KWAME NKRUMAH UNIVERSITY OF SCIENCE AND TECHNOLOGY, KUMASI, GHANA

Assessing the impact of introducing rapid diagnostic testing on malaria case detection at retail pharmacies in Ghana

by

Audu Rauf

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DECLARATION

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

Audu Rauf
Student Name & ID 20292113

……
Signature

……
Date

Certified by:

Prof. Berko Panyin Anto
Supervisor

……..
Signature

……
Date

Certified by:
Prof. Kwame Ohene Buabeng
Head of Department

……
Signature

……
Date

ABSTRACT

Background

In 2010, the World Health Organization issued a guideline that called for a shift from presumptive malaria treatment to test-based treatment. However, test-based treatment is still unpopular in a number of community pharmacies in Ghana. The purpose of this study was to assess the use of malaria rapid diagnostic testing in the management of suspected malaria cases at retail pharmacies in Ghana.

Methods

This study was done in 3 phases. The first was exploratory baseline study, in which a questionnaire was used to interview patients exiting on mode of diagnosis to establish the malaria diagnostic practices, understanding of the treatment and satisfaction of health care services. An interview also with retail pharmacists to assess their acceptance of mRDTs at their facilities.

The second was an intervention study evaluating mRDTs (intervention) and PD (control) at retail pharmacies, and assessing pharmacists' level of adherence to test results.

The third phase was assessing the cost-benefit of mRDTs at private retail pharmacies using Willingness-To-Pay payment technique and direct and indirect cost approach.

Results

Most of the practitioners diagnosed malaria presumptively (83.0%, n = 44) as against (17.0%, n = 9). About 50% of pharmacists agreed to implement mRDTs. Sensitivity and specificity of the mRDTs were 90.68 $\pm$ 11.18% and 98.68 $\pm$ 1.19%, respectively. The Positive Predictive Value and Negative Predictive Value were both 98.0%; and false discovery rate, and false omission rate, were both 2.0%. Patients tested negative with

mRDTs, 212 (62.0%) received ACTs. The benefit- cost ratio obtained for using mRDTs was 1.11.

Conclusions

Malaria diagnosis is largely presumptive. Generally, the patients have shown good understanding of treatment and satisfaction of health care services received. However, an indication to implement test-based diagnosis by pharmacist has been expressed, in spite of not routinely using diagnostic results. The performance of mRDTs in private retail pharmacies has shown much better accuracy than presumptive diagnosis in detecting malaria illness. Treatment based on tests result was not properly adhered to, and the cost benefit analysis of using mRDT was shown to be beneficial with much better economic value.

DEDICATION

Dedicate to my parents, family and siblings.

ACKNOWLEDGEMENT

First and foremost, I give glory and thanks to Almighty, Allah (SWT) for reaching this far. I gratefully register my indebtedness to my supervisor, Prof. Berko Panyin Anto, whose rich guidance, patience and encouragement contributed immensely to this successful and memorable journey.

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1. Rauf Audu, Berko Panyin Anto, George Asumeng Koffuor, Akua Afriyie Abruquah, Kwame Ohene Buabeng (2016). Malaria rapid diagnostic test evaluation at private retail pharmacies in Kumasi, Ghana. *J Res Pharm Pract*, 5: 175 – 80.
2. Rauf Audu, Berko Panyin Anto, George Asumeng Koffuor, Kwame Ohene Buabeng, Mohammed Abdul-Kabir (2014). Introducing Malaria Rapid Diagnostic Testing (MRDTs) at registered retail pharmacies in Ghana: Practitioners' perspective. *Br J Pharm Res*. 4(8): 943-53.
3. Rauf Audu, Anto BP, Koffuor GA, Buabeng KO, Abdul-Kabir M (2014). Assessing the diagnosis of uncomplicated malaria after introduction of malaria rapid diagnostic tests. *Br J Med Res*, 4: 3167-78.

ABBREVIATIONS AND TERMS

ACT	Artemisinin-based Combination Therapy
AIDS	Acquired Immunodeficiency Syndrome
ADR	Adverse Drug Reactions
AV	Average Value
AS/AQ	Artesunate/Amodiaquine
ARPCS	Ashanti Regional Pharmacy Council Secretariat
BCR	Benefit-Cost Ratio
CRF	Case Reporting Form
CD	Clinical Diagnosis
CBQ	Cost-Benefit Questionnaire
CHW	Community Healthcare Workers
CHIM	Centre for Health Information Management
CI	Confidence Interval
DALYs	Disability Adjusted Life Years
DFID	Danish Fund for International Development
DNA	Deoxyribonucleic acid
DOR	Diagnostic Odds Ratio
ELISA	Enzyme-Linked Immunosorbent Assays
FP	False Positive
FN	False Negative
FGV	Fairly Good Value
FDR	False Discovery Rate
FOR	False Omission Rate
FDA	Food and Drug Authority
GDP	Gross Domestic Product
GSS	Ghana Statistical Service
GHS	Ghana Health Service
HIV	Human Immunodeficiency Virus
ICT	Information and Communication Technology
HRP-2	Histidine-Rich Protein-2
IFA	Immunofluorescence Antibody Assay
IMCI	Integrated Management of Childhood Illnesses

IDSR	Integrated Disease Surveillance and Response
KNUST	Kwame Nkrumah University of Science and Technology
LR	Likelihood Ratio
LLHF	Lower Level Health Information Management
mRDTs	Malaria Rapid Diagnostic Tests
MOH	Ministry of Health
NMCP	National Malaria Control Programme
NPV	Negative Predictive Value
NGO	Non-Governmental Organization
NMFI	Non-Malarial Febrile Illnesses
NHIS	National Health Insurance Scheme
OPD	Out Patient Department
UNICEF	United Nation International Children Educational Fund
USAIDS	United States Agency for International Development
UKAIDS	United Kingdom Agency for International Development
PRP	Private Retail Pharmacy
PD	Presumptive Diagnosis
PR	Principal Researcher
PAQ	Pharmacist Assessment Questionnaire
PC	Pharmacy Council
PPV	Positive Predictive Value
PCR	Polymerase Chain Reaction
PEQ	Patient Exit Questionnaire
pLDH	parasite Lactate Dehydrogenase
RBC	Red Blood Cell
RBM	Roll Back Malaria
QBC	Quantitative Buffy Coat
R & D	Research & Development
SPSS	Statistical Package for Social Science
WHO	World Health Organization
WTP	Willingness-To-Pay
USD	United States Dollar

CHAPTER 1

1.1 Introduction

Malaria is among the commonest forms of febrile illness diagnosed in most countries in sub-Saharan Africa (WHO 2003), and case management is reported as one of the key strategies in controlling malaria (WHO 2010). In view of that, several global efforts to prevent, control and treat malaria have been rolled out. These included Roll Back Malaria (RBM) 1999, Abuja Declaration 2001, and WHO's T3 (Test.Treat. Track) initiative; Countries within the sub-Saharan Africa have made some improvement towards country specific strategies and plans for malaria control over the years. The overall objective in recent initiatives have been to achieve a universal access to diagnostic testing of all suspected malaria cases in both public and private health sectors (WHO 2012, 2013).

Malaria diagnostic testing makes a significant contribution in advancing global health. This is useful in guiding treatment decisions towards appropriate prescriptions of medicines and economic gains, particularly at the point-of-care. Evidently, malaria disease presents a significant public health challenge, which has been recognized as a factor in high morbidity, mortality, and of a substantial economic burden to endemic countries. Malaria Rapid Diagnostic Tests, (mRDTs) have shown to be a better alternative to the method of diagnosing patient based on clinical signs or in some instances microscopy, where very good quality microscopy services are not readily available. Changes in treatment protocols to the more expensive multi drug regimens have increased the importance of obtaining an accurate diagnosis based on the evidence of parasitaemia prior to treatment.

Presumptive diagnosis and management of malaria (initiating treatment without a confirmed diagnosis) is practiced in many malaria endemic countries. This was as a result

of the inadequate access to laboratory facilities, absence of diagnostic kits, availability of relatively affordable antimalarials and the urge of averting malaria deaths (Amexo et al. 2004, D'Acremont et al. 2011). Evidence have shown that presumptive diagnosis of malaria is ineffective and could contribute to missing cases of malaria and endangering the condition of non-malaria febrile patients (Bisoffi et al. 2009). This strategy, therefore leads to a significant over-diagnosis of malaria because of possible overlaps of symptoms of malaria and non-malaria febrile conditions. However, Presumptive Diagnosis (PD) has been reported as being successful in malaria endemic areas (Genton et al. 1994, Rogier, Henry, and Spiegel 2001).

In 1999 the World Health Organization published a report titled "*New Perspectives in Malaria Diagnosis*". This report revealed the potential usefulness of the innovation of mRDTs. Then, in 2006, the WHO, issued its first guidelines for malaria case management involving the compulsory use of a parasitological test with microscopy or mRDTs before treatment (WHO 2006). Since then, most malaria endemic countries have progressively updated their malaria treatment policies in a paradigm shift from clinical signs and symptoms to evidenced-based. In its second edition of the guidelines in 2010, the WHO recommended that confirmatory diagnosis should be done for all persons including children under 5 years. Presumptive diagnosis and treatment of malaria was to be considered only if a parasitological diagnosis was not accessible (WHO 2012).

Though these policy directives by the WHO have resulted in an increase in the proportion of malaria cases that gets tested before treatment since 2010, especially in sub-Saharan Africa, the coverage of confirmatory diagnosis is quite low especially in the private sector (WHO 2014). In this regard, expanding malaria diagnosis in private sector with

implementable policy using mRDTs is very necessary and urgent to achieving universal access to effective case management.

Many countries within sub-Saharan Africa have accordingly changed their first-line malaria treatment to a relatively costly Artemisinin-based Combination Therapy (ACT), increasing the financial implications of wasted antimalarial drugs. Parasite-based diagnosis, using mRDTs or microscopy, can ensure appropriate use of ACTs. Studies have shown the economic benefit of using mRDTs before administering ACTs. However, the challenge has been the adherence to the test results by health care practitioners. (Hamer et al. 2007).

In practice however, some studies have reported a distrust of test results by health care practitioners and patients and a seeming lack of alternative treatment for fever patients (Williams et al. 2008, Mangham et al. 2011, Onwujekwe et al. 2009, Uzochukwu et al. 2011) as some of the factors identified in influencing the effective uptake of comfirmatory diagnosis before treatment in many malaria endemic countries.

In 2009, the National Malaria Control Programme (NMCP) of the Ghana Health Service reviewed its policy on malaria case management in keeping with current WHO recommendations (WHO 2010). This replaced the presumptive management of malaria in Ghana. Presumptive treatment of fevers as malaria is no longer encouraged because it can lead to misdiagnosis of malaria and irrational use of antimalarial drugs (Amexo et al. 2004). With the adoption of mRDTs in routine health care service delivery in Ghana. It was expected that malaria testing will no longer be a preserve of areas with laboratories. Given the limitations associated with scaling up of microscopy services, mRDTs policy is increasingly gaining much attention for its practical advantages in relation to ease of

training and use. The NMCP reported that Ghana has made some progress implementing malaria case management programme, but challenges are significant (NMCP 2009).

With these varied opinions in mind, this research was set out to establish malaria diagnostic procedures used in health facilities, establish the overall patients' assessment of malaria managements at study sites, and evaluate the cost-benefit of using mRDTs in registered private retail pharmacies.

1.2. Problem statement

Though the WHO recommendation on malaria case management has led to an increase in the use of malaria diagnostics the coverage has been low in endemic countries (WHO 2011). This remains a challenge, against the backdrop of decreasing incidence of malaria in Ghana and many other malaria endemic countries.

Despite an increase in coverage of malaria rapid diagnostic tests from fewer than 200,000 in 2005 to more than 160 million in 2013, its usage in diagnosing malaria remains very low in Africa (WHO 2014). Research has demonstrated that prescribers are very reluctant in refraining from treating malaria after a negative test (Reyburn et al. 2007, Hamer et al. 2007).

The over usage of antimalarials resulting from misdiagnosis of malaria could cause an increase in drug budget, and speed up the development of resistence to the antimalarials currently used in the management of malaria [WHO, 2012].

Malaria patients who are wrongly diagnosed or inappropriately treated have the higher probability to develop severe malaria, given the transmission intensity and age [WHO, 2013].

Private retail pharmacies play an important role in malaria case management and it is reported that up to 80% of malaria cases are initially managed in the informal health sector (Nankabirwa et al. 2009). It is therefore, critical to map out effective context-based intervention programs on diagnostic testing using mRDTs.

1.3. Justification of study

Ghana has adopted the WHO recommendation on malaria case management which requires a mandatory comfirmatory test using microscopy or mRDT before treatment (WHO 2010). This recommendation was aimed at improving malaria case management, which hitherto was characterized by overprescription of antimalarials (Amexo et al. 2004, Reyburn et al. 2007, Bloland, Ringwald, and Snow 2003). Additionally, presumptive diagnosis may delay the diagnosis of other non-malaria febrile illnesses (Chandramohan, Jaffar, and Greenwood 2002, Ndyomugyenyi, Magnussen, and Clarke 2007).

In addition, the wide-spread approach where all febrile illnesses are treated as malaria could accelerate the development of resistance with ACTs (Amexo et al. 2004, Hamer et al. 2007, Reyburn et al. 2007, Wiseman et al. 2006). Furthermore, the cost of the overprescription and use of antimalarials to the patient and its effect on the entire country's economy may be devastating, especially in resource-poor countries (Rafael et al. 2006). A comprehensive evaluation of estimates of the costs and benefits of a malaria diagnostic method used in health care facilities may be timely. Moreso, evidence on the cost-benefit impact of malaria case management in retail pharmacies is patchy and weak.

However, it is difficult achieving confirmatory test using microscopy since the service is only available in larger health institutions where there are skilled trained staff. A rapid diagnostic testing for malaria has the potential in reducing these problems (Bell and Peeling 2006, Lubell et al. 2007).

This research therefore set out to establish the diagnostic practices after the recommendations of WHO of test-based policy in an exploratory baseline study, evaluate the performance of malaria diagnostic procedures, and the cost-benefit of using mRDTs at registered retail pharmacies in Ghana.

1.4. Aims and objectives

The aim of this study was to assess the diagnostic procedures used to manage malaria cases in retail pharmacies.

The study was in three main stages:

Stage 1: An exploratory baseline studies, in which malaria diagnostic procedures, understanding of malaria treatment and satisfaction of healthcare services were explored, experiences and perspectives of pharmacists in relation to malaria case management was assessed.

Stage 2: An intervention study (malaria rapid diagnostic testing, as intervention, and presumptive diagnosis as control) to evaluate the diagnostic procedures and adherence to tests results in the management of malaria in registered private retail pharmacies.

Stage 3: An evaluation of cost-benefit of using malaria diagnostic testing at registered private retail pharmacies.

In achieving the above aim, this study had five specific objectives.

i. To identify the diagnostic procedures used in malaria case management in hospitals/clinics and registered private retail pharmacies.
ii. To assess the patients' understanding of malaria case management and their satisfaction of care services at the study sites.
iii. To assess practitioners' perspectives and their performance in conducting and adhering to the mRDT results

iv. To evaluate the diagnostic procedures used in private retail pharmacies.

v. To determine the cost-benefit of the diagnostic practices.

CHAPTER 2

LITERATURE REVIEW

2.1. Malaria

Malaria is reported as one of the most important parasitic infection in the world, ranking among the major health and developmental challenges, particularly for poor countries of the world (Sachs and Malaney 2002). Until recently, only four species that were known to cause malaria in humans, namely *P. falciparum, P. vivax, P. malariae and P. ovale*. However, in 2008, *Plasodium knowlesi*, known to be associated in infecting only apes of the genous Macaque, was recognized by the WHO as the fifth *Plasmodium* species that infect humans (WHO 2014). It is however acknowledged, that *Plasmodium falciparum* is responsible for most malaria cases and mortality (Greenwood et al. 2005). Malaria is a mosquito-borne disease transmitted largely in Africa by the female Anopheles mosquito to humans (Figure 2.1).

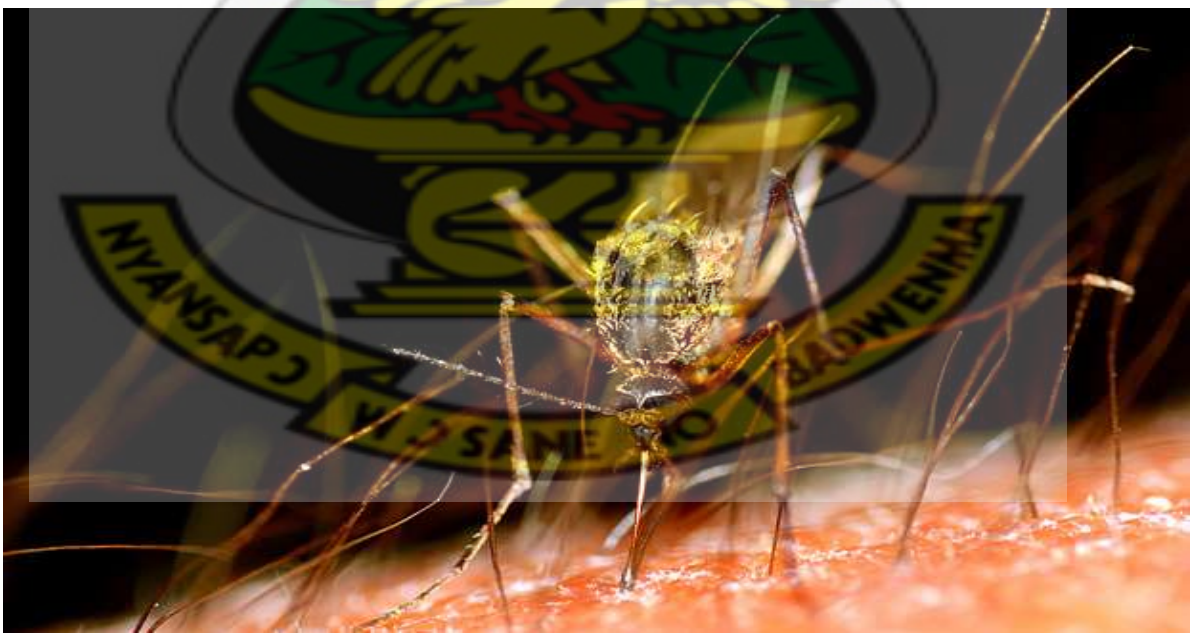

Figure 2.1: Picture of a female Anopheles Mosquito

Source: www.cdc.gov.

Records revealed that there are over 400 different species of the mosquitoes. Out of which 30 species of the Anopheles is believed to be malaria vectors. These malaria transmitting Anopheles species bite at night between dusk and dawn. The female Anopheles mosquitoes requires a human blood meal before it can lay eggs. The eggs are laid into cleaned stagnant waters, hatch into larvae, develop into pupa and eventually as adult mosquitoes. Malaria transmission is generally higher in comunities where the life cyle of the Anopheles mosquito is uninterrupted. This paves a way for the parasite to have time to complete its development inside the mosquito.

The life cycle of the mosquito (Figure 2.2) is similar in all the five kown species that infect humans. The life cycle is in three phases:

i. Infection stage
ii. Asexual reproduction stage
iii. Sexual reproduction stage

The first two phases occur exclusively in the human body, while the third phase commences in human but ends in the mosquito. The first stage is where an infected female Anopheles bites human to tranfer sporozoites in its saliva into the blood stream of humans for the asexual reproduction phase to commence.

The asexual reproduction phase occurs in two stages as follows:

i. pre-erythrocytic
ii. erythrocytic

In about 30 – 60 minutes after the transfer of the malaria parasites into man, the sporozoite passes through the blood stream to the liver. In the liver the sporozoites start dividing into schizonts within six to seven days. Each schizont produces thousands of merozoites that

are released back into the blood stream. This then marks the end of the exoerythrocytic phase of the asexual reproduction. In some instance, however, the schizonts may become dormant in the liver.

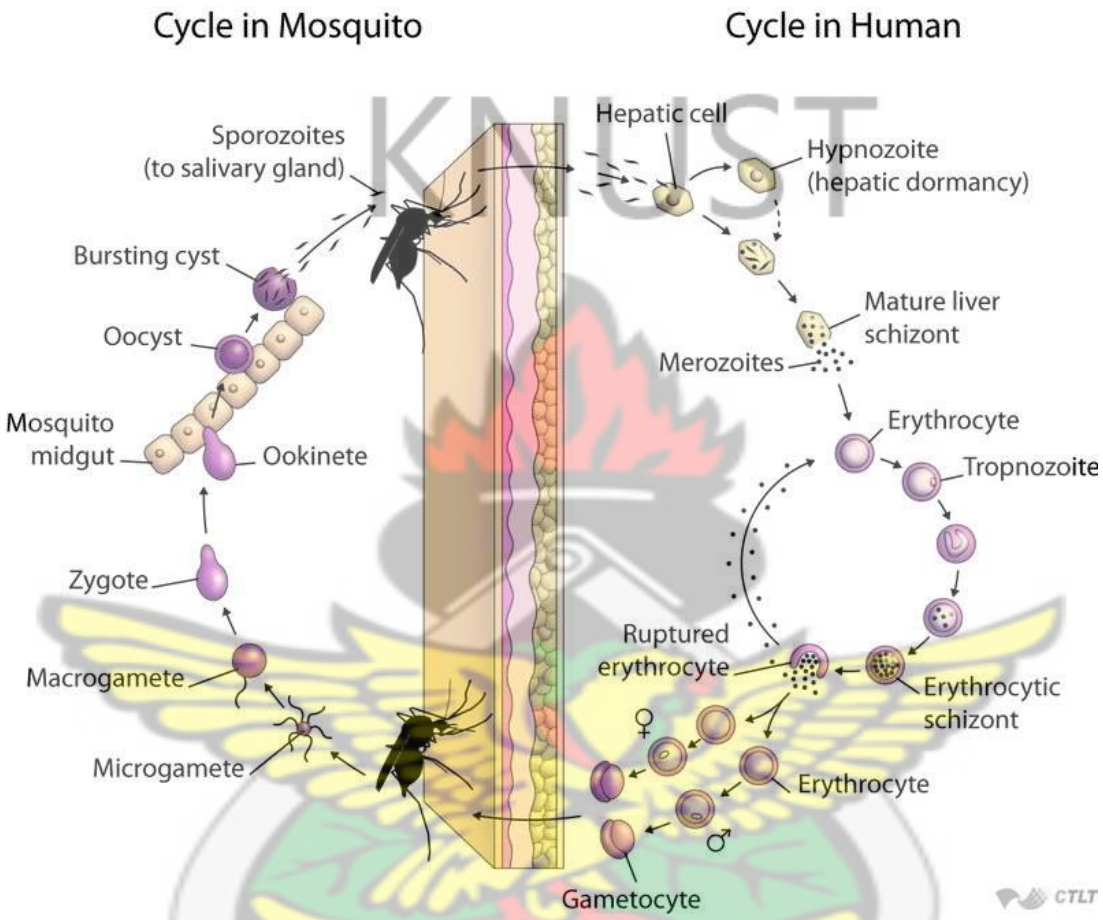

Figure 2.2: Plasmodium life cycle

Source: www.malwest.gr

The dormant schizonts may become activated after weeks, months or even years. The pre-erythrocytic phase is therefore non-pathogenic, and hence doe not produce symptoms of the disease. The erythrocytic phase begins when the merozoites targets are the red blood cells (RBCs). A ring stage that evolves into trophozoite is the first stage after the invasion. Trophozoites are unable to digest haem so they are converted into haemozoine but could digest the globin which is used as a source of amino acids for their reproduction.

Erythrocytic schizont, which initially appeared immature, then mature into schizonts. The mature schizont reproduces new generation of merozoites i.e. erythrocytic schizogony. This occur after the ruptured RBCs, are released in the blood stream and subsequently invading other RBCs. At this stage parasitaemia occurs resulting into clinical manifestations.

The next stage of the life cycle occurs in the RBCs of the infected person characterized by the differentiation of the parasite into male and female gametocytes. When the female Anopheles mosquito bites an infected person, it takes up these gametocytes with the blood meal. The gametocyte then matures into microgamete (male) and macrogamete (female) during a process of gametogenesis in the mosquito. The time needed for these processes varies among the different plasmodium species, i.e. 3 – 4 days for *P. vivax* and *P. ovale*, 6 – 8 days for *P. malariae* and 8 – 10 days for *P. falciparum*.

Microgamete nucleus divides three different times producing eight nuclei in the gut of the mosquito. Each nucleus fertilizes a macrogamete leading to the formation of a zygote. The zygote, after the process of fusion of nuclei and fertilization, becomes the ookinete. The ookinete then penetrates the gut wall of the mosquito to form an oocyst. The oocyst, then rupture releasing thousands of sporozoites who find their way into its salivary glands of thee mosquito. This marks the end of the sexual reproduction phase which usually lasts for 8-15 days.

2.1.2. Signs and Symptons of Malaria

Symptoms usually begin after 10 to 15 days of being bitten by an infected mosquito. It is reported that a poorly treated persons may have recurrences of the malaria disease months later (WHO 2014). For those who survive the malaria disease, may have re-infection

usually with milder symptoms. This form of partial immmunity disappears over months to years if the persons have no continuous exposure to malaria (Caraballo and King 2014).

2.1.2.1 Uncomplicated Malaria

The signs and symptoms of uncomplicated malaria as shown in figure 2.3, typically begins 8-25 days after a bite of an infected female Anopheles mosquito (Fairhurst and Wellems 2010).

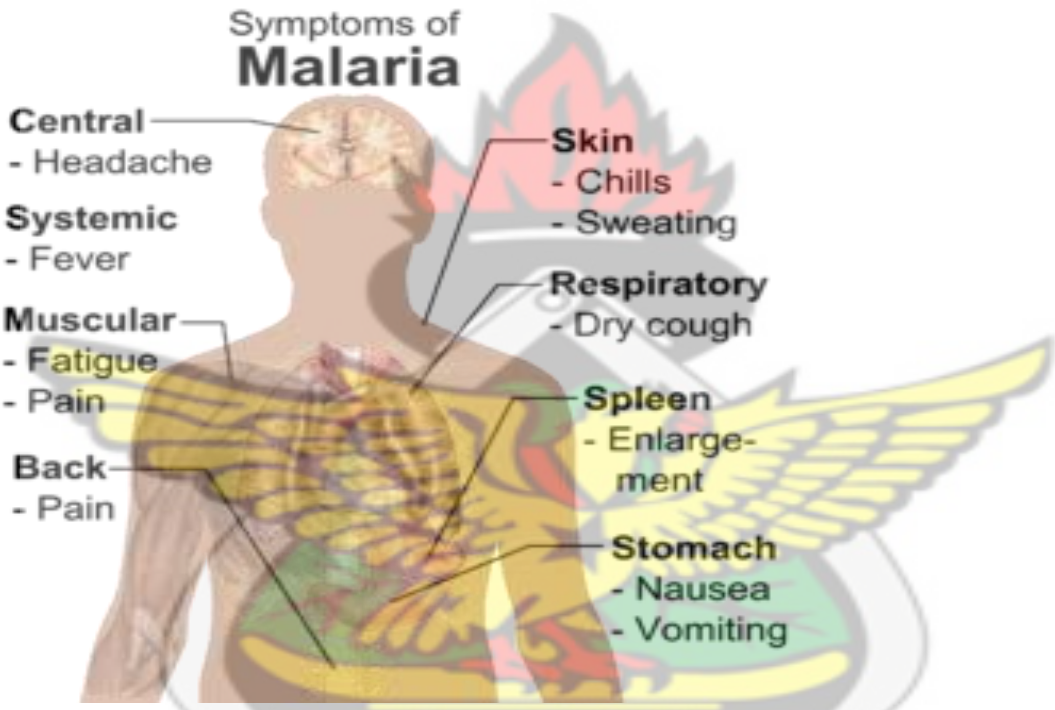

Figure 2.3: Diagrammatic presentation of symptoms of uncomplicated malaria.

Source: Commons.m.wikimedia.org

The initial manifestations of malaria is common to all the *Plasmodium* species, and are similar to flu-like symptoms (Bartoloni and Zammarchi 2012). Uncomplicated malaria presents commonly with the following signs and symptoms fever, headache, shivering, vomiting, joint pain, jaundice, haemolytic anaemia, retinal damage and convulsions (Beare et al. 2006, Ferri 2009).

2.1.2.2. Severe Malaria

Malaria has several serious complications. Development of respiratory distress is one of such complications which may occur in up to 25% of adults and 40% of children reported with severe malaria (Taylor et al. 2012). The respiratory compensation of metabolic acidosis, pulmonary oedema, concomitant pneumonia, and severe anaemia are the most possible causes. These complications are known to be rare in young children with severe malaria. It is also shown that acute respiratory distress syndrome occurs between 5 to 25% of adults and up to 29% of pregnant women (Taylor et al. 2012). It is also established that cerebral malaria, splenomegaly, hepatomegaly and renal failure, could be a form of malaria complication. A feature of blackwater fever manifests, where haemoglobin from lysed red blood cells leak into the urine (Beare et al. 2006, Beare et al. 2011, Bartoloni and Zammarchi 2012) .

2.1.3 Malaria Epidemiology and Burden.

Malaria endemic countries are those within a minimal transmission to an intense all year-round transmission (WHO 2009). Figure 2.4 describes the risk profile of *P. falciparum* malaria transmission pattern as follows; no risk is represented by light grey, unstable risk - medium grey and stable risk with endemicity displayed as a continuum of yellow to red.

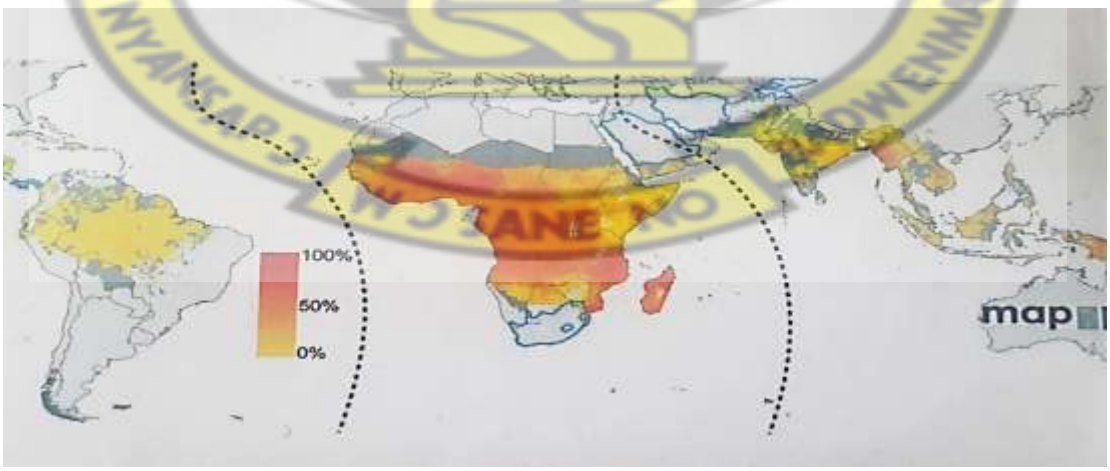

Figure 2.4: *P. falciparum* transmission

Source: Gallup JL, Sachs JD. The Economic Burden of Malaria (2001)

Various malaria transmission descriptions are used, such as holoendemic which is an intense transmission all year and characterized with parasite prevalence of above 60-70% of children under 5 years. Hyperendemic is an intense, but with periods of lower transmission during the dry season and parasite prevalence above 50% but below 70%. Mesoendemic is characterized with regular seasonal transmission, whilst hypoendemic has a very low or intermittent parasite transmission of less than 10% in children under 5 years.

It is known that, in malaria endemic countries, the transmission rates could vary considerably within different geographical areas, depending on height above sea-level (Drakeley et al. 2005), rainfall patterns and urbanization (Keiser et al. 2004).

It is estimated globally that 3.3 billion people in 97 countries are believed to be at risk of malaria. According to a WHO report, 198 million cases of malaria occurred globally in 2013. In an earlier WHO report in 2000, the disease led to 584,000 deaths representing a decrease in malaria case incidence and mortality rates of 30% and 47%, respectively. The risk is shown to be heavy in WHO African Region, where it is estimated that about 90% of malaria mortality occur and children aged under 5 years accounted for 78% of all malaria deaths (WHO 2014).

The burden posed by malaria remains a significant public health challenge (WHO 2009). Usually, malaria disease burden is measured using metrics ranging from incidence of clinical cases to malaria deaths and disability adjusted life years (DALYs). Accurate estimate of the true burden is difficult to determine because:

i. In stable transmission areas, the levels of malaria immunity are high.
ii. The signs and symptoms of fever may be as a result of malaria or other infections leading to an overestimation of the prevalence of malaria.
iii. Many fevers are treated at informal health system so do not get reported.

iv. Inaccurate diagnosis may be reported, and the national reporting systems may also be incomplete (Hay et al. 2010).

Therefore, figures for disease burden are likely to vary widely, because of these disparities in data sources and analysis.

2.2. Malaria in Africa

In spite of the several years of research and development efforts by the governments in malaria endemic countries, most malaria deaths occur in the Africa region. Although, country studies and WHO reports show a gradual decline in the malaria disease burden in many countries in sub-Saharan Africa (O'Meara et al. 2010).

A country-wide surveillance in Ethiopia and Eritrea, reported a 70% reduction in malaria morbidity. Similarly, in the coastal area of Kenya a 75% decline in admissions of children with malaria was reported between 2003 and 2007 (Okiro et al. 2007). In another study conducted in five healthcare facilities in Gambia, a decline of 35% in prevalence of malaria was recorded between 2003 and 2007 (Ceesay et al. 2008), a trend which continued in 2009 (Ceesay et al. 2010). This declining trend in malaria cases was also reported in similar studies conducted in Zanzibar, Tanzania, Zambia, South Africa, Mozambique, Ethiopia and Rwanda of a decline in malaria cases (Bhattarai et al. 2007, Mmbando et al. 2010, Barnes, Chanda, and Ab Barnabas 2009, Otten et al. 2009).

In contrast, available information from Central Africa indicated a little changes in malaria burden in Brazzaville-Congo and DRC (Guerra et al. 2010, WHO 2010). In the central and western parts of Africa, where malaria burden is great, the disease still exists with no evidence of decline in malaria cases (WHO 2010).

In north Saharan Africa, malaria is obviously for practical purposes, and no longer a public health problem (WHO 2008). It is reported that countries in this region e.g. Algeria and Morocco have eliminated malaria while others are awaiting certification of elimination (WHO 2014).

In general, health care delivery in the public sector is organized across administrative districts into Community Health Planning Services (CHPS) compounds, health facilities, district and regional hospitals. Although the public health facilities are not only the point of contact for many patients with fever, they have been the main focal point for surveillance and data collection than private drug outlets (Sabot et al. 2009). It was reported that data from Ministries of health regarding distribution of mRDTs, examination of patients using microscopy or mRDTs usually cover only the public sector. Although, studies have also proven that 40% of malaria patients worldwide seek treatment in the private sector (Abuya et al. 2007, Djangmah and Esena 2013).

The WHO has long believed that retail pharmacy practitioners could make a greater contribution towards providing better health care (WHO 1988, 1996). Particularly in developing countries where the health needs are much greater and provision of public-sector health care services is limited. The dearth of pharmaceutical care providers and the inadequate access to medications creates multiple disease management challenges in sub-Saharan Africa, where 25% of the world's disease burden but with only 1.3% of the world's health care providers. In preventing and treating malaria and other febrile illnesses, there is the urgent need to train and build the capacities of health workers.

It is evident that retail pharmacy outlets are internationally and widely recognized to have the potential to enhance contribution to health care delivery (Smith 2004). In practice, the majority of underprivileged people and those at higher risk of malaria do not often use

formal health services for treatment of malaria. It is because their first entry point in seeking healthcare delivery is usually the informal sector, which included the retail pharmacies (Rutebemberwa et al. 2009, Moerman et al. 2003).

2.3 Malaria in Ghana

The control of malaria in Ghana began in the 1950s. Interventions adopted included the use of residual insecticide, mass chemoprophylaxis with pyrimethamine tablets and improving the drainage systems. Inspite of all these, malaria continued as one of the leading cause of illness in Ghana.

In 1999, Ghana committed itself to the Roll Back Malaria (RBM) initiative which led to the development of a strategic framework to guide its implementation. Generally, the RBM emphasized on strengthening health care through multi and inter sectoral partnerships. Therefore, making prevention strategies and treatment more widely available. Four major strategies pursued were:

i. Promoting preventive measures which included the use of treated mosquito bed nets, environmental management and chemoprophylaxis.
ii. Improving malaria case management at all levels of health care.
iii. Encouraging evidenced-based research in malaria control to come up with effective and reliable interventions.
iv. Improving and facilitating collaboration with related stakeholders.

Though, Ghana made some progress in implementing the RBM initiative, gaps still exist in achieving the targets. Lessons learned informed other programs, such as the National Malaria Strategic Plan Monitoring and Evaluation, 2008 to 2015. This was aimed at reducing malaria deaths and morbidity by 75% by 2015 in accordance with the Millennium Development Goals, MDGs.

The UKAID Department for International Development working document, titled "Malaria: burden and intervention" in 2010, indicated that, 900,000 out of the 3.2 million malaria cases reported in 2008 were children below the ages of five years. However, only 26% (832,000) of the 3.2 million malaria cases were parasitologically confirmed. In 2014, there were 2,506 malaria deaths out of 1.6 million confirmed malaria cases in Ghana (WHO 2014).

In Ghana, malaria accounted for 37.5% of outpatient illnesses, 36% of admissions and 33.4% of malaria deaths in children under five years. Malaria in pregnancy accounted for 13.8% of outpatient attendants, 10.6% of admissions and 9.4% of deaths. The most vulnerable groups are children under 5 years and pregnant women who constitute 20% and 4% respectively of the general population (NMCP 2009).

It is worth noting that, Ghana has systems of malaria surveillance but they are however fragmented. The sources of routine surveillance information are the Centre for Health Information Management (CHIM), the Integrated Disease Surveillance and Response (IDSR), the sentinel sites, the national pharmacovigilance centre and the National Malaria Control Programme (NMCP).

To make the health sector more responsive, both the public and private health institutions should be made responsible for their activities such as planning, budgeting, implementation, monitoring and evaluation. The private and non-governmental organization (NGO) sectors provide over 40% of health care delivery in Ghana.

Qualified health care providers are essential requirement of any functioning health care system together with effective malaria control programmes. Yet, this remains a critical weakness in most low and middle-income countries including Ghana. The causes of the shortage and inequitable distribution of trained staff are multifactorial with varying scale

and impact on health outcomes. It is reported that training of healthcare workers require adequate supervision, workforce planning and reliable health care infrastructure that can support effective implementation of health policies (Smith et al. 2009, WHO 2001).

Even though malaria contributed 30 – 40% of outpatient visits at health facilities and 25% of deaths in children under five years (GSS 2008), most of these patients were not tested for malaria. This was because majority of the health facilities especially health centres are not well- equipped to perform laboratory investigations. Where the health facility is even well-equipped, malaria microscopic examination is sometimes not even done (Polage et al. 2006, English et al. 2004), despite the WHO recommendation of test-based treatment with ACTs. With such diagnostic practices and the adoption of expensive ACTs as first-line for malaria treatment, it is obvious the cost of managing the disease will increase. Unfortunately, the average budget for malaria treatment in many malaria endemic countries most countries was less than US$ 20 per person annually, whilst a single course of ACT for a child costs between US$ 0.9 and US$1.4 (Whitty et al. 2008). However, it has been demonstrated that if costs of ACT fell to US$ 0.5, then using mRDTs will averts over US$ 200 million in unnecessary malaria treatments in children alone. (Whitty et al. 2008). Accordingly, Zikusooka et al., 2008 suggested that restricting antimalarial treatment to only mRDT positive patients will save up to US$ 2.12 per person, especially if mRDT and ACT were sold at a retail prices of US$ 0.95 and US$ 2.40 respectively.

Additionally, an assessment of malaria deaths is very necessary for monitoring the impact and case management using interventions, such as mRDTs and advocacy. Unfortunately, most countries in sub-Saharan Africa where malaria burden remains high have low coverage and weak monitoring systems (Murray and Lopez 1997, Murray et al. 2001, Mathers et al. 2005).

2.4 Economic Burden of Malaria

Empirical and theoretical evidences to measure socio-economic impact of malaria abounds. A survey conducted in Zambia by Utzuger et al., 2003, showed that investments in malaria control during the colonial period reduced worker's absenteeism in copper production which led to a general improvement in economic development and growth in Zambia (Epidemics, In, and Abdullateef). Indicating that malaria disease can potentially slow down productivity within the households. Currently, malaria afflict mostly the poorest and deprived communities in Africa, often with devastating consequences. (Remme et al. 2006, Mharakurwa et al. 2012, Hotez and Kamath 2009).

Examining the relationship between malaria burden and the economies of many malaria endemic countries reveals a strong relationship, though with varying magnitude of effect among countries (Sachs and Malaney 2002). A study by Laxminarayan in 2004, confirmed the relationship between the decline in malaria prevalence and the improvements in living standards. Malaria burden is therefore not just linked with poverty, but rather a cause of poverty (Gollin and Zimmermann 2007).

Many studies have estimated the direct costs of treatment and prevention including transportation to treatment centre and special foods. Other studies have focused on the indirect costs of time lost by the sick individual, caretaker and death.

An earlier study by Onwujekwe et al., 2000, showed the cost of treating malaria amounted to 49.87% of curative health care costs incurred by the households (Onwujekwe, Chima, and Okonkwo 2000).

In its entirety, the economic impact of malaria in Africa has been estimated to cost US$12 billion every year (Chima, Goodman, and Mills 2003). This include cost of health care,

days lost in education, working days lost due to sickness, lost of productivity, and loss of investment (Greenwood et al. 2005). A study in rural Kenya revealed that the direct costs of malaria were 7.1% and 5.9% of the total household expenditure in the wet and dry seasons respectively (Chuma, Thiede, and Molyneux 2006).

The WHO in its report confirmed that the cost of malaria is substantial on health care delivery systems in endemic countries, where three out of every ten hospital beds are occupied by patients with malaria (WHO 2005a). A study by Muula et al in Malawi, found that by treating 65% - 85% of falciparum malaria cases led to using 8.9% - 12.2% of the health budget or 22.2% to 33.2% of the whole national drug budget (Muula et al. 2007). Again, an estimated 39% of the total health care expenditure in Tanzania was earmarked for malaria prevention and care (Jowett and Miller 2005). Similarly, in Nigeria the malaria disease was estimated to retard gross domestic product, GDP, by 40% annually and costing up to US$1.5 billion (Ezennia, Nduka, and Ekwunife 2017).

2.5. Test-based diagnostic practice and artemisinin-based combination therapy

Currently, the Artemisinin Combination Therapies, ACTs, hold much promise for effective treatment of malaria as has been demonstrated in many studies (Barnes, Chanda, and Ab Barnabas 2009, Bhattarai et al. 2007). The ACTs are now being heavily promoted as the first line treatment option for uncomplicated malaria across sub-Saharan Africa. (WHO 2001, Arrow et al. 2004, WHO 2006).

The World Health Organization recommends that all malaria cases must be parasitologically confirmed before treatment either by mRDTs or microscopy (WHO 2010). This recommendation has been adopted by many countries (WHO 2014).

This has led to an increase in malaria testing especially in the WHO Africa region where it has doubled since 2010, translating into 52% of malaria cases tested in 2013 (WHO 2014). The quantity of malaria test kits sold has increased from 46 million in 2008 to 319 million in 2013, as reported by manufacturers.

2.6. Malaria diagnosis

The strategy in diagnosing malaria in many countries ranges from basic empirical clinical diagnostic algorithms to laboratory examination using either microscopy or mRDT.

2.6.1 Presumptive/Clinical Diagnosis

Presumptive diagnosis (PD) or Clinical diagnosis (CD) of malaria is a process of establishing malaria disease condition of a patient based on clinical suspicions which are often dictated by practical considerations. These are usually characterized by patient's physical examinations based on clinical signs and symptoms. The most common symptoms and signs used in presumptive diagnosis of malaria include headache, fever, bitterness in the mouth and general weakness in the body. Though, in malaria endemic population where many of the people are chronically parasitaemic, malaria maybe responsible for the febrile illness in majority of cases.

However, it is difficult to distinguish between fever and headache as a result of malaria from that arising from other etiologies. (Chandramohan, Jaffar, and Greenwood 2002, Dorsey et al. 2000, Kockaerts et al. 2001, Casalino et al. 2002).

The accuracy of presumptive diagnosis therefore varies with the level of endemicity, malaria season, and age group (Ruebush et al. 1995, Dicko et al. 2005). A study conducted in 2006 revealed that children in high-transmission areas could be managed by

presumptive diagnosis in accordance with the Integrated Management of Childhood Illnesses (IMCI) guidelines (Reyburn et al. 2006, WHO 2000).

Several studies on presumptive diagnosis in populations from different malaria-related environment, such as Phillipines, Thailand, Sri Lanka, Mali, Tanzania, Chad, and Kenya have shown 40 – 80% varying range of malaria over-diagnosis with associated potential for economic loss (Ruebush et al. 1995, Dicko et al. 2005, Wongsrichanalai et al. 2007, Othnigué et al. 2006).

Generally, the management of febrile patients in sub-Saharan Africa, is typically characterized by presumptive diagnosis. Such practices has consequently become more problematic, as treatment failures resulting from the development of resistance by the malaria parasite has necessitated the introduction of new antimalarial regimens such as artemisinin combination therapies (Agnamey et al. 2005, Zurovac et al. 2008, Malik et al. 2006).

2.6.2 Biologic Diagnosis

In 1904 Gustav Giemsa, introduced the principle of microscopic examination using Giemsa-stained blood smears, which subsequently became the reference or gold standard for malaria diagnosis. The performance of microscopy as a diagnostic method is a function of multiple factors including techniques in slide preparation, skills of the microscopist, workload, state of the microscope, and quality of other laboratory accessories. Also studies have shown that even with same microscope and training the results of two microscopists may vary significantly (Lalloo and Naraqi 1992, Thomson et al. 2000). Developed countries are not exempted from the scarcity of expert malaria microscopists (Maguire et al. 2006, Lalloo and Naraqi 1992, Thomson et al. 2000). The threshold in detecting the Giemsa-stained thick blood film are likely to be higher in remote settings where there may

be less skilled microscopists and relatively poor state of equipment exist (Levine, Wardlaw, and Patton 1989, Demirev et al. 2002, Payne 1988).

The preparation of the stained blood film for microscopy requires expertise and this may influence the accuracy and specificity of the result as the blood film may be contaminated several foeign matter (Johnston et al. 2006, Houwen 2002). Improving the training of miroscopists to enhance the quality of slide preparation is critical in reducing false positive results. However the probability of reading a false negative result increases with a decrease in parasite density (Maguire et al. 2006).

Other alternative biological diagnostics for malaria used were the indirect Immunofluorescence Antibody assay (IFA) and the Enzyme-Linked Immunosorbent assays (ELISA), for detecting malaria antibodies (Fleischer 2004, Sulzer, Wilson, and Hall 1969). Later, immunochromatographic assay was developed which technology forms the basis of the mRDTs (Spencer et al. 1979, Shiff, Minjas, and Premji 1994).

2.6.3 Rapid Diagnostic Test

The mRDT was developed over 20 years ago based on immunochromatographic assay technology to detect the malaria parasite antigen in the affected human blood as shown in Figure 2.6. The result appears as a coloured test line usually in 5-20 minutes (less than an hour). The device requires no extensive investment or electrical power, and very simple to perform and interpret. The malaria RDT formats (fig. 2.6) is easy to use in diverse settings and where there are no microscopes.

Figure 2.6: A malaria RDT kit showing the various possible results.

In sub Saharan Africa, most malaria RDT kits are Histidine-Rich Protein 2 (HRP-2) which detects only *P. falciparum* since about 90% of malaria cases are due to *P. falciparium*. However, there are those that contain either aldolase or lactate dehydrogenase enzymes that can detect the other non-falciparum species alone or in combination (Miller et al., 2001). Other major group of targeted antigens is the parasite lactate dehydrogenase (pLDH) enzymes available for detecting *P. ovale*, and *P. vivax*. The *P. vivax*- specific assay is new and yet to be adequately evaluated.

The HRP-2 is reported to persists in the patient's blood for some weeks even after treatment, and therefore pLDH may be more appropriate for targeted treatment (Moody et al. 2000). The persistence of HRP-2 on the other hand, could be an advantage in detecting low parasitaemia malaria cases (Bell, Wilson, and Martin 2005). However, other studies have reported instances where plasmodial gametocytes also produced pLDH which remained giving rise to a positive test despite clearing of the malaria parasite (Miller, McDaniel, and Wongsrichanalai 2001). Both the HRP-2 and pLDH-based tests have been employed in detecting malaria in pregnancy with peripheral and placental blood specimens

with variable outcomes (Leke et al. 1999, Singer et al. 2004). For mRDT to be a useful malaria diagnostic tool, its sensitivity must exceed 95% (WHO 2000).

Table 2.1: Malaria 'zones' by parasite species and type of RDT kit recommended

Zone	Common malaria parasites	Geographical area	Appropriate mRDT kit type
1	*P. falciparum* only or with other species for mixed infection	Sub-Saharan Africa, Lowland Papua New Guinea	HRP-2 RDT kits
2	*P. falciparum* and *P. vivax*.	Asia, Americas and Ethiopia highlands	Combined HRP-2 and pLDH RDT kits
3	Non-falciparum	East and Central Asia; some other highland areas	pLDH RDT kits only

Technological developments have paved way for more and new malaria rapid diagnostic test kits to be used in diagnosing malaria. It has also proven to be promising for improved management and control of malaria. However, the usefulness of these tests in any setting can best be answered only through evaluations in the appropriate laboratory, clinical or field settings. This is because many variables can influence the performance of tests in different settings including differences in the characteristics of the population or the infectious agent. Again, disease prevalence and genetic variation of the host, as well as the test methodology have also shown to influence test performance. Although, several new rapid diagnostic techniques have been developed and evaluated, the rate of introduction, withdrawal, and modification of these tests kit has rendered these reviews largely obsolete (Dicko et al. 2005, Ruebush et al. 1995, Mwangi et al. 2005).

Other limitations observed with HRP2-based RDTs are genetic diversity described among African *P. falciparum* isolates (Baker et al. 2010, Wurtz et al. 2013), and false HRP2 negative result due to prozone effect (Gillet et al. 2009). To date, no genetic LDH

diversity/deletion has been observed which presupposes that LDH-based RDTs are not susceptible to any prozone effect (Maltha et al. 2010, Talman et al. 2007).

With the increased number of malaria RDTs in the market, the most driving factor for decision-makers in their considerations has been the context within which the testing would be appropriately performed. Of these are qualities of the malaria RDT kit, sensitivity, specificity, shelf-life, heat sensitivity, storage and cost.

2.6.4. Consequences of overdiagnosis of malaria

Febrile illnesses treated as malaria account for approximately 20% - 40% of outpatient visits in SSA (Chima, Goodman, and Mills 2003). However, there is inadequate data concerning the exact break down into malaria and other non-malaria febrile illnesses. There are a number of studies conducted in SSA suggesting that malaria is being grossly over diagnosed, especially in low transmission areas (Makani et al. 2003, Reyburn et al. 2007). This has raised concern regarding detrimental consequences for patients suffering from receiving antimalarials instead of appropriate treatment (Makani et al. 2003).

From the public health perspective, the confusion surrounding case definition and diagnosis also results in considerable variation in total estimates of morbidity and mortality, with the speculated number of clinical episodes of malaria ranging from 400 million to five billion clinical episodes annually, leading to about 1 to 3 million deaths a year (Breman, Alilio, and Mills 2004). The magnitude of even the lowest of these estimates justifies placing malaria high on the health agendas; however, this uncertainty can also lead to pursuit of highly inappropriate strategies, where billions of clinical episodes might be incorrectly treated and up to two million lives might be lost every year after incorrect diagnosis with malaria.

The assessment of the true burden of malaria is continuously challenged by factors such as urbanization, climate change (Tanser, Sharp, and Le Sueur 2003), and the widespread implementation of interventions such as insecticides treated bed-nets (Curtis et al. 2003). These all affect transmission intensity and consequently prevalence of malaria and host immunity, posing substantial difficulties to policy makers considering treatment and diagnostic strategies, and raises concerns as to how they might account for such variation in their decision-making process.

2.7. Review of relevant malaria documents and diagnostic practices

Most of the malaria RDTs diagnostic studies that appear in the literature were limited to global malaria endemic regions due to the severity of the problem and much resource allocated to malaria research in those regions. In this study, criteria employed in identifying studies included the outcomes measures at community level, use of rigorous design i.e. experimental, quasi-experimental or pre/post interventional evaluation, and a minimum sample size of 100.

2.7.1. Search strategy

The sources that were used for identifying related journal articles on malaria RDTs was PubMed (MEDLINE). Other sources such as biomed central, google scholar, and cochrane database of systematic reviews, WHO reports and government publications and websites were used. The search was conducted only on studies published in English. The key terms searched were rapid diagnostic test, malaria, sensitivity, specificity, microscopy, cost-effectiveness, cost-benefit, evaluation, positive predictive value, negative predictive value, false-negative, over-diagnosis, misdiagnosis, and study design. These words were used either single or in combination.

The initial search resulted in about 124 related malaria documents largely from 2000 to 2012. Among the searched documents were 'malaria literatures' which was defined in this study as, all commentaries, correspondence, documentaries and booklets; 'malaria reports' defined as malaria authoritative and scientific papers, directives, policies and seminars; 'malaria research articles/papers' represented study reports, papers, trials. The intention was to review only the literature that evaluates the performance characteristics of mRDTs and implementation at health care facilities. Therefore, descriptive studies, demographic and epidemiological malaria data were excluded. Figure 2.6 illustrates the categories of malaria documents reviewed in this research, an overview of which is given in Appendix 2.1.

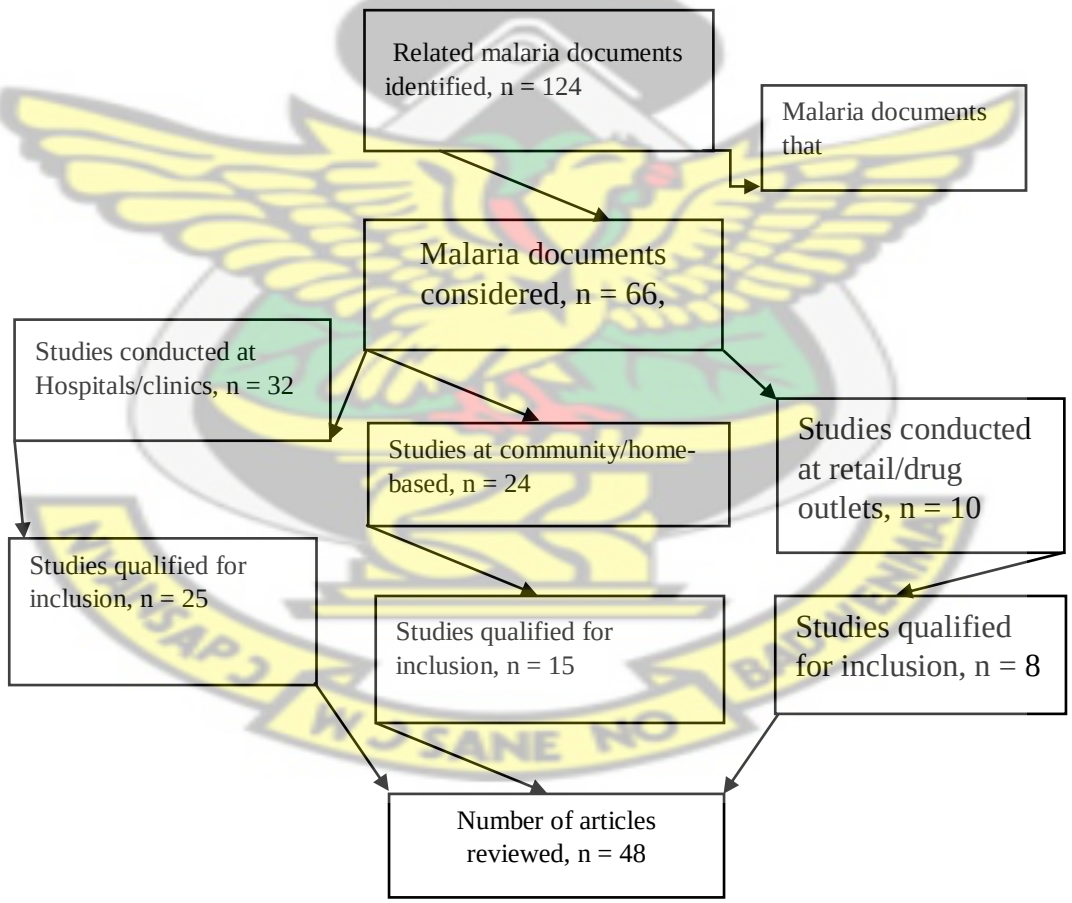

Figure 2.5: Frame work for sampling and inclusion of study documents.

2.7.2 Assessment of diagnostic accuracy.

Diagnostic tests such as mRDTs is making significant contribution to global health. Several studies that support this fact have been shown in (Appendices 2.1a, b, c, and d). They are essential in guiding treatment decisions towards ensuring appropriate use of medicines. In 2013, the WHO reported of investments in scaling-up of mRDTs through NMCPs in certain reviewed malaria documents, to achieve desired outcome. Evidence to date shows mixed programme success (Bastiaens, Bousema, and Leslie 2014).

When the malaria diagnostic procedure is followed appropriately one can easily distinguish between patients with or without malaria. In 2015, Mbonye et al. demonstrated in his study conducted in drug shops in Mukono district, Uganda, that majority of febrile patients who received ACTs were properly diagnosed as having malaria, while some in the control arm, also assumed same. However, an earlier study by Diarra et al. in 2012, assessing the performance of mRDTs kit in children under in Burkina Faso, observed that the overall sensitivity and specificity were very encouraging with high values of positive and negative predictive values. During high transmission periods, sensitivities were higher within children with axillary temperature of 37.5℃ or more. However, sensitivities of the RDT kits drop during low transmission season. The differences in sensitivity between the high and low malaria transmission seasons were found to be statistically significant (Diarra et al. 2012). In contrast, specificity decreases marginally in low transmission season, and same trends were observed for the positive and negative predictive values. Therefore, a perfect test of mRDTs will only show an inference that always indicate malaria disease or excluding the disease. Unfortunately, a perfect test is not very practical and therefore diagnostic procedures only indicate distinction between patients with or without the disease. A longitudinal study by Ishengoma et al. in Tanzania, assessed the performance of mRDTs with microscope found the overall sensitivity and specificity of mRDTs to be

88.6% and 88.2% respectively. However, in the cross-sectional surveys, the sensitivity was lower, while the specificity was higher when compared to the longitudinal study (Ishengoma et al. 2011). This presupposes that values classifying malaria are not always the case. These are termed false positive (FP) values. Additionally, it was shown the same study that the risk of FP mRDTs values were significantly higher in cases with fever compared to afebrile cases.

However, several studies have shown that, patients considered not to have malaria after a malaria rapid diagnostic test were confirmed to have malaria after microscopy. These patients are examples of false negatives (FN). Therefore, this dichotomy on patients with and without malaria are classified in four subgroups:

i. True Positive (TP) is where patient with malaria disease is with the value of interest.
ii. False Positive (FP) is where patient without malaria disease is with the value of interest.
iii. True Negative (TN) is where patient without malaria disease is with the value of interest.
iv. False Negative (FN) is where patient with malaria disease with the value of interest.

It is important, therefore to identify the implications of all the four values in designing a study involving a screening test which determines who qualify to be considered diseased and who will be considered disease-free. This decision clearly reflects the repercussions of classifying individuals as false negatives or false positives. For example, a screening tool for early stage breast cancer. There are considerable consequences for both false positives and false negatives. On one hand, a patient with a false positive may be referred for unnecessary testing that is painful and expensive, as well as emotionally taxing. On the

other hand, a false negative also has serious implications, since the patient may not receive any treatment until the disease has progressed much farther.

Circumstances that could lead to such situations have been demonstrated in several studies, one of which was by Aladenika et al. in Nigeria which revealed marked difference in sensitivity of test kits to adult sample compared with children sample. A higher rate of false negative results were found in the adult sample than the kids sample (Aladenika et al. 2012). This confirms previous findings from Kenya, Madagascar, and Uganda where the positives in mRDTs were found to be associated with higher parasite load (Cooke et al. 1999, Iqbal, Khalid, and Hira 2002, Kyabayinze et al. 2008, Wanji et al. 2008) . Thus, increasing the possibility of false negative and false positive rates. However, unlike a previous study by Gasser et al., 2005, which reported no significant difference in sensitivity of the test kit. Reviewing a field evaluation of mRDTs in Yaounde, Cameroon, by Rachida et al., 2012, the results indicated most false-negatives occurred in samples with low parasitaemia (<500 asexual parasites/µL). It was observed that the performance of mRDTs was better at higher parasitaemia (>500 asexual parasites/µL). The study concluded that, one weakness of the mRDT-based strategy in Cameroon was inadequate sensitivity for low parasitaemia. However, Diarra et al., 2012, used 2 community clinics, to compare the performance of mRDTs using microscope as standard. Similarly, malaria RDTs showed the ability to accurately diagnose malaria as microscopy.

Therefore, the reliability and accuracy of mRDT has made it an important tool in malaria control programmes (WHO 2013). These were exemplified in a Cochrane review, where mRDTs testing for falciparum malaria were specific within the range of 92 – 100%. Meaning that only 0 – 8% of patients who tested positive would not actually have the disease (Abba et al. 2011). Furthermore, the test was shown to be very sensitive (range of

about 91 – 99%) meaning that only 1 – 9% of the patients with falciparum malaria would get a negative test result (Abba et al. 2011).

A similar study in Ghana by Baiden et al demonstrated that mRDTs have high-level sensitivity and specificity compared with microscopy. Another related study evaluating the performance of mRDTs in different countries with microscopy as standard. The results showed a sensitivity range of 47.5 to 95.5% and a specificity range of 64.3 to 98.5%, indicating different performance for both falciparum and non-falciparum malaria detection (Mens et al. 2007, Endeshaw et al. 2008, Endeshaw et al. 2012, Nigussie et al. 2008, Ashton et al. 2010). Similarly, a reduced sensitivity in detecting non-falciparum malaria, compared to falciparum detection, in combined HRP-2 and pLDH RDT kits have been reported (Mohon et al. 2012, Alam et al. 2011, Kosack et al. 2013, Eibach et al. 2013).

It was also noted in some trials of mRDTs in diverse populations (Table 2.1), of varying sensitivity and specificity after microscopic examinations. The HRP-2 malaria test kits usually show a sensitivity of greater than 90% in *P. falciparum* clinical cases (Fernando, Karunaweera, and Fernando 2004, Forney et al. 2003, Marx et al. 2005, Buchachart et al. 2004, Kilian et al. 1997, Kilian et al. 1999, Guthmann et al. 2002). However, when accompanied by an aldolase assay, the non-falciparum sensitivity is usually lower (Forney et al. 2003, Fernando, Karunaweera, and Fernando 2004, Tjitra et al. 1999, Guthmann et al. 2002, Min-Naing and Gatton 2002).

Table 2.2. Comparing malaria parasite density, sensitivity and specificity after microscopy examinations

First author/ publication year	Parasite density (parasite/mcL)	Sensitivity	Specificity	Comments
Buchachart, 2004	>80	*Pf* 96%	*Pf* 93%	Previously diagnosed malaria patients only.
Fernando, 2004	9% of *Pv* and 48% of *Pf* had ≤1000	*Pf* 100% *Pv* 70%	*Pf* 100% *Pv* 70%	Test line intensity and parasite density correlation noted for *Pv*.
Forney, 2003	15% of *Pf* had ≤500 23% of *Pv* had ≤ 500	*Pf* 98% *Pv* 87%	*Pf* 93% *Pv* 87%	83% sensitivity for *Pf* ≤ 500/mcL 55% sensitivity for *Pv* ≤ 500/mcL
Mboera, 2006	≥40	*Pf* 90%	*Pf* 97%	Asymptomatic patients and mRDT storage conditions noted.
Pattanasin, 2003	28% of *Pf* and 38% of *Pv* had ≤500	*Pf* 90%	*Pf* 96%	Studies explained the false positive test results (N=9)
Iqbal, 2003	12% (all species combined) had < 500	*Pf* 88% *Non-Pf* 65% *Pf* 85% *Pv* 76%	Pf 92% Non-Pf 99% Pf 99% Pv 99%	Sensitivity for Pf was 70% and 64% for non-Pf with densities 100-500/mcL. Performance of mRDTs was better than microscopy at remote clinics.

It is known that the identification of parasite by microscopy mainly depends on good stains and microscopes. Further, the technical expertise of the microscopist and time spent on reading slides are factors worthy also of consideration (McMorrow et al. 2008). This means that an expansion of microscopic diagnosis of suspected malaria patient to satisfy WHO recommendation appeared to be an unrealistic option. However, the bulk of evidence proves that with reasonable care, rapid diagnostic testing for malaria provides

viable alternative as shown by Abba et al., 2011. Other studies have shown that the accuracy of mRDTs normally exceeds 95% sensitivity and 90% specificity when compared with expert slide readings (Table2.3).

Table 2.3: Malaria RDT kit brands for sub-Saharan Africa verified with microscopy.

RDT Brands	Study (n) Cohort	Patients (n)	P. falciparum Cases(n)	Pooled sensitivity (95% CI)	Pooled specificity (95% CI)	Test
Paracheck-Pf	27	22,319	6,929	93.2 (89.7, 95.6)	95.6 (92.8, 97.3)	P = 0.15
ParaSight-F	17	12,521	3,261	94.1 (89.9, 96.6)	94.6 (90.4, 96.8)	
ICT Malaria-Pf	16	2,955	1,200	97.6 (95.5, 98.8)	94.5 (90.5, 96.9)	
ParaHIT-F	4	1,119	192	92.3 (74.9, 98.0)	98.9 (94.9, 99.8)	
Determine Malaria-Pf	1	526	262	98.2 (85.4, 99.8)	86.8 (35.1, 98.8)	
PATH	2	378	180	96.6 (83.8, 99.3)	93.3 (68.6, 98.9)	
Rapid Test Malaria	1	306	36	97.8 (70.1, 100.0)	96.1 (65.6, 98.9)	
DiaSpot Malaria	1	153	63	71.8 (23.1, 95.6)	82.6 (27.3, 98.4)	
Hexagon Malaria	1	119	32	100.0	65.7 (13.4, 96.0)	

Study findings also from Uganda, where expert slide results were compared with polymerase chain reaction indicated HRP-2 mRDTs to be more sensitive than expert slide reading (Hopkins et al. 2008, Bell, Wilson, and Martin 2005). In addition to the low-density discordance as noted, there are other reports of antigenic variation in *Pf* HRP. This

gives more details for a relatively rare but consistent findings of high-density of *P. falciparum* infections, therefore remaining negative to testing with HRP-2 RDT kits (Lee et al. 2006).

2.7.3. Diagnostic practices and antimalarial therapy

The validity of test-based intervention has been reported in different studies. In some studies, decrease in antimalarial treatment with the introduction of mRDTs were reported (Bruxvoort et al. 2013, Bastiaens, Bousema, and Leslie 2014, Yukich et al. 2012, Thiam et al. 2011). An evidenced based decision and prioritization should be paramount in settings with limited resources. For instance, limiting ACTs to mRDT positive and microscopy positive cases alone could reduce the number of children who would have received ACTs because they are suspected to have malaria by more than 50% (Reyburn et al. 2007). Implying, costs incurred in the treatment could possibly be halved. Unfortunately, others indicated frequent antimalarial prescriptions despite a negative test results (Koenker et al. 2014, Mubi et al. 2011, Juma and Zurovac 2011, Kyabayinze et al. 2010). In other words, some research show widespread prescriptions of other antimalarial (Zurovac et al. 2008, D'Acremont et al. 2011, Skarbinski et al. 2009) drugs to test-negative patients contrary to established guidelines. In effect, presumptive treatment of fever as malaria without any confirmatory test is widely practiced.

It has been shown in other studies that more than 50% of patients found to be microscopic negative were treated for malaria (Reyburn et al. 2007, Reyburn et al. 2004). This over-diagnosis of malaria occurs in both private and public health institutions, resulting in administration of anti-malarial drugs to people who do not need them. Additionally, the detection and treatment of substantial number of non-malaria febrile illnesses are delayed or missed (Berkley et al. 2005). Similarly, studies conducted in Ethiopia and Thailand

using mRDTs led to the reduction in malaria morbidity and mortality (Carrara et al. 2006, Lemma et al. 2010). Also, a cluster randomized trial in children aged less than 5 years in Zambia, reported a decline in the overuse of antimalarials (Yeboah-Antwi et al. 2010). A study in Nigeria, also demonstrated a 42% reduction in the chances of purchasing antimalarial after using mRDT (Ikwuobe et al. 2013).

2.7.4. Diagnostic practices and treatment

Several studies related to ACTs, have shown much evidence for effective treatment of malaria as has been demonstrated in much of Southeast Asia and more recently in a number of locations in Africa (Bhattarai et al. 2007, Barnes, Chanda, and Ab Barnabas 2009). The arguments in favour of improving diagnostic practices have coincided with the increasing availability of malaria rapid diagnostic tests, which are competing with the traditional use of microscopy for the detection of parasitaemia.

With the increased demand for ACTs and mRDTs, and a vast rise in available funding from donor organizations (Waddington, Martin, and Walford 2005), a growing variety of ACTs and mRDTs are becoming available on the market. This increase in antimalarials and diagnostic tools is accompanied by a host of evaluations considering their efficacy, effectiveness and costs in a variety of settings. These data, however, are not amenable for use by decision makers due to their fragmentation in three main areas: (1) the specific antimalarial or mRDTs; (2) the target sub-groups in the population; (3) the geographical location.

Regarding the target population in diagnosis, there are a number of factors relating to patient profiles that will influence the diagnostic interventions' effectiveness. The patient's age for instance might determine how susceptible they are to infection and subsequent development of disease due to acquired immunity (Greenwood et al. 2005). This will

influence both the efficiency of the treatment used, and also the utility of using diagnostic tests to confirm the existence of malaria parasites.

Other patient characteristics that might influence efficiency are HIV status and pregnancy. The interaction between HIV and malaria is garnering attention and is likely to influence the efficiency of both diagnostics and treatment (Kublin and Steketee 2006, Laufer et al. 2006, Van Geertruyden et al. 2006). Pregnant women can lose their immunity to malaria, therefore fast and accurate demonstration of parasitaemia is critical. Furthermore, there have been concerns regarding the safety of certain antimalarials for this subgroup, therefore presumptively treating them where prevalence is low may be inappropriate (Breman, Alilio, and Mills 2004, Brentlinger, Behrens, and Micek 2006).

Regional differences such as those in transmission patterns and resistance to partner drugs will also influence intervention effectiveness. Artemisinin-based combination therapies, ACTs, will be less effective when the partner drug in the combination is one that is locally failing in monotherapy (Whitty and Staedke 2005). Presumptive treating all febrile patients where transmission is very low is also unlikely to be efficient. Competing interventions and health needs, as well as the available health budget, will all impact on whether the use of specific malaria diagnostics and treatments are an efficient use of resources. These are all factors that vary widely by location.

Many of these factors are highly temporally dynamic, adding a further complication. Treatment efficacies for instance vary, as do transmission intensities and host immunity in the poplation. These variations are due to factors such as emerging resistance, urbanization and climate change. Given these circumstances it is clear that no single choice of drugs, diagnostic, or case-management strategy will be appropriate for all patients, at all times and all locations. An expensive ACTs may not be the most appropriate first line drug in

all settings, for instance, in the treatment of semi-immune adults in areas of low resistance to cheaper drugs. On the other hand, its use in presumptively treating subgroups, such as young children in high transmission areas, may be beneficial.

There is a sense of urgency to these issues, both to curb the ongoing toll of malaria and other non-malaria febrile illnesses in the most vulnerable populations in sub-Saharan Africa, but also to temper the drive for the immediate widespread deployment of ACTs and mRDTs across sub-Saharan Africa. Health care systems already buckling under the strain of illnesses such as malaria cannot afford to pursue ill-suited strategies to tackle them.

A study conducted in Iganga district of Uganda by Mukanga et al, 2010, showing the acceptance of mRDTs by the community, identified the need for proper training of community health workers, CHWs, regular technical supervision and logistical support, as gaps affecting the implementation. However, the study employed a communication theory, by using communication skills of health care providers to develop rapport with the patients. By this perspective, an equal relationship between the patients and the health care providers were established (Mukanga et al. 2010). These were strategy in allaying fears of being stigmatized in drawing blood to perform the test, in respect ofthe beliefs in witchcraftand the perceptions and suspicions of Acquired Immune Deficiency Syndrome (Mukanga et al. 2010). Another study conducted in central Cote d'Ivoire established that socio-cultural factors might be barriers for implementing mRDTs in general health services, such as the societal representations of malaria and HIV/AIDS with reference to blood taking and blood-related diseases (Ouattara et al. 2011). Despite efforts made in introducing mRDTs and subsequent acceptance by the target users, the implementation process of mRDTs is contingent on user beliefs, attitudes and perceptions (Mukanga et al.

2010, Danquah et al. 2016). Therefore, it is critical for the health system to provide the enabling environment to facilitate the integration of diagnostic tools into routine health care delivery.

A study in Ghana examining how mRDTs can achieve their potentials showed that with insufficient incentive package, mRDTs were variously interpreted and used. This explains how the health workers had learnt to use rapid diagnostic tests results (Chandler, Whitty, and Ansah 2010). To encourage health care providers in the face of negative mRDT results, it was recommended that a supporting package includes, local innovation, clarity of guidelines, information on alternative causes of disease, and constant support and interaction with health workers (Chandler, Whitty, and Ansah 2010). However, equitable access and universal coverage of efficient interventions remain limited due to the prevailing challenges in the health care system of resource-limited malaria settings in Africa (WHO 2013). Therefore, efficient health care delivery systems devoid of basic challenges are most needed for efficacious interventions in minimizing malaria related morbidity and mortality among the most vulnerable population.

A study conducted by Baiden et al in Ghana which assessed the acceptability of mRDT use among caregivers of under-five children in rural Ghana showed a widespread acceptance of the mRDT and its implementation. However, identified gaps that needed to be improved, were quality of caregiver-health worker interaction (Baiden et al. 2012). Another related study in Gabon, considered mRDTs as an alternative to microscopy, allowing not only an efficient and reliable malaria diagnosis in primary health institutions. It also provides basis for advancing changes in antimalarial prescribing and use habits (Mawili-Mboumba et al. 2010). In South-East Nigeria, Ezeoke et al., 2012, explored healthcare providers and the community perceptions and experiences with mRDT. It came

to light that they were familiar with malaria diagnostic tests as very important step to detect malaria from other non malaria febrile illnesses. This constituted an appropriate means of delivering malaria treatment (Ezeoke et al. 2012). Similar community-based studies conducted in Zambia has established the effectiveness and safety of oral treatment of malaria. This enhances the opportunity of improving access to confirmatory diagnosis and appropriate treatment in malaria endemic areas.

In Ethiopia, it was demonstrated that the use of mRDTs by Community Health Workers (CHWs) was not only feasible but associated with the potential of reducing malaria burden (Lemma et al. 2010). It was also realized that adequately trained CHW can perform and interpret mRDTs, and give treatment for malaria in Zambia (Yeboah-Antwi et al. 2010). This finding was consistent with a study in Cambodia (Yasuoka et al. 2010). Another scale-up study, which aimed at communities assessing the impact of mRDTs in the formal health sector, suggested a promising strategy to improve access of diagnostic procedures to remote populations. Ultimately, the improved access to diagnostics may lead to effective management of uncomplicated malaria and decrease mortality due to malaria (Thiam et al. 2012). Despite these, the logic in test-directed policy was dependent on cost of test and lack of testing facilities.

Two districts with prevailing difference in the level of malaria endemicity in Madagascar, i.e. Manakara, with high malaria transmission and Moramanga with low malaria transmission, was studied on the reliability of mRDTs by CHW. The study indicated that deploying mRDTs which is easy-to-use diagnostic tools at the community level seems an efficient strategy for improving malaria induced febrile conditions and reduction in excessive use of anti-malarial drugs (Ratsimbasoa et al. 2012). Similarly, a study by Ukwaja et al., 2011, in urban health centre in Ogun, Nigeria, which examined 50 children with malaria-pneumonia symptoms and treated presumptively (control arm) and other 50

children using mRDTs (intervention arm). It was observed that mRDT-based treated children had much lower tendency of receiving antimalarial compared to presumptively treated (Ukwaja, Aina, and Talabi 2011). In rural Dangme West District of Southern Ghana, Ansah et al., 2010, revealed in a study where microscopy already exists, deploying mRDTs had limited impact on prescriber behavior. However, where there were no microscopes, using mRDTs led to a marked reduction in overprescription of antimalarials. In Tanzania also, Williams et al., 2008, used the dispensary-based piloting system of implementing mRDTs to evaluate the acceptance and usage of mRDTs. It was deduced from health care providers and patients that overprescriptions decrased over the period of study. A study by Masaninga et al., 2012, in Livingstone district, Zambia, indicated a large decline in ACTs consumptionwith the introduction of mRDTs, and malaria mortality declined to zero. This indicated the effectiveness of the new diagnostic regime. In another study by Yukich et al., 2012, assessing ACTs consumption after nationwide routine exercise in scaling-up mRDTs, concluded that mRDTs contributed immensely in rationalizing treatment of febrile illnesses and reduction in the rate of consuming antimalarial drugs; however, their impact may be greater in low transmission areas.

Suggestions have been made to introduce mRDTs to staff of retail community pharmacies in recognition of the important role they play in the treatment of malaria (Chandler et al. 2011) (Cohen and Dickens 2012). Ikwuobe et al., 2013, showed that having the mRDT before treatment reduces the possibility of dispensing antimalarials to patients with symptoms of uncomplicated malaria in a community pharmacy by 42%. Similarly, other studies recorded as high as 77% (D'Acremont et al. 2011) and 96% (Msellem et al. 2009) reduction in antimalarial prescriptions with mRDTs use. However, it was found that restricting the sales of antimalarials to only mRDTs positive patients may be very

challenging, if alternative sources of income is not made available to community pharmacies (Zikusooka, McIntyre, and Barnes 2008).

2.7.5. Adherence to diagnostic test results

The assumption that prescribers and other healthcare providers will adhere to the malaria test results may be highly questionable based on study findings from several countries and settings. Several studies have shown varying degrees of adherence to test results (Appendix 2.1b). A study by Ndiaye et al., 2013 revealed an overall adherence to test-results of 85.6%, with test-positive patients, 90.1% receiving treatment and 24.8% of test-negatives clients receiving malaria treatment (Ndiaye et al. 2013). A systematic review of 27 articles, also revealed that, CHW correctly performed mRDTs, although the specificity levels vary. The study showed high level of adherence to test results, though, sizeable proportion of test negative patients received malaria treatment (Ruizendaal et al. 2014). In another systematic review recently conducted, which evaluated health worker compliance with malaria rapid diagnostic tests results showed a compliance levels of 97.0% and 78.0% of patients with positive and negative test results respectively (Kabaghe et al. 2016). The community health workers were more likely to comply with mRDTs-negative results (95.0%) compared with clinicians (75.0%) and nurses (87.0%). It was also observed in another study that the use of mRDTs at the community level was not well documented, and the few studies carried out indicated that a much smaller fraction (5.8%) were prescribed with ACTs even when the mRDTs results were negative (Mukanga et al. 2012, Mukanga et al. 2011, Mubi et al. 2011).

Therefore, deploying mRDTs needs to be done with updated clinical protocols that provide clear rules in treating patients with negative malaria test results (Mangham et al. 2011). In spite of this suggestion accessibility to effective management of non-malaria febrile illness

(Shillcutt et al. 2008, Msellem et al. 2009). Some other studies have also questioned, whether the deployment and use of mRDTs on a large scale will have a significant impact on the management of febrile illnesses (Bisoffi et al. 2009, Reyburn et al. 2007). Consistent with other findings, successful implementation is contingent on modification of long-standing community and health care practitioner attitude and perception of the causes and management of febrile illnesses (Msellem et al. 2009, Ansah et al. 2010, Williams et al. 2008, Harvey et al. 2008). However, in other studies the reportage was basically on quantitative or qualitative assessment of factors associated with compliance to mRDTs (Mbonye et al. 2015, Mubi et al. 2011, Bisoffi et al. 2009, Uzochukwu et al. 2011, Manyando et al. 2014).

It was reported that drug shops vendors adhered to mRDTs, thus reducing over-treatment of malaria (Mbonye et al. 2015). However, in a similar study, poor adherence to negative mRDTs results has been reported (Diggle et al. 2014). In Zambia, despite the routine use of mRDTs antimalarials were continuously prescribed to over one-third of patients with negative test results (Hamer et al. 2007). In Tanzania, a randomized trial in low transmission areas, found that over 90% of all antimalarials prescribed were for patients with negative test results, irrespective of the diagnostic method used (Reyburn et al. 2007).

The reasons for ignoring both mRDTs and microscopy negative test results have been explored by Chandler et al., who identified several factors contributing to the practice of overdiagnosis of malaria (Chandler et al. 2008). The study identified, firstly the spheres of influence on clinicians, such as training programmes, patient expectations and peer – pressure, followed by the mind-lines, meaning the thought patterns that are assumed to lead to overdiagnosis. These consist of the ease and acceptability of diagnosing malaria; and the fact that missing a case of malaria appears indefensible in the face of both peers

and patients, and particularly so given the extensive emphasis placed on treating malaria through promotion and training campaigns.

2.7.6. Economic evaluation of malaria rapid diagnostic testing

Economic evaluations are often based on single study from a particular setting, and then seek to generalize results to other settings. The data input into these evaluations can consist of an intervention costs, the effectiveness, target population characteristics, similar data for comparator interventions, and the value placed on outcomes. The values of these input parameters are, however, rarely completely fixed and known. Some of the uncertainty stems from limited data. While some variation will be due to heterogeneity, i.e. genuine differences in the intervention costs and effectiveness, and other characteristics of the location and target population (Briggs, Claxton, and Sculpher 2006). For instance, in the context of malaria, transmission intensity can vary widely within small areas (Yé et al. 2007), resulting in significant implications for population susceptibility to infection and the predictive values of diagnostic tests.

Literature reviews have highlighted some approaches in estimating the cost of malaria on two key determinants:

(i) direct cost resulting from expenditure on prevention and treatment and an indirect cost arising from productive time lost due to malaria morbidity and mortality

(ii) estimating the economic impact by summing the direct and indirect cost components (Shepard et al. 1991, Ettling and Shepard 1991, Ettling et al. 1994, Sauerborn et al. 1991, Guiguemde et al. 1994, Leighton and Foster 1993, Asenso-Okyere and Dzator 1997).

However, other studies have assessed a third determinat of cost refered to as the 'intangible cost' resulting from the suffering and grief an individual goes through when infected by the disease (Byford, Torgerson, and Raftery 2000). Generally, this has been found not to have substantive value in tangible economics because it is not measurable.

The direct costs of malaria, as defined in some literature refers to the cost involve in the prevention and treatment of malaria by households. In this definition, households use a range of preventive methods, i.e. aerosol sprays, mosquito coils, mosquito repellents and bed nets, to a different degree in different areas. In another definition, the direct cost consisted of medical and non-medical costs. The medical costs included registration fees, diagnosis, diagnostics, medicines, continuing care, hospitalization and rehabilitation. The non-medical costs are transportation to hospital and any other form of informal payments (Gold 1996).

The indirect cost of an illness covers those related to productivity or loss of income. This is of monetary value to the patient or caregiver as a result of the income lost in absenting from work due to illness (Goossens et al. 2000). Further, the loss of productivity and working time are significantly affected by the type of illness (Babu et al. 2002). It has been argued that this productivity losses can therefore be valued from either the societal, individual/household or employer perspective (Boccuzzi 2003). In some other studies, the evidence available on household monthly expenses per capita on malaria preventive methods, ranges between $0.05 per person in rural Malawi and $2.10 in urban Cameroon. This translates to an equivalent of between $0.24 and $15 per household (Kirigia et al. 1998). For malaria-related costs, a substantial variation between settings is expected. This is attributed to epidemiological conditions, such as the *Plasmodium* species, levels of

immunity, and socio-economic conditions such as income levels, accessibility to healthcare, and disease -related beliefs.

In Africa, the expenditures on malaria prevention and treatment are generally incurred by governments in the health care institutions. These are termed as the second component of direct cost. Unfortunately, the overall public expenditure on prevention and treatment of malaria is difficult to estimate. Estimation is therefore, hampered due to the fact that health care institutions cater for most of the expenditures involving treatment. Therefore, expenditures related to malaria are not separated from other health service cost during budgeting and accounting processes. Data available has confirmed that direct costs to government on malaria treatment are likely to be substantial. This is because of the increasing number of patients seeking care for suspected malaria in relation to an estimated unit cost of treatment. It has been estimated that 20 – 40% of outpatient visits in health care facilities in sub-Saharan Africa are for fever (Brinkmann and Brinkmann 1991, Najera, Hempel, and Organization 1996). Although the proportion of these that are malaria will greatly vary in areas and seasons. Similarly, suspected malaria amongst inpatients ranges from 0.5 to 50% of admissions.

In Malawi, an equivalent of US$1.00 was found to be the average recurrent cost for an outpatient visit of a suspected malaria in public and faith-based health facilities (Ettling and McFarland 1992). However, in Tanzania a relatively higher cost ranging between US$1.54 and US$4.49 was obtained. Further, the cost of in-patient admissions due to malaria was between $3.05 and $21.29, which was dependent on patient age group and the type of facility. As indicated, the age of a patient contributed in determining recurrent cost for malaria-related hospital admissions, i.e. it ranged from US$ 9.00 in Malawi to US$154.00 in Senegal for patients under 15 years of age with cerebral malaria (Faye et al.

1995). The average cost of hospital admissions for children with severe malaria in the Kilifi district hospital was US$68.00 whilst in the adjacent Malindi sub-district hospital, it costed US$36.00 (Kirigia et al. 1998). These estimations constituted 15% and 9% of annual recurrent expenditure of Kilifi district hospital and Malindi sub-district hospital respectively.

In some related studies the approximations used for unit cost were more general. For instance, in Rwanda, an average cost of an outpatient visit due to malaria was considered to be same as the average cost of all hospital visits, and estimated between US$1.56 and US$3.12, depending on the source of care. Generally, cost per day for malaria-related in-patient was estimated as two-thirds the average cost, multiplied by the average length of stay for malaria patients, giving an estimated cost per admission between US$ 8.73 and US$ 37.60 (Ettling and Shepard 1991). Another similar study divided the total health care budget by the total number of hospital visits per year, without distinguishing between in-patients and outpatients (Sauerborn et al. 1991). By using this approximation, the unit costs of malaria treatment by the Rwandan Ministry of Health was found to be 19% of operating budget (Ettling and Shepard 1991). In some countries, a portion of this total cost may be recouped through facility user fees system. A caution associated with this analysis was that, data ought to be used such that a decline in the number of malaria cases will lead to financial savings (Kirigia et al. 1998).

A research conducted by Mooney (1977) which assessed the contribution of human life in health service delivery, identified three types of approaches in deriving monetary values for human life:

a. Implied value or revealed preference approach. This is based on the values implied by past healthcare decisions.

b. Human capital approach or lost output approach. This equates the value of human life to the value of livelihood.
c. Willingness to pay or contingent valuation approach.

Although, these approaches have have their own strengths, they also exhibit some form of weaknesses, as exhaustively discussed by (Mooney 1977, Jones-Lee 1982).

The willingness to pay approach usually approximates the cost components of the disease by determining the value placed on avoiding the disease. However, this valuation concept is subject to interpretation with an assumption that economic choices are rational and related to cost and other consequences. Nonetheless, the willingness to paying to avoid a disease, is much reliable and a useful measure of how important a disease is, and can therefore influence be public policy on a particular disease.

In Nigeria, a study by Jimoh et al. assessed the economic burden of malaria using the willingness to pay approach where households were willing to pay an average minimum cost of N1,112 per month (Jimoh et al. 2007). With a population of about 140 million in Nigeria, this translates to billions of Naira in a year, with its associated impact on economic growth. In another study by Uzochukwu et al., 2009 which compared the cost-effectiveness of malaria rapid diagnostic testing with syndromic diagnosis among a study population with malaria prevalence of 43.1%. These patients with fever were diagnosed as having malaria by health workers in urban and rural districts of Nigeria and the increase in cost-effectiveness ratio of rapid diagnostic tests versus presumptive treatment was US$221 per death averted, indicating malaria rapid diagnostic test to be more cost-effective than other diagnostic strategies for malaria treatment (Uzochukwu et al. 2009). Similarly, another study evaluated the impact of malaria prevalence on the cost-effectiveness of diagnostic strategies in Kenya (Zurovac et al. 2008). The study showed

that rapid diagnostic tests is likely to improve malaria treatment by reducing the percentage of overtreatment between 30% and 50%. However, in areas where malaria prevalence is low, rapid diagnostic tests are more likely to yield minor reductions in overtreatment (Zurovac et al. 2008). In an earlier study by Zurovac in 2005, the results indicated an increase in frequency of ACT prescriptions over 2 years. This increase coincided with the expansion of rapid diagnostic test capacity in Zambia (Zurovac et al. 2005).

Evaluation of the cost effectiveness of rapid diagnostic test has never accounted for the degree to which clinicians adhere to the test results. Such a parameter could be difficult to quantify, and is likely to vary widely under different contexts (Amexo et al. 2004, Reyburn et al. 2007). An evaluation of the cost effectiveness of mRDT without accounting for the degree to which test results are adhered to, will misinform policy makers on the desirability of the deployment of mRDTs.

CHAPTER 3

3.0 METHODOLOGY

3.1 Study area

This study was conducted in Kumasi Metropolis, Ejisu-Juabeng Municipal, and Asokore-Mampong Municipal Assemblies of Ashanti Region of Ghana. These areas were conveniently selected in the municipal and metropolitan administrative areas.

3.2 Study setting

The three administrative settings were conveniently sampled as the study areas, where study participants were drawn at different stages during the research, with different sampling techniques. This sampling method is more economical as it provides an opportunity to select to represent the study site than including all healthcare facilities of interest. Additional advantage is when there is no sampling list. It has been shown that this approach is a less precise method of sampling with a higher standard error (Bowling 2014).

The hospitals/clinics selected to pilot the first phase of the study were, Kwame Nkrumah University of Science and Technology (KNUST) hospital, Paradise Clinic in Ejisu and Manhyia Regional Hospital in Kumasi.

i. The KNUST hospital is an out-patient quasi-governmental set-up with well-equipped laboratory and pharmacy facilities. The health care practitioners worked on shift policy, and thus made the health care facility very operational during the period of study.

ii. Paradise Clinic is a private health facility in Ejisu. Which is a peri-urban community of Ejisu-Juaben Municipality of Ashanti region. The facility attends to patients from Ejisu and surrounding villages. It had laboratory and

dispensary facilities. It was noted from the clinic registry that almost 20-25% of the monthly attendance were suspected malaria cases.

iii. Manhyia Regional Hospital, is a public health facility owned by government. It is located in Kumasi which is within the Kumasi Metropolitan Authority and provide services to the surrounding communities. The hospital registry indicated between 25-30% of monthly OPD cases to be malaria.

The retail pharmacies selected as study settings at different stages of the research were:

a. Kama health services a private registered pharmacy located at the commercial area of KNUST – Kumasi. It was supervised by a registered clinical pharmacist. It provided pharmaceutical care services by retailing to the University community and surrounding environs. It was assumed that majority of clients would be public servants and students.

b. Bandy Chemist is a private registered retail and wholesale pharmacy situated at Adum, in Kumasi, Ashanti Region. It provides pharmaceutical care services mostly to the business community in Kumasi metropolis.

c. Paso Health Services is a registered retail pharmacy situated at Roman Hill, near the Kumasi central market. It mostly provides pharmaceutical care services to the market community in the metropolis.

d. AAB Pharmacy is a registered retail pharmacy situated at Ejisu, within Ejisu-Juaben Municipality. It was assumed that patronage would predominantly be within the community.

e. Sawaba Pharmacy, located at Sawaba a community within Asokore-Mampong Municipal Assembly. The community is densely-populated, with people from northern part of Ghana being the majority. A lot of schools are within the

community. Sawaba Pharmacy, was assumed to be mostly patronized by people from the community.

f. Kama Health Services, Adum branch, was registered to provide both retail and wholesale pharmaceutical services to clients. It is situated in Adum, the commercial city of Kumasi, Ashanti Region, under Kumasi Metropolitan Assembly. It was assumed that majority of the clients might be traders.

Other criteria considered in the selection of the retail pharmacies, included;

a) a facility within a reasonable range to a laboratory.
b) a well patronized retail facility to achieve the desired sample
c) a facility that has operated for a minimum of 5 years
d) a facility with a Superintendent Pharmacist having a minimum of 5 years working experience
e) a facility already using mRDT or health care providers were willing to be trained on the use of mRDT.
f) a facility with a minimum of 8 working hours, especially between 7.00 am to 10.00 pm, from Monday to Saturday.
g) a facility with an adequate stock level of medications (antimalarial drugs) and diagnostic kits.

3.3. Study design

This was a three-phase study consisting of an exploratory baseline study in which patients were interviewed to establish diagnostic practices, understanding of malaria treatment and level of satisfaction of care services at health institutions, as a pilot. Then, pharmacists at registered retail pharmacies were also interviewed to explore their perspectives and willingness to implement malaria rapid diagnostic testing at their practice sites.

This was followed by an intervention study designed to evaluate the malaria diagnostic procedures. It was a longitudinal and prospective study with cross-over validation period of two (2) weeks, using Presumptive Diagnosis (PD) as the control arm and malaria rapid diagnostic testings as the intervention arm. The study compared the performance of PD and mRDTs, using microscopy as the standard. The study design also elicited both the trend of diagnostic procedures and pattern of practice of the care providers.

The third phase of the study assessed the cost-benefit of malaria diagnostic practices at the study sites. A contingent valuation process was employed using the payment card technique to estimate the maximum average cost patients were willingness-to-pay, among the study participants. An open-ended Cost-Benefit Questionnaire (CBQ) was self administered, and developed in providing information needed to analyse the cost-benefit of the malaria rapid diagnostic practices at registered retail pharmacies. The format in determining the participants' willingness to pay was the payment scale or card. This presented ranged of values to choose. These payment scales were allocated randomly in the study population to avoid range bias.

3.4 Ethical Considerations

Ethical approval was sought from Pharmacy Council (PC – 147) [3.11] in conducting the study. Additionally, informed consent was obtained from all the participants either from themselves or their care-givers prior to the engagement.

The information generated from the patient exit interviews were filed in locked filling cabinets. The data was double entered into an excel template and stored in a password protected Dropbox Network for safety and retrieval as and when necessary. Inductive coding system was employed after the diagnostic procedures to prevent untraced samples at the retail pharmacy and laboratory.

3.5 Study Limitation

The sampling strategy of Bennet *et al*., 1991, was based on calculations of precisions, and variability in treatment between health care facilities. This study assumed that the figures on precisions and variability were exact as those of Bennet *et al*., 1991.

3.6. Sample size determination

3.6.1. Baseline Survey Sampling

The sample size used was based on research findings of Bennett et al., 1991. It suggested that a minimum of 20 clinical cases with same diagnostic approach in hospitals/clinics was enough to confirm the pattern of practice in managing that clinical case, with precision of +/- 13%. An intra-cluster correlation of 0.3 was assumed (Bennett et al. 1991).

For private retail pharmacy outlets, Bennett et al., 1991, revealed a minimum of 14 patients. Implying that, if the same diagnostic procedure was applied to manage 14 patients then it was enough to confirm the practice in those health care institutions, provided, the precision was +/- 6.6% and with the same degree of variation (Bennett et al. 1991).

With these analyses, 65 patients exit questionnaires, PEQ, were used for the baseline study. Although, 53 were retrived (35 from hospitals/clinics and 18 from retail pharmacies), which satisfied the minimum requirements by Bennett et al., 1991.

3.6.2. Pharmacists Assessment Interview Sampling

The 'rule of thumb' was applied as a sampling technique in the second model. In this rule, the sample size should be a factor of five, ten, or twenty times the number of variables in any multivariable and factor analyses (Norman, Monteiro, and Salama 2012). In computing the sample size, 5 was used as a factor multiplied by 20 variables obtained from Pharmacists Assessment Questionnaire, PAQ (5x20 = 100). According to Norman et al., 2012, sample size of 100 participants meets the most standard 'rule of thumb'. A sample

size of 100 pharmacists were used which met this requirement. The first and last 50 pharmacists to register for private pharmacies with the regulatory body, i.e. Pharmacy Council in Ashanti Region were conveniently sampled as respondents of PAQ.

3.6.3. Sampling strategy for the intervention study

A convenience sampling method was used in the second phase of the study in examining the performance of the diagnostic practices. Six study sites (pharmacy) were conveviently sampled. Two-hundred, 200, suspected malaria patients per study site. One-hundred, 100, of the suspected malaria patients were diagnosed presumptively, PD, while the other 100 were tested using mRDTs. Being in either group was dependent on the type of diagnosis on the day of visit. In all, one thousand two hundred (200 x 6 = 1200) suspected malaria patients were involved in the study. The sampling method also considered expectation of approximately 34% of study population who were diagnosed and confirmed of malaria (Causer et al. 2004).

3.6.4. Post Intervention Study Sampling

Part of the third phase of the study was to analyse the cost-benefits of the diagnostic practices. Fifty (50) suspected malaria patients were randomly sampled from each of the six, 6, registered private retail pharmacies (6 x 50 = 300) for an interview using CBQ.

3.7. Materials for the second phase of study

The BlueAid Malaria Test Kit (Core Technology Co., Ltd., Beijing, China), which uses the Histidine Rich Protein-2 RDT detection system, was used for the research without any preference apart from availability. The test kit package contained new unopened test packet, alcohol swabs, lancet, capillary tube and desiccant sachet. Set of new disposable hand gloves were made available for use in attending to each patient to avoid possible blood contaminations. Sharps box for discarding lancet and capillary tubes were provided

to all the study facilities for the disposal of sharps after conducting the mRDT. Non-sharp waste containers for disposing used hand gloves, alcohol swab, and desiccant sachet were also provided to all the study facilities. Additionally, 3% Giemsa stains, Leica DM 750 light microscope and slides were used in the standard laboratories involved in this research.

3.7.1. Malaria RDT (mRDT) procedure

For uniformity, a common Malaria *Pf/Pv* rapid test devise, "BlueAid Malaria Test Kit" format devise was used. This was to minimize the challenges of variations because of multiple products in the market, i.e. more than 200 malaria rapid diagnostic tests kit from about 60 manufacturers (WHO 2011). About 10 µL of blood from the 4th fingertip of the participants' left hand, was picked with a plastic micropipette into the test well with a solubilized conjugated antibody. Three (3) drops of buffer was then added. The mixture migrated into the results window until the blood cleared, usually within 15 minutes. The result of the test kit was recorded negative, when the control line only appeared; or positive, when both control and test lines appeared irrespective of the intensity of the test line. A non-conclusive mRDTs, i.e. when only the test line appeared without the control line, and these were usually repeated. Patients with positive mRDTs were given a free package of ACTs as an incentive.

Malaria RDT results were recorded as True Positive (TP), True Negative (TN), False Positive (FP), or False Negative (FN). The malaria disease prevalence of the study setting was determined based on TP and FN in relation to the total study population. The test's sensitivity (Se), specificity (Sp), positive predictive value (PPV), along with false discovery rate (FDR); the negative predictive value (NPV), along with the false omission rate (FOR) were then calculated. A Diagnostic Odds Ratio (DOR) was computed and

employed to measure effectiveness of the diagnostic test (Glas et al. 2003). For each value, a 95% confidence interval (CI) was used.

3.7.2. Thick blood smear procedure

Microscopy was used as a 'gold standard' for confirmation of mRDTs and PD conducted at the registered private retail pharmacies in the second stage of the study. These were done, according to the WHO standard protocol, in agreed accredited medical laboratories. The blood films of suspected malaria patients, after mRDTs (positive or negative) were stained (within 3 days of collection) for 30 minutes with 3% Giemsa. The films were examined independently by two experienced laboratory technicians. For the thick film examination, parasites were counted against 200 – 500 White Blood Cells by microscopists. They were blinded to the mRDT results while reading the smears with a Leica DM 750 light microscope (Leica Microsystems CM5 GmbH, Wetzlar - Germany) under oil immersion (× 1000 magnification). The smear was negative if the examination did not reveal any parasites. The discordant results were checked and confirmed by a senior technician.

3.7.3. Operational quality control measures

The mRDT kits used for the study were those approved by the NMCP in accordance with WHO quality control standards. It uses histidine-rich protein-2 (HRP-2) detection system for *P. falciparum*. HRP2-based RDTs show a sensitivity of 82 - 97% (Iqbal, Khalid, and Hira 2002, Hopkins et al. 2008, Nicastri et al. 2009). The storage condition of the test kits was in accordance with the recommendation of the manufacturer (in a sealed pouch; humidity, heat and direct sunlight were avoided) and used within the recommended shelf life. The average storage temperature of the retail pharmacies was 19 – 25 ^{o}C (manufacturer's recommendation: 2 - 30 ^{o}C). The standard storage conditions were

enforced by the supervisory staff. The results were coded and recorded, and the kits kept for comparison with microscopy results. Afterwards, the used test kits were disposed using special containers designed for that purpose.

An accredited microscopists, stationed at the selected laboratories for that purpose, reviewed blood films and results collated by the Principal Researcher. Discordant results were resolved by another microscopist. Microscopists were blinded to both the results of the corresponding mRDTs and that of other microscopists.

3.8. Data collection process

The first specific objective examined malaria diagnostic practices at healthcare institutions and explored the understanding of treatment and satisfaction of the care service provided. Therefore, Patient Exit Questionnaire, PEQ, was designed to provide that information. Of the 65 PEQ, 53 (81.54%) were received with no explanable reasons for attrition. The interview using the PEQ was conducted while patient was exiting, upon consent, between March and April, 2013. This data collated provided adequate information required to address the specific objective. Which includes reasons of visit (signs/symptoms), mode of diagnosis, drug therapy, motivational factors, and demograhics of patients.

The second specific objective was to establish the acceptance and willingness of healthcare practitioner in implementing WHO recommendations of test-based policy of malaria diagnosis at healthcare institutions. A Pharmacists Assessment Questionnaire, PAQ, was employed to provide information from a retail pharmacy practitioner. This data collation exercise transverse between September and November, 2013. The information provided by PAQ was categorized to respond to this objective. Which includes characteristics of practitioner, knowledge and experience of the test kit, acceptance and willingness of using

it and challenges with the kit. As explained in the sampling method, 100 practitoners were the respondents.

The final specific objective examines the performance, assess adherence to tests results and determining cost-benefit of mRDTs and PD at registered private retail pharmacies. A prospective, longitudinal, and 2-weeks cross-over validation study was conducted in retail pharmacy outlets at Kumasi Metropolis, Ejisu-Juaben Municipal Assembly and Asokore-Mampong Municipal Assembly, in Ashanti Region, Ghana, from April to September, 2014.

Some of the practitioners were trained prior to the commencement of the survey. The training was on the technique and usage of mRDTs kit, approved by the National Malaria Control Programme, in accordance with the WHO quality control standards [Appendix 5.1].

The trained staff were assigned the role of daily consultations with the eligible patients. A total of 1200 patient, as explained in the sampling technique, who presented with fever (axillary temperature $\geq$ 37.5 ℃ or history of fever in the preceding 48 hours, were enrolled.

The patients were categorized into two, i.e. control arm (PD) and intervention arm (mRDTs). Six hundred, 600, each for the control-arm and the intervention-arm, as explained in the sampling technique. Initial consultation was done to collate information on participants such as demographic characteristics, frequency of visit for medical attention, profession and educational background.

Following this consultation, a finger-prick blood sample of patients from both arms of the study (mRDTs and PD) was collected to prepare a thick and thin blood film for malaria microscopy (gold standard). The prepared slides were labeled, dated and coded. The

patients categorized for mRDTs went through the processes of testing, while presumptively diagnosed patients, PD, went for medical attention after the blood sampling procedures. The results were recorded in a standardized Case Reporting Form (CRF) [Appendix 3.1]. These CRF were kept by the accredited pharmacy staff, which was inspected and verified by the Principal Researcher (PR) to collate information at both pharmacies and laboratories. The daily results of mRDTs, and the prepared thick and thin blood film (for both mRDTs and PD set-ups) after microscopic examination at the laboratories were separately and sequentially coded. Serial number codes were used to define and indicate daily activities and consigned into coding boxes. These were further recorded for cross assessment and verification. Pregnant women, persons presenting with extremely elevated body temperature, chills, and rigor, and those refusing or unable to provide informed consent were excluded from the study.

The CBQ facilitated data collation on willing-to-pay, WTP. The maximum amount willing to pay for treatment including diagnostic testing, was perceived as the monetary benefit with regards to the service or intervention to the individual. This is in line with economic theory of welfare, which explains the benefit of a service or intervention. The interview with CBQ was after a short briefing on the concept of test-based before treating malaria patients.

3.8.1. Data analysis

All filled questionnaires, PEQ, PAQ and CBQ received were checked for completeness, coded before data entry. Data collated were double-entered to minimize data entry errors and secured on a password-protected computer. The analysis was done using SPSS Version 19.

At baseline, bivariate analysis was used to identify relationships between explanatory variable such as health care facilities and method of diagnosis, patient' understanding of treatment and satisfaction with health services provided at a p-value ≤ 0.05.

At the intervention, analysis started with the manual transcription of data from the completed PAQ, which were identified with codes. The statistical parameter used in establishing the significance of the themes were logistic regression. The level of significance was also fixed at 5%. The results were termed as true positive, TP, true negative, TN, false positive, FP, or false negative, FN. A TP or TN is the event where the mRDTs makes a positive or negative prediction, and the subject also obtains a positive or negative result under the gold standard. While a FP or FN is the event where the mRDTs makes a positive or negative prediction, and subject has opposite result under the gold standard. The sensitivity, Se, and specificity, Sp, positive predictive value, PPV, along with false discovery rate, FDR, and negative predictive value, NPV, along the false omission rate, FOR, were computed, and employed to measure the performance of the diagnostic tests. Malaria disease prevalence, MDP, of the study calculated based on TP and FN in relation to the total study population. For each value, a 95% confidence interval, CI, was used.

Formulae for the calculation of the parameters mentioned above were as follows:

MDP = T_{dx} /T_{sp} x 100, where T_{dx} = number of individuals with disease, T_{sp} = total study population; Se = TP/(TP + FN) X 100; Sp = TN/(TN + FP) X 100; PPV = TP/(TP + FP) = TP/number of positive calls; FDR = (1 – PPV) or FP/(TP + FP); NPV = TN/(TN + FN) = TP/number of negative calls; FOR = (1 – NPV) or FN/(TN + FN); DOR = Se x Sp/([1 – Se] x [1 – Sp]).

In assessing the adherence level to tests result, the monetary value was studied. The study established differences in malaria treatment cost, i.e. based on presumptive diagnosis and

confirmed by microscopy and by mRDTs. Two different cost situations were involved. First, the cost of antimalarial drugs for patients diagnosed presumptively. This cost was for only ACTs prescribed without the cost of services provided. The other cost which was calculated separately included cost of tests kit with the cost of ACTs, as cost of the treatment for the intervention arm (mRDTs).

At the post intervention stage, the cost component was calculated from care providers' perspective. These included, the average salary of pharmacists working at retail pharmacies at the study settings, and cost of the 15 minutes of pharmacists' time spent on administering mRDTs services (Zurovac et al. 2006, Uzochukwu et al. 2009). The average cost price of the tests kit from pharmaceutical distributors in Ashanti Region was also used in this calculation. The calculation on cost-benefit of treating patient using mRDTs kit was done. Thus, by dividing benefits over costs, referred to as a benefit-cost ratio, BCR. A ratio greater than one is a demonstration of a positive return on investment. In this study, the potential benefit used was the willingness to pay for mRDTs service, and the cost was the pharmacist time used in administering mRDTs plus cost of the kit.

CHAPTER 4

4.0. RESULTS

4.1 Baseline Studies (First stage)

4.1.1 Demographic Characteristics of Patients

A total of 53 patients were enrolled into the study. Twenty-five (47.2%) were males while 28 (52.8%) females. The median age was 30.0 years (range 17 – 66 years). Fifty-two (98%) gave information on their educational status, with tertiary having 24 (46.2%), second-cycle 9 (17.3%), basic education 14 (26.9%) and without formal education 5 (9.6%).

4.1.2. Demographic characteristics of practitioners

Table 4.1 shows the detailed characteristics of the 99 practitioners whose questionnaires were retrieved. Of the type of practitioner involved in the study, pharmacists were the highest (67%)

Table 4.1. Demographic characteristics of practitioners involved in the study

Characteristics	number	Percentage
Practitioner type		
Pharmacists	67	67.7
Pharmacy Technician	14	14.1
Pharmacy intern	11	11.1
Medicine Counter Assistant	7	7.1
Highest educational level		
Graduate degree	63	63.6
Post graduate degree	17	17.1
HND	13	13.1
MCA	6	6.1
Age (years)		
31-40	43	43.4
20-30	29	29.3
Above 40	27	27.3
Years worked as a practitioner		
Above 5 years	59	60
3 - 5years	18	22
Less than 3 years	15	18
Sex		
Males	66	67.0
Females	33	33.0

4.1.3. Mode of Diagnosis to establish practice

Forty-four out of the 53 patients were diagnosed of malaria presumptively in the first phase of the study, while 9 patients were diagnosed through test-based.

4.1.4. Drug Therapy

All the 53 suspected malaria patients received antimalarial drug, i.e. Artemisinin-based Combination Therapy, ACTs. It means ACTs was the main antimalarial drug being used.

4.1.5. Patients Understanding of Treatment and Satisfaction of Care Service

Twenty-five (47.2%) out of the 53 patients in the first phase study indicated very good understanding of treatment and 37 (69.8%) patients were very satisfied with the health care services. Six, 6 (11.3%) indicated very poor understanding of treatment, while 2 (3.8%) were very dissatisfied for the care services received.

By stratification, 15 out of 35 patients (42.9%) who sought medical attention at hospitals/clinics, had very good understanding of treatment, and 4 (11.4%) expressed their understanding as very poor. For the 18 patients who attended private retail pharmacies, 10 (55.6%) had very good understanding of their treatment, and 2 (11.1%) had very poor understanding of treatment. Twenty-two, 22 (62.9%) were very satisfied with care services at the hospitals/clinics, while 1 (2.9%) was very dissatisfied. Details are shown in Table 4.2.

Table 4.2. Patients understanding of the treatment and level of satisfaction of services.

	Rating	Hosp/clinics, n(%)	Retail pharm, n(%)	Total, n (%)
Understanding	AV	8 (22.9)	1 (5.6)	9 (17.0)
	FGV	7 (20.0)	4 (22.2)	11 (20.0)
	SPV	1 (2.9)	1 (5.6)	2 (3.8)
	VGV	15 (42.0)	10 (55.6)	25 (47.2)
	VPV	4 (11.4)	2 (11.1)	6 (11.3)
Satisfaction	AS	3 (8.6)	0 (0.0)	3 (5.7)
	NSD	1 (2.9)	0 (0.0)	1 (1.9)
	SS	8 (22.9)	2 (11.1)	10 (18.9)
	VD	1 (2.9)	1 (5.6)	2 (3.8)
	VS	22 (62.9)	15 (83.3)	37 (69.8)

VPV: Very Poor Value; VGV: Very Good Value; SPV: Somehow Poor Value; VGV: Very Good Value; VPV: Very Poor Value; AV: Average Value. The 'value' stands for 'understanding'

Peason Chi-Square Test (Value: 2.76; df: 4). Asymp. Significance (2-sided): 0.599, Monte Carlo Significance (2-sided): 0.624, 99% confidence interval (lower boundary: 0.612, Upper boundary: 0.637.

AS: Average Satisfy; NSD: Neither Satisfied nor Dissatisfied; SS: Somehow Satisfied; VD: Very Dissatisfied; VS: Very Satisfied

Peason Chi-Square Test (Value: 3.8; df: 4). Asymp. Significance (2-sided): 0.269, Monte Carlo Significance (2-sided): 0.431, 99% confidence interval (lower boundary: 0.418, Upper boundary: 0.444).

Hosp/cl: Hospitals/clinics; PRP: Private Retail Pharmacy.

In assessing patients' satisfaction for care services, 'convenience' in accessing the service was very prominent, 35 (66.0%) and brands of drug, 4 (7.5%) [Figure 4.1].

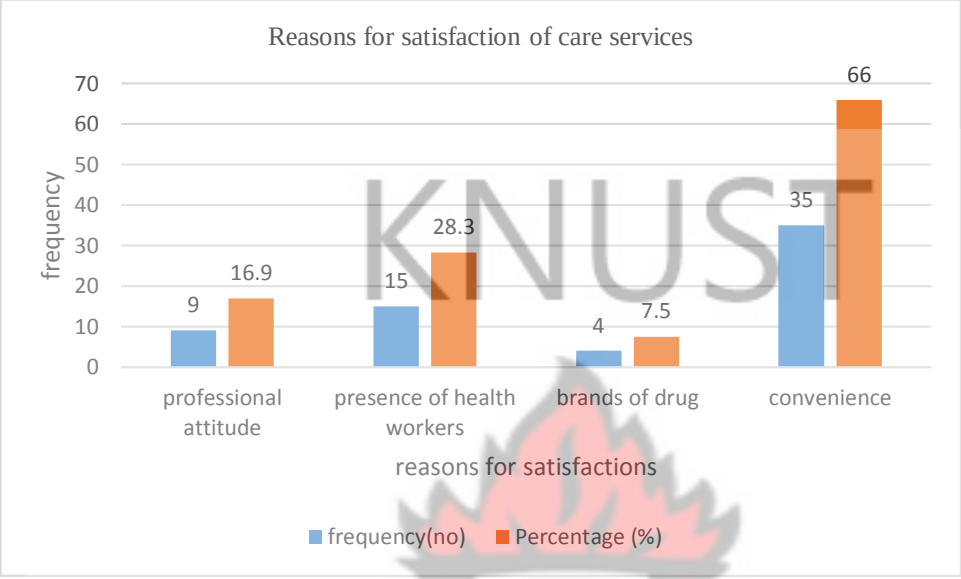

Figure 4.1: Reasons for the expression of satisfaction of care services.

4.1.6. Patients understanding of treatment and educational level

Patient's educational level was shown to influence or have effect on the understanding of treatment (Table 4.1). Fourteen, 14 (58.3%) of the 25 patients who expressed very good understanding of treatment had tertiary education.

Table 4.3. Patients understanding of treatment with education level

Understanding (%)	No formal n (%)	1 n (%)	2 n (%)	3 n (%)	Total n
AV	0 (0.0)	3 (21.4)	1(11.1)	5(20.8)	9 (17.3)
FGV (21.2)	1 (20.0)	2 (14.3)	3 (33.3)	5 (20.8)	11
SPV	0 (0.0)	1(7.1)	1(11.1)	0 (0.0)	2 (3.8)
VGV (48.1)	1 (20.0)	6 (42.9)	4 (44.4)	14 (58.3)	25
VPV	3 (60.0)	2 (14.3)	0 (0.0)	0 (0.0)	5 (9.6)

VPV: Very Poor Value; VGV: Very Good Value; SPV: Somehow Poor Value; FGV: Fairly Good Value; AV: Average Value. Pearson Chi-Square Test (Value: 23.309; df: 12). Asymp. Significance (2-sided): 0.026.

4.1.7. Pharmacist Awareness and Experience with mRDTs

Majority of the pharmacists (96.03%) were aware of mRDTs as diagnostic tool. Pharmacists who indicated using the diagnostic kit always were 0.99%; and those who never used the tests kit were 58.41%, 38.61% sometimes use it, and those who usually used it were 0.99%.

Among the pharmacists, 45 (70.3%) became aware of the test through workshops, 7 (10.9%) in print/electronic media, 7 (10.9%) through professional colleagues, 1 (1.6%) in medical journals, 1 (1.6%) through patient and 3 (4.7%) had no knowledge of the tests kit. A logistic regression was employed in determining the statistical significance of medium of information, and usage of test. This was done by keeping educational level constant, and Pearson Chi-Square of 0.751 and Likelihood Ratio (LR) of 0.540 was obtained, at $p \leq 5$.

4.1.8. Pharmacists Acceptance and Willingness to use mRDT

Above forty-eight percent (47.52%) of the practitioners strongly agree to implement the mRDTs testing as an index of acceptance, and 48.51% also agreed to implement mRDTs, while 0.99% disagreed. As an indication of willingness to use the tests kit, 32 (66.7%) of the practitoners were definite suggesting to colleagues, as they believe mRDTs will enhance treatment by targeting the malaria parasite. A subset of practitioners, 15 (33.3%), were probably willing to implement the tests, because they believed it was a good policy aimed at accurate diagnosis [Table 4.4].

Table 4.4: Reasons to suggest malaria rapid diagnostic tests to professional colleague

Reasons for suggestions	Definitely, n (%)	Probably, n (%)	Not sure, n(%)	Probably not, n (%)	Total n
Perceived barriers	0 (0.0)	1 (50.0)	1 (50.0)	0 (0.0)	2
Not very enthused about deployment procedure	0 (0.0)	3 (75.0)	1 (25.0)	0 (0.0)	4
Enhance treatment by targeting the malaria parasite	32 (66.7)	15 (31.3)	1 (2.1)	0 (0.0)	48
Very good policy aimed at accurate diagnosis	29 (64.4)	15 (33.3)	1 (2.2)	0 (0.0)	45
Perceived threat of missing malaria cases	0 (0.0%)	0 (0.0)	2 (66.7)	1 (33.3)	3

4.1.9. Practitioners' Challenges towards the Use of mRDTs

Of the practitioners, 40.0% identified additional cost as a challenge in accepting and willing to implement mRDTs testing, 44.4% felt presumptive diagnosis was a huge challenge, 22.0% were not sure of regular supply of tests kit and 13.0% thought socio-cultural and religious beliefs in drawing blood pose a challenge to implementing mRDTs 13.0% [Figure 4.2].

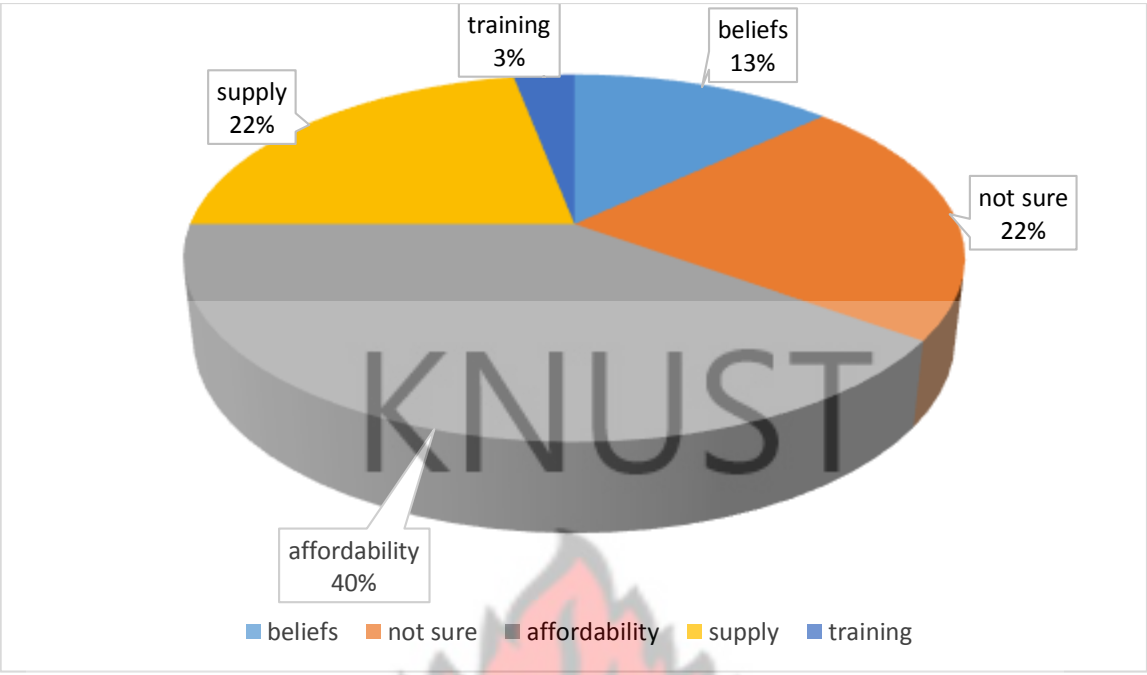

Figure 4.2: Practitioners' challenges to accepting mRDTs

4.2. Intervention Study Results (Second stage)

4.2.1 Diagnostic results and antimalarial therapy provided

The 600 suspected malaria patients subjected to mRDTs (intervention), 258 (43.0%) tested positive while 342 (57.0%) tested negative. All the 258 (43.0%) participants who tested positive to the mRDT received Artemisinin-based Combination Therapy (ACT) consisting of artemether-lumefantrine. A total of 212 (62.0%) of the 342 mRDTs negative patients were also given antimalarial. The cost of treatment on the negative tested patients was US$ 576.64 [Table 4.5: under mRDT]. The remaining 130 (38.0%) of mRDTs negative patients did not receive antimalarial therapy.

Another set of 600 suspected malaria patients who were diagnosed using PD (control), 589 (98.2%) were treated with artemether-lumefantrine. The sum cost of ACTs used on the 589 patients was US$ 1071.98. However, microscopy examination confirmed 178 (29.7%) as positive (level of agreement) while 422 (70.3%) were negative (level of disagreement).

The cost incurred on patients confirmed negative by microscopic but treated with ACTs was US$ 768.04 [Table 4.5: under microscopy].

Table 4.5: Diagnostic method used and its effect on cost of malaria treatment

Variable N = 600

Diagnostic Method		Test Results		Test negative patients supplied with ACTs	Cost of treatment US$ (95% CI)
		Negative	Positive		
Age group	No. of Patients	n(%)	n(%)	n(%)	n(%)
mRDT					
< 5yrs	20	17 (85.0)	3 (15.0)	17 (100.0)	46.24
6-10yrs	100	70 (70.0)	30 (30.0)	50 (71.4)	136.00
11-15yrs	180	85 (47.2)	95 (52.8)	65 (76.5)	190.40
>16yrs	300	170 (56.7)	130 (43.3)	80 (47.0)	204.00
Total		342 (57.0)	258 (43.0)	212 (62.0)	576.64
		PD negative	**PD positive**		
Microscopy					
< 5yrs	50	34 (68.0)	16 (32.0)		61.88
6-10yrs	150	112(74.7)	38 (25.0)		203.84
11-15yrs	180	120 (80.0)	60 (33.3)		218.40
>16yrs	220	156 (70.9)	64 (29.1)		283.92
Total		422 (70.3)	178 (29.7)		768.04
Presumptive Diagnosis, PD					
< 5yrs	50	0	50 (100.0)	50 (100.0)	91.00
6-10yrs	150	2 (1.3)	148 (98.7)	148 (98.7)	269.36
11-15yrs	180	9 (5.0)	171 (95.0)	171 (95.0)	311.22
>16yrs	220	0	220(100.0)	220 (100.0)	400.40
Total		11 (1.8)	589 (98.2)	589 (98.2)	1071.98

Note: A United States Dollar, US$, rate during study period was equivalent to GHc 3.30. (i) mRDT: Cost of malaria treatment was the cost of antimalarial drug + cost of diagnostic method. Average cost of a generic antimalarial drug was GHc 6.00 and cost of test kit was GHc 3.00. [GHc 9.00 = US$ 2.72]. (ii) PD: The cost of treatment was the cost of antimalarial drugs minus cost of test kit [GHc 6.00 = US$ 1.82].

4.2.2. Comparing mRDT results with microscopy as gold standard

All the 3 patients under 5-years category, who tested positive with mRDTs maintained their status as positive with microscopy (TP). The 17 patients within the same age categories who tested negative with mRDTs, 16 (94.1%) of them remained negatives after

microscopic examination [TN]. By computation, the sensitivity, Se and specificity, Sp, of mRDTs within that age categories were 75% and 100% respectively. Similarly, of the 30 patients within 6 – 10 years category who tested positive with mRDTs, 28 (93.3%) was confirmed TP after microscopic examinations. The 70 patients within the same age category, who tested negative with mRDTs, 3 (4.3%) was FN and 67 (95.7%) was TN. The Se and Sp were 90.3% and 97.1% respectively (Table 4.7).

Table 4.6: Comparing the results of malaria rapid diagnostic test positive patients with their microscopy results to determine 'sensitivity' and 'specificity'

Age (yrs)	mRDT (+)	TP	FP	mRDT (-)	FN	TN	Se (%)	Sp (%)
≤ 5	3	3 (100)	0	17	1(5.9)	16(94.1)	75	100
6-10	30	28 (93.3)	2(6.7)	70	3(4.3)	67(95.7)	90.3	97.1
11-15	95	94 (98.3)	1(1.1)	85	1(1.2)	84(98.8)	98.9	98.6
≥ 16	130	128 (98.5)	2(1.5)	170	2(1.2)	168(98.8)	98.5	98.7
Total	258	253(98.1)	5(1.9)	342	7(2.0)	335(97.9)		

Data presented as frequency (%) of patients. mRDT= malaria rapid diagnostic test, Se=Test's Sensitivity, Sp=Test's specificity, TP=True Positive, FP=False Positive, FN=False Negative, TN=True Negative

Table 4.6 shows the level of agreement between mRDTs testing and microscopic examination to be 98.1%, i.e the TP.

The performance of mRDTs at the study sites was computed using standard procedures such as malaria prevalence, sensitivity and specificity of mRDTs, PPV, FDR, NPV, FOR and DOR [Table 4]. Appendix 3.10 showed details of the computation.

Table 4.7: Summary of key parameters used in the evaluation of mRDTs and its corresponding value obtained

Parameter	Formula used	Value
Disease prevalence	T_{dx} / T_{sp} x 100	43.3 %
Sensitivity of mRDT (Se)	TP / (TP + FN) x 100	90.68 ±1.18 %
Specificity of mRDT (Sp)	TN / (TN + FP) x 100	98.68 ± 1.19 %
Positive Predictive Value (PPV)	TP / (TP + FP)	98.0 %
False Discovery Rate (FDR)	(1 – PPV) or FP / (TP + FP)	2.0 %
Negative Predictive Value (NPV)	TN / (TN + FN)	98.0 %
False Omission Rate (FOR)	(1 – NPV) or FN / (TN + FN)	2.0 %
Diagnostic Odds Ratio (DOR)	Se x Sp / [(1 – Se) x (1 – Sp)]	2,366.43

The T_{dx} represents the number of individuals with malaria disease, and T_{sp} is the total study population.

4.3. Post Intervention Study

4.3.1. Benefit estimate: Willingness-to-pay for malaria rapid diagnostic test treatment.

A total of 285 out of the 300 respondents (95%) answered the question on willingness-to-pay. Of this subset, 205 (71.92%) stated that they prefer malaria rapid test before treatment while 80 (28.07%) prefered presumptive treatment. The reasons given by most of the participants for rejecting the malaria testing and prefering presumptive treatment were mainly financial considerations. Implying, those who were not willing to pay for mRDTs may have prefered it, if it was without cost to the client.

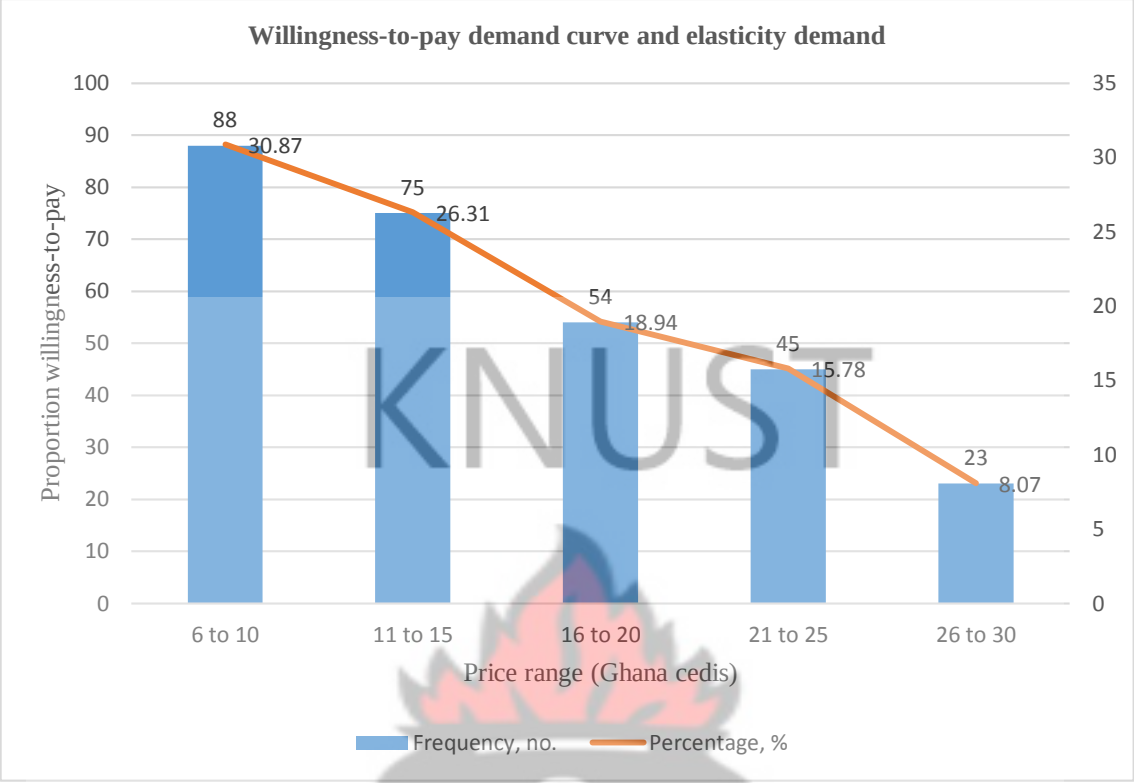

Figure 4.3: Willingness-to-pay on the cost of treatment with malaria rapid diagnostic test

Figure 4.3 shows a demand curve on the willingness to pay. It illustrated a relationship between a price of treatment with rapid diagnostic test kit and the percentage of patients willing to get tested. A total of 88 respondents (30.87%) indicated paying an amount between GHc6.00 to GHc10.00 for treatment with the test kit. The demand curve exhibited a negative slope which is consistent with the law of demand. This means that an increase in the price of treatment with the test kit, will cause a decrease in the percentage of patients willing to pay.

4.3.2. Cost estimate

It was estimated that the average salary of a pharmacist during the study was GHc 1,800.00. The cost of 15 minutes of the pharmacist's time used in conducting a malaria test and the average distributor's price for a mRDT kit (GHc 3.00) in the study area were

used to estimate the total cost to the patient. By calculation, 15 minutes is 0.25 hours; and 26 working days =GHc 1800. A working day would be = GHc 1800/26 = GHc 69.23 (24 hours). Therefore, 0.25 hours = 0.25 x 69.23/24 = GHc 6.00. Thus, the total cost involved = GHc 3.00 + GHc 6.00 = GHc 9.00. The United States Dollar, US$, equivalent in Ghana cedi at the time of study was: US$1 = GHc3.30. Therefore, if GHc3.30 was US$1.00, then GHc9.00 total treatment cost will be US$2.72.

4.3.3. Benefit-cost estimates

The cost-benefit of rapid diagnostic testing from community pharmacists' perspective was estimated by dividing the benefits over costs, termed as a benefit-cost ratio, BCR. In this study, 88 (30.87%) participants agreed to pay within a range of GHc 6 – 10 (figure 4.3). The cost as stated above was GHc 9.00 (US$ 2.72) Using the upper limit of WTP in the mostly agreed range, i.e. GHc 10.00 which was equivalent of US$ 3.02, the BCR in US$ = 3.02/2.72 = 1.11.

CHAPTER 5

5.0. DISCUSSION

5.1 Baseline Studies (First phase)

It was discovered in this study that the median age of the patients was 30.0 years. This could be said to be within the productive age range. So therefore if a greater percentage of the study population visiting health facilities for malaria care then their productivity is likely to be affected by malaria morbidity and mortality. Studies conducted by Gallup and Sachs in malaria endemic countries have demonstrated comparable adverse impact on economic activities, particularly related to productivity. This was because direct and indirect costs of illness and worker productivity impede economic growth (Gallup and Sachs 2001). It has been reported that malaria played a major role in causing poverty and low productivity in Ghana, accounting for about 32.2% of hospital visits at out-patient-department, and 48.8% of under-five years hospital admissions in the country (NMCP 2014). So, it is essential to deploy prompt and efficient methods of man malaria case management to reverse the adverse effects of malaria on the economy of Ghana. Therefore, effective malaria treatment guidelines and its implementation can result into maximizing the potential of improving an efficient therapy for malaria and reduce the economic burden of malaria control in Ghana.

Though both the NMCP of Ghana and the WHO new treatment guidelines for malaria case management demand a parasite-based confirmation before initiating malaria therapy, seven years after the deployment mRDTs in health facilities in Ghana, this survey revealed at baseline that only 18% of malaria diagnosis at the retail outlets were based on confirmatory diagnosis. Even where microscopes were readily available, the health care

providers were not making use of them. Largely confirming presumptive diagnosis as the most common diagnostic practice.

This presumptive diagnosis has long been the practice in Ghana. Which has created a diagnostic uncertainty and has reduced the level of accuracy of malaria diagnosis coupled with the declining prevalence of malaria across many regions in Ghana (NMCP 2009, Chandramohan, Jaffar, and Greenwood 2002, Greenwood et al. 2005, Weber et al. 1997). As a result, a number of non-malaria febrile illnesses may be missed and treated as malaria as reported in many other similar studies (Whitty et al. 2008, A-Elgayoum et al. 2009). Strengthening diagnostic testing by effectively deploying mRDTs use in all health facilities and supporting it with effective behavior change communication will substantially improve health care delivery and enhance economic development.

It was also observed at baseline that all the patients who sought medical care for fever were all treated for malaria using Artemisinin-based Combination Therapies without any confirmatory diagnostic test. Though this is in line with the recommendations of NMCP and WHO, the malaria drug therapy as observed in this study suggests a wholesale treatment with ACTs, regardless of the test-based treatment directives. It has been reported that such excessive use of antimalarials lead to wastage of antimalarial drugs and the cost effectiveness of the diagnostic tests is also reduced (Lubell et al. 2008, Zurovac et al. 2008). This practice has the potential of accelerating drug resistance development and also possibly encourage influx of substandard and counterfeit ACTs because of the excessive patronage.

The study also showed at baseline that less than 50% of the patients had good understanding of their treatments at the study sites with patients of private retail pharmacies indicated higher score on understanding of the treatment, despite malaria being

one of the most common disease condition in Ghana. This is encouraging because most patients use private retail pharmacies as their first port of entry to health care delivery (Rutebemberwa et al. 2009, Moerman et al. 2003). However, the level of understanding of the treatment regimen among educated respondants was higher in this study. This suggest that the educational background of the respondant influenced the level of understanding of the treatment received as reported in similar studies (Leventhal and Cameron 1987). This could probably be linked to the medium of communication and the confidence of asking questions. Therefore, it would be more appropriate to counsel patients using the language which is more understandable to the patients, because it could maximize therapeutic benefits, and create an environment of mutual understanding and respect between the patient and health care provider.

Assessing the level of satisfaction of health care services and the factors which contribute to their preference, majority of patients indicated that the convenience of access to health facilities was ranked highest, followed by the presence of the health workers at the facility, the professional attitude of the health worker and the availability of medicines in the facility. Stratifying the study sites, respondants or patients from the private retail pharmacies had the highest satisfaction score of health care services from facilities. This is a significant finding which supports the international recognition of the contribution of private retail pharmacies in health care delivery (WHO 2014).

When practitioners' views and perceptions about the deployment and use of mRDTs in health facilities was explored, only 1% had ever used the malaria test kit. Majority of the private retail pharmacy practitioners (97%) were rather aware of mRDT use in other health facilities such as hospitals and clinics. However, the private retail pharmacy practitioners were willing to use mRDTs in their facilities inspite of their varied opinions and

perceptions which were likely to negatively influence the deployment of RDTs in private retail pharmacies. Therefore, sustainable approaches such as interactive training and routine support supervision visits would be required for the scale up of the mRDT implementation.

It was evidently clear from the study results that most practitioners were satisfied with the introduction of the mRDTs in their facilities. However, some practitioners were not very sure of regular supply of the tests kit. This could be a challenge to its implementation. It is therefore necessary a set of coordinated activities is put in place to ensure regular supply of the tests kit. By this suggestion, malaria rapid diagnostic testing will ultimately have an equitable public health impact (Brooks et al. 2009).

Other factors that were found militating against the deployment of malaria rapid diagnostic testing were affordability, specificity and sensitivity of the kits, and cultural, religious and traditional beliefs. Affordability in this study stood for cost and convenience. This was similarly observed in a study by Hansen et al., 2009. Affordability as a cost in private pharmacies is a major driving factor for patronage. The use of mRDTs was perceived to have the potential of increasing the cost of treatment and could therefore affect their profit margins as reported in a similar study (Labhardt et al. 2009).

Despite the practitioners' strong will to implement mRDTs in their facilities, some expressed their reservation on the sensitivity and specificity of the tests kit. However, several studies have sufficient proves on the effectiveness and potential of mRDTs, with respect to sensitivity and specificity. Where the tests clearly delineate non-malaria febrile illnesses and improve management of such cases (D'Acremont et al. 2009, Msellem et al. 2009, Moody 2002, Murray et al. 2003).

Some of the practitioners indicated that some patients had a strong cultural, religious and traditional beliefs against drawing blood for the malaria test which in their view could pose a challenge to the deployment of mRDTs in private retail pharmacies. This was because drawing of blood is associated with witchcraft in traditional African society, and the rumour could impede adherence (Mbonye et al. 2010). A similar study reported of a client perception that the blood test was for HIV/AIDS and not malaria in Uganda and Tanzania (McMorrow et al. 2008, Williams et al. 2008). It is therefore important that appropriate methods of education and counseling is employed to manage this perception.

5.2 Intervention Studies (Second phase)

The study showed that when the malaria test was conducted on febrile patients, the probability of patients with malaria having a positive test result (PPV) was 70.3% and the probability of patients without malaria having a negative malaria test results (NPV) was 29.7%. Interestingly, these findings are consistent with those obtained from similar studies in Uganda and Zimbabwe, although NPVs were generally higher than PPVs in those studies (Hopkins et al. 2008, Kyabayinze et al. 2008) and the variation here, depended on the malaria transmission rate (Hopkins et al. 2008). High NPVs are extremely useful for clinicians who can then find another cause for fever, thereby reducing misdiagnosis and mortality due to misdiagnosis (Opoka et al. 2008).

However, when the patients were diagnosed presumptively, 98.2% of the patients were presumed to have malaria and therefore treated with ACTs (Table 4.5). This contrary finding suggests that, when presumptive diagnosis is used, febrile patients are misdiagnosed and inappropriately treated and this has been reported in other studies in Africa (Lubell et al. 2008, Polage et al. 2006, Reyburn et al. 2007, Reyburn et al. 2004, WHO 2011). Restricting the use of antimalarials to patients with positive test results only

is important in slowing the development of antimalarial drug resistance. Accurate diagnosis of malaria through parasitological test is therefore of immense importance as malaria prevalence is declining in many endemic countries such as Ghana (Feachem et al. 2010, Moonen et al. 2010). However, in comparing the malaria test results of patients in the mRDTs arm of the study with microscopic examination of thin blood films from the same patients in a standard laboratory revealed a same positive predicted value and negative predicted value of 98.0% (Table 4.6). This high predictive value obtained indicates that many of the test results are accurate and hence, patients who tested positive will actually have malaria and those testing negative will not have malaria.

In addition, the PPV and NPV are not intrinsic to the test alone, but also a function of the disease prevalence as obtained in this study (43.3%). However, there are other parameters such as the False Discovery Rate (2.0%) and the False Omission Rate (2.0%) that were used in this study to complement the PPV and NPV respectively. The lower the False Discovery Rate (FDR) and False Omission Rate (FOR) values, the better the predictive values (PPV and NPV) obtained.

Furthermore, in establishing the effectiveness and accuracy of the malaria rapid diagnostic test kit used in this study, the Diagnostic Odds Ratio (DOR) was computed as 2,366.43 (Refer Table 4.7). This was comparable to DOR figures computed in similar studies (Glas et al. 2003). Unlike the PPV and NPV, the significance of DOR was to determine the test performance without recourse to disease prevalence. It ranges from zero to infinity. However, the higher the DOR value, the better the test performance. Therefore, the performance of the mRDT kit used in this study was encouraging and could be a factor for consideration in scaling up mRDT deployment in private retail pharmacies. However, the usefulness of a diagnostic test is determined by whether the test results can be and are used

in such a way that morbidity and mortality rates are directly or indirectly reduced by the application of the test results.

The sensitivity of the mRDT kit used in this study was 90.68 ± 1.18%. This sensitivity value obtained is consistent with the manufacturer's (91.3%) and WHO recommendations (95.0%) (WHO 2005b). The specificity of the mRDTs kit was found to be 98.68 ± 1.19%. This compares favourably with a similar study published in 2007 (Ratsimbasoa et al. 2007).

In spite of these, some studies have reported the inability of the mRDTs kit to sometimes detect high parasitaemia (Ratsimbasoa et al. 2007, Palmer et al. 2003). These anomalies may be linked to the presence of mutation or deletion within the HRP2 and pLDH genes (Mariette et al. 2008, Baker et al. 2005). Consequently, these anomalies may result in low specificity of the mRDTs kit. Another possibility for low specificity, though controversial, could be that mRDTs are more sensitive than microscopy. This probably could mean that false positives mRDT results obtained were actually true positives as has been reported in other studies (Ratsimbasoa et al. 2007).

5.3 Post Intervention Studies (Third phase)

The findings from the study showed that a little over 78% preferred malaria rapid diagnostic testing before treatment, indicating a high demand for the mRDT service, whilst a little over 28% preferred presumptive diagnosis. Here, their preference was largely due to financial considerations. This affirms what some private retail pharmacy practitioners thought at baseline when their willingness to accept mRDT deployment was explored.

Majority of the patients, who preferred testing before treatment agreed with the least payment scale of GHc 6.00 to GHc 10.00, as illustrated in Figure 4.2. This could mean that, if the treatment package is subsidized to a lesser amount, those who preferred

presumptive diagnosis to mRDTs, would agree to pay since financial constraints was a major reason for their decline. The demand curve obtained from this study had a negative slope which is consistent with the law of demand and supply. This strengthens the financial consideration and hence as the cost of treatment with the test kit increases, the percentage of patients willing to pay decreases, all things being equal.

This trend not withstanding, a number of factors may have influenced those who rejected the testing. This may include difficulty in placing value on an extra cost in addition to the cost of medication, thus perceiving it as unaffordable. This reinforces the importance of creating more awareness and education on malaria case management among communities. Finally, the benefit-cost ratio obtained was more than one. This imply that malaria testing at the private retail pharmacies was a worthwhile investment.

CHAPTER 6

6.1 Conclusion

Malaria diagnosis was predominantly presumptive at the health care institutions after WHO and NMCP recommendations. Patients have expressed good understanding of malaria treatment and satisfaction in the health care service delivery at the health facilities. The retail pharmacists have indicated their willingness, and acceptance in implementing the malaria rapid diagnostic testing at their practice sites.

The performance of mRDT in private retail pharmacies has shown much better accuracy than presumptive diagnosis. However, study indicated some level of non-adherence to test results.

Patients have shown willingness to pay a minimum cost for the tests kit. The cost-benefit analysis indicated that using malaria tests kit was worth the costs involved.

6.2. Recommendation

Successful implementation of mRDTs will require a systematic capacity building approach in addressing all the relevant challenges identified especially the increasing cost of the mRDTs kit and the emphasis on the ills of stigmatization of drawing blood for the test. It is recommended that health care practitioners are periodically trained and the provision of the RDT service be restricted to only practitionerswho have received training on mRDT use. Finally, the use of algorithms should be employed to mitigate the non adherence to test results.

It was observed in this study that efforts to improving the diagnostic coverage and accuracy will be undermined without concurrent interventions to change understanding, behaviour, and practice among the health care practitioners. Therefore, strategies are urgently needed

to improve health worker attitudes if a major health intervention like mRDTs are to be well-accepted by the communities that intended to benefit from it.

Successful implementation of mRDTs, therefore require a systematic capacity building approach in addressing all the relevant challenges identified. By these, local-level algorithms for actions would be useful. Although, will be an additional responsibility regarding educating patients/clients, it would guide on the consequences of presumptive treatment which has been the practice for many years in Ghana.

Emphasis should be made in addressing the ills of stigmatization of drawing blood to perform the tests and sensitize patients on potential increase in the cost of care due to the inclusion of mRDTs. The cost of diagnosis might increase coupled with the fact that private retail pharmacies have profit motives. Integrating the cost of the tests and kit into national health insurance scheme would be vital in making the policy attractive at the retail pharmacies in Ghana. There are proposals by WHO for the developers of mRDT kits to check the quality of mRDTs at point-of-care (Bell and Peeling 2006, Lon et al. 2005). Until then, care must be taken on the brands of mRDTs that are procured for use in Ghana. Thus, the need for improved malaria surveillance, and continued collaboration between programme managers (NMCP), regulatory authorities (Food and Drugs Authority, Pharmacy Council) and health care practitioners. This would be intended to ensure safety and quality whilst ensuring that the public has timely access to the diagnostic device. Achieving these goals will require major and long-term investments through well established and innovative funding programms, as well as increased and sustained domestic funding earmarked for malaria disease control.

It was observed that ACTs were prescribed as first-line to all suspected malaria patients after presumptive analysis and even with the mRDTs negative patients. Over the years,

significant resources have been committed to developing new, safer and more effective antimalarial agents. However, each scientific advance has been followed by the evolution of parasite and emergence of drug resistance. It is important to be prudent in our prescribing habit and stick to the positive tested patient to avoid promoting antimalarial drug resistance.

In this new health policy intervention, it is highly commendable in regularizing national surveys with distinct idea of measuring the policy progress at the informal sectors, such as the private retail pharmacies. This is because health systems vary widely depending on being formal or informal sector, and hence best-practices model needs to be designed and adopted for a particular sector and environment.

6.3. Implication for policy and practice

The thesis revealed that the cooperation between public and private health sectors is crucial for the deployment of any health care intervention. If the conduct of the malaria rapid diagnostic testing in the private retail pharmacies is to be restricted to only trained practitioners, then there must be some policy changes to guarantee the enforcement of same since there are currently no guidelines on who qualifies to work in a private retail pharmacy in Ghana. This is necessary to ensure public safety and prevent untrained practitioners from possibly perpertuating harm to the public.

6.4. Further research work

Considering the numerous brands of mRDT kits available on the Ghanaian market, it would be prudent to evaluate the individual performance of these brands in terms of their sensitivity and specificity to inform policy.

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APPENDICES

Appendix 2.1.a. Overview of malaria rapid diagnostic tests studies

Reference	Site	Study design	Results
Mbonye *et al*., 2015	20 clusters of drug shops in Mukono district, Uganda.	10 clusters as intervention (RDTs followed by ACTs) and 10 clusters as control arm (PD followed with ACTs).	Proportion of febrile patients who received appropriate ACT treatment was 72.9% vrs 33.7% in the control arm; a difference of 36.1% (95% CI: 21.3% - 50.9%), p< 0.001. Drug shops vendors adhered to the malaria RDT, reducing over-treatment of malaria by 72.6% (95% CI: 46.7 – 98.4), P<0.001) compared with drug shop vendors using PD (control arm).
Briggs *et al*., 2014	2 regions in Tanzania (Mtwara & Mwanza)	Cross-sectional survey i. Interview ii. Client exit interview	High proportion of ACTs going to persons without malaria demonstrates a need to better targeting who receives ACTs in the drug shops.
Zurovac *et al*., 2014	Health facilities, Kenya	i. Cross-sectional survey of health facilities (172-176). ii. Health workers interviews between	i. Comparing baseline and the last survey results, all readiness indicators showed significant (p<0.005) improvements. ii. Availability of parasitological diagnosis (55.2% to 90.7%). iii. Testing increased by 34.0% (23.9% to 57.9% at p<0.001). iv. Testing and treatment according to test result increased by

		216-237 iii. Output consultations for 1,208-2,408 febrile patients across 6 surveys	34.0% (15.7% to 49.9%; p<0.001). v. Treatment adherence for test positive patients improved from 83.3% to 90.3% (p=0.138) and for test negative patients from 47.9% to 83.4% (p<0.001).
Diggle *et al*., 2014	Greater Garissa, Kenya	i. FGD with community members from HFs ii. Indepth Interview (IDIs) and FGD with HCWs.	Poor adherence to negative RDTs results, unfamiliarity and distrust of RDT, and inconsistent RDT supply were the main challenges.
Ruizendaal *et al*., 2014		Systematic review using databases of Medline, Embase, the Cochrane library. 27 articles were included.	Community Health Workers, CHW, correctly performed RDTs, although the specificity levels varies. They showed high adherence to test results, however, a substantial group of negatives receive treatment. Uptake and acceptance by The community was high, but negative-tested patients did stay away from referral advice.
Mboye *et al*., 2013	Mukono district, Central Uganda.	Cluster randomized trial with structured Questionnaire.	Proportion of patients receiving appropriate ACTS treatment at drug shops was low, due to Presumptive Diagnosis (PD).

Rachida *et al*., 2013	Nlongkak Catholic Mission, Yaounde, Cameroon.	Evaluated RDTs available with Microscopy.	The validity, ease of use, and cost of HRP2-based tests were comparable. However, weaknesses identified was inadequate sensitivity for low parasitaemia.
Bruxvoort *et al*., 2013	Mwanza, Mbeya and Mtwara regions, Tanzania.	Randomly selected health facilities were interviewed. Using probability proportional to malaria output utilization.	Rollout of malaria RDT dramatically improved diagnostic testing for malaria and reduced overuse of ACTs for patients without parasitaemia. Stock-outs of ACTs and malaria RDTs were important problems.
Mubi *et al*., 2013	Public Health Centre Kibaha district, Tanzania.	i. Exit interviews with fever patients. ii. Interview with prescribers	Antimalarial drugs were prescribed to all patients with positive test results and 14.0% of negative patients.
Blanas *et al*., 2013	Saraya district, South-Eastern Senegal.	FGD with villages, and pre- and post-training questionnaire.	Community approved of community case management, but expressed concern about other general barriers to care, e.g., transportational challenges. Sizeable minority did not understand the RDT algorithm.
Ekong Udoh *et al*., 2013	Health facilities in Cross River State, Nigeria.	Patients' Case Records using pretested data extraction forms.	Appropriate dose of ACT was instituted in 300 (64.8%), wrong dose in 109 (23.5%), and inappropriate treatment in 41 (8.9%). The utilization of ACTs for treating uncomplicated malaria in

			State has improved, however the clinical assessment and laboratory confirmation of diagnosis were suboptimum.
Ikwuobe *et al*., 2013	2 pharmacies in Gwagwalada, Nigeria.	Interventional arm and control arm.	Having RDT test reduced the chance of purchasing antimalarial by 42% (95% CI: 38%-46%) compared to not having the test. 51.6% (276) in spite of being RDTs negative still purchased antimalarials, especially if antimalarials had been recommended by health worker (58.9%) compared to self-referral (44.2%) (p=0.001).
Mangham *et al*., 2012	Yaounde and Bamenda in Cameroon.	Cross-sectional cluster Survey.	Introduction of RDTs needs to be accompanied by updated clinical guidelines that provide clear guidance for the treatment of patients with negative results.
Aladenika *et al*., 2012	South-south, Nigeria	Evaluation of 5 commonly used malaria RDT kits, with microscopy.	Range of sensitivity 96.0% - 99.0% and specificity of 97.0% - 99.0%, for children. In adult, general reduction in sensitivity of the test kits: 30.0% - 78.0%. This inform the need to re-evaluate kits before introducing into Nigeria market.
Albertini *et al*., 2012	6 sites in Africa, South-east Asia, South America.	Questionnaires	Availability of RDTs were limited. And RDTs demonstrated inadequate sensitivity.

Toby *et al*., 2012	22 clinics in two Afghan provinces	Prospective observational study	i. Although 413 of 414 patients were negative by reference slide, 412 (99%) received malaria drug in Health centres with PD. ii. Clinics with microscopy, 37% (75/202) of negative patients by reference slide received malaria drug. iii. Specificities established of the microscopy were 72.9% and 79.9%.
Joao *et al*., 2012	District health centres,	Key informant interview, Focus group discussion, and survey at community/ hospitals.	Factors that impeded the implementation of the new malaria protocol included: i. Inadequate introduction and training around the revised protocol. ii. Unclear phase out and phase in of revised treatment protocol. iii. Lack of supervision. iv. Lack of adherence to the revised guidelines. v. Insufficient understanding of the rapid diagnostic test and untimely supply of diagnostic tests kit further hampered it.
Asiimwe *et al*., 2012	21 health centres in Uganda	Cross-sectional study	Malaria RDT found to be acceptable. Guidelines for management of febrile patients with negative test outcomes should be provided along the new health technology.

Masanga *et al*., 2012	Livingstone district, Zambia.	Retrospective study	Large decline in malaria cases and in ACTs consumption. Adherence and/or use of RDT was still not adequate.
Diarra *et al*., 2012	2 community clinics	Malaria diagnosis by Microscopy and RDTs.	Malaria RDTs showed similar ability (61.2%) to accurately diagnose malaria as microscopy (61.1%). Malaria RDT showed a high level sensitivity and specificity, compared with microscopy. With a sensitivity of 92.9% vrs. 74.9% and a specificity of 77.2% vrs 87.5%.
Baiden *et al*., 2012	Kintampo hospital in rural Ghana.	Evaluated RDTs kit using microscopy as reference.	RDT showed good sensitivity and specificity. However, minority of children who did not receive ACT based on RDT results developed clinical malaria within short period in high transmission settings. It could undermine confidence in the new guidelines. Improving the quality of management of non-malarial febrile illnesses should be a priority in the era of test-based management of malaria.
Ratsimbasoa *et al*., 2012	Region of high malaria transmission	In parallel, retrospective	Deploying of easy-to-use diagnostic tools, such as RDTs, at community level appears to be effective strategy for improving

(Manakara district)	parasitological and region of low malaria transmission (Moramanga district), Madagascar.	diagnosis by microscopy and PCR	febrile patient management. Additionally reduce over-usage of anti-malarial drugs.
Comoe *et al*., 2012	Health centres in Bozi and Yoho in rural Cote d'Ivoire.	Interview with pre-tested questionnaire On practice and Perception.	Only 34 out of 100 patients offered for RDTs. Others perceived blood as sacred body fluid and less likely to comply. Strong relation was established between acceptance and the idea that an RDTs was a pre-text to know HIV status (Odd Ratio =16.61, 95% CI =1.03-268.5).
Ishengoma *et al*., 2011	6 villages of Korogwe and Muheza districts, Tanzania.	Longitudinal and cross-sectional surveys, and performance of RDT was compared with microscope.	Overall sensitivity and specificity of RDTs in the longitudinal study were 88.6% and 88.2% respectively. In cross-sectional surveys, the sensitivity was significantly lower (63.4%; $x^2 = 3.67.7$, $p< 0.001$) while the specificity was significantly higher (94.3%; $x^2 = 143.1$, $P< 0.001$), when compared to the longitudinal study. The risk of false positive RDT was significantly higher in cases with fever compared to afebrile cases (OR $\geq$2.40, $p < 0.001$). Using RDTs reduced antimalarials dispensing from 98.9% to 32.1% in cases aged $\geq$ 5 years.

Wijesinghe *et al*., 2011	Rural and urban villages of Malaita Province, Solomon Islands.	12 FGDs and 12 Key Informant Interview (KII)	Lack of access to microscopy or distrust in the accuracy of diagnostic tools were reported, therefore more reasons for presumptive treatment of malaria. Lack of confidence in RDT accuracy has negatively impacted its acceptability.
Chandler *et al*., 2011	Mukono districts, Uganda.	Formative qualitative Study: In-depth interview with drug shop workers and districts assistant drugs inspectors. FGD with the community.	Drug shops were seen to provide an important health services. Diagnostic testing was deemed useful in theory, and community members were curious about the results. The appeal of the tests waned due to cost and results conflicts with presumed diagnosis.
Chandler *et al*., 2010	Dangme West District, Southern Ghana.	In-depth interview and purposive sample of health workers.	Different modes of participation led to change in practice for some health workers, and reinforced existing practice for others. Certain characteristics of RDTs were realised to be inherently conducive to change. However, limited support, lack of system antecedents for change and limited system readiness for change were apparent in the analysis.

Ansah *et al*., 2010	Rural Dangme West District, Southern Ghana.	RCT, Open label clinical trial	Where microscopy already exists, deploying RDTs had limited impact on prescriber behaviour. However, where there was no microscopes, using RDTs led to a significant reduction in the overprescription of antimalarials, without any evidence of clinical harm, and to better targeting of antibiotics.
Ukwaja *et al*., 2010	Urban health centre in Ogun, Nigeria.	50 children with malaria-pneumonia symptoms treated presumptively (control arm) and other 50 using RDTs (intervention arm).	Malaria RDT-based treated children had lower risk of receiving antimalarial compared to those treated presumptively (48.0% vrs 100.0%), (p= <0.001; relative risk 2.08, CI 1.56 to 2.78).
Mawuli-Mboumba *et al*, 2010.	Oyem and Owendo Gabon.	Evaluation study	Both RDTs had similar sensitivity (94.0%; 95% CI, 92-96). Likewise the Negative Predictive Values were high and Comparable (>98%). Overtreatment with antimalarial drugs was 12%. These tests should be considered as a good alternative to Microscopy.

Mukanga *et al*., 2010.	Iganga district, Uganda.	Focus Group Discussion with Community Medicine Distributors, CDM, Key Informant Interview, KII, with health workers and community leaders.	CDMs were trusted because of access, and their perceived effectivenss of antimalarial drugs. Some community expressed fear that the blood collected could be used for HIV testing, the procedure could infect children with HIV, and blood used for witchcraft. Caregivers insisting on treatment despite the results and de-tested referral.
Skarbinski *et al*., 2009	Governments health facilities in 3 districts in Kenya.	Pre-post cluster randomized controlled trial.	88.0% of RDTs positive and 9.0% of RDTs negative patients were treated with AL, respectfully. Overtreatment was low in both arms and was not significantly reduced by the provision of RDTs (-12.0% -points, p = 0.30).
Dodoo *et al*., 2009	Pharmacies of health facilities, Accra, Ghana.	Cohort-event monitoring study.	This study shows that though first-line therapy recommendation may change, clinical practice may still be affected by factors other than the decision or ability to diagnose. This has implications for adherence to policy changes, and suggest a potential positive impact of increased access to testing for malaria.

Williams *et al*., 2008	6 Tanzanian public dispensaries.	Baseline data collated using standardized exit interview.	Of the 595 patients aat baseline, 200 (33%) diagnosed clinically with malaria but had negative RDTs. Among the 2519 RDTs performed during implementation, 289 (11.5%) had negative results and antimalarial prescribed. The proportion of 'over-prescriptions' at baseline was 54.8% (198/365). At weeks 4 and 8, decreased to 16.1% (27/168) and 16.4% (42/256) respectively.
Reyburn *et al*., 2007	OPDs in northeast Tanzania.	Randomized to RDTs and microscopy.	1030 (86.0%) tested negative for malaria; 523 (51.0%) of these were treated with an antimalarial drug. Of 1193 patients randomized to RDTs, 1005 (84.0%) tested negative; 540 (54.0%) of these were treated for malaria (odds ratio, 1.13, 95% CI 0.95 to 1.34; p= 0.18.
Rowe *et al*., 2006	6 sub-populations	Systematic review	Estimates based on the available data and methods, clearly demonstrated malaria's enormous mortality burden.

Appendix 2.1. b. Adherence to test results by Community Health Workers (CHWs)

Study	Target Population	Treatment	Adherence Overall*	Positives treated	Negatives treated
Ndiaye *et al*., 2013***	Patients of all ages, care Seeking	NS	85.6%	90.1%	24.8%
Ndiaye *et al*., 2013***	Patients of all ages, care Seeking	NS	93.9%	95.3%	24.8%
Hamer *et al*., 2012	Children 6 months -5 years, fever	AL	99.3%	98.5%	0.4%
Mukanga *et al*., 2012****	BF: 6-59 months, (history of) fever	AL	99.0%	100.0%	4.8%
Mukanga *et al*., 2012****	Gh: 6-59 months, (history of) fever	AA	99.5%	100.0%	3.3%
Mukanga et al., 2012****	Ug: 4-59 months (history of) fever	AL	99.0%	99.9%	7.6%
Chanda *et al*., 2011	All ages, care seeking	AL, SP <5 Kg	99.9%	99.3%	0.2%
Chanda *et al*., 2011	All ages, care seeking	AL, SP <5 Kg	99.9%	99.3%	0.2%
Ishengoma *et al*., 2011	≥5 years with (history of) fever	AL	95.8%	98.9%	5.4%
Mubi *et al*., 2011	> 3 months (history of) fever. Exclusion: severe malaria	AL	96.8%	99.7%	6.1%
Mukanga *et al*., 2011	Children <5 (history of) fever no danger signs.	AL	97.8%	98.6%	4.8%
Chinkhumba *et al*., 2010	>5 years, (history of) fever	NS	86.9%	98.0%	58.0%
Yeboah-Antwi *et al*., 2010	Children 6 months-5 years fever	AL	99.3%	98.5%	0.4%

= adherence percentages calculated from study data, *= CHWs attended review meetings with study team each month discussing non-adherence to diagnostic and treatment algorithm with CHWs, HF= health facility, NS= not specified, AL= artemether-lumefantrine, SP= sulphadoxine-pyrimethamine.

Appendix 2.1.c. Morbidity and mortality outcomes of RDT based Community Case Management of malaria, CCMm, strategies

Study	Design	Intervention	Control	Outcome
Thiam *et al*., 2012	NRCT	RDT-based CCMm	No CCMm	Malaria related hospitalization reduced by 43.1% in intervention arms and 40.99% in control arms. malaria related deaths reduced by 62.5% in intervention arms (significant reduction) and 23.4% in control arms (no significant reduction).
Ruta *et al*., 2012	Pre-post Study	RDT-based CCMm (with AL)	Comparison with pre-intervention period (Presumptive CCMm with SP)	A drop of >72.0% in malaria slide positivity rate to a persistent low level of <10% was found in the period of study.
Mubi *et al*., 2011	RCT	RDT-based CCMm	Presumptive CCMm	Increased perception of recovery in control group versus intervention group (93.3%) at day 7.P=0.000
Elmardi *et al*., 2009	Pre-post study	RDT-based CCMm (with AS/SP)	Comparison with pre-intervention period (no CCMm, health centres treated with AS/SP)	24% fever episodes in last two weeks pre-intervention and 8.5% fever episodes post intervention (p=0.000).

RCT= randomized control trial, AS= artesunate, SP= Sulphadoxine-Pyrimethamine, NRCT= non-randomized control trial, AL= artemether-lumefantrine, CCMm= community case management of malaria,

Appendix 2.1.d. Interpretation and execution of RDTs by CHWs

Study	CHW training	Outcome interpretation	Outcome execution
Counihan *et al*., 2012 and	Half-day training. At 3 months CHWs received a poster-seized job aid and a photographic guide on RDT interpretation.	(i) RDT test results correctly read by 95.1, 98.3 and 98.3% of the CHWs at 3, 6 and 12 months after training respectively. (ii) Correct interpretation of positive RDT results was found to be 96.5% at 3 months, 98.3% at 6 months and 90.5% at 12 months. (ii) Correct interpretation of negative RDT results was found as 94.3% at 3 months, 97.9% and 94.7%, for 6 and 12 months respectively. (ii) Faint positive lines were correctly read by 89.7% within 3 months, at 6 months 96.7% and dropped to 76.7% at 12 months.	19-item checklist, interpretation, and 8 items were considered critical. Median correctly performed critical steps were 87.5%, 100% and 100% at 3, 6, 12 months respectively. 40.3, 61.7 and 79.7% of CHWs correctly performed critical RDT steps at 3, 6 and 12 months respectively.

Mukanga *et al*., 2011	An 8-day training by experienced trainers. Job aid provided.	100% of RDTs were correctly interpreted shortly after less than 2 weeks training.	96.3% of RDTs were correctly Performed shortly after less than 2 weeks in a 14-item checklist, interpretation excluded.
Mubi *et al*., 2011	1 week training	99.7% of positive tests were correctly interpreted in the 5 months of study.	
Hawkes *et al*., 2009	1-day training, and pictorial job aid provided.	100% of CHWs correctly interpreted the RDT directly after training.	Median score on a WHO 16-item assessment of RDT performed was 100% (range of 94-100%) directly after training.
Harvey *et al*., 2008	Group 1: use manufacturers' Instructions. Group 2: only use of job aid. Group 3: 3-hour training on RDTs+ job aid.	(i) 72, 86, and 96% of CHWs correctly interpreted RDT results for group 1, 2 and 3 respectively. (ii) 54, 82 and 93% of tests were correctly interpreted for group 1, 2 and 3 respectively.	57%, 80% and 90% of steps were correctly performed by group 1, 2 and 3 respectively, at the same day of instructions, job aid or training in a 16-item checklist.

(i) Based on assessment of RDTs
(ii) Based on photographic assessment.

Appendix 3.1: Questionnaire Covering Letter

The Superintendent Officer,

Health Care Facility……

Date…….

Dear Sir/Madam,

LETTER OF REQUEST

I humbly request the use of your facility to undertake a study. The aim is to collate information on diagnostic procedures from patients treated for uncomplicated malaria, while exiting the premise after consultations. The choice of your facility is informed by your tremendous support and service to the community. Confidentiality of any information is assured.

I thank you, and questionnaires will be collected at the end of the study period (1st April to 30th June, 2013), either completed or not.

Yours faithfully,

Sign……

Pharm. Audu Rauf

(Principal Researcher).

Appendix 3.2: Patient Exit Questionnaire, PEQ.

Please, kindly spare a moment of your time to assist in completing this questionnaire. It is a survey to gather information on the management of malaria from out-patient perspective. Your response will help address issues you may have. The confidentiality of your information is guaranteed.

Patient's telephone number: …….. Date: …….....

Patient's Demographics

1. a. Age: …… b. Sex: (Male) (Female)
2. What is the educational level of the patient?
   i. No formal education
   ii. Primary education
   iii. Secondary education
   iv. Tertiary

Motivational Factors

1. Was this your first time of visiting the health care facility?
   i. Yes
   ii. No
2. What motivated you to sought medical attention at this facility?
   i. Quality of services
   ii. Presence of health care providers
   iii. Recognized quality drugs
   iv. Convenience

Signs and Symptoms

1. What was/were the signs/symptoms presented to the health care provider? [Can choose more than one].
    a. Febrile
    b. Headache
    c. Joint pains
    d. Chills
    e. Cough
    f. Vomiting
    g. Others……

Diagnostic Procedure

1. What mode of diagnosis was used on the patient?
    a. Presumptive Diagnosis, PD
    b. Parasitological-based confirmation
2. If the above was (b), which type was used?
    a. Microscopy
    b. Rapid Diagnostic Tests, RDT
3. If question (2) was (b), were you surcharged for the RDTs services?
    a. Yes
    b. No
4. If question (3) was (a), how much were you charged?
    a. Under 1 cedi
    b. Between 1 – 2 cedis
    c. Between 2 – 3 cedis
    d. Above 3 cedis

Prescription of antimalarial drugs

1. Was the microscopy or RDTs done prior prescription?
    a. Yes
    b. No
2. What antimalarial drugs were prescribed?
    a. Artemisinin-based Combination Therapy, ACT
    b. Artemisininmonotherapy
    c. Amodiaquine
    d. Quinine
    e. Sulphadoxine-Pyrimethamine, SP
    f. Others……
3. If question (2) was (a), which of the following were prescribed?
    a. Artesunate/Amodiaquine, AA
    b. Artemether/Lumefantrine, AL
    c. Dihydroartemisinin/Piperaquine, DHAP
    d. Artesunate/Sulphadoxine-Pyrimethamine, AS/SP

Understanding of treatment

1. Does the patient asked for a particular brand of antimalarial drug?
    a. Yes
    b. No
2. If question (1) was (a), which brand was asked……
3. Which of the following best described the reason(s) for the brand requested?
    a. Recognized brand name
    b. Convenience to adhere todosage regime
    c. High quality drug

d. Influence of media promotion

e. Affordable and available

4. How does patient rated understanding of treatment?

a. Very Poor Value, VPV

b. Somewhat Poor Value, SPV

c. Average Value, AV

d. Fairly Good Value, FGV

e. Very Good Value, VGV

Satisfaction of health care delivery

1. How satisfied was the patient with the health care services delivered?

a. 5…… Very Satisfied, VS

b. 4……. Somewhat Satisfied, SS

c. 3……. Neither Satisfied nor Dissatisfied, NSND

d. 2……Very Dissatisfied

Thank you for the support, and may probably contact you to solicit further information.

Please for any information regarding this discussion, contact this number: 0209403927.

Appendix 3.3: Covering letter for Pharmacist Assessment Questionnaire, PAQ.

The Superintendent Officer

Health care facility

Date……

Dear Sir/Madam

LETTER OF REQUEST

I would like to humbly request for your service. I am embarking on a project on deploying malaria rapid diagnostic tests, mRDTs, at retail pharmacies. It is intended to be used as diagnostic tool and hope you will be of assistance as respondent. Your choice as facilitator was based on the immense contribution of pharmaceutical care to the community.

Confidentiality of any information is highly guaranteed. The study period extends from 1st September, 2013 to 30th November, 2013, and all questionnaires collected after the expiration of study period.

Counting on your support.

Yours faithfully,

……

Pharm. Audu Rauf (Principal Researcher).

Appendix 3.4: Pharmacist Assessment Questionnaire, PAQ

Please, kindly spare some moment of your time to assist in filling this questionnaire. It is a survey to solicit the views of retail pharmacy practitioners on the acceptability and the willingness to implement malaria rapid diagnostic testing. Your response could be of help in addressing certain issues you may have. The confidentiality of any information provided is guaranteed.

Characteristics of Retail Pharmacy Practitioner

1. Practitioner's telephone number…… Date ……
    a. Male
    b. Female
    c. Name o facility …….
2. What is your age?
    a. Less than 20 years
    b. Between 20 – 30 years
    c. Between 30 – 40 years
    d. Above 40 years
3. What is your professional status?
    a. Pharmacist
    b. Intern Pharmacist
    c. Dispensing Technician
    d. Medicine Counter Assistant
    e. Others ……..
4. What is your educational level?
    a. Post-graduate degree
    b. Graduate degree

c. Higher National Diploma

d. Certificate in Medicine Counter Assistance

e. Others ……

5. How long have you been practicing your profession?

a. Less than 3 years

b. Between 3 – 5 years

c. Above 5 years

6. What is your employment status?

a. Full-time

b. Part-time

c. Internship

d. Others ……..

e. Prefer not to answer

Retail Pharmacy Practitioner's knowledge and experience

1. How many malaria patients do you attend to per week?

a. Less than 5 patients

b. Between 5 – 10 patients

c. Between 10 – 15 patients

d. Above 15 patients

2. Have you heard of the new technology of rapidly diagnostic testing of malaria?

a. Yes

b. No

c. Not very sure

3. If question (2) was (a), through what means?
    a. Conference/seminar/workshop
    b. Media reportage
    c. Medical and scientific journals
    d. Professional colleague
    e. Patient
4. Are you well informed on the use of malaria rapid diagnostic tests, mRDTs?
    a. Very well informed
    b. Somehow well informed
    c. Neither well informed nor uninformed
    d. Somehow uninformed
    e. Very much uninformed

Retail Pharmacy Practitioner's acceptance and willingness

1. How interested are you in the new technology of mRDTs?
    a. Very interested
    b. Interested
    c. Neutral
    d. Uninterested
    e. Very uninterested
2. As a retail pharmacy practitioner, would you agree to implement mRDTs in your premise?
    a. Strongly agree
    b. Agree
    c. Neutral
    d. Disagree

e. Strongly Disagree

3. In general, how would you rate the introduction of mRDTs as diagnostic method?
   a. Excellent
   b. Very Good
   c. Good
   d. Fair
   e. Poor
   f. Don't know

4. Have you ever used the mRDTs to determine the presence or otherwise of the parasite?
   a. Always
   b. Never
   c. Sometimes
   d. Usually
5. Would you suggest the policy to a professional colleague?
   a. Definitely
   b. Probably
   c. Not sure
   d. Probably not
   e. Definitely not
6. Why do you feel that way about the suggestion? [Don't tick more than 2]
   a. Because of perceived barriers
   b. Not very enthused about the deployment procedure
   c. Enhance treatment by targeting the malaria parasite
   d. Very good policy aimed at accurate diagnosis

e. Perceived threat of missing malaria cases

7. Do you foresee the success and sustenance of mRDTs in the retail pharmacy practice?
   a. Definitely
   b. Probably
   c. Not sure
   d. Probably not
   e. Definitely not

Retail Pharmacy Practitioner's challenges and recommendations

1. What would be the most important challenging factor in implementing mRDTs in your premise? (Please, check any 1)
   a. Cultural, religious and traditional beliefs in using blood during the process
   b. Not very sure of the sensitivity and specificity of the test
   c. Affordability (cost component)
   d. Convenience at the premise
   e. Not sure of regular supply and storage of mRDT kit
   f. Always training of new staff
2. How satisfied are you with the Presumptive Diagnosis for which mRDTs is replacing?
   a. 5 ……. Very Satisfied
   b. 4 ……. Somewhat Satisfied
   c. 3 …….. Neither Satisfied nor Dissatisfied
   d. 2 …….. Somewhat Dissatisfied
   e. 1 …….. Very Dissatisfied

3. Are you sure malaria patients would accept the mRDTs?
    a. 5 …… Very Sure
    b. 4 …… Somehow sure
    c. 3 …… Neither Sure nor Unsure
    d. 2 …….. Somehow unsure
    e. 1 …….. Not Very Sure
4. What additional comment(s) would you like to provide in relation to the mRDTs?

    ……..

    ……..

    ……..

    ……

Thank you for the contribution. May solicit for more information as and when necessary.

Please for any inquiry, contact: 0208403927

Appendix 3.5: Covering letter for diagnostic studies

The Pharmacist

Facility ……

Date ……

Dear Sir/Madam

LETTER FOR PERMISSION

I would honourably like to request for permit to undergo a study at your premise. The study entails your participation as well. The objective is to evaluate malaria diagnostic practices, with the intent of implementing malaria rapid diagnostic testing at pharmacies. Your participation is a measure of the valuable pharmaceutical care services you are rendering to communities, and hope this request receive appropriate attention.

It is hoped to span between 1st April to 30th September, 2014. The confidentiality of information is assured, and unused kits and antimalarial drugs after the exercise would be left for the usage of the pharmacy.

Thank you.

Yours faithfully,

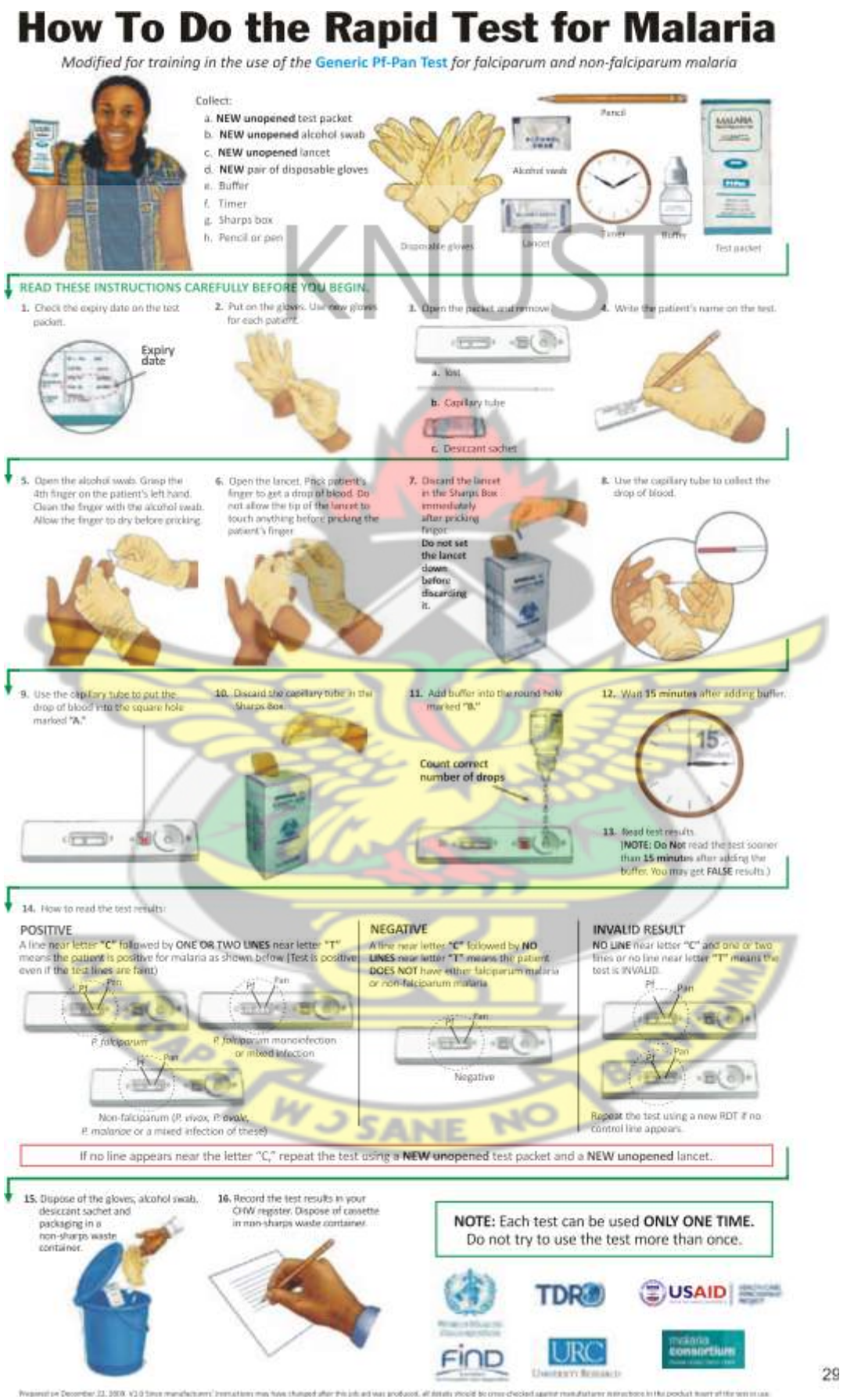
……

Pharm. Audu Rauf (Principal Researcher)

Appendix 3.6: Case Reporting Form, CRF.

Serial code numbers	mRDT results at pharmacy	mRDTs results confirmation by microscopy	Serial code numbers	PD treated patients	Microscopy Confirmation results

Appendix 3.7: Manual for rapid test for malaria



Appendix 3.8: Covering letter for Cost-Benefits studies

The Superintendent Pharmacist

Facility…….

Date ……

Dear Sir/Madam

LETTER FOR PERMISSION

I would like to request for a permission to solicit for information from suspected malaria patients in your pharmacy. This is a follow-up of an earlier one, on malaria diagnostic practices. It is intended to assess the willingness-to-pay for malaria diagnostic test kits, if deployed in retail pharmacy.

Your assistance would be appreciated, and confidentiality of information is guaranteed.

Thank you

Yours faithfully

…….

Pharm. Audu Rauf (Principal Researcher)

Appendix 3.9: Cost Benefit Questionnaire, CBQ

Please, kindly spare a moment of your time to help in this study. It is intended to gather information on the willingness-to-pay for malaria rapid diagnostic test at retail pharmacy. Your response will help address the issue. Confidentiality of your information is assured.

Patient's telephone number…… Date……..

1. a. Age:…… b. Sex: (Male) (Female)
2. What is your educational level
   a. No formal education
   b. Primary education
   c. Secondary education
   d. Tertiary
3. Do you currently pay for your malaria treatment?
   a. Yes
   b. No
   c. Insurance scheme
4. What price do you currently pay, if question 3 is (a).
   a. GHc 3.00
   b. GHc 4.00
   c. GHc 5.00
   d. GHc 8.00
   e. GHc 10.00
   f. Above GHc 10.00
5. Would you pay an increase if a malaria testing kit is introduced before medication?
   a. Yes
   b. No

6. If question 5 is (a) Yes, proceed to the next question
7. What is the highest price you are willing to pay?
    a. GHc 6 – 10
    b. GHc 11 – 15
    c. GHc 16 – 20
    d. GHc 21 – 25
    e. GHc 26 - 30

Appendix 3.10: Computations on evaluating the performance of mRDTs

The disease prevalence was calculated as: T_{dx} / T_{sp} X 100.

Where T_{dx} = number of individuals with disease; T_{sp} = Total study population

T_{dx} = TP + FN = 260

T_{sp} = 600

Therefore, 260/600 X 100 = 43.3%

The sensitivity, specificity, predictive values and diagnostic odds ratio are the basis to assess the accuracy of mRDTs, with results confirmed by microscopic examination.

Sensitivity, Se, is the probability that a test will indicate 'disease' among those with the disease. Therefore,

Se = TP/ (TP + FN) X 100

= 253/ (253 + 7) X 100

Se [95% CI, 0.95 – 0.99] = 97.3%

Specificity, Sp, is the fraction of those without disease who will have a negative test results. Therefore,

Sp = TN/ (TN + FP) X 100

= 335/ (335 + 5) X 100

Sp [95% CI, 0.95 – 0.99] = 98.5%

Positive Predictive Value, PPV, = TP/ (TP + FP)

= TP/ number of positive cells

Where TP [true positives] is the event that the test makes a positive prediction and the subject has a positive result under the gold standard, and FP [false positive] is the event that the test makes a positive prediction, and the subject has a negative result under the gold standard.

PPV = 253/ (253 + 5) = 0.98

Therefore, at 95% CI, PPV = 0.98 X 100 = 98.0%

False Discovery Rate, FDR. It is the complement of the PPV:

FDR = 1 – PPV

= 1 – 0.98 = 0.02

Or

FDR = FP/ (TP + FP)

= FP/ number of positive calls

= 5/258 = 0.019 = 0.02

Therefore, at 95% CI, FDR = 2.0%

Negative Predictive Value, NPV = TN/ (TN + FN)

= TN/ number of negative call

Where a TN [true negative] is the event that the test makes a negative prediction, and the subject has a negative result under the gold standard, and a FN [false negative] is the event that the test makes a negative prediction, and the subject has a positive result under the gold standard.

NPV = 335/ (335 + 7)

= 0.98

Therefore, at 95% CI, NPV = 0.98 X 100 = 98.0%

False Omission Rate, FOR: Is the complement of the NPV:

Therefore, FOR = 1 – NPV

= 1 – 0.98 = 0.02

Or,

FOR = FN/ (TN + FN)

= 7/ (340 + 7) = 0.02

Therefore, at 95% CI: FOR = 0.02 X 100 = 2.0%

In a medical testing using binary classification, the Dianostic Odds Ratio, DOR, is defined as a measure of the effectiveness of a diagnostic test. It is the ratio of the odds of the test being positive if the subject has a disease relative to the odds of the test being positive if the subject does not have the disease.

DOR = Se X Sp/ [(1 – Se) X (1 – Sp)]

= 0.973 X 0.985/ [(1 – 985)]

= 0.958405/0.000405

= 2,366.43.

The DOR ranges from zero to infinity, although for useful tests it is greater than 1, and higher DOR are indicative of better test performance.

Appendix 3.11: Ethical approval from Pharmacy Council

PHARMACY COUNCIL
GHANA
P. O. Box 10344, Accra-North. Tel: (0302) 680150, 681929 Fax: (233) 681931 Website: www.pcghana.org E-mail: info@pcghana.org

PC – 147

10TH June, 2013

THE HEAD OF DEPARTMENT
CLINICAL & SOCIAL PHARMACY
FACULTY OF PHARMACY & PHARMACEUTICAL SCIENCES.
KNUST

Dear Madam,

RE-AUTHORIZATION FOR STAFF OF COMMUNITY PHARMACIES TO PERFORM MALARIA RAPID DIAGNOSTIC TEST AS PART OF A PHD STUDY BY AUDU RAUF

The Pharmacy Council acknowledges your letter dated 4th June, 2013 on the above subject matter.

Your request has been granted for staff of community pharmacies in the Ashanti Region to be involved in the above study to assess the impact of introducing rapid diagnostic testing on malaria case detection at retail pharmacies.

Please kindly furnish the Pharmacy Council on the personnel to be enlisted for the study after your service provider training for accreditation.

Thank you.

Yours faithfully

PHARMACY COUNCIL
P. O. BOX AN 10344
ACCRA-NORTH

KENNETH SIMONS
REGIONAL MANAGER

Greater Accra Reg. Office	P.o. Box AN 10344, Accra-North, Ghana	Tel: (233) (0302) 681929, 680150	Fax: (233) (0302) 681931
Eastern Regional Office	P.o. Box KF 2228, Koforidua,	Tel: (03420) 23205	Fax: (233) (03420) 24699
Volta Regional Office	P.o. Box HP 1266, HO,	Tel: (03620) 26324	Fax: (233) (03620) 26324
Central Regional Office	P.o Box CC 1339, Cape Coast.	Tel: (03321) 33233	Fax: (233) (03320) 33233
Western Regional Office	P.o. Box 1216, Takoradi.	Tel: (03120) 46391	Fax: (233) (03120) 46391
Ashanti Regional Office	P.o. Box KS 778, Kumasi.	Tel: (03220) 31636, 41455	Fax: (233) (03320) 31636
Brong Ahafo Reg. Office	P.o. Box 744, Sunyani.	Tel: (03520) 26551, 26490	Fax: (233) (03520) 26551
Northern Reg. Office	P.o. Box TL 1777, Tamale	Tel: (03720) 23061	Fax: (233) (03720) 23061
Upper East Reg. Office	P. o. Box BG 869, Bolgatanga	Tel: (03820) 29208	Fax: (233) (03820) 29208
Upper West Reg. Office	P. o. Box 179, Wa	Tel: (03920) 22842	Fax: (233) (03920) 22842