (Osun urban) D (Osun rural)

Figure 3.15: Graphs showing antimalarial drug type used for treatment and dosage completion across the four regions; A (Lagos urban), B (Lagos rural), C (Osun urban) and D (Osun rural).

3.3.20 Statistical analyses of the data

Table 3. 2: Association of socio-economic variables with treatment practice in Lagos urban area.

Variable		Appropriate diagnosis			ACT use		
		X^2	df	P-value	X^2	df	P-value
Total							
Age	**16-20**	44.321	6	<0.001	5.495	3	0.139
	21-25						
	26-30						
	30+						
Sex	**M**	3.148	2	0.207	1.162	1	0.281
	F						
Education	**none**	35.870	6	<0.001	13.191	3	0.004
	Primary						
	Secondary						
	Tertiary						
Marital status	**Single**	5.046	2	0.80	0.224	1	0.636
	Married						
Employment	**Yes**	13.770	2	0.001	6.430	1	0.011
	No						
Salary	**<₦50,000**	19.992	2	<0.001	7.730	1	0.005
	>₦50,000						
WTP	**>₦500**	11.636	2	0.003	5.971	1	0.015
Treated	**Hospital**	32.065	2	<0.001	4.623	1	0.032
	Pharmacy	14.845	2	0.001	2.911	1	0.088
	PPMV	0.453	2	0.797	6.769	1	0.451

Table 3. 3: Association of socio-economic variables with treatment practice in Lagos rural area.

Variable		Appropriate diagnosis			ACT use		
		X^2	df	P-value	X^2	df	P-value
Total							
Age	**16-20**	9.564	6	0.144	3.562	3	0.313
	21-25						
	26-30						
	30+						
Sex	**M**	0.011	2	0.994	0.679	1	0.410
	F						

Education none	11.147	6	0.084	5.456	3	0.141
Primary						
Secondary						
Tertiary						
Marital status Single	3.699*	4	0.448	1.288	2	0.525
Married						
Employment Yes	2.333	2	0.311	0.106	1	0.745
No						
Salary <₦50,000	4.705	2	0.095	0.628	1	0.428
>₦50,000						
WTP >₦500	3.306	2	0.191	1.292	1	0.256
Treated Hospital	14.416	2	0.001	9.334	1	0.002
Pharmacy	3.380*	2	0.184	1.242	1	0.265
PPMV	2.103	2	0.349	0.33	1	0.856

Table 3. 4: Association of socio-economic variables with treatment practice in Osun urban area.

Variable	**Appropriate diagnosis**			**ACT use**		
	X^2	df	P-value	X^2	df	P-value
Total						
Age 16-20	26.755*	6	<0.001	3.365	3	0.339
21-25						
26-30						
30+						
Sex M	9.648	2	0.008	0.004	1	0.952
F						
Education none	21.827*	6	0.001	20.781*	3	<0.001
Primary						
Secondary						
Tertiary						
Marital status Single	8.317	2	0.016	0.504	1	0.478
Married						
Employment Yes	10.862	2	0.004	11.926	1	0.001
No						
Salary <₦50,000	7.725	2	0.021	7.490	1	0.006
>₦50,000						
WTP >₦500	8.975	2	0.11	3.207	1	0.073
Treated Hospital	39.159	2	<0.001	6.050	1	0.014
Pharmacy	8.509	2	0.055	2.299	1	0.129
PPMV	25.340	2	0.008	7.424	1	0.006

Table 3. 5: Association of socio-economic variables with treatment practice in Osun rural area.

Variable	Appropriate diagnosis			ACT use		
	X^2	df	P-value	X^2	df	P-value
Total						
Age 16-20	3.496*	6	0.743	6.753	3	0.080
21-25						
26-30						
30+						
Sex M	7.930	2	0.019	0.326	1	0.568
F						
Education none	2.811*	6	0.832	6.007	3	0.209
Primary						
Secondary						
Tertiary						
Marital status Single	4.804	2	0.127	0.254	1	0.705
Married						
Employment Yes	3.653	2	0.238	1.129	1	0.482
No						
Salary <₦50,000	1.749	2	0.482	2.036	1	0.213
>₦50,000						
WTP >₦500	0.177*	2	0.873	2.986	1	0.084
Treated Hospital	15.552	2	<0.001	3.306	1	0.018
Pharmacy	6.634	2	0.034	0.081	1	0.775
PPMV	18.336	2	<0.001	10.458	1	0.001

Chi squared result to determine an association between SES variables such as education level, stated WTP, and recommended treatment practice across the four regions are summarized in Table 3.2 to 3.5. In the Lagos urban region, there is an association between age and self-medication but no association with the use of ACTs; a similar result was also recorded in Osun urban region. Both rural regions did not show an association between age and treatment practice. It can also be seen that the use of ACTs is not associated with any age group; meaning all age groups run the risk of improper treatment of malaria with a non-ACT as recommended. Also, in the entire four regions as seen in table 3.2 to 3.5 there is no association between gender and treatment practice, meaning both genders are at equal risk of poor malaria treatment practice. There is however a strong association between education level and diagnosis ($P<0.001$) in Lagos urban area, and an association with the use of an ACT in the same region. This is also found in the urban area of Osun State; however, there was no association between education level and

treatment practice in the rural areas (Ikorodu, Iwo). No association was also found between marital status and treatment across the four regions; however, employment status showed a positive association with self-medication and the use of ACTs in the urban regions only. Lagos urban region and Osun state urban region shows that there is an association between employment and salary earned by participants and mode of treatment; this can be largely due to the ability to afford effective treatment. WTP as much as ₦500 as stated by participants did not have an association with actual payment for ACTs except for Lagos urban region; this shows that other factors such as affordability, trust, and access can also affect the use of ACTs even if participants are willing to pay a particular amount for malaria treatment. An association between treatment received at the hospital and appropriate diagnosis is recorded across the four regions; with three of them having a strong association ($P<0.001$). A statistically significant association was also found between hospital visits and appropriate treatment with ACTs across the four regions. However, treatment in PPMV stores in Osun rural region showed a significant association with appropriate diagnosis before treatment and sale of ACTs. To further investigate the association found between education status and treatment patterns, an LSD test was done.

LSD (Least Significant Difference) is the value at a particular level of statistical probability (e.g. $P\leq0.01$- means with 99% accuracy) when exceeded by the difference between two varietal means for a particular characteristic, then the two varieties are said to be distinct for that characteristic at that or lesser levels of probability. When an analysis of variance (ANOVA) gives a significant result, this indicates that at least one group differs from the other groups. Yet, the omnibus test does not indicate which group differs. In order to analyze the pattern of difference between means, the ANOVA is often followed by specific comparisons, and the most commonly used involves comparing two means (the so called “pairwise comparisons”). Fisher's LSD method is used in ANOVA to create confidence intervals for all pairwise differences between factor level means while controlling the individual error rate to a significance level specified. Fisher's LSD method then uses the individual error rate and number of comparisons to calculate the simultaneous confidence level for all confidence intervals. This simultaneous confidence level is the probability that all confidence intervals contain the true difference.

LSD analysis (Table in Appendix) shows in detail what educational group has an effect or an association with the use of ACTs. People that are educated to a tertiary level in Lagos urban are

very likely ($p < 0.001$) to use an ACT to treat malaria compared to other type of educational level. This might be expected because people in this group usually get the best jobs and are generally paid a higher salary. Though the use of ACTs is very encouraging, it is also worrying that there is no relationship found between any educational group and appropriate diagnosis with either RDT or microscopy which indicates that a lot of negative cases could have been treated with ACTs. Also, a similar result was found in Osun state urban region, however, people with secondary education also showed a significant association with ACT ($p < 0.05$)

3.4 Discussion

Having in mind that Nigeria has the largest number of cases of malaria in the world (Dawaki *et al.,* 2016) continuous effort has been made over years to reduce this epidemic. Also, most of the interventions and targets attached to achieving a particular aim in regards to treatment and prevention have not been achieved (Amoran *et al.,* 2013; Umaru *et al.,* 2015); this is a threat to planned eradication of malaria. As much as malaria infection is a problem, over the years, effective treatment of infected people has proved a challenge in all areas of the country (Omo-Aghoja *et al.,* 2008; Jeu, 2013; Uzochukwu *et al.,* 2010). As recommended by WHO and the FMOH, effective treatment can be achieved by following two major steps of appropriate diagnosis and treatment using recommended ACTs. However, incompliance with stated recommendations and guidelines to treatment for one reason or the other are major barriers and threat to eradication or effective management of malaria.

With respect to the data presented in this chapter, the null hypothesis stated that there is no association between participants' socio-demographics in these regions (as defined by age, educational level, residence, and stated willingness to pay) and their malaria treatment-seeking behaviour (as defined by percentage of people who self-medicate or/and are treated with drugs outside the adopted recommendations. According to Etika (2018), nearly 70% of Nigeria's population of 180 million people are aged below 35. For this reason, this study has divided the age categories into four groups and purposely done to concentrate more on the youths as defined by Alhasan & Tyabo, (2013); which is between the age of 16 and 35. By doing this, the study is able to concentrate more on the age groups where most of these treatments are believed to be done. Also, because of the difference in population density between these two regions, more participants were approached in Lagos compared to Osun State. The result of this study showed

that not all the variables under consideration were significantly associated with treatment practices. In other words, the null hypothesis can be accepted for some variables and rejected for other variables in the different study regions.

For example, treatment practices including diagnosis and ACT use are significantly associated with some socio-economic factors such as education level, WTP, salary earned and treatment received in hospitals in the Lagos urban region. In the Lagos rural region, most of these significant associations were not found; only treatment received in the hospital showed an association with recommended treatment practice. When compared, urban region in Osun showed the similar result as Lagos urban and the rural region in Osun, like Lagos, showed an association between hospital treatment; however, in Osun, an association was also found between PPMVs and appropriate treatment practice. Low level of education and awareness in the Osun rural region could mean that clients totally depend on the expertise of the medicine seller. Although the treatment practice in Lagos PPMVs conforms with the results of Isiguzo *et al.,* (2014), the Osun PPMV data is different; with most patients visiting the hospital as opposed to medicine retail outlets. Osun State hospitals provide free treatment for uncomplicated malaria, although this is practised in Lagos State, the process is more reliable in Osun State and the waiting time in Osun is generally shorter compared to Lagos with a much larger population. Earning less in a region where hospital treatment is free could be a leading reason why people in Osun State preferred hospital treatment compared to a busy State as Lagos, where patients want to rush in, get their drugs, and be on their way. Overall, the results show a similar trend in treatment practice in the urban regions of both States and in the rural regions. People that reside in the urban regions of these two States, who earn up to ₦50,000, are very likely to treat with an ACT, and those who receive treatment in the hospitals are likely to be treated and diagnosed appropriately. This is a massive improvement for the hospital caregivers and shows that training that has been offered over the years is now beginning to yield results. Chapter 4 and 5 further investigates practices in the health sector and this is discussed in more detail. However, this result further lays emphasis for more specific intervention programs rather than general programs, so barriers can effectively be tackled at a more focused level.

3.4.1 Compliance with ACT use

Overall, across both communities, ACTs were preferred as the treatment of first choice among participants in the urban region and a small number of participants in the rural region; which corroborates findings by Magham *et al.,* (2011). This could be good news considering that the recommended first-line treatment method for malaria is the use of ACTs; however, a reason for concern is the low acceptance in the rural regions and the high rate of self-medication among clients that actually use ACTs. There is a high possibility that the majority of people using ACTs without a prior diagnosis do not actually have a malaria infection; this inappropriate use may contribute in the long term to *Plasmodium* drug resistance. With regard to the use of ACTs, as explained by Bablola *et al.,* (2007) the high cost of ACTs is a primary reason for people using chloroquine and SP as a first line treatment for malaria despite the reduced efficacy or known reactions to these drugs. The preference of ACTs in the urban communities may be because of the awareness through TV adverts and intervention programs in the environment, or expectation of efficacy. The findings of this study show an improvement with the use of ACTs in both States which confirms the findings by Ezenduka *et al.,* (2014) in the eastern part of Nigeria (it should however be noted that most of the participants in this study also used ACTs to treat an unconfirmed case of *Plasmodium*). Malaria symptoms are often assumed in Nigeria if one has a headache and elevated body temperature. Awareness of ACT use is a major factor that can improve malaria treatment, aside from intervention programs- mouth to mouth advice, TV and radio adverts, and health provider advice has helped increased awareness of ACTs in the urban areas. However, this effort has not been replicated with regard to ensuring diagnosis before treatment. As discussed by Onwujekwe *et al.,* (2005), treatments through medical outlets are mostly based on clinical symptoms which have led to 50% non-malaria cases being treated as a malaria infection.

Findings from this study showed that self-medication is still a common practice among both communities where this study was carried out. Self-medication was observed among all age groups, sex, urban and rural regions and across all social economic status. This result confirms the findings of Babalola *et al.,* (2007) and Chipwaza *et al.,* (2014). However, there is an association between education level and appropriate diagnosis in the urban areas of both States. As mentioned by McCombie (2002), inappropriate prescription and use of antimalarials will increase the risk of developing parasite resistance. This study shows that a lot of self-medication

happens in the PPMVs, confirming the findings of Metta *et al*., (2014), McCrombie (2002), Goodman *et al*., (2007). It also shows that the majority of the participants have either got their treatment from pharmacy stores or a PPMVs, which is consistent with previous studies (Afolabi, 2008; Ranno *et al.,* 1988). As most pharmacy stores in Nigeria are privately owned and are for profit, owners would rather yield to a customer request regardless of government recommendations and policies than to see the customer leave. The result, however, further strengthens the fact that the use of ACTs for malaria treatment is the way forward towards eradication of malaria in Nigeria since it has been recorded that a majority of Nigerians would have at least 4 -5 cases of malaria in one year. If the use of ACTs can be embraced by everyone and strong measures are in place to ensure its authenticity and safety, then barriers to effective case management can be removed**.**

3.4.2 SES and adherence to recommendations

Affordability is a major issue and barrier to the effective management of health care, especially treating malaria in endemic regions. Drug cost constitutes the bulk of expenses on malaria treatment (Salawu *et al.,* 2016). As pointed out by Chuma *et al.,* (2010), lack of money contributes to poor drug compliance and people who can't afford the recommended treatment are often given other types of treatment because they are cheaper than the recommended antimalarial. Although essential, the price of a particular drug is not the only factor to be considered while discussing cost of treatment; in some areas, cost of treatment is largely affected by transportation, hospital or health care charges among other factors. The total mean price for the most available antimalarial at the time this study started was ₦500. Willingness to pay is the maximum or comfortable amount an individual is willing to pay or sacrifice to procure a service or avoid something undesirable. Willingness to pay is an integral part of malaria intervention programs to improve treatment and eradication and it has been used in various studies including Uganda (Hansen *et al.,* 2012), Nepal (Morey *et al.,* 2003) and Nigeria (Onwujekwe *et al.,* 2010).

This study also used salary earned by respondents to determine if they are willing to pay up to ₦500 for malaria treatment; the findings showed that even among people that earned over ₦50,000 monthly, a small percentage are willing to pay. This result showed that in the rural regions, majority of those in employment and earning at least ₦50,000 still don't treat malaria properly; showing that treatment practice in rural areas is generally not affected by amount

earned, but low awareness to recommended treatment pattern might be a barrier (Bamiselu *et al.*, 2016). This finding is in contrast to Chuma *et al.,* (2010) which state that lack of cash was the reason why people are not seeking appropriate treatment. It should be noted however that this study was done in 2010 and a lot has changed in Nigeria since then; especially with the country's economy going into recession recently. Also, the decision to subsidize ACTs has not improved people's willingness to pay for them; as a matter of fact, within the two years of data collection in Nigeria, the price of Coartem (one of the most used and most effective antimalarial drugs in Nigeria) increased from ₦650 to ₦1850. Most ACTs are above ₦500, which means people are forced to pay for these drugs at that price and those that can't afford it would simply go for an alternative such as chloroquine. In a study by Uzochukwu *et al.,* (2010) the willingness to pay for RDTs by respondents was positive; 90.7% in rural areas and 89% in urban. However, the mean WTP in urban areas during this study was ₦372.30 and ₦296.28 in rural areas; both of which are less than ₦500 that was used in this study.

There was a statistically significant association between those who stated a willingness to pay ₦500 or more and actual payment; this is supported in a study by Aizuddin *et al.,* (2012) where factors such as age, education, income, locality rural/urban are factors that can affect an individual's WTP for healthcare. However, this study did not check for an association between willingness to pay and actual payment. For example, as mentioned by Jimoh *et al.,* (2007) economic burden plays an important role in people's actual adherence to practices they are willing to engage in. This study found that participants who are in employment and reside in urban areas are more likely to be willing to pay as much for treatment; however, although this can be observed in Figures 3.2-3.5, there is no statistically significant result to support this. Considering the resources available to people living in rural areas and the high rate of malaria cases, it is not surprising to see that most people are not willing to pay as much for treatment of one case of malaria. A significant association between salary earned and place where treatment was recorded was only found in Lagos urban region, with other regions showing no significant association. This result is similar to what was found by Onwujekwe *et al.,* (2011), where there was no statistically significant difference across SES groups and place where treatment was received. Educational level and social economic status to an extent appear to have a positive impact on the treatment practices among both communities. This corroborates the findings of Jombo *et al.,* (2010). A large number of respondents had a formal education with a small

percentage having just primary and no education at all. The south west region has a high level of western education compare to the northern region (Gobir *et al.*, 2014).

3.4.3 Treatment centres and adherence

With regard to treatment completion, treatments obtained from drug stores and pharmacy stores cannot be monitored, due to the fact that most people receive treatment from drug stores, it explains why a lot of patients do not complete their dosage as observed in this study. This was also observed by Gobir *et al.,* (2014). Most participants from rural areas receive treatments from hospitals and drug vendors, which may be due to the facts that these rural areas do not have a lot of legal pharmacy stores around them. Primary health care centres which are located in the rural areas would have been the cheapest option to receive treatment, but poor services, shortage of medicines and attitude towards patients by health care providers is one of the reasons people sought alternative treatment. There was no correlation observed between educational status of people living the rural areas and hospital treatment of malaria. This finding is in contrast to previous studies (Habeeb *et al.,* 1993. Sayeed, 1998. Abosede, 1994). This study also found that in cases where pharmacists or PPMVs were in a place to influence the decision of a client, most have influenced them to buy an ACT. This confirms the finding of Okeke *et al*., (2009) that claims that drug vendors can also give correct verbal advice to patients, and strongly advises the inclusion of PPMVs in malaria control strategies. Monotherapy was used more in PPMVs compared to hospitals and pharmacy stores, which also confirms the finding of Ezenduka *et al.*, (2014).

A clear preference for drug outlets was recorded in this study. This is also supported by Landscape of Antimalarial Medicines in Nigeria (2016) and other studies (Isiquzo, *et al.,* 2014; Goodman *et al.,* 2007) where over 70% of malaria treatments were received at a medicine store. Reasons for these visits include; long waiting times at the hospital (Ogunnowo *et al.,* 2015; Umar and Umar, 2011), affordability of drugs (Chuma *et al.,* 2010) and the ability to influence treatment (Prach *et al.,* 2015). However, medicine outlets have a history of improper treatment practices, including high rates of self-medication (Prach *et al.,* 2015; Goodman *et al.,* 2007), counterfeit drugs (Liu *et al.,* 2016; Afolabi, 2008) and substandard drugs (Beyeler *et al.,* 2015). PPMVs have been described to be the worst place to be treated in Nigeria; for example, Berendes *et al.,* (2012) in a study to describe the effectiveness of PPMVs in malaria control

found that all drug vendors in the district failed to stock and sell first-line antimalarials, replacing them with drugs such as chloroquine, sulphadoxine-pyrimethamine and oral artesunate. This practice is common among PPMVs (Beyeler *et al.,* 2015; Prach *et al.,* 2015; Goodman *et al.,* 2007) and calls for an urgent need to regularly monitor and improve the quality and availability of medicines sold by these sellers.

Also, the only venue for treatment that has a statistically significant association in the study area ($P<0.001$ in three of the four regions) with proper diagnosis and ACT use was the hospital. This compliance with recommendation was not recorded in any drug store, which confirms the worrying state of adherence to policy among medicine sellers. However, this improvement in adherence recorded in the hospitals, which was also found by Ezenduka *et al.,* (2014), suggests that over the years, hospital treatment is continually improving from what was described by Saka and Fakeye (2015) were poor adherence to guidelines for children in rural health facilities of Southwest Nigeria was found. Although there was no statistically significant association across SES groups and where individuals received treatment, there is a significant association between those that visited hospitals for treatment and being treated appropriately in line with the WHO recommendations.

3.5 Conclusion

Findings from this study indicate that there is a high level of self-reported malaria across all SES groups and geographic areas, with the better-off SES groups in general reporting more malaria than worse-off SES groups, and with more malaria reported in urban areas compared to the rural areas. Formal education impacts on the use of appropriate antimalarial drugs but it does not relate to adequate awareness of appropriate treatment practices, including diagnosis and completion of dosage as advised.

The drug prescription pattern in the hospitals is improving while no meaningful improvement can be seen in the prescription pattern at medicine outlets. The prescription of CQ, SP including monotherapy artesunate in drug stores will undermine the attainment of the Millennium Development Goal. Although rural and urban individuals are quite aware of the recommendations for treatment, increasing drug prices is a major barrier to adherence. Success recorded over the years with effective malaria treatment, when ACTs were sold at a subsidised rate, is being threatened by the continuous price increase in ACTs, thereby making even people

in higher SES groups opt for cheap antimalarials against recommendations. Drug vendors are major health providers in Nigeria and it has been advised that they should be made partners in the health care network because they are likely to continue as a major source of antimalarial drugs for most rural communities in the foreseeable future. However, evidence has shown that adherence by drug vendors has not improved over a long time and it decreases the chance of eradication. Therefore, efforts should be made towards improving malaria eradication by educating caretakers and drug vendors while provision of more functional primary health care facilities with readily available drugs and improving the conditions of roads with a good transportation network may improve accessibility to appropriate health care in rural areas. Hospitals and primary health centres where recommendations are being followed should be at the forefront of malaria treatment until drug vendors can be trusted to treat every case appropriately.

Overall, malaria public enlightenment efforts need to be intensified and effective malaria preventive and treatment methods should be affordable and support should be provided to make malaria diagnosis and treatments at hospitals free.

Policy makers and programme managers should develop distribution channels for malaria prevention and treatment which can better protect everyone from malaria. This is in accordance with the notion of universal access to malaria control interventions, since targeting the poor and other supposedly vulnerable groups may not adequately cover the true picture of people who require malaria control services and expose them to increased burden of the disease and potentially catastrophic costs that could lead to impoverishment or further impoverishment. This means that to substantially decrease the burden of the disease, there should be mass deployment of malaria control intervention tools such as Artemisinin-based combination therapy (ACTs) and RDTs, without preference to any SES group or people residing in different geographic locations.

CHAPTER 4: TREATMENT PRACTICES IN HOSPITALS, PHARMACIES AND PROPRIETARY PATENT MEDICINE VENDORS (PPMVs)

4.1 Introduction

Drug stores are believed to be the most popular place for Nigerians to seek treatment. Isiquzo *et al.,* (2014) and Goodman *et al.,* (2007) claim that nearly 60% of all treatment for malaria happens at a drug store; either a pharmacy store or a PPMV (owner-operated drug retail outlets are known as patent and proprietary medicine vendors). The WHO and Federal Ministry of Health (FMOH) currently recommend confirmatory blood tests for all suspected malaria cases prior to treatment. Furthermore, treatment should only be with an ACT upon confirmation of parasitaemia (this includes not administering ACTs to patients or buyers with unconfirmed blood tests) (FMOH, 2004; WHO, 2010). Considering the proportion of patients that visit both pharmacy stores and PPMVs for malaria treatment compared to other places, this means that the efficacy of malaria treatment and the road to eradication largely depends on adherence to recommendations and policies at these outlets.

Efforts have been made to help promote effective case management in pharmacy stores and PPMVs by providing Rapid Diagnostic Tests (RDTs) to improve point-of-care diagnosis; however, this is not seen to be practical as a lot of drug vendors either do not have RDTs available or they are not well trained to use them. Also, a reasonable proportion of consumers purchase medication for a relative or friend, who is probably too weak from the symptoms to visit the store. There is a huge difference in practice between pharmacy stores and PPMVs; the pharmacy stores are predominantly privately owned and staffed by formally trained pharmacists and are usually patronized by people of higher economic class. However, the PPMVs, which are commoner pharmacy stores, are either owned or staffed by untrained vendors. Also, from a business perspective, the PPMVs are lower scale investments that offer little return and hence they are loosely regulated and often found in the more rural regions of the country (Beyeler *et al.,* 2015). Due to the fact that PPMVs invest in cheaper drugs, the quality of health service that they provide is poor and less trusted compared to pharmacy stores. PPMVs are only licensed to sell over-the-counter medicines, but in a bid to allow and ensure equitable access of the larger

population to chemotherapy, antimalarials were included in the drugs they may sell. Goodman *et al.,* (2007) however assessed that these stores do not stock ACTs and they have little or no awareness of the recommended treatment guidelines; which is why many health care providers continue to prescribe and sell less effective and unsafe drugs such as chloroquine. This is a significant problem considering that up to 60% of household members reported with fever received treatment from a PPMV (Oyeyemi *et al.,* 2015; National Population Commission, 2012). Predictably therefore, 58% of malaria deaths occur amongst people that reside in the rural regions (Gwatkin and Guillot, 1999).

In May 2005, Nigeria adopted a new malaria drug policy to combat issues regarding malaria diagnosis and treatment. While policies and recommendations are more likely to be adhered to in the hospitals and clinics, and may provide a better quality treatment due to the qualifications of health providers, other factors such as long waiting and travel times are common reasons as to why patients often seek other faster but non-conventional methods. An assessment of indirect cost of treatment of malaria by Obieche & Odili (2016) showed that more than 50% of the 254 patients studied spent 2-4 hours at the hospital before they got to the pharmacy for their medications. Confirmatory malaria microscopy testing is one of the advantages of seeking malaria treatment at the hospital; however, as rightly suggested by Salawu *et al.,* (2016), the cost of hospital services are unaffordable for many families and may account for the delays observed in accessing hospital services for medical treatment. Indeed, the average cost for treatment of uncomplicated malaria in private hospitals among adults, children and pregnant women was ₦3,941 (Salawu *et al.,* 2016). About ₦406 (10.3%) of the treatment cost was spent on consultation, ₦1064 (27.7%) was spent on laboratory investigations and ₦2,444 (62%) was spent on antimalarial drugs. These consultation and laboratory testing costs are more than a patient would pay for antimalarials sourced from a pharmacy store or a PPMV.

This chapter therefore seeks to describe and compare profiles of patients and treatment practices in the PPMV, pharmacy store and hospital settings; including where patients are more likely to self-medicate and where patients are more likely to be correctly treated with the use of ACTs in line with the newly adopted treatment policy. Findings can be used to describe in detail, the barriers to the effective management of malaria cases by health providers at the diagnosis and treatment stages.

4.2 Objective

This chapter aims to better characterize the practice of presumptive treatment of malaria in Nigerian drug stores and hospitals, in order to evaluate reasons for failure of effective case management practices and to determine where interventions for malaria treatment delivery should be targeted.

4.2.1 Research question 2 and hypothesis:

Does the type of drug store (defined as pharmacy stores and PPMVs) where treatment is delivered influence adherence to recommended malaria treatment practices?

H_0: there is no association between type of drug store and adherence to recommended malaria treatment-seeking practices.

H_1: there is an association between type of drug store and adherence to recommended malaria treatment-seeking practices.

4.2.2 Research question 3 and hypothesis:

Are hospital caregivers adhering to the recommended treatment policies?

H_0: there is no association between hospitals (including private and public) where treatment is received and adherence to recommended malaria treatment-seeking practices.

H_1: there is an association between hospitals (including private and public) where treatment is received and adherence to recommended malaria treatment-seeking practices.

4.3 Results

4.3.1 Evaluation of treatment practices in pharmacy stores and PPMVs

A total of 10 pharmacy stores and 10 PPMV stores were evaluated in each state. This sampling was carefully chosen to cover the drug stores in both States and regions that have a high patient load. The medicine retail outlets were strategically selected to cover all parts of the urban regions and also the rural regions of each State selected for this study, with 20 people targeted at 10 outlets in each region. Even though 10 of each type of drug store was chosen in each State, 20 responders were expected for each store in Lagos, while 15 responders were targeted for each store in Osun State. This was done to create a more representative sampling of responders,

considering that Lagos State has a higher population that Osun state. The respondent success rate in Lagos State was 75% and 80% in Osun State. With the use of a questionnaire (refer to section 2.4.1) questions asked included the pharmacist's influence on the drug purchased by the buyer. This question was included because in some cases, patients rely on the expertise of the drug seller and they ask them which drug is best. The pharmacist can now advise on the range of drugs that they think will be appropriate. However, the buyer's decision can still be influenced by the price of the drug. Tables 4.1- 4.2 below shows the socio-graphic distribution results in both States, while Figures 4.3 – 4.4 shows sociographic distribution according to region.

Table 4. 1: Treatment practices at pharmacy and PPMV stores in Lagos State

Characteristics		**Pharmacies**	**PPMVs**	**Total**			
		Patients **(N/%)**	Patients **(N/%)**	Patients **(N/%)**	X^2	df	P-value
Respondents		165 (74)	57 (26)	222 (100)			
Sex	Female	95 (57.7)	43 (75.4)	138 (62.2)	8.241*	1	0.004
	Male	70 (42.3)	14 (24.6)	84 (37.8)			
Drug used	ACT	147 (89.1)	20 (35.1)	167 (75.2)	47.720**	1	P<0.001
	Non-ACT	18 (10.9)	37 (64.9)	55 (24.8)			
Self-medication		136 (82.4)	57 (100)	193 (86.9)	4.518***	1	0.034
Drug seller's influence	ACT	104 (70.7)	17 (85)	121 (72.5)	1.001****	1	0.317
	Non-ACT	5 (27.8)	31 (83.8)	36 (65.5)			

[2]

Table 4.1 shows that out of a total of 222 patients that visited both pharmacies and PPMVs in this region, 57 (26%) visited PPMVs while 165 (74%) visited pharmacies. In total, there were 95 (57.7%) female and 70 (42.3%) male clients that visited the pharmacy stores, while 43 (75.4%) female and 14 (24.6%) male clients visited the drug vendors. As such, though female clients sought malaria treatment more than males, a larger proportion of females received their treatment from drug vendors. Of all the clients that visited pharmacy stores, 136 (82%) were self-medicating compared to 193 (86.9%) of those that visited drug vendors. A significantly higher

[2] * Association between gender and place where treatment was received. ** Association between type of antimalarial purchased and where treatment was received. *** Association between self-medication and place where treatment was received. **** Association between sellers influence and drug purchased.

percentage of the patrons of pharmacies (147/165, 89%) purchased an ACT with 18 (11%) opting for a non-ACT treatment. In contrast, 20 (35.1%) clients bought an ACT at a drug vendor while 37 (70%) clients bought a non-ACT drug. Even though all the drug sellers in this area admitted that they are aware of malaria treatment drug policy and they usually prescribe an ACT to a client seeking malaria treatment, this knowledge does not translate into practice as not only did a whole lot of drug sellers sell non-ACTs to clients, they sometimes influenced the use of non-ACTs. 71% of the ACTs sold in the pharmacy store were influenced by the pharmacist but so was the 29% of the non-ACTs used. Also, 85% of ACTs purchased at a drug store were influenced by the seller and 84% of non-ACTs.

Table 4. 2: Treatment practices at pharmacy and PPMV stores in Osun State

Characteristics		**Pharmacies**	**PPMVs**	**Total**			
		Patients **(N/%)**	Patients **(N/%)**	Patients **(N/%)**	X^2	df	P-value
Respondents		141 (40.5)	96 (59.5)	237 (100)			
Sex	Female	36 (25.5)	54 (56.3)	90 (38)	0.187*	1	0.665
	Male	105 (74.5)	42 (43.7)	147 (62)			
Drug used	ACT	91 (64.5)	47 (49.0)	140 (59.5)	0.081**	1	0.776
	Non-ACT	50 (35.5)	49 (51.0)	99 (40.5)			
Self-medication		82 (58.2)	73 (76.0)	155 (65)	15.574***	1	P<0.001
Drug seller's influence	ACT	40 (28.4)	34 (35.4)	74 (52.9)	2.478****	1	0.317
	Non-ACT	14 (9.9)	29 (30.2)	43 (43.4)			

[3]

Table 4.2 shows that in Osun State, during the period of data collection, recruited PPMVs attended to a total of 96 (59.5%) malaria treatment cases and licensed pharmacists attended to a total of 141 (40.5%) individual malaria treatments. In total, there were 36 (40%) female and 105 (71.4%) male clients that visited the pharmacy stores, while 54 (60%) female and 42 (28.6%) male clients visited the drug vendors. This contrasts with the Lagos State data showing females

[3] * Association between gender and place where treatment was received. ** Association between type of antimalarial purchased and where treatment was received. *** Association between self-medication and place where treatment was received. **** Association between sellers influence and drug purchased.

sought treatment more than males. However, similar to Lagos State, men visited pharmacy stores more than PPMVs and a larger proportion of female clients received malaria treatment from drug vendors. Of all the clients that visited pharmacy stores, 82 (58.2%) were self-medicating compared to 73 (76%) of those that visited drug vendors. The number of ACTs used in pharmacy stores was 91 (64.5%) with 50 (35.5%) opting for a non-ACT. In contrast, 47 (49%) clients purchased an ACT at a drug vendor, while 49 (51%) clients bought a non-ACT drug. The sale of non-ACTs by these sellers, who had previously admitted and showed an awareness of the recommended policy with regard to treatment type shows that their awareness does not translate into practice. 40% of the ACTs sold in the pharmacy store were influenced by the pharmacist but so was the 14% of non-ACTs used. Also, 72.3% of ACTs purchased at a PPMV was influenced by the seller and 59.2% of non-ACTs.

Table 4. 3: Comparison of the treatment practices at pharmacy and PPMV stores in Lagos and Osun State urban areas

Characteristics		Lagos urban					Osun urban				
		Pharmacies **(N/%)**	PPMVs **(N/%)**	X^2	df	P-value	Pharmacies **(N/%)**	PPMVs **(N/%)**	X^2	df	P-value
Respondents		84 (78.5)	23 (21.5)				88 (68.2)	41 (31.8)			
Sex	Female	44 (52.4)	12 (52.2)	3.548*	1	0.986	30 (34.1)	18 (43.9)	1.152	1	0.283
	Male	40 (47.6)	11 (47.8)				58 (65.9)	23 (56.1)			
Drug used	ACT	77 (91.7)	7 (30.4)	40.118**	1	P<0.001	65 (73.9)	15 (36.6)	16.500	1	P<0.001
	Non-ACT	7 (8.3)	16 (69.6)				23 (26.1)	26 (63.4)			
Self-medication		75 (89.3)	21 (91.3)	0.080***	1	0.778	44 (50)	24 (58.5)	0.818	1	0.366
Drug seller's influence	ACT	54 (70.1)	3 (42.9)	1.926****	1	0.165	36 (55.4)	6 (40)	2.445	1	0.118
	Non-ACT	5 (71.4)	11 (68.8)				11 (47.8)	10 (38.5)			

[4]

[4] * Association between gender and place where treatment was received. ** Association between type of antimalarial purchased and where treatment was received. *** Association between self-medication and place where treatment was received. **** Association between sellers influence and drug purchased.

Table 4.4: Comparison of the treatment practices at pharmacy and PPMV stores in Lagos and Osun State rural areas

Characteristics		Lagos rural					Osun rural				
		Pharmacies **(N/%)**	PPMVs **(N/%)**	X^2	df	P-value	Pharmacies **(N/%)**	PPMVs **(N/%)**	X^2	df	P-value
Respondents		35 (30.4)	80 (69.6)				38 (34.9)	71 (65.1)			
Sex	Female	25 (71.4)	57 (71.3)	3.442	1	0.984	24 (63.2)	18 (25.4)	13.571	1	P<0.001
	Male	10 (28.6)	23 (28.7)				14 (36.8)	53 (74.6)			
Drug used	ACT	9 (25.7)	27 (33.8)	16.101	1	P<0.001	16 (42.1)	22 (30.9)	7.445	1	0.006
	Non-ACT	26 (74.3)	53 (66.2)				22 (57.9)	49 (69.1)			
Self-medication		18 (51.4)	77 (96.3)	34.047	1	P<0.001	32 (84.2)	56 (78.9)	0.453	1	0.505
Drug seller's influence	ACT	9 (100)	14 (51.9)	3.552	1	0.505	8 (50)	13 (59.1)	0.252	1	0.144
	Non-ACT	11 (42.3)	39 (73.6)				18 (81.8)	30 (61.2)			

[5]

[5] * Association between gender and place where treatment was received. ** Association between type of antimalarial purchased and where treatment was received. *** Association between self-medication and place where treatment was received. **** Association between sellers influence and drug purchased.

Tables 4.3 and Table 4.4 provide information on the treatment practices in similar regions of both States. In the urban regions of Lagos and Osun State there is a strong significant association between the type of antimalarial used and type of medicine retailer visited (pharmacy or PPMVs) (Table 4.3). This result shows that people that visited pharmacy stores are more likely to buy a recommended ACT for malaria treatment compared to those that visited a PPMV store, where they are likely to use a non-ACT, against the WHO recommendations. A similar finding with regard to type of antimalarial used and store where it was purchased was also observed in the rural regions of Lagos and Osun States (Table 4.4). There was also a strong association ($p < 0.001$) for self-medication and place where antimalarial was purchased in the Lagos rural region which was not observed in the Osun rural region. Also, gender of client had a significant association ($p < 0.001$) with the type of store where treatment was received in Osun rural area but not in Lagos rural area.

4.3.2 Evaluation of treatment practices in hospitals

The type and number of hospitals used in both regions has been previously described in section 2.3 of the thesis. The rate of malaria when compared between an urban region and a rural region is usually higher in the rural areas; however, the number of cases is usually higher in the urban regions due to the overall population density of the towns and cities. Urban regions in Nigeria, especially in both States where this research was done, have more learned people, better access to and options for treatment. In addition, higher socio-economic status enhances affordability of treatment and preventive measures compared to the rural regions in which people are generally less well educated and living in poor housing conditions. As confirmed in the table below (Table 4.3), the total malaria incidence in the rural regions (=1057) is less than the number recorded in the urban regions (=1172).

Table 4.5: Hospital clinical records (Lagos State and Osun State)

	LAGOS STATE		OSUN STATE	
HOSPITAL DATA (MAY - SEPTEMBER 2015)	URBAN	RURAL	URBAN	RURAL
Number of patients suspected to have malaria	1546	941	1359	456
Suspected malaria patients in whom any test was carried out	1546	941	1327	456
Suspected malaria patients assessed clinically only	74	9	30	0
Suspected malaria patients tested by microscopy	0	0	45	20
Suspected malaria patients tested by RDT	1472	932	1300	440
Cases appropriately tested using (RDT + Microscopy)	0	0	45	20
Suspected malaria patients found to be negative	769	253	691	87
Confirmed negative cases treated with antimalarial	140	0	15	0
Negative cases not given antimalarial	629	253	1173	87
Cases found to be malaria positive	536	688	636	369
Positive cases appropriately treated with ACT	449	597	564	290
Positive cases treated with quinnine	51	57	30	45
Positive cases treated with SP	36	34	42	34
Positive cases not treated with antimalarial	0	0	0	0

A clinical examination is standard in all of the hospitals and usually precede other forms of examination; this includes checking the body temperature with the use of a thermometer, asking questions about symptoms that the patient has noticed and sometimes also checking the patient's blood pressure. During the period of data collection, the number of patients suspected to have malaria was 1546 in Lagos urban hospitals, 941 in Lagos rural hospitals, 1359 in Osun urban hospitals and 456 in Osun rural hospitals. In the Osun urban area 98% of patients were tested with an appropriate malaria diagnostic test; in the other three areas, all patients were suitably tested. In Lagos urban area 1472 (95%) patients were tested clinically and with RDT only; none of these patients were tested with a combination of RDT and microscopy. 769 (50%) were negative and 140 (18%) were given an antimalarial. 449 (84%) of the positive cases in this region were treated with an ACT, 51 (10%) were administered quinine and 36 (7%) people were given SP. In Lagos rural, 932 (99%) were tested clinically and with RDT only, similar to Lagos urban, none of the patients in Lagos rural were tested with a combination of RDT and microscopy. Of the patients tested, 253 (27%) tested negative and none of these people were offered an ACT for treatment. 597 (87%) of those that tested positive were given an ACT, 57 (8%) were give quinine while 34 (5%) were given SP. In Osun Urban, 1300 (98%) were tested clinically and with the use of RDT, 45 (3.4%) patients were tested with the combination of RDT and microscopy in this region. Of the patients tested during this period in Osun urban, 691 (52%)

tested negative and of these negative cases, 1% were treated with an antimalarial. 564 (84%) of the positive cases in this region were treated with an ACT, 30 (5%) were given quinine and 34 (5%) were given SP. In Osun rural region, 440 (97%) were tested clinically and with RDT while 20 (4.4%) were tested using a combination of RDT and microscopy. Of the patients tested during this period, 87 (19%) were negative and none of these people were given an antimalarial. 290 (79%) of the positive cases were treated with an ACT, 45 (12%) were treated with quinine and 34 (9%) were treated with SP. in Osun rural. All of the four regions treated all positive malaria cases with an antimalarial.

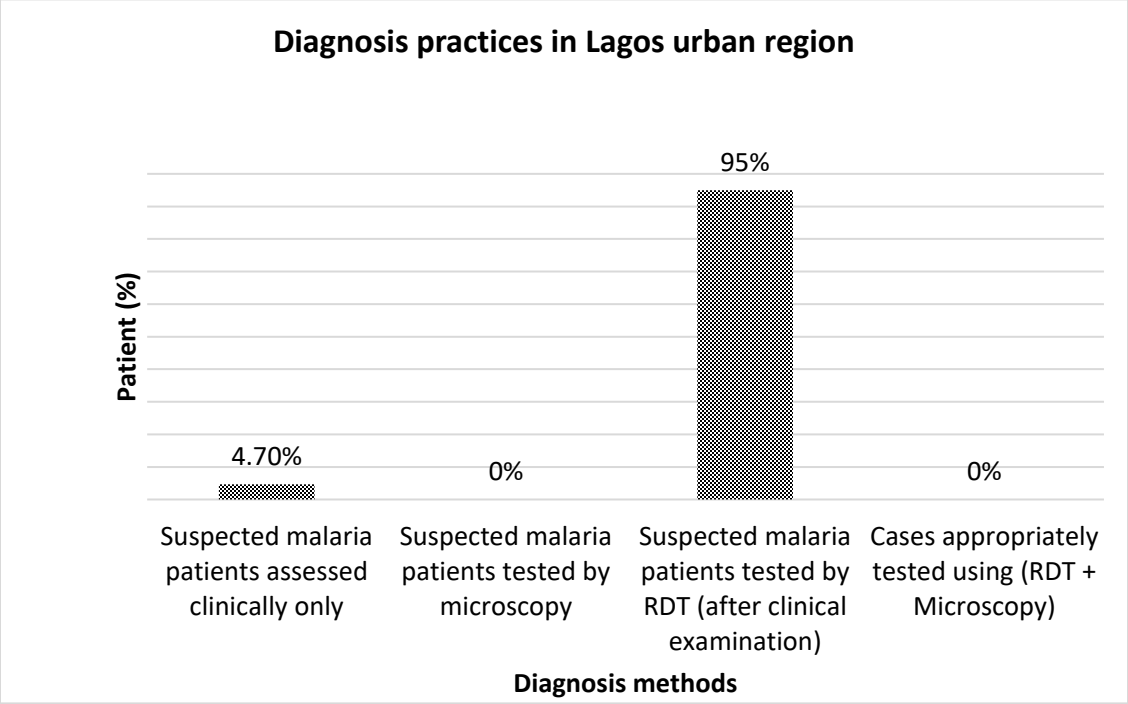


Figure 4.1: Graphical representation of diagnosis practices in selected hospitals in Lagos urban region. An encouraging adherence to recommendation can be seen in this region with 95% patients tested clinically and with the use of RDTs.

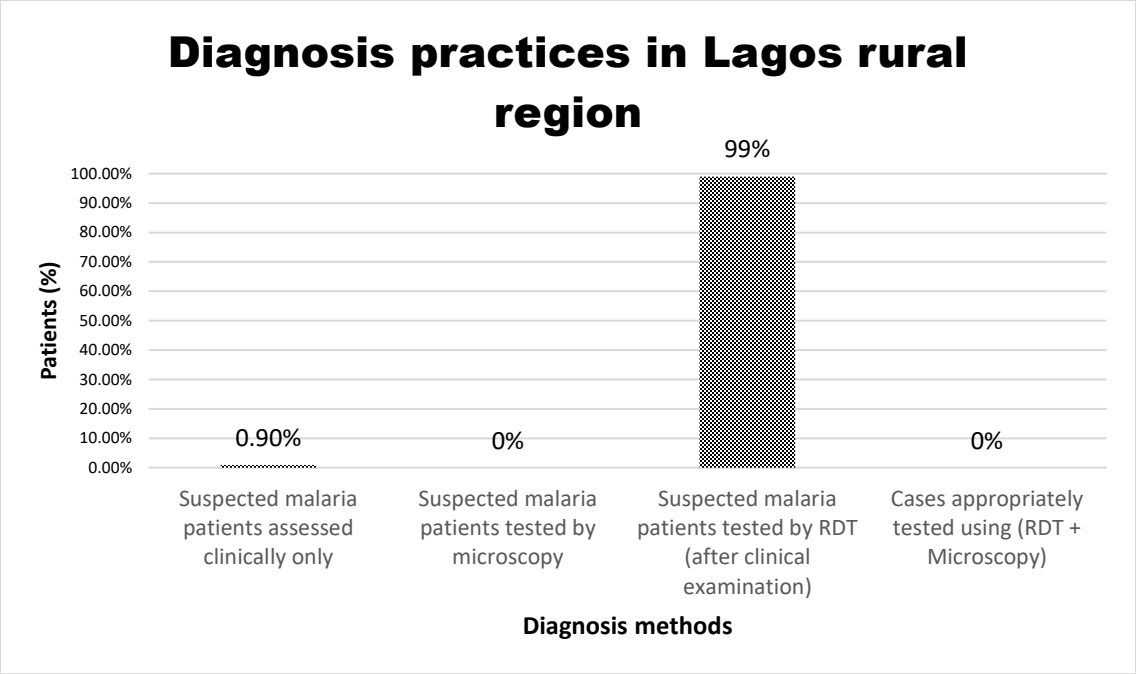


Figure 4.2: Graphical representation of diagnosis practices in selected hospitals in Lagos rural region. An encouraging adherence to recommendation can be seen in this region with 99% patients tested clinically and with the use of RDTs

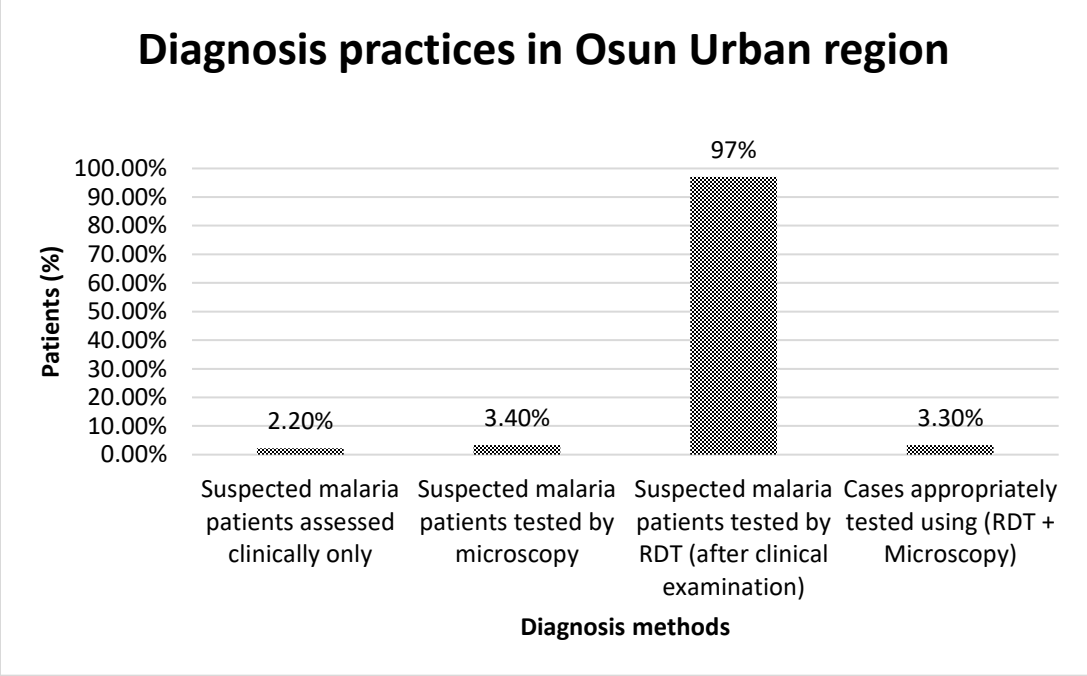


Figure 4.3: Graphical representation of diagnosis practices in selected hospitals in Osun urban region. An encouraging adherence to recommendation can be seen in this region with 97% patients tested clinically and with the use of RDTs

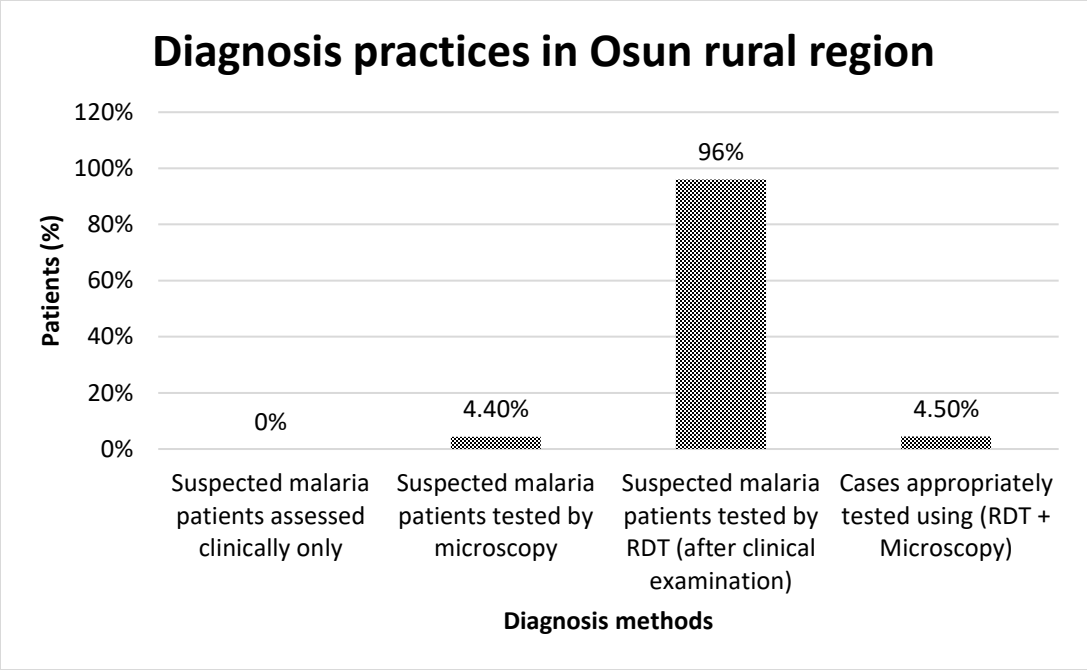


Figure 4.4: Graphical representation of diagnosis practices in selected hospitals in Osun rural region. An encouraging adherence to recommendation can be seen in this region with 96% patients tested clinically and with the use of RDTs.

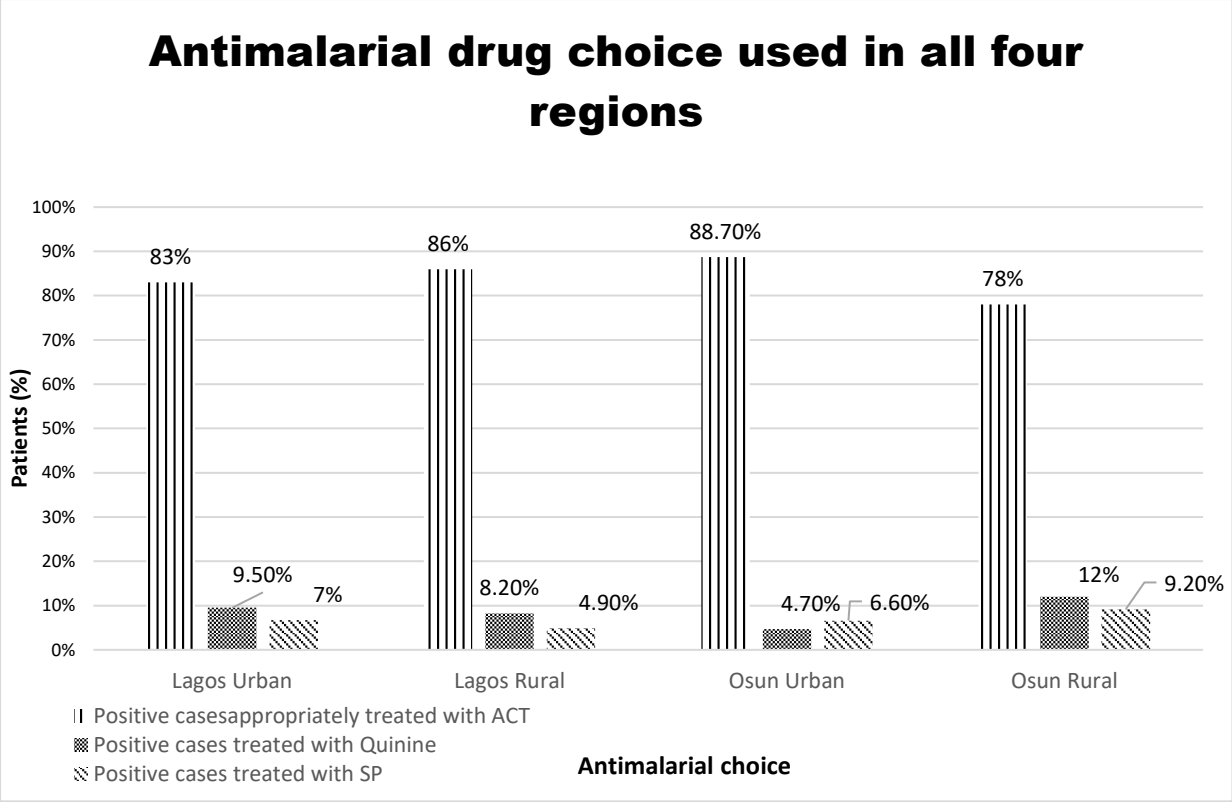


Figure 4.5: Graphical representation of antimalarial drug used to treat malaria cases in selected hospitals across the four regions. Most cases were treated with ACTs even though a small percentage were treated with chloroquine and SP.

As seen in Figure 4.5, Diagnosis practice in recruited hospitals in Lagos urban areas shows that majority of the hospitals diagnosed visiting patients by clinical examination and then using RDT to confirm parasite in the body of patients. The rate of ACT use across the four regions can be seen in Figure 4.9 where it shows that a lot of hospitals are accepting and showing their awareness towards the use of ACT for malaria treatment even though there are still cases of prescriptions that are not in accordance to the WHO and FMOH recommendations.

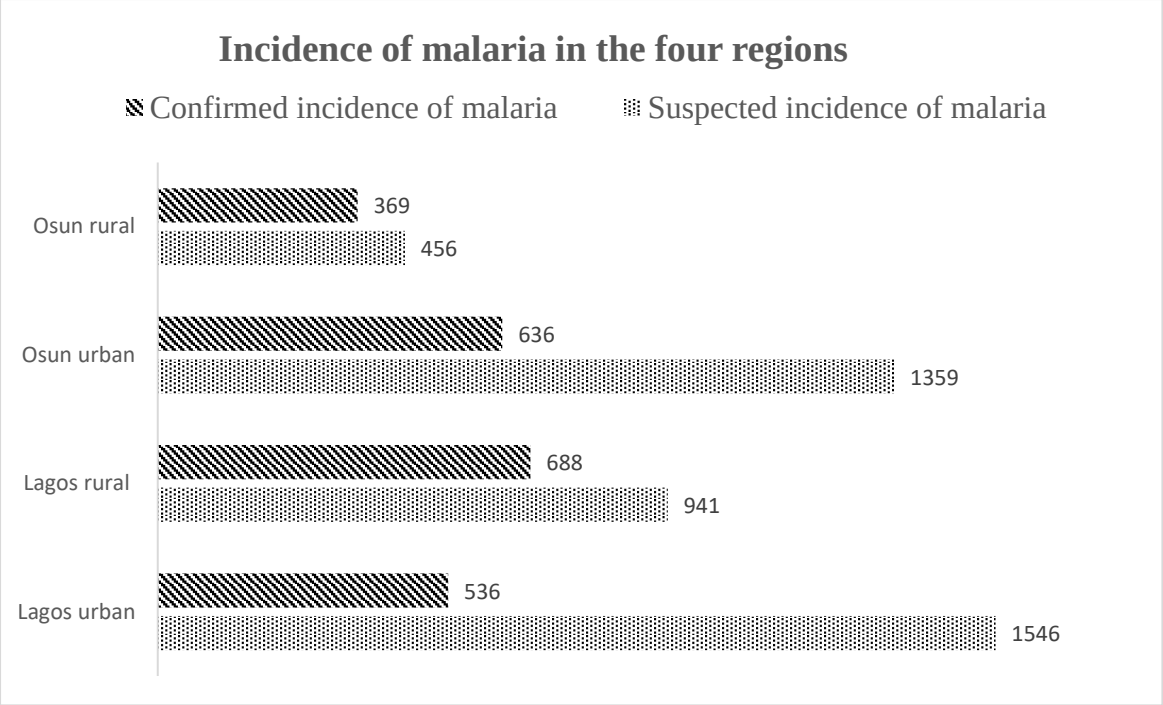


Figure 4.6: Graphical representation of the incidence of malaria compared to the suspected cases of malaria in selected hospitals across the four regions.

Figure 4.10 shows the confirmed incidence of malaria to be 81% in Osun rural hospitals, 47% in Osun urban hospitals, 73% in Lagos rural hospitals, and 35% in Lagos urban hospitals. Figure 4.10 can also be interpreted to show the dangers of self-medication; especially in the urban areas.

4.4 Discussion

4.4.1 Treatment practices in pharmacy stores and PPMVs in Osun and Lagos State

This study documents the case management of drug dispensers for treatment of malaria fever at community pharmacies and PPMVs in Lagos State and Osun State. This study has provided insight and expanded the current limited evidence around the effect drug dispensers (pharmacies and PPMVs) have on effective management of malaria. As most studies on the presumptive management of malaria have been done in one region or State of the country, this study compares the management of malaria at two different regions at the same time. As Lagos State and Osun State are both in the Southwest region, Lagos is a large commercial state with a lot of 'high class' residents compared to the more 'quiet' Osun State where socio-economic status is generally low, being that most residents are either farmers, market women, low scale business owners and civil servants. As such, one would expect attitude and

practices related to malaria treatment to be different in these two regions. Many studies have confirmed that drug outlets are the main access for many health-care products and services, especially drug vendors (WHO, 2004; Ladner *et al.,* 2017). Drug vendors are only allowed to sell 'off-the-counter' drugs; however, there is an exception for antimalarials. This was introduced to reduce the huge pressure on hospitals and other public health services. However, due to the fact that most of these stores are low scale businesses and mostly patronised by people of lower economic status, vendors invest and stock cheap drugs of lower quality (Beyeler *et al.,* 2015). Also, studies further mentioned that most of these poor people that patronise the PPMVs also depend on them for advice and guidance with regard to diagnosis and treatment methods (Ajayi *et al.,* 2002; Ross-Degnan *et al.,* 1996).

All of the providers in this study stated a preference for ACT as a treatment regime for uncomplicated malaria in contrast to what was reported by Goodman *et al.,* (2007) and Ajayi *et al.,* (2013). However, the reason for this could not be confirmed and it was unclear whether it was awareness of policy change or because of an experience-driven awareness of the efficacy of ACTs compared to other antimalarials. Also, in contrast to Goodman *et al.,* (2007), and Mangham-Jefferies *et al.,* (2014) there is no difference in pharmacy store owners and PPMVs with regard to the type of antimalarial the sellers preferred and prescribed; with all of them admitting to preferring ACTs for malaria treatment. This result is encouraging and has shown a positive in comparison to earlier studies where awareness of ACTs as first line treatment of malaria was very low among drug vendors. This shows that awareness programmes such as 'Roll Back Malaria, which has been ongoing over the years in Nigeria, are beginning to yield positive results with regard to the awareness of recommended malaria drug regimes. This awareness of the drug sellers can undoubtedly positively influence clients and patients directly, or indirectly, if managed properly.

Gender predominance for malaria treatment was different in the two locations where this study was done. The predominance of the female gender in Lagos State is consistent with many studies (Ezenduka *et al.,* 2014; Meremikwu *et al.,* 2011; Sears *et al.,* 2013) showing that more females sought out malaria treatment. However, a contrasting result was found in Osun State where more males patronised a drug store for treatment; Lampietti *et al.,* (1999) explains that in some cases or areas, a restricted mobility upon women may impede their attendance at health centres. Also, exposure patterns and gender norms could have been responsible for the difference in treatment pattern by gender in the two States. As explained by WHO (2007), exposure patterns and infection can be affected by gender norms if men are

more likely to be working in fields/farms at dusk, or if women are expected to fetch water from streams in the morning. Therefore, as rightly put by Ricci (2012) 'A cautious understanding of the gender-related dynamics of treatment seeking behaviour, as well as of decision making, resource allocation and financial authority within households is key to ensuring effective malaria control programmes.' Health interventions in malaria over the years (WHO, 2006), have mostly concentrated on awareness for women more than men, which has made a massive impact on health promotion among women; especially in cases of malaria in pregnancy. However, it is critical to start including men in these intervention programs because recent studies are beginning to reveal that there is no longer a significant difference with regard to seeking treatment for malaria between the two genders. Also, in most cases, whoever is buying drugs from a drug store might be buying it on behalf of a sick individual, which means everyone has to be part of these awareness programs and intervention programs to truly be able to effectively manage malaria across every household.

Adherence to the policy of confirming malaria cases by RDT and microscopy before treatment is very poor in this study. Drug outlets are meant to either follow a prescription from a doctor showing that diagnosis has been arrived at clinically, or they are required to perform one in stores. However, up to 82% of patients that visited Lagos pharmacies are suspected to be self-medicating, and all of the patients that visited PPMVs in Lagos State did not have any proof of diagnosis and were still treated for malaria. A similar result was found in Osun State where 58.2% of patients at pharmacies and 76% at PPMVs self-medicated. These findings are similar to data published in other studies in Nigeria (Oyeyemi *et al.,* 2015; Ezenduka *et al.,* 2014; Meremikwu *et al.,* 2007; Uzochukwu *et al.,* 2010). The findings also corroborate a more recent study by Ladner *et al.,* (2017), where the use of ACTs, or any antimalarial drug, was not dependent on the patient having a confirmed diagnosis of malaria or an antimalarial prescription. Table 4.1 and Table 4.2 also shows that there is evidence of an association between the type of drug store where treatment is received and self-medication in both States; a result supported by Chipwaza *et al.,* (2014). The level of self-medication across these two regions shows the high probability of over-diagnosis and over-use of antimalarial drugs at these stores as opposed to the current treatment guidelines; the consequences of which include, high rates of morbidity and mortality (Mulenga and Kawimbe, 2015), an increase in parasite resistance (Quedraogo *et al.,* 2008; Awad *et al.,* 2005) and a diminishing trust of malaria treatment.

This study also clearly demonstrates that the knowledge of policy may not translate into actual adherence to recommended guidelines for treatment of malaria by vendors in both states. The result showed that even though all of the drug sellers stated an ACT as the drug preferred, the sale of ACTs in Lagos pharmacies was 89%, 35% in PPMVs and 65% in Osun pharmacies and 49% in PPMVs. This result shows that awareness is not commensurate with practice. This can be linked to what was previously observed by Oyeyemi *et al.,* (2015). The power of buyers to influence their own treatment due to affordability, or trust in a particular drug, was clearly evident. As these stores are for profit, sellers would rather succumb to the buyer's choice of treatment than see them walk out to the next store where their choice would be granted. So, in this case, seller's awareness can only lead to advice or suggestions and it is ultimately left to the patient to decide what course of treatment suits them best. This was also observed by Mangham-Jefferies *et al.,* (2014), where there was evidence in Nigeria and Cameroon of provider's choice dependence on their patient. In some cases, patients tell the seller how much they have and it's left to the seller to find a drug that fits the client's price range (which most times is not an ACT). This is evident in this study which observed that store owners who have already admitted awareness of ACTs as first-line antimalarials still influence a client's use of other drugs such as chloroquine and SP. It should be noted however, that the use of ACTs has improved compared to what was earlier recorded in Nigeria (Okeke *et al.,* 2006; Erhun *et al.,* 2004; Ezedinachi *et al.,* 1991); however, to totally eradicate malaria or effectively manage it, a total compliance to the recommended drug has to be used for every confirmed malaria incidence. Treatments in pharmacy stores can be more easily monitored and influenced than practices in PPMVs because most PPMVs fail to register under the Pharmacist Council of Nigeria; which is the regulatory body for both pharmacists and drug vendors. For this reason, information about health awareness and promotion can more easily be passed across pharmacy stores. Also, education level is required for specified laws governing the licensing of pharmacists but not necessarily in PPMVs. Consequently, anyone can start a PPMV business regardless of their background or training they have that is connected to having adequate knowledge of illness perception and management, which in turn contributes to dispensing of antimalarials (Beyeler *et al.,* 2000).

ACTs are approximately ten times more costly than previously used monotherapies so the use of RDTs prior to treatment may improve cost-effectiveness. Furthermore, in a study by Ezennia *et al.,* (2017), the cost benefit of malaria diagnostic tests among pharmacists showed that RDT-based malaria treatment is cost-beneficial for pharmacy practitioners. Also,

Azikiwe *et al.,* (2012) did a comparative study on the two methods of diagnosis; rapid diagnostic tests (RDTs) and microscopy. Result showed that RDTs based on the malaria antigen (whole blood) method is as specific as traditional microscopy and even appears more sensitive than microscopy. The subsidised provision of RDTs, similar to ACTs subsidy, should be assessed to examine the impact on the uptake of RDTs in the health sector.

4.4.2 Treatment practices in hospitals in Osun and Lagos State

A major disadvantage of retrospective evaluation is the inability to randomize and standardize the experiment, which necessitates both careful interpretation and tentative application of results to the general population (Lazarski *et al.,* 2001). Also, important questions or data could have been missed at the time the data was collected. However, retrospective studies have the ability to cover larger study populations, longer follow-up periods, and often are shielded from bias because data was often collected for reasons other than the study (Lazarski *et al.,* 2001). Also, because of the time constraint on the current study, retrospective data that covered as far back as 12 months was determined to be the best approach. Hospitals in Osun State and Lagos State were conveniently sampled due to the availability of secondary data which is the foundation of the retrospective evaluation. Secondary data are data collected by someone other than the user or researcher.

The WHO recommends that before any suspected case of malaria is treated, the presence of *Plasmodium* species must first be confirmed in the patient's body (FMOH, 2011). It was further recommended that confirmation should be done with the use of both RDT (Rapid Diagnostic Test) and microscopy after clinical assessment has been carried out (Udoh *et al.,* 2013). It is encouraging that over 90% of people that visited the hospitals during the time of this study were tested both clinically and with the use of RDT. This is an improvement compared to a study by Ughasoro *et al*., (2013) and Udoh *et al.,* (2013) describing up to 98% of children in the study being treated just on a presumptive basis as a result of a high notion held by doctors that most fever cases are malaria. Also, Uzochukwu *et al.,* (2010) recorded 31% of RDT use in a hospital in Nigeria; while Barat *et al.,* (1999) claimed that clinicians rely on clinical symptoms instead of microscopic diagnosis. The high use of RDTs in this area for diagnosis could mean that distribution and acceptance has increased over the years. However, total compliance with the WHO recommendations, which includes the use of microscopy tests, must be strictly adhered to so as to achieve meaningful results with regard to effective case management and the eradication of malaria. The WHO has also advised that

malaria rapid diagnostic tests (RDTs) can help with providing a quick, effective and accurate diagnosis in cases where demonstration of parasitaemia has previously been unavailable or where microscopy-based diagnosis may be unreliable, as noted by Tagbo *et al.,* (2007).

To enable effective diagnosis of all malaria cases, the diagnostic method used must be accurate and available at the point of care. This could be the motivation behind the recent huge increase in the use of RDTs at the hospital with little importance placed on microscopic diagnosis. Another factor to be considered in this case is the recent effort by the government to provide cheap and accessible RDTs at the hospitals to ease diagnosis and to improve treatment methods (Bamiselu *et al.,* 2016). One of the frequent reasons for over-treatment of malaria, as highlighted in the introduction, is the assumption of infection through symptoms only. As discussed by Cohen *et al.,* (2015), after a long exposure to malaria, especially in endemic countries, 'familiar' symptoms are easily assumed to be malaria and treatment is provided when unnecessary. Indeed, data in this chapter shows a high level of suspected malaria cases being negative following testing; particularly in Lagos urban region. Similar to a study by Ughasoro *et al.,* (2013), this common practice is responsible for the continuous wastage of drug, health complications, decrease in confidence for antimalarial drugs due to presence of symptoms after dosage completion and eventually *P. falciparum* resistance. This further places emphasis on the benefits of diagnostic and microscopy testing before treatment. The data in this chapter show that Osun State rural area is the most challenging place to have malaria, considering the fact that not only is treatment practice poor but the presence of counterfeit and substandard drugs in the market exacerbate the problems. With about 81% of the people who suspected that they had malaria being confirmed infected following hospital diagnosis in Osun State rural region, this does not only promote the use of accurate diagnostic methods, but also highlights the urgent need to promote recommended treatment practice in this region. A similar result was found in Lagos rural region. Housing conditions and structures, environmental factors and awareness are factors that increases exposure to the disease in rural areas, but if treatment practices can be done appropriately as recommended, this will reduce the barriers of effective malaria treatment. In both urban areas, there are less confirmed malaria cases, with 65% and 53% in Lagos and Ousn respectively. However, this does illustrate the danger of self-medication that occurs when patients visit pharmacy stores and drug vendors. This study shows that more people in the rural areas of both States might malaria compared to the urban regions where less than half of suspected cases were confirmed. This is more worrying for people living in the rural regions

because of the already established poor treatment practices by people who reside in these regions (discussed in Chapter 3). Asides a high level of self-medication, poor access to effective treatment, preference of non-ACT antimalarials due to affordability, and the high level of counterfeit and substandard drugs that they are exposed to (this is better discussed in Chapter 5 and 6). Figure 4.11 shows 65% and 53% falsely suspected malaria cases in Lagos urban and Osun urban areas respectively, and with an average of 50% of individuals self-medicating (as discussed in Chapter 3), it highlights the large number of ongoing cases of wrong treatment in urban areas. This in turn, will lead to over use of ACTs and would encourage drug resistance

Also, the data in this chapter showed that in some areas, cases found to be negative were still treated with an antimalarial as opposed to the policy and recommendations to not treat negative cases with antimalarial. This is similar to what was observed by Bottieau *et al.,* (2012); indeed, this abuse of ACTs in negative cases will result in a negative clinical and economic impact (Skarbinski *et al.,* 2009). As recorded in previous studies the treatment of unconfirmed malaria has a dangerous effect, ranging from drug resistance of the parasite to medical complications on the user's part (Ocan *et al.,* 2015; Okeke *et al.,* 2005; Mehta *et al.,* 2007). If this practice is not checked over time, there is the risk of losing the only drug that is presently trusted to effectively treat malaria; just like chloroquine (Wellems and Plowe, 2001; Grigg *et al.,* 2016) and SP (World Health Organization 2001; Okell *et al.,* 2016).

Since ACT is the recommended first line treatment of malaria in Nigeria, data with regard to treatment choice was also collected from hospitals in the areas where research was done. The results showed that there is an encouraging rate of ACT prescription and treatment method in the hospitals; both in the urban regions and in the rural areas. About 83% of the antimalarials used in the hospitals on the island in Lagos were ACTs, 86% in Ikorodu, 88.7% in Osogbo and 78% in Iwo. This shows that there is a strong awareness about the recommended and effective method of treatment across these regions.

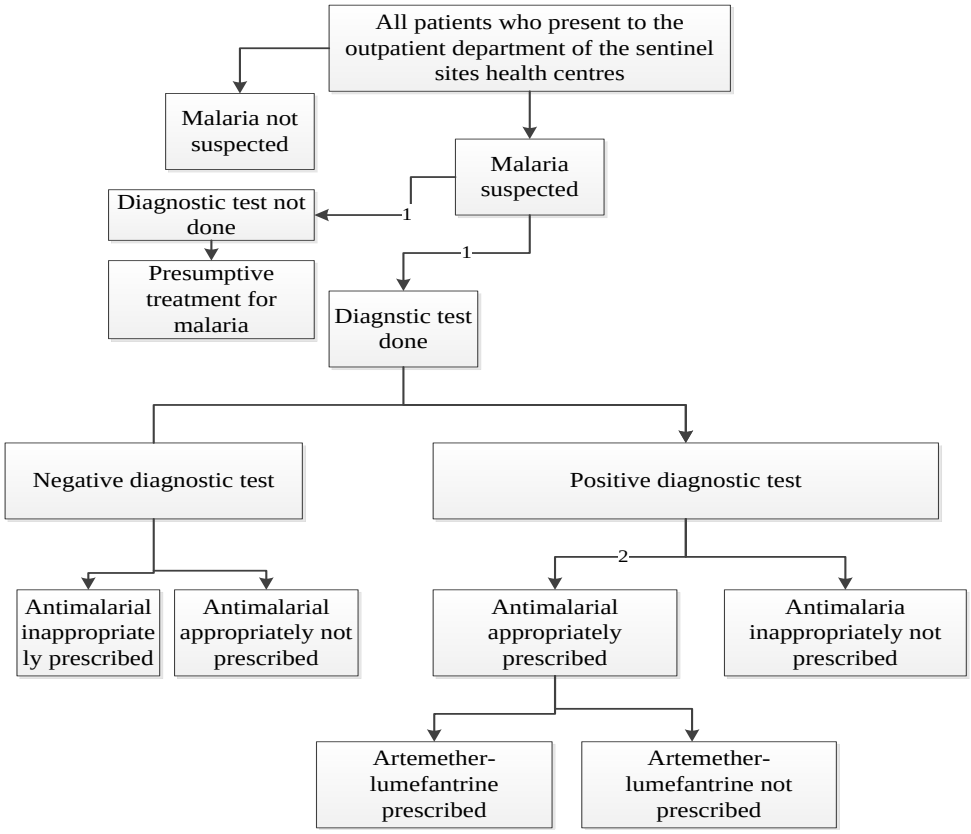
However, even though only a few instances were noted, some cases of malaria are still treated with Chloroquine and SP. These two drugs have been banned in Nigeria as a first-line treatment therapy and only ACTs are to be used to treat malaria. Over 10% of the total patients in the period of this survey were treated outside the recommendation of WHO and the Ministry of Health and this would be a barrier to malaria effective case management and the eradication of malaria in Nigeria. As much as this is an improvement from earlier studies,

were the use of chloroquine and SP was a lot higher (Olurishe *et al.,* 2007; Mokuolu *et al.,* 2007), the reduction observed in this study is similar to that observed by Udoh *et al* (2013). However, it should be noted that chloroquine injections are still allowed and effective in Nigeria for urgent cases of malaria; also, as explained by doctors interviewed, some patients are administered chloroquine if there is no health improvement after being treated with ACT, or they react negatively to ACTs.

Since RDTs have shown a high success rate, more efforts should be introduced to encourage its use across all hospitals and drug stores. There is still the argument of practices in public and private health sectors; for example, in a study by Bamiselu *et al.,* (2016) RDT kits were more available in the public health facilities (82%) than private health facilities (19.2%). Also, considering that a higher patient load in public health facilities could make adherence to recommendations difficult, health providers in public health facilities tend to receive more training support from government agencies than their counterparts in private facilities and may be expected to adhere better to practice guidelines; however, Adesanya *et al.,* (2012) argues that reverse is actually the case.

In general, this study showed a better level of awareness and adherence to the national treatment guideline among health providers, as reported by Bamiselu *et al.,* (2016). This contrasts with Ogochukwu *et al* (2010) which revealed that Nigerian hospital prescribers had poor adherence to national antimalarial treatment guidelines and policy. Also, only 15.5% of health workers in Tanzania were aware of the government's health policy (Minzi, & Haule, 2008); this shows that over the years, there has been an improvement in the awareness and adherence of health workers to health guidelines. Even though more still needs to be done, the use of RDTs has increased in hospitals as well as the use of ACTs. However, the availability and use of the recommended ACT in the hospitals in both regions is commendable and shows the level of confidence the health facilities has in ACT and to some extent, the effect of initiatives such as affordable medicine facility for malaria (AMFm). This is a positive finding in the push to improve the case management of malaria in the state. It also indicates the progress made over the years when compared to results of a study on malaria control practice done in 2010, which showed that less than a fifth of the primary and secondary health facilities used the recommended. The malaria treatment regime is depicted in table 4.5 below.

Table 4.6: The WHO recommended malaria treatment procedure



4.5 Conclusion

Twelve years after the change in antimalarial treatment policy in Nigeria, a substantial increase in the awareness of health providers has been recorded. However, awareness among drug sellers in PPMVs and pharmacy stores has not translated to practice. Adherence to prescription and recommended treatment practices was lower among drug sellers than it was in the hospitals. Even though an individual is more likely to be treated with a non-ACT at a PPMV store, the sale of non-ACTs is also considerably high in the pharmacy stores and this is a cause for concern. This study has further shown that patients are at the driving point of treatment decisions at these stores. Even though more awareness is needed across all health providers, hospital providers are generally showing an increase in policy adherence. Deteriorating practices at the drug stores, in contrast to the improvements recorded in the hospitals, therefore suggest that malaria treatment seekers should be encouraged to visit hospitals. For this to occur, increased effort should be made to provide a conducive environment for treatment; this includes reduced waiting periods and subsidised treatment. Since there is an increase in the awareness of drug dispensers about the recommended

antimalarials, these stores should be empowered and made to operate under strict laws to comply with the recommendations of treatment. Moreover, old/out-of-date antimalarials should be taken off the counter across all stores and replaced with subsidised ACTs.

Although the role of provider-patient relationships in hindering or promoting access to medicines is well documented, interventions to improve the situation are inadequately considered in policy design, particularly in low income countries. Training and periodic re-training of drug sellers to enable them to provide correct and full therapy for uncomplicated malaria, appreciate the importance of giving verbal advice to care-givers and recognize and refer promptly all severe malaria cases is recommended. The effectiveness of such training has been recorded in different settings (Kassam *et al.,* 2015).

CHAPTER 5: INVESTIGATING THE QUALITY OF ANTIMALARIAL DRUGS USING FOURIER TRANSFORM INFRARED SPECTROSCOPY (FT-IR)

5.1 Introduction

The FT-IR process can be used to identify a compound or the composition of a sample and it is based on the fact that chemical bonds have specific frequencies of vibrations when infrared radiation is absorbed. The resulting spectrum is dependent upon the molecule possessing specific features that change its dipole movement during vibration; the greater the change then the more intense the absorption will be. For example, as homonuclear diatomic molecules have a dipole moment of zero, no matter how long the bond, such a molecule does not have a vibrational spectrum. Infrared spectroscopy is used more often for qualitative analysis than it is for quantitative. For a conclusive identification of a group of samples (antimalarial drugs in this case) features of spectra across all samples must match the spectrum observed for a reference standard.

The infrared spectrum is rich in structural information; the spectral lines are produced by the absorption of incident radiation by the vibrational modes of functional groups in the molecule; these absorptions adhere to the Beer-Lambert law and hence intensify as a function of solute concentration which provides a means for determining the concentration of mixture components. The FT-IR spectrometer measures the infrared absorption and transmittance spectrum to check vibrational frequencies and provides details on chemical structure and bonding type. The presence of multiple bond dipoles within a typical organic molecule, the possibility for several vibrational modes being associated with each dipole, and the coupling of vibrational and rotational transitions gives rise to a pattern of absorptions and a corresponding characteristic infrared fingerprint for a compound

There are different types of measurement methods which can be performed using infrared spectroscopy including the diffuse reflection method and the attenuated total reflection method. To achieve the best result, a measurement method that fits with the sample form must be selected. From the sample viewpoint, it is possible to use more than one method to measure an infrared spectrum for a single sample. However, for the purpose of this research,

attenuated total reflection (ATR) was adopted. Attenuated total reflection (ATR) is a method that allows the direct measurement of powder samples and avoids the need to solubilise powder samples in potassium bromide (KBr) or liquid paraffin (Elmer, 2005). The attenuated total reflection (ATR) method involves pressing the sample against a high-refractive-index prism and measuring the infrared spectrum using infrared light that is totally internally reflected in the prism. In comparison with other methods of FT-IR spectroscopy, the ATR method is an excellent method for obtaining infrared information for the powder sample surface. However, care is required with the wavenumber dependency of the absorption peak intensity and with the peak deformation towards the first-order differential form due to the anomalous dispersion of the refractive index for inorganic and other high-refractive-index samples (Elmer, 2005). It is important to have a reference spectrum (possibly spectrum of one of the drugs that has been previously analysed) so as to be able to compare spectra and find out the quality of the sample drugs. Antimalarial tablets for analysis in this chapter were kept according to manufacturer's instructions in dry, sealable, rubber sachets at room temperature until analysed. To analyse, samples were carefully ground and kept away from light and humidity. Ground samples were placed on the FT-IR machine and 3 different spectra for 3 different days were recorded. Drugs were labelled to include name of tablet, artemether/lumefantrine ratio, date, place purchased and price of drug.

5.1.1 FT-IR Spectra analysis.

After the FT-IR machine had been used to analyse the antimalarials, spectra results were analysed with respect to group frequencies. There are three different groups: mid-infrared region, near-infrared region and far-infrared region.

Mid-Infrared region (4000-400cm^{-1}): is divided into four sub-regions and the nature of group frequency can be determined by the region that it is located.

1) X-H stretching region (4000-2500cm^{-1})

- O-H stretching produces a broad band in the region 3700-3600cm^{-1}
- N-H stretching are observed in the region 3400-3300cm^{-1}
- C-H stretching bands from aliphatic compounds will be observed in the region 3000-2850 cm^{-1}, and C-H stretching bands adjacent to a double will be observed in the range 3100-3000cm^{-1}.

2) Triple bond region (2500-2000cm^{-1})

- C≡C absorb in the range 2300 and 2050cm^{-1}, and its stretching is normally weak
- C≡N are observed between 2300 and 2200cm^{-1}, and its stretching is of medium intensity

3) Double-bond region (2000-1500cm^{-1})

- C=O stretching usually occurs in the 1830-1650cm^{-1} region
- C=c stretching occurs around 1650 cm^{-1} and its much weaker
- C=N stretching occur in the same region but stronger.

4) Finger print region (1500-650 cm^{-1}).

Near-infrared region (13000-4000 cm^{-1}): The absorptions seen in this region are overtones or combinations of the fundamental stretching bands, which occur in the 3000-1700 cm^{-1} region. They are commonly due to C-H, N-H, or O-H stretching.

Far-infrared region (400-100 cm^{-1}): This region provides information about molecules that contain heavy atoms, molecular skeleton vibrations, molecular torsions and crystal lattice vibrations. This region is not as useful as the mid-infrared region but it can provide some information about the vibration of the molecule.

An example spectrum showing the absorbance spectra of erythromycin is seen in Figure 5.1 below.

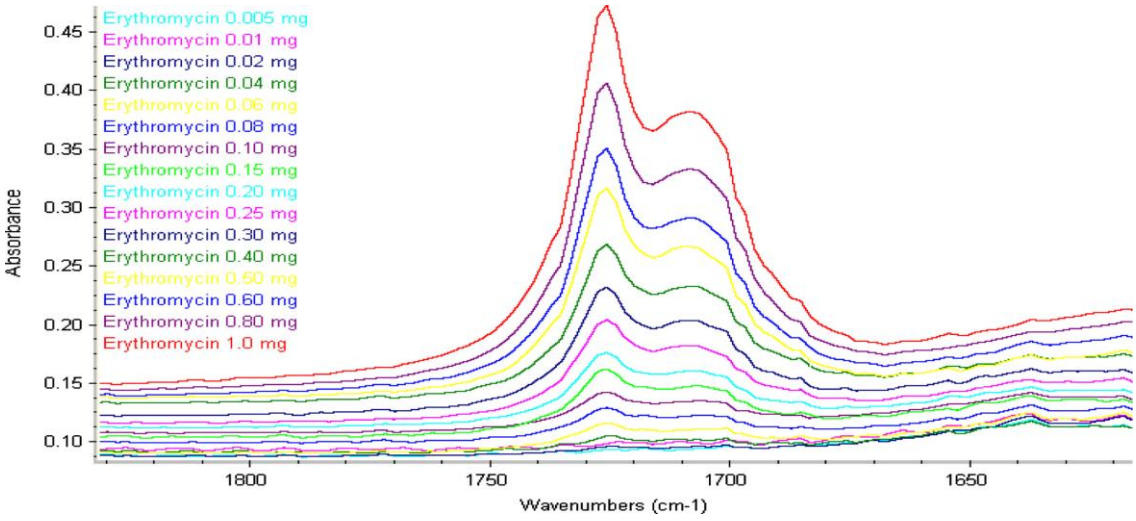


Figure 5.1: An example of the FT-IR spectra of different concentrations of erythromycin showing an absorption peak between the region 1700 cm^{-1} and 1750 cm^{-1} where the C=O stretching occurs. (Source: Ali *et al*., 2012).

FT-IR data can also be viewed as a transmittance spectrum, as seen with artemether in Figure 5.2.

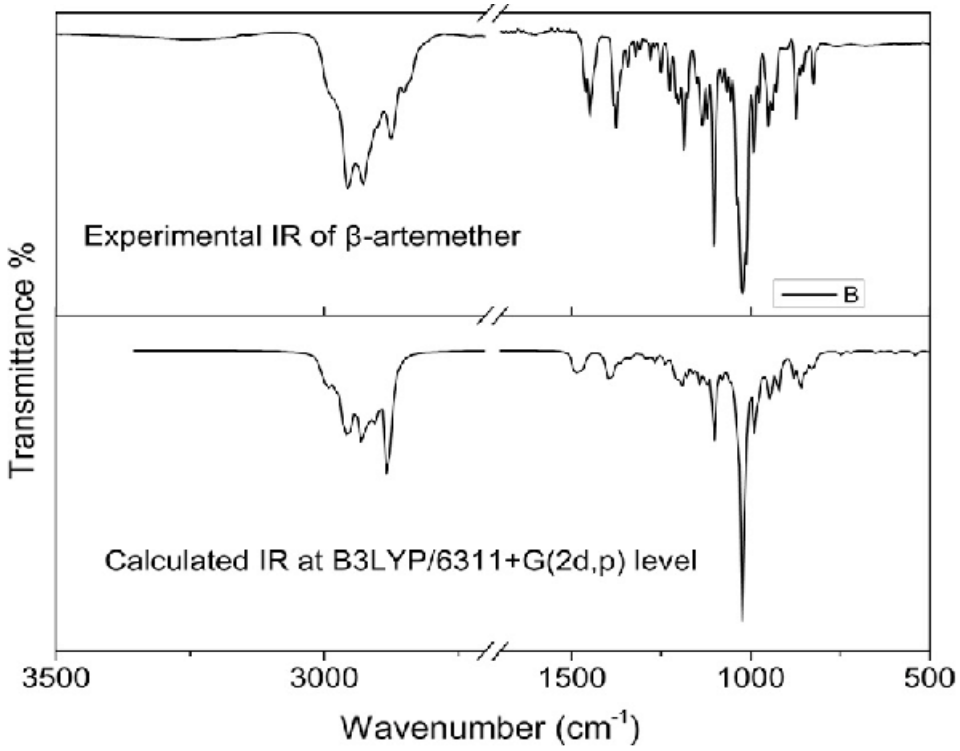


Figure 5.2: An example of the FT-IR spectrum of artemether showing a transmittance peak between the region 3000-2850cm^{-1} where the C-H stretching bands usually occur (Source: Wang *et al*., 2015).

Antimalarial drugs target malaria parasites to eradicate them and thereby stop their multiplication and also, the reoccurrence of the disease. Unless an effective drug is used, little or no reduction in the multiplication of parasite can be expected. This makes drug efficacy in malaria treatment an important factor and all drugs must meet standard expected by the Ministry of Health or the regulatory organisation of the country concerned.

5.2 Objectives

One of the recommendations of the WHO and the Federal Ministry of Health (FMOH) is to treat every case of malaria appropriately using artemether/lumefantrine combination therapy (ACT). This chapter will qualitatively investigate the threat of poor quality and counterfeit drugs that are sold in the market in the two study regions (Osun and Lagos) using FT-IR spectroscopy to provide a basis for spectral comparisons of the antimalarials being used with their reference standards. This would not only show the level of discrepancy existing within the drug groups but also within the regions where this study is being carried out.

5.3 Results

All drug samples were analyzed within their recommended shelf life periods through FT-IR and the spectra below are the results of the sample drugs. The experiment was repeated thrice over three days to establish stable spectral signatures and then one spectrum was used to represent samples. Not all of the drugs sampled are ACTs, and non-ACT drugs showed absorption at different wavelengths.

5.3.1 Artemether

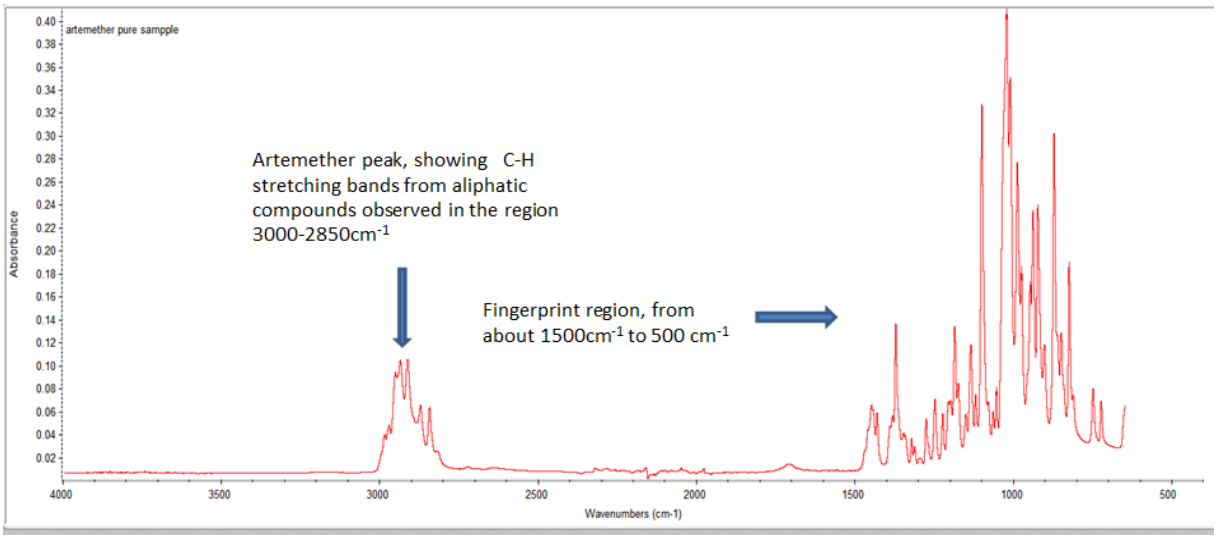


Figure 5.3: Artemether FT-IR Spectrum (pure reference sample from Novartis UK). Shows C-H stretching bands from aliphatic compounds observed in the region 3000-2850cm^{-1}, and a fingerprint region, from about 1500cm^{-1} to 500 cm^{-1}.

Artemether, an artemisinin derivative, is a medication used to treat uncomplicated malaria caused by *P. falciparum*. For ACT regimes, it is used in combination with lumefantrine which has a longer mode of action in the human body. This combination therapy exerts its effects against the erythrocytic stages of *Plasmodium* species and may be used to treat infections caused by *P. falciparum* and unidentified *Plasmodium* species, including infections acquired in chloroquine-resistant areas. The spectral result of artemether from this study, as shown in Figure 5.3, shows C-H stretching bands from aliphatic compounds observed in the region 3000-2850cm^{-1} which is consistent with spectra from previous studies (Yu *et al.*, 2012). This broad band observed is the most important part of the artemether FT-IR spectrum, as the fingerprint region does not reflect on the efficacy of the drug itself. The fingerprint region, to the right-hand side of the spectrum (from about 1500 to 500 cm^{-1}), usually contains a very complicated series of absorptions. This is because of the various bending vibrations within the molecule. It is much more difficult to pick out individual bonds

in this region than it is in the "cleaner" region at higher wavenumbers. The importance of the fingerprint region is that each different compound produces a different pattern of troughs in this part of the spectrum.

5.3.2 Lumefantrine

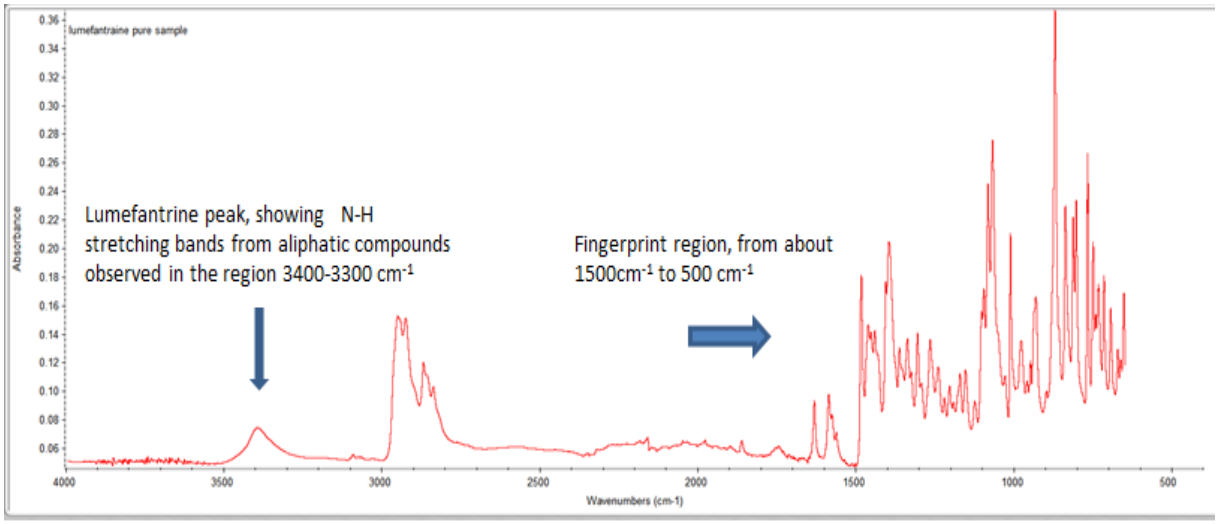


Figure 5.4: Lumefantrine FT-IR spectrum (pure reference sample from Novartis UK). Shows N-H stretching bands from aliphatic compounds observed in the region 3400-3300cm^{-1}, and a fingerprint region, from about 1500cm^{-1} to 500 cm^{-1}.

Lumefantrine is a dichlorobenzylidine derivative that is also very effective for the treatment of various species of *Plasmodium*, including multi-drug resistant strains of *P. falciparum*. When combined with artemether (ACT), it serves as the first-line treatment for uncomplicated malaria in many malaria endemic countries. It has a primary action as a blood schizontocidal and a secondary action as an inhibitor of nucleic acid and protein synthesis within the malarial parasite, thus providing a longer duration of antimalarial action (Ezzet *et al.*, 2000; Hamrapurka *et al.*, 2010). This therefore makes lumefantrine an important drug in the struggle for eradication and effective case management of malaria. Figure 5.4 shows the FT-IR spectrum of lumefantrine with a broad N-H stretching that can be observed in the region 3400-3300cm^{-1}.

5.3.3 Coartem reference sample

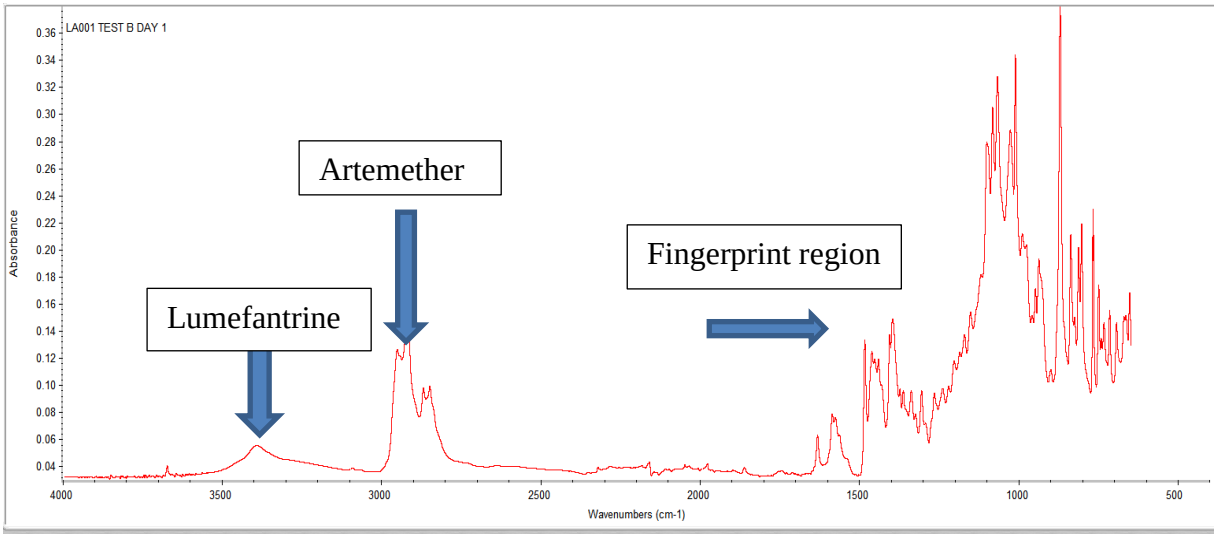


Figure 5.5: Coartem reference sample FT-IR spectrum (pure reference sample from J Jeckor Pharmacy in Lagos urban region). Shows lumefantrine in the region 3400-3300cm^{-1}, artemether in the region 3000-2850cm^{-1} and a fingerprint region, from about 1500cm^{-1} to 500 cm^{-1}.

Since artemether and lumefantrine are two different derivatives, one can decipher which drug contains both medications by observing the broad FT-IR spectra at the artemether region and the lumefantrine region. For example, one of the most popular globally used ACT combinations is Coartem. Coartemether (Riamet™ in Europe, Coartem in Africa and the United States) is a combination of artemether and lumefantrine (20/120mg or 80/480mg) used for the treatment of uncomplicated malaria in adults and children weighing > 4.5kg and it is becoming widely distributed in Africa. Coartem is generally well tolerated though there are some adverse effects, including gastrointestinal upset, headache, and dizziness. Figure 5.5 illustrates the FT-IR spectrum of ACTs located in the mid-infrared region (4000-400 cm^{-1}); the presence of O-H groups in the drugs is indicated by a broad band in the region 3600-3400 cm^{-1} and C-H stretching bands from aliphatic compounds overlap with this band in the range 3000-2850 cm^{-1}. The spectrum also indicates strong C=O stretching bands at 1650 and 1550 cm^{-1} showing that the molecule contains carbonyl groups. The spectrum for each drug also indicates strong bands at 1400-1350 cm^{-1}. The 1500-650cm^{-1} region represents a fingerprint region in which each band in the spectrum can be specified to a particular deformation of the molecule.

5.3.4 Lonart reference Sample

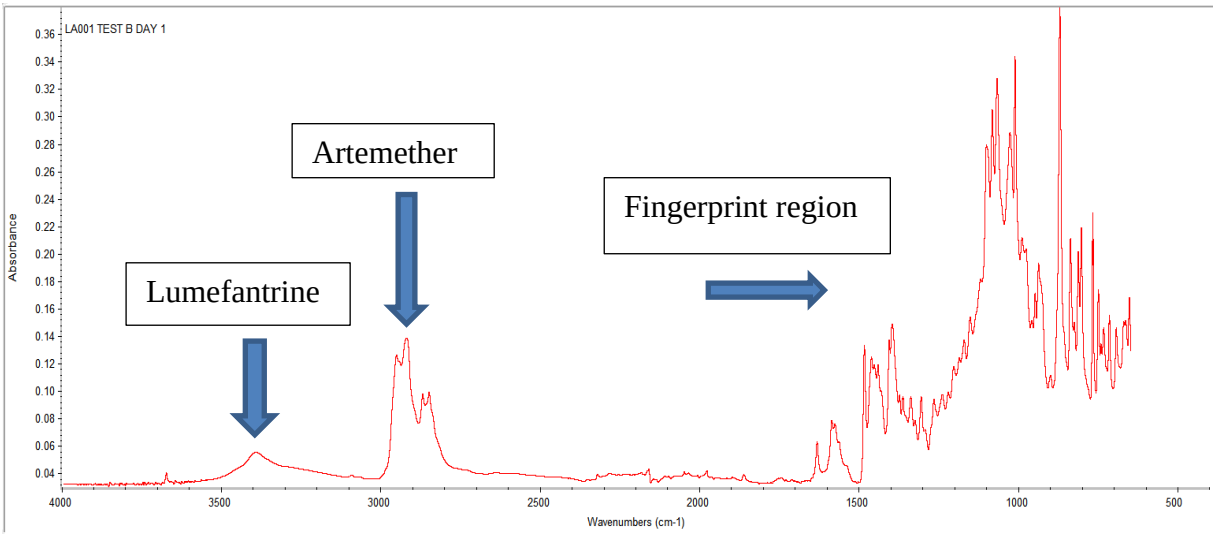


Figure 5.6: Lonart reference sample FT-IR spectrum (pure reference sample from Bliss JVS Ltd in Lagos urban region). Shows lumefantrine in the region 3400-3300 cm^{-1}, artemether in the region 3000-2850 cm^{-1} and a fingerprint region, from about 1500 to 500 cm^{-1}.

Lonart is one of the most commonly used antimalarial drugs in Nigeria and it also contains artemether and lumefantrine in the ratio 1:6 respectively (20/120mg or 80/480mg). The Lonart FT-IR spectrum (Figure 5.6) is as expected from an ACT drug; lumefantrine is represented by a broad N-H stretching band observed in the region 3400-3300$cm^{-1}$and artemether C-H stretching bands are seen in the region 3000-2850cm^{-1}. The fingerprint region can be affected by other substances in the drug (eg. colouring, sweetener etc.); however, the fingerprint for each type of drug should be the same and differ across different types of ACT (or other groups).

5.3.5 Amatem reference sample

Amatem is a common antimalarial drug used in Nigeria and it contains artemether and lumefantrine in the 1:6 amount (20/120mg or 80/480mg). The Amatem FT-IR spectrum (Figure 5.7) is consistent with results observed for other ACT drugs; lumefantrine is indicated by the broad N-H stretching observed in the region 3400-3300$cm^{-1}$and artemether C-H stretching bands are seen in the region 3000-2850cm^{-1}. As expected, the fingerprint region of Amatem shows a spectrum that is different from Lonart and Coartem.

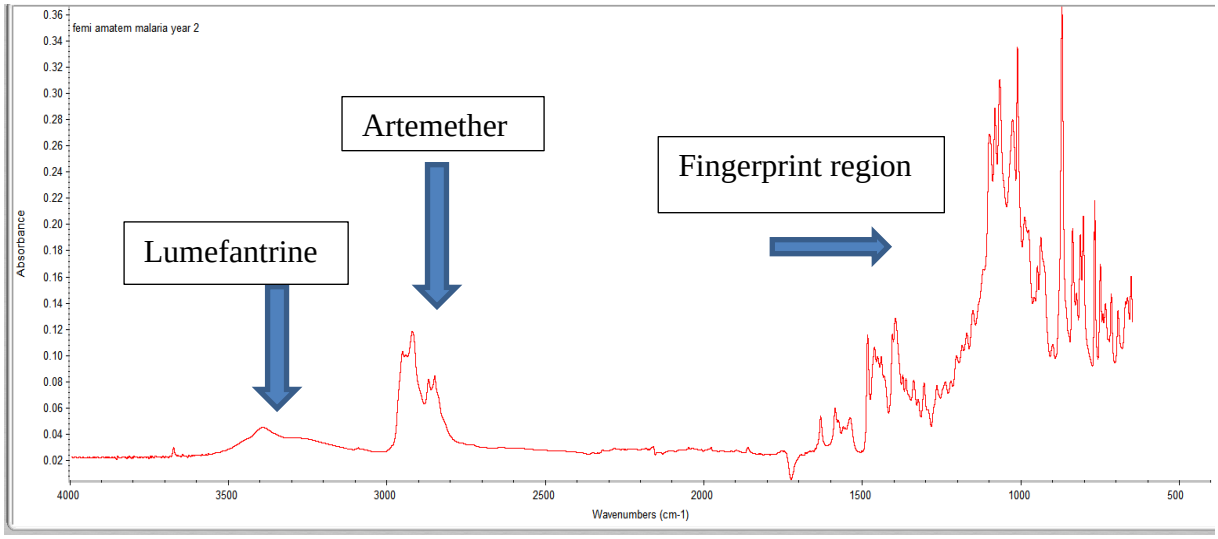


Figure 5.7: Amatem reference sample FT-IR spectrum. Shows lumefantrine in the region 3400-3300 cm^{-1}, artemether in the region 3000-2850 cm^{-1} and a fingerprint region, from about 1500cm^{-1} to 500 cm^{-1}.

5.3.6 ACT drug spectra (Pharmacy and PPMVs)

Table 5.1: Antimalarial brands that are commonly used in the study area.

ANTIMALARIAL	ACT Yes/No	CONTENT	EXPIRY DATE
Combisunate	Yes	Artemether/Lumefantrine	Jul-18
Chloroquine	No	Chloroquine phosphate	Jun-18
Fansidar	No	Sulfadoxine/Pyrimethamine	Oct-19
Lonart	Yes	Artemether/Lumefantrine	Jun -18
Lumartem	Yes	Artemether/Lumefantrine	Feb-17
Coartem	Yes	Artemether/Lumefantrine	Jun-19
Artesunate	No	Artesunate	Sep-17

Table 5.1 shows a list of the mostly used antimalarial drugs that were purchased from the research area. These drugs include ACTs and non-ACTS and they were sampled across pharmacy stores and PPMVs in both Osun and Lagos States.

All ACTs that were purchased from pharmacy stores and drug vendors had spectra consistent with the reference drugs that were acquired from the drug manufacturers/ licensed distributors. The presence of lumefantrine was confirmed bythe broad N-H stretching bands in the region 3400-3300cm^{-1}artemether was shown by the C-H stretching bands in the region

3000-2850 cm^{-1}(Figure 5.7 - Figure 5.14,). The fingerprint regions also have the same troughs for the same drugs but differences are apparent between the types of ACT (Figures 5.7 – Figure 5.14). For example, Lonart drugs which were purchased from Osun state urban and rural regions and Lagos state urban and rural regions were compared and the spectra result was consistent across all regions (Figures 5.8 and 5.9). It should be noted that the fingerprint region of both urban and rurally sourced drugs is also the same.

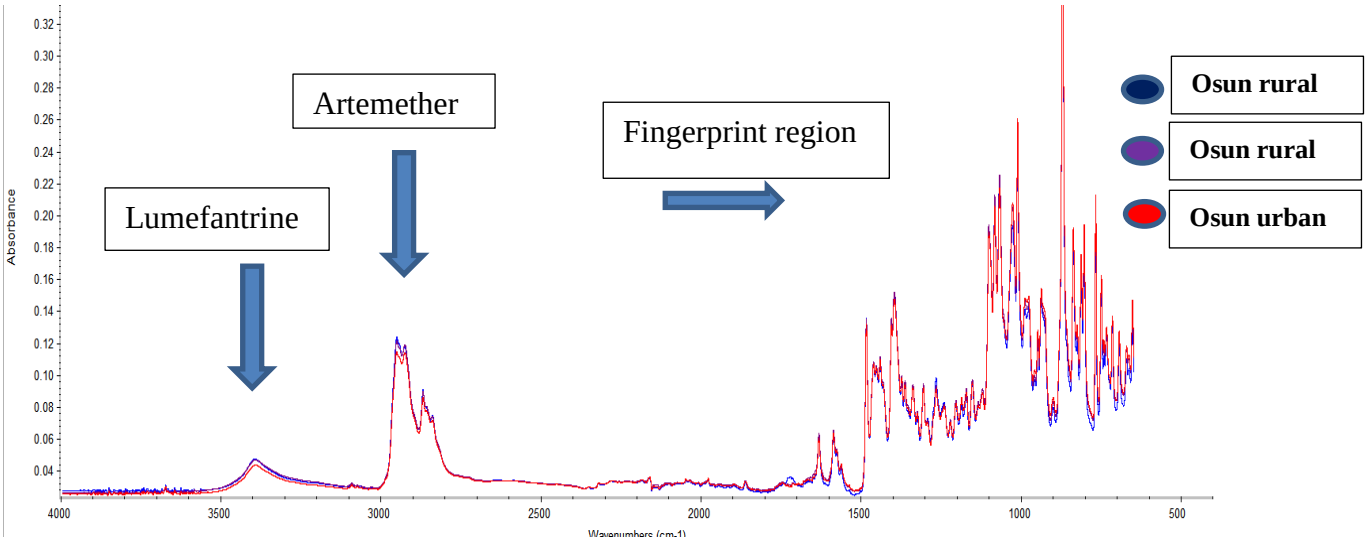


Figure 5.8: Lonart FT-IR spectra from Osun rural and urban regions (rural, rural, and urban). The presence of lumefantrine in the region 3400-3300 cm^{-1}, artemether in the region 3000-2850 cm^{-1} and a fingerprint region, from about 1500 to 500 cm^{-1} can be observed.

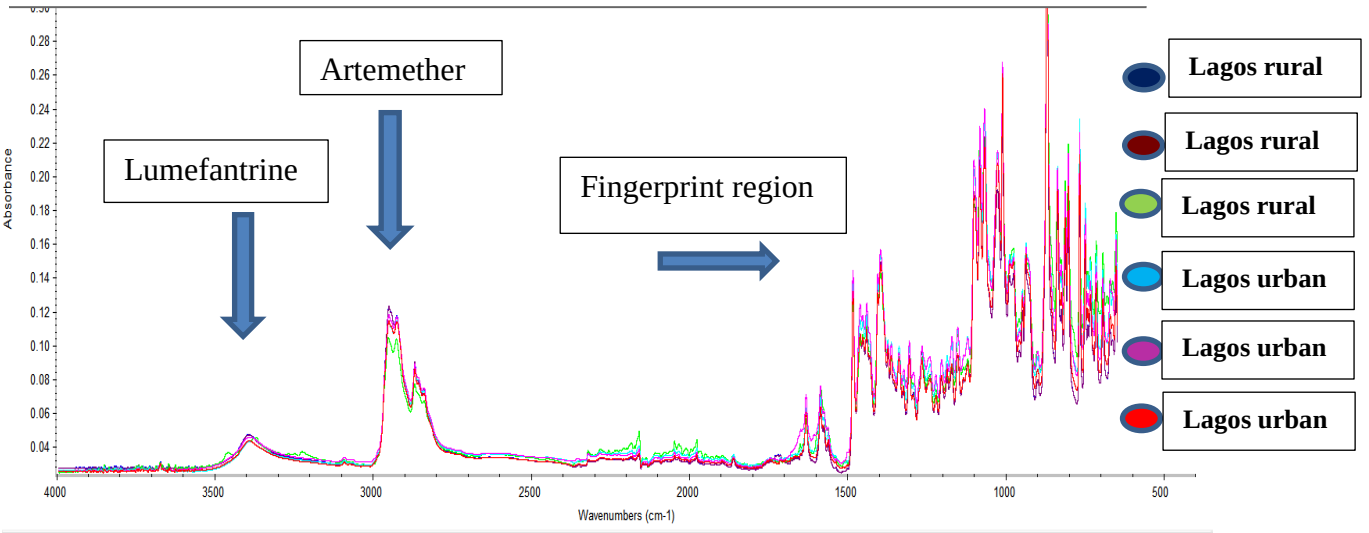


Figure 5.9: Lonart FT-IR spectra from Lagos rural and urban regions (rural, rural, rural, urban, urban, and urban). The presence of lumefantrine in the region 3400-3300 cm^{-1}, artemether in the region 3000-2850 cm^{-1} and a fingerprint region, from about 1500 to 500 cm^{-1} can be observed.

Coartem drugs in Osun State were also cross referenced and the result showed consistent troughs across the State, including the fingerprint region (Figure 5.10). The presence of lumefantrine and artemether can be confirmed by broad N-H stretching in the region 3400-3300cm^{-1} and C-H stretching bands from in the region 3000-2850cm^{-1} respectively.

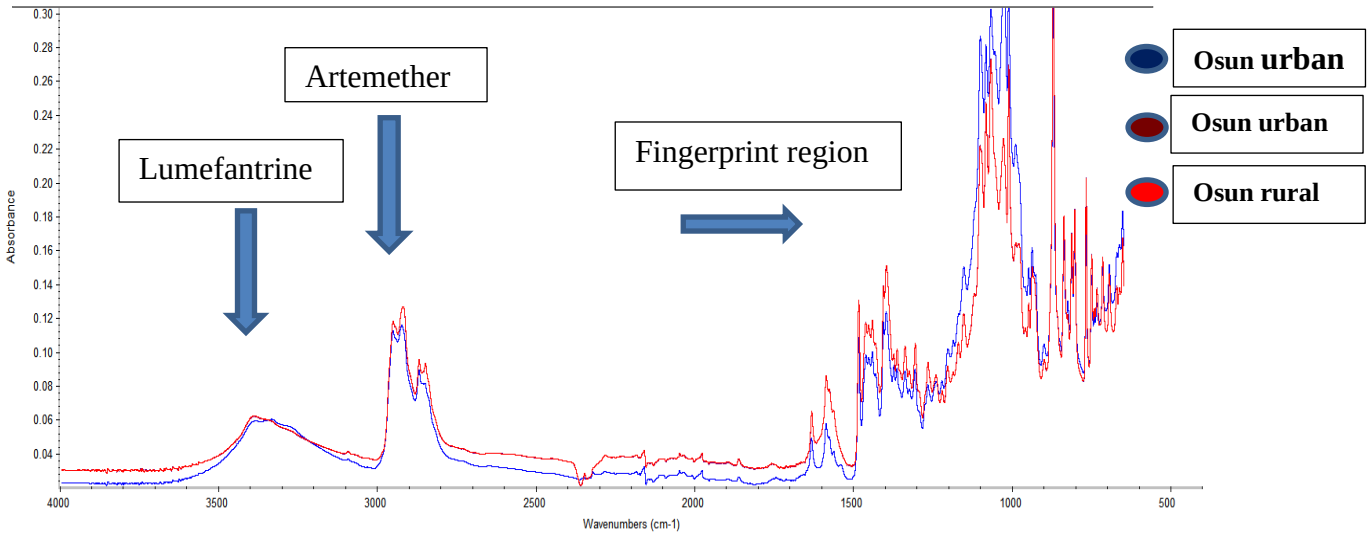


Figure 5.10: Coartem FT-IR spectra from Osun urban and rural regions (urban, urban, and rural). The presence of lumefantrine in the region 3400-3300 cm^{-1}, artemether in the region 3000-2850 cm^{-1} and a fingerprint region, from about 1500 to 500 cm^{-1} can be observed.

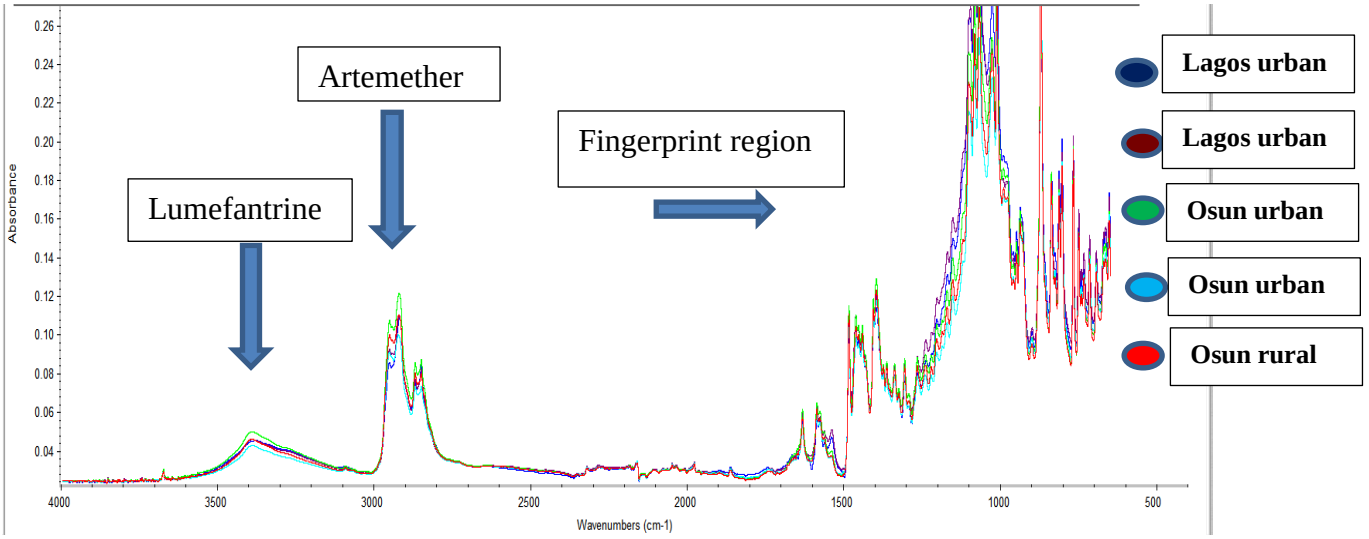


Figure 5.11 Combisunate FT-IR spectra from Osun and Lagos urban and rural regions. The presence of lumefantrine in the region 3400-3300 cm^{-1}, artemether in the region 3000-2850 cm^{-1} and a fingerprint region, from about 1500 to 500 cm^{-1} can be observed.

Combisunate drugs in Lagos State urban and rural areas, when cross referenced, showed consistent troughs across the State, including the fingerprint region (Figure 5.11).

All ACTs drug samples, when compared by urban and rural region of both states showed the same consistency as expected. Some of these drugs are represented in Figure 5.12 – Figure 5.15.

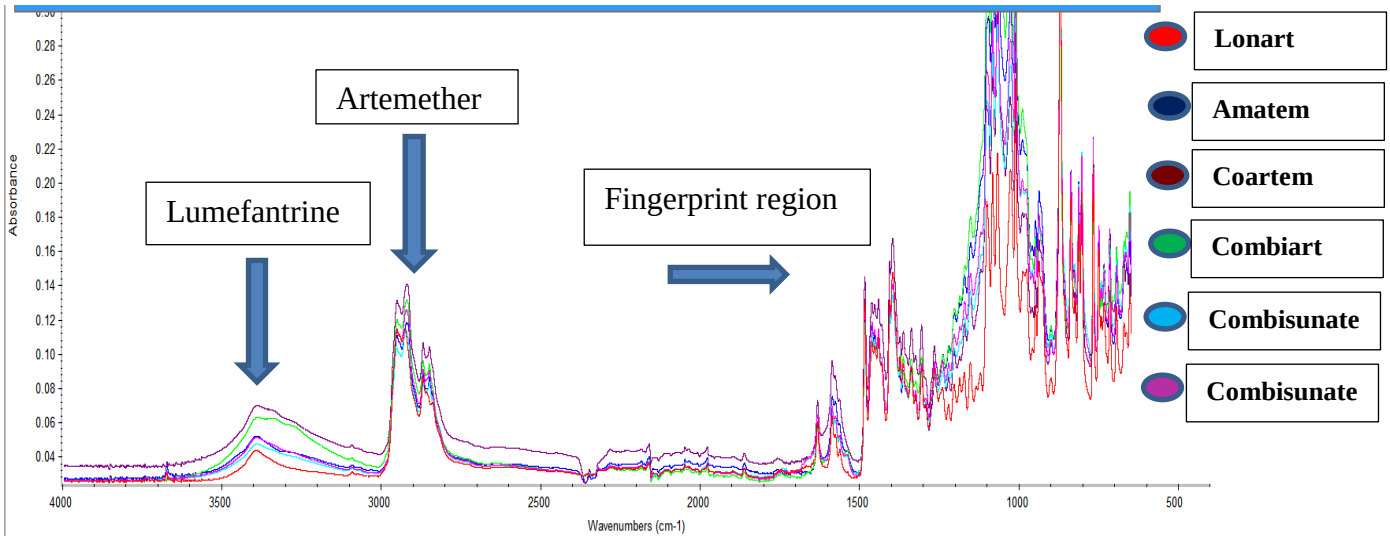


Figure 5.12: FT-IR spectra from ACT samples purchased from stores in Osun urban region. The presence of lumefantrine in the region 3400-3300 cm^{-1}, artemether in the region 3000-2850 cm^{-1} and a fingerprint region, from about 1500 to 500 cm^{-1} can be observed. (Lonart, Amatem, Coartem, Combiart, Combisunate, Combisunate).

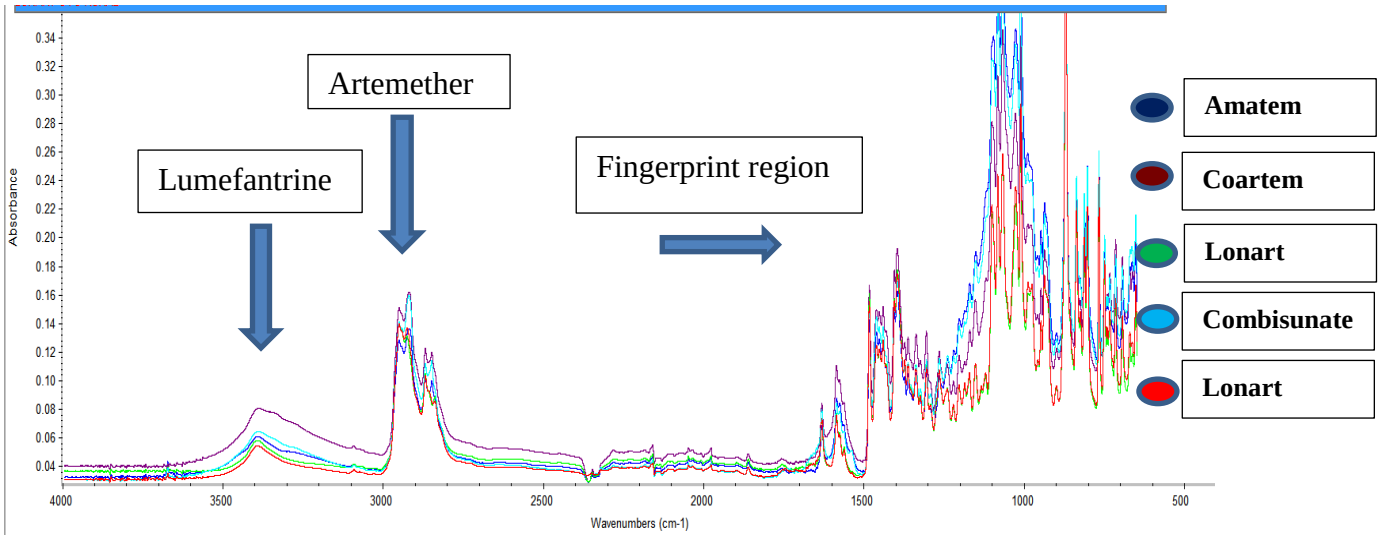


Figure 5.13: FT-IR spectra from ACT samples purchased from stores in Osun rural region. The presence of lumefantrine in the region 3400-3300 cm^{-1}, artemether in the region 3000-2850 cm^{-1} and a fingerprint region, from about 1500 to 500 cm^{-1} can be observed (Amatem, Coartem, Lonart, Combisunate, Lonart).

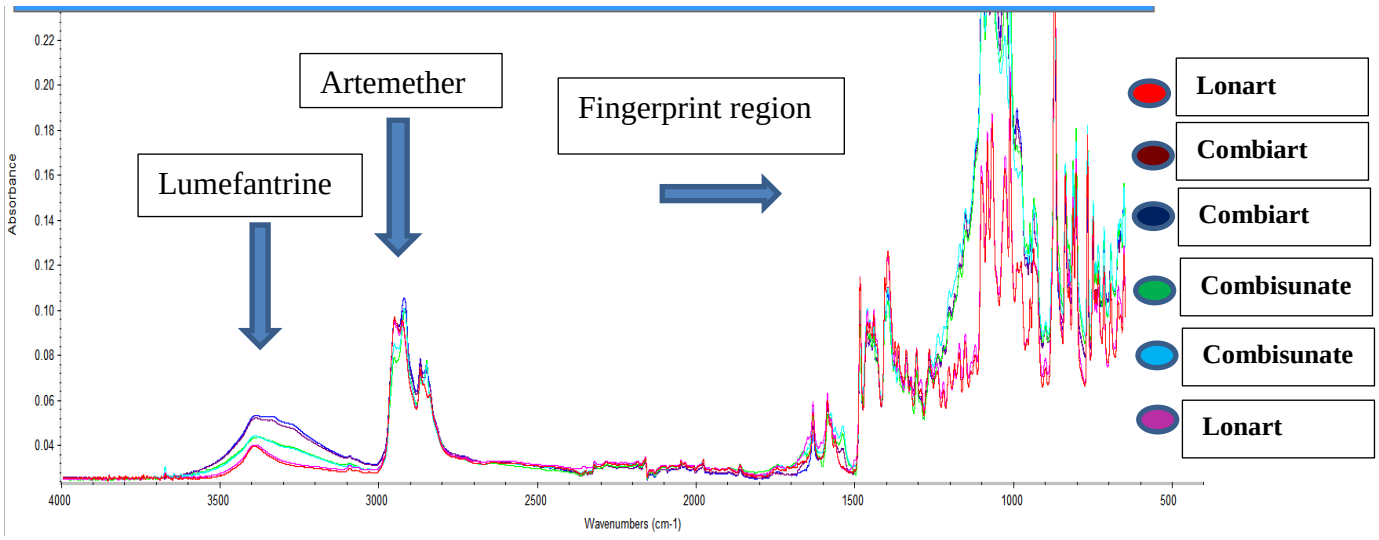


Figure 5.14: FT-IR spectrum from ACT samples purchased from stores in Lagos urban region. The presence of lumefantrine in the region 3400-3300 cm^{-1}, artemether in the region 3000-2850 cm^{-1} and a fingerprint region, from about 1500 to 500 cm^{-1} can be observed (Lonart, Combiart, Combiart, Combisunate, Combisunate, Lonart).

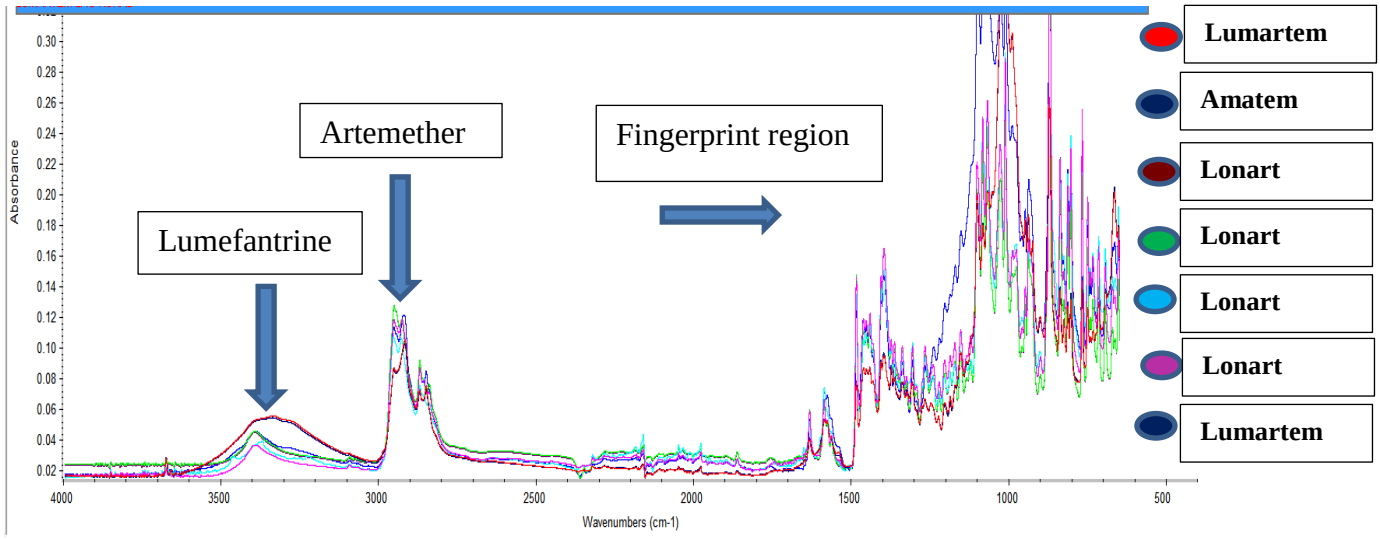


Figure 5.15: FT-IR spectrum from ACT samples purchased from stores in Lagos rural region. The presence of lumefantrine in the region 3400-3300 cm^{-1}, artemether in the region 3000-2850 cm^{-1} and a fingerprint region, from about 1500 to 500 cm^{-1} can be observed (Lumartem, Amatem, Lonart, Lonart, Lonart, Lonart, Lumartem).

5.3.7 Artesunate drug spectra

As described by the WHO, artesunate is a water-soluble hemi-succinate derivative of Artemisinin. Although artesunate is a derivative of artemisinin, it is not an artemether-lumefantrine combination. Artesunate has been reported to clear fever in patients with severe *P. falciparum* malaria 16-25 hours after parenteral administration and hence it is a very effective drug against malaria. The following results show the spectra recorded from artesunate that were purchased from the study area.

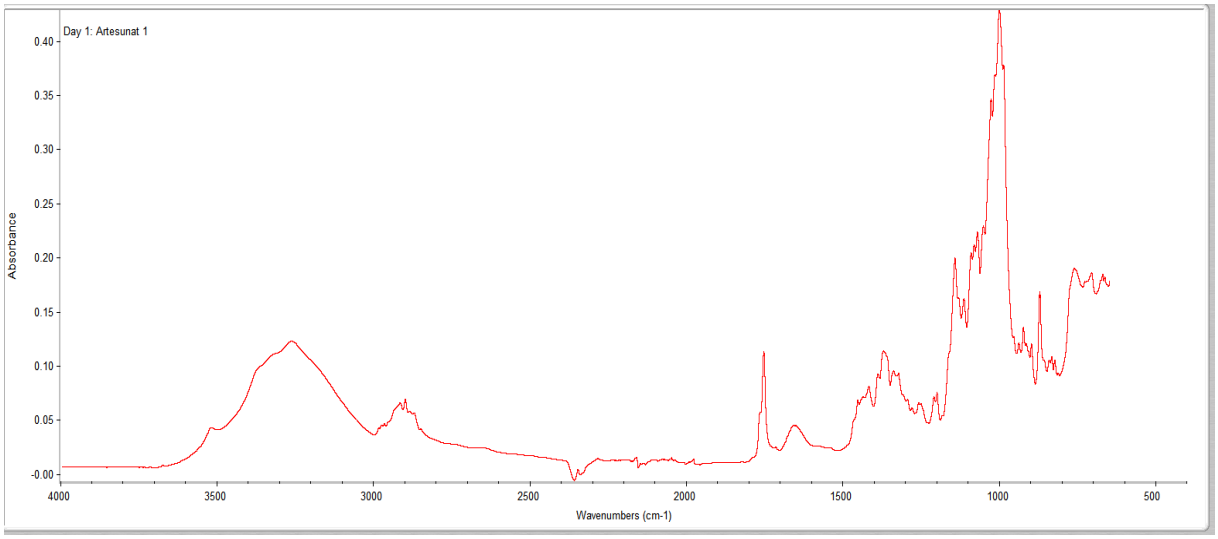


Figure 5.16: Artesunate reference sample (Pure reference sample from Phat Pharm Pharmaceuticals in Lagos urban region) FT-IR spectrum. Shows absorbance in the region 3500-3000 cm^{-1} and in the region 3000-2850 cm^{-1} and a fingerprint region, from about 1500 to 500 cm^{-1}.

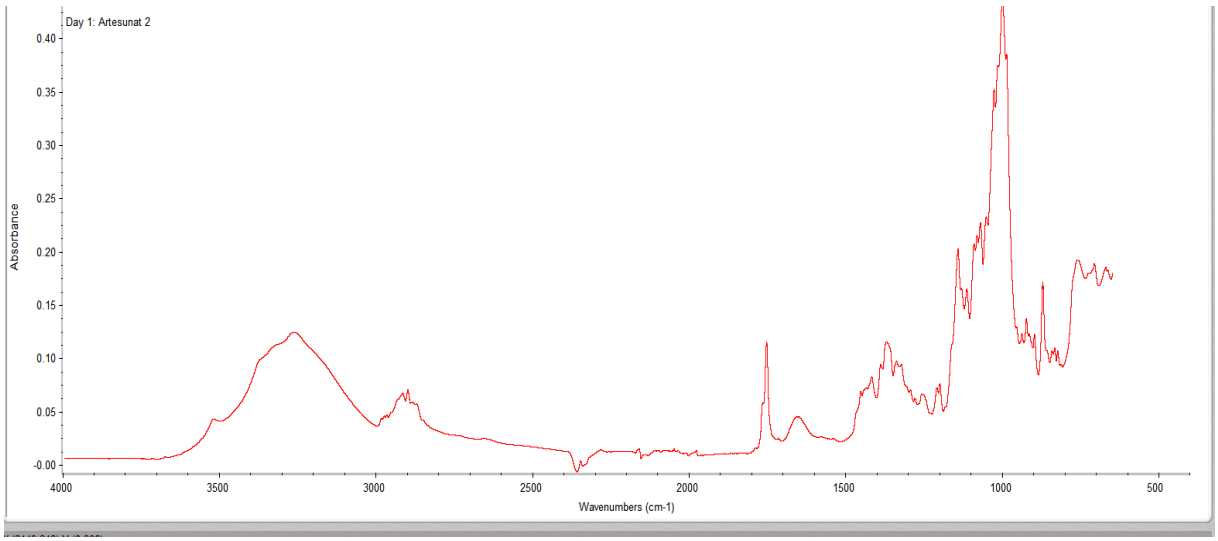


Figure 5.17: FT-IR spectrum of artesunate (Lagos urban). Shows absorbance in the region 3500-3000 $cm^{-1}$and in the region 3000-2850 cm^{-1} and a fingerprint region, from about 1500 to 500 cm^{-1}.

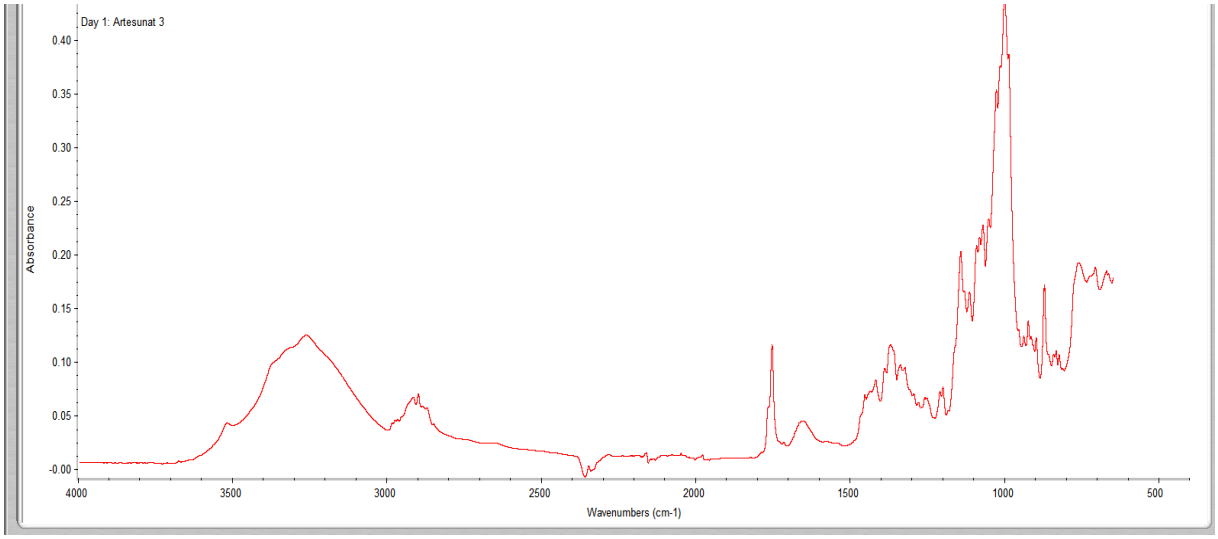


Figure 5.18: FT-IR spectrum of artesunate (Osun urban). Shows absorbance in the region 3500-3000 $cm^{-1}$and in the region 3000-2850 cm^{-1} and a fingerprint region, from about 1500 to 500 cm^{-1}.

3.3.8 Chloroquine spectra (Albert healthcare Ltd)

Chloroquine (7-chloro-4-(4-diethylamino-l-methylbutylamino) quinoline) is a very common chemotherapeutic agent for the prevention and clinical treatment of malaria in Nigeria. Years after its development, the efficiency, safety, stability, low cost and ease of manufacture of chloroquine have all contributed to making it the most widely used synthetic antimalarial drug (Slater, 1993). Therefore, because of its easy accessibility and cheapness, it is vital to include chloroquine spectra in this study to examine if similar results will be observed across different regions. The spectra below show all chloroquine samples that were tested in both Lagos and Osun State.

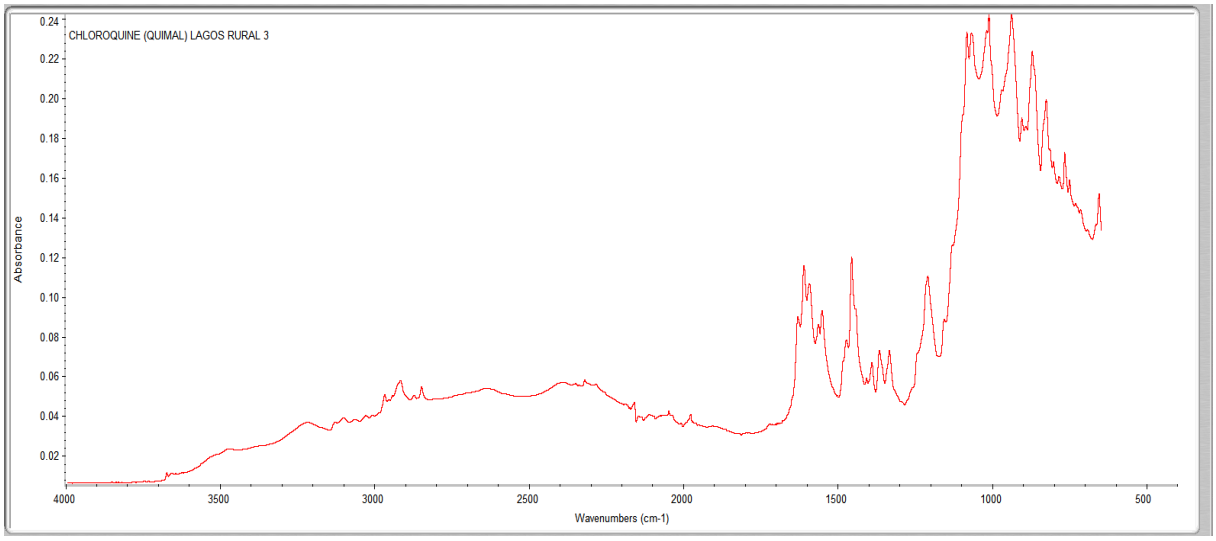


Figure 5.19: FT-IR Spectrum of a chloroquine reference sample (pure reference sample from Albert healthcare Ltd).

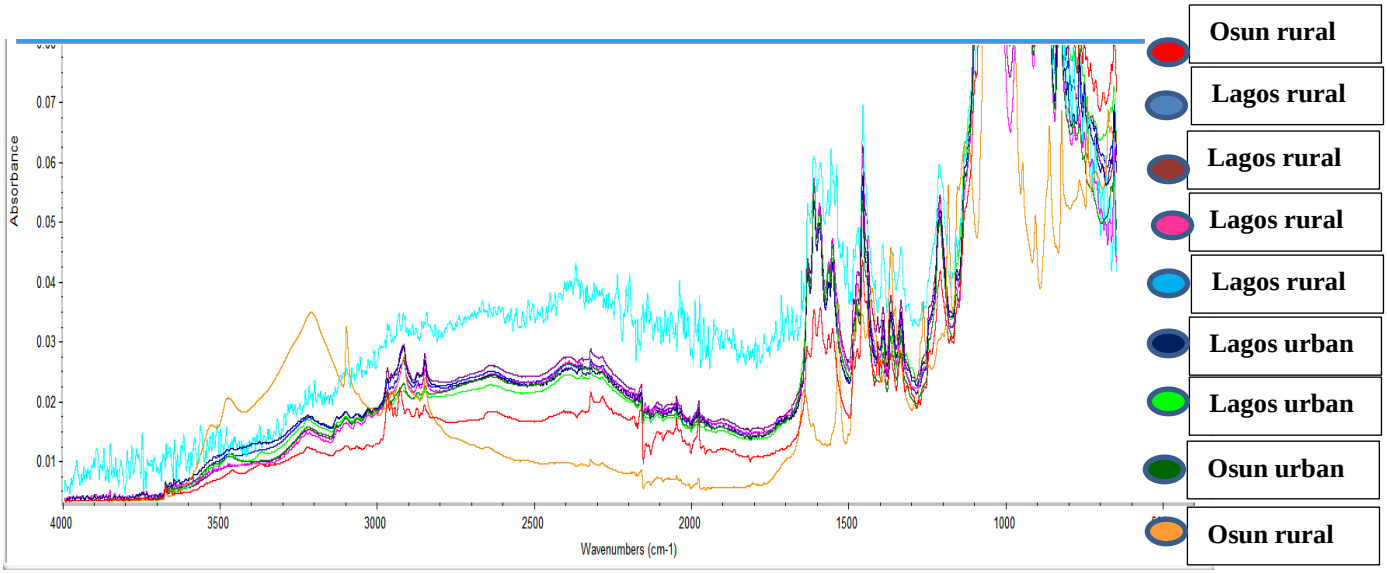


Figure 5.20: Chloroquine FT-IR spectra across the four regions (Lagos rural, Lagos rural, Lagos rural, Lagos urban, Lagos urban, Lagos rural, Osun Urban, Osun rural, Osun urban)

As shown (Figure 5.20), not all chloroquine samples produced the expected spectrum across both States; particularly one of the samples from Lagos rural region. These discrepancies in the spectra of chloroquine highlight the level of counterfeit or substandard drugs in the field; especially among non-ACTs. The samples purchased from Osun state shows that only two spectra were as expected. Chloroquine spectra of drugs from Lagos showed that five samples had the same spectra, including the fingerprint region, whilst one showed a totally different spectrum. The inconsistency in chloroquine spectra (Figure 5.20), shows that the content of some of these drugs have been mislabelled; whether intentionally or not, and they are therefore fake drugs.

5.3.9 Fansidar spectra (Swiss Pharma Ltd)

Fansidar is an antimalarial from the SP group and it is commonly a treatment choice for malaria in Nigeria because of its cheap price compared to ACTs. It is also the recommended treatment drug for pregnant women in their 3rd trimester. The spectrum of a Fansidar tablet that was purchased from an authorised distributor (Figure 5.21) was compared with randomly collected samples from the field of study. Although not as much as ACT samples tested, one of the few Fansidar samples tested was found to be inconsistent with the reference sample and the other samples (Figure 5.22).

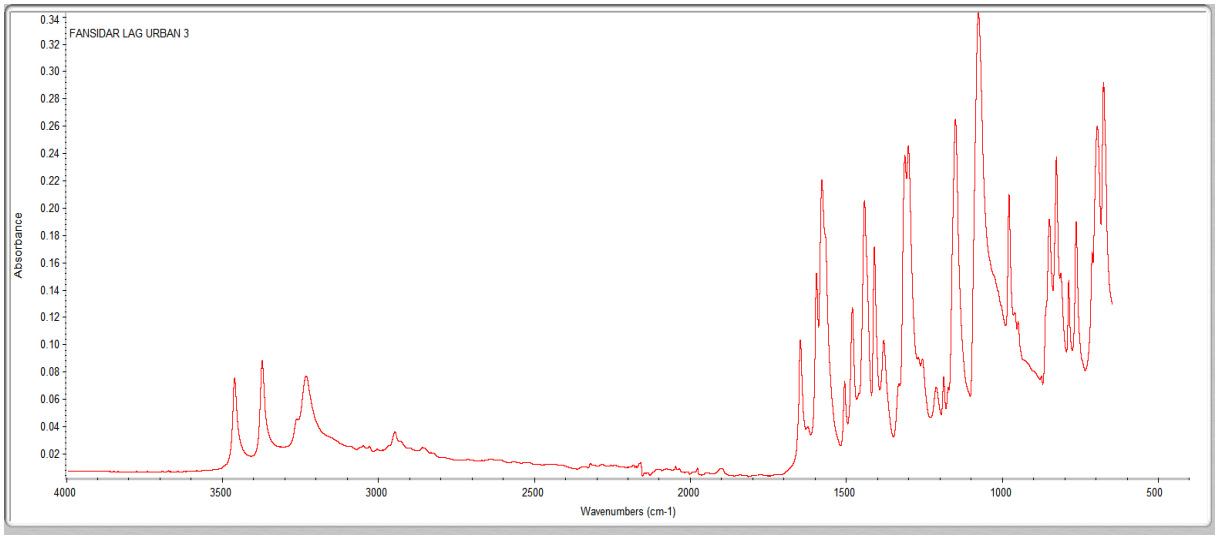


Figure 5.21: FT-IR Spectrum of the Fansidar reference sample (pure reference sample from Swiss Pharma Ltd).

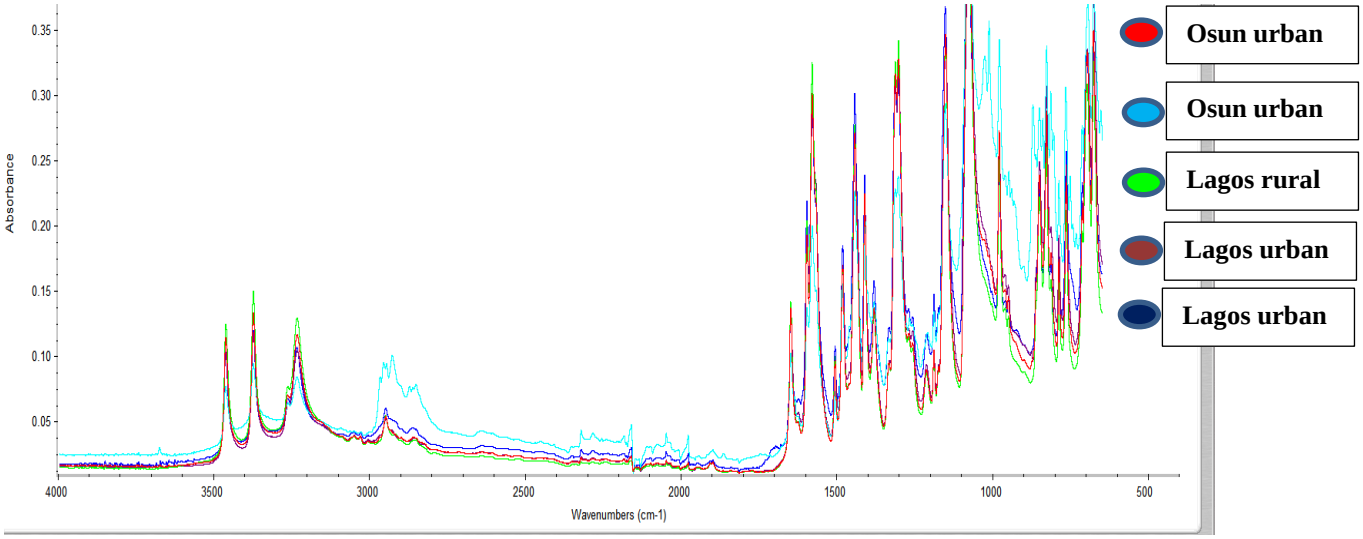


Figure 5.22: Fansidar FT-IR Spectra across the four regions. Shows that one of the five Fansidar spectra from Lagos and Osun is not consistent with the reference spectrum and with spectra from other samples

Table 5.2 is a summary of the FT-IR analysis that was done on different antimalarial drugs that are preferred by participants from the four different regions of the study. It should however be noted that there is a limit to what can be concluded from this result. The quick drug sampling that was done included the purchase of about 60 drugs across the four regions of the research to show the possibility of the presence of counterfeit drugs in this region and to create a link with the already flawed treatment practices in these regions.

Table 5.2: Summary of the antimalarial drug quality across the study area as assessed by FT-IR analysis.

LOCATION	SP		CHLOROQUINE		ARTESUNATE (Monotherapy)		ACT (AL)	
	Total	Failed	Total	Failed	Total	Failed	Total	Failed
Lagos urban	2	0	3	0	2	0	6	0
Lagos rural	2	0	3	1	0	0	7	0
Osun urban	1	1	2	0	1	0	6	0
Osun rural	0	0	1	1	0	0	5	0
Grand total	5	1	9	2	3	0	24	0

5.4 Discussion

The continuous increase in malaria prevalence and the threat of *P. falciparum* resistance to monotherapies lead to the WHO 2006 guidelines that specifically recommend combination therapy of ACTs for effective treatment of malaria cases caused by *P. falciparum* (Mosha *et al.,* 2014; Makanga & Koudsood, 2009). Since artemether acts quickly by reducing the biomass of the parasite by approximately 10,000 times per sexual life cycle (Premji, 2009) another antimalarial that lasts longer to eliminate residual parasites after artemether is also needed. This combination is needed to avoid recrudescence and the parasite developing resistance to either of the drug in combination. However, a major setback to the effective control of malaria through appropriate treatment is the issue of counterfeit and substandard drugs. Counterfeit or substandard pharmaceutical formulations are a serious public health concern to communities, individuals, and to the government. WHO defines counterfeit drugs as "*a drug that has been deliberately and fraudulently mislabelled with respect to identity and/or source*". National and international authorities have different ways of defining terms relating to medicine quality. The WHO has used the term 'substandard, spurious, falsely labelled, falsified and counterfeit' (SSFFC) to encompass the range of poor-quality medicines (WHO, 2016). However, recent years have brought a new dimension and attention to the difference between the terms 'falsified' and 'substandard' medicines. As defined by (Newton *et al.,* 2011; Nayyar *et al.,* 2012) 'falsified' medicine is deliberately and fraudulently

mislabelled with regard to its identity or source. Therefore, falsification can apply to both branded and generic products and refer to medicines in which the active pharmaceutical ingredients (API) could theoretically be correct, wrong, insufficient, or absent, or be a result of fake packaging. This is the definition adopted for this study and will be used interchangeably with fake drugs and counterfeit drugs. A 'substandard' medicine on the other hand, is a genuine drug product that does not meet quality specifications because of manufacturing error or that degrades over time within the recommended shelf-life (Bassat et al., 2016; Attaran *et al.*, 2012).

Keledis *et al* (2007) describes a continuous increase in the number of counterfeit and substandard drugs reported in the last decade, most of which were found in developing countries. In Nigeria, few studies have been published to describe fake drugs in the context of API although some studies (Pincock, 2003; Ahmad, 2004) have shown that diseases with greater risk of death, such as AIDS, and malaria, are targets for counterfeit producers. As seen from different studies on drug efficacy, different techniques can be used to determine fake and substandard drugs; from physical to laboratory analyses. In addition to physical differentiation (packaging, tablet colour, text on pack etc.) the quality of antimalarial drugs can be tested in the laboratory using FT-IR (Sundaramoorthi *et al.,* 2017; Kiruthika *et al.,* 2015), NMR (Holzgrabe 2017; Siddiqui *et al.,* 2017) and HPLC (Nikolin *et al.*, 2004; Siddiqui *et al.*, 2017) among others. For this study however, FT-IR was used to qualitatively determine the presence of artemether/lumefantrine in ACTs and consistency in drug content across all groups and regions. This study is the first study to use FT-IR as a qualitative method to test drug quality from Nigeria, however, a more detailed study that examines up to 200 drug samples in each region will provide a richer result through which a definite conclusion can be reached.

The reference drugs that were purchased from trustworthy manufacturers or distributors showed consistent spectra with a pure AL combination (Figure 5.4 - Figure 5.6). The spectra result of all AL drugs that were acquired from urban and rural regions showed the presence of artemether and lumefantrine peaks at their expected IR regions. However, it should be noted that even though FT-IR confirms that these drugs have artemether and lumefantrine, there is the question of API to consider since the presence of the right substance does not guarantee the right quantity of this substance.

The spectra of chloroquine drug samples that were purchased from all drug outlets in Osun state and Lagos state showed that one sample lacked drug. The spectra of chloroquine acquired from medical outlets in Osun state showed that three samples from the urban area as well as two samples from the rural area do not have a spectra that is consistent with the reference sample. In Lagos state, the FT-IR spectra showed that one chloroquine sample from the rural area was inconsistent with the others and with the reference sample. Following the recommendations of WHO and the adoption of ACTs as the first-line treatment for malaria in Nigeria since January 2015, chloroquine tablets are not meant to be used for malaria treatment. Not only has *P. falciparum* resistance to chloroquine been recorded in many studies (Onwujekwe 2009; Sidhu *et al.,* 2002; Mekonenn *et al.,* 2014), it is also a target for counterfeit producers because it is cheap and easy to buy. With Fansidar (SP group), out of the 5 of the samples that were tested, four of the drugs were consistent with the reference sample and the sample from Osun urban region showed a different IR absorption peak in the region 2800-3000 cm^{-1} showing C-H stretching bands from aliphatic compounds which isn't found in other samples.

The drugs that did not pass the FT-IR test in this context either did not have the expected active ingredients or they had other active ingredients that are not expected. The results of this study are similar to that reported by Onwujekwe *et al.,* (2009) in the Southeast region of Nigeria using HPLC chromatography. In this study (Onwujekwe *et al.,* 2009) a large number of SP drugs (40.7%) and chloroquine (53.6%) failed the quality test (did not meet the tolerance limit for quality test) and all ACTs passed the quality test. One major concern with the noticeable increase in fake SP formulations is the danger it poses to pregnant women in Nigeria since the national policy on malaria control prescribes the use of intermittent preventive treatment with SP for chemoprophylaxis against malaria in pregnant women (Ugwu *et al.,* 2013).

In contrast to Onwujekwe *et al.,* (2009), this study does not provide enough information to conclude that there are more counterfeit drugs in the urban regions compared to rural regions or in Lagos State compared to Osun State. However, the pattern of fake drugs that was found in this study has equity implications for appropriate treatment of malaria in Nigeria. As rightly decided by health authorities to make ACTs the trustworthy mode of malaria treatment, the high cost of these drugs means the poor people of lower socio-economic status groups are left to treat malaria with cheap and easily accessible drugs like chloroquine and SP formations. Despite the fact that ACTs are sold at a subsidised rate in malaria endemic

countries, the price between most ACTs and commonly used SP formations and chloroquine is still very high and this is why chloroquine is regarded as a poor people's drug. Similar to what was recorded by Kelesidis & Falagas (2015), the most common substandard/counterfeit antimicrobials include beta-lactams (among antibiotics) and chloroquine; this study therefore strengthens opinion that cheap and commonly used drugs by poor people are major targets of the counterfeit drug producers and it disagrees with researchers that believe inexpensive drugs like chloroquine are not targets. For example, Whitty *et al.,* (2008) said completely fake drugs are rare where drugs are cheap. The fact that there are more poor people in Nigeria makes cheap counterfeit antimalarials a business target for counterfeit producers.

Although Newton *et al.,* (2006) found in Cambodia that out of 133 drug vendors 71% had counterfeit artesunate, Onwujekwe *et al.,* (2009) also found an increasing rate in counterfeit artemether monotherapy such as artesunate sold in drug outlets; for example, 25% of artemisinin monotherapy tested did not meet the tolerance limit for quality test. However, this was not found to be the case in this study, as all the artesunate samples tested passed even though not enough artesunate were tested to firmly draw a conclusion. In support, a study by Ofori-Kwakye *et al.,* (2008) was carried out to evaluate the quality of artesunate tablets sold in retail and wholesale pharmacies in Kumasi, Ghana. Artesunate tablets were purchased from pharmacies in Kumasi to check for mechanical properties of the tablets such as uniformity of weight, breaking strength and the rate of disintegration in aqueous medium; before colorimetric methods were used to determine the presence of artesunate. Results of this study showed that none of the artesunate tablets sampled was found to be counterfeit.

ACTs in this study showed a 100% pass rate, this result compares well with those from other studies such as Onwujekwe *et al.,* (2009), where all ACTs met the USP tolerance limits for quality test. However, Newton *et al.,* (2014) found no artemether, lumefantrine or any other pharmaceutical ingredients in the drugs labelled "artemether-lumefantrine" tablets that were seized in Luanda, Angola. Compared to other types of antimalarial, fake ACTs are not yet prevalent in the drug market; for this reason, urgent intervention should be developed and implemented so as to quickly curb counterfeit producers from infiltrating the ACT market,

To improve on the quality treatment available to malaria patients, drug quality must definitely be improved; therefore, it is imperative to increase educational intervention for health providers, and patients to be able to identify between quality drugs and fake drugs. This is important because studies have shown that even healthcare providers, including doctors,

sometimes do not follow the procedures and guidelines of patient treatment. For example, a study by Ugwu *et al*., (2013) showed that 54.5% of general practitioners prescribed other antimalarials for acute treatment of malaria in the first trimester instead of quinine as recommended by the World Health Organization and the national malaria control programme of the Federal Ministry of Health (FMOH) (2012). This shows that with the effective treatment of malaria, even the GPs may not be abreast with a new concept of treatment of acute malaria in the first trimester where quinine is the drug of choice and is also currently the only anti-malaria drug that is effective and safe for use in the first trimester of pregnancy.

More emphasis and more campaigns need to be established to advise people to steer clear of chloroquine as a treatment for malaria. The fact that some of the chloroquine samples in this study did not have the same spectrum as the reference sample is very worrying considering the prevalence of malaria in this region. A lot of patients can be exposed to this and could develop a worse complication, or even die as a result.

If the use of ACTs for malaria treatment is being promoted among citizens then the fight against counterfeiting should also be taken more seriously. If more people believe in the use of ACTs but cannot afford them because of their huge price, they can then be easily lured into buying fake ACTs at a cheaper price. This will in turn increase the amount of ACTs in the market and this will eventually be hard to control.

5.4.1 ACT potential target for modern counterfeiters

As one of the most potent antimalarials that has been well-tolerated, ACT is a major target for drug counterfeiters. It takes nearly six months to grow the plant Qinghao, which produces artemisinin and from which the combination ACT comes. The huge prevalence of malaria leads to a massive demand for artemisinin which is in short supply (Newton *et al.,* 2006). The major reason why ACTs are usually targeted in developing countries is mainly because of its market price. ACT is relatively expensive; the cost of a course for an adult and a young child is US$ 1.20-3.50 (Karunamoorthi, 2014) (it had increased to about $5 by the time this study was being concluded). In a country where the poverty level is extremely high, there is a call for cheaper trusted drugs to treat a disease which some people have more than 10 times in a year. In Third World countries, citizens usually face high exposure to different diseases because of lack of amenities and when combined with corruption, insufficient drug regulation and weak law enforcement, it becomes a very frustrating situation were people can give or receive treatment without any form of monitoring. This creates a huge opportunity and it’s a

major driving force to establish a counterfeit anti-malarial industry to produce and distribute fake antimalarials. This is usually the case in Nigeria, in addition to insufficient amenities and ability to detect and identify the quality of antimalarials, poor consumer and health worker knowledge about these drugs and lack of punitive action against counterfeiters make these drugs attractive targets for counterfeiters. In Nigeria, much investment, or money, is not needed to start a counterfeiting business and fake drugs can be produced in the backyard of houses, or in a small room.

In the case of ACTs where drug prices of medicines are high and the difference in price with other identical products exists there is a huge possibility for the consumer to seek medicines outside the normal supply system. Some rural areas in Nigeria lack transport and there is no easy connection to the urban areas. This reduces their access to original drugs that can be purchased from trustworthy pharmacy stores and therefore patients resort to local stores who might only be licensed to sell off the counter drugs. Poverty, and the lack of an official supply chain, are major factors in creating markets for counterfeit products (Bamitale, 2013)

5.4.2 Consequences of counterfeit medicine

Effective and appropriate drug use is the key to treatment in public health. In this case, fake antimalarials, which usually contain no, or less active ingredients, either lead to patients being at substantial risk of developing severe malaria or dying from complications. A prediction by Seiter (2009) to quantify the cost of ineffective antimalarials from prior estimates states that in a country of about 20 million people, there may be four million treatments and nearly 800,000 cases treated with poor quality antimalarials, causing up to 4,000 childhood deaths. Fake antimalarials will lead to recrudescence of disease and can also lead to resistant parasites. Evidently, the recent emergence of artemisinin resistance or tolerance of a *P. falciparum* strain in the Thailand-Cambodia border makes protection of an effective drug supply imperative. This means the drug does not help the patient get better and can also be harmful to the patient. For example, the treatment of uncomplicated malaria with this type of drug can lead to severe malaria and this may result in death. Another type of counterfeit drug is the drugs that have no active ingredient but contain harmful ingredients. For example, a tragedy occurred on a larger scale in Panama when a Chinese chemical manufacturer sold diethylene glycol, the active ingredient in antifreeze, as pharmaceutical-grade glycerin to a European company Buckley and Gostin (2013). Because this is often used as the solvent in cough syrup, it led to kidney failure in the people who ingested it. A total of about 60,000 bottles were sold to people and as a result, more than 219 people lost their lives

to kidney failure brought on by diethylene glycol poisoning (Núñez, 2011); some news reported more than 500 deaths. Another case of a counterfeit drug is that of a GlaxoSmithKline's over-the-counter weight-loss medication "Orlistat" which was distributed in the United States. The counterfeit contained the controlled substance sibutramine instead of Orlistat (Blackstone *et al.,* 2014).

Substandard and counterfeit antimalarials are directly or indirectly associated with higher morbidity, mortality and stunted socio-economic growth due to additional healthcare costs because of treatment failure and they impose a severe burden of disability adjusted life years (DALYs) at the national level. Even when patients are treated with genuine drugs, no response is seen due to resistance caused by the previous intake of fake drugs (Akunyili, 2004).

In Nigeria, counterfeit antimalarials cannot be easily identified from genuine drugs which has led to a steady diminishing of the confidence of the public healthcare providers and systems at large. The problem of counterfeit drugs has embarrassed the Nigerian healthcare providers and denied the confidence of the public on the nation's healthcare delivery system. The following are notable recorded occurrences in Nigeria that shed more light on how devastating the consequences of counterfeit drugs can be. Starting in 1989, some poorly manufactured chloroquine syrup killed a number of children in U.N.T.H, Enugu; of which there are no statistics, partly because many of the deaths were not even reported (Akunyili, 2004). Later in 1990, the "Paracetamol syrup" disaster occurred when 109 children died in Ibadan and Jos, after taking paracetamol/cough syrup produced with the toxic ethylene glycol solvent instead of propylene glycol (Itodo and Oyinye, 2017). During a meningitis epidemic in Niger in 1995, more than 50,000 people were inoculated with fake vaccines resulting in 2,500 deaths. Also, Odion (2017) recorded that in 2002, 3 patients reacted adversely to infusions manufactured by a Nigerian company. Some of the adverse reactions exhibited by the patients were severe rigor, vomiting, sweating, restlessness, seizure, impaired level of consciousness, etc. The reactions stopped immediately after the administration of the infusions were discontinued. Investigations by NAFDAC on the offensive infusions collected from the hospital revealed that three batches were heavily contaminated.

In 2003, counterfeit adrenaline was reported to have contributed to the death of three children during open-heart surgery in Nigeria. Further investigations by NAFDAC revealed that the suxamethonium used in the surgical procedure was a counterfeit product. Later in 2004, some

hospitals reported cases of adverse reactions from the use of contaminated infusions produced by four Nigerian companies. Consequently Bamitale (2013) sampled infusions and water for injection from all over the country and results confirmed that some batches of infusions produced by the companies were heavily contaminated with microorganisms. The extent of counterfeit problems in Nigeria is better described by the fact that counterfeit products (drugs, food, cosmetics, medical devices, chemicals, and water including all drinks but mostly pharmaceuticals) prized at over N8b ($60 million) were seized and destroyed in Nigeria by the National Agency for Food and Drug Administration and Control (NAFDAC) between April 2001 and December 2004.

5.4.3 Drug law-enforcing agency in Nigeria (NAFDAC)

The problems of fake drug proliferation in Nigeria have affected the credibility of the healthcare system and can exert very harmful effects on the consumer resulting in illness, disability and even death; anyone can be a victim. Some of the incidents have resulted in death even among children because most times the consumers do not know the quality of what they are buying or taking. This makes it imperative that there is a need to intensify effort in fake drug eradication. The National Agency for Food and Drug Administration and Control (NAFDAC) is Nigeria's equivalent of the US Food and Drug Administration (FDA). The main purpose for creating this agency is to protect public health in Nigeria by maintaining the safety of food, cosmetics, vaccines, drugs, veterinary products, herbal preparation and so on. National Agency for Food and Drug Administration and Control (NAFDAC) is the government agency in Nigeria that is fully empowered to regulate and control the importation, exportation, manufacture, advertisement, distribution, sale and use of drugs in order to ensure that safe and quality drugs are available to the public. As NAFDAC tasks herself dutifully in fighting fake drugs, more challenge come from unscrupulous drug dealers who sometimes have the backings of lawmakers and politicians making the stipulated drug laws and standard unattainable

Legislative measures taken on counterfeit medicines, including revised approaches to ensure that standards for quality, safety and efficacy are implemented and distribution chains effectively controlled. In many countries regulatory oversight of pharmaceuticals is ineffective, especially of distribution channels. Coordinated action at the local level is essential between health authorities, police, customs, and judiciary institutions to ensure proper regulation, control, investigation and prosecution. IMPACT will help countries with

weak regulatory systems to strengthen them by improving collaboration and drawing from the experience, capacity and resources of all IMAPCT stakeholders.

5.5 Conclusion

Weak policies and translating existing policies into practice have proved very challenging in all departments in developing countries including Nigeria. Even though there isn't a widespread occurrence of fake ACTs at the moment compared to chloroquine and Fansidar, these drugs were once the first-line drug choice for malaria treatment and after a period of time were hugely invaded by counterfeit producers. This means ACTs are even at greater risk considering the more advanced technology in the world now and the higher number of counterfeit producers compared to the 1980's. Prior to the introduction of ACT, it was already known that many, and the majority in some settings; especially rural, struggled to afford the market price of antimalarials. This was the motivation behind counterfeiting the available drugs; transitioning into the use of ACT for existing first-line antimalarials, even if completely effective, was therefore likely to have little impact, although limited impact is far better in this case to no impact at all. The impact of ACTs cannot be felt if their distribution is not channelled to reach both rich and the poor; if this is achieved, it could lead to lasting health gains. New approaches or interventions need to be developed; it cannot safely be assumed that some of the strategies, which worked when malaria was by far the most common cause of potentially fatal febrile illness, will necessarily, remain appropriate.

One of the major strategies through which counterfeit products are stopped in developed countries and which developing countries struggle with is the government's lack of ability to stop fake medicines from entering the private market through customs and policing. The recommended actions for improving the quality of drugs for effective malaria treatment should include refresher and fresh training and capacity building for all policy makers, providers and consumers but with special and priority emphasis on PPMVs who are usually the first point of contact for patients in the rural areas, or urban areas that want cheap genuine drugs; so as to enhance the quality of drug acquisition. As such, information about the quality of drugs used in the co-packaging or co-prescriptions as ACT is very useful for improving malaria case management. In addition to this, the government needs to invest in forensic chemical analysis and simple field tests which will enhance drug quality monitoring. Improved access to inexpensive genuine medicines, strong support of drug regulatory authorities, vigorous law enforcement, and international cooperation with determined

political leadership will also improve access to genuine drugs. The National Agency for Food, Drug Administration and Control (NAFDAC) will be able to tackle the high incidence of counterfeit drugs if they are decentralised and are able to perform at the Local Government Areas (LGA) level as opposed to working from the Federal level. In this case, NAFDAC can collaborate with the State Ministry of Health (SMOH) in each State for easy and more effective monitoring. This will help improve on the fight of NAFDAC against counterfeit drugs that has been recorded in the urban areas over the years but haven't had any impact in rural areas against substandard and counterfeit drugs.

An effective approach would have been to take all malaria drugs off the counter and make sure only registered pharmacy stores have access to buy and can sell to patients. However, even though this can help monitor channels of drug distributions, it will put a lot of pressure on case management because of the huge number of people that seek treatment daily.

CHAPTER 6: INVESTIGATING THE QUALITY OF ACT ANTIMALARIAL DRUGS USING *IN-VITRO* CULTURE.

6.1 Introduction.

The continuous spread of substandard antimalarials in malaria endemic regions, including Nigeria, is one of the major barriers to public health and is a threat to the usefulness of antimalarial drugs.

Bearing in mind that malaria drug resistance has been recorded across most antimalarial groups, two important factors that can also lead to resistance to the new ACTs include the continuous use of counterfeit/falsified drugs for treatment and also the use of substandard drugs for treatment. It should however be noted that counterfeit drugs are not the same as substandard drugs. As defined by WHO, substandard drugs are "genuine medicines produced by manufacturers authorized by the NMRA (National Medicine Regulatory Authority) which do not meet quality specifications set for them by national standards" (WH0, 2008). To further add, substandard drugs can also be as a result of the way the drugs have been handled after they have been manufactured correctly.

To minimise the emergence of drug resistance to new antimalarial drugs, the WHO in 2001 recommended the use of ACTs as a first line treatment of malaria; a policy that in 2005 was adopted by the Nigerian government (Ojurongbe *et al.,* 2013). Combination therapy is seen to be an effective approach to reducing the probability of resistance of parasites to the used antimalarial; particularly if the mode of action of the two drugs in the combination is different. As explained by Gupta *et al.,* (2002), the idea is to combine a fast acting and short half-life drug with a slowly eliminated drug that maintains a minimum inhibitory concentration level for at least 7 days. However, developing countries usually lack advanced, or even basic techniques to effectively test and ascertain the standard and quality of antimalarials in the market, thereby leading to a high exposure of citizens to counterfeit and substandard drugs. This factor led Newton *et al.,* (2006) to describe Africa as the next likely destination for counterfeit and substandard drug producers; an accurate description, as we can see now in 2018 (Siva, 2010; Burns, 2006; Sambira, 2013).

Different studies have reported cases of substandard antimalarial drugs in African countries, such as Cameroon (Basco *et al.*, 2014), Tanzania (Minzi *et al.*, 2003) and Ghana (El Duah and Ofori-Kwaye, 2012). In addition, a trend of studies in Nigeria has consistently found the existence of substandard drugs in the market. In 2008, the WHO collected drug samples from six Sub-Saharan countries for evaluation. 63.9% of the 28.5% (n=1437) of drugs that failed were from Nigeria (WHO, 2011). Analysis of drug samples by Onwujekwe *et al.*, (2009) in Anambra State, South-eastern Nigeria, found the 37% of antimalarial drugs tested did not have the required amount of active ingredients; most samples that failed were primarily quinine and SP. The authors concluded *"our study highlights the need for increased pharmacovigilance and greater regulatory control on local ACT production, importation, drug storage, and provision"* (Onwujekwe *et al.*, 2009). . In 2012, NAFDAC reported 19.6% of samples around the country were not up to standard, and more recently, Kaur *et al.*, (2015) found 9.3% of substandard drugs in Enugu State.

Over the years, focus has been placed on falsified drugs with little attention given to substandard medicines (Johnston and Holt, 2014). Like counterfeit drugs, substandard medicines also reach patients and affect effective treatment because of poor manufacturing and quality control practices even though the production of the drug is genuine. Also, storage patterns in hospitals and medicine stores have the tendency to reduce the potency of the drugs. The inability to afford or access "high price" ACTs has been a contributing factor to the booming counterfeit and substandard drug market in Nigeria. This makes the rural and poor areas a major target for producers. The distribution and production of substandard drugs in Nigeria is a vast and underreported problem. Asides from the morbidity and mortality it causes, it is also a factor behind the loss of confidence in drug treatment practices.

6.2 Objectives.

As one of the recommendations of the WHO and also the federal Ministry of Health (FMOH) is to treat every case of malaria appropriately using artemether/lumefantrine combination therapy (ACT). This chapter will investigate the threat of substandard ACTs that are sold in the market in the two study regions (Osun and Lagos) by using *in-vitro* culture methods to compare the percentage of *P. falciparum* cleared by each drug. This approach should highlight the level of discrepancy within each drug product and also within the regions where this study is being carried out.

6.3 Methods

Refer to Chapter 2 for detailed methodology. Note, all tested drugs were solubilised in chloroform prior to *in vitro* assays being carried out.

Table 6. 1: List of drugs tested, including weights and concentrations (all drugs were tested using FT-IR spectroscopy and they all showed the presence of Artemether/Lumefantrine).

Region	Drug name (Code)	Drug weight	Artemether/lumefantrine ratio	Expiry date
Lagos rural	A	230 mg (0.23g)	20/120 mg	July-2018
	B	730 mg (0.73g)	80/480 mg	June-2018
	C	250 mg (0.25g)	20/120 mg	June-2018
	D	680 mg (0.68g)	80/480 mg	February-2017
	E	680 mg (0.68g)	80/480 mg	May 2017
	F	230 mg (0.23g)	20/120 mg	July-2018
	1F	250 mg (0.25g)	20/120 mg	May 2017
	1D	230 mg (0.23g)	20/120 mg	Sept 2017
Lagos urban	G	950 mg (0.95g)	80/480 mg	July-2018
	H	250 mg (0.25g)	20/120 mg	Sept 2017
	I	250 mg (0.25g)	20/120 mg	June-2018
	J	680 mg (0.68g)	80/480 mg	June-2019
	K	680 mg (0.68g)	80/480 mg	July-2018
Osun rural	L	230 mg (0.23g)	20/120 mg	September 2017
	M	960 mg (0.96g)	80/480 mg	June-2018
	N	730 mg (0.73g)	80/480 mg	Sept 2017
	O	680 mg (0.68g)	80/480 mg	July-2018
	1K	250 mg (0.25g)	20/120 mg	May 2017
Osun urban	P	230 mg (0.23g	20/120 mg	June-2018
	Q	680 mg (0.68g)	80/480 mg	May 2017
	R	730 mg (0.73g)	80/480 mg	July-2018
	S	250 mg (0.25g)	20/120 mg	May 2017
	T	730 mg (0.73g)	80/480 mg	June-2018

6.4 Results.

In vitro drug assays were carried out in triplicate at 5 nM, 10 nM and 20 nM concentrations. Figure 6.1 shows a reduction in parasitaemia at 20 nM concentration for all the sampled drugs. Indeed, at 20 nM drug A appears to be the most efficacious, with almost 60% parasitaemia reduction in comparison to a 30-40% reduction for the other drugs. Moreover, it can be seen that drug A also shows a parasitaemia reduction of almost 40% at 10 nM concentration; this efficacy is not recorded in the other drugs. Indeed, drugs B and D showed no reduction at 10 nM concentration while drugs C, E and F showed about 15% reduction in parasitaemia. This data confirms that even though all of the drugs tested contain the recommended Artemether/Lumefantrine, the concentration at which they are effective may vary.

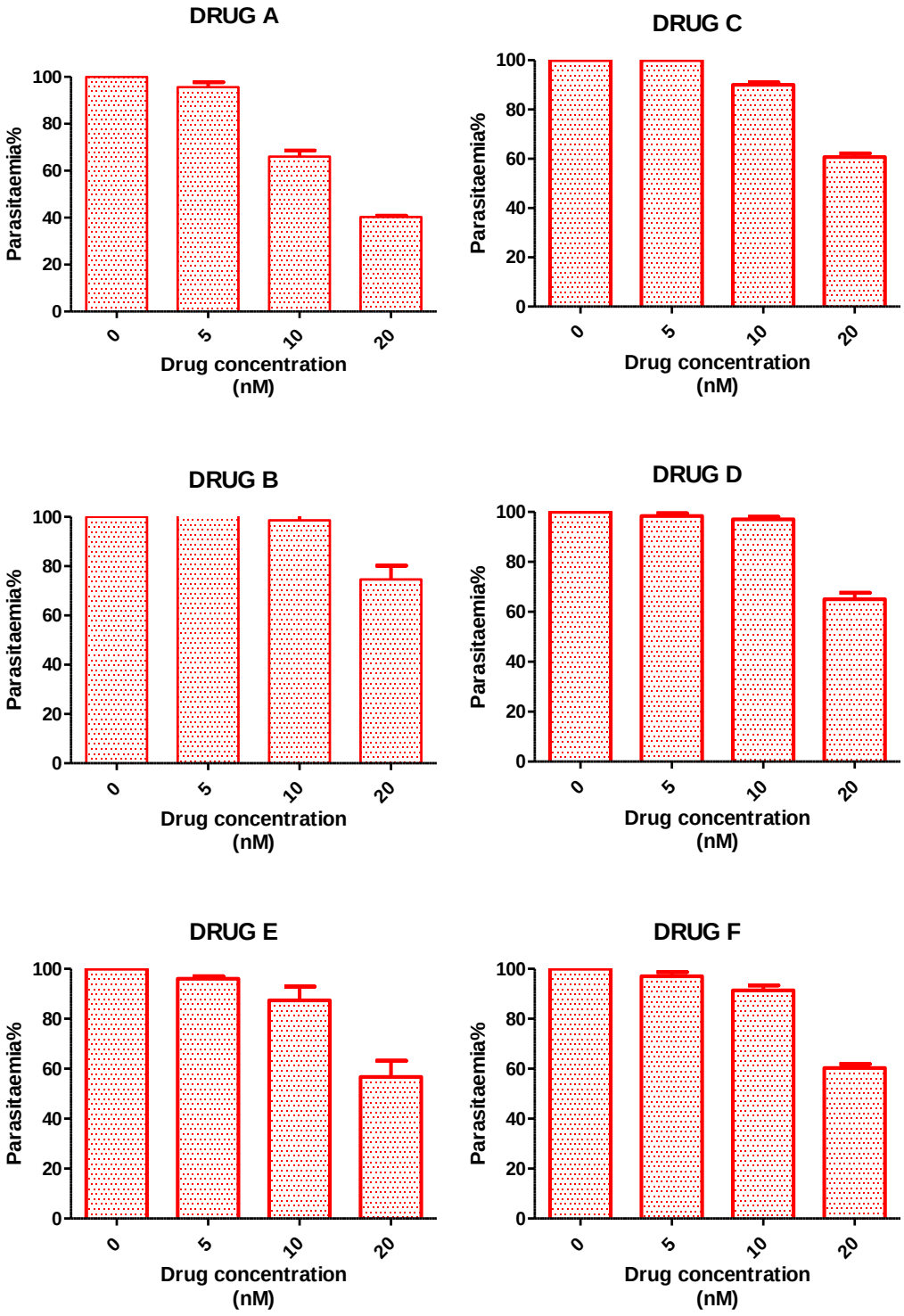


Figure 6.1: The effects of 6 (A-F) ACTs on parasiteamia %. A range of ACTs concentrations were incubated with 1% ring stage cultures of *P. falciparum* multi-drug resistant K1 strain 72 hours under the conditions described previously. Tests were done in triplicate and were analysed using SYBR Green-based methodology.

For this reason, 20 nM drug concentrations was chosen for subsequent assays as shown below.

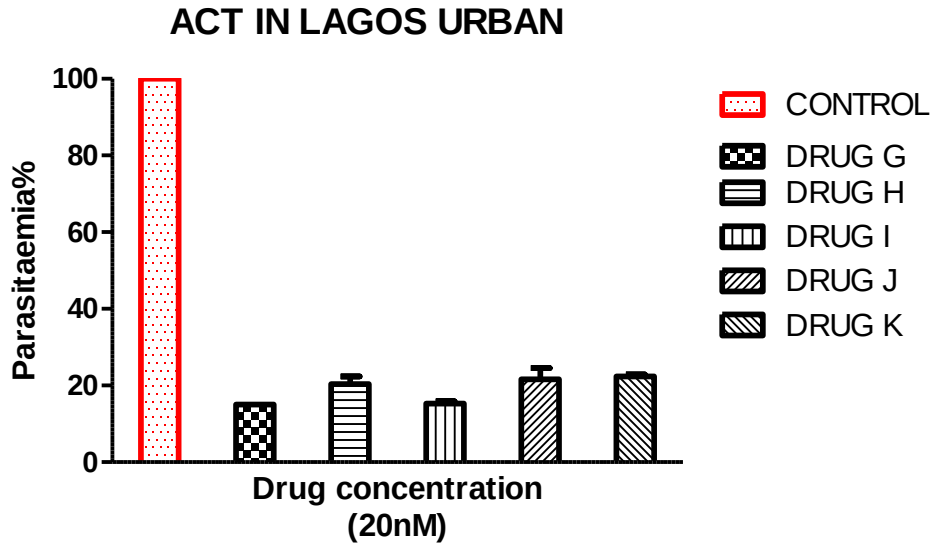


Figure 6.2: Analysis of sampled ACTs (20 nM concentration) in Lagos urban region against P. falciparum multidrug resistant K1 strain. Each drug was assayed in triplicate and standard error of the mean is shown.

As shown (Figure 6.2), all drugs sampled from the Lagos urban region resulted in an approximate 80 % reduction in parasitaemia. This shows that all the sampled drugs from this area, regardless of brand (H and I are the same brand and J and K are the same brand), are of the expected standard.

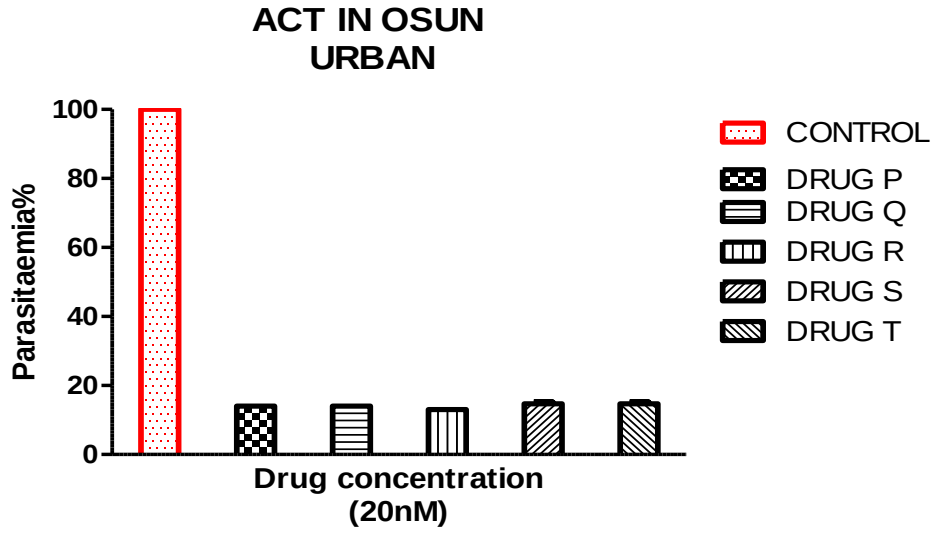


Figure 6.3: Analysis of sampled ACTs (20 nM concentration) in Osun urban region against P. falciparum multidrug resistant K1 strain. Each drug was assayed in triplicate and standard error of the mean is shown.

As shown (Figure 6.3), all drugs sampled from the Osun urban region showed about 80% reduction in parasitaemia. This confirms that the drugs, regardless of brand (drugs R and T are the same brand), are all of the expected standard.

In contrast to the above, the drugs tested at 20 nM concentration from the Osun rural region (Figure 6.4) were more inconsistent in their efficacy to reduce levels of parasitaemia. Indeed, drug 1K appeared to reduce parasitaemia to approximately 70% of control levels compared to the approximate 80% observed for other drugs tested; this includes drug M, which is the same brand as 1K.

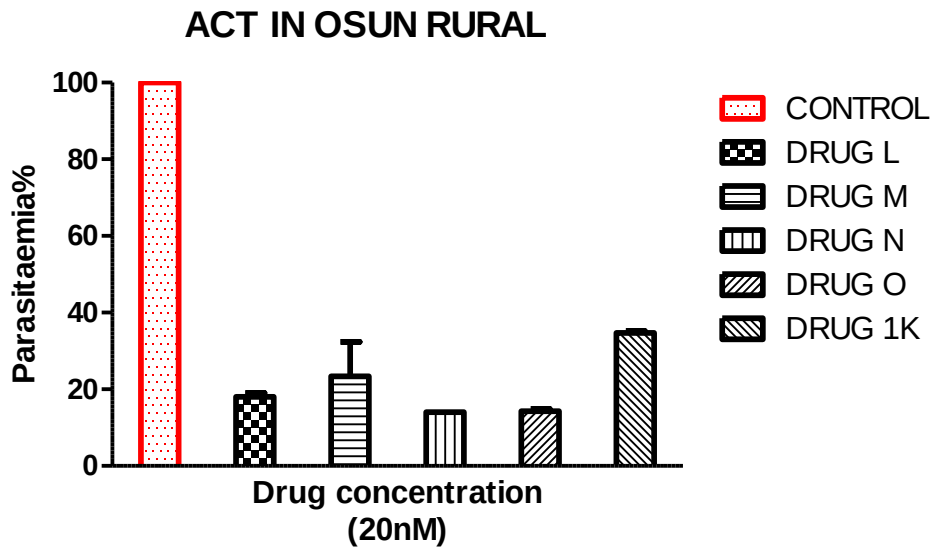


Figure 6.4: Analysis of sampled ACTs (20 nM concentration) in Osun rural region against P. falciparum multidrug resistant K1 strain. Each drug was assayed in triplicate and standard error of the mean is shown.

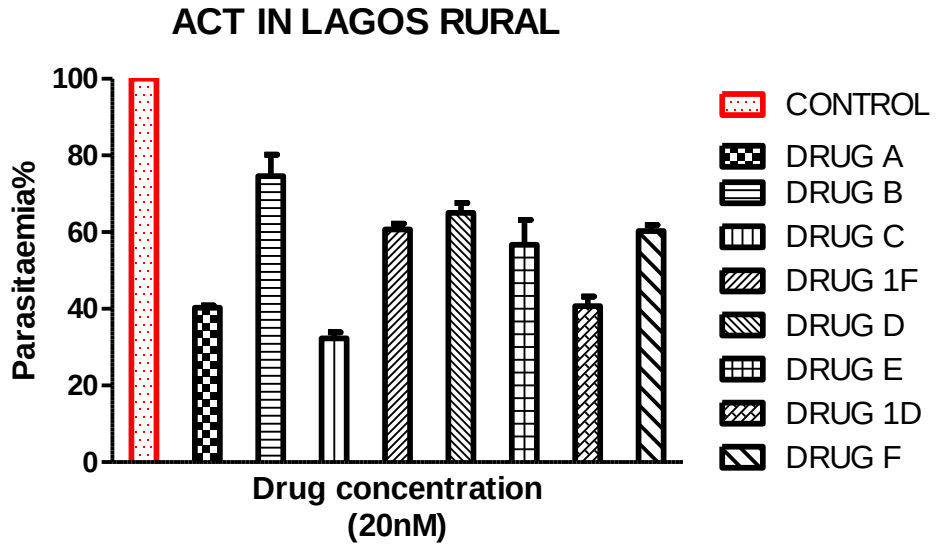


Figure 6.5: Analysis of sampled ACTs (20 nM concentration) in Lagos rural region against P. falciparum multidrug resistant K1 strain. Each drug was assayed in triplicate and standard error of the mean is shown.

The *in vitro* drug assays that contrasted most with the other tests were those carried out with the samples from Lagos rural region (Figure 6.5). The most efficacious drug from this area (drug C) produced an approximate 70% reduction in parasitaemia, others showed an approximate 50% reduction in parasitaemia and drug B was least effective; parasitaemia was reduced by approximately 25%. Moreover, drug B is the same brand as drugs N, R and T (Osun rural and urban regions; Figures 6.4 and 6.3) and drug C is the same brand as drugs H, S and M (Osun rural and urban, Lagos urban; Figures 6.4, 6.3 and 6.2). This demonstrates that the Lagos rural region is particularly susceptible to substandard ACTs in the marketplace relative to the other study areas.

6.5 Discussion

There is very little research done to describe the quality of antimalarial drugs and reports are not available for the majority of malaria endemic countries (Tabernero *et al.*, 2014; Kaur *et al*., 2015). Use of the term substandard is less controversial and there is consensus among most organizations that substandard drugs are those that fail to meet established quality specifications. When a regulator approves a drug, they approve a quality standard, outlined in the accepted pharmacopeia or in the manufacturer's approved dossier. As the WHO explains, substandard products are the drugs that "do not meet the quality specifications set for them in national standards" (WHO, 2009).

Even though most studies have concentrated on counterfeit drugs in Nigeria (Salisu *et al.,* 2017; Adeyemi *et al.,* 2017; Joda *et al.,* 2017), very few have checked for a combination of counterfeit and substandard drugs. In a study by Kaur *et al.,* (2015) to assess the quality of ACTs purchased from pharmacies, PPMVs and other public health facilities in Enugu metropolis, Nigeria, 9.2% of the drugs purchased were of poor quality, with 1.2% falsified, 1.3% degraded and 6.8% substandard in one or more of the APIs. A limitation of this study is the relatively low number of drugs tested across each region; however, the proportion of substandard drugs that was found is in broad agreement with that observed by Bate (2012) where antimalarial samples from pharmacy stores in Lagos were assayed by Raman spectrometry between 2007-2012 and 23% of ACTs were substandard. More recently an evaluation of the quality of anti-hypertensive drugs in Lagos State by using HPLC showed that of 102 drug, samples, up to 76% did not meet quality standard Ndichu (2018). Interestingly, it was further reported that most of the drugs that did not meet the drug purity standards were from low social economic status areas Ndichu (2018). This is also the case in the current study since findings clearly show more substandard drugs in the rural area of Lagos compared to the other urban areas. It can be suggested that the prevalence of substandard drugs is determined by the type of disease, or ailment, and also, the awareness of a target group. For example, a disease with high prevalence among people of low economic status, residing in rural areas, might attract more counterfeit and substandard drugs. Awareness and the ability to afford and decipher between authentic and substandard drugs is also a factor that helps the sale of substandard drugs in these areas. Although one would expect the urban areas to be a primary target of substandard drugs because of the profits that could be accumulated if these drugs are exposed to large urban markets, control and monitoring measures that are present in the urban areas will to a large extent limit the sales of counterfeit and substandard drugs. For example, most pharmacy stores in the urban areas obtain their drugs from an accredited distributing company and this is not always the case in rural areas. Another factor that can be responsible for substandard drugs is the storage methods. Certain drugs should be stored in at a particular temperature and exposure to heat and sunlight must be avoided otherwise the efficacy of such drugs will be compromised.

Results from this study highlight the importance for the need to carry out a larger scale study to provide a more thorough representation of the rate of substandard drugs in each community and to provide suitable intervention approaches that meet the needs of each community. Data in this chapter also corroborates the study of Kaur *et al.,* (2015) which

suggests that the prevalence of poor quality drugs in sub-Saharan Africa could be overestimated. However, where it is prevalent, the consequences of substandard drugs can be seen on an individual (patient) level, or in a more general (community level).

6.5.1 Consequences of substandard antimalarials

Consequences of substandard ACTs and counterfeit drugs are usually similar, and in the long run can affect patients directly or indirectly, affect communities and also, reduce trust in the drugs in question. Substandard/counterfeit antimalarials may have serious consequences for both patients and global health, such as increased antimalarial resistance, treatment failure, and side effects (Nwokike *et al.,* 2018; Newton *et al.,* 2017).

6.5.1.1 Consequences for patients

Substandard drugs pose a very serious public health concern for patients as they can directly result in death (Johnson and Holt, 2014) even though falsified drugs receive more attention with respect to causing unnecessary deaths. As described by Keldeis and Falagas (2015), using an excessive dose of the active ingredient in low-quality antimicrobials may be toxic to humans, especially in children, or with antimicrobials with a narrow therapeutic range, such as quinine. Developed countries have measures in place to put in check the quality of drugs that citizens are exposed to (see Appendix). A drug with insufficient API may also lead to la ack of clinical response if not death; an example of this has been recorded by Newton *et al.,* (2006) and Keoluangkhot *et al.,* (2008) in antimalarial treatment failing because the drugs contained less than the stated dose of API. There is an extensicve literature to show that in some cases, substandard drugs have caused devasting morbidity in humans (IMPACT, 2010; Newton *et al.,* 2011; Harris *et al.,* 2009).

6.5.1.2 Consequences for the community

Very importantly, substandard antimicrobial medicines, in this case antimalarials, may promote parasite drug resistance (Thu *et al.,* 2017; Blasco *et al.,* 2017). Keldeis and Falagas (2015) describe that emergence of antimicrobial resistance as a result of low-quality antimicrobials has been reported with antimicrobials that are often used in combination therapy; as antimalarials are often used. On a more general level, low-quality antimalarials may significantly decrease confidence in the efficacy of some antimalarials. It has been recorded in some cases were poor-quality drugs have led to physicians losing confidence in specific antibiotics and thus opting for other antibiotics as the drugs of choice for infections. When therapeutic failure or adverse events occur, patients may also experience a loss of

confidence in health systems, health professionals as well as registered pharmaceutical products and brands (Gautam *et al.,* 2009). This can be easily linked with antimalarials, leading to the prescription of more 'trusted' expensive antimalarials that patients in developing countries are not able to afford. Also, when these people cannot afford the treatment, they either find other ways to treat or they stay untreated; posing a risk of infection to other people in the community that are not infected.

Cases of substandard antiviral drugs being responsible for the emergence of drug resistant viruses including HIV have been documented (Wertheimer & Norris, 2009; Jordan *et al.,* 2008) and substandard anthelmintics have been implicated in the development of drug-resistant human helminths (Geerts & Gryseels, 2001), thus further aggravating the economic burden of treating infectious diseases.

6.6 Conclusion

Like counterfeit antimalarial drugs, substandard drugs also create an expanding problem throughout developing countries with possible devastating consequences for global public health if not checked with ultimate urgency. To begin with, appropriate design studies need to be implemented to fully understand the magnitude of the problem as mere speculations would not suffice. In addition, initiatives have been developed to counteract counterfeiting and these should be encouraged; including collaboration between patients, health workers, local, national, and international organizations, and industry. It is also imperative to invest in technologies that can effectively assist in detecting substandard drugs as the lack of this resource in developing countries limits the implementation of many measures to combat the production of substandard drugs. As expected, the rate of malaria incidence in Nigeria over the years and the huge amount attached to its treatment has led to the increase of substandard drugs in the country. Where economic and regulatory environments are less structured, supply chain security strategies that fixate on 'counterfeits' often fail in limiting the prevalence of poor quality medicines.

CHAPTER 7: GENERAL DISCUSSION.

7.1 Overview

Malaria is a long-standing global health issue and many efforts have been made to eliminate and control the disease. Around the world, 113 countries have eliminated malaria and 34 middle-income and some low-income countries are in the malaria elimination phase (Zelman *et al.,* 2014). However, most low-income countries in malaria-endemic regions of the world are still undergoing malaria control programs (Zelman *et al.,* 2014). Malaria disproportionately affects low-income countries, such as those of Sub-Saharan Africa, where 47 of 54 countries are malaria endemic and most are currently in malaria control programmes (Omumbo, *et al.,* 2013). The malaria story in Nigeria is one that is complex and unique, usually because of a complex national health system and a population with huge religious and cultural differences. Although there is a very active private and public health sector that is generally available to the people, because of a very poor public health system and poor adherence to regulations, treatment practices continue to deteriorate over years in the presence of numerous intervention programs. A dwindling economy also plays an important role in health care allocation which is usually skewed towards urban areas, leaving half of Nigeria's population, who live in rural areas, with limited access to health care facilities and pharmacists (SFH, 2012). In most cases, the ability to afford appropriate treatment is not guaranteed as willingness to pay for appropriate drugs can be affected by the ability to also afford other important everyday expenses in each household.

Thirteen years after a change in antimalarial treatment policy, the high awareness among PPMVs was yet to translate to a commensurate increase in the sale of the newly adopted drugs (ACTs). Chloroquine, Fansidar, and other artemisinin monotherapy drugs still flood the medicine stores with urgent consequences for malaria control. Profit is the main motivation behind the sale of drugs for these sellers; so to an extent, awareness of treatment policies does not matter as much in treatment patterns. Having recorded that similar factors such as knowledge of treatment policies that affect medicine stores also affect the clients; exorbitant prices of the ACTs means that most clients wouldn't demand them and this leads to sellers not stocking these drugs. Also, the continued availability of older ineffective antimalarial drugs in the market has created options for malaria treatment and this needs to be addressed in order to optimize the effect of ACTs in fighting the disease.

Nigeria's domestic pharmaceutical production is a growing industry, and it represents about 30% of the country's pharmaceutical needs (SFH, 2012); however, the other 70% is primarily imported from China and India via drug traders who have a reputation for smuggling drugs through Niger and Benin, or repackaging expired drugs from neighbouring countries (Oluwatuyi and Ileri, 2014). Hospitals are also vital in the treatment of malaria, especially where there is short waiting time and the location is easily accessible (Salawu *et al.*, 2016).

The purpose of the quantitative, descriptive, non-experimental part of this research was to investigate the association between residents of two Southwestern states (Lagos and Osun) and factors that can act as barriers to effective malaria case management such as (a) socio-demographics of residents and (b) stated willingness to pay for the ACT and actual payment. The quality of antimalarial drugs normally available for residents at the medicine stores (including pharmacies and drug vendors) in these areas were further investigated using FT-IR and *in vitro* culture to check for counterfeit and substandard drugs respectively.

7.2 Research question 1

Does the socio-demographics of residents in these regions, as defined by age, educational level, residence, and stated willingness to pay, have an association with barriers to malaria case effective management and their malaria treatment-seeking behaviour (as defined by percentage of people who self-medicate or/and are treated with drugs outside the adopted recommendations)?

Self-medication is still a very common practice in Nigeria and it is a major barrier to malaria case effective management. This study found a statistically significant association ($p < 0.01$) between education level, employment status, salary earned monthly and appropriate diagnosis before treatment in urban areas. However, this significant association was not recorded in the studied rural areas and hence all residents of the rural areas have an equal probability of self-medicating. The results of this study align with a study conducted by Onwujekwe *et al.*, (2009) that found that home-based care and self-prescribing were common practices amongst adults and child caretakers, with patients often starting self-treatment with drugs from the commercial sector and then turning to the formal health providers, if needed. Also, in a study by Jombo *et al.,* (2011), low educational levels, low family incomes, and lack of jobs were important contributory factors towards the people's resolve to self-medication for malaria. This study has shown that not only is self-medication more prevalent in the rural areas of Nigeria; in confirmation with what was recorded by Arikpo *et al.,* (2009), Abasiubong *et al.*,

(2012), Bonti, (2017), and Ayanwale *et al.,* (2017), education level and employment status does not play a role in influencing treatment practice. Numerous intervention programmes in the urban areas are positively influencing residents with regard to malaria diagnosis. A similar result was also found with regard to antimalarial used for treatment since there was a statistically significant association ($p < 0.01$) between education level, employment status, salary earned monthly and appropriate malaria treatment with an ACT only in urban areas; as also noted in other studies (Chatio *et al.,* 2015); Efunshile *et al.,* 2013). The lower salary range of people who reside in the rural areas compared to those that live in the urban areas means that affordability of recommended drugs in the rural areas is a challenge. The cost of ACTs is up to 20 times that of other conventional antimalarial drugs such as chloroquine and sulphadoxine-pyrimethamine used for the treatment of uncomplicated malaria. As a consequence, people in rural areas are unable to afford the high cost of ACT, bearing in mind that being in employment in rural areas is not as economically advantageous as in urban areas. However, when association was calculated using salary earned, there was still no significant association.

7.3 Research Question 2

Is the type of medicine store where treatment is sought (pharmacy store and PPMV) associated with adherence to recommended malaria treatment practices?

This part of the research was done to illustrate the practical realities in the treatment of uncomplicated malaria in public and private health facilities in Nigeria, which bears a major impact on implementation of malaria treatment guidelines. This study has shown that drug sellers still maintain a treatment pattern that is outside the WHO recommendations. Pharmacists are expected to run a legal and trusted business; however, this is not always the case. PPMVs usually do not have the necessary qualifications but have been allowed to administer antimalarials for better coverage of treatment. A lot of these sellers are introduced to the business from a variety of backgrounds unconnected with having adequate knowledge of illness perception and management, making effective malaria control impracticable (Treleaven *et al.,* 2015; Beyeler *et al.,* 2015). Also, some pharmacists leave their stores to be manned by an inexperienced apprentice, potentially exposing visiting patients to wrong prescriptions. These factors are likely to contribute to inappropriate dispensing of antimalarial drugs, especially where some of the clients do not have a prescription and are naïve of what malaria first-line treatment is. Supported by Isiguzo *et al.,* (2004), pharmacy stores are more

likely to stock and sell ACTs than PPMVs, which would have been encouraging if more people didn't visit PPMVs for treatment. Also, self-medication was high in both medicine stores across the four regions which was also found by others (Ayanwale *et al.,* 2017; Babatunde *et al.,* 2016). This undermines therapeutic efficacy and may promote the emergence and further spread of drug-resistance. In reality, access to ACTs is still very poor and most cases of malaria are still treated with chloroquine by the PPMVs. Furthermore, chloroquine drugs and other monotherapy were administered commonly, a finding consistent with earlier studies in Nigeria (Onwujekwe *et al.,* 2009). This large number of chloroquine and SP treatments indicates that clients have a bigger influence in dictating the drugs they want and sellers are primarily motivated by their need to make profit and not by any wish to provide a public health good. It was encouraging to observe in this study that the preference for ACTs by the sellers was increased from that recorded by Mangham-Jefferies *et al.,* (2014) were 69% of providers had a preference for ACT; though alternatives included quinine and artemisinin-monotherapy, which according to the WHO recommendations, should be reserved for cases of severe malaria, and sulphadoxine-pyrimethamine, which was the former first-line treatment. However, awareness and preference of ACTs did not prevent some sellers from selling unrecommended drugs. Training can have an effect that goes beyond informing providers about treatment policy and can influence their preferences over different treatments; as having access to guidelines is not a good predictor that providers will supply the recommended treatment. The results of this study however suggest that more punitive and strict measures are required to ensure that medicine sellers adhere to the recommendations of the WHO and FMoH.

7.4 Research Question 3

Are hospital caregivers adhering to the recommended treatment policies?

The results of this study show an encouraging pattern of adherence to the Test, Treat, and Track strategy (3Ts) as recommended by the WHO. The 3Ts strategy was initiated to effectively manage all suspected cases of malaria; starting with proper diagnosis with the use of RDTs or microscopy, treatment with recommended ACT if the result is positive and then full documentation. In this study, a high rate (mean = 97.25% across the four regions) of compliance to this recommendation was observed; an improvement from what was recorded by Meremikwu *et al* (2007), which reported a laboratory test rate of 45%. The use of laboratory techniques for diagnosis has proven to be effective (Mukry *et al.,* 2017; WHO,

2006; Odugbemi *et al.*, 2018), however over the years its use has been generally poor; whether due to limited availability, or lack of trust. This has been a major barrier to the effective management of suspected malaria cases. For example, Ezenduka *et al.*, (2014) describes the use of laboratory diagnosis for malaria treatment in the two facilities where a study was done to be limited to 49%, with health providers depending on presumptive diagnosis, contrary to the test and treat recommendations of current guidelines. This result can be linked with the high rate of over-diagnosis (Ezenduka *et al.*, 2014) and wrong prescription methods (Uzochukwu *et al.*, 2010; Chitakata *et al.*, 1998) in the hospitals in Nigeria. It also reflects the level of confidence and popularity to which prescribers attach to presumptive malaria treatment. Findings by Onwujekwe *et al*., (2009) and Uzochukwu *et al*., (2010), confirm this, in which over 80% and 51.1% respectively, of healthcare providers are confident in clinical diagnosis of malaria, including those at the hospitals. This therefore shows that there is an improvement since these studies have been done. However, it should be noted that these studies were conducted in the south-eastern part of the country, so other factors such as level of awareness could have affected the difference. Aside from time wastage; morbidity and drug resistance are very common consequences that have been attributed to wrong diagnosis. This accentuates the urgent need for intensified efforts at promoting the use of RDTs to detect malaria parasites before treatment is offered. In addition, the findings of this study showed a clear preference for ACT as the drug of choice for uncomplicated malaria at these facilities, which is an indication of compliance with policy recommendation. However, some negative cases were still treated with an antimalarial, contrary to the recommendations of the WHO. Reasons why some negative cases were treated for malaria are believed to include the unreliability of laboratory results due to poor laboratory reagents and also RDT insensitivity.

Finally, a larger percentage of participants in the rural regions that suspected that they had malaria were actually confirmed to have malaria. This observation is undoubtedly a wake-up call for policy makers and the government (both nationally and locally), to intensify their effort in these regions on the eradication of malaria. The link provided in this study is that those who live in the rural areas are more prone to malaria infection and unfortunately, they mostly self-medicate, seek cheap treatment from unlicensed providers and are more likely exposed to counterfeit or substandard drugs.

7.5 Substandard/fake antimalarial drugs

In a country where nearly half the population is illiterate, poverty is still rampant and consumer awareness is low, the spread of fake and substandard drugs is a cause for alarm. The presence of counterfeit drugs shown in this study corroborates earlier reports (Bassat *et al.,* 2016); albeit, this research has only found some SPs and chloroquine tablets to be counterfeit. Although this study did not find an ACT to be counterfeit, similar to Izevbekhai *et al.,* (2017) it should be noted that the number of drugs assessed is smaller than those tested in other studies. However, of concern was the finding that some ACTs acquired from the rural regions showed less efficacy when compared to other ACTs (either same or different brands). This also confirms the report of Kelesidis, & Falagas, (2015) that cheap drugs are major targets for counterfeit makers because, in a poor region, there is a bigger market for fake and cheap drugs. The situation is worsened by the fact that the government and many pharmaceutical companies are reluctant to publicize the problem to health staff and the public, apparently motivated by the belief that the publicity will harm the sales of brand-name products in a fiercely competitive business. They argue that publicly attacking these fake drugs could prevent patients taking their genuine medicines (Cookburn 2005). This is unacceptable, as the continuous use of these drugs has potentially killed a number of citizens, or at the very least worsened, or caused, their illness. It is, however, imperative that the physicians, government, regulatory authorities, and pharmaceutical companies prioritize a habit of alerting key audiences, stakeholders and the general public about counterfeit medicines in communities and across countries. This would send a signal across borders that the health and good living of patients takes priority over the reputation of pharmaceutical companies. In support of this, Cockburn *et al.,* (2007) urges a change to mandatory reporting to governmental authorities, which should also have a legal duty to investigate, issue appropriate public warnings, and share information across borders. This is not a role for the pharmaceutical industry due to a serious conflict of interest.

7.5.1 Actions to reduce fake drugs

Considering that some fake drugs were found from the small sample size of drugs tested, the need for a more intensive fight against drug proliferation cannot be over-emphasised. Also, there is an urgent need for data of sufficient sample size with random sampling design to reliably estimate the prevalence of poor-quality medicines in these regions and across the country as a whole. In a study by Oladepo *et al.,* (2007) asking for suggestions from PPMVs on how to stop the counterfeit market, a substantial proportion of PPMVs (64%) said that

stronger government regulation was needed to minimise the availability of fake drugs, while nearly a quarter called for PPMV self-regulation through the associations. It is vital to invest in the strengthening of medicine regulatory authorities, especially NAFDAC. The mandate of the NAFDAC, which includes safeguarding the health of the public, increase supply of quality medicines into the Nigerian health system and fight against counterfeit and sub-standard medicines in the drug supply chain has been boosted by the collaboration with the United States Pharmacopeia (USP), with the assistance of the United States Agency for International Development (USAID), in an agreement to work on a road map that will act as a guide towards ensuring the quality monitoring of medicines in Nigeria. Also, determination from political office holders and a clear coordinated role between the police, customs officials and NAFDAC is crucial. The benefit of this has been recorded by the successful investigation into counterfeit medicine in other countries (Newton *et al.*, 2008; Cockburn *et al*., 2007). Unfortunately, being a poor developing country, there is limited access to the wide range of sophisticated quality-assurance markers and machines have been developed in other developed countries. As rightly mentioned by Newton *et al.*, (2010), support for Medicine Regulated Authorities (MRAs) and the development of regional laboratories to allow the regulation of the drug supply will be crucial to allow interventions. The good news is that not as much effort in combating counterfeit drugs is needed to curb substandard drugs. Actions required in this case may be more direct because malicious/criminal intent is not involved; however, these interventions will involve costly improvements in manufacturing companies and periodical inspections.

7.5.2 Possible intervention actions

Possible intervention actions to improve the present situation will have to address a number of inter-related factors. Very importantly, interventions need to address the lack of knowledge about appropriate diagnosis and treatment, which will require continuous training of medicine sellers (PPMVs and pharmacy store owners) and educating the public. As this research has shown an improved adherence to treatment policy in the hospitals in the two study regions, it highlights that continuous training and the ability to hold treatment providers responsible when they go against recommendations should be adopted. This will involve the design of strategies for communicating with a variety of audiences including government regulators, boards of pharmacists and PPMVs, doctors, and community members. These strategies will have to take into account the fact that a substantial proportion of PPMVs obtain information from drug suppliers, rather than government. They also need to take into account the many

inter-state differences in the characteristics of PPMVs and the market within which they operate. Better still, pharmacy stores and hospitals should be better equipped and managed to have the capacity for treating malaria on a larger scale. This will mean that PPMVs can continue to sell only 'over the counter medicine' which was the initial plan when they were created. As Oladepo (2017) has advised, measures like this may require innovative approaches to explain reasons for radical changes in what has been proposed as appropriate treatments for malaria. If this can be successfully achieved, then there would be less worry over the spread of counterfeit and substandard drugs that are usually supplied by PPMVs. With regard to fake and substandard drugs, a lot of work will be required to promote effective partnerships between government regulators and these associations. A study has shown that strong support by PPMVs, government policy-makers and members of the community for an increased role of communities in monitoring drug quality (Beyeler *et al.*, 2015). To successfully achieve this, community members should be trained and have enough information on how to identify fake drug packages and what to look out for. This will also involve training people to undertake these tasks, which could include looking for NAFDAC registration and expiry dates. Technology wise, it is high time the country invested in new simple technologies for testing drugs or scanning product identification, or for utilising information and communications technology to be able to provide real-time support to PPMVs and regulators could also be considered. Something like this was introduced recently that enables a reference number on a drug to be sent to a number and this provides information about the drug, including the expiry date. Unfortunately, although this in an improvement, the drug information is received following a delay (up to 24 hours) and this is not good enough considering the urgency required for treating malaria infections. Within this time frame, a patient could have used a fake antimalarial, or an expired antimalarial. The impact of subsidy of ACTs cannot be over-emphasised and people have argued that instead of subsidy at local level, it should be done globally (Laxminarayan *et al*., 2006; Arrow *et al*., 2005). The issue with this is, even with endemic regions, economic status plays a vital role in the treatment pattern. ACT subsidy needs to be a function of a particular group of people to understand how much most people would be able to afford. For example, the price at which ACT subsidy would make a significant difference in treatment pattern in Lagos urban would not necessary make an impact in Osun rural.

7.6 Conclusions, recommendations and future directions

Studies of this nature are intended to provide insight for further investigation and intervention and are often therefore limited in what they are able to conclude. The study involved cross-sectional and retrospective assessments and hence follow-up studies will be needed to capture changes over time to better identify factors that are causally related to improve knowledge or treatment of malaria. The inferences in this study were derived from interviews and observations of communities, drug outlets and hospitals. Notwithstanding these limitations, these studies allowed identification of more focused questions for research and intervention, which remains challenging in a weakly regulated environment. Also, later studies should recruit a larger number of participants than this study has, to create a larger sample set to be analysed; results would then be more conclusive. In addition, a more representative drug sample set should be tested for *in vitro* efficacy to allow conclusions on what is happening across regions and therefore allow more widespread recommendations to be provided.

It has been established that ACT is the best and most effective antimalarial on the market. It is also the recommended first line therapy for uncomplicated malaria in several countries, especially sub-African countries. Although limited, the preliminary findings of this study on the field is that the ACT regulations have been good over the years. This is good news considering ACTs have been the first line treatment drugs for malaria; however, a depreciating economy means the price of ACTs are unbearable in the region; forcing citizens to go for cheaper drugs. This therefore moves the spotlight to other non-ACTs and thus creates malpractices; for example, they become a target for counterfeiting. The benefits of subsidised ACTs, which was noticed in the past, are beginning to wear out because of the recent huge increase in ACT price; forcing even working people to struggle with its use. Malaria control programs should put into consideration the findings of this study while developing targeted interventions to improve treatment pattern. To begin with, the government needs to implement programmes that will make ACTs more affordable to the people as well as creating awareness and educating citizens of the recommended drugs and the dangers of using other antimalarials that are not ACTs. As already advised by Oyeyemi *et al.*, (2015), the Pharmacists Council of Nigeria (PCN) should without further delay revise the approved list of antimalarial drugs that PPMVs are allowed to sell and the government should initiate effort to withdraw non-ACT antimalarials from the market. Also, to maintain long-term efficacy there is a need to train healthcare providers on appropriate dosing and dispensing of ACTs. The poor adherence that was recorded in this study, especially in the

retail sector, calls for more efforts to improve adherence to ACTs both in the urban and rural areas. Barriers to adherence should be addressed because nonadherence could be a platform for the development of antimalarial resistance. At community level people should be educated on the adverse effects and implications of poor adherence to ACT. Healthcare providers, policy makers, and other stakeholders involved in malaria control programs should take note of these findings when designing targeted interventions to improve ACT adherence. Educational programmes to increase awareness and understanding of ACT dosing regimen are interventions urgently needed to improve adherence to ACTs. Patients, or caregivers, should be provided with an adequate explanation at the time of prescribing and/or dispensing ACTs. Prescribers, dispensers, and vendors should, therefore, give a clear and comprehensible explanation on how to use ACTs. User-friendly packaging (e.g., blister packs) should be used to encourage completion of the treatment course and correct dosing.

8 APPENDIX

Appendix I: Consent and Questionnaires

Community perspective on malaria treatment.

The main aim of this research is to qualitatively and quantitatively analyse malaria chemotherapeutic practices and outcomes at an individual and community level in three selected states (Lagos, and Osun) in the Southwest region of Nigeria in a bid to define barriers to effective malaria case management.

SECTION 2: CONSENT FORM

I confirm that I have read/been explained to and understood the information presented above about the purpose and nature of this study.

I have also had the opportunity to clarify any doubts with _____.

I understand that my participation will involve answering some questions related to my knowledge and opinions about malaria treatment.

I understand that my participation is voluntary and that I can withdraw my consent at any time without prejudice to my rights.

I understand that the interviews will be noted down in the questionnaire for the purpose of analysis.

I understand that my confidentiality will be protected.

I hereby consent to participate voluntarily in this study.

----------	----------	----------
Name of Participant	Signature of Participant	Date
----------	----------	----------
Name of witness	Signature of witness	Date

State…….

GPS location……

Rural/Urban……

Code…….

1**. Sex**: Male □ Female □

2. **Age group**: 16-20 □ 20-25 □ 26-30 □ 30 and above □

3. **Marital status:** Single □ Married □ Divorced/Widowed □

4. **Educational level:** Primary □ Secondary □ Tertiary □ none □

5. **Socio-economic status:** *(Please tick which of the following you possess)*

Car □ Television □ Generator □ Computer □ Owned apartment □

Employed □ Unemployed □

Salary earned per Month: ₦0 - ₦10,000 □ ₦10,000 - ₦50,000 □ ₦50,000 and above □

6. **How much are you willing to pay for treatment?**

Less than ₦500 □ More than ₦500 □

7. **When was the last time you had malaria?**

Within the past 1 month □ within the past 6 months □ within the last 1 year□ can't remember □.

8. **How often do you have malaria in a year?**

Less than 5 times in a year □ Between 5 and 10 times a year □ More than 10 times in a year □

9. **Treatment sorted**: Amatem □ Coartem □ Leonart □ combiart □

choloquine □ Fansidar □ Herbal (*please name*)……. others *(please name*……..

10**. Were you diagnosed before treatment? (Microscopic and others)**

Yes □ No □ I don't know □

11. Where did you get treatment from?

Hospital □ Drug vendors □ Pharmacy store □ did not get treated □ others □

12. How often do you complete your antimalarial dosage?

Always □ Most times □ I stop when I feel better □

Pharmacy store questionnaire

The main aim of this research is to qualitatively and quantitatively analyse malaria chemotherapeutic practices and outcomes at an individual and community level in three selected states (Oyo, Lagos, and Osun) in the Southwest region of Nigeria in a bid to define barriers to effective malaria case management.

SECTION 2: CONSENT FORM

I confirm that I have read/been explained to and understood the information presented above about the purpose and nature of this study.

I have also had the opportunity to clarify any doubts with _____.

I understand that my participation will involve answering some questions related to my knowledge and opinions about malaria treatment.

I understand that my participation is entirely voluntary and that I can withdraw my consent at any time without prejudice to my rights.

I understand that the interviews will be noted down in the questionnaire for the purpose of analysis.

I understand that my confidentiality will be protected.

I hereby consent to participate voluntarily in this study.

| --- | --- | --- |
Name of Participant	Signature of Participant	Date
Name of witness	Signature of witness	Date

State…….

GPS location……

Rural/Urban……

Code…….

1. Educational level of pharmacist/drug vendor: Primary □ Secondary □ Tertiary □ none □
2. Which Antimalarial drug do you mostly prescribe to clients?

Amatem □ Coartem □ Leonart □ combiart □ choloquine □ Fansidar □

Others *(please provide with the name)* ……..

……

3. Sex of client: Male □ Female □
4. Has the client shown any proof of diagnosis? Yes □ No □
5. Is the client self-medicating? Yes □ No □
6. Which Antimalarial drug was purchased by client?

Amatem □ Coartem □ Leonart □ combiart □ choloquine □ Fansidar □

Others *(please provide with the name)* ……..

7. Did the pharmacist influence the decision in which drug to buy?

Yes □ No □

8. Price of Antimalarial drug purchased by client? ₦……..

Hospital questionnaire

The main aim of this research is to qualitatively and quantitatively analyse malaria chemotherapeutic practices and outcomes at an individual and community level in three selected states (Oyo, Lagos, and Osun) in the Southwest region of Nigeria in a bid to define barriers to effective malaria case management.

SECTION 2: CONSENT FORM

I confirm that I have read/been explained to and understood the information presented above about the purpose and nature of this study.

I have also had the opportunity to clarify any doubts with _____.

I understand that my participation will involve answering some questions related to my knowledge and opinions about malaria treatment.

I understand that my participation is entirely voluntary and that I can withdraw my consent at any time without prejudice to my rights.

I understand that the interviews will be noted down in the questionnaire for the purpose of analysis.

I understand that my confidentiality will be protected.

I hereby consent to participate voluntarily in this study.

----------	----------	----------
Name of Participant	Signature of Participant	Date
----------	----------	----------
Name of witness	Signature of witness	Date

State…….

GPS location……

Rural/Urban……

Code…….

Number of patients suspected to have malaria…….

Suspected malaria patients in whom any test was carried out…….

Suspected malaria patients assessed clinically only…….

Suspected malaria patients tested by microscopy……

Suspected malaria patients tested by RDT……...

Cases appropriately tested using (RDT + Microscopy)……...

Suspected malaria patients found to be negative……..

Confirmed negative cases treated with antimalarial…….

Negative cases not given antimalarial……..

Cases found to be malaria positive……...

Positive cases appropriately treated with ACT……

Positive cases treated with quinine……...

Positive cases treated with SP……..

Positive cases not treated with antimalarial…….

Appendix II: Ethical Approvals

Academic Audit and Governance Committee

College of Science and Technology Research Ethics Panel (CST)

To **Oluwafemi Olanrewaju AKINSOLA (and Dr Niroshini Nirmalan / Dr Debapriya Mondal)**

cc: **Professor Judith Smith, Head of School of ELS**

MEMORANDUM

From **Nathalie Audren Howarth**, **College Research Support Officer**

Date 27/07/2015

Subject: **Approval of your Project by CST**

Project Title: **Qualitative and Quantitative Evaluation of Antimalarial Chemotherapeutic Practices and Outcomes in the Southwest Region of Nigeria.**

REP Reference: **CST 15/32**

Following your responses to the Panel's queries, based on the information you provided, I can confirm that they have no objections on ethical grounds to your project.

If there are any changes to the project and/or its methodology, please inform the Panel as soon as possible.

Regards,

[redacted]

Nathalie Audren Howarth

College Research Support Officer

MINISTRY OF HEALTH, OSOGBO

HEALTH PLANNING RESEARCH AND STATISTICS DEPARTMENT

PRIVATE MAIL BAG NO. 4421, OSOGBO, OSUN STATE OF NIGERIA

Your Ref. No.....
All communication should be addressed to the
Permanent Secretary quoting

12th August, 2015

OSHREC/PRS/569T/48

Dr. Olufemi Olanrewaju Akinsola,
Plot 16B Adedapo Adejoke Street,
Oroki Estate,
Osogbo, Osun State.

THE QUANTITATIVE AND QUALITATIVE EVALUATION OF MALARIA CHEMOTHERAPEUTIC

I wish to inform you that the Osun State Health Research Ethics Committee (OSHREC) has granted you an approval to proceed on the above exercise.

The approval lasts one (1) year spanning August 4, 2015 and 10 August 2016. You are to inform the committee the starting date of the exercise. If there is any delay in starting, kindly inform the Committee to enable it adjust the date accordingly. This will equally allow for monitoring by designated representative of the Committee.

Regard this letter as Certificate of OSHREC approval.

Thank you.

[redacted]
Dr. Tope Oladele
Chairman
(OSHREC)

LAGOS STATE MINISTRY OF HEALTH

INSTITUTION REVIEW BOARD, LAGOS STATE UNIVERSITY TEACHING HOSPITAL
P.M.B 21005, IKEJA, LAGOS STATE, NIGERIA
Website: www.lasuth.org.ng

Ref. No: LREC/10/15/418

Date: 23rd November, 2015

Olufemi Olanrewaju Akinsola,
Plot 16B Adedapo Adejoke Street,
Oroki Estate,
Osogbo, Osun State.

THE QUANTITATIVE AND QUALITATIVE EVALUATION OF MALARIA CHEMOTHERAPEUTIC

This is to inform you that the Institution Review Board of the Lagos State University Teaching Hospital through the office of the Permanent Secretary, Ministry of Health, Lagos State has approved that you can proceed on your research as above.

The research approval will be for a period of one year only from the 23rd of November, 2015 to 25th of November, 2016. Please be informed that you will be guided and monitored accordingly during this process by representatives of the board.

Thank you.

[redacted]
Dr. Modele Osunkiyesi
Permanent Secretary

Appendix III: Tables showing hospital data, community data, and drug store data

	LAGOS STATE		OSUN STATE	
HOSPITAL DATA (MAY - SEPTEMBER)	URBAN	RURAL	URBAN	RURAL
Number of patients suspected to have malaria	1546	941	1359	456
suspected malaria patients in whom any test was carried out	1546	941	1327	456
suspected malaria patients assessed clinically only	74	9	30	0
suspected malaria patients tested by microscopy	0	0	45	20
suspected malaria patients tested by RDT	1472	932	1300	440
cases appropriately tested using (RDT + Microscopy)	0	0	45	20
suspected malaria patients found to be negative	769	253	691	87
confirmed negative cases treated with antimalarial	140	0	15	0
negative cases not given antimalarial	629	253	1173	87
cases found to be malaria positive	536	688	636	369
positive cases appropriately treated with ACT	449	597	564	290
positive cases treated with quinnine	51	57	30	45
positive cases treated with SP	36	34	42	34
positive cases not treated with antimalarial	0	0	0	0

Community result Lagos Urban

Participan	Sex M/F	Age group	M.status	Education	Employer	Salary	propertie	WTP (₦)	History	cases/yea	Treatment	Diagnosed?	Place where treated	completion of dosage?
1	F	1	S	S	U	2		₦500	2	2	Fansidar	No	Drug vendors	I stop when I feel better
2	M	2	S	S	U	2		₦500	0	1	Fansidar	No	Drug vendors	Most times
3	F	3	S	T	E	3		>₦500	3	1	Amatem	No	Drug vendors	Always
4	M	4	M	S	E	2		₦500	2	1	Herbal (Agbo iba)	No	Others	Most times
5	F	3	S	T	E	3		>₦500	0	1	Coartem	No	Pharmacy store	Always
6	M	4	M	T	E	3		>₦500	1	1	Amatem	No	Pharmacy store	Always
7	F	3	S	S	E	2		₦500	0	1	Chloroquine	No	Drug vendors	Most times
8	M	4	M	T	E	3		>₦500	0	1	Lonart	Yes	Hospital	Always
9	M	4	M	T	E	3		>₦500	0	1	Lonart	Yes	Pharmacy store	Always
10	M	4	M	T		3		>₦500	0	1	Lonart	Yes	Hospital	Always
11	F	4	M	T	E	3		>₦500	2	1	Coartem	Yes	Hospital	Always
12	M	3	S	T	E	3		>₦500	0	1	Coartem	Yes	Hospital	Always
13	M	4	M	T	E	3		>₦500	0	1	Lonart	Yes	Hospital	Always
14	F	4	M	T	E	3		>₦500	0	1	Coartem	No	Pharmacy store	Always
15	F	3	S	T	E	3		>₦500	0	1	Amatem	Yes	Hospital	Always
16	M	4	M	T	E	3		>₦500	0	1	Lonart	Yes	Hospital	Always
17	M	4	M	T	E	3		>₦500	0	1	Coartem	No	Pharmacy store	Always
18	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
19	F	3	S	T	E	3		>₦500	1	1	Chloroquine	Yes	Hospital	Always
20	M	2	S	S	U	2		₦500	0	1	Fansidar	No	Drug vendors	Most times
21	M	3	S	T	E	3		>₦500	0	1	Fansidar	No	Pharmacy store	Most times
22	M	4	S	T	E	3		>₦500	0	1	Amatem	Yes	Hospital	Always
23	M	4	M	T	E	3		>₦500	2	1	Herbal (Agbo iba)	No	Others	I stop when I feel better
24	M	3	S	T	E	3		₦500	2	1	Lonart	No	Pharmacy store	Most times
25	F	2	M	N	U	1		<₦500	1	2	Chloroquine	No	Drug vendors	I stop when I feel better
26	F	4	S	T	E	3		<₦500	0	1		I don't know	No treatment	
27	F	4	S	T	E	3		>₦500	1	1	Chloroquine	Yes	Hospital	I stop when I feel better
28	M	4	M	T	E	3		>₦500	2	1	Coartem	Yes	Hospital	Always
29	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Pharmacy store	I stop when I feel better
30	M	2	S	T	U	1		₦500	2	1	Fansidar	No	Drug vendors	I stop when I feel better
31	F	4	M	T	E	3		₦500	0	1	Amatem	Yes	Hospital	I stop when I feel better
32	M	4	S	T	E	3		>₦500	2	1	Coartem	Yes	Pharmacy store	Always
33	F	4	M	T	E	3		>₦500	0	1	Fansidar	No	Hospital	Always
34	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
35	F	4	M	T	E	3		<₦500	0	1	Amatem	No	Pharmacy store	Always
36	F	4	M	T	E	3		>₦500	2	1	Chloroquine	Yes	Hospital	Always
37	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
38	M	3	S	T	E	3		>₦500	0	1	Fansidar	Yes	Pharmacy store	Always
39	F	3	M	T	E	3		>₦500	0	1	Coartem	Yes	Hospital	Always
40	F	3	S	T	S	3		>₦500	0	1	Coartem	Yes	Hospital	Always
41	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
42	M	4	M	S	E	3		₦500	2	1	Amatem	I don't know	Hospital	I stop when I feel better
43	M	4	M	T	E	3		>₦500	0	1	Lonart	Yes	Hospital	Always
44	M	2	M	S	U	1		<₦500	1	2	Fansidar	No	Drug vendors	Most times
45	F	4	M	T	E	3		>₦500	0	1	Chloroquine	Yes	Hospital	Always
46	M	4	M	T	E	3		>₦500	2	1	Lonart	No	Pharmacy store	Always
47	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
48	M	4	M	T	E	3		>₦500	3	1	Lonart	No	Pharmacy store	Always
49	M	3	S	T	E	3		>₦500	2	1	Lonart	No	Pharmacy store	Most times
50	F	3	S	T	E	3		<₦500	2	1	Lonart	Yes	Hospital	Always
51	M	3	S	T	S	3		<₦500	2	1	Coartem	No	Pharmacy store	Always
52	F	3	S	T	E	3		<₦500	2	2	Lonart	Yes	Pharmacy store	Most times
53	F	2	S	T	E	2		₦500	2	1	Amatem	No	Hospital	I stop when I feel better
54	M	1	S	T	U	1		<₦500	2	1	Artesunate	I don't know	Pharmacy store	Most times
55	F	3	S	T	E	3		>₦500	2	2	Lonart	Yes	Pharmacy store	Always
56	M	3	S	T	E	3		>₦500	0	1	Amatem	Yes	Pharmacy store	Always
57	M	4	S	T	E	3		>₦500	0	1	Chloroquine	No	Pharmacy store	Most times
58	M	3	S	T	E	3		>₦500	1	1	Lonart	Yes	Hospital	Always
59	M	3	S	T	E	3		>₦500	2	1	Amatem	Yes	Drug vendors	Most times
60	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
61	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
62	M	3	M	T	E	3		>₦500	2	1	Fansidar	No	Pharmacy store	Always
63	M	3	S	T	S	3		>₦500	0	3	Amatem	No	Drug vendors	Most times
64	M	4	M	T	E	3		>₦500	0	1	Lonart	Yes	Hospital	Always
65	M	4	M	T	E	3		>₦500	0	1	Fansidar	Yes	Hospital	Most times
66	F	4	M	T	E	3		>₦500	0	1	Fansidar	No	Hospital	Always
67	M	1	S	N	S	1		<₦500	1	2	Chloroquine	No	Pharmacy store	I stop when I feel better
68	F	4	S	T	E	3		>₦500	0	1	Fansidar	No	Pharmacy store	I stop when I feel better
69	M	3	S	T	E	3		>₦500	0	1	Lonart	Yes	Hospital	Always
70	M	3	S	T	E	3		>₦500	0	1	Lonart	No	Pharmacy store	I stop when I feel better
71	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
72	M	2	S	S	S	2		₦500	0	3	Amatem	No	No treatment	
73	F	3	S	T	E	3		>₦500	0	1	Fansidar	No	Pharmacy store	Always
74	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
75	M	4	M	T	E	3		>₦500	0	2	Lonart	Yes	Pharmacy store	Most times
76	M	3	S	T	E	3		>₦500	0	2	Lonart	Yes	Pharmacy store	Most times
77	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
78	M	3	M	T	E	3		>₦500	2	2	Amatem	Yes	Hospital	Most times
79	M	4	M	T	E	3		>₦500	0	2	Coartem	No	Pharmacy store	I stop when I feel better
80	M	3	S	S	E	2		₦500	2	3	Herbal (Agbo iba)	No	Others	I stop when I feel better
81	M	2	S	N	U	1		<₦500	1	2	Chloroquine	No	Drug vendors	I stop when I feel better
82	M	4	M	T	E	3		₦500	0	1	Coartem	Yes	Hospital	Always
83	M	3	S	T	E	3		>₦500	0	1	Coartem	Yes	Pharmacy store	Most times
84	M	4	M	T	E	3		>₦500	2	1	Fansidar	No	Pharmacy store	Always
85	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
86	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
87	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
88	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
89	F	3	M	T	U	1		<₦500	0	1	Fansidar	No	Others	I stop when I feel better
90	F	4	M	T	U	2		>₦500	2	2	Fansidar	Yes	Hospital	Most times

91	F	4	M	S	E	2		<₦500	2	1	Chloroquine	No	Pharmacy store	Always
92	F	3	S	T	E	1		<₦500	1	1	Coartem	Yes	Hospital	Most times
93	F	2	S	S	E	1		<₦500	2	1	Amatem	I don't know	Hospital	I stop when I feel better
94	M	2	S	T	E	1		<₦500	0	1	Chloroquine	No	Drug vendors	I stop when I feel better
95	M	2	S	T	E	1		<₦500	1	2	Lonart	No	Pharmacy store	Always
96	M	4	M	T	E	2		<₦500	1	1	Herbal	No	Pharmacy store	Always
97	F	4	M	T	E	2		>₦500	0	1	Chloroquine	Yes	Hospital	Always
98	M	3	S	T	E	3		>₦500	1	1	Coartem	No	Drug vendors	Always
99	F	3	M	T	E	2		<₦500	1	1	Chloroquine	Yes	Drug vendors	Always
100	F	4	S	T	U	1		<₦500	1	2	Chloroquine	No	No treatment	
101	M	2	S	T	U	1		<₦500	0	3	Lonart	I don't know	Pharmacy store	I stop when I feel better
102	M	1	S	S	U	1		<₦500	0	3	Chloroquine	Yes	Hospital	I stop when I feel better
103	F	1	S	S	U	1		>₦500	0	1	Herbal	I don't know	Hospital	Always
104	M	1	S	S	U	1		<₦500	0	1	Coartem	I don't know	Others	I stop when I feel better
105	F	2	S	S	U	1		<₦500	1	1	Amatem	Yes	Hospital	I stop when I feel better
106	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
107	F	3	S	S	U	1		<₦500	0	1	Fansidar	I don't know	Pharmacy store	I stop when I feel better
108	F	2	S	S	U	1		>₦500	2	1	Herbal	Yes	Drug vendors	Always
109	F	3	S	N	U	2		>₦500	1	2	Lonart	Yes	Pharmacy store	Most times
110	F	4	S	T	E	1		<₦500	0	1	Chloroquine	Yes	Hospital	I stop when I feel better
111	M	1	S	S	U	1		<₦500	2	1	Coartem	Yes	Drug vendors	I stop when I feel better
112	M	1	S	S	U	1		<₦500	0	1	Chloroquine	Yes	Hospital	Always
113	F	2	M	N	U	1		<₦500	1	2	Chloroquine	No	Drug vendors	I stop when I feel better
114	M	4	S	T	U	1		<₦500	2	1	Herbal	I don't know	Drug vendors	I stop when I feel better
115	M	2	S	T	E	1		<₦500	0	1	Lonart	I don't know	Hospital	I stop when I feel better
116	F	3	M	T	E	2		>₦500	1	1	combiart	I don't know	Drug vendors	I stop when I feel better
117	F	2	S	P	U	1		<₦500	1	2	Fansidar	No	Pharmacy store	I stop when I feel better
118	F	1	S	S	E	2		<₦500	1	1	Chloroquine	Yes	Drug vendors	Most times
119	F	4	S	T	E	2		>₦500	1	2	Herbal	No	Pharmacy store	Always
120	F	1	S	S	E	2		>₦500	1	2	Lonart	I don't know	Hospital	I stop when I feel better
121	M	3	M	T	E	2		<₦500	1	2	Chloroquine	Yes	Drug vendors	Most times
122	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
123	M	4	M	S	S	2		>₦500	0	1	combiart	I don't know	Hospital	I stop when I feel better
124	F	3	M	T	E	2		>₦500	2	2	Chloroquine	I don't know	Hospital	I stop when I feel better
125	F	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
126	F	2	S	T	U	2		>₦500	0	1	Herbal	I don't know	Hospital	I stop when I feel better
127	M	2	S	T	E	2		>₦500	1	2	Fansidar	Yes	Drug vendors	Most times
128	F	2	S	T	E	1		<₦500	0	1	Chloroquine	No	Drug vendors	Most times
129	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
130	M	2	S	T	U	1		<₦500	0	1	Chloroquine	Yes	Pharmacy store	Always
131	M	3	M	T	E	2		>₦500	2	2	Coartem	Yes	Drug vendors	I stop when I feel better
132	M	2	M	S	U	1		<₦500	1	2	Fansidar	No	Drug vendors	Most times
133	F	3	S	T	E	1		<₦500	0	1	Fansidar	No	Drug vendors	I stop when I feel better
134	M	4	M	T	E	2		>₦500	1	1	Chloroquine	Yes	Hospital	Always
135	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
136	F	1	S	S	U	1		<₦500	0	1	Amatem	No	Pharmacy store	Always
137	F	1	S	S	U	1		<₦500	0	2	Chloroquine	I don't know	Pharmacy store	I stop when I feel better
138	M	4	M	T	E	3		<₦500	2	1	Other	Yes	Drug vendors	Most times
139	F	1	S	P	E	2		<₦500	1	1	Chloroquine	No	Hospital	Always
140	M	1	S	S	E	1		<₦500	1	1	Amatem	I don't know	Hospital	Always
141	F	2	S	T	E	2		<₦500	2	1	Amatem	No	Hospital	I stop when I feel better
142	M	1	S	T	U	1		<₦500	0	1	Chloroquine	I don't know	Pharmacy store	Always
143	M	1	S	S	U	1		<₦500	0	1	Coartem	I don't know	Pharmacy store	Always
144	M	1	S	P	U	1		<₦500	0	1	Chloroquine	No	Hospital	I stop when I feel better
154	F	4	M	T	E	2		<₦500	0	1	Coartem	I don't know	Pharmacy store	I stop when I feel better
146	F	4	M	S	U	2		>₦500	0	1	Coartem	No	Hospital	Always
147	M	1	S	S	E	1		<₦500	0	1	Chloroquine	Yes	Hospital	I stop when I feel better
148	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
149	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
150	M	2	S	T	U	2		<₦500	2	1	combiart	Yes	Hospital	I stop when I feel better
151	M	1	S	S	E	2		<₦500	2	2	combiart	No	Hospital	I stop when I feel better
152	M	3	M	N	U	1		<₦500	1	3	Chloroquine	Yes	Drug vendors	Most times
153	F	4	M	P	E	3		>₦500	1	2	Fansidar	Yes	No treatment	Most times
154	F	2	M	S	U	1		<₦500	2	3	Lonart	Yes	Drug vendors	Always
155	F	2	S	S	U	1		<₦500	0	1	Amatem	Yes	Hospital	Always
156	F	3	S	T	S	1		<₦500	0	1	Chloroquine	Yes	Hospital	I stop when I feel better
157	F	2	S	T	U	1		<₦500	0	1	Chloroquine	No	Drug vendors	Most times
158	F	4	S	S	S	1		>₦500	0	1	Chloroquine	No	Pharmacy store	I stop when I feel better
159	F	4	M	P	S	2		<₦500	1	1	Amatem	I don't know	Drug vendors	I stop when I feel better
160	M	4	M	N	U	1		>₦500	1	1	Amatem	No	Pharmacy store	Always
161	F	4	M	N	S	2		>₦500	0	2	Fansidar	No	Pharmacy store	Always
162	M	4	M	S	S	1		>₦500	2	1	Chloroquine	I don't know	Pharmacy store	Always
163	M	4	M	T	E	1		<₦500	0	1	Lonart	No	Drug vendors	Always
164	M	3	M	S	E	2		<₦500	0	2	Coartem	Yes	Hospital	I stop when I feel better
165	M	4	M	S	U	2		>₦500	1	2	Herbal	No	No treatment	Always
166	M	3	M	S	S	2		>₦500	0	2	Chloroquine	Yes	Hospital	Always
167	F	2	S	T	U	2		>₦500	1	3	Chloroquine	No	Hospital	Most times
168	M	2	S	P	U	1		<₦500	0	1	Chloroquine	No	Hospital	Most times
169	F	2	S	S	U	1		<₦500	1	2	Herbal	No	Pharmacy store	Always
170	M	3	S	S	U	3		>₦500	2	1	Chloroquine	Yes	Drug vendors	Always
171	F	4	M	S	S	1		>₦500	2	2	Amatem	I don't know	Drug vendors	I stop when I feel better
172	M	3	S	T	U	1		<₦500	2	1	Lonart	I don't know	Drug vendors	I stop when I feel better
173	F	4	D	P	E	1		<₦500	0	3	Chloroquine	I don't know	Pharmacy store	Most times
174	F	2	S	P	E	1		<₦500	0	1	Lonart	Yes	Drug vendors	Most times
175	F	1	S	P	U	2		<₦500	1	1	Amatem	I don't know	No treatment	Most times
176	F	1	S	S	E	1		<₦500	0	1	Chloroquine	I don't know	Drug vendors	I stop when I feel better
177	F	1	S	S	U	1		<₦500	0	1	Coartem	No	Drug vendors	I stop when I feel better
178	F	2	S	S	S	1		<₦500	0	1	Chloroquine	No	Drug vendors	Most times

Community result Lagos rural

Participan	Sex M/F	Age group	M.status	Education	Employen	Salary	properties	WTP (₦)	History	cases/yea	Treatment	Diagnosed?	Place where treated	completion of dosage?
1	F	3	M	P	U	1		<₦500	1	2	CHLOROQUINE	No	Pharmacy store	I stop when I feel better
2	F	2	M	P	U	1		>₦500	1	1	CHLOROQUINE	No	Drug vendors	I stop when I feel better
4	F	3	M	T	U	1		<₦500	2	2	FANSIDAR	Yes	Hospital	Always
5	M	2	S	P	U	1		<₦500	0	1	FANSIDAR	No	Drug vendors	Most times
6	M	3	S	S	U	1		<₦500	2	2	CHLOROQUINE	No	Hospital	Always
7	F	4	M	P	U	1		<₦500	2	1	LONART	No	Hospital	Most times
8	M	4	S	P	U	1		<₦500	0	1	CHLOROQUINE	No	Drug vendors	Always
9	M	4	M	P	E	1		<₦500	1	2	NONE	No	Pharmacy store	I stop when I feel better
10	F	4	S	S	E	2		<₦500	2	1	LONART	Yes	Hospital	Always
11	F	4	M	T	U	2		₦500	0	1	CHLOROQUINE	I don't know	Pharmacy store	I stop when I feel better
12	F	3	S	S	E	2		<₦500	0	1	FANSIDAR	No	Hospital	Always
13	F	3	M	P	E	1		>₦500	1	1	NONE	I don't know	Drug vendors	Always
14	F	2	M	S	U	1		<₦500	0	1	NONE	Yes	Hospital	Most times
15	M	3	S	P	E	1		<₦500	0	2	FANSIDAR	Yes	Drug vendors	Always
16	F	2	M	P	S	1		<₦500	2	1	FANSIDAR	No	Pharmacy store	I stop when I feel better
17	M	1	S	S	S	1		<₦500	2	1	COARTEM	I don't know	Others	Most times
18	F	2	M	S	U	1		<₦500	1	2	AMATEM]	Yes	Hospital	I stop when I feel better
19	F	1	S	T	U	1		<₦500	1	2	FANSIDAR	No	Drug vendors	Most times
20	F	2	M	T	U	1		>₦500	0	1	CHLOROQUINE	No	Pharmacy store	Always
21	F	1	M	N	S	1		>₦500	1	1	CHLOROQUINE	I don't know	Drug vendors	I stop when I feel better
22	M	2	S	N	U	1		<₦500	2	2	COARTEM	I don't know	Hospital	I stop when I feel better
23	M	3	S	N	E	1		>₦500	0	2	CHLOROQUINE	No	Hospital	Always
24	M	3	M	N	E	2		<₦500	0	1	CHLOROQUINE	I don't know	Drug vendors	Always
25	M	3	M	N	U	1		<₦500	0	1	AMATEM	Yes	Hospital	Always
26	F	2	M	N	U	1		<₦500	1	2	CHLOROQUINE	No	Drug vendors	I stop when I feel better
27	F	4	D	T	U	1		<₦500	2	1	CHLOROQUINE	I don't know	no treatment	I stop when I feel better
28	M	4	M	P	E	1		<₦500	1	1	FANSIDAR	No	Pharmacy store	I stop when I feel better
29	F	4	M	N	U	1		<₦500	0	2	FANSIDAR	I don't know	Hospital	Always
30	M	4	S	T	U	1		<₦500	1	2	FANSIDAR	No	Pharmacy store	I stop when I feel better
31	F	3	M	P	S	1		<₦500	2	1	FANSIDAR	I don't know	Drug vendors	Always
32	F	3	M	N	S	2		>₦500	0	1	HERBAL	No	Others	I stop when I feel better
33	F	3		T	U	1		<₦500	2	2	NONE	No	Hospital	Always
34	M	3	M	P	U	1		<₦500	2	1	NONE	No	Pharmacy store	Always
35	M	2	S	P	S	1		<₦500	1	2	HERBAL	No	Drug vendors	I stop when I feel better
36	M	3	M	N	U	1		<₦500	0	1	FANSIDAR	I don't know	Hospital	I stop when I feel better
37	M	2	M	N	U	1		<₦500	0	1	COARTEM	Yes	Hospital	Always
38	F	2	S	P	U	1		<₦500	1	2	FANSIDAR	No	Drug vendors	I stop when I feel better
39	F	2	S	N	N	2		>₦500	1	1	CHLOROQUINE	I don't know	Pharmacy store	I stop when I feel better
40	F	2		T	E	2		>₦500	0	2	CHLOROQUINE	I don't know	Drug vendors	Always
41	M	2	M	P	N	1		<₦500	2	1	CHLOROQUINE	No	Drug vendors	I stop when I feel better
42	M	2	S	N	U	1		<₦500	1	2	FANSIDAR	No	Drug vendors	I stop when I feel better
43	M	3	M	N	U	1		<₦500	0	1	LONART	I don't know	Hospital	Always
44	F	1	S	N	E	2		<₦500	0	1	COARTEM	Yes	Hospital	I stop when I feel better
45	F	2	S	N	U	1		<₦500	1	2	AMATEM	No	Drug vendors	Most times
46	M	4	S	N	U	1		<₦500	0	1	FANSIDAR	I don't know	Hospital	Most times
47	F	1	M	S	U	1		<₦500	0	1	FANSIDAR	No	Drug vendors	Always
48	M	2	S	P	S	2		<₦500	1	2	CHLOROQUINE	No	Drug vendors	Most times
49	F	2	M	P	E	1		>₦500	0	1	NONE	Yes	Hospital	Always
50	F	2	S	P	U	1		<₦500	1	1	NONE	No	Hospital	Always
51	M	3	M	P	S	1		<₦500	2	1	HERBAL	Yes	Hospital	I stop when I feel better
52	F	2	S	T	S	2		<₦500	0	1	CHLOROQUINE	No	Hospital	Most times
53	M	2	M	P	U	1		>₦500	1	1	CHLOROQUINE	I don't know	Drug vendors	Always
54	F	4	S	N	U	1		<₦500	2	1	HERBAL	Yes	Drug vendors	Always
55	M	1	M	S	S	1		<₦500	0	2	HERBAL	No	Drug vendors	Most times
56	F	1	M	N	U	1		<₦500	2	1	HERBAL	I don't know	Hospital	Most times
57	M	3	M	S	U	1		<₦500	0	1	FANSIDAR	I don't know	Hospital	Always
57	F	4	D	P	S	2		<₦500	0	1	NONE	No	Hospital	Most times
57	F	1	S	S	U	1		>₦500	2	1	NONE	Yes	Hospital	Always
57	F	4	S	N	E	1		>₦500	0	2	NONE	Yes	Hospital	Always
61	M	3	M	N	E	2		<₦500	1	2	FANSIDAR	No	Drug vendors	I stop when I feel better
62	F	2	S	T	U	1		<₦500	2	1	FANSIDAR	No	Drug vendors	Most times
63	M	1	S	N	U	1		>₦500	2	1	CHLOROQUINE	No	Pharmacy store	Most times
64	F	1	S	S	U	1		<₦500	1	1	COARTEM	No	Drug vendors	I stop when I feel better
65	M	4	D/W	N	U	1		<₦500	0	1	FANSIDAR	No	Drug vendors	I stop when I feel better
66	M	4	D/W	P	U	1		<₦500	0	1	AMATEM	No	Drug vendors	I stop when I feel better
67	F	3	M	P	S	1		<₦500	2	1	NONE	No	others	Always
68	F	2	M	S	U	2		>₦500	1	1	LONART	Yes	Hospital	Always
69	M	4	M	T	E	3		<₦500	2	1	AMATEM	Yes	Hospital	Always
70	M	2	S	N	U	1		<₦500	1	1	CHLOROQUINE	No	Pharmacy store	I stop when I feel better
71	M	2	S	N	U	1		<₦500	2	1	CHLOROQUINE	No	Drug vendors	I stop when I feel better
72	F	1	S	N	E	1		<₦500	1	2	COMBIART	No	Drug vendors	Most times
73	F	2	S	S	U	2		>₦500	2	1	CHLOROQUINE	No	Drug vendors	Always
74	F	4	M	N	S	2		>₦500	0	2	Fansidar	No	Pharmacy store	Always
75	M	4	M	S	S	1		>₦500	2	1	Chloroquine	I don't know	Pharmacy store	Always
76	M	4	M	T	E	1		<₦500	0	1	Lonart	No	Drug vendors	Always
77	M	3	M	S	E	2		<₦500	0	2	Coartem	Yes	Hospital	I stop when I feel better
78	M	4	M	S	U	2		>₦500	1	2	Herbal	No	No treatment	Always
79	M	3	M	S	S	2		>₦500	0	2	Chloroquine	Yes	Hospital	Always
80	F	2	S	T	U	2		>₦500	1	3	Chloroquine	No	Hospital	Most times

81	M	2	S	P	U	1		<₦500	0	1	Chloroquine	No	Hospital	Most times
82	F	2	S	S	U	1		<₦500	1	2	Herbal	No	Pharmacy store	Always
83	M	3	S	S	U	3		>₦500	2	1	Chloroquine	Yes	Drug vendors	Always
84	F	4	M	S	S	1		>₦500	2	2	Amatem	I don't know	Drug vendors	I stop when I feel better
85	M	3	S	T	U	1		<₦500	2	1	Lonart	I don't know	Drug vendors	I stop when I feel better
86	F	4	D	P	E	1		<₦500	0	3	Chloroquine	I don't know	Pharmacy store	Most times
87	F	2	S	P	E	1		<₦500	0	1	Lonart	Yes	Drug vendors	Most times
88	F	1	S	P	U	2		<₦500	1	1	Amatem	I don't know	No treatment	Most times
89	F	1	S	S	E	1		<₦500	0	1	Chloroquine	I don't know	Drug vendors	I stop when I feel better
90	F	1	S	S	U	1		<₦500	0	1	Coartem	No	Drug vendors	I stop when I feel better
91	F	2	S	S	S	1		<₦500	0	1	Chloroquine	No	Drug vendors	Most times
92	M	4	M	T	E	2		<₦500	1	1	Herbal	No	Pharmacy store	Always
93	F	4	M	T	E	2		>₦500	0	1	Chloroquine	Yes	Hospital	Always
94	M	3	S	T	E	3		>₦500	1	1	Coartem	No	Drug vendors	Always
95	F	3	M	T	E	2		<₦500	1	1	Chloroquine	Yes	Drug vendors	Always
96	F	4	S	T	U	1		<₦500	1	2	Chloroquine	No	No treatment	
97	M	2	S	T	U	1		<₦500	0	3	Lonart	I don't know	Pharmacy store	I stop when I feel better
98	M	1	S	S	U	1		<₦500	0	3	Chloroquine	Yes	Hospital	I stop when I feel better
99	F	1	S	S	U	1		>₦500	0	1	Herbal	I don't know	Hospital	Always
100	M	1	S	S	U	1		<₦500	0	1	Coartem	I don't know	Others	I stop when I feel better
101	F	2	S	S	U	1		<₦500	1	1	Amatem	Yes	Hospital	I stop when I feel better
102	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
103	F	3	S	S	U	1		<₦500	0	1	Fansidar	I don't know	Pharmacy store	I stop when I feel better
104	F	2	S	S	U	1		>₦500	2	1	Herbal	Yes	Drug vendors	Always
105	F	3	S	N	U	2		>₦500	1	2	Lonart	Yes	Pharmacy store	Most times
106	F	4	S	T	E	1		<₦500	0	1	Chloroquine	Yes	Hospital	I stop when I feel better
107	M	1	S	S	U	1		<₦500	2	1	Coartem	Yes	Drug vendors	I stop when I feel better
108	M	1	S	S	U	1		<₦500	0	1	Chloroquine	Yes	Hospital	Always
109	F	2	M	N	U	1		<₦500	1	2	Chloroquine	No	Drug vendors	I stop when I feel better
110	M	4	S	T	U	1		<₦500	2	1	Herbal	I don't know	Drug vendors	I stop when I feel better
111	M	2	S	T	E	1		<₦500	0	1	Lonart	I don't know	Hospital	I stop when I feel better
112	F	3	M	T	E	2		>₦500	1	1	combiart	I don't know	Drug vendors	I stop when I feel better
113	F	2	S	P	U	1		<₦500	1	2	Fansidar	No	Pharmacy store	I stop when I feel better
114	F	1	S	S	E	2		<₦500	1	1	Chloroquine	Yes	Drug vendors	Most times
115	F	4	S	T	E	2		>₦500	1	2	Herbal	No	Pharmacy store	Always
116	F	1	S	S	E	2		>₦500	1	2	Lonart	I don't know	Hospital	I stop when I feel better
117	M	3	M	T	E	2		<₦500	1	2	Chloroquine	Yes	Drug vendors	Most times
118	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
119	M	4	M	S	S	2		>₦500	0	1	combiart	I don't know	Hospital	I stop when I feel better
120	F	3	M	T	E	2		>₦500	2	2	Chloroquine	I don't know	Hospital	I stop when I feel better
121	F	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
122	F	2	S	T	U	2		>₦500	0	1	Herbal	I don't know	Hospital	I stop when I feel better

Community result Osun urban

Participan	Sex M/F	Age group	M.status	Education	Employen	Salary	propertie	WTP (₦)	History	cases/yea	Treatmen	Diagnosed	Place where treated	completion of dosage?
1	F	3	M	T	U	1		₦500	0	1	Fansidar	No	Others	I stop when I feel better
2	M	4	M	T	U	2		>₦500	2	2	Fansidar	Yes	Hospital	Most times
4	F	4	M	S	E	2		₦500	2	1	Lonart	No	Pharmacy store	Always
5	F	3	S	T	S	1		<₦500	1	1	Coartem	Yes	Hospital	Most times
6	F	2	S	S	S	1		₦500	2	1	Amatem	I don't kn	Hospital	I stop when I feel better
7	F	2	S	T	S	1		<₦500	0	1	Coartem	No	Drug vendors	I stop when I feel better
8	F	2	S	T	U	1		₦500	1	2	Herbal	No	Pharmacy store	Always
9	M	4	M	T	E	2		<₦500	1	1	Coartem	No	Pharmacy store	Always
10	F	4	M	T	E	2		>₦500	0	1	Amatem	Yes	Hospital	Always
11	M	3	S	T	E	3		>₦500	1	1	Coartem	No	Hospital	Always
12	M	3	M	T	E	2		<₦500	1	1	Chloroqui	Yes	Drug vendors	Always
13	M	4	S	T	U	1		<₦500	1	2	Herbal	No	No treatment	
14	F	2	S	T	E	1		₦500	0	3	Lonart	I don't kn	Pharmacy store	I stop when I feel better
15	M	1	S	S	U	1		<₦500	0	3	Fansidar	Yes	Hospital	I stop when I feel better
16	F	1	S	S	U	1		>₦500	0	1	Coartem	I don't kn	Hospital	Always
17	M	1	S	S	U	1		₦500	0	1	Coartem	I don't kn	Others	I stop when I feel better
18	F	2	S	S	E	1		₦500	1	1	Amatem	Yes	Hospital	I stop when I feel better
19	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
20	F	3	S	S	U	1		<₦500	0	1	Fansidar	I don't kn	Pharmacy store	I stop when I feel better
21	M	2	S	S	U	1		>₦500	2	1	Amatem	Yes	Pharmacy store	Always
22	F	3	S	N	E	2		>₦500	1	2	Lonart	Yes	Pharmacy store	Most times
23	F	4	M	T	E	1		₦500	0	1	Chloroqui	Yes	Hospital	I stop when I feel better
24	F	1	S	S	U	1		<₦500	2	1	Coartem	Yes	Hospital	I stop when I feel better
25	M	1	S	S	U	1		₦500	0	1	Amatem	Yes	Hospital	Always
26	F	2	M	N	U	1		<₦500	1	2	Chloroqui	No	Drug vendors	I stop when I feel better
27	M	4	M	T	U	1		₦500	2	1	combiart	I don't kn	Drug vendors	I stop when I feel better
28	M	2	S	T	E	1		₦500	0	1	Lonart	I don't kn	Hospital	I stop when I feel better
29	M	3	M	T	E	2		>₦500	1	1	combiart	I don't kn	Hospital	I stop when I feel better
30	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Pharmacy store	I stop when I feel better
31	F	1	S	S	E	2		₦500	1	1	Chloroqui	Yes	Hospital	Most times
32	F	4	M	T	E	2		>₦500	1	2	Coartem	No	Pharmacy store	Always
33	F	1	S	S	E	2		>₦500	1	2	Lonart	I don't kn	Hospital	I stop when I feel better
34	F	3	M	T	E	2		₦500	1	2	Lonart	Yes	Hospital	Most times
35	M	2	S	P	U	1		<₦500	1	2	Herbal	No	Drug vendors	I stop when I feel better
36	M	4	M	S	S	2		>₦500	0	1	combiart	I don't kn	Hospital	I stop when I feel better
37	M	3	M	T	E	2		>₦500	2	2	combiart	I don't kn	Hospital	I stop when I feel better
38	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
39	M	2	S	T	U	2		>₦500	0	1	Coartem	I don't kn	Hospital	I stop when I feel better
40	M	2	S	T	E	2		>₦500	1	2	Fansidar	Yes	Pharmacy store	Most times
41	M	2	S	T	E	1		<₦500	0	1	Chloroqui	No	Pharmacy store	Most times
42	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
43	M	2	S	T	U	1		₦500	0	1	Chloroqui	Yes	Pharmacy store	Always
44	M	3	M	T	E	2		>₦500	2	2	Coartem	Yes	Hospital	I stop when I feel better
45	M	2	M	S	U	1		<₦500	1	2	Fansidar	No	Drug vendors	Most times
46	M	3	S	T	E	1		<₦500	0	1	Fansidar	No	Drug vendors	I stop when I feel better
47	F	4	M	T	E	2		₦500	1	1	Chloroqui	Yes	Hospital	Always
48	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
49	M	1	S	S	U	1		₦500	0	1	Amatem	No	Pharmacy store	Always
50	F	1	S	S	U	1		<₦500	0	2	Chloroqui	I don't kn	Pharmacy store	I stop when I feel better
51	F	4	M	T	E	3		₦500	2	1	Other	Yes	Hospital	Most times
52	F	1	S	P	E	2		<₦500	1	1	Amatem	No	Hospital	Always
53	M	1	S	S	E	1		₦500	1	1	Amatem	I don't kn	Hospital	Always
54	F	2	S	T	E	2		₦500	2	1	Amatem	No	Hospital	I stop when I feel better
55	M	1	S	T	U	1		<₦500	0	1	Amatem	I don't kn	Pharmacy store	Always
56	F	1	S	S	U	1		<₦500	0	1	Herbal	I don't kn	Pharmacy store	Always
57	F	1	S	P	U	1		₦500	0	1	Herbal	No	Hospital	I stop when I feel better
58	F	4	M	T	E	2		<₦500	0	1	Coartem	I don't kn	Pharmacy store	I stop when I feel better
57	F	4	M	S	U	2		>₦500	0	1	Coartem	No	Hospital	Always
60	F	1	S	S	E	1		₦500	0	1	Chloroqui	Yes	Hospital	I stop when I feel better
61	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
62	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
63	M	2	S	T	U	2		₦500	2	1	combiart	Yes	Hospital	I stop when I feel better
64	M	1	S	S	E	2		₦500	2	2	combiart	No	Hospital	I stop when I feel better
65	M	3	M	T	E	2		₦500	1	1	combiart	No	Hospital	I stop when I feel better
66	M	3	M	T	E	2		>₦500	2	1	combiart	I don't kn	Hospital	Most times
67	F	1	S	S	U	2		₦500	1	1	combiart	I don't kn	Hospital	I stop when I feel better
68	M	1	S	N	S	1		<₦500	1	2	Chloroqui	No	Pharmacy store	I stop when I feel better
69	F	1	S	S	U	1		<₦500	1	1	Fansidar	Yes	Hospital	I stop when I feel better
70	M	4	M	T	E	3		>₦500	2	1	Lonart	Yes	Hospital	Most times
71	F	4	S	T	U	1		>₦500	2	1	Amatem	Yes	Hospital	Always
72	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
73	M	4	M	T	E	2		>₦500	0	1	Lonart	Yes	Pharmacy store	Most times
74	M	2	S	S	E	2		<₦500	0	1	Amatem	No	Drug vendors	Most times
75	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
76	M	4	M	T	E	3		<₦500	2	1	Fansidar	Yes	Drug vendors	I stop when I feel better
77	M	3	S	T	E	3		>₦500	0	2	Lonart	Yes	Pharmacy store	Most times
78	M	2	S	P	U	1		<₦500	1	2	Fansidar	No	Drug vendors	I stop when I feel better
79	M	4	M	T	E	3		>₦500	2	1	Lonart	Yes	Hospital	Most times
80	F	4	M	T	E	2		>₦500	2	1	Lonart	Yes	Hospital	I stop when I feel better

81	M	4	M	T	E	3		₦500	1	1	Coartem	No	Pharmacy store	Always
82	M	2	S	N	U	1		<₦500	1	2	Chloroqui	No	Drug vendors	I stop when I feel better
83	M	4	M	T	E	2		>₦500	1	2	Coartem	Yes	Pharmacy store	Always
84	M	4	M	T	E	2		<₦500	0	1	Coartem	No	Hospital	Always
85	M	4	M	T	U	1		<₦500	1	1	Fansidar	No	Pharmacy store	Most times
86	F	4	M	T	S	1		<₦500	1	2	Fansidar	Yes	Hospital	Always
87	F	2	S	S	U	2		<₦500	0	1	Fansidar	Yes	Hospital	I stop when I feel better
88	M	4	M	T	E	1		<₦500	1	1	Coartem	No	Pharmacy store	Most times
89	M	2	S	T	E	1		<₦500	1	1	Amatem	I don't kn	Pharmacy store	I stop when I feel better
90	M	4	M	N	U	1		<₦500	0	2	Chloroqui	No	Drug vendors	I stop when I feel better
91	F	4	M	T	E	1		<₦500	1	2	combiart	No	Pharmacy store	Always
92	M	4	D	T	E	2		₦500	0	2	Herbal	Yes	Pharmacy store	I stop when I feel better
93	M	3	M	T	S	2		<₦500	0	2	combiart	No	Hospital	Most times
94	F	2	S	S	E	1		<₦500	2	1	Amatem	I don't kn	Pharmacy store	Always
95	M	3	M	S	S	1		>₦500	0	1	Lonart	Yes	Hospital	I stop when I feel better
96	F	4	M	S	S	1		>₦500	2	2	Fansidar	No	Drug vendors	I stop when I feel better
97	M	1	S	T	E	1		>₦500	0	2	Lonart	Yes	Pharmacy store	Always
98	M	1	S	T	E	1		<₦500	1	1	Amatem	Yes	Hospital	I stop when I feel better
99	F	2	S	S	S	1		>₦500	0	1	Lonart	No	Drug vendors	I stop when I feel better
100	M	2	S	S	E	1		>₦500	0	3	Herbal	No	Pharmacy store	Always
101	F	2	S	T	S	1		<₦500	0	3	Lonart	Yes	Pharmacy store	I stop when I feel better
102	F	3	M	S	S	1		<₦500	1	2	Amatem	Yes	Hospital	Most times
103	M	4	D	P	S	2		>₦500	0	1	Chloroqui	Yes	Pharmacy store	I stop when I feel better
104	F	3	S	T	S	1		>₦500	0	3	Fansidar	Yes	Pharmacy store	I stop when I feel better
105	M	3	M	T	S	1		<₦500	1	2	Lonart	Yes	Hospital	Most times
106	M	3	M	S	E	2		>₦500	0	3	Lonart	No	Hospital	I stop when I feel better
107	F	4	M	S	E	2		<₦500	1	2	Coartem	Yes	Pharmacy store	I stop when I feel better
108	F	4	D	S	S	2		<₦500	1	2	Lonart	No	Pharmacy store	Always
109	M	2	S	T	S	2		<₦500	1	3	Amatem	Yes	Pharmacy store	I stop when I feel better
110	F	3	M	T	S	2		>₦500	0	1	Fansidar	Yes	Drug vendors	I stop when I feel better
111	M	3	M	T	U	1		<₦500	0	2	Fansidar	Yes	Hospital	I stop when I feel better
112	F	4	M	S	U	2		>₦500	0	1	Lonart	No	Hospital	I stop when I feel better
113	M	3	S	T	S	1		<₦500	2	2	Lonart	No	Drug vendors	Most times
114	M	4	M	P	S	1		<₦500	2	1	Amatem	Yes	Hospital	I stop when I feel better
115	F	2	S	T	E	2		>₦500	1	2	Chloroqui	Yes	Hospital	I stop when I feel better
116	M	4	M	T	S	2		>₦500	0	2	Fansidar	Yes	Pharmacy store	Most times
117	M	3	S	T	U	1		<₦500	2	2	Coartem	No	Drug vendors	I stop when I feel better
118	M	4	M	T	E	2		<₦500	0	1	Herbal	No	Hospital	Always
119	F	3	S	S	E	2		>₦500	1	2	Lonart	Yes	Pharmacy store	I stop when I feel better
120	F	3	M	T	E	2		>₦500	0	2	Chloroqui	Yes	Hospital	I stop when I feel better
121	F	3	S	T	S	1		>₦500	0	2	Lonart	Yes	Pharmacy store	Most times
122	M	4	M	T	S	2		<₦500	0	1	Amatem	No	Hospital	I stop when I feel better
123	F	4	M	T	S	1		<₦500	1	2	Fansidar	Yes	Pharmacy store	Most times
124	F	4	M	T	S	2		<₦500	2	2	Lonart	Yes	Hospital	I stop when I feel better
125	M	4	M	T	U	2		>₦500	0	3	combiart	No	Pharmacy store	I stop when I feel better
126	F	2	M	T	U	2		<₦500	0	3	Coartem	Yes	Drug vendors	Most times
127	F	3	M	P	S	1		<₦500	2	1	Chloroqui	Yes	Hospital	I stop when I feel better
128	F	4	M	T	U	2		<₦500	0	1	Lonart	Yes	Drug vendors	Always
129	M	4	M	T	S	2		>₦500	1	2	Fansidar	No	Hospital	I stop when I feel better
130	F	4	M	T	E	1		<₦500	2	2	Amatem	No	Pharmacy store	I stop when I feel better
131	F	3	M	T	E	1		<₦500	2	3	Chloroqui	Yes	Hospital	Most times
132	M	4	M	S	S	1		>₦500	1	2	Lonart	Yes	Drug vendors	I stop when I feel better
133	F	4	M	S	S	1		<₦500	0	2	Chloroqui	Yes	Hospital	Most times
134	M	2	S	T	S	2		<₦500	0	1	Coartem	No	Pharmacy store	I stop when I feel better
135	F	2	M	T	S	1		<₦500	0	1	Lonart	Yes	Hospital	Always
136	M	4	M	T	E	1		<₦500	2	1	Amatem	Yes	Hospital	I stop when I feel better
137	M	4	M	T	E	2		>₦500	0	2	Coartem	No	Pharmacy store	Always
138	M	4	M	T	S	2		>₦500	1	2	Chloroqui	No	Hospital	I stop when I feel better
139	F	3	S	S	U	2		<₦500	0	2	Herbal	Yes	Drug vendors	I stop when I feel better
140	F	3	M	T	S	2		<₦500	2	2	Herbal	Yes	Pharmacy store	Most times
141	F	3	M	T	E	1		<₦500	1	3	Coartem	Yes	Hospital	I stop when I feel better
142	F	3	S	T	E	1		>₦500	0	1	Lonart	No	Drug vendors	Most times
143	M	4	M	T	E	2		<₦500	1	3	Coartem	No	Hospital	Most times

Community result Osun rural

Participan	Sex 0/1	Age group	Marital St	Education	Employme	Salary	propertie	WTP (₦)	History	cases/yea	Treatment	Diag0sed?	Place where treated	completion of dosage?
1	1	1	0	1	0	0		0	0	0	Amatem	1	0	0
2	1	2	1	0	0	0		0	0	0	Chloroquine	0	2	2
4	1	2	1	0	0	0		0	2	0	Chloroquine	1	0	0
5	0	3	1	0	1	1		0	0	0	Fansidar	1	0	0
6	0	2	0	1	1	1		0	2	0	Chloroquine	1	0	0
7	1	2	1	0	0	0		0	2	0	Coartem	1	0	0
8	0	0	0	1	0	0		0	0	0	combiart	0	0	0
9	0	2	1	1	1	0		0	2	0	Amatem	0	2	2
10	0	3	1	1	1	1		0	2	0	Lonart	1	0	0
11	0	3	1	3	0	0		0	0	0	Chloroquine	2	2	2
12	1	2	1	1	1	1		0	0	0	Fansidar	1	0	0
13	1	2	1	0	0	0		0	1	0	Chloroquine	2	0	0
14	1	1	1	1	0	0		0	0	0	Amatem	1	0	0
15	0	0	0	1	1	0		0	0	0	Lonart	1	0	0
16	1	1	1	0	2	0		0	2	0	Fansidar	0	2	2
17	0	0	0	1	0	0		0	0	0	Coartem	2	4	2
18	1	1	0	1	0	0		0	1	0	Amatem	1	0	2
19	0	1	0	0	0	0		0	1	1	Fansidar	0	1	2
20	1	1	1	0	0	0		0	0	0	Coartem	0	2	2
21	1	2	1	3	2	0		0	0	0	Chloroquine	2	2	2
22	1	1	1	0	0	0		0	2	0	Coartem	2	0	2
23	1	1	1	0	0	0		0	0	0	Fansidar	1	0	0
24	1	2	1	0	1	0		0	0	0	Coartem	2	0	0
25	1	2	1	1	0	0		0	0	0	Amatem	1	0	0
26	1	1	1	3	0	0		0	1	1	Chloroquine	0	1	2
27	1	1	1	1	0	0		0	2	0	Coartem	2	3	2
28	0	2	1	0	1	0		0	0	0	Chloroquine	0	2	2
29	1	2	1	3	0	0		0	0	0	Chloroquine	2	0	0
30	0	1	0	0	0	0		0	1	1	Fansidar	0	2	2
31	1	2	1	0	1	0		0	2	0	Fansidar	2	0	0
32	0	2	1	3	0	1		1	0	0	herbal	2	4	2
33	1	0	1	0	0	0		0	2	0	Chloroquine	0	0	0
34	0	2	1	1	0	0		0	2	0	Chloroquine	0	2	0
35	0	1	0	0	1	0		0	1	1	Fansidar	0	1	2
36	1	2	1	1	0	0		0	0	0	Fansidar	2	0	2
37	0	2	1	0	0	0		0	0	0	Coartem	1	0	0
38	0	1	0	0	0	0		0	1	1	Fansidar	0	1	2
39	1	0	0	0	1	0		1	0	0	Chloroquine	2	2	2
40	1	1	1	2	2	1		1	0	0	Fansidar	2	0	0
41	1	1	1	0	0	0		0	2	0	Coartem	2	2	2
42	0	1	0	0	0	0		0	1	1	Fansidar	0	1	2
43	0	2	1	0	0	0		0	0	0	Coartem	2	0	0
44	1	1	0	2	1	0		0	0	0	Coartem	1	0	0
45	0	1	1	1	0	0		0	1	1	Fansidar	0	1	1
46	0	3	1	0	0	0		0	0	0	Amatem	2	0	2
47	0	3	1	1	0	0		0	0	0	Coartem	2	0	0
48	0	1	0	0	2	0		0	1	1	Fansidar	0	1	2
49	1	1	1	1	0	0		0	1	0	Coartem	1	0	0
50	1	0	0	1	0	0		0	0	0	Amatem	1	0	0
51	1	2	1	1	2	3		0	2	0	Coartem	1	0	0
52	1	1	1	1	2	0		0	0	0	Amatem	1	0	0
53	1	1	1	1	0	0		0	0	0	Chloroquine	2	0	0
54	1	0	0	1	1	0		0	0	0	Coartem	1	0	0
55	0	0	0	1	2	0		0	1	0	Fansidar	0	2	2
56	1	0	0	1	0	0		0	2	0	Coartem	2	0	0
57	0	2	1	1	0	0		0	0	0	Coartem	2	0	0
58	1	2	1	0	2	0		0	0	0	Fansidar	1	0	2
57	1	0	0	1	0	0		0	2	0	Amatem	1	0	0
60	0	1	0	1	1	0		0	0	0	Amatem	1	0	0
61	0	1	0	2	0	0		0	1	1	Fansidar	0	1	2
62	1	3	1	2	1	1		1	2	0	Fansidar	1	1	1
63	0	0	0	1	1	0		0	0	0	Coartem	0	2	2
64	0	2	1	1	0	0		1	1	1	Chloroquine	0	2	1
65	1	0	0	0	0	0		0	2	2	Coartem	1	1	2
66	0	3	1	0	1	0		0	2	0	Fansidar	0	0	1
67	1	3	1	2	0	0		0	2	0	Chloroquine	0	1	2
68	0	3	1	1	0	0		0	0	0	Chloroquine	1	0	1
69	1	2	1	1	2	1		1	1	0	Chloroquine	0	2	2
70	1	3	1	0	0	0		0	0	1	Lonart	0	0	0
71	1	3	0	1	1	0		0	0	0	Coartem	1	0	2
72	0	2	0	2	1	1		0	0	0	Chloroquine	0	1	2
73	0	2	1	1	0	0		0	1	2	Amatem	1	2	1
74	1	2	1	0	2	1		1	0	1	Chloroquine	0	2	1
75	1	3	0	1	0	0		0	0	0	Chloroquine	1	0	2
76	0	1	1	0	1	0		0	0	0	Lonart	1	0	0
77	0	3	1	1	0	0		0	1	0	Lonart	0	2	1
78	1	3	1	1	2	0		1	2	1	Fansidar	1	2	2
79	0	2	0	1	1	0		0	0	0	Chloroquine	0	0	2
80	1	3	1	1	0	1		0	1	2	Amatem	1	2	1
81	1	3	1	0	0	0		0	0	0	Chloroquine	0	0	2
82	1	3	1	1	2	0		0	0	0	Chloroquine	0	2	0
83	0	3	1	2	1	1		1	1	1	Coartem	1	1	1
84	0	3	1	1	1	1		0	0	0	Chloroquine	0	2	2
85	1	1	0	0	2	0		0	2	0	Chloroquine	1	0	1
86	1	2	0	1	0	0		1	2	0	Chloroquine	0	2	2
87	1	3	1	2	0	0		0	1	0	Fansidar	0	0	0
88	0	1	0	1	2	1		0	1	2	Chloroquine	0	2	1
89	0	3	0	0	0	0		0	0	0	Chloroquine	1	0	2
90	1	3	0	1	2	0		1	1	1	Lonart	1	0	1
91	0	2	1	1	0	0		0	1	1	Fansidar	0	0	2

Pharmacy data Lagos

	Education of pharmacist	Urban/Rural	Antimalarial mostly prescribed	sex of client	proof of diagnosis	self-medicating?	Antimalarial purc	ACT?	influenc	price
Client 1	Tertiary	Urban	Lonart	F	Y	Y	Chloroquine	N	N	₦80
Client 2	Tertiary	Urban	Lonart	F	N	Y	Fansidar	N	Y	₦160
Client 3	Tertiary	Urban	Lonart	F	Y	N	lonart	Y	Y	₦850
Client 4	Tertiary	Urban	Lonart	F	Y	N	Amatem	Y	Y	₦600
Client 5	Tertiary	Urban	Lonart	F	Y	N	Chloroquine	N	N	₦80
Client 6	Tertiary	Urban	Lonart	M	Y	N	lonart	Y	Y	₦850
Client 7	Tertiary	Urban	Lonart	F	N	N	lonart	Y	N	₦850
Client 8	Tertiary	Urban	Lonart	F	N	N	Amatem	Y	Y	₦600
Client 9	Tertiary	Urban	Lonart	F	N	N	Amatem	Y	Y	₦600
Client 10	Tertiary	Urban	Lonart	F	N	Y	lonart	Y	Y	₦850
Client 11	Tertiary	Urban	Lonart	M	Y	N	Chloroquine	N	N	₦80
Client 12	Tertiary	Urban	Lonart	M	Y	N	Coartem	Y	Y	₦850
Client 13	Tertiary	Urban	Lonart	F	N	N	lonart	Y	Y	₦850
Client 14	Tertiary	Urban	Lonart	M	N	N	Fansidar	N	Y	₦170
Client 15	Tertiary	Urban	Lonart	F	Y	Y	Fansidar	N	N	₦170
Client 16	Tertiary	Urban	Lonart	F	N	Y	Coartem	Y	Y	₦600
Client 17	Tertiary	Urban	Lonart	F	N	Y	Chloroquine	N	N	₦80
Client 18	Tertiary	Urban	Lonart	F	Y	N	lonart	Y	Y	₦850
Client 19	Tertiary	Urban	Lonart	F	Y	N	lonart	Y	Y	₦850
Client 20	Tertiary	Urban	Lonart	F	Y	N	Fansidar	N	N	₦170
Client 21	Tertiary	Urban	Lonart	M	Y	N	Chloroquine	N	Y	₦80
Client 22	Tertiary	Urban	Lonart	F	Y	N	Chloroquine	N	N	₦80
Client 23	Tertiary	Urban	Lonart	M	N	Y	lonart	Y	N	₦850
Client 24	Tertiary	Urban	Lonart	F	N	Y	lonart	Y	Y	₦850
Client 25	Tertiary	Urban	Lonart	F	Y	N	lonart	Y	Y	₦850
Client 26	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Y	Y	₦250
Client 27	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Y	N	₦250
Client 28	Tertiary	Urban	Coartem/Amatem	F	N	Y	Amatem	Y	Y	₦500
Client 29	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Y	N	₦250
Client 30	Tertiary	Urban	Coartem/Amatem	F	Y	N	Coartem	Y	Y	₦250
Client 31	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	N	₦250
Client 32	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Y	Y	₦250
Client 33	Tertiary	Urban	Coartem/Amatem	M	N	Y	Amatem	Y	Y	₦500
Client 34	Tertiary	Urban	Coartem/Amatem	M	N	Y	Amatem	Y	Y	₦500
Client 35	Tertiary	Urban	Coartem/Amatem	M	N	Y	Amatem	Y	Y	₦500
Client 36	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	N	₦250
Client 37	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Y	N	₦250
Client 38	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Y	N	₦250
Client 39	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	Y	₦250
Client 40	Tertiary	Urban	Coartem/Amatem	F	N	Y	Amatem	Y	Y	₦500
Client 41	Tertiary	Urban	Coartem/Amatem	F	Y	N	Amatem	Y	Y	₦500
Client 42	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Y	Y	₦250
Client 43	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	Y	₦250
Client 44	Tertiary	Urban	Coartem/Amatem	F	N	Y	Amatem	Y	Y	₦500
Client 45	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	N	₦250
Client 46	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	N	₦250
Client 47	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	N	₦250
Client 48	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Y	N	₦250
Client 49	Tertiary	Urban	Coartem/Amatem	F	N	Y	Amatem	Y	Y	₦500
Client 50	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	Y	₦250
Client 51	Tertiary	Urban	Coartem/Amatem	F	N	Y	Lonart	Y	Y	₦700
Client 52	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	N	₦250
Client 53	Tertiary	Urban	Coartem/Amatem	M	Y	N	Lonart	Y	N	₦700
Client 54	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Y	Y	₦250
Client 55	Tertiary	Urban	Coartem/Amatem	M	N	Y	Amatem	Y	Y	₦500
Client 56	Tertiary	Urban	Coartem/Amatem	M	N	Y	Amatem	Y	Y	₦500
Client 57	Tertiary	Urban	Coartem/Amatem	M	N	Y	Amatem	Y	Y	₦500
Client 58	Tertiary	Urban	Coartem/Amatem	M	N	Y	Amatem	Y	Y	₦500
Client 59	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Y	Y	₦250
Client 60	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	N	₦250
Client 61	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	Y	₦250
Client 62	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	Y	₦250
Client 63	Tertiary	Urban	Coartem/Amatem	M	Y	N	Coartem	Y	N	₦250
Client 64	Tertiary	Urban	Coartem/Amatem	F	Y	Y	Coartem	Y	Y	₦250
Client 65	Tertiary	Urban	Coartem/Amatem	M	N	Y	Amatem	Y	Y	₦500
Client 66	Tertiary	Urban	Coartem/Amatem	F	N	Y	Lonart	Y	Y	₦700
Client 67	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	Y	₦250
Client 68	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	Y	₦250
Client 69	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Y	Y	₦250
Client 70	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Y	Y	₦250
Client 71	Tertiary	Urban	Coartem/Amatem	F	N	Y	Amatem	Y	Y	₦500
Client 72	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Y	Y	₦250
Client 73	Tertiary	Urban	Coartem/Amatem	F	Y	N	Coartem	Y	Y	₦250
Client 74	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	Y	₦250
Client 75	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Y	Y	₦250
Client 76	Tertiary	Urban	Coartem/Amatem	M	N	Y	Amatem	Y	N	₦500
Client 77	Tertiary	Urban	Coartem/Amatem	M	N	Y	Amatem	Y	N	₦500
Client 78	Tertiary	Urban	Coartem/Amatem	M	N	Y	Amatem	Y	Y	₦500
Client 79	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	Y	₦250
Client 80	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Y	Y	₦250
Client 81	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Y	Y	₦250
Client 82	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	Y	₦250
Client 83	Tertiary	Urban	Coartem/Amatem	F	N	Y	Amatem	Y	Y	₦500
Client 84	Tertiary	Urban	Coartem/Amatem	F	Y	N	Amatem	Y	Y	₦500
Client 85	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Y	Y	₦250
Client 86	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	Y	₦250
Client 87	Tertiary	Urban	Coartem/Amatem	F	N	Y	Amatem	Y	Y	₦500

Client 88	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	Y	₦250
Client 89	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	Y	₦250
Client 90	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	Y	₦250
Client 91	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Y	Y	₦250
Client 92	Tertiary	Urban	Coartem/Amatem	F	N	Y	Amatem	Y	N	₦500
Client 93	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	Y	₦250
Client 94	Tertiary	Urban	Coartem/Amatem	F	N	Y	Lonart	Y	N	₦700
Client 95	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	Y	₦250
Client 96	Tertiary	Urban	Coartem/Amatem	M	Y	N	Lonart	Y	Y	₦700
Client 97	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Y	Y	₦250
Client 98	Tertiary	Urban	Coartem/Amatem	M	N	Y	Amatem	Y	Y	₦500
Client 99	Tertiary	Urban	Coartem/Amatem	M	N	Y	Amatem	Y	Y	₦500
Client 100	Tertiary	Urban	Coartem/Amatem	M	N	Y	Amatem	Y	Y	₦500
Client 101	Tertiary	Urban	Coartem/Amatem	M	N	Y	Amatem	Y	Y	₦500
Client 102	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Y	Y	₦250
Client 103	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	Y	₦250
Client 104	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	Y	₦250
Client 105	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	N	₦250
Client 106	Tertiary	Urban	Coartem/Amatem	M	Y	N	Coartem	Y	N	₦250
Client 107	Tertiary	Urban	Coartem/Amatem	F	Y	Y	Coartem	Y	Y	₦250
Client 108	Tertiary	Urban	Coartem/Amatem	M	N	Y	Amatem	Y	Y	₦500
Client 109	Tertiary	Urban	Coartem/Amatem	F	N	Y	Lonart	Y	Y	₦700
Client 110	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	Y	₦250
Client 111	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Y	Y	₦250
Client 112	Tertiary	Rural	Amatem/Coartem/Lonart	M	N	Y	Chloroquine	N	N	₦80
Client 113	Tertiary	Rural	Amatem/Coartem/Lonart	F	N	Y	Coartem	Y	Y	₦250
Client 114	Tertiary	Rural	Amatem/Coartem/Lonart	M	N	Y	Coartem	Y	Y	₦250
Client 115	Tertiary	Rural	Amatem/Coartem/Lonart	F	N	Y	Amatem	Y	Y	₦450
Client 116	Tertiary	Rural	Amatem/Coartem/Lonart	F	N	Y	Amatem	Y	Y	₦450
Client 117	Tertiary	Rural	Amatem/Coartem/Lonart	F	N	Y	Chloroquine	N	N	₦80
Client 118	Tertiary	Rural	Amatem/Coartem/Lonart	F	N	Y	Chloroquine	N	N	₦80
Client 119	Tertiary	Rural	Amatem/Coartem/Lonart	M	N	Y	Amatem	Y	Y	₦450
Client 120	Tertiary	Rural	Amatem/Coartem/Lonart	F	N	Y	Amatem	Y	Y	₦450
Client 121	Tertiary	Rural	Amatem/Coartem/Lonart	F	N	Y	Coartem	Y	Y	₦250
Client 122	Tertiary	Rural	Amatem/Coartem/Lonart	M	N	Y	Chloroquine	N	Y	₦80
Client 123	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Fansidar	N	Y	₦180
Client 124	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Coartem	Y	Y	₦250
Client 125	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Chloroquine	N	Y	₦80
Client 126	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Fansidar	N	Y	₦180
Client 127	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Coartem	Y	Y	₦250
Client 128	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Fansidar	N	Y	₦180
Client 129	Secondary	Rural	Amatem/Coartem/Lonart	M	N	Y	Fansidar	N	N	₦180
Client 130	Secondary	Rural	Amatem/Coartem/Lonart	M	N	Y	Coartem	Y	N	₦250
Client 131	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Coartem	Y	Y	₦250
Client 132	Tertiary	Rural	Amatem/Coartem/Lonart	F	N	Y	Chloroquine	N	Y	₦80
Client 133	Tertiary	Rural	Amatem/Coartem/Lonart	F	N	Y	Lonart	Y	Y	₦700
Client 134	Tertiary	Rural	Amatem/Coartem/Lonart	F	N	Y	Amatem	Y	Y	₦450
Client 135	Secondary	Rural	Amatem/Coartem/Lonart	M	N	Y	Lonart	Y	Y	₦700
Client 136	Secondary	Rural	Amatem/Coartem/Lonart	M	N	Y	Fansidar	N	Y	₦180
Client 137	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Chloroquine	N	N	₦80
Client 138	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Coartem	Y	Y	₦450
Client 139	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Amatem	Y	Y	₦450
Client 140	Secondary	Rural	Amatem/Coartem/Lonart	M	N	Y	Chloroquine	N	Y	₦80
Client 141	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Chloroquine	N	N	₦80
Client 142	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Chloroquine	N	Y	₦80
Client 143	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Chloroquine	N	N	₦80
Client 144	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Amatem	Y	Y	₦250
Client 145	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Lonart	Y	N	₦700
Client 1	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Yes	Y	₦250
Client 2	Tertiary	Urban	Coartem/Amatem	M	N	Y	Lonart	Yes	Y	₦250
client 3	Tertiary	Urban	Coartem/Amatem	F	N	Y	Amatem	Yes	Y	₦500
Client 4	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Yes	Y	₦250
Client 5	Tertiary	Urban	Coartem/Amatem	F	Y	N	Coartem	Yes	Y	₦250
Client 6	Tertiary	Urban	Coartem/Amatem	F	N	Y	Lonart	Yes	Y	₦250
Client 7	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Yes	Y	₦250
Client 8	Tertiary	Urban	Coartem/Amatem	M	N	Y	Amatem	Yes	Y	₦500
Client 9	Tertiary	Urban	Coartem/Amatem	M	N	Y	Amatem	Yes	Y	₦500
Client 10	Tertiary	Urban	Coartem/Amatem	M	N	Y	Chloroquine	No	Y	₦500
Client 11	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Yes	Y	₦1850
Client 12	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Yes	Y	₦1850
Client 13	Tertiary	Urban	Coartem/Amatem	M	N	Y	Lonart	Yes	Y	₦250
Client 14	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Yes	Y	₦1850
Client 15	Tertiary	Urban	Coartem/Amatem	F	N	Y	Amatem	Yes	Y	₦500

Client 16	Tertiary	Urban	Coartem/Amatem	F	Y	N	Amatem	Yes	Y	₦500
Client 17	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Yes	Y	₦1850
Client 18	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Yes	Y	₦250
Client 19	Tertiary	Urban	Coartem/Amatem	F	N	Y	Amatem	Yes	Y	₦500
Client 20	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Yes	Y	₦1850
Client 21	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Yes	Y	₦1850
Client 22	Tertiary	Urban	Coartem/Amatem	F	N	Y	Lonart	Yes	Y	₦250
Client 23	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Yes	Y	₦1850
Client 24	Tertiary	Urban	Coartem/Amatem	F	N	Y	Chloroquine	No	Y	₦500
Client 25	Tertiary	Urban	Coartem/Amatem	F	N	Y	Fansidar	No	Y	₦250
Client 26	Tertiary	Urban	Coartem/Amatem	F	N	Y	Lonart	Yes	Y	₦700
Client 27	Tertiary	Urban	Coartem/Amatem	F	N	Y	Chloroquine	No	Y	₦250
Client 28	Tertiary	Urban	Coartem/Amatem	M	Y	N	Lonart	Yes	Y	₦700
Client 29	Tertiary	Urban	Coartem/Amatem	M	N	Y	Coartem	Yes	Y	₦1850
Client 30	Tertiary	Urban	Coartem/Amatem	M	N	Y	Amatem	Yes	Y	₦500
Client 31	Tertiary	Urban	Coartem/Amatem	M	N	Y	Amatem	Yes	Y	₦500
Client 32	Tertiary	Urban	Coartem/Amatem	M	N	Y	Amatem	Yes	Y	₦500
Client 33	Tertiary	Urban	Coartem/Amatem	M	N	Y	Amatem	Yes	Y	₦500
Client 34	Tertiary	Urban	Coartem/Amatem	M	N	Y	Lonart	Yes	Y	₦250
Client 35	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Yes	Y	₦1850
Client 36	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Yes	Y	₦1850
Client 37	Tertiary	Urban	Coartem/Amatem	F	N	Y	Lonart	Yes	Y	₦250
Client 38	Tertiary	Urban	Coartem/Amatem	M	Y	N	Coartem	Yes	Y	₦1850
Client 39	Tertiary	Urban	Coartem/Amatem	F	Y	Y	Coartem	Yes	Y	₦1850
Client 40	Tertiary	Urban	Coartem/Amatem	M	N	Y	Amatem	Yes	Y	₦500
Client 41	Tertiary	Urban	Coartem/Amatem	F	N	Y	Lonart	Yes	Y	₦700
Client 42	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Yes	Y	₦1850
Client 43	Tertiary	Urban	Coartem/Amatem	F	N	Y	Coartem	Yes	Y	₦1850
Client 1	Secondary	Rural	Amatem/Coartem/Lonart	M	N	Y	Chloroquine	No	Y	₦80
Client 2	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Coartem	Yes	Y	₦250
client 3	Secondary	Rural	Amatem/Coartem/Lonart	M	N	Y	Coartem	Yes	Y	₦250
Client 4	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Amatem	Yes	Y	₦450
Client 5	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Amatem	Yes	Y	₦450
Client 6	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Chloroquine	No	Y	₦80
Client 7	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Chloroquine	No	Y	₦80
Client 8	Secondary	Rural	Amatem/Coartem/Lonart	M	N	Y	Amatem	Yes	Y	₦450
Client 9	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Amatem	Yes	Y	₦450
Client 10	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Coartem	Yes	Y	₦250
Client 11	Secondary	Rural	Amatem/Coartem/Lonart	M	N	Y	Chloroquine	No	Y	₦80
Client 12	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Fansidar	No	Y	₦180
Client 13	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Coartem	Yes	Y	₦250
Client 14	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Chloroquine	No	Y	₦80
Client 15	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Fansidar	No	Y	₦180
Client 16	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Coartem	Yes	Y	₦250
Client 17	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Fansidar	No	Y	₦180
Client 18	Secondary	Rural	Amatem/Coartem/Lonart	M	N	Y	Fansidar	No	Y	₦180
Client 19	Secondary	Rural	Amatem/Coartem/Lonart	M	N	Y	Coartem	Yes	Y	₦250
Client 20	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Coartem	Yes	Y	₦250
Client 21	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Chloroquine	No	Y	₦80
Client 22	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Lonart	Yes	Y	₦700
Client 23	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Amatem	Yes	Y	₦450
Client 24	Secondary	Rural	Amatem/Coartem/Lonart	M	N	Y	Lonart	Yes	Y	₦700
Client 25	Secondary	Rural	Amatem/Coartem/Lonart	M	N	Y	Fansidar	No	Y	₦180
Client 26	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Chloroquine	No	Y	₦80
Client 27	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Coartem	Yes	Y	₦250
Client 28	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Amatem	Yes	Y	₦450
Client 29	Secondary	Rural	Amatem/Coartem/Lonart	M	N	Y	Chloroquine	No	Y	₦80
Client 30	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Chloroquine	No	Y	₦80
Client 31	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Chloroquine	No	Y	₦80
Client 32	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Chloroquine	No	Y	₦80
Client 33	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Amatem	Yes	Y	₦250
Client 34	Secondary	Rural	Amatem/Coartem/Lonart	F	N	Y	Lonart	No	Y	₦700

Pharmacy data Osun

	Education of pharmacist	Urban/Rural	Antimalarial mostly prescribed	sex of clie	proof of diagnosis	self-medicating?	Antimalarial purchased	ACT?	influence of pharmacist?	price
Client 1	Tertiary	Urban	Lonart/Combiart	M	Y	N	Lonart	Y	Y	₦950
Client 2	Tertiary	Urban	Lonart/Combiart	F	N	Y	Fansidar	N	Y	₦250
Client 3	Tertiary	Urban	Lonart/Combiart	F	N	Y	Fansidar	N	N	₦250
Client 4	Tertiary	Urban	Lonart/Combiart	M	Y	N	Lonart	Y	Y	₦950
Client 5	Tertiary	Urban	Lonart/Combiart	F	Y	N	Lonart	Y	Y	₦950
Client 6	Tertiary	Urban	Lonart/Combiart	F	N	Y	Lonart	Y	N	₦950
Client 7	Tertiary	Urban	Lonart/Combiart	M	Y	N	Chloroquine	N	N	₦80
Client 8	Tertiary	Urban	Lonart/Combiart	F	Y	N	Other		Y	₦1400
Client 9	Tertiary	Urban	Lonart/Combiart	M	N	Y	Fansidar	N	N	₦250
Client 10	Tertiary	Urban	Lonart/Combiart	F	N	Y	Lonart	Y	N	₦950
Client 11	Tertiary	Urban	Lonart/Combiart	M	N	Y	Fansidar	N	N	₦250
Client 12	Tertiary	Urban	Lonart/Combiart	F	Y	N	Lonart	Y	N	₦950
Client 13	Tertiary	Urban	Lonart/Combiart	M	N	Y	Coartem	Y	Y	₦1200
Client 14	Tertiary	Urban	Lonart/Combiart	F	N	Y	P-Alaxin	N	Y	₦600
Client 15	Tertiary	Urban	Lonart/Combiart	F	N	Y	Fansidar	N	N	₦250
Client 16	Tertiary	Urban	Lonart/Combiart	F	N	Y	Coartem	Y	Y	₦1200
Client 17	Tertiary	Urban	Lonart/Combiart	M	N	Y	Chloroquine	N	N	₦80
Client 18	Tertiary	Urban	Lonart/Combiart	F	Y	N	Lonart	Y	Y	₦950
Client 19	Tertiary	Urban	Lonart/Combiart	M	N	Y	Fansidar	N	N	₦250
Client 20	Tertiary	Urban	Lonart/Combiart	F	N	Y	Fansidar	N	N	₦250
Client 21	Tertiary	Urban	Lonart/Combiart	F	N	Y	Lonart	Y	Y	₦950
Client 22	Tertiary	Urban	Lonart/Combiart	F	N	Y	Lonart	Y	N	₦950
Client 23	Tertiary	Urban	Lonart/Combiart	M	Y	N	Lonart	Y	N	₦950
Client 24	Tertiary	Urban	Lonart/Combiart	M	Y	N	Chloroquine	N	N	₦80
Client 25	Tertiary	Urban	Lonart/Combiart	F	N	Y	Chloroquine	N	N	₦80
Client 26	Tertiary	Urban	Lonart/Combiart	M	N	Y	Coartem	Y	Y	₦1200
Client 27	Tertiary	Urban	Lonart/Combiart	F	N	Y	Fansidar	N	N	₦250
Client 28	Tertiary	Urban	Lonart/Combiart	F	N	Y	Chloroquine	N	N	₦80
Client 29	Tertiary	Urban	Lonart/Combiart	F	N	Y	Lonart	Y	N	₦950
Client 30	Tertiary	Urban	Lonart/Combiart	M	Y	N	Lonart	Y	N	₦950
Client 31	Tertiary	Urban	Lonart/Combiart	M	N	Y	Chloroquine	N	N	₦80
Client 32	Secondary	Rural	Amatem/Coartem	F	N	Y	Fansidar	Y	Y	₦1250
Client 33	Secondary	Rural	Amatem/Coartem	F	Y	N	Chloroquine	N	Y	₦1250
Client 34	Secondary	Rural	Amatem/Coartem	F	N	Y	Amatem	Y	Y	₦550
Client 35	Secondary	Rural	Amatem/Coartem	F	N	Y	Coartem	Y	Y	₦1250
Client 36	Secondary	Rural	Amatem/Coartem	M	N	Y	Chloroquine	N	Y	₦1250
Client 37	Secondary	Rural	Amatem/Coartem	F	Y	N	Coartem	Y	Y	₦1250
Client 38	Secondary	Rural	Amatem/Coartem	M	N	Y	Amatem	Y	Y	₦550
Client 39	Secondary	Rural	Amatem/Coartem	F	N	Y	Coartem	Y	Y	₦1250
Client 40	Secondary	Rural	Amatem/Coartem	F	N	Y	Chloroquine	N	Y	₦50
Client 41	Secondary	Rural	Amatem/Coartem	F	N	Y	Fansidar	Y	Y	₦1250
Client 42	Secondary	Rural	Amatem/Coartem	F	N	Y	Amatem	Y	Y	₦550
Client 43	Secondary	Rural	Amatem/Coartem	F	N	Y	Coartem	Y	Y	₦1250
Client 44	Secondary	Rural	Amatem/Coartem	F	N	Y	Chloroquine	N	Y	₦50
Client 45	Secondary	Rural	Amatem/Coartem	M	N	Y	Lonart	Y	Y	₦600
Client 46	Secondary	Rural	Amatem/Coartem	F	N	Y	Chloroquine	N	Y	₦950
Client 47	Secondary	Rural	Amatem/Coartem	F	N	Y	Coartem	Y	Y	₦1250
Client 48	Secondary	Rural	Amatem/Coartem	M	N	Y	Amatem	Y	Y	₦550
Client 49	Secondary	Rural	Amatem/Coartem	F	N	Y	Coartem	Y	Y	₦1250
Client 50	Secondary	Rural	Amatem/Coartem	F	N	Y	Coartem	Y	Y	₦1250
Client 51	Secondary	Rural	Amatem/Coartem	M	N	Y	Chloroquine	N	Y	₦1250
Client 52	Secondary	Rural	Amatem/Coartem	M	N	Y	Amatem	Y	Y	₦550
Client 53	Secondary	Rural	Amatem/Coartem	F	N	Y	Coartem	Y	Y	₦1250
Client 54	Secondary	Rural	Amatem/Coartem	M	Y	N	Lonart	Y	Y	₦950
Client 55	Secondary	Rural	Amatem/Coartem	F	N	Y	Fansidar	N	Y	₦550
Client 56	Secondary	Rural	Amatem/Coartem	F	N	Y	Fansidar	N	Y	₦1250
Client 57	Secondary	Rural	Amatem/Coartem	M	N	Y	Coartem	Y	Y	₦1250
Client 58	Tertiary	Urban	Combisunate/Coartem	M	Y	N	Lonart	Y	Y	₦950
Client 59	Tertiary	Urban	Combisunate/Coartem	F	N	Y	Fansidar	N	Y	₦250
Client 60	Tertiary	Urban	Combisunate/Coartem	F	N	Y	Fansidar	N	N	₦250
Client 61	Tertiary	Urban	Combisunate/Coartem	M	Y	N	Lonart	Y	Y	₦950
Client 62	Tertiary	Urban	Combisunate/Coartem	F	Y	N	Lonart	Y	Y	₦950
Client 63	Tertiary	Urban	Combisunate/Coartem	F	N	Y	Lonart	Y	N	₦950
Client 64	Tertiary	Urban	Combisunate/Coartem	M	Y	N	Chloroquine	N	N	₦80
Client 65	Tertiary	Urban	Combisunate/Coartem	F	Y	N	Other	N	Y	₦1400
Client 66	Tertiary	Urban	Combisunate/Coartem	M	N	Y	Fansidar	N	N	₦250
Client 67	Tertiary	Urban	Combisunate/Coartem	F	N	Y	Lonart	Y	N	₦950
Client 68	Tertiary	Urban	Combisunate/Coartem	M	N	Y	Fansidar	N	N	₦250
Client 69	Tertiary	Urban	Combisunate/Coartem	F	Y	N	Lonart	Y	N	₦950
Client 70	Tertiary	Urban	Combisunate/Coartem	M	N	Y	Coartem	Y	Y	₦1200
Client 71	Tertiary	Urban	Combisunate/Coartem	F	N	Y	P-Alaxin	Y	Y	₦600
Client 72	Tertiary	Urban	Combisunate/Coartem	F	N	Y	Fansidar	N	N	₦250
Client 73	Tertiary	Urban	Combisunate/Coartem	F	N	Y	Coartem	Y	N	₦1200
Client 74	Tertiary	Urban	Combisunate/Coartem	M	N	Y	Chloroquine	N	N	₦80
Client 75	Tertiary	Urban	Lonart/Combiart	F	Y	N	Lonart	Y	Y	₦950
Client 76	Tertiary	Urban	Lonart/Combiart	M	N	Y	Fansidar	N	N	₦250
Client 77	Tertiary	Rural	Lonart/Combiart	F	N	Y	Fansidar	N	N	₦250
Client 78	Tertiary	Rural	Lonart/Combiart	F	N	Y	Lonart	Y	Y	₦950
Client 79	Tertiary	Rural	Lonart/Combiart	F	N	Y	Lonart	Y	N	₦950
Client 80	Tertiary	Rural	Lonart/Combiart	M	Y	N	Lonart	Y	N	₦950
Client 81	Tertiary	Rural	Lonart/Combiart	M	Y	N	Chloroquine	N	N	₦80
Client 82	Tertiary	Rural	Lonart/Combiart	F	N	Y	Chloroquine	N	N	₦80
Client 83	Tertiary	Rural	Lonart/Combiart	M	N	Y	Coartem	Y	Y	₦1200
Client 84	Tertiary	Rural	Lonart/Combiart	F	N	Y	Fansidar	N	N	₦250
Client 85	Tertiary	Rural	Lonart/Combiart	F	N	Y	Chloroquine	N	Y	₦80
Client 86	Tertiary	Urban	Lonart/Amatem	F	N	Y	Lonart	Y	Y	₦950
Client 87	Tertiary	Urban	Lonart/Amatem	M	Y	N	Lonart	Y	Y	₦950

Client 88	Tertiary	Urban	Lonart/Amatem	M	Y	N	Lonart	Y	Y	₦950
Client 89	Tertiary	Urban	Lonart/Amatem	M	Y	N	Coartem	Y	N	₦1200
Client 90	Tertiary	Urban	Lonart/Amatem	M	Y	N	Amatem	Y	N	₦550
Client 91	Tertiary	Urban	Lonart/Amatem	M	Y	N	Chloroquine	N	N	₦80
Client 92	Tertiary	Urban	Lonart/Amatem	M	Y	N	Chloroquine	N	N	₦80
Client 93	Tertiary	Urban	Lonart/Amatem	M	Y	N	Amatem	Y	N	₦550
Client 94	Tertiary	Urban	Lonart/Amatem	M	N	Y	Lonart	Y	N	₦950
Client 95	Tertiary	Urban	Lonart/Amatem	M	N	Y	Lonart	Y	N	₦950
Client 96	Tertiary	Urban	Lonart/Amatem	M	Y	N	Chloroquine	N	Y	₦80
Client 97	Tertiary	Urban	Lonart/Amatem	M	Y	N	Fansidar	N	Y	₦250
Client 98	Tertiary	Urban	Lonart/Amatem	M	Y	N	Lonart	Y	Y	₦950
Client 99	Tertiary	Urban	Lonart/Amatem	M	Y	N	Lonart	Y	N	₦950
Client 100	Tertiary	Urban	Lonart/Amatem	M	Y	N	Amatem	Y	N	₦550
Client 101	Tertiary	Urban	Lonart/Amatem	M	N	Y	Lonart	Y	N	₦950
Client 102	Tertiary	Rural	Lonart/Combiart	M	Y	N	Chloroquine	N	N	₦80
Client 103	Tertiary	Rural	Lonart/Combiart	M	Y	N	Lonart	Y	N	₦950
Client 104	Tertiary	Rural	Lonart/Combiart	M	N	Y	Chloroquine	N	N	₦80
Client 105	Tertiary	Rural	Lonart/Combiart	M	Y	N	Amatem	Y	N	₦550
Client 106	Tertiary	Rural	Lonart/Combiart	M	Y	N	Fansidar	N	N	₦250
Client 107	Tertiary	Rural	Lonart/Combiart	M	N	Y	Fansidar	N	N	₦250
Client 108	Tertiary	Rural	Lonart/Combiart	M	N	Y	Fansidar	N	N	₦250
Client 109	Tertiary	Rural	Lonart/Combiart	M	Y	N	Chloroquine	N	N	₦80
Client 110	Tertiary	Rural	Lonart/Combiart	M	N	Y	Other	N	N	₦973
Client 111	Tertiary	Rural	Lonart/Combiart	M	N	Y	Coartem	Y	N	₦1200
Client 112	Tertiary	Rural	Lonart/Combiart	M	N	Y	Amatem	Y	N	₦550
Client 113	Tertiary	Rural	Lonart/Combiart	M	Y	N	Amatem	Y	N	₦550
Client 114	Tertiary	Rural	Lonart/Combiart	M	Y	N	Chloroquine	N	N	₦80
Client 115	Tertiary	Urban	Lonart/Amatem	M	Y	N	Chloroquine	N	N	₦80
Client 116	Tertiary	Urban	Lonart/Amatem	M	Y	N	Lonart	Y	Y	₦950
Client 117	Tertiary	Urban	Lonart/Amatem	M	Y	N	Amatem	Y	N	₦550
Client 118	Tertiary	Urban	Lonart/Amatem	M	Y	N	Amatem	Y	N	₦550
Client 119	Tertiary	Urban	Lonart/Amatem	M	Y	N	Amatem	Y	N	₦550
Client 120	Tertiary	Urban	Lonart/Amatem	M	Y	N	Lonart	Y	N	₦950
Client 121	Tertiary	Urban	Lonart/Amatem	M	Y	N	Amatem	Y	N	₦550
Client 122	Tertiary	Urban	Lonart/Amatem	M	Y	N	Chloroquine	N	N	₦80
Client 123	Tertiary	Urban	Lonart/Amatem	M	Y	N	Amatem	Y	Y	₦550
Client 124	Tertiary	Urban	Lonart/Amatem	M	N	Y	Chloroquine	N	N	₦80
Client 125	Tertiary	Urban	Lonart/Amatem	M	N	Y	Fansidar	N	N	₦250
Client 126	Tertiary	Urban	Lonart/Amatem	M	N	Y	Lonart	Y	N	₦950
Client 127	Tertiary	Urban	Lonart/Amatem	M	Y	N	Lonart	Y	N	₦950
Client 128	Tertiary	Urban	Lonart/Amatem	M	N	Y	Amatem	Y	N	₦550
Client 129	Tertiary	Urban	Lonart/Amatem	M	Y	N	Amatem	Y	N	₦550
Client 130	Tertiary	Urban	Lonart/Amatem	M	Y	N	Amatem	Y	N	₦550
Client 131	Tertiary	Urban	Lonart/Amatem	M	Y	N	Amatem	Y	N	₦550
Client 132	Tertiary	Urban	Lonart/Amatem	M	Y	N	Chloroquine	N	N	₦80
Client 133	Tertiary	Urban	Lonart/Amatem	M	N	Y	Amatem	Y	Y	₦550
Client 134	Tertiary	Urban	Lonart/Amatem	M	Y	N	Amatem	Y	Y	₦550
Client 135	Tertiary	Urban	Lonart/Amatem	M	N	Y	Lonart	Y	Y	₦950
Client 136	Tertiary	Urban	Lonart/Amatem	M	Y	N	Chloroquine	N	Y	₦80
Client 137	Tertiary	Rural	Combisunate/Amatem	M	N	Y	Lonart	Y	N	₦950
Client 138	Tertiary	Rural	Combisunate/Amatem	M	N	Y	Combisunate	Y	N	₦950
Client 139	Tertiary	Rural	Combisunate/Amatem	M	N	Y	Combisunate	Y	N	₦950
Client 140	Tertiary	Rural	Combisunate/Amatem	M	N	Y	Lonart	Y	N	₦950
Client 141	Tertiary	Rural	Combisunate/Amatem	M	N	Y	Chloroquine	N	Y	₦80
Client 142	Tertiary	Rural	Combisunate/Amatem	M	N	Y	Lonart	Y	Y	₦950
Client 143	Tertiary	Rural	Combisunate/Amatem	M	N	Y	Combisunate	Y	Y	₦950
Client 144	Tertiary	Rural	Combisunate/Amatem	M	N	Y	Amatem	Y	N	₦550
Client 145	Tertiary	Rural	Combisunate/Amatem	M	N	Y	Fansidar	N	N	₦250
Client 146	Tertiary	Rural	Combisunate/Amatem	M	N	Y	Lonart	Y	N	₦950
Client 147	Tertiary	Rural	Combisunate/Amatem	M	N	Y	Combisunate	Y	Y	₦950
Client 148	Tertiary	Rural	Combisunate/Amatem	M	N	Y	Chloroquine	Y	N	₦80
Client 149	Tertiary	Rural	Combisunate/Amatem	M	N	Y	Chloroquine	N	N	₦80
Client 150	Tertiary	Rural	Combisunate/Amatem	M	N	Y	Chloroquine	N	N	₦80
Client 151	Tertiary	Rural	Combisunate/Amatem	M	Y	N	Chloroquine	N	Y	₦80
Client 152	Tertiary	Rural	Combisunate/Amatem	M	N	Y	Fansidar	N	N	₦250
Client 153	Tertiary	Rural	Combisunate/Amatem	M	N	Y	Lonart	Y	N	₦950
Client 154	Tertiary	Rural	Combisunate/Amatem	M	N	Y	Amatem	Y	Y	₦550
Client 155	Tertiary	Rural	Combisunate/Amatem	M	Y	N	Amatem	Y	Y	₦550
Client 156	Tertiary	Rural	Combisunate/Amatem	M	N	Y	Amatem	Y	Y	₦550
Client 157	Tertiary	Rural	Combisunate/Amatem	M	N	Y	Amatem	Y	Y	₦550
Client 158	Tertiary	Rural	Combisunate/Amatem	M	N	Y	Combisunate	Y	N	₦950
Client 159	Tertiary	Rural	Combisunate/Amatem	M	N	Y	Combisunate	Y	N	₦950

Client 160	Tertiary	Urban	Lonart/Amatem	M	N	Y	Chloroquine	N	Y	₦80
Client 161	Tertiary	Urban	Lonart/Amatem	M	Y	N	Lonart	Y	N	₦950
Client 162	Tertiary	Urban	Lonart/Amatem	M	Y	N	Lonart	Y	N	₦950
Client 163	Tertiary	Urban	Lonart/Amatem	M	Y	N	Lonart	Y	Y	₦950
Client 164	Tertiary	Urban	Lonart/Amatem	M	N	Y	Lonart	Y	N	₦950
Client 165	Tertiary	Urban	Lonart/Amatem	M	N	Y	Amatem	Y	N	₦550
Client 166	Tertiary	Urban	Lonart/Amatem	M	N	Y	Amatem	Y	Y	₦550
Client 167	Tertiary	Urban	Lonart/Amatem	M	Y	N	Amatem	Y	N	₦550
Client 168	Tertiary	Urban	Lonart/Amatem	M	Y	N	Coartem	Y	N	₦1200
Client 169	Tertiary	Urban	Lonart/Amatem	M	Y	N	Coartem	Y	N	₦1200
Client 170	Tertiary	Rural	Lonart/Coartem	M	Y	N	Lonart	Y	N	₦950
Client 171	Tertiary	Rural	Lonart/Coartem	M	N	Y	Lonart	Y	N	₦950
Client 172	Tertiary	Rural	Lonart/Coartem	M	N	Y	Lonart	Y	N	₦950
Client 173	Tertiary	Rural	Lonart/Coartem	M	Y	N	Fansidar	N	Y	₦250
Client 174	Tertiary	Rural	Lonart/Coartem	M	Y	N	Fansidar	N	Y	₦250
Client 175	Tertiary	Rural	Lonart/Coartem	M	N	Y	Lonart	Y	Y	₦950
Client 176	Tertiary	Rural	Lonart/Coartem	M	N	Y	Lonart	Y	Y	₦950
Client 177	Tertiary	Rural	Lonart/Coartem	M	N	Y	Amatem	Y	Y	₦550
Client 178	Tertiary	Rural	Lonart/Coartem	M	N	Y	Lonart	Y	Y	₦950
Client 179	Tertiary	Rural	Lonart/Coartem	M	N	Y	Coartem	Y	Y	₦1200
Client 180	Tertiary	Rural	Lonart/Coartem	M	Y	N	Lonart	Y	Y	₦950
Client 1	Secondary	Rural	Amatem/Coartem	F	N	Y	CHLOROQUINE	No	Y	₦50
Client 2	Secondary	Rural	Amatem/Coartem	F	Y	N	CHLOROQUINE	No	Y	₦50
client 3	Secondary	Rural	Amatem/Coartem	F	N	Y	Amatem	Yes	Y	₦550
Client 4	Secondary	Rural	Amatem/Coartem	F	N	Y	FANSIDAR	No	Y	₦250
Client 5	Secondary	Rural	Amatem/Coartem	M	N	Y	FANSIDAR	No	Y	₦250
Client 6	Secondary	Rural	Amatem/Coartem	F	Y	N	AMATEM	Yes	Y	₦550
Client 7	Secondary	Rural	Amatem/Coartem	M	N	Y	CHLOROQUINE	No	Y	₦50
Client 8	Secondary	Rural	Amatem/Coartem	F	N	Y	Coartem	Yes	Y	₦1250
Client 9	Secondary	Rural	Amatem/Coartem	F	N	Y	CHLOROQUINE	No	Y	₦50
Client 10	Secondary	Rural	Amatem/Coartem	F	N	Y	CHLOROQUINE	No	Y	₦50
Client 11	Secondary	Rural	Amatem/Coartem	F	N	Y	AMATEM	Yes	Y	₦550
Client 12	Secondary	Rural	Amatem/Coartem	F	N	Y	CHLOROQUINE	No	Y	₦50
Client 13	Secondary	Rural	Amatem/Coartem	F	N	Y	CHLOROQUINE	No	Y	₦50
Client 14	Secondary	Rural	Amatem/Coartem	M	N	Y	LONART	Yes	Y	₦600
Client 15	Secondary	Rural	Amatem/Coartem	F	N	Y	COARTEM	Yes	Y	₦1250
Client 16	Secondary	Rural	Amatem/Coartem	F	N	Y	COARTEM	Yes	Y	₦1250
Client 17	Secondary	Rural	Amatem/Coartem	M	N	Y	CHLOROQUINE	No	Y	₦80
Client 18	Secondary	Rural	Amatem/Coartem	F	N	Y	CHLOROQUINE	No	Y	₦1250
Client 19	Secondary	Rural	Amatem/Coartem	F	N	Y	COARTEM	Yes	Y	₦1250
Client 20	Secondary	Rural	Amatem/Coartem	M	N	Y	FANSIDAR	No	Y	₦250
Client 21	Secondary	Rural	Amatem/Coartem	M	N	Y	FANSIDAR	No	Y	₦250
Client 22	Secondary	Rural	Amatem/Coartem	F	N	Y	CHLOROQUINE	No	Y	₦80
Client 23	Secondary	Rural	Amatem/Coartem	M	Y	N	CHLOROQUINE	No	Y	₦80
Client 24	Secondary	Rural	Amatem/Coartem	F	N	Y	FANSIDAR	No	Y	₦250
Client 25	Secondary	Rural	Amatem/Coartem	F	N	Y	FANSIDAR	No	Y	₦250
Client 26	Secondary	Rural	Amatem/Coartem	M	N	Y	CHLOROQUINE	No	Y	₦80
Client 1	Tertiary	Urban	Lonart/Combiart	M	Y	N	Lonart	Yes	Y	₦950
Client 2	Tertiary	Urban	Lonart/Combiart	F	N	Y	Fansidar	No	Y	₦250
client 3	Tertiary	Urban	Lonart/Combiart	F	N	Y	Fansidar	No	N	₦250
Client 4	Tertiary	Urban	Lonart/Combiart	M	Y	N	Lonart	Yes	Y	₦950
Client 5	Tertiary	Urban	Lonart/Combiart	F	Y	N	Lonart	Yes	Y	₦950
Client 6	Tertiary	Urban	Lonart/Combiart	F	N	Y	Lonart	Yes	N	₦950
Client 7	Tertiary	Urban	Lonart/Combiart	M	Y	N	Chloroquine	No	N	₦80
Client 8	Tertiary	Urban	Lonart/Combiart	F	Y	N	Other		Y	₦1400
Client 9	Tertiary	Urban	Lonart/Combiart	M	N	Y	Fansidar	No	N	₦250
Client 10	Tertiary	Urban	Lonart/Combiart	F	N	Y	Lonart	Yes	N	₦950
Client 11	Tertiary	Urban	Lonart/Combiart	M	N	Y	Fansidar	No	N	₦250
Client 12	Tertiary	Urban	Lonart/Combiart	F	Y	N	Lonart	Yes	N	₦950
Client 13	Tertiary	Urban	Lonart/Combiart	M	N	Y	Coartem	Yes	Y	₦1200
Client 14	Tertiary	Urban	Lonart/Combiart	F	N	Y	P-Alaxin	Yes	Y	₦600
Client 15	Tertiary	Urban	Lonart/Combiart	F	N	Y	Fansidar	No	N	₦250
Client 16	Tertiary	Urban	Lonart/Combiart	F	N	Y	Coartem	Yes	N	₦1200
Client 17	Tertiary	Urban	Lonart/Combiart	M	N	Y	Chloroquine	No	N	₦80
Client 18	Tertiary	Urban	Lonart/Combiart	F	Y	N	Lonart	Yes	Y	₦950
Client 19	Tertiary	Urban	Lonart/Combiart	M	N	Y	Fansidar	No	N	₦250
Client 20	Tertiary	Urban	Lonart/Combiart	F	N	Y	Fansidar	No	N	₦250
Client 21	Tertiary	Urban	Lonart/Combiart	F	N	Y	Lonart	Yes	Y	₦950
Client 22	Tertiary	Urban	Lonart/Combiart	F	N	Y	Lonart	Yes	N	₦950
Client 23	Tertiary	Urban	Lonart/Combiart	M	Y	N	Lonart	Yes	N	₦950
Client 24	Tertiary	Urban	Lonart/Combiart	M	Y	N	Chloroquine	No	N	₦80
Client 25	Tertiary	Urban	Lonart/Combiart	F	N	Y	Chloroquine	No	N	₦80
Client 26	Tertiary	Urban	Lonart/Combiart	M	N	Y	Coartem	Yes	Y	₦1200
Client 27	Tertiary	Urban	Lonart/Combiart	F	N	Y	Fansidar	No	N	₦250
Client 28	Tertiary	Urban	Lonart/Combiart	F	N	Y	Chloroquine	No	N	₦80
Client 29	Tertiary	Urban	Lonart/Combiart	F	N	Y	Lonart	Yes	N	₦950
Client 30	Tertiary	Urban	Lonart/Combiart	M	Y	N	Lonart	Yes	N	₦950
Client 31	Tertiary	Urban	Lonart/Combiart	M	N	Y	Chloroquine	No	N	₦80

Appendix IV: List of drugs

ANTIMALARIAL	ACT?	STATE	URBAN/RURAL	STORE	CONTENT	RATIO	MANUFACTURER	EXPIRY DATE	SOLUBILITY	DOSAGE	WEIGHT PER TABLET
Combisunate	ACT	Osun	Rural	Pharmacy	Artemether/Lumefantrine	20/120	Ajanta pharma ltd	Jul-18	Chloroform	4tablet 1st dose 4 tablet 8 hours after 1st dose 4 tablet 24 hours after 1st dose 4 tablet 36hours after 1st dose 4 tablet 48 hours after 1st dose 4 tablet 60 hours after 1st dose	0.25g
Chloroquine	Quinine	Osun	urban	Pharmacy	quinine		Alben Healthcare Ltd	Jun-18	freely soluble in water	4 tablets per day for the 1st two days 2 per day for the next two weeks	0.33g
Fansidar	SP	Osun	Rural	vendor	sulfadoxine/pyrimethamine	500/20mg	swiss pharma ltd	Oct-19		3 tablets (one dose)	0.70g
Lonart	ACT	Osun	Rural	vendor	Artemether/Lumefantrine	80/480	Bliss GVS		Chloroform	1 tablet 1st dose 1 tablet 8 hours after 1st dose 1 tablet 24 hours after 1st dose 1 tablet 36hours after 1st dose 1 tablet 48 hours after 1st dose 1 tablet 60 hours after 1st dose	0.70g
Lumartem	ACT	Osun	urban	Pharmacy	Artemether/Lumefantrine	20/120	Cipla ltd	Feb-17	Chloroform	4tablet 1st dose 4 tablet 8 hours after 1st dose 4 tablet 24 hours after 1st dose 4 tablet 36hours after 1st dose 4 tablet 48 hours after 1st dose 4 tablet 60 hours after 1st dose	0.37g
Chloroquine	Quinine	Osun	Rural	vendor	quinine		jopan pharmaceutical	Jun-19	freely soluble in water	4 tablets per day for the 1st two days 2 per day for the next two weeks	0.33g
Lonart	ACT	lagos	urban	Pharmacy	Artemether/Lumefantrine	80/480	Bliss GVS	Sep-17	Chloroform	1 tablet 1st dose 1 tablet 8 hours after 1st dose 1 tablet 24 hours after 1st dose 1 tablet 36hours after 1st dose 1 tablet 48 hours after 1st dose 1 tablet 60 hours after 1st dose	0.70g
Combisunate	ACT	lagos	urban	Pharmacy	Artemether/Lumefantrine	20/120	Ajanta pharma ltd	Sep-17	Chloroform	4tablet 1st dose 4 tablet 8 hours after 1st dose 4 tablet 24 hours after 1st dose 4 tablet 36hours after 1st dose 4 tablet 48 hours after 1st dose 4 tablet 60 hours after 1st dose	0.25g
Fansidar	SP	lagos	rural	Pharmacy	sulfadoxine/pyrimethamine		swiss pharma ltd	Dec-19		3 tablets (one dose)	0.70g
Chloroquine	Quinine	lagos	Rural	Pharmacy	quinine				freely soluble in water	4 tablets per day for the 1st two days 2 per day for the next two weeks	0.33g
Chloroquine	Quinine	lagos	urban	Pharmacy	quinine		dana pharmaceuticals	Dec-17	freely soluble in water	4 tablets per day for the 1st two days 2 per day for the next two weeks	0.33g
Fansidar	sp	lagos	urban	Pharmacy	sulfadoxine/pyrimethamine		Swiss pharma ltd	Jan-20		3 tablets (one dose)	0.70g
Lonart	ACT	Osun	urban	Pharmacy	Artemether/Lumefantrine	80/480	Bliss GVS	Nov-18	Chloroform	1 tablet 1st dose 1 tablet 8 hours after 1st dose 1 tablet 24 hours after 1st dose 1 tablet 36hours after 1st dose 1 tablet 48 hours after 1st dose 1 tablet 60 hours after 1st dose	0.70g
Lonart	ACT	lagos	urban	vendor	Artemether/Lumefantrine	80/480	Bliss GVS	Nov-17	Chloroform	1 tablet 1st dose 1 tablet 8 hours after 1st dose 1 tablet 24 hours after 1st dose 1 tablet 36hours after 1st dose 1 tablet 48 hours after 1st dose 1 tablet 60 hours after 1st dose	0.70g
Chloroquine	Quinine	lagos	Rural	vendor	quinine		Alben Healthcare Ltd	Sep-17	freely soluble in water	4 tablets per day for the 1st two days 2 per day for the next two weeks	0.33g
Combisunate	ACT	Osun	urban	vendor	Artemether/Lumefantrine	20/120	Ajanta pharma ltd	Jul-17	Chloroform	4tablet 1st dose 4 tablet 8 hours after 1st dose 4 tablet 24 hours after 1st dose 4 tablet 36hours after 1st dose 4 tablet 48 hours after 1st dose 4 tablet 60 hours after 1st dose	0.25g

Lonart	ACT	Osun	Rural		Artemether/Lumefantrine	80/480		Nov-17	Chloroform	1 tablet 1st dose 1 tablet 8 hours after 1st dose 1 tablet 24 hours after 1st dose 1 tablet 36hours after 1st dose 1 tablet 48 hours after 1st dose 1 tablet 60 hours after 1st dose	0.70g
Amatem	ACT	Osun	urban		Artemether/Lumefantrine	80/480	elbe pharma	Feb-18	Cloroform	1 tablet 1st dose 1 tablet 8 hours after 1st dose 1 tablet 24 hours after 1st dose 1 tablet 36hours after 1st dose 1 tablet 48 hours after 1st dose 1 tablet 60 hours after 1st dose	0.70g
Coartem	ACT	lagos	urban	Pharmacy	Artemether/Lumefantrine	20/120		Oct-18	Cloroform	4 tablets 1st dose 4 tablets 8 hours after 1st dose 4 tablets 24 hours after 1st dose 4 tablets 36hours after 1st dose 4 tablets 48 hours after 1st dose 4 tablets 60 hours after 1st dose	0.25g
Coartem	ACT	lagos	urban	Pharmacy	Artemether/Lumefantrine	80/480		Oct-17	Cloroform	1 tablet 1st dose 1 tablet 8 hours after 1st dose 1 tablet 24 hours after 1st dose 1 tablet 36hours after 1st dose 1 tablet 48 hours after 1st dose 1 tablet 60 hours after 1st dose	0.99g
Coartem	ACT	lagos	urban	Pharmacy	Artemether/Lumefantrine	20/120		Oct-18	Chloroform	4 tablets 1st dose 4 tablets 8 hours after 1st dose 4 tablets 24 hours after 1st dose 4 tablets 36hours after 1st dose 4 tablets 48 hours after 1st dose 4 tablets 60 hours after 1st dose	0.25g
Coartem 2	ACT	lagos	urban	Pharmacy	Artemether/Lumefantrine	80/480		Oct-17	Chloroform	1 tablet 1st dose 1 tablet 8 hours after 1st dose 1 tablet 24 hours after 1st dose 1 tablet 36hours after 1st dose 1 tablet 48 hours after 1st dose 1 tablet 60 hours after 1st dose	0.99g
Fansidar	SP	lagos	urban	Pharmacy	sulfadoxine/pyrimethamine	500/25mg		May-21		3 tablets (one dose)	
Lonart	ACT	lagos	urban	Pharmacy	Artemether/Lumefantrine	80/480		Aug-17	Chloroform	1 tablet 1st dose 1 tablet 8 hours after 1st dose 1 tablet 24 hours after 1st dose 1 tablet 36hours after 1st dose 1 tablet 48 hours after 1st dose 1 tablet 60 hours after 1st dose	0.70g
Amatem	ACT	lagos	urban	Pharmacy	Artemether/Lumefantrine	80/480		Nov-17	Chloroform	1 tablet 1st dose 1 tablet 8 hours after 1st dose 1 tablet 24 hours after 1st dose 1 tablet 36hours after 1st dose 1 tablet 48 hours after 1st dose 1 tablet 60 hours after 1st dose	0.70g

Chloroquine	Quinine	lagos	urban	Pharmacy	quinine	250mg		Apr-19	freely soluble in water	4 tablets per day for the 1st two days 2 per day for the next two weeks	
Amatem	ACT	lagos	urban	Pharmacy	Artemether/Lumefantrine	80/480		Nov-17	Chloroform	1 tablet 1st dose 1 tablet 8 hours after 1st dose 1 tablet 24 hours after 1st dose 1 tablet 36hours after 1st dose 1 tablet 48 hours after 1st dose 1 tablet 60 hours after 1st dose	
Lonart	ACT	lagos	urban	Pharmacy	Artemether/Lumefantrine	80/480		Aug-17	Chloroform	1 tablet 1st dose 1 tablet 8 hours after 1st dose 1 tablet 24 hours after 1st dose 1 tablet 36hours after 1st dose 1 tablet 48 hours after 1st dose 1 tablet 60 hours after 1st dose	0.70g
Fansidar	ACT	lagos	urban	Pharmacy	sulfadoxine/pyrimethamine	500/25MG		May-21		3 tablets (one dose)	
Lonart	ACT	lagos	urban	Pharmacy	Artemether/Lumefantrine	80/480		Mar-17	Chloroform	1 tablet 1st dose 1 tablet 8 hours after 1st dose 1 tablet 24 hours after 1st dose 1 tablet 36hours after 1st dose 1 tablet 48 hours after 1st dose 1 tablet 60 hours after 1st dose	0.70g
Combisunate	ACT	lagos	urban	Pharmacy	Artemether/Lumefantrine	80/480		Nov-17	Chloroform	4tablet 1st dose 4 tablet 8 hours after 1st dose 4 tablet 24 hours after 1st dose 4 tablet 36hours after 1st dose 4 tablet 48 hours after 1st dose 4 tablet 60 hours after 1st dose	0.25g
Chloroquine	Quinine	lagos	urban	Pharmacy	quinine	250mg		Apr-19	freely soluble in water	4 tablets per day for the 1st two days 2 per day for the next two weeks	0.33g
Maladar											
Combiart	ACT	Osun	Rural	Pharmacy	Artemether/Lumefantrine	80/480				1 tablet 1st dose 1 tablet 8 hours after 1st dose 1 tablet 24 hours after 1st dose 1 tablet 36hours after 1st dose 1 tablet 48 hours after 1st dose 1 tablet 60 hours after 1st dose	0.70g
Artesunate	ACT	lagos	urban	Pharmacy					Methanol Water	4 tablets 1st day 4 tablet 8 hours after first dose 4 tablets daily afterwards	0.25g

Appendix V: Drug calculation

Region	Drug name (Code)	Drug weight	Artemether/lumefantrine ratio	Quantity needed in 1 ml for 5 nM solution
Lagos rural	A	230 mg (0.23g)	20/120 mg	17.1565 mg
	B	730 mg (0.73g)	80/480 mg	13.6133 mg
	C	250 mg (0.25g)	20/120 mg	18.6483 mg
	D	680 mg (0.68g)	80/480 mg	12.6809 mg
	E	680 mg (0.68g)	80/480 mg	12.6809 mg
	F	230 mg (0.23g)	20/120 mg	17.1565 mg
	1F	250 mg (0.25g)	20/120 mg	18.6483 mg
	1D	230 mg (0.23g)	20/120 mg	17.1565 mg
Lagos urban	G	950 mg (0.95g)	80/480 mg	17.7160 mg
	H	250 mg (0.25g)	20/120 mg	18.6483 mg
	I	250 mg (0.25g)	20/120 mg	18.6483 mg
	J	680 mg (0.68g)	80/480 mg	12.6809 mg
	K	680 mg (0.68g)	80/480 mg	12.6809 mg
Osun rural	L	230 mg (0.23g)	20/120 mg	17.1565 mg
	M	960 mg (0.96g)	80/480 mg	17.9024 mg
	N	730 mg (0.73g)	80/480 mg	13.6133 mg
	O	680 mg (0.68g)	80/480 mg	12.6809 mg
	1K	250 mg (0.25g)	20/120 mg	18.6483 mg
Osun urban	P	230 mg (0.23g	20/120 mg	17.1565 mg
	Q	680 mg (0.68g)	80/480 mg	12.6809 mg
	R	730 mg (0.73g)	80/480 mg	13.6133 mg
	S	250 mg (0.25g)	20/120 mg	18.6483 mg
	T	730 mg (0.73g)	80/480 mg	13.6133 mg

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