Cost and cost-effectiveness analysis of the available strategies for diagnosing malaria in outpatient clinics in Zambia

by

Pascalina Chanda

May 2006

Dissertation Submitted to the Health Economics Unit, School of Public Health and Family Medicine at the University of Cape Town in partial fulfilment of the requirements for the Masters of Public Health (in Health Economics).

DECLARATION

I declare that this work is my own. It has not been previously submitted in whole, or in part, for the award of any degree. Each significant contribution and quotation in this dissertation from the works of other people has been acknowledged and referenced.

Signature: Signed by candidate Date: 15th November 2006

PASCALINA CHANDA

This paper has been submitted for examination with my approval as the University Supervisor

Signature: Signed by candidate Date: 27-Nov-2006

Ms MARIANELA CASTILLO

ACKNOWLEDGEMENTS

The process towards the beginning and finishing of this work has benefited greatly from the patience and help of many individuals.

I would like to extend my utmost gratitude to my supervisor whose tireless efforts and suggestions have been crucial from the inception to the completion of this work. Thank you Marianela.

A big thank you to Dr F. Masiye and Mr B. Chitah for their technical support and encouragement in pursuing the masters programme.

I am indebted to the support of my colleagues at work (Dr N. Sipilanyambe, Ms P. Wamulume, Dr M. Kango, Mr E. Chanda, Ms M. Mwanza) and fellow students in Master of Public Health (Health Economics) programme. To Moonga Hawela and Patrick Banda who were instrumental in the data collection process, thank you.

My appreciation goes to the Swedish International Development Aid (SIDA) for the financial support for the entire programme.

I also extend special thanks to Mutale and Mambwe for being a source of inspiration. Finally, am grateful to my family and friends for their invaluable support.

Pascalina Chanda

TABLE OF CONTENTS

LIST OF ACRONYMS

ACER	Average Cost Effectiveness Ratio
ACTs	Artemisinin-Based Combination Therapies
AL	Artemether-lumefantrine
BHCP	Basic Health Care Package
CBA	Cost Benefit Analysis
CBOH	Central Board of Health
CDD	Cases Correctly Diagnosed
CDEs	Commissioned Daily Employees
CEA	Cost Effectiveness Analysis
CHWs	Community Health Workers
CMA	Cost Minimisation Analysis
CQ	Chloroquine
CUA	Cost Utility Analysis
DALY	Disability Adjusted Life Year
DDT	Dichloro-diphenyl-trichloroethane
DHMBs	District Health Management Boards
DHO	District Health Office
EHT	Environmental Health Technicians
FSP	Finacial Sustainability Plan
HMIS	Health Management Information System
HRP-2	Histidine-Rich Protein-2
ICER	Incremental Cost effectiveness Ratio
IMCI	Integrated Management of Childhood Illnesses
IRS	Indoor Residual Spraying
ITN	Insecticide Treated Net
MOH	Ministry of Health
NHSP	National Health Strategic Plan
NMCC	National Malaria Control Centre
pLDH	Parasite-specific Lactate Dehydrogenase

RBM	Roll Back Malaria
RDTs	Rapid Diagnostic Tests
SP	Sulphadoxine-pyrimethamine
SSA	Sub Sahara Africa
USD	United States Dollars
WHO	World Health Organisation
ZDHS	Zambia Demographic Health Survey
ZMK	Zambian Kwacha

LIST OF TABLES

LIST OF FIGURES

DEFINITIONS

Presumptive treatment
Prescribing treatment based on clinical assessment in the absence of confirmatory tests.

Pallor
Refers to paleness of skin caused by illnesses such as anaemia .

Sensitivity
Ability of a test to detect cases with the disease or outcome of interest

Specificity
The ability of a test to detect cases without the disease or outcome of interest.

Pre-test probability
The probability that a given case has the disease of interest before a diagnostic test is performed.

Post-test probability
The probability that a given patient has the disease of interest after a diagnostic test is performed.

Likelihood ratio
The probability that a given test result would be expected in a patient with the targeted outcome compared with the probability that the same result would be expected in patient without the targeted outcome.

Accuracy
Ability of a test to correctly identify positive and negative cases in any given sample or population (Sum of true positives and true negative divided by total cases tested).

Gini Coefficient
Standard measure of the relative inequality in a population on a scale of 0 to 1. Where 1 indicates perfect equality and 0 represents perfect inequality.

Fever
Temperature greater or equal to 37.5°C.

Asymptomatic
Refers to the presence of detectable infection but absence of manifested clinical disease (carrier).

ABSTRACT

Introduction

Malaria is a major public health problem in Zambia accounting for more than 3 million clinical cases and about 33,000 deaths annually. Artemether-lumefantrine, (a relatively expensive drug) is being used for first line treatment of uncomplicated malaria. However, diagnostic capacity in Zambia is low, which has both economical, and health implications for the health system. The current alternatives for diagnosis of malaria are clinical, microscopy and rapid diagnostic tests (RDTs). This study consists of an economic evaluation of the alternative malaria diagnosis methods in outpatient facilities in Zambia. The study is expected to contribute to effective decision-making in Zambia, especially when considering scaling up malaria diagnosis in health facilities.

Methods

A cost and cost effectiveness evaluation of clinical, microscopy and rapid diagnostic test (RDT) diagnosis of malaria was conducted in 12 facilities in 4 districts in Zambia from the providers' perspective. Effectiveness was measured as cases correctly diagnosed by each strategy. Retrospective data (epidemiological and on costs) was collected from facility registers from March to November 2005. Principles of cost effectiveness analysis were applied to determine average and incremental cost effectiveness ratios of the alternatives, which were evaluated under routine conditions in health facilities. Based on the results, annual cost and effect extrapolations were made to estimate the potential impact of implementing the most cost effective method at district level.

Results

RDTs were found to be more cost effective (USD 6.5) than either microscopy (USD 11.9) or clinical diagnosis (USD 17.1) for malaria. The incremental cost per case correctly diagnosed and treated was found to be USD 2.6 for RDT and USD 9.6 for microscopy with clinical diagnosis as baseline. The findings were robust to changes in

assumptions and various parameters. The annual incremental cost of implementing RDTs at district level was estimated at USD 356,821. Cost savings on treatment were not significant in facilities with confirmatory strategies mainly due to prescription practices that include treating with antimalarials cases found negative. However, if the diagnostic strategy were to influence treatment decisions, savings on drugs of at least 56% could be achieved in the RDT and microscopy strategies.

CHAPTER ONE

1.0 INTRODUCTION

1.1 Background

The global burden of malaria today is estimated in terms of the epidemiological indicators and economic consequences. Malaria is a major public health problem in the world where at least 3.2 billion people are at risk of the disease annually (WHO 2000a). In its 2005 report, World Health Organisation (WHO) estimates that 60% of the cases and 80% of malaria related mortality occurs in Sub Sahara Africa (SSA) (WHO 2005). This shows that most malaria morbidity and mortality is being experienced utmost in an area geographically defined as the hub of poverty. Further, the true burden of the disease in SSA is expected to be sub-estimated as a result of under-reporting. For example it has been shown that as much as 70% of malaria cases in the region occur in the community (Amexo et al 2004), thus such cases are not incorporated into facility figures and therefore not officially reported on.

The consequence of such a huge burden of the disease has translated into economic losses by both individuals and health systems. When disability-adjusted life years (DALYs) are used to measure the burden of disease, WHO estimates that up to 45 million DALYs are lost due to malaria in Africa (WHO 2000a). In Africa alone, malaria would account for 12 billion US Dollars loss due to health care related costs and a reduction in the production potential due to an episode of malaria (WHO 2005). It has also been reported that malaria slows economic growth. Malaria endemic countries show a reduction from 0.25% to 1.3% in Gross National Product (GNP) per capita when compared to non-malaria endemic countries (Sachs 2001, Greenwood et al 2005).

Zambia has not been spared by the malaria burden. The disease is endemic countrywide and about 95% of all cases are caused by the mostly deadly species of the parasites *Plasmodium falciparum* (National Malaria Control Centre 2000). Health Management

Information System (HMIS) in 2004 showed that malaria accounts for 3 million clinical cases and 33,000 deaths annually.

Uncomplicated cases of malaria could turn into severe malaria if cases are not promptly diagnosed and treated. Therefore, it is critical, in malaria case management, to be able to detect signs and symptoms of malaria early and thereafter treat with an effective antimalarial. It is for this reason that the Roll Back Malaria (RBM) emphasizes improved malaria case management as one of the pillars of reducing malaria disease burden (WHO 2000b).

It is against this background that in 2003, the national antimalarial drug policy in Zambia was revised. This led to the replacement of the failing chloroquine (CQ) and Sulphadoxine-pyrimethamine (SP) with artemisinin-based combination therapy (ACTs) for the treatment of uncomplicated malaria. Currently, ACTs have been scaled up countrywide to treat uncomplicated cases of malaria. ACTs have been reported to be highly efficacious in treating uncomplicated malaria and consequently reducing the transmission of resistant genes (Omari et al 2002, Chanda et al 2004, WHO 2005). It is therefore expected that by ensuring the efficacious drug is available countrywide, patients will receive effective treatment so as to avoid fatal outcomes.

Nonetheless, malaria diagnostic capacity plays a pivotal role in correctly identifying malaria cases from non-malaria cases. This depends on the accuracy of a diagnostic test, which is determined by its sensitivity and specificity. Sensitivity is defined as the ability of a test to correctly identify those with the disease, while specificity is the ability of a test to correctly identify those without the disease of interest (Grimes and Schulz 2002). However apart from the test accuracy, other characteristics need to be considered, such as resources and time needed to perform that test (Moody 2002). With an effective diagnostic tool for malaria, only true cases would be prescribed an antimalarial. This helps in channelling antimalarial drugs to those that need them and at the same time provides the non-malaria cases an opportunity to be examined for other causes of illness.

However, due to lack of diagnostic capacity to detect parasite presence in the patients, most fevers are being diagnosed clinically to be malaria. Consequently, antimalarial prescriptions are normally given to patients without any laboratory confirmation. Algorithms for fever management based on the integrated management of childhood illnesses (IMCI) guidelines are also being applied to ensure that other causes of fever are excluded (Gove 1997, Chandramohan et al 2002). Nonetheless, such IMCI guidelines are misapplied and only a few (33%) frontline health workers have actually been trained in IMCI (NMCC 2005). Further clinical algorithms have been unsuccessful in improving malaria diagnosis (Chandramohan 2002). This may be a contributing factor to poor patient management and has repercussions for the outcome of an event of malaria, especially in children aged five years and below in whom progression to severe malaria occurs rapid.

The NMCC (2001) estimates show that in Zambia, only 34% of the facilities have laboratory facilities for microscopy services. Of these only 60% (about 20.4% of facilities countrywide) have functional laboratories. This is mainly due to the health system resource constraint to revamp the capital, human and other resource needs for this program. A recent survey, which was conducted in public health facilities in Zambia, with the aim of estimating the proportion of malaria cases being laboratory confirmed, showed that the proportion of malaria patients receiving treatment after laboratory confirmation was at 11%. Furthermore it was shown that where laboratory diagnosis was introduced, there was a 31% reduction in antimalarial use when compared to the times when there was no capacity to confirm malaria (NMCC 2005). This implies that relevant health personnel need to be equipped with the capacity to distinguish malaria cases from non-malaria cases through confirmatory tests such as microscopy or Rapid Diagnostic Tests (RDTs).

There is a challenge now that Coartem® a fixed dose combination of Artemether-lumefantrine (AL), which is being used to treat uncomplicated malaria, is more expensive than the former monotherapies. The cost of a full treatment course per adult has been

estimated to be USD 2.4 for AL while that of CQ and SP is USD 0.10 to USD 0.20 respectively (Yeung et al 2004). Due to the shift to a more expensive drug, the malaria drug budget in Zambia has increased from USD 579, 300.32 in 2003 (when SP was first line treatment) to USD 4,474,017.72 in 2005 (672.7% or 7.72 times). Without microscopy, it is difficult to exclude fevers, which are not due to malaria, thus the true burden of the disease proves difficult to quantify. This is leading to wastage of drugs on unnecessary treatment and one can also anticipate inappropriate patient management to be rampant. Therefore, it is necessary to assess the economic implication of continuing to rely on clinical diagnosis as opposed to the introduction of a more accurate (and probably more expensive) diagnostic method in this era of ACTs.

1.2 Rationale

New technologies have introduced RDTs, which work on the principle of antigen detection methods. These immunochromatographic dipsticks can be sensitive to two basic antigens of the malaria parasites; the histidine-rich protein-2 (HRPII) or parasite lactate dehydrogenase (pLDH) (Hanscheid 2003). These tests are now being thought of as a viable option for defining malaria parasite presence in the patients suspected of having malaria. Compared to expanding microscopy services, RDTs can be easy to implement in the short term. This is because in order to have functional laboratory capacity, various inputs are needed such as trained laboratory personnel, a microscope, a building (where no structure already exists), reagents and other supplies such as slides and lancets (Moody 2002, WHO 2000c). RDTs however, can easily be used by any frontline health workers and do not need extra infrastructure (Guerin et al 2002). All that is required is someone who is able to draw a blood sample and read the test strips based on appearance of lines. (More details on RDTs are provided in Chapter 3, Section 3.3). There is a need therefore to come up with recommendations based on a systematic analysis of the diagnostic needs for malaria case management in Zambia. This study therefore seeks to compare the cost and cost-effectiveness of the three available options (clinical, microscopy and RDTs) for diagnosis of malaria in light of ACTs as first line

treatment. The cost implications of false positives (cases diagnosed as malaria in absence of the parasite) and false negatives (cases diagnosed as non-malaria in the presence of the parasite) will be determined.

This study contributes to new knowledge on the economics aspects of malaria management. This is relevant since economic evaluations on malaria interventions, especially in Zambia, are scarce. Only two studies have been conducted so far in the Copperbelt province on integrated malaria control interventions and environmental management (Utzinger et al 2001, Utzinger et al 2002). The results of this analysis will serve to inform policy makers on which alternatives will be most efficient in reducing malaria misdiagnosis by taking into account both the costs and effects of each strategy. Further options for research are also discussed.

1.3.0 Aim and Objectives

1.3.1 Aim

The aim of this research is two fold, firstly to assess the cost and cost-effectiveness of clinical, microscopy and RDTs techniques for diagnosing malaria in outpatient clinics in Zambia. This involved using primary data sources on costs and effects from 12 facilities in 4 study districts. The second aim is to use this data to estimate the net impact on costs (cost of technology minus the saving on treatment) and effects of scaling up cost-effective malaria diagnosis up to district level.

1.3.2 Specific Objectives

1. To determine the mean cost per patient with each diagnostic method in each facility.
2. To determine the monthly cost of false positives for each diagnostic method.
3. To determine the monthly cost of false negatives for each diagnostic method.
4. To determine the proportion of cases successfully diagnosed by each method.

5. To determine the cost per correctly diagnosed case with each diagnostic method.
6. To analyse health workers prescription behaviour along with the diagnostic method used.
7. To determine the most cost effective of the three diagnostic methods along with incremental analysis between strategies.
8. To draw recommendations for policy decisions in the light of the results obtained

CHAPTER TWO

1.0 COUNTRY PROFILE – ZAMBIA

2.1 Demographic and Economic Features

According to World Bank estimates of world economies, Zambia is among the low developed countries in SSA. The country's population estimate for 2004 was 11.5 million inhabitants (http://siteresources.worldbank.org). 51% of the population are male and 49% female. Children under the age of five years account for about 17.5% of the population. The majority of the population lives in rural areas (65%). The annual population growth rate is estimated to be 2.9% and the average household size is 5.4. The crude birth rate is 41.46 births per 1,000. The national literacy rate is estimated at 63% for males and 50% for females Zambia Demographic Health Survey (ZDHS) 2001/2002). The life expectancy is at 47.5 years for males and 51.7 for females, and the total fertility rate is at 5.9 (ZDHS 2001/2002).

The climate in Zambia is typical of the sub tropics region. The three main seasons are defined as cool dry winter (May to August), hot dry season (September and October), and warm wet season (November to April) (ZDHS 2001/2002).

Administratively, the country is divided into nine provinces namely Lusaka, North Western, Northern, Luapula, Eastern, Western, Central, Southern and Copperbelt. Of these provinces, only Lusaka and Copperbelt are considered to be urban and form the main hub of economic activity in Zambia (ZDHS 2001/2002). The provinces are further divided into a total of 72 districts countrywide.

The economic activity has since the early nineteenth century been centred on the mining industry with copper as the main output. Other industries include manufacturing, agriculture, trade and tourism. The Ministry of Finance and National Planning (MFNP)

reported a positive real economic growth rate of 4.6% in 2004. This meant that there was a consequent increase in funding to social sectors such as health. Nevertheless, the high inflation rate (17%) continues to have a negative impact on the real value of health sector funding by government (MFNP 2004).

The reported increase in Gross Domestic Product (GDP) is also negated by an increase in population making real GDP growth almost non-existent. In 2002, GDP per capita was estimated at 865 international dollars[1]. The National Health Accounts (NHA) analyses have also shown that general government expenditure on health (GEH) has remained almost stagnant from 1998 to 2002 at just around 52% *(WHOSIS,* http://www.who.int/nha/country/en*)*. Expenditure on health as a proportion of gross domestic product (GDP) is only 5.8%[1].

Unemployment continues to be high generally due to the negative effects of the economic reforms. This was during the privatisation process of formerly government owned parastatals, which began in 2001 (NHSP 2005). It is not surprising then that even in the health sector, a human resource crisis is looming. A Human Resource Development Review in 2004 showed that about 50% of the required core health worker positions (at all levels of health care) were still vacant (MOH 2001). This has made it difficult to manage the growing needs for patient care mainly due to malaria, HIV/AIDS and Tuberculosis (TB) to mention but a few.

It is estimated that about 70% of the population lives on less than USD1 per day, which the World Bank has defined as the poverty line. Income is inequitably distributed (Gini coefficient = 0.57)[2] with the rural areas being more equitable (0.42) than the urban areas (0.61) (CSO/LCMS 2002-2003). There are noticeable differences in health status between the rural and urban areas. This is also partly due to the fact that poverty levels

[1] WHOSIS, available at http://www.who.int/nha/country/ZMB.xls, accessed 5th October 2005.
[2] Gini coefficient measures the income inequality in a population and ranges on a scale of 0 to 1. With 1 implying highest inequality while 0 indicates no inequality.

are worse off in the rural areas (80%) as compared to urban areas (50%) (MOH 2003). Inequities in health service delivery exist among rural and urban areas. For example, the doctor to patient ratio was 1:5000 in Lusaka Province (urban) whereas it was 1:43000 in rural Luapula Province in 2004 (MOH 2004).

2.2 The Health System Context

2.2.1 Health System Structure

The health system decentralization policy was implemented in Zambia since 1998. What this meant was that the MOH, the umbrella body for all health activities was responsible for the legislature, setting policy direction and financing of the health system. Whereas the Central Board of Health (CBOH), a technical body ratified by parliament to implement government health programmes, has been delegated to manage the district action plans of the health sector. This led to the formation of 72-district health management boards (DHMBs), which were responsible for implementing health programmes (Bossert et al 2003). This purchaser-provider split was seen as a way of ensuring that the policy and operations roles are carried out more effectively. The jurisdiction of the DHMBs includes District Hospitals, health centres, health personnel training institutions and the community level neighbourhood health committees (NHCs) which is the lowest entry point into the structure of health service (Bossert et al 2003). The community level is defined as a level that

"*brings health care as close to the family as possible. Community health workers (CHWs) are expected to promote preventive measures, provide individual counseling and group education, detect cases of fever and pregnancy, provide simple case management and prophylaxis, and know when to refer*". (NHSP 2005). Due to human resource shortages, CHWs sometimes have ended up operating at health centres (especially in rural areas).

However, attempts are being made now to devolve functions to local authorities in the district councils (political administrators), which would in turn manage the districts affairs including health programmes (MOH NHSP 2005) and would be supervised by the

provincial office and central level. However, decision-making may revert to a system similar to a centralized health system. By March 2006, an Act of Parliament was repealed allowing the dissolution of CBOH. Even so, there is no further information as to what the next steps will be and the DHMTs have continued to operate as per decentralized structure.

2.2.2 Health Care Provision and Financing

The overall goal of the health system in Zambia is *"to provide Zambians with equity of access to cost-effective, quality health care as close to the family as possible."* (MOH-NHSP 2005). In line with this goal, the basic health care package is provided through public service based on the priority disease burden. User fees are charged to patients at the point of seeking care. An exemption policy however, exists for the treatment of chronic illnesses, sexually transmitted diseases, family planning services, treatment of epidemics, children under five and adults older than 65 years of age (CBOH 1998). However effective implementation of user fees policy has proved difficult due to the extent of poverty. Most people are unable to pay and only a few urban-based facilities have managed to raise some income (Bossert et al 2003). Plans are now under way to remove the user fee policy in lower level health facilities.

There are about 1,327 health facilities, 1,124 are government owned, 115 are private sector clinics and 88 are mission facilities (CBOH 2002). The major causes of illness in these facilities include, malaria (which is endemic countrywide), respiratory infections, diarrhoea, pneumonia and trauma. Other common diseases include HIV/AIDS, TB, urinary tract infections, sexually transmitted diseases and non-communicable diseases (MOH NHSP 2005). The maternal mortality rate is among the highest in the world (729 per 100,000 live births), whereas under five mortality rates is at 163 per thousand population (MOH NHSP 2005). Table 2.1 illustrates some of the key health indicators. The estimates for SSA have also been incorporated to allow for comparative understanding of the health status of the country in relation to the region.

Table 2.1 Key Health Indicators for Zambia and Sub Saharan Africa

Indicator	Zambia 2003	SSA Average 2004**
Life expectancy (Years)	43	46.2
Infant Mortality Rate (per 1000 live births)	95	100.5
Maternal Mortality Rate (per 1000 live births)	729	870
Child Mortality Rate (per 1000 live births)	168	168.2
Low Birth Weight (for every 25 births at facility)	1	..
Fully Vaccinated Children (FVC) (%)	74	64.5
HIV Prevalence (% among those suspected)	15.6	..
Malaria Prevalence (HMIS 2003)*	428/1000	..

Sources: Zambia Health and Demographic Survey (2001/2), Annual Health Statistics Bulletin (2003), *HMIS estimates (including both confirmed and unconfirmed cases), **World Bank[3]

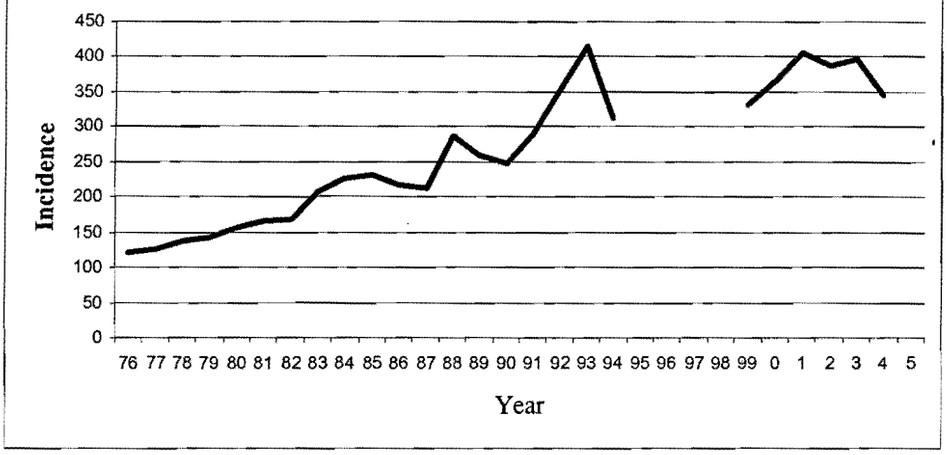
2.3.0 Malaria Situation Analysis in Zambia

2.3.1. Malaria Burden

According to the ZDHS, malaria is the leading cause of mortality and morbidity, accounting for 37% of all out patient attendances at health facilities (ZDHS 2002, MOH 2004). Current trends show at least 3 million clinical cases and 33,000 deaths are reported annually from all public health facilities. It is anticipated that these cases could be more if unreported cases of disease and community deaths are included. By 2004, the CBOH reported a prevalence of 428 cases per thousand populations countrywide. Furthermore, malaria is responsible for 40% of the under five deaths and 20% of maternal mortality (CBOH 2004). The incidence of malaria has been fluctuating over the past years. However, the general trend is an increase in cases from about 120 per thousand population in 1976 to more than 300 cases per thousand population in 2004 as shown in figure 2.1 below. Note that the period 1994 to 1998 shows a data gap due to the structural changes in the reporting system from the previous health services information systems to the current HMIS (NMCC 2000).

[3] http://devdata.worldbank.org/external/CPPrrrofile.asp?PTYPE=CP&CODE=SSA

Figure. 2.1 Reported Number of Malaria Cases per Thousand (Incidence)



Source: National Malaria Control Strategic Plan, 2006 (NMCC 2005). The number of malaria cases includes both confirmed and unconfirmed cases at the facility level.

The vector species, which are responsible for the transmission of malaria, are the *Anopheles gambiae, Anopheles arabiensis and Anopheles funestus complex* (NMCC 2000). These are known to be very efficient in transmission of the malaria parasites. *Plasmodium falciparum* is the most prevalent in Zambia accounting for about 95-98% of the malaria cases, whereas *P. malariae* and *P. ovale* have been reported in about 5% of the cases countrywide. *Plasmodium vivax* is said not to be a causal agent for malaria in Zambia (NMCC Situation Analysis 2000). The prevalence of the most deadly form of the malaria parasite and the most efficient vectors coupled with a warm climate has made malaria control in Zambia a big challenge.

As early as 1944, the then Rhodesian government instituted the Mosquito Extermination Act to control malaria in the then Northern Rhodesia. The primary requisite of this Act was to warn the communities of any accumulation of water in their surroundings contributing to mosquito breeding resulting in malaria. Failure to do so attracted a penalty

in form of a fine instituted by the city council (NMCC 2000). This not only prevented malaria but also other water borne diseases. The copper mining industry, early in the 1950s, had also invested significantly in malaria control in the urban areas, given the good economic performance at that time (Utzinger et al 2002). The rural areas were using chemoprophylaxis for malaria prevention in school children. Thus, in the mid 19th century, malaria became a notifiable disease in the Copperbelt and the City of Lusaka, while the rest of the country had very low prevalence of malaria (NMCC 2000).

The decline in copper prices in the late 1970s and the Stockholm Convention ban on the use of DDT for malaria control in 1972 brought about the beginning of increase in malaria incidence from 137 per thousand populations in 1976 (NMCC 2000) to 428 cases per thousand populations in 2003 (CBOH 2003). The increase in incidences has consequently increased expenditure on malaria and this has created a resource burden on the under funded health system (NMCC 2000).

CQ and SP were the main drugs used to treat malaria. However, the recent times have seen an increase in multidrug resistance to commonly used antimalarials. Sentinel site surveillance of the therapeutic efficacy of antimalarials have been conducted in country based on the recommended WHO protocol (WHO 2003). These have shown that treatment failure to CQ is greater than 50% while that of SP show as high as 32% in certain parts of the country (Barat et al 1998, Chanda et al 2004a, Chanda et al 2004b). The consequences of drug resistance have been reported to be prolonged illnesses, increased morbidity and mortality, thus negating malaria control efforts being made by countries (Phillips & Phillips-Howard 1996).

As a result of the myriad of factors mentioned above, malaria control is now high on the nation's health agenda. The following section discusses the various malaria control interventions which are being implemented in order to effectively reduce malaria related illnesses and deaths.

2.3.2 Malaria Control Efforts

In April 2000, the Abuja Declaration for RBM was instituted and, malaria endemic countries reaffirmed their commitment to prioritise malaria control so as to halve the disease burden by 2010 (WHO 2000a). Zambia as country is a signatory to the Abuja Declaration and thus ascribes to its ideals and goals. To this effect, the National Malaria Control Programme (NMCP) in Zambia has embarked on a strategic process of implementing the RBM objectives. The interventions, which have been adopted by the NMCP, include vector control, improved case management, behaviour change communication, partnership strengthening and, monitoring and evaluation, including research.

2.3.2.1 Improved Case Management

Under this component, efforts are being made to ensure early detection and treatment of malaria. Due to increase in parasite resistance to CQ and SP, the antimalarial drug policy has been revised. AL has been declared a first line treatment for uncomplicated malaria except for children under 10 kg and pregnant women, in whom SP is being used. By December 2004, AL was available in all public facilities in the 72 districts (Mudondo et al 2005, NHSP 2005). Quinine is still being used as second line treatment. For malaria in pregnancy, Quinine is being used in the first trimester of pregnancy, SP in the second and third trimester for treatment and also for intermittent presumptive treatment (IPT).

2.3.2.2 Integrated Vector Management

Indoor residual spraying (IRS) is carried out in selected districts in Zambia based on level of urbanisation and malaria incidences. The insecticides being used are pyrethroids and DDT. Currently 15 districts are implementing this intervention under the auspices of malaria control programme in collaboration with various partners. The partners involved in the spraying operation include the private sector, bilateral and multilateral organisations. A total of 324,137 individuals (91.4% of targeted population) were

protected at an average direct cost of USD 1.41 per person and USD6.55 per household protected in the 2004 season (NMCC 2004a).

The Insecticide Treated Nets (ITNs) programme in Zambia is another strategy being used for personal protection against mosquitoes. Taxes and tariffs on mosquito nets and insecticide for re-treatment have been removed (NMCC 2004b). The delivery mechanisms use different approaches to reach various target groups based on disease burden and also on socio-economic status. According to ZDHS, 27.2% of households surveyed owned at least a bed net. However, those who owned ITNs were 17.7% (ZDHS 2001/2002). It is expected that by now, these rates have improved given the scaling up efforts. The school health programme is another initiative in which ITNs are being provided to all boarding schools countrywide in a bid to revamp malaria control efforts in schools. Re-treatment campaigns for all ITNs in the community are intensified during Child Health Week activities.

2.3.2.3 Information, Education and Communication

Information dissemination is key for malaria control. The Information, Education and Communication (IEC) department at NMCC works with various partners in order to provide useful information to different audiences on malaria control aspects in Zambia. A communication strategy has been developed with collaboration from bilateral and multilateral partners. This is to ensure that information is disseminated in a systematic way. Communication channels being used include television, radio, leaflets, pamphlets and drama. Translation of information guides into the main local languages is also done.

2.3.2.4 Monitoring, Evaluation and Research

The NMCC has developed a strong emphasis on monitoring the progress and impact of malaria control interventions. This helps to provide the necessary and timely information to suit the programme needs and serve as evidence base for policy decisions and advocacy. The malaria research-working group sets the agenda for research every year

based on NMCC recommendation. The group coordinated by NMCC is composed of partners from universities (local and foreign), research institutions, private sector and NGOs. Quarterly meetings help to disseminate research areas among institutions and also to report on programmes monitoring progress. Various studies have been conducted on antimalarial drug use (efficacy and compliance), knowledge, attitudes and practices of malaria (KAP studies), insecticide resistance monitoring, and IRS monitoring and other areas. Draft guidelines for malaria research in the districts have been produced to demystify research and encourage district level staff to engage in applied research.

Close collaboration of the surveillance office with HMIS and Central Statistics Office (CSO) and other regions helps to integrate efforts in information collection, analysis and presentation. Epidemic preparedness is also another key area because some areas in Zambia are prone to epidemics especially those near major rivers and lakes where floods occur frequently.

2.3.2.5 Resources for Malaria Control

Financing of malaria control in Zambia is made possible by support from government and partners. About 32% of the malaria expenditure is government funded while various donors fund the larger proportion. These include multilateral, bilateral, the private sector and other local partnerships. Broadening the partnership base is key to ensure that the resource needs for scaling up malaria control are available.

CHAPTER THREE

2.0 LITERATURE REVIEW

3.1 Theoretical Background of Malaria Diagnosis

Malaria is transmitted through a mosquito bite by an infected female *Anopheles sp* mosquito. When the parasites have been injected in the body, they multiply in the liver and then get released in the blood stream leading to a myriad of symptoms. These symptoms include one or more of the conditions as shown in Table 1 (first column). At this stage malaria is considered to be uncomplicated or simple.

Table 3.1 Signs and Symptoms of Uncomplicated and Severe Malaria

Uncomplicated Malaria	***Severe Malaria***
Fever	Convulsion, unconsciousness
Chills	Cerebral malaria
Sweats	Severe anaemia due to haemolysis
Headache	Haemoglobirunia
Nausea and Vomiting	Acute respiratory distress
Body aches	Cardiovascular collapse and shock, etc
Body malaise	
Splenomegally	
Enlarged liver	
Increased respiratory rate, etc	

Adapted from Zambia Malaria Foundation website: http://www.malaria.org.zm/treatment.hml

Severe (or complicated) malaria on the other hand, occurs when the initial uncomplicated malaria is either not resolved (due to treatment failure) or not detected early. Late detection of malaria could be due to patient health care access problems, the stage at which the detection is performed, the type of test being used and or health worker performance capacities on diagnosis. Some of the complications of severe malaria are shown in Table 3.1 above – right column.

It has been said that the failure to effectively control malaria is in part due to *"inability to deliver appropriate case-management to a significant proportion of patients, particularly at the periphery of health systems"* (Guerin et al 2002). This observation is true because in order for a case of malaria to be detected, the diagnostic method must be *appropriate* (sensitive to the parasites in question). Furthermore, for the identified case of malaria to be successfully treated, the treatment given to the patient must be *appropriate* (have sufficient efficacy to clear parasites from the blood). Additionally, being able to correctly identify those with the disease will not only cure them, but is said to help reduce malaria transmission by clearing parasite reservoirs of the infected person (Mendiratta et al 2006). In this way malaria diagnosis serves both as a curative and preventive strategy.

WHO, in its "New Perspectives for Malaria Diagnosis" (2000c, page 5) paper emphasises the need for *"prompt and accurate diagnosis"* of malaria as a prerequisite to successfully care for malaria patients. It is therefore important that health workers and the caretakers of patients are aware of this important fact. However, the objective of *"prompt and accurate diagnosis"* of malaria (WHO 2000c, page 5) is affected by other health system factors. For example good access to health care services provided by trained personnel is limited and where these exist, specifically laboratory services may be unavailable (Guerin et al 2002). At this stage, it is possible to see why malaria diagnosis is usually described to be a challenging issue by several authors (Moody 2002, WHO 2000c, Hanscheid 2003).

Moody (2002), in his review of malaria diagnosis points out that the main challenges of malaria diagnosis include: Morphological variations in the parasite itself at the different stages of its life cycle, these changes also vary with the emergence of drug resistance, the parasites diversity and complexity of blood collection techniques. These issues are key in determining the quality of a diagnostic service.

Different methods of diagnosing malaria have been outlined in literature. Currently, various approaches have been defined by WHO (2000c). These include clinical diagnosis, light microscopy, fluorescent microscopy, antigen detection (RDT), polymerase chain reaction (PCR) and haemozoin-containing leukocytes-automated full blood count analyser. These methods differ in technique, capacity and effectiveness. Of these alternatives, PCR, fluorescent microscopy and full blood count analysers are not used in routine conditions. The choice of which strategy to implement depends on several factors as outlined in Table 3.2 below.

Table 3.2 Factors Affecting Choice of a Diagnostic Method

• The extent of malaria endemicity
• The prevalence of drug resistance
• Geographical access to health services
• Socio economic situation
• The level of infrastructure in the health system under consideration
• The availability of diagnostic tools

Source: Adapted from WHO 2000c.

The following review will concentrate on the three strategies, which are commonly used in Zambia and are the subject of this study.

3.2 Clinical Diagnosis of Malaria

Clinical diagnosis of malaria is a strategy of malaria diagnosis based on signs and symptoms of malaria (WHO 2000c). The commonly used symptoms include a history of fever, increased breathing rate, anaemia, convulsions, inability to feed, to mention but a few have been outlined in Snow et al, (2003). The IMCI strategy is one of the tools

developed by WHO to improve clinical detection of childhood illnesses. IMCI guidelines recommend that children with fever or history of fever and or pallor qualify for antimalarial treatment (Tarimo et al 2001). Other predictions of malaria have included the use of fever with a previous history of malaria coupled with absence of cough, presence of enlarged spleens (commonly referred to as splenomegally) or pallor (Muhe et al 1999).

An extensive prospective evaluation conducted by Luxemburger et al (1998) in Thailand also identified other combinations for predicting malaria infection. These included fever, nausea, clinical anemia, palpable spleen, palpable liver, headache and, absence of cough and diarrhoea. Among these factors, the study showed that vomiting, confirmed fever, splenomegally and hepatomegally were by themselves risk factors for *Plasmodium falciparum* malaria. They however concluded that these methods were unsuccessful in accurately detecting malaria infections.

Evidence from Malawi (Redd et al 1996) demonstrated that even though all children with fever were supposed to be treated as malaria, there was a need to include splenomegally and pallor. This would make the diagnosis even more effective. It was thought that by better defining malaria cases, the concerns of over-treatment would be averted.

Despite all the possible determinants of clinical diagnosis for malaria discussed above, the most widely used is fever greater or equal to 37.5 degrees Celsius (febrile), or history of fever and pallor. The presence of these symptoms may indicate uncomplicated malaria. On the other hand, convulsions or history of convulsions, unconsciousness and severe anaemia are good indicators of severe malaria (WHO 2004, NMCC 2004c).

In Africa, it has been reported that fever is often the main feature of clinical diagnosis of malaria (WHO 2000c). This is so, mostly because access to health facilities is still a problem in many countries on the continent. Furthermore, according to Amexo et al (2004) most cases may occur in the community. These patients lack access to trained medical personnel. Yet, even where medical personnel exist, laboratory services in these facilities may not be available. In these instances, it has been argued that clinical

In order to try and improve the effectiveness of clinical diagnosis, approaches are being made to pre-test various algorithms. The main aim is to improve the specificity (i.e. reducing false positives) of clinical malaria diagnosis. In order to achieve this, various researchers have tried to combine one or more of the other signs and symptoms of malaria with the widely used fever.

A study was conducted by Mwangi et al, (2005) in Kenya to assess the effectiveness of clinical algorithms in diagnosing malaria in different age groups. The study took place in Kilifi (an area of moderate malaria transmission) with 1602 participants reporting fever or history of fever in an out patient clinic. Clinical diagnosis was compared with microscopy confirmation of malaria. The main conclusions were that when age specific algorithms were used as basis for treatment, 16% of those aged five years and below, 44% of those aged 6-14 years and 66% adults eligible for antimalarial treatment would not receive any treatment. This was despite these cases having a history of fever and parasitaemia. This study demonstrated that in an effort to improve specificity, false negatives were increased. Thus there was a concern that clinical diagnosis using algorithms may not be useful in targeting treatment to the most vulnerable groups and may increase prolonged malaria morbidity.

In Pakistan, a study was conducted in low malaria endemic area among patients aged 6-12 months in a rural health centre (Hozhabri et al 2002). Different combinations of signs and symptoms were assessed and compared with microscopy at predicting *Plasmodium falciparum* malaria. Fever in the past three days or more and absence of cough or rigours was found to have a sensitivity of 100% and 63% specificity. However, WHO recommends that malaria detection be conducted within 24 hours of onset of symptoms. So, if the more than 3 days history of fever was adopted, a lot of cases could be missed from being detected and this would consequently increase incidence of severe malaria, which is more difficult and expensive to manage.

Chandramohan and colleagues (2002) conducted a review of several studies that used clinical algorithms to diagnose malaria. They assessed different epidemiological zones to establish the risks and benefits of the algorithms. They concluded that in low endemic settings, the risk of false negatives was low. They also reported that the savings on over treatment was not significant in low malaria transmission areas. However, in endemic areas, the false negatives increased with an increase in prevalence. They concluded that clinical algorithms were inaccurate and could not be used as a basis for treatment. This was also found in India where different combinations of clinical symptoms were used to get the highest possible score based on ability to predict malaria correctly in adults and children (Chandramohan et al 2001). The highest scoring algorithms had 60% sensitivity. They further said that the IMCI recommendation of treating all febrile cases (or history of fever) was better than other clinical algorithms if microscopy confirmation could not be within reach. It was concluded that clinical diagnosis was poor in predicting malaria. It was also suggested that microscopy confirmation is needed so as to improve the accuracy of malaria diagnosis.

Other studies have used various signs/symptoms and differences in endemicities. In low malaria transmission Luxemburger et al (1998) evaluated several signs and symptoms of malaria to assess their association with a true malaria diagnosis in Thailand. 1527 children were prospectively followed up and 9 signs and symptoms were evaluated. Using history of fever, headache and absence of cough was 51% sensitive and 72% specific. History of fever and oral temperature greater or equal to 38 degrees Celsius gave a 51% sensitivity and 71% specificity. However when using fever greater or equal 37.5 degrees Celsius in a low transmission area in Zambia clinical diagnosis of malaria when compared with microscopy was found to be 70.6% sensitive and 35.6% specific. Conversely, in a high transmission area, it was 93.3% sensitive and 25.5% specific (Ndhlovu et al 2004. MOH Report unpublished). These studies show that clinical diagnosis produces different accuracy depending on the definition used and the endemicity of malaria in a given area.

Other studies have compared clinical diagnosis with either RDTs or microscopy. In Tanzania, a study was conducted to compare the IMCI strategy (treating all fever and or pallor cases) with RDTs (validated by microscopy) in a low endemic area (Tarimo et al 2001). 395 children who were identified to receive antimalarial treatment using the IMCI strategy were tested for malaria parasites using microscopy and RDTs. 70% of these actually had malaria parasites (30% false positive). Fever was found to have a sensitivity of 93% and 15.5% specificity. However, pallor had a sensitivity of 72.2% and 50.8% specificity. The ICT brand of RDTs were found to be 100% sensitive and 74% specific, while the OptiMal brand was 100% sensitive and 100% specific (Please see RDTs section 3.3 for more details on the differences between these brands). The study concluded that financial limitations might inhibit the use of RDTs for routine malaria diagnosis if the antimalarial drug is cheap. But if the drug of choice is expensive, the opposite may be true.

In Ethiopia, Muhe et al (1999) assessed the improvement of malaria prediction by including pallor and splenomegally to fever or history of fever. Microscopy was used as a gold standard. The study included a total of 2490 children between 2-59 months in low and high transmission seasons. It was found that pallor and splenomegally improved malaria prediction capacity both in the low and high transmission seasons. Fever and pallor reported sensitivity and specificity of 83% and 75% respectively in the high transmission season. During the low transmission season, the effectiveness of diagnosis reduced showing a sensitivity of 51% and 60% specificity. However, fever and splenomegally were 80% sensitive and 69% specific in the high transmission season. But during the low transmission season, fever and splenomegally were 65% sensitive and 81% specific.

One of the earliest evaluations of IMCI was conducted in Kenya during a high malaria transmission season (Perkins et al 1997). 1795 children aged 2months to 5 years were enrolled over a 7 months period. 67% had microscopically confirmed malaria and 80% had anaemia (haemoglobin <11g/dl). The assessor was a health worker trained in IMCI and was compared to a paediatrician with laboratory support. The IMCI strategy was

found to be 100% sensitive and 0% specific. Based on these, recommendations were made to revise the IMCI strategy. Malaria was found to have symptoms and signs similar to pneumonia and malnutrition. This shows implementing IMCI still results in poor malaria prediction even by trained personnel. Thus, health workers who are not even trained in IMCI should be expected to perform even worse.

3.3 Microscopy Diagnosis of Malaria

Malaria diagnosis using microscopy (light microscopy to be specific), under ideal conditions is up to date considered to be the gold standard (Guerin et al 2002, Hanscheid 2003). Unlike clinical diagnosis of malaria where only one clinician is involved, this strategy needs a minimum of two personnel: a clinician and a laboratory technician. The initial stage involves a clinical diagnosis of the patient by a clinician. The clinical diagnosis is performed based on the signs and symptoms that a patient may present with (as discussed in Chapter One - section 1.1 above) at the facility. If a clinician suspects malaria, the patient is sent to the laboratory to obtain a confirmation of malaria infection. Once laboratory investigation for malaria is complete, armed with a laboratory result, a clinician may decide to treat or not treat.

In order for the laboratory personnel to be able to detect malaria parasites, there are basic steps that are supposed to be accurately followed. Initially, blood is collected by way of a finger prick or otherwise using a sterile lancet. The drop of blood is then smeared on glass slide manufactured for this purpose, then the slide is dried by either a heater of blower. After that, the slide is stained in a standard dilution of Giemsa stain for up to 15 minutes (for a quick count) or 30 minutes (for a slow count). Quick counts usually serve the purpose of identification of parasite presence and are used in routine clinical practice, where as slow counts are used in monitoring therapeutic efficacy and help to make better estimations of parasite counts. After staining, the slide is then read under oil immersion using a conventional light microscope. Details of this procedure have been described in detail elsewhere (Moody 2002, WHO 2000c).

(1998), it was said that malaria endemic countries expenditure on health are too low to allow for extensive investments in malaria microscopy. This has led to a situation where only a few facilities in main referral centres and hospitals are actually able to provide the service. It has been observed that most of microscopy services are not widely available in most areas where they are needed especially in the SSA region (Guerin et al 2002, Moody 2002).

Furthermore, where services are available, the possibility of attaining high sensitivity levels under routine conditions is questionable. This is because in a typical clinic setting, a lot of people may be waiting for results. Thus a laboratory person may be likely to rush through the tedious procedures. Human resource constraints may also lead to heavy workloads and thus concentration is disturbed. Under these conditions, it is likely that the quality of laboratory results may be compromised (Guerin et al 2002).

WHO estimates also show that sensitivity of microscopy diagnosis of malaria under routine conditions may be 10% less than the expected sensitivity of expert microscopy (WHO 2000c). Other studies have also reported that only up to 90% of all routine microscopy diagnoses were correct (Milne at al 1994 in Hanscheid et al 2003).

Another issue of concern is that laboratory procedures take a longer time to perform, thereby contributing to long waiting hours. The minimum time it takes to get results may be 30 minutes and more. Due to this, it has been reported that clinicians are more likely to treat without laboratory results. Hence, the investigation ends with no role in the decision making process of the clinician (Moody 2002). Therefore, the extra cost of conducting laboratory investigations (for unutilised results) and the opportunity costs for the microscopists are a drain on the limited resources of the health system. Amexo et al (2004) have pointed out that misdiagnosis of malaria have negative consequences on the illness outcomes and poverty.

In the case of highly endemic countries, it has been reported that members of a population may have parasites but not clinical disease (Guerin et al 2002, WHO 2002c).

In these cases, a malaria positive laboratory result may not be predictive of the actual reason for visit to the health centre. This also may be an ingredient for patient mismanagement.

Moody (2002) has further outlined other threats to the validity of microscopic results. These include the observation of a negative slide when in the actual fact; parasites are sequestered in body tissues and not circulating in peripheral blood. This may lead to false negatives and thus misdiagnosis of malaria. Lastly, dead parasites may be observed (post treatment) and this may be misinterpreted as treatment failure. It is for this reason that laboratory personnel need to have a better understanding of the various dynamics of malaria (Hanscheid et al 2003).

Various studies have been conducted in which microscopy has been recommended to be the better method for malaria diagnosis and disease estimation. In Malawi, microscopy confirmation of malaria was estimated to lead to about USD14, 000.00 savings on annual drug costs when compared to presumptive treatment during the rainy season (Jonkman et al 1995). Such savings could help in reprogramming of resources to other areas of need.

Additionally, field evaluations in several countries have shown that microscopy was able to detect fewer cases than those detected by clinical investigation only. In Tanzania, when IMCI diagnosis was compared with microscopy and RDTs in an endemic situation, only 70% of those treated presumptively were found positive by microscopy (30% false positives according to microscopy) (Tarimo et al 2001). In a study by Guthman et al (2002), in Uganda, in an out- patient setting, only 57% of those who were clinically suspected of having malaria were positive with microscopy. Another study conducted in Thailand by Stephens et al (1999), showed that clinical diagnosis overestimated the malaria burden. Only 32% of the cases clinically diagnosed as having malaria were positive with microscopy.

In Zambia, a study was conducted by random selection of health centres during high malaria transmission season. It was found that of the 239/335 (71.13%) clinically

diagnosed malaria cases, only 74/335 (22.09%) actually had malaria parasites detected by expert microscopy methods. Hence 49.25% (165) would have been false positives (Ndhlovu et al 2004). Thus, diagnosis of malaria using microscopy has a major role to play in correctly identifying mono-infections from mixed infections and that if correctly interpreted and utilised, microscopy can assure treatment within 30 minutes and avoid secondary illness (Penine et al 1998).

However, the true sensitivity and specificity of microscopy under routine conditions has not been well documented. Colin et al (2002) have argued that since most of the times microscopy is the reference method, its poor performance in routine settings is difficult to estimate. In the same paper, the authors demonstrated that in trial settings, *basic microscopy* (routine) was found to be 91% sensitive and 71% specific when compared with expert microscopy.

3.4 Rapid Diagnostic Test Malaria Diagnosis

RDTs are immunochromatic dipsticks used to diagnose malaria. They are a relatively new technology in malaria, which uses "non-microscopic methods", and as the name suggests they are rapid. It is possible to get results within 5-15 minutes, depending on the type of RDTs (WHO 2000c, Guerin et al 2002).

The RDTs detection methods are based on immunology, where the monoclonal antibodies are fixed on the test strip (or dip stick immunochromatographic paper) during the manufacturing process. When these come into contact with infected blood, they bind to specific antigens produced by malaria parasites. The main antigens, which have been used, include HRP-2 and pLDH (Guerin et al 2002). The HRP-2 antigen is common on the membranes of *Plasmodium falciparum* especially in the asexual and young gametocytes. Unlike HRP-2, the pLDH protein can detect isomers for each of the four types of parasites that exist (Moody 2002). Hence pLDH can be used to detect any of the malaria parasite species. Furthermore, pLDH can distinguish *Plasmodium falciparum*

infections from those caused by the other three species (P. *malariae, ovale and vivax*) (WHO 2000c).

The steps involved in performing RDT malaria diagnosis have been outlined elsewhere (WHO 2000c) and are summarised in the following account. Like in microscopy, the finger prick is the starting point so as to generate a blood sample. The blood sample is then mixed with a buffer solution in a capillary tube (or test wells). The buffer contains agents, which are able to haemolyse, the red blood cells so as to release the contents of these cells. Once haemolysis is complete, the antibodies on the capillary binds to the parasite antigens present in the blood so as to form antigen-antibody complex. This complex then moves along the test strip migrates by capillary action and after some time, the control line appears on the test strip. Then, if parasites are present, a second line (test line) appears thereafter. Moody et al (2002), provide more detail on the scientific basis for each of these steps.

WHO acknowledges that RDTs are increasingly gaining attention for their practical use given the limitations of scaling up microscopy services (WHO 2000c). These sentiments have been observed by other researchers working in malaria due to the various advantages RDTs have over microscopy.

RDT diagnosis of malaria has been said to be rapid and requiring less inputs than microscopy (Guerin et al 2002). In the case of microscopy, at least a clinician and trained laboratory personnel is required whereas the RDT method only needs a clinician or a nurse. This is an opportunity for health systems where staff shortage is raging. Additionally, it has been reported that no specialised personnel are required to perform this test (Moody 2002, Guerin et al 2002). Moody (2002) has expressed that RDTs have the potential to move diagnosis services from central level laboratories to areas where patients need them.

The applicability of RDTs in areas or situations where malaria microscopy is not feasible is another advantage. RDTs have been reported to be useful in emergencies or epidemics

(WHO 2003), mobile clinics and in rural areas where electricity supplies may be non-existent (Guerin et al 2002). Other situations in which RDTs would be more applicable than microscopy have been reported to be in travellers, military forces and organised workforces in malarious countries (WHO 2000c). These situations have demonstrated that RDTs are more practical than microscopy.

Since RDTs are relatively easier to use and take less time to produce results (10-15 minutes) (WHO 2000bc), they have the potential to reduce the long waiting time at health facilities. This will go a long way in improving malaria case management especially in rural areas where microscopy services may not be readily accessed.

However, the perception that RDTs are simple to use should be interpreted with care. Hanscheid (2003) stated that health workers should at least be aware of various dynamics involved in malaria transmission. This is so because a failure to get a test line may not necessarily mean the patient does not have malaria.

Disadvantages of RDTs have been widely debated thereby presenting policy makers with the main issues to consider when deciding among diagnosis strategies. WHO estimates have shown that the cost per unit of RDT ranges from USD0.60 to USD2.50 (WHO 2000c). Other estimates have reported the unit cost per RDT to be USD 0.50 to USD 3.00 (Guerin et al 2002). In a study conducted in Uganda in 2002, the cost per test using RDT (Paracheck Pf) was USD 0.50 (Guthman et al 2002). Rolland et al (2006) also estimated the cost of Paracheck Pf to be USD 0.50. The differences in cost may be due to variations in suppliers and exchange rates across time and regions. Nonetheless, all these figures are more expensive than microscopy, which in 2000 prices was estimated to be about USD 0.12 to USD 0.40 per test (WHO 2000c). Therefore, in as much as RDTs are viable, the cost of the test may be a barrier for some countries. In Zambia, the current unit cost per Paracheck Pf test is estimated at USD1.50.

The other important disadvantage of RDTs, especially if HRP-2 based antigen is used, is the prevalence of false positives post treatment. WHO have reported that this may be a

problem for high endemic areas where drug resistance may be suspected, while in the actual fact, the RDT may pick the antigen released form already dead parasites (WHO 2000c). This may lead to overestimation of treatment failures and lead to indiscriminate use of second line antimalarials such as quinine. The consequences of over treatment have been outlined by Amexo et al (2004) to be inflating of the drug budget and encourage the emergence of drug resistance due to increased drug pressure. Therefore HRP-2 based antigens are not useful in assessing drug efficacy but their use could be limited to detection of new cases of malaria.

Other cases in which RDTs are prone to false positives have been said to be when gametocytaemia is high (WHO 2000c, Hanscheid 2003). This is termed false positive because the gametocytes do not lead to clinical disease and are usually not cleared by antimalarials that target asexual parasites (WHO 2000c).

The other limitation of using RDTs has been reported to be the inability of obtaining quantitative information (WHO 2000c). An RDT will only detect if parasites are present or not but may not provide insight into the level of parasitaemia. Knowing how much parasitaemia is present has implications for diagnosing severe malaria. Another disadvantage is the inability to differentiate among species except for *Plasmodium falciprum* (WHO 2000c).

There are various brands of commercially available RDTs, which use either the HRP-2 or the pLDH antigen detection methods. These are:

- Paracheck Pf, ParaSightF, ParaHITf, ICT Pf or Pf/Pv and PATH Falciparum Malaria IC test. These tests use the HRP-2 antigen.
- OptiMal and KAT use the pLDH antigen.

Even though the brands are different, the evaluations are usually conducted based on the type of antigen the RDT uses.

HRP-2 based RDTs have been evaluated in various countries in comparison with microscopy. In a study by Mendiratta et al (2006) in India, 443 patients were diagnosed using RDTs (Paracheck Pf) and microscopy (read by two independent microbiologists). Paracheck Pf. was found to have a sensitivity of 92.6% and 98.6% specificity. The false negatives by were found to be in 7.4% of the samples. Singh et al (2005) also assessed the usefulness of RDTs (Paracheck Pf and ParaHITf). Paracheck Pf was more senisitive (93%) than ParaHITf (87.5%) in detecting placental malaria.Thesed studies showed that concluded that detection of malaria using HRP-2 based RDTs might have a role in routine diagnosis. However, clinical diagnosis may override a negative RDT result if malaria is strongly suspected.

In Uganda, a high transmission area, Guthman et al (2002) conducted an outpatient-based assessment of RDTs in comparison with microscopy. 742 patients who were clinically suspected to have malaria were enrolled. Paracheck Pf was not only found to be highly sensitive (97%) but was also reliable, user friendly and relatively cheap (USD0.5 per test). The sensitivity of Paracheck Pf was higher than that of ParaSight F (88.9%), which was found by Shiff et al (1993) in a high transmission area in East Africa. In the Tanzanian study, Shiff et al 1993 also demonstrated the extent to which HRP-2 antigens persist in the blood of treated patients. Ten days after treatment, it was found that 10% of those treated still tested positive and this persisted up to 14 days after treatment. Nonetheless, the test was said to be accurate enough to warrant its use in rural centres where microscopy services are not available.

Other studies have evaluated RDTs in the context of special groups such as refugees and travellers returning from endemic countries. In Cambodia, Causer et al (2005) evaluated the role of RDTs in a refugee setting. 902 refuges were screened for malaria using RDTs, microscopy and PCR. When compared with microscopy, RDTs were found to be 100% sensitive and 99% specific at a prevalence of 1%. They further observed that RDTs were useful in providing timely, sensitive diagnosis and treatment in a refugee setting. In Honduras, Palmer et al (1998) evaluated the performance of an OptiMal test in an epidemic setting. Among 202 patients in whom malaria was suspected, two species were

identified to be the causal agents. For *P. falciparum*, OptiMal was found to be 94% sensitive and 99% specific whereas for *P. vivax* sensitivity was 88% and specificity was 100%. Based on these findings, it was concluded that OptiMal tests could be useful in detecting malaria in epidemic situations.

Marx and colleagues (2005) conducted a meta-analysis of RDTs in travellers returning from endemic countries. They reviewed studies, which were looking at diagnostic accuracies in non-immune patients with microscopy as the gold standard and stratified results into either antigens group (HRP-2 or pLDH). After reviewing 21 studies they found that HRP-2 based assays were more accurate than pLDH assays. They also found that there was more evidence regarding *Plasmodium falciparum* species than the other three (*malariae, ovale and vivax*). This may be due to the fact that most malaria is caused by *P.falciparum* species hence the concentration of research in this area.

Buchachart et al (2004) evaluated the performance KAT (pLDH-based) in diagnosing malaria as compared to microscopy in a hospital setting. The KAT test was found to have a sensitivity of 96% and 92% specificity in diagnosing both falciparum and non-falciparum species (mixed infections). In Kuwait, two commercial assays (ICT Malaria Pf/Pv tests and OptiMal) with expert microscopy for malaria diagnosis in local health centres among 750 participants (Iqbal et al 2002). The specificities for both tests were found to be 98%. The sensitivities varied depending on the species. They also reported that when parasite density decreased to less than 500/ microlitre of blood, the sensitivity of both tests was reduced. pLDH based performed better than HRP-2 based assays. This conforms to observations that RDTs sensitivity is reduced in very low parasite density (WHO 2000c, Palmer et al 1998).

In the Philippines, trials were performed among health workers in a remote area comparing clinical diagnosis, RDTs (ICT Pf/Pv) and local microscopy (Bell et al 2001). The three approaches were compared to 'expert microscopy'. ICT Pf/Pv tests were found to be 97.9% sensitive, clinical diagnosis was found to be 95.4% sensitive but only 16.5% specific. It was also found that the low parasite density that could not be detected by local

microscopy was detected by RDT. An assessment of local health workers (non-medical workers) found that they were able to accurately perform ICT Pf/Pv tests after a brief training on how to use the malaria test. These observations are important in demonstrating the role of RDTs at low levels of health care.

Other factors which have been assessed with regard to RDTs in the degree of agreement among different users and the occurrence of false negatives. Lema et al (1999) showed the high degree of agreement (99%) among five different microscopists. Mills et al (1999) compared the accuracy of RDTs (PATH Falciparum Malaria IC Strip) with microscopy and PCR. They found that false negatives were likely to occur in samples with less than 100 parasites per microlitre of blood.

3.5 Economic Evaluations in Malaria Control Including Malaria Diagnosis

As pointed out by Foster and Phillips (1998) the role of economics in malaria control is by far and large becoming useful in providing insights for decision-making. The increase in the burden of disease not only impacts negatively on potential economic gains due to absenteeism from school and work (Breman et al 2004, Utzinger et al 2002) but it also increases costs for the health systems. More so in third world countries, which are said to be struggling to meet the need for increased funding of health programmes (Yeung et al 2004, De Savigny and Binka 2004). Evans and Hurley (1995) have stated that, the lack of adequate resources to meet the increasing demand entails making choices among competing interests to achieve desired goals.

Furthermore, the discovery of new technologies for malaria control is also coming at a greater cost. Goodman et al (1999) have observed that more effective interventions are seemingly expensive to implement. This situation is currently being experienced in Zambia where for instance, there has been an eight-fold increase in the malaria drug budget. This was mainly due to changing the first line treatment from SP to AL (Personal Communication with DR M Kango, Case Management Specialist – NMCC). It will be

important to establish whether such budgetary expenditure is translating into more health effects. Such is the role of cost effectiveness analysis in health care.

Cost effectiveness analysis (CEA) is a form of economic evaluation in which the costs and effects of specific interventions are evaluated jointly. Thus, cost effectiveness ratios refer to the cost for a unit of effect. For example, cost per malaria case detected or cost per malaria case prevented. Note that the methods for economic evaluations are reviewed in details in chapter 4.

Various studies have been conducted in SSA to show the cost and cost-effectiveness of malaria control interventions such as vector control and case management options. In a community randomised control trial in India, Bhatia et al (2004) compared the cost effectiveness of IRS and ITNs in a low malaria endemic area. The cost per case prevented was found to be lower for ITNs (USD 52) than IRS (USD 87). In another cost effectiveness study in Kwa Zulu Natal (South Africa) AL was compared with SP for malaria treatment from a providers' perspective (Muheki et al 2004). It was found that the cost per malaria out patient visit was USD 9.77 when using SP and USD 17.38 for AL. Further, using a decision tree analysis model; the average cost per life saved was almost 9 times lower for AL (USD 18) than SP (USD 158).

Goodman et al (1999) conducted a modelling of the cost effectiveness of malaria control interventions based on a hypothetical setting. They found that the cost per DALY averted was USD 19–85 for ITNs, USD 32-58 for IRS conducted twice a year, USD 3-12 for children chemoprophylaxis, USD 4-29 for IPT in pregnancy and USD 1–8 for improved casemanagement.

In Thailand, Kamolratanakul et al (2001) compared the cost effectiveness of malaria prevention (ITNs and DDT) with surveillance in a malaria endemic area. The cost of preventing a case of malaria using ITNs was found to be USD1.54, whereas that of DDT was found to be USD1.87 per case prevented. However, when compared to control areas (where only malaria surveillance was being conducted), the prevention methods (DDT

and ITN) were more cost-effective since surveillance attracted a cost of USD2.50 per case prevented. Based on these results, malaria prevention is more cost-effective than surveillance in malaria endemic areas.

Goodman and Mills (1999) conducted an extensive review of 14 studies, which were addressing the cost effectiveness of malaria control interventions. Among the findings, it was observed that improving treatment was highly cost effective. These observations may be attributed to the preventive and curative effects of treatment. In curing the patient, morbidity is reduced (and finally mortality is prevented) and hence increases the number of cases successfully treated. But also the treatment given to the patient reduces parasite pool available for transmission to other uninfected individuals.

Rajab et al (2005) conducted cost effectiveness evaluation of pre-transfusion screening of donor blood when compared to antimalrial prophylaxis of recipients. The study was conducted in both low and high transmission areas. The outcome measure was the prevalence of malaria in donor units. It was found that pre-transfusion screening was more cost effective than prophylaxis with SP. The former had a cost of USD 0.03 per case prevented, whereas prophylaxis costs per case prevented were USD 0.69 for children and USD 1.4 for adults. However, using ACT for prophylaxis instead of SP increased the cost of preventing malaria to about USD 7.79 for adults and USD 5.84 for children. Screening blood units for malaria prevented the disease in the recipient at a far much lower cost than prophylaxis and much more if the drug of choice was ACTs.

In Guinea, Jha et al (1998) conducted a cost-effectiveness evaluation of forty health interventions from a provider's perspective. These interventions included prevention and treatment in primary and secondary care. The final outcome measure was life year saved . They found no systematic difference in costs by level of care. Among the interventions evaluated, IMCI for pneumonia, malaria and diarrhoea (proxy for clinical diagnosis of malaria) had a cost effectiveness of USD 8 per life year saved. Treating paediatric malaria was USD 13/life year saved and outreach programmes for ITNs were found to be USD43/life year saved. From these results, it can be seen that IMCI malaria diagnosis

was more cost effective than using ITNs in this context. They suggested an increase in government expenditure on health if health objectives were to be achieved. However comparing these results to other settings is difficult due to the use of different outcome measures.

Rolland et al (2006) carried out a study to evaluate the cost effectiveness of RDTs (Paracheck Pf) in comparison with presumptive treatment (clinical diagnosis). They used a hypothetical epidemic setting with a cohort of 10,000 febrile patients in a month. The treatment options were either Artesunate-amodiaquine (AS+AQ) or AL and three malaria prevalence levels were assumed (25%, 50% and 75%). The main outcome measure was incremental cost per false positive averted, and the secondary outcome measure was cost per true malaria case detected. The cost per true malaria case detected was found to be similar with either treatment options and at all levels of prevalence. RDTs however, were found to be more cost effective at reducing false positives in the AL treatment option (at prevalence less than 75%). But it was less effective in the AS+AQ option at all the three prevalence levels. The RDT strategy was found to have a positive incremental cost at a prevalence of 21% or higher for artesuante amodiaquine and 55% or higher for AL. However, this threshold increased to 58% and 70% respectively if an incremental cost of €1 per false positive averted was tolerated. These findings suggest that the cost effectiveness of a diagnostic strategy would be affected by malaria prevalence, the cost of the drug and the cost of the diagnostic strategy. As reported elsewhere (Lee et al 2002) the usefulness of new diagnostic technologies will depend on the cost, ease of use, specificity and sensitivity, time, purpose and setting.

However, researchers have expressed concern on the lack of consistency in methods and outcomes used in cost effectiveness analysis (Goodman et al 1999). This tends to limit the external validity of study findings. They have also observed that many interventions suffer from a lack of information on costs and effects. It is therefore difficult to compare results from different studies and across countries. Furthermore, Goodman et al (1999) have also argued that factors such as disease transmission patterns, price of commodities, infrastructure and behaviour issues have an impact on the cost effectiveness of an

intervention. They also pointed out that even though an intervention is proved to be cost effective, the operational and financial feasibility might affect its implementation.

3.6 Summary of the Evidence

It is evident from the literature that an enormous body of information exists on malaria in general. This is because malaria has continued to be a priority public health problem due to failures of eradication campaigns, its complexity and high control costs. The level of poverty in the regions where the disease is prevalent exacerbates the situation.

Malaria diagnosis still remains a challenge under current health system structures. History shows a heavy reliance on microscopy in health facilities and yet these services are unavailable to most people who need them. The inputs required for setting up a functional malaria laboratory represent a considerable financial burden. New technologies to complement microscopy services have been developed. However, these are met with issues of cost, accuracy and malaria endemicity. Clinical diagnosis of malaria, though widely practised, has led to overestimation of the disease burden and is costing health systems potentially avoidable drug costs. The consequent result of this practice is poor patient management.

Despite the relatively wide range of studies on economic evaluations in malaria, those specifically addressing malaria diagnosis are rare. In the case of Zambia, no such studies were available. This gap in information needs to be addressed seeing that the role of economics in malaria is vital. More especially that policy decision-making needs to be based on evidence. Table 3.3 summarises the evidence on the sensitivity and specificity of each of the three diagnostic strategies. This particular evidence was selected to represent the values, which will be used in the analysis of this study. The sensitivity and specificity was chosen from settings similar to the Zambian context in terms of type of diagnosis strategy and the level of malaria transmission. These studies were further considered because expert microscopy was used as the gold standard. The studies on clinical diagnosis in Ethiopia used both low and high transmission seasons, hence the two

different sets of findings. Studies, which compare basic microscopy tests to expert microscopy, are rare and so only one could be accessed (Colin et al 2002). For the RDT strategy, the studies specifically using Paracheck Pf were selected since this is the type of RDT, is currently in use in Zambia.

Table 3.3 Summary of Reported Sensitivity and Specificity of Malaria Diagnosis Strategies

Diagnosis Strategy	Sensitivity %	Specificity %	Sample	Source
Clinical	100	63	438	Hozhabri et al 2002, Pakistan
	93	15.5	395	Tarimo et al 2001, Tanzania
	83	75	1245	Muhe et al 1999, Ethiopia
	51	60	1245	Muhe et al 1999, Ethiopia
	80	32.9	1210	Ndhlovu et al 2004, Zambia
Microscopy	91	71	204	Colin et al 2002, Indonesia
RDT	92.6	98.6	443	Mendiratta et al 2006, India
	97	88	742	Guthman et al 2002, Uganda

CHAPTER FOUR

3.0 METHODOLOGY

4.1 Theoretical Background on Economic Evaluation

Economic evaluation has been defined as *"the comparative analysis of alternative courses of action in terms of both their costs and consequences."(Drummond et al 1987).* Economic evaluation has gained considerable attention due to the scarcity of resources for health care (Evans and Hurley 1995). There are never enough resources to cater for the growing health needs of a population, which are further increased by technological development in the medical field. Economic evaluation use standardised methods to assess the relationship between resources for programmes and their outcome. Thus, economic evaluation in health care constitutes a relevant input in the policy process in terms of the efficiency implications of alternative health programmes.

Efficiency in health care is used to determine how the given resources (inputs) are utilised to produce better health (output). There are two broad terms, which are used to define efficiency: *technical* and *allocative* efficiency. *Technical efficiency* determines whether the available resources are being used to maximise the desired outcomes (Palmer and Torgerson 1999). For example, if two diagnostic strategies A and B are compared, and it is found that B costs less per case correctly diagnosed than A, then B is said to be technically efficient. Thus measuring technical efficiency is applied to a situation where the programme of interest is already defined, but there is a need to determine how best to implement the programme. On the other hand, *allocative efficiency* considers the efficient allocation of resources across different interventions. Thus a programme is allocatively efficient if resources are allocated *"to maximise the welfare of the community"* (Drummond 1991).

In economical terms, the term cost is defined as *"the value of resources used to produce something"* (Creese and Parker 1994). The costs can be measured from two different perspectives: The *societal perspective* and the *provider perspective*. The societal perspective takes into consideration all the direct and indirect costs (including intangible

costs) whereas the provider perspective only considers the direct costs to the programme (Schmid 1995). The costing perspective will determine which costs to include or exclude and how to further evaluate the costs (Luce and Elixhauser 1990). Costing involves a systematic identification, measurement and valuation of various resources for the programme under consideration. These resources can further be grouped by level of in put as *capital* or *recurrent* costs. Capital costs refer to resources, which last more than one year while recurrent resources last less than one year and are frequently purchased (Creese and Parker 1994).

Outcome measures are concerned with the output of the intervention. *Intermediate* or *final* outcome measures can be used. Intermediate outcomes relate to those outcomes, which form part of the process that leads to improving health but are not in themselves, the final outcome (Evans and Hurley 1995). Examples of intermediate outcome measures include number of cases detected, number of ITNs distributed, number of patients treated, etc. Final outcomes measures on the other hand relate to the *"final improvement in health"* (Evans and Hurley 1995). These include indicators such as lives saved, deaths averted, DALYs prevented, Health Year Equivalent (HYE), or Quality adjusted life years (QALYs). HYEs, QALYs and DALYs are generic measures of outcome that combine life expectancy and quality of life in only one indicator. Generic measures of outcome allow direct comparisons to be made among different conditions or healthcare programmes.

There are four main types of economic evaluation namely: Cost minimisation analysis (CMA), cost effectiveness analysis (CEA), cost utility analysis (CUA) and cost benefit analysis (CBA). All these methods use cost in monetary terms, the main difference lies in the approach to assess the outcomes. CMA and CEA use natural outcome measures which are disease specific while CUA uses generic natural outcome measures such as DALYs , QALYs, HYEs and CBA measures outcomes in monetary terms (Drummond et al 1987). CMA, CEA measure technical efficiency while CUA and CBA are concerned with allocative efficiency.

It is important to note that in economic evaluation, there has to be at least two interventions to be compared in terms of their inputs and outputs. These variables (inputs and outputs) can be measured in natural and monetary units depending on the form of evaluation.

Some common challenges in economic evaluations have been identified. These include methodological heterogeneity, lack of credible data for estimates of effectiveness (Hutubessy et al 2003) and where such data exists usually its from a trial setting which differs significantly from actual field setting (Drummond 1992). Differences in methods and study populations affect the extent to which findings of one study can be generalised. This is further compounded by differences in the costs of interventions in different settings (Briggs et al 1994). Nevertheless, these uncertainties in economic evaluation can be dealt with through sensitivity analysis. Sensitivity analysis explores how changes in different assumptions and specific parameters impact on the baseline results (see section 4.9 below).

To overcome some of these challenges just described above, a comprehensive economic evaluation is recommended. In an economic evaluation, the recommendation of an intervention will depend on the quality of the data used and the accuracy in the definition of various interactions. The latter can be health system and epidemiology related. The basic principles on how to conduct an economic evaluation as outlined in Drummonds et al (1987) are:

The question under consideration needs to be specific as to what interventions are being compared and the possible outcomes. For example are bed nets more cost effective than IRS in preventing malaria cases? The alternatives to be evaluated need to be comprehensively described. This will favour potential applicability in other settings. The evidence on programme effectives needs to be demonstrated; this implies that sample sizes, observation methods and analysis of the effectiveness need to be clearly

established. All relevant costs and consequences (according to the study perspective) need to be identified, measured and properly valued. In this stage, it is key to use the economic concept of *cost*. Costs and consequences need to be adjusted by differential timing by discounting; this process is grounded in the principle of time preference. After the average cost per outcome is analysed, incremental costs and consequences need to be analysed. This allows measuring the additional costs required to produce additional outcomes. Sensitivity analysis is then performed on major variables to show changes in assumptions and parameters affect the results. Finally, the feasibility in terms of financial, logistics and programme design is discussed to guide policy makers with a broad view of underlying factors.

These steps are useful in guiding researchers on how best to conduct these evaluations and allow readers to assess the validity of their findings. Further it offers an opportunity for others to either adapt the findings or replicate the study in their specific context.

4.2.0 Study Design

4.2.1 Type of Economic Evaluation

The study is a cost effectiveness evaluation of the malaria diagnosis alternatives in health facilities in Zambia. This study is concerned with technical efficiency rather than allocative efficiency. That is to say, malaria is already a health priority in Zambia. Therefore, this research aims to answer the question: Which is the most cost effective method to diagnose malaria in outpatient facilities in Zambia? There are three available options for malaria diagnosis (clinical, microscopy and RDTs). These strategies have different capacities to correctly diagnose malaria cases as well as different costs. The outcome measure being used "the proportion of cases correctly diagnosed" is an intermediate one, which cannot be used either for cost benefit or cost utility analysis, before converting it into final outcome measure.

4.2.2 Description of Interventions Under Comparison

The conceptual framework of malaria diagnosis in Zambia (as shown figure 4.1 below) presents no major departure from what is known in the literature. The strategies available for malaria diagnosis include: clinical, microscopy and RDTs.

4.2.2.1 Clinical Diagnosis of Malaria

Firstly, when a patient arrives at the out patient department (ODP), the first point of contact is usually a nurse or a clinical officer (or a community health worker at some rural health centres and health posts). These are frontline health workers who have the capacity to screen patients and provide the necessary health services. In the case of a suspected malaria visit, a patient history of symptoms will be taken to ascertain the reason for the visit. The minimal requirements for this strategy of diagnosis are simply a thermometer (for measurement of axillary temperature) and a stethoscope where applicable. If temperature is above or equal to 37.5^{o}C or where a history of fever exists and malaria is suspected, treatment is commenced and the patient returns home. Thus it is possible for a trained health worker to exclude fevers from malaria based on signs and symptoms the patient presents with. This allows the health worker to manage the case as non-malaria. Thus, it is possible to have cases found negative for malaria after clinical diagnosis.

4.2.2.2 Microscopy Diagnosis of Malaria

Where microscopy facilities were available, a clinical officer, nurse or a Commissioned Daily Employee (CDE) initially assessed patients. If malaria is suspected, the patient is sent to the laboratory for malaria investigation. The laboratory facilities are usually located within the clinic complex but in a different room or wing. At the laboratory, the laboratory technician or microscopists analyses the patients' blood sample for malaria

infection. Once the laboratory investigation is complete, the results are recorded in the patients file and the patient is instructed to return to the screening room with the laboratory results.

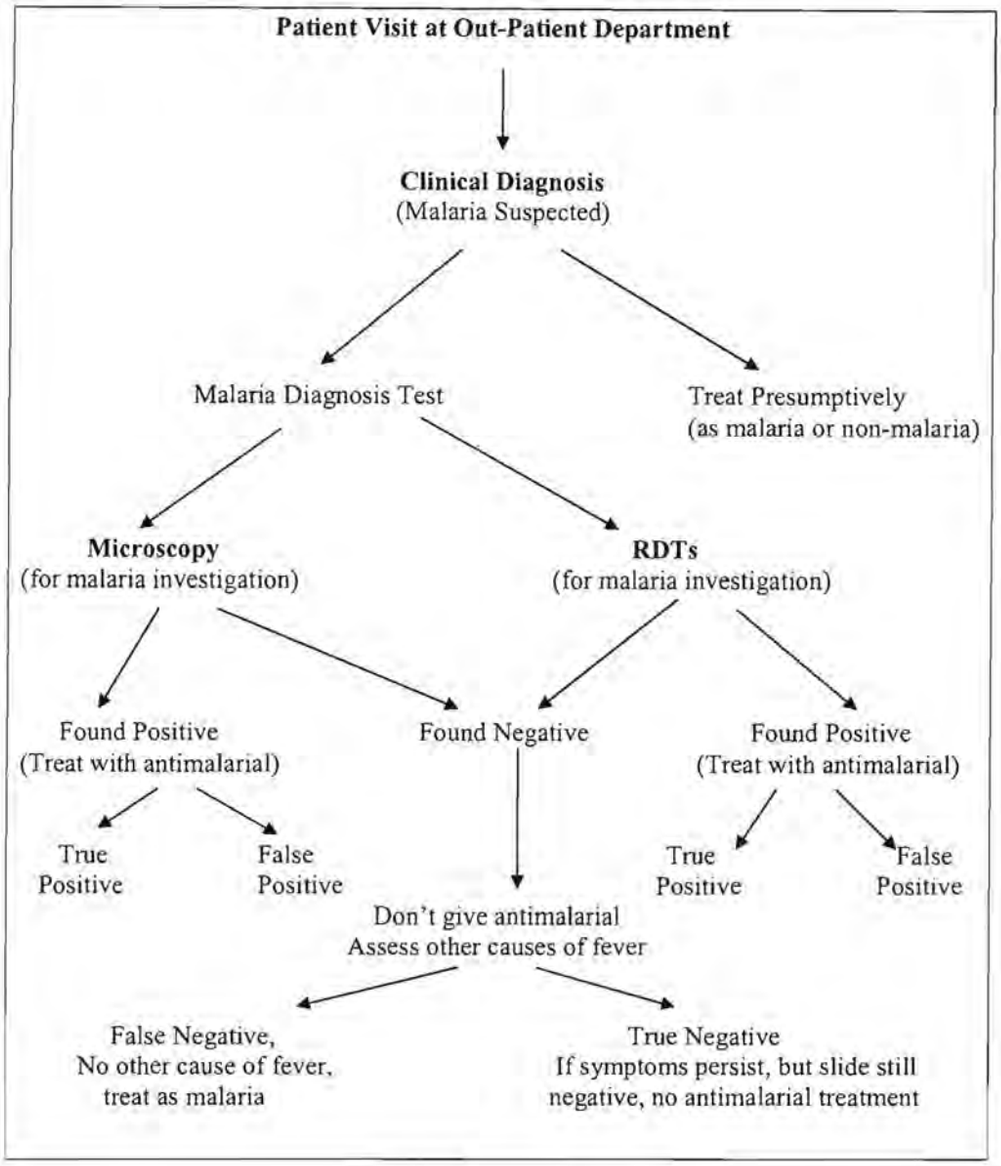
The clinician then is supposed to prescribe antimalarial treatment based on the laboratory result and the clinical presentation of the patient at that time. The inputs required for one patient to be microscopically examined for malaria parasites include: 1 clinical officer or nurse (3 – 15 minutes per patient), 1 trained microscopist or laboratory technician, laboratory space, a functional microscope, reagents, electricity supply, water supply and other consumables such as lancets, blood slides. Microscopy diagnosis results could be obtained after at least 30 minutes.

4.2.2.3 RDT Diagnosis of Malaria

In the case of facilities with RDTs, the assessment of the patient is performed by either of the available health workers as mentioned above. Once malaria is suspected, parasitological confirmation of malaria infection is performed with an RDT. Depending on the results, the clinician may then prescribe an antimalarial. It should be noted here that the screening health worker performs both the clinical assessment and RDT. This is unlike in microscopy facilities where laboratory personnel are involved in the diagnosis of malaria. The minimum requirements for this diagnostic strategy are:

1 Paracheck Pf kit (which contains a test dip stick, desiccant, sample applicator, buffer solution and collection capillary tubes) and 1 clinical officer or nurse (or CHW in some rural areas) with minimum orientation on how to use the RDT. Lancets, methylated spirit and cotton wool were some of the supplies needed but did not come with the kit; they need to be bought separately.

Figure 4.1 Conceptual Framework of Malaria Diagnosis in Zambia



Among the three diagnostic strategies, clinical diagnosis is widely used, followed by microscopy and least of all RDTs (recently introduced). Microscopy centres are found mainly in major health centres such as tertiary hospitals, district level hospitals and a

small proportion of urban health centres. However, effective treatment in form of ACT (AL) is available countrywide. This treatment is more expensive than previously used CQ or SP. Guidelines for malaria diagnosis and treatment are available and are supposed to be the guiding principle in malaria case management. To ensure adherence to these guidelines, provincial health officers in each region have the mandate to carry out performance assessments in order to monitor health worker practices. In-service training and orientations are held from time to time to help sustain good clinical practice. A few health workers (33%) have also been trained in IMCI.

4.3 Study Populations and Sample Size

The analysis included all malaria related visits (suspected or confirmed), which occurred from March to November 2005 in 12 facilities in the four study districts. The 8-month study period was used because that was the available time frame for data collection in the districts under financial sustainability study (see section 4.4 below). This period captured both the low and high transmission seasons of malaria. Patients were stratified according to age, month of attendance and the diagnostic strategy used on the day of their consultation. There were no exclusions by age, sex and pregnancy status. In this study the term malaria may be used interchangeably when referring to either uncomplicated or severe malaria (unless explicitly stated otherwise).

4.4 Study Sites

The study was undertaken in four districts namely Chingola (Copperbelt Province), Kabwe (Central Province), Kalomo (Southern Province) and Chongwe (Lusaka Province). Malaria is meso to hyper endemic in these districts (National Malaria Control Centre 2001). In each of these districts, three facilities were used to collect data for the study, bringing the total of facilities sampled to 12. Table 4.1 below summarises the major characteristics of the district where the study took place. These sites are also part of

the sentinel sites surveillance system for malaria so the research findings will be representative of the various malaria epidemiological zones currently in Zambia.

Table 4.1 Characteristics of Study Districts

District	Chongwe	Chingola	Kabwe	Kalomo
Province	Lusaka	Copperbelt	Central	Southern
Setting	Rural	Urban	Urban	Rural
Population**	157,664	196,685	196,828	181,379
Total number of health facilities***	26	10	23	24
Malaria Incidence/1000 population ****	129.8	56.57	111.45	80.76
Number of health facilities with microscopy services*	2	4	5	2
Number of facilities with trained laboratory technicians*	2	4	4	1
Number of facilities using RDTs*	1	1	2	4

Sources:*NMCC 2005, **DHS 2001-2002, ***CBOH 2002, ****HMIS 2004 (Malaria incidence refers to the number of new malaria episodes per thousand population)

The districts and their respective facilities were purposively chosen because; they were part of the larger study collecting information on the "financial sustainability plan (FSP)" for scaling up malaria control activities. The FSP study is being developed by NMCC based on the recommendations of the MOH to identify resources needed and financing gaps for the malaria strategic plan to be implemented. This provided the means of collecting quality and reliable data from these facility registers under routine conditions.

In the context of the FSP study, 3 facilities in each of the 6 districts were allocated to pilot one of each of the malaria diagnostic approaches: microscopy, clinical and rapid

diagnostic tests. This diagnostic model was being piloted in these sites and not in the entire country. All the patients suspected of malaria were being recorded in the facility's outpatient malaria registers and received confirmatory diagnosis based on the allocated method in that facility. In all the six districts and country wide, AL was being used as first line treatment for malaria. However, due to resource constraints, data on costs, diagnosis and treatment were collected in four out of the six districts. The summary of diagnostic strategies by district and facilities is shown in table 4.2 below. The defined catchment area of each facility is provided in brackets.

Table 4.2 Summary of Diagnostic Strategies by Study Site

DISTRICT	FACILITY/DAIGNOSTIC TOOL (Catchment Area)		
	Microscopy	RDT's	Clinical
Chongwe	Chongwe (15486)	Chalimbana (6596)	Chinyunyu (8281)
Kabwe	Makululu (28951)	Kawama (6886)	Natuseko (19873)
Kalomo	Namwianga (6140)	Mukwela (6140)	Kalonda (4262)
Chingola	Kabundi (31857)	Kasompe (14638)	Kalilo (5212)

4.5 Data Collection

Data was collected from primary sources as opposed to hypothetical settings, which have been widely used in economic evaluations through modelling (Hanson et al 2004, Goodman and Mills 1999). The advantage of field-based data is that it incorporates the inherent differences in practice, settings and seasons, which cannot be found in hypothetical or trial settings. This is cardinal because effectiveness data collected in trial settings has limited applicability to true population setting (Luce and Elixhauser 1990).

Morbidity data (malaria suspected outpatient visits and confirmed malaria cases) was collected retrospectively using facility registers. Patients were diagnosed in each facility based on the diagnostic strategies being used. The type of treatment administered and laboratory related characteristics were also reviewed. Cost information was obtained from facilities, central level sources and suppliers of commodities where applicable. Secondary data from published literature was used to determine the sensitivity of clinical, microscopy and RDTs in diagnosing malaria.

4.6.0 Costing Perspective and Approaches

The costs were analysed from a providers' perspective. This is because the cost of implementation of diagnostic services for malaria is largely borne by the health system. The basic health care package, which includes malaria, is provided for free especially in the lower level facilities where the data was collected (NHSP 2005). The ingredient approach combined with step-down approach to costing was used to estimate average costs per month and per year (Drummond et al 1987).

Data collection forms (Appendix I) were developed to conduct inventories on capital and recurrent costs related to malaria diagnosis. Health staffs at each of these facilities were also interviewed to obtain information on the types and estimated quantities of resources they use in daily management of malaria patients. Financial reports, cash receipts, malaria outpatient registers, district action plans, procurement units, market prices of commodities and various data sources were reviewed for measurement and valuation of the resources used. Cost data, which was obtained from facilities related to expenditures that are managed by the peripheral centres and their respective district offices.

However, full costs of salaries, unit cost of drugs and vehicles are usually purchased centrally and then distributed to the respective facilities. As such, such cost data was obtained from central level sources, expenditure reports and market prices of goods. The

cost of distribution was estimated from main government distributors and was added to the unit cost.

4.6.1 Capital Costs

Capital resources (i.e. items which have a useful life of more than one year) were annualised based on the replacement value, its estimated useful life and the official discount rate used in Zambia (5%)[4]. This allowed the equivalent annual cost of equipment to be calculated (Johns et al 2003). The useful lifespan of the different assets included can be seen in table 4.3 below. Capital costs included:

- Equipment (such as microscopes, furniture in laboratory and screening room, etc)
- Vehicles (including motor bikes or bicycles)
- Buildings (Laboratory, screening room and storage rooms)

Table 4.3 Useful Life Span of Capital Costs

Item	Useful Life (in years)
Vehicles	5
Motorbike	5
Bicycle	3
Building	30
Microscope	30
Furniture	5
Sink	30
Stethoscope	5
Digital thermometer	3
Training	5

Source: BHCP 2005, Expert Opinion

The allocation of capital costs to malaria diagnosis was done according to the utilisation rate of malaria OPD visits (see table 4.4). However, laboratory related capital costs such as a microscope and cost of a laboratory building were allocated based on the number of

[4] MOH Planning Unit, Zambia (personal communication).

patients attending the laboratory for malaria as a proportion of laboratory visits for all other diseases.

4.6.2 Recurrent Costs

Personnel costs were measured based on number and categories of each type of staff (nurse, clinical officer, medical doctor, community health worker, etc) and their respective annual salaries. These were then allocated based on utilisation of facilities by suspected malaria patients (see table 4.4 below). The malaria cases reported for these facilities account for both confirmed and unconfirmed cases as captured by district information offices.

Table 4.4. Allocation Factors for Each Facility Based on Malaria OPD Visits.

District	Facility	Suspected Malaria OPD Visits*	All Diseases OPD Visits	Suspected Malaria as % of total OPD
Chingola	Kalilo	634	3093	20.5
	Kabundi	6306	27417	23.0
	Kasompe	1604	6416	25.0
Chongwe	Chinyunyu	3276	7254	45.2
	Chongwe	8847	20087	44.0
	Chalimbana	4310	10448	41.3
Kalomo	Kalonda	4176	11926	35.0
	Mukwela	3733	8647	43.2
	Namwianga	11155	42569	26.2
Kabwe	Natuseko	3950	8831	44.7
	Kawama	2753	8311	33.1
	Makululu	4147	14301	29.0

Sources: District Information Offices. * Malaria related visits regardless of diagnosis strategy and whether they turn out to be negative or positive after diagnosis.

The data presented in table 4.5 above refers to all OPD visits from January to December for 2005. On average, facilities in Chingola district recorded the lowest proportions of malaria attendance at OPD. The highest attendance was recorded by facilities in Chongwe district. All the strategies had a mixture of both low and high malaria attendance at OPD.

Some recurrent costs such as supplies, and utilities were valued using a step-down approach to costing and allocated based on facility utilisation by malaria patients. However, costs unique to malaria (such as cost of the diagnostic technique) were fully allocated as such. Further, the districts are also allowed up to 15% of their total expenditures on administration costs (or overheads). Therefore in the absence of better sources of administrative expenditures, it was assumed that on average, 15% of malaria related expenditure would be on administrative costs such as fuel, communications, cleaning materials, stationery and other utilities. For simplicity, all other recurrent costs (non-personnel or malaria specific) are termed overheads in this study.

All prices in Zambian Kwacha were converted into United States Dollars (USD) equivalent using the existing average exchange rate of **K4, 512.51 = 1USD** for the data collection period March to November 2005 (http://www.aonda.com). The unit cost per patient was then derived for each diagnostic intervention. All the costs were analysed into averages per facility and strategy.

4. 7 Outcome Measures

A diagnostic test performed on a group of patients will give two categories of results: positive (those found with the condition of interest) and negative (those found not to have the condition of interest). However, since tests are not 100% accurate, an accepted gold standard is used as a comparator in order to evaluate how effective a test is at correctly diagnosing the condition of interest. When comparisons with the gold standard are made,

the test results are then summarised into four categories: True positives, false positives, true negatives and false negatives (as shown in table 4.5 below). Thus in this study, malaria diagnosis accuracy of each technique was evaluated by its ability to increase cases correctly diagnosed (true positives and true negatives) and the ability to decrease cases incorrectly diagnosed (false positives and false negatives). These were calculated from the total number of patients screened, the screening results, the underlying malaria prevalence and sensitivity of the diagnostic strategy used. Table 4.5 below shows the '2 x 2 Table' (which is based on Bayesian theory applied on screening methodology) used to carry out these calculations.

Table 4.5 '2 x 2 Table' for Assessing Sensitivity and Specificity

		True Malaria Prevalence	
		Positive	Negative
Diagnostic Test Results	Positive	True Positive	False Positive
	Negative	False Negative	True Negative
Total		True Positive + False Negative	False Positive + True Negative

The main outcome measure was the number and proportion of malaria cases correctly diagnosed by each diagnostic strategy. To estimate the number of cases correctly diagnosed by each diagnosis strategy, evidence from the literature (see table 3.3 in section 3.7) was weighted up according to sample size and relevance for the Zambian setting. For the purpose of this study, sensitivity was used as the input variable, whereas specificity was an output variable. This is because sensitivity and specificity vary with prevalence, and the districts under study had varying underlying prevalence as shown in table 4.6 below. For clinical diagnosis, the sensitivity for two sites (Kalilo and Kalonda) was assumed at 100%, because almost all the suspected malaria visits were classified as

positive for malaria. For the remaining two clinical sites (Chinyunyu and Natuseko), which at least reported on some negative cases, the average sensitivity was assumed at about 90%. These figures were similar to sensitivity analysis from literature (Hozhabri et al 2002, Tarimo et al 2001).

Microscopy is assumed to be the gold standard only under ideal conditions. However, routine microscopy in itself has been found to have sensitivity of 91% and specificity of 71% (Colin et al 2002) when compared to expert microscopy. Therefore, when determining cases correctly diagnosed, the sensitivity of microscopy evaluated was based on the trial results of Colin et al (2002).

For RDT tests, the weighted average of the sensitivity was calculated from studies that used Paracheck Pf brand and performed field evaluations by comparing RDT to expert microscopy (Guthman et al 2002, Mendiratta et al 2006). The sample size of each study determined the weight used in the calculation of the average sensitivity. The two studies were selected based on clinical and methodological similarities. In this way, it was hoped that statistical heterogeneity would be reduced. The weighted average sensitivity for RDT was 95.36%.

The underlying prevalence in the districts was obtained from survey data conducted by the NMCC. These surveys are conducted as part of the malaria information systems monitoring system and the RBM surveys. The surveys use standardised methods and sample sizes. An important aspect of these surveys is that they incorporate the 2-9 years who are the standard group for estimating malaria parasite prevalence (NMCC RBM Survey 2005 Report). In the case of Chongwe, Kabwe and Chingola, the prevalence figures were obtained from the 2005 parasitological surveys, whereas for Kalomo, the 2004 figure was used in the absence of any latest estimates. The prevalence for each district was estimated to be 22.0% (Chongwe), 10.6% (Kabwe), 18.8% (Chingola) and 26.3% (Kalomo). These prevalence values are assumed to approximate the true annual prevalence of malaria among patients suspected of malaria seeking care at the facility.

Thus based on the sensitivity of each strategy and the underlying prevalence in each district, the following equations (derived from Bayesian theory) were used to estimate true positives, false positives, true negatives and false negatives and consequently the total negative and positive:

1. True positives = prior prevalence * visits * sensitivity
2. False positives = found positive - true positives
3. False negatives = (prior prevalence * total visits) - true positives
4. True negatives = found negative – false negatives
5. Cases correctly diagnosed = true positives + true negatives
6. Accuracy = number of cases correctly diagnosed/total visits.

After obtaining the main results, other variables of the tests were estimated such as specificity and likelihood ratios. Likelihood ratios measure the probability that a given test result (positive or negative) would be expected in a patient with the condition of interest compared with the probability that the same result would be expected in a patient without the target disorder (www.cebm.net/likelihood-ratios.asp). Thus;

7. Specificity = true negative / (false positive + true negative)
8. Likelihood ratio positive = sensitivity/(1-specificity)
9. Likelihood ratio negative = (1-sensitivity)/specificity

A diagnostic test translates a pre-test probability (prior prevalence) of a condition in the population into a post-test probability on an individual patient. The direction and strength of the post-test probability depends on the sensitivity and specificity of the test. Post- test probability was estimated by applying the prior prevalence and likelihood ratios to the standard nomogram developed by Fagan (1995).

4.8 Average Cost Effectiveness and Incremental Cost Effectiveness Analysis

After establishing the costs and consequences of each alternative, the average cost per case diagnosed as well as the average cost per case correctly diagnosed were calculated for each strategy. Average costs were calculated with and without treatment costs. However, the relevant cost effectiveness ratio has been defined as the average cost per case correctly diagnosed and treated, as follows:

1. Cost per case correctly diagnosed (CCD) = $[\mathbf{C_d + C_t}] / \mathbf{CCD}$. Where,

   C_d = Cost of diagnosis

   C_t = Cost of all treatment

   CCD = Number of cases correctly diagnosed.

2. The incremental cost per additional case correctly diagnosed was calculated based on the changes in the costs and effects of moving from the strategy that costs less per patient diagnosed to the next alternative in order of the rank of costs per patient.

Thus: ICER = change in cost/ change in cases correctly diagnosed.

4.9 Sensitivity Analysis

Sensitivity analysis in economic evaluations is a way of handling uncertainties, which arises form various assumptions in the input variables for costs and effects. There are various types of uncertainties, which have been described in literature. These relate to data requirements, extrapolation, generalisability and analytic methods (Briggs et al 1994). These forms of uncertainty may impact on the validity of the estimates.

Briggs et al (1994) have outlined four major forms of sensitivity analysis. These include simple sensitivity analysis, threshold analysis, extreme scenario analysis and probabilistic analysis. In this study, simple sensitivity analysis will be used to measure uncertainty. In this study, simple (one-way) sensitivity analysis will be used on parameters such as discount rate, sensitivity value of clinical diagnosis, accuracy of diagnostic tests, personnel costs, allocation factor, and changing the unit costs of RDTs and AL. The ACER will be recalculated according to the observed treatment practices. It has been demonstrated elsewhere that some of these variables might impact on results of a study (Drummond et al 1987, Rolland et al 2006, Creese and Parker 1994). Furthermore, personnel costs were chosen as a variable for sensitivity analysis because they were a major cost component in all the facilities.

4.10 Data Entry and Analysis

The data collected for this study was entered into two software. Morbidity data was entered and analysed in STATA version 8. Cost data was entered and analysed in excel based on principles of cost analysis (Drummond et al 1987, Creese and Parker 1994) as described in section 4.6 above. The number of cases correctly diagnosed for each intervention and the proportion of false positives and false negatives were calculated from the '2x2' table using the equations already defined in section 4.7 above. The cost of treatment was estimated from the unit cost of antimalarials and the number of patients treated by each type of antimalarial. The cost of implementing the most cost effective strategy was analysed based on implementing the most cost effective method on the already existing structures and resources. Sensitivity analysis was performed on various variables as mentioned in section 4.9. Table 4.6 below summarises the various assumptions and parameters used in the analysis of costs and cases correctly diagnosed.

Table 4.6 Parameter Assumptions and Data Sources

Description	Assumption	Source
Exchange Rate (8- month average)	1USD = ZMK4512.51	http://www.aonda.com
Discount rate	5%	MOH Planning Unit
Overhead costs	15% (Of district recurrent expenditure)	District Health Office (DHO)
Personnel costs	Gross earnings (Taken from central level)	MOH/DHO
Cost of drug	AL = 2.45USD SP = 0.18 USD Quinine= 0.84 USD	NMCC, (weighted average cost per person/course including storage and distribution costs).
Cost/test	RDT = 1.50USD Microscopy = 1.00 USD	NMCC (excludes personnel and capital costs).
Laboratory utilisation	60%	Expert opinion
Sensitivity (clinical)	100%, 90%	Current study data from clinical sites and Hozhabri et al 2002, Tarimo et al 2001.
Sensitivity (microscopy)	91%	Colin et al 2002
Sensitivity (RDTs)	95.4%	Guthman et al 2002, Mendiratta et al 2006.
Prevalence (Chingola)	18.8%	NMCC 2005
Prevalence (Chongwe)	22.0%	NMCC 2005
Prevalence (Kalomo)	26.3%	NMCC 2004
Prevalence (Kabwe)	10.6%	NMCC 2005

Note: The malaria prevalence refers to the proportion of people with detectable malaria parasites in their peripheral blood, approximated from the average annual parasite prevalence surveys among the 2-9 years old in each district.

CHAPTER FIVE

5.0 RESULTS

5.1 Summaries from Morbidity Data

Between March and November 2005, more than 23,600 suspected malaria visits were made at the 12 out-patient clinics in the four districts. Of these reported attendances, 6520 (28%) were at clinical facilities. 10460 (44%) visited microscopy facilities and 6685 (28%) visits were made at the RDTs facilities. Table 5.1 shows the aggregated diagnostic results for the entire study period per each facility. The highest number of malaria related visits were recorded at Natuseko health centre (3661) in Kabwe district. On the other hand, the lowest number of malaria attendances was found at Kalilo health centre in Chingola (409). Children under five years accounted for 51.08% of all attendances.

Table 5. 1 Facility Visits and Diagnostic Results

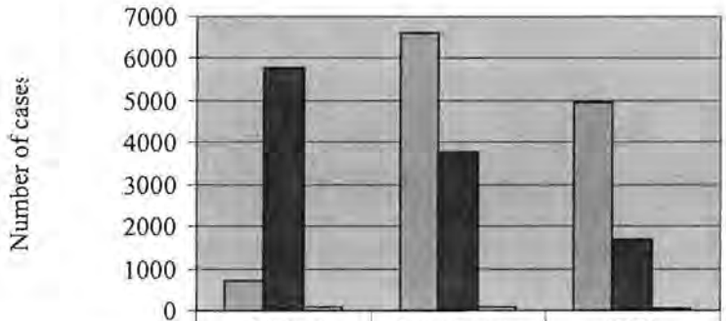
District	Health Facility	Total Visits	Diagnostic Result			% found Negative of total visits	Diagnostic Method
			Positive Uncomplicated	Positive Severe	Negative		
Chingola (Urban)	Kalilo	409	378	29	2	0.49	Clinical
	Kabundi	3084	1552	15	1517	49.19	Microscopy
	Kasompe	1187	281	6	900	75.82	RDT
Chongwe (Rural)	Chinyunyu	1430	1367	11	52	3.64	Clinical
	Chongwe	3338	1130	46	2162	64.77	Microscopy
	Chalimabana	2634	928	35	1671	63.44	RDT
Kalomo (Rural)	Kalonda	1020	1018	2	0	0.00	Clinical
	Namwianga	1975	813	0	1162	58.84	Microscopy
	Mukwela	874	263	1	610	69.79	RDT
Kabwe (Urban)	Natuseko	3661	3003	21	637	17.4	Clinical
	Makululu	2063	282	0	1781	86.33	Microscopy
	Kawama	1990	216	1	1773	89.1	RDT
TOTAL		23665	11231	167	12267	51.84	-

Overall, regardless of diagnostic strategy, 51.84% (N=12,267) were found not to have malaria. Another, 48.2% (N=11398) were found to have malaria. Of those found with

malaria, 98.5% were considered to be uncomplicated malaria and 1.5% (N=167) were diagnosed with severe malaria.

When the cases were stratified by diagnostic method, there were significant differences in the proportions of uncomplicated and negatives malaria cases, especially between clinical compared to microscopy and RDT. The overall proportion of patients found negative with clinical diagnosis was 11%, 63% with microscopy and 74% with RDT diagnosis. Severe malaria was diagnosed in 1% of those diagnosed clinically and 0.6% in both microscopically and RDT diagnosed patients respectively. Figure 5.1 shows the overall diagnosis results per diagnostic method.

Figure 5.1 Malaria Cases as Diagnosed by Each Diagnostic Strategy



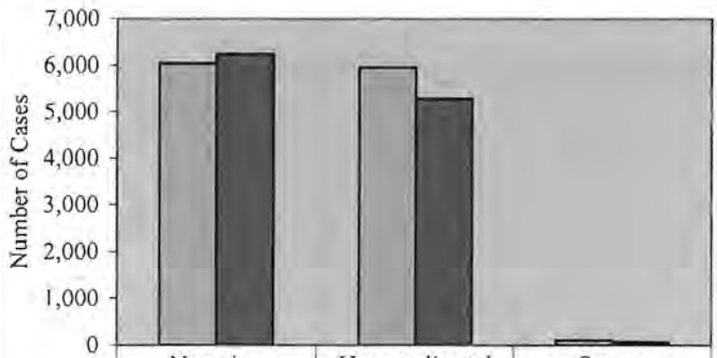
	Clinical	Microscopy	RDT
Negative	691	6622	4954
Uncomplicated	5766	3777	1688
Severe	63	61	43

The proportions of clinically diagnosed malaria were more than that diagnosed by either RDT or microscopy.

Among the total attendances recorded in all the 12 facilities, 60.5% of the severe cases and 53.0% of uncomplicated malaria were found in children under five years of age (see

figure 5.2 below). This showed that malaria was more prevalent in the under five children than in those over five years of age.

Figure 5.2 Malaria Visits Stratified by Age



	Negative	Uncomplicated	Severe
<5	6,035	5,953	101
>5	6,232	5,278	66

The proportion of suspected malaria visits in relation to the catchment population was found to differ among facilities. Facilities in Chingola district recorded the least malaria related visits, while the rest were relatively similar (see table 5.2 below).

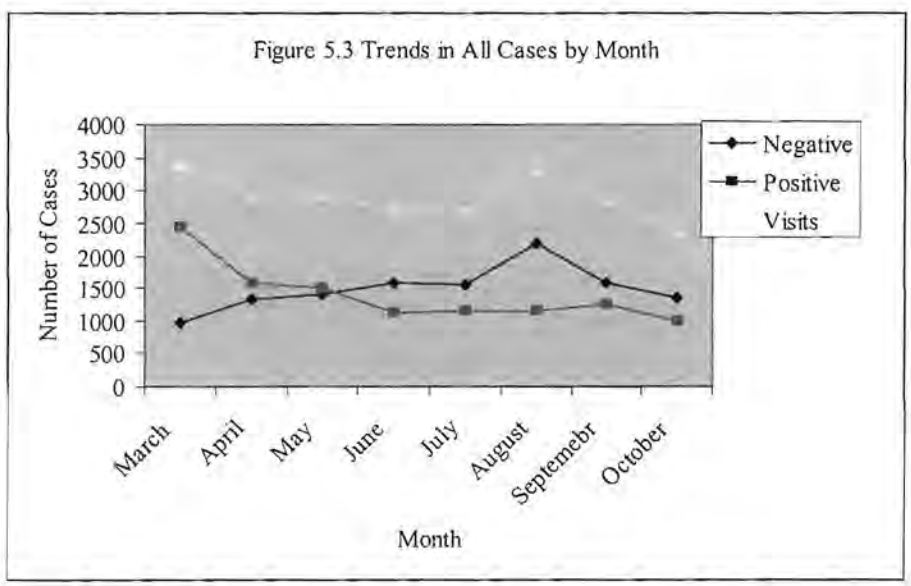
Looking at facilities individually, Chalimbana recorded the highest proportion of suspected malaria visits per catchment population (40%), while the least malaria related visits were recorded in Makululu (7%). There was no clear relationship between malaria visits per catchments population by either setting or diagnosis strategy. However, it should be noted that two facilities (Kabundi and Kasompe) in Chingola and one facility in Kabwe (Makululu) are located in areas where vector control using IRS is being conducted. This may explain the relatively lower malaria related visits per population. Additionally, these districts are also located in the urban parts of the country where malaria prevalence is expected to be relatively lower than in the rural areas.

Table 5.2 Malaria Visits per Catchment Population From March to November 2005

District	Health Facility	Catchment Population	Total Malaria Visits	% Malaria Visits	Diagnostic Method
Chingola (Urban)	Kalilo	5212	409	8	Clinical
	Kabundi	31857	3084	10	Microscopy
	Kasompe	14638	1187	8	RDT
Chongwe (Rural)	Chinyunyu	8281	1430	17	Clinical
	Chongwe	15486	3338	22	Microscopy
	Chalimabana	6596	2634	40	RDT
Kalomo (Rural)	Kalonda	4262	1020	24	Clinical
	Namwianga	6140	1975	32	Microscopy
	Mukwela	6140	874	14	RDT
Kabwe (Urban)	Natuseko	10873	3661	34	Clinical
	Makululu	28951	2063	7	Microscopy
	Kawama	6886	1990	29	RDT
TOTAL		145322	23665	16	-

The trends in the diagnosis of malaria cases for all the 12 facilities during the 8-month period are illustrated in figure 5.3 below.

Figure 5.3 Trends in All Cases by Month



As observed in figure 5.3, during March there were more cases of uncomplicated malaria (and severe malaria) found than at any other time. From June to August, the number of malaria cases reported by the facilities remained almost the same at just above 1000 cases. During the hotter and dry months beginning September and October, the cases were observed to be generally lower than during the wetter months (March and April). 'Visits' in the figure above refers to the total number of suspected malaria visits in the facilities.

In terms of seasons, November to April is referred to as the rainy season, May to August are cooler and dry months, while September and October are hot and dry months (ZDHS 2001/2002). Therefore, the rainy season months are expected to have higher malaria transmission (with the peak April/May) than both the cooler and hotter months. The negative malaria cases were lowest around March, but increased steadily until about August and started to decline thereafter.

Microscopically confirmed malaria cases showed characteristic peaks in March (48%) and May (as shown in figure 5.4 below). By June, the proportion of malaria began to reduce steadily and reached the low level in August, where only around 20% of suspected cases were confirmed as malaria.

Figure 5.4 Microscopy Diagnoses of Malaria Over Time

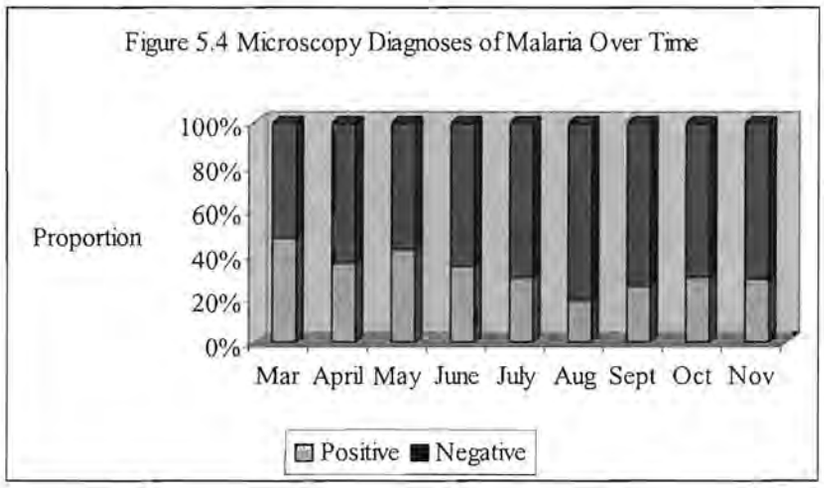
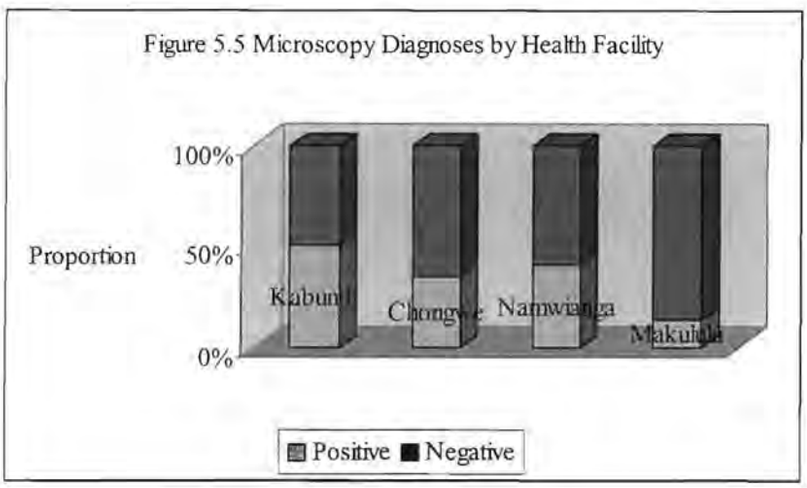
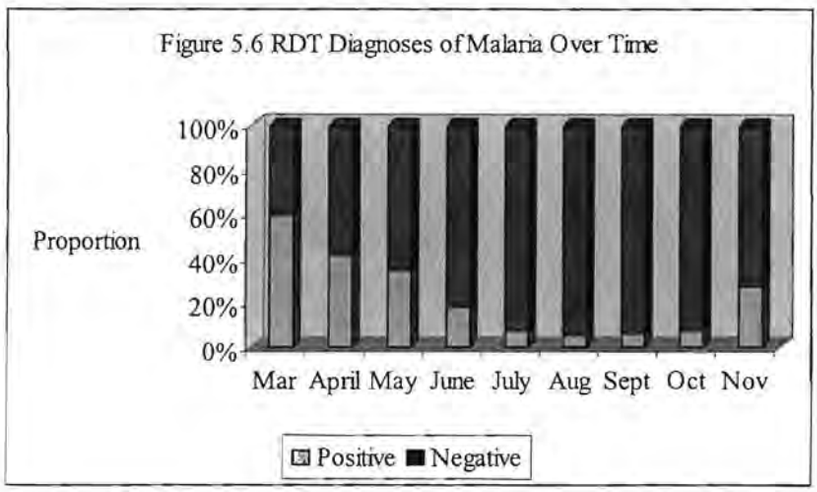


Figure 5.5 below depicts the proportion of positive cases in each study facility where microscopy was being used. Kabundi (urban) and Namwianga (rural), which, are supposed to be located in low transmission districts, recorded higher proportions of malaria positive cases. This could be because reducing transmission leads to a consequent decline in partial immunity making the population more susceptible to malaria infection (Personal Communication, Dr M. Kango, Malaria Case Management Specialist - Lusaka). Chongwe (rural) and Makululu (urban) that are high malaria transmission areas recorded lower proportions of cases. On the other hand Kabundi and Makululu are both areas in which IRS is being implemented.

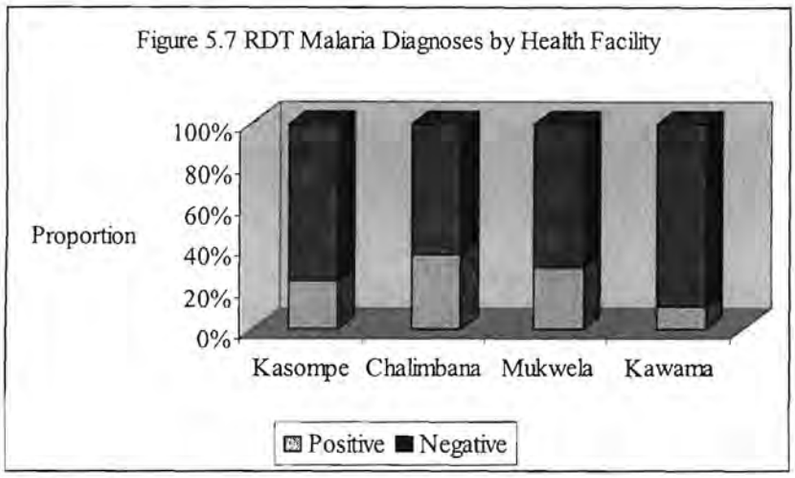


The proportion of RDT confirmed cases showed a gradual decline from a higher number of cases in March to fewer cases in the drier and cooler months (see figure 5.6 below). This is very different from microscopy trends, which showed a peak in March and May. These differences could be attributed to differences in detection capacities of RDT and microscopy. Nevertheless, the trends in the transmission patterns by RDT confirmed malaria showed the expected patterns of malaria transmission in Zambia.



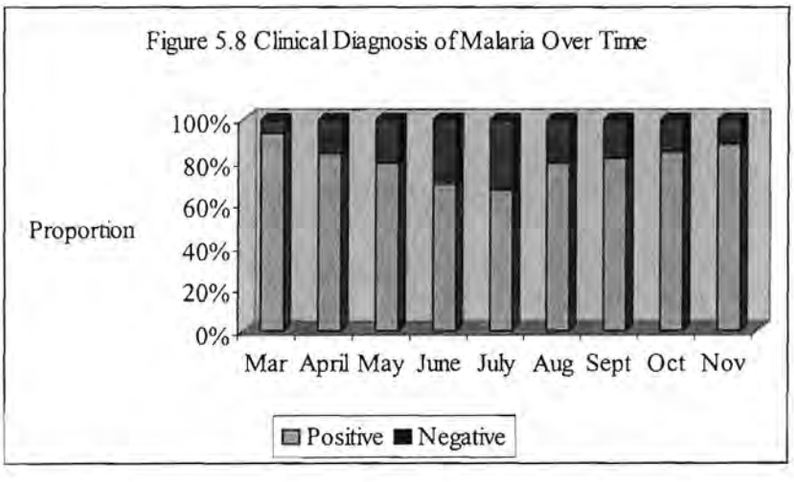
Chalimbana recorded a higher proportion of malaria than any other RDT site as shown in figure 5.7 below. Further Chalimbana also recorded the highest proportion of malaria related visits per catchment population (as shown in table 5.2 above). Kawama however, showed the lowest proportion of malaria cases despite the facility being located in an area said to be a high transmission area. One explanation could be due to the area being one of the few places in Kabwe where indoor residual spraying was conducted. However, as mentioned earlier, high transmission areas tend to have more asymptomatic cases. A note worthy feature is that Chalimbana also offers health services to some boarding schools and a teachers training college in the vicinity. So even if the catchment population was low, the actual number of patients seen from the college and boarding school might have increased the malaria related OPD visits.

Figure 5.7 RDT Malaria Diagnoses by Health Facility



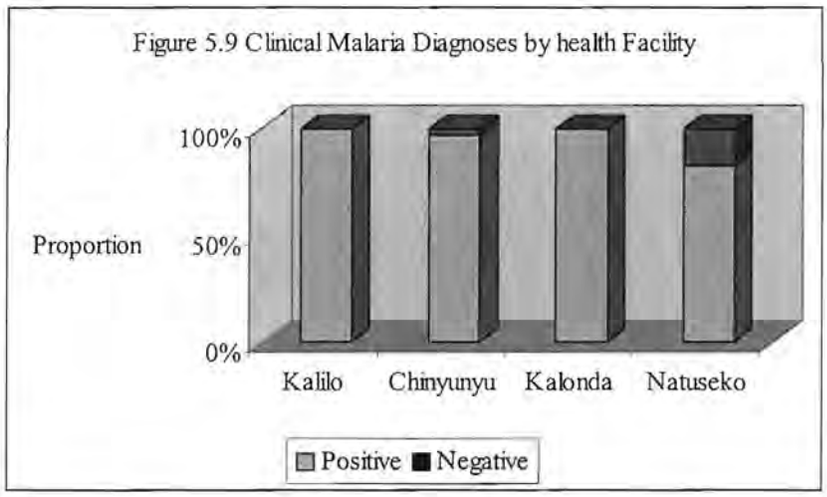
The proportion of cases clinically diagnosed as malaria presented trends, which were different from those seen in microscopy and RDT sites. The cases seem too high all through out the study period (see figure 5.8). A slight decrease was noticed between April and July. However, on average the proportion of malaria cases were higher than expected. This general trend in the clinical cases affected the overall trend in all malaria cases as shown in figure 5.3 above (all cases over time).

Figure 5.8 Clinical Diagnosis of Malaria Over Time



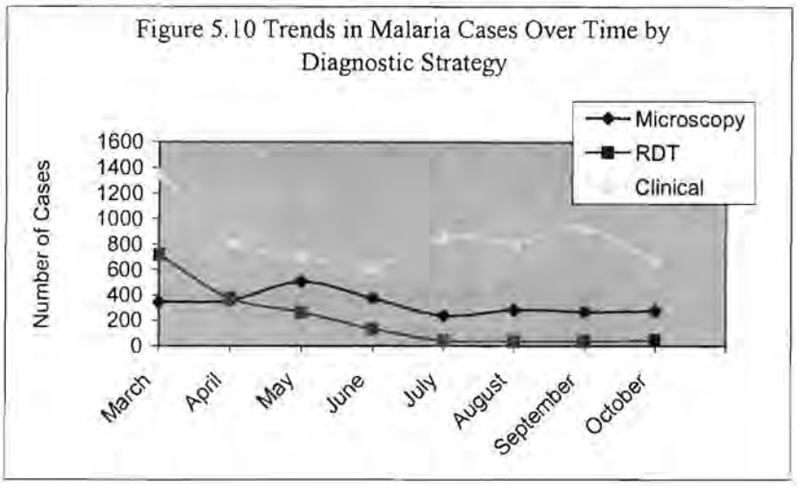
Kalilo (99.5%) and Kalonda (100%) recorded the highest proportion of clinical cases than any of the other three clinical sites (see figure 5.9 below). Natuseko recorded a relatively lower proportion of malaria found positive than other facilities. Clinical diagnosis of malaria in these facilities led to all or almost all of the cases suspected of malaria being thought to have malaria.

Figure 5.9 Clinical Malaria Diagnoses by health Facility



The trends in malaria cases over time when stratified by diagnostic strategy are presented in figure 5.10 below. RDT and microscopy showed almost similar trends with a peak in the wetter months and lesser cases in the cooler and drier months. Clinically diagnosed cases showed different trends from what is expected of malaria transmission patterns in Zambia.

Figure 5.10 Trends in Malaria Cases Over Time by Diagnostic Strategy



5.2 Number of Cases Correctly Diagnosed

The number of cases correctly diagnosed by each strategy was calculated using the '2x 2 table' shown in table 4.5 in methods section. In this section the details of these estimations are shown for each of the facilities as well as the average according to the diagnostic strategy used. Note that this is based on the assumptions on the sensitivity of each diagnostic strategy, which in turn were based on the available studies as shown in table 4.6 (methods section).

Table 5.3 Cases Correctly Diagnosed (CCD) by Clinical Strategy

	Kalilo	Kalonda	Chinyunyu	Natuseko	Total
Visits	409	1020	1430	3661	6520
Test Results					
Found Positive	407	1020	1378	3024	5829
Found negative	2	0	52	637	691
Estimations of Accuracy					
True Positive	77	268	284	348	977
False Positive	330	752	1094	2676	4852
True Negative	2	0	21	598	621
False Negative	0	0	31	39	70
CCD	79	268	305	946	1598
Accuracy %	19.3	26.3	21.3	25.8	24.5
Prior Prevalence%	18.8	26.3	22	10.6	16.1

The average accuracy (proportion of cases correctly diagnosed out of all diagnoses) of malaria diagnosis among clinically diagnosed patients was found to be 24.5%, as shown in table 5.3 above. This means that for every 10 malaria suspected patients clinically diagnosed, the number of cases correctly diagnosed would be less than 3. The highest accuracy of clinical diagnosis was found in Kalonda (26.3%) and the lowest was in Kalilo (19.3%). On average 17% of the patients clinically diagnosed to have malaria would actually have it. Conversely, about 10% of the patients who were found not to have malaria by clinical diagnosis would have had malaria (false negatives). A 'real positive' malaria case was as likely as a 'real negative' malaria case to be found positive when diagnosed clinically (Likelihood ratio=1.05).

The average accuracy of microscopy in diagnosing malaria patients was found to be about 79% (see table 5.4 below). This proportion was more than that which was observed in clinical diagnosis but less than the accuracy of RDT diagnosis of malaria. About 51% of the patients who were microscopically diagnosed to have malaria may not have had it. Similarly, around 2.8% of the patients who were diagnosed negative by microscopy technique may have had malaria.

Table 5.4 Cases Correctly Diagnosed (CCD) by Microscopy Strategy

	Kabundi	Namwianga	Chongwe	Makululu	Total
Visits	3084	1975	3338	2063	10460
Test Results					
Found Positive	1567	813	1176	282	3838
Found negative	1517	1162	2162	1781	6622
Estimations of Accuracy					
True Positive	528	472	668	199	1866
False Positive	1039	341	508	83	1972
True Negative	1465	1115	2096	1761	6437
False Negative	52	47	66	20	185
CCD	1993	1587	2764	1959	8303
Accuracy %	64.6	80.3	82.8	94.9	79.4
Prior Prevalence	18.8	26.3	22	10.6	20

As shown in table 5.4 above, the diagnostic accuracy of microscopy was highest in Makululu (94.9%) and lowest in Kabundi (64.6%). Kabwe district (Makululu health facility) uses trained malaria microscopists as opposed to the conventional laboratory technicians. These microscopists receive a short course (one month) on basic malaria microscopy and are employed on a part time basis by the district office.

Among the RDT diagnosed cases, the proportion of cases correctly diagnosed (accuracy) was found to be 91% (see table 5.5). The highest accuracy among the RDT sites was found in Kawama (98.7%), while the lowest accuracy was found in Chalimbana (83.4%). Among the patients diagnosed by RDT, 8% were wrongly diagnosed to have malaria when they probably did not have had it. This was much less than any of the proportions found in both the microscopically and the clinically diagnosed cases. The proportion of false negatives diagnosed by RDT was found to be about 1%. The variations in accuracy among the sites may be due to human errors during sample preparation and reading of results. The same brand of RDTs was used in all the facilities.

Table 5.5. Cases Correctly Diagnosed (CCD) by RDT

	Kasompe	Mukwela	Chalimbana	Kawama	Total
Visits	1187	874	2634	1990	6685
Test Results					
Found Positive	287	264	963	217	1731
Found negative	900	610	1671	1773	4954
Estimations of Accuracy					
True Positive	213	219	553	201	1186
False Positive	74	45	410	16	545
True Negative	890	599	1644	1763	4896
False Negative	10	11	27	10	58
CCD	1103	819	2197	1964	6082
Accuracy %	92.9	93.7	83.4	98.7	91
Prior Prevalence	18.8	26.3	22	10.6	18.6

The aggregated results on cases correctly diagnosed by each strategy are summarised in table 5.6 below. The table also shows the average prevalence, likelihood ratios and post-test probabilities for each strategy.

Table 5.6 Summary of Average Effectiveness of Each Strategy

Strategy	Clinical	Microscopy	RDT
Total Visits	6520	10460	6685
Test Results			
Found Positive	5829	3838	1731
Found Negative	691	6622	4954
Estimations of Accuracy			
True Positives	977	1866	1186
False Positives	4852	1972	545
True Negative	621	6237	4896
False Negative	70	186	58
Sensitivity (%)- input	93.3	90.9	95.3
Specificity (%)- output	11.3	76.5	90
Cases correctly diagnosed	1598	8303	6082
Accuracy (%)	24.5	79.4	91.0
Estimations of Reliability			
Likelihood ratio positive	1.1	3.9	9.5
Likelihood ratio negative	0.6	0.1	0.1
Positive post-test probability	17%	53%	70%
Negative post-test probability	10%	3%	2%

Clinical diagnosis of malaria was found to have very low accuracy in diagnosing malaria when compared to either microscopy or RDT methods. The proportion of false positives in clinical diagnosis was four times more than those by microscopy and nine times more than those observed by RDT strategy. As indicated in the table, the RDT diagnosis led to less false negatives (<1%), while clinical and microscopy were responsible for 1.1% and 1.8% false negatives respectively. A lower proportion of false negatives are desirable in malaria diagnosis due to the negative consequences of leaving malaria untreated.

For clinical diagnosis likelihood ratio positive indicates that a 'real positive' malaria case was as likely as a 'real negative' malaria case to be found positive when diagnosed clinically (Likelihood ratio = 1.1). On the other hand, the likelihood ratio negative indicates that a 'real negative' malaria case was 0.6 times as likely as a 'real positive' malaria case to be found negative when diagnosed clinically. Thus, with clinical diagnoses a malaria case found positive will have only 17% probability of being truly positive. The clinical diagnosis translates the pre-test to post test probability of malaria in a patient by just 1% (from 16% to 17%). This is not useful in malaria diagnosis as shown

by a positive likelihood ratio of about 1. Negative post-test probability indicates that a negative result on clinical diagnosis has a 10% chance of being a malaria case (false negative).

A positive malaria case diagnosed microscopically will have a 53% certainty that it is a true positive malaria case, while a negative result is 3% likely to be a true malaria case (false negative). Thus a negative malaria result diagnosed by microscopy would be more reliable than a positive result.

As shown in table 5.6 above, a positive malaria result on RDT has a 70% chance of being a true malaria case, while a negative result has only a 2% likelihood of being a true malaria case. Both the positive and negative likelihood ratios of the RDT test were high indicating that a malaria test result on RDT is more reliable.

5.3 Cost of Malaria Diagnosis for Each Strategy

The costs of malaria diagnosis were grouped into five main categories. These were personnel, capital costs, diagnostic technique and overheads. At this stage treatment cost had not been included. These categories were further specified for each diagnostic strategy and facility. All costs are expressed in USD. In each table the catchment area and total visits (malaria suspected) have been added so that total costs can be related to utilisation and total inputs.

Table 5.7 below shows the estimates in costs for clinical diagnosis sites. The major cost components for clinical diagnosis of malaria were personnel (83%) and overheads (13%). The later included administrative costs and utilities such as water, electricity and telephone bills. In all the four clinical sites, personnel costs were by far the highest contributor to malaria expenditure, accounting for an average of 83%. Non- laboratory related capital costs were the least contributor to clinical diagnosis of malaria. There were no other diagnostic related recurrent or capital costs in the clinical facilities.

Table 5.7 Cost Estimates for Clinical Diagnosis (in USD)

	Kalilo	Kalonda	Chinyunyu	Natuseko	Total	
a. Catchment population	5212	4262	8181	10873	28528	
b. Visits	409	1020	1430	3661	6520	
Utilisation rate (b/a)	0.08	0.24	0.17	0.34	0.23	
Costs						
Personnel	994	1,326	3,426	9,152	14,899	
Capital (Routine)	83	93	343	160	678	
Capital (Laboratory)	-	-	-	-	-	
Diagnostic Technique	-	-	-	-	-	
Overheads	149	199	514	1,425	2,287	
Total costs	**1,226**	**1,618**	**4,282**	**10,737**	**17,864**	**%**
Unit cost per type of resource						
Personnel	2.4	1.3	2.4	2.5	2.3	83%
Capital (Routine)	0.2	0.1	0.2	0.0	0.1	4%
Capital (Laboratory)	-	-	-	-	-	
Diagnostic Technique	-	-	-	-	-	
Overheads	0.4	0.2	0.4	0.4	0.4	13%
Cost per visit	**3.0**	**1.6**	**3.0**	**2.9**	**2.7**	**100%**

The average cost of clinical diagnosis of malaria was USD 2.7 per patient (ranging from USD 1.6 to USD 3) as shown in table 5.7 above. Kalonda was found to have the lowest cost per visit. However, the remaining three facilities had similar costs per patient despite having different catchment populations and utilisation rates.

As shown in table 5.8 below, personnel costs were a major cost contributor to microscopy malaria diagnosis (65%). The highest personnel related costs per visit were found in Kabundi (urban) and Chongwe (rural). These sites had more health workers than any of the other two sites and on average more than any of the clinical and RDT sites. Namwianga health centre was associated with lower costs, which can be partly explained by its highest utilisation rate and low expenditure in personnel.

Diagnostic specific costs (recurrent and capital costs) accounted for 14% the total costs as shown in table 5.8 below. Overheads expenditure was 13% of the total costs. Microscopy sites tended to have more resources than the clinical and RDT sites. This is to some extent because these facilities usually engage in the provision of more complex

interventions and serve a much larger population. However, in the light of the population size (catchment area) and utilisation, these increases in resources are more than proportional to the population they serve.

Table 5.8 Cost Estimates for Microscopy Diagnosis (in USD)

	Kabundi	Namwiang	Chongwe	Makululu	Total	
a.Catchment	31857	6140	15486	28951	82434	
b.Visits	3084	1975	3338	2063	10460	
Utilisation rate (b/a)	0.10	0.32	0.22	0.07	0.16	
Costs						
Personnel	18,946	2,977	27,095	6,328	55,347	
Capital (Routine)	1,160	1,279	4,197	501	7,136	
Capital (Laboratory)	243	256	304	251	1,054	
Diagnostic Technique	3,423	2,192	3,705	2,290	11,611	
Overheads	3,584	853	5,226	1,293	10,956	
Total Costs	**27,355**	**7,558**	**40,528**	**10,663**	**86,103**	
Unit cost per type of resource						**%**
Personnel	6.1	1.5	8.1	3.1	5.3	65%
Capital (Routine)	0.4	0.6	1.3	0.2	0.7	9%
Capital (Laboratory)	0.1	0.1	0.1	0.1	0.1	1%
Diagnostic Technique	1.1	1.1	1.1	1.1	1.1	13%
Overheads	1.2	0.4	1.6	0.6	1.0	12%
Cost per visit	**8.9**	**3.8**	**12.1**	**5.2**	**8.2**	**100%**

The overall unit cost per visit was USD 8.2 (ranging from USD 3.8 to USD 12.1). However, controlling for the extra cost of diagnosis, the average unit cost is USD 7. This demonstrates that diagnosis related cost reach up to USD 1.2 per visit. The cost per visit was highest in Chongwe (rural) and lowest in Namwianga (rural). Except from diagnosis specific costs, there were considerable variations in unit costs across the resources. However the major source of cost variation was personnel.

Table 5.9 below shows the major cost components of RDT diagnosis. Personnel costs accounted for 50% of the total costs. Kawama (urban) and Mukwela (rural) had the highest personnel costs per visit while Chalimbana showed the lowest. The extra time

required by a health worker to prepare an RDT accounted for 2% of the total costs (assuming 5 minutes per patient for preparation of RDT sample).

There were no laboratory related capital expenditure but routine capital costs accounted for about 2% of the total costs (see table 5.9). Compared to microscopy unit costs across facilities seem to be more homogeneous. For example the unit cost of routine capital costs was similar in all the four facilities. Expenditure on the diagnostic technique was found to be high at an average 33% of the total costs. Overhead costs were at 14%.

Table 5.9 Cost Estimates for RDT Diagnosis (in USD)

	Kasompe	Mukwela	Chalimbana	Kawama	Total	
a. Catchment	15638	6140	6596	6886	35260	
b. Visits	1187	874	2634	1990	6685	
Utilisation rate (b/a)	0.08	0.14	0.40	0.29	0.19	
Costs						
Diagnostic Technique	1,829	1,347	4,059	3,067	10,302	
Personnel	2,709	2,805	4,242	6,072	15828	
Personnel (extra time)	90	64	192	144	490	
Capital (Routine)	69	125	226	204	625	
Capital (Laboratory)	-	-	-	-	-	
Overheads	805	709	1,245	1,504	4,293	
Total Cost	**5,502**	**5,050**	**9,965**	**10,991**	**31,508**	
Unit cost per type of resource						**%**
Diagnostic Technique	1.5	1.5	1.5	1.5	1.5	33%
Personnel	2.3	3.2	1.6	3.1	2.4	50%
Personnel (extra time)	0.1	0.1	0.1	0.1	0.1	2%
Capital (Routine)	0.1	0.1	0.1	0.1	0.1	2%
Capital (Laboratory)	-	-	-	-	-	
Overheads	0.7	0.8	0.5	0.8	0.6	14%
Cost per visit	4.6	5.8	3.8	5.5	4.7	100%

As shown in table 5.9, the unit cost of RDT diagnosis was USD 4.7 (ranging from USD 3.8 to USD 5.8). Excluding the extra costs related to RDT diagnosis (USD 1.6) brings the unit cost to about USD 3.1. The differences in the unit cost per patient among the RDT facilities were mainly due to variations in personnel.

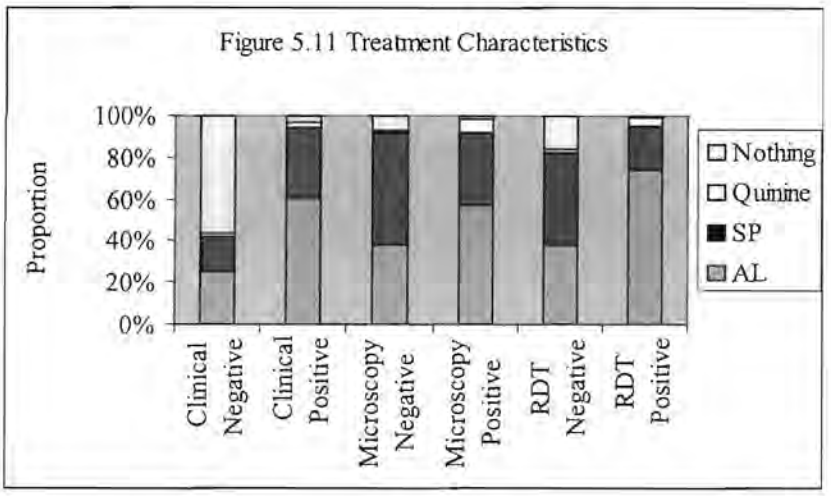
Personnel costs were clearly an important cost component among the three strategies. While clinical and RDT personnel costs were similar at about USD 2.3 – 2.4 per visit, microscopy personnel costs were found to be the highest at USD 5.3 per visit (with considerable variation across facilities). Routine capital costs were also similar for clinical and RDT strategies but for microscopy they were 7 times higher. There was no cost associated to the diagnostic technique for clinical strategy, USD 1.2 for microscopy and higher for RDT at USD 1.6. Overheads were lowest in the clinical strategy and highest in the microscopy strategy.

Overall, the unit cost per visit was USD 2.7, USD 8.2 and USD 4.7 for clinical, microscopy and RDT strategy respectively. Some of the differences in the costs may also be attributed to variations in the utilisation rates in facilities.

5.4 Treatment Characteristics

As demonstrated in this section it was established that malaria treatment patterns are not necessarily driven by diagnostic results. It was unlikely that physicians do not prescribe some malaria treatment, even if patients were considered or found negatives. Out of the 12267 malaria cases found negative, only 17% (2113) did not receive any antimalarial, while 83% (9990) did receive antimalarial treatment. There was no provision to determine what the cases found negative received when they were affected by other (non-malaria) conditions and returned to the clinic. This is because such details were not recorded in the malaria register; hence it was difficult to link them with their prior malaria visit.

Figure 5.11 Treatment Characteristics



As shown in figure 5.11 above, the chance of a patient getting any of the three types of antimalarials depended upon the malaria status and the diagnostic strategy. Negative and positive malaria cases diagnosed by clinical methods were more likely to receive AL treatment than SP. However, in the microscopy and RDT strategies, cases diagnosed to be negative for malaria, were more likely to get SP than AL. Cases diagnosed positive by microscopy and RDT, were treated with AL more than SP. Across all the three strategies Quinine was prescribed more to the cases found positive than negative. Furthermore, a case clinically diagnosed to be negative (although these were very few) had less chance of being prescribed an antimalarial than a negative case diagnosed by either microscopy or RDT.

Of all the cases visiting the facilities, 10% did not receive any treatment. Among this 10% (2422), 2113 (87%) had been diagnosed malaria negative, 309 (13%) had been found to be positive for malaria. The reason for not treating some of the cases diagnosed malaria positive was not stated. However, this may be attributed to the cases being referred for further management at the next level of health care or a lack of drugs (stock outs) at the time of the diagnosis.

5.5 Cost of Treatment by Diagnostic Strategy

The cost of antimalarial treatment was based on the number of patients treated and the type of antimalarial used. The recommended antimalarials for malaria in Zambia are AL, SP and Quinine (as described in section 2.3.2.1). In principle, healthcare workers are supposed to provide malaria treatment to those found positives (whatever the diagnostic method)

The cost on other drugs (non-antimalarial treatment) was not considered in this study because such information was not systematically recorded.

Table 5.10 below shows the estimated expenditure on antimalarial treatment in the clinical sites. "Number treated" refers to all the cases that were prescribed an antimalarial regardless of the test results (positive or negative). "Found positive" refers to the number who should have been treated if treatment were dependent upon the test result. The observed probability of being treated by SP, AL or Quinine when a case was found positive was used to estimate the cost of treating only those patients found positive.

Table 5.10 Treatment Costs for Clinical Sites (USD)

	Kalilo	Kalonda	Chinyunyu	Natuseko	Total
Visits	409	1020	1430	3661	6520
Number treated	407	1020	1351	2842	5620
Cost patients treated	614	1518	2379	4910	9422
Av. unit cost observed	0.80	1.07	1.91	1.35	1.66
Found positives	407	1020	1378	3024	5829
Cost treating found positives	614	1518	2426	4871	9429
Av. Unit cost found positive	1.51	1.49	1.76	1.61	1.62
Potential saving (%)	0%	0%	-2%	0.8%	-0.1%

As shown in table 5.10 above, clinical diagnosis did not show any potential saving in antimalarial treatment, in fact the opposite occurs. This is because apart from the fact that nearly 100% of the cases are found positive, some cases found positives had not been treated in the first place (refers to section 5.4). In Natuseko, a saving of less than 1% was observed where as in Chinyunyu 2% more was spent when only those found positive are treated as opposed to treating all the cases. The average unit cost of treatment was higher when only positives are treated as opposed to when both positives and negatives are treated. This difference in costs is related to the fact that AL, an expensive drug was more likely to be given to a positive case than SP. The average difference in the unit costs resulting from those treated and the scenario when only positives are treated was found to be small (USD 0.03).

Table 5.11 below summarises the costs of antimalarial treatment in facilities where microscopy diagnosis of malaria was available. On average 56% (USD 7,118) of antimalarial treatments given to the patients could have been avoided if only the found positive were treated. As mentioned earlier, it is clear that most of the negative malaria cases are being given antimalarials. This seems to suggest that the treatment of patients may not be guided by microscopy results. Namwianga health centre showed the lowest savings. However, this is because most of the negative cases were given the cheaper SP while AL was mostly given to the found positive. Nevertheless, the fact that negative cases were prescribed a cheaper antimalarial (SP) than more expensive (AL) shows that in some way, a diagnostic tool helped to rationalise drug use. As explained earlier, the differences in costs for the two scenarios (observed treated and only found positives treated) is due to the differential of using AL more in the positive cases and SP was used more in the negative cases. The last column of figure 5.11 shows that the difference between the unit costs for the observed and scenario treatment costs (USD 0.16) was five times higher than that which was found under clinical diagnosis.

Table 5.11 Treatment Costs for Microscopy Sites (USD)

	Kabundi	Namwianga	Chongwe	Makululu	Total
Visits	3084	1975	3338	2063	10460
Number treated	3075	1774	3325	1485	9659
Cost patients treated	2459	1901	6344	2003	12708
Av. unit cost observed	0.8	1.07	1.91	1.35	1.32
Found positives	1563	771	1175	277	3786
Cost treating found positive	1436	1523	2247	384	5590
Av unit cost	0.92	1.98	1.91	1.39	1.48
Potential saving	42%	20%	65%	81%	56%

Table 5.12 below illustrates the treatment costs for RDT sites. The RDT facilities were observed to generate similar results to microscopy. Almost 60% of unnecessary antimalarial treatment could have been avoided if health workers prescribed antimalarials only to cases they found positive. The potential savings were very low in Mukwela because most negatives were treated with SP, which is cheaper than AL. On average, the difference in the unit cost of treatment between the observed and treating only positive scenario (USD 0.44) was relatively higher than both microscopy and clinical. As shown in figure 5.11, this is attributed to the finding that in the RDT strategy, clinicians were more likely to use more AL for positive cases than either microscopy or clinical strategies.

Table 5.12 Treatment Costs for RDT Sites (USD)

	Kasompe	Mukwela	Chalimbana	Kawama	Total
Visits	1187	874	2634	1990	6685
Number treated	934	536	2484	1576	5530
Cost patients treated	1726	568	4504	1120	7918
Av. Unit cost observed	1.85	1.06	1.81	0.71	1.43
Found positives	287	261	960	213	1721
Cost treating found positive	516	483	1842	384	3226
Av unit cost found positive	1.87	1.85	1.92	1.80	1.87
Potential saving	70%	15%	59%	66%	59%

In the 8-month study period, approximately USD 11, 803 was spent on treating non-malaria cases in all the 12 facilities. However, this figure could be almost double if only the true malaria cases (true positive and false negatives) were considered (USD 22, 886). Although it was observed that malaria treatment patterns were not entirely based on the test results, these were used to some extent in microscopy and RDT facilities. For example, SP (a cheaper drug) was systematically prescribed more to cases found negative while AL (the more expensive drug) was prescribed more to cases found positive (see figure 5.11). The fact that 28% of patients in the clinical sites were treated with SP while 65% were treated with AL also demonstrates that clinicians would discriminate among patients found positive. Some of them would be considered more likely to really have malaria and hence they get AL while others would be less likely to have it and they get SP.

The overall cost of treatment per visit was estimated by dividing the total cost of treatment by total visits for each strategy. Thus, the average cost of treatment per visit was 1.44 for clinical, 1.21 for microscopy and 1.18 for RDT strategy. This showed that RDT led to about USD 0.26 less than clinical and USD 0.03 less than microscopy on drug costs per patient visit. This saving may be because in the RDT strategy, clinicians were able to target treatment better than in clinical and microscopy strategies.

5.6 Monthly Cost of False Positives and False Negatives

In this section the costs on treatment associated with the inaccuracy of the different diagnosis methods is assessed. The cost on antimalarials given to false positives was estimated using the number of false positives estimated for all the facilities and stratified by diagnostic tool. Additionally, the mean unit cost per treatment was found using the observed probabilities that a person found positive receive either drug (none, SP, AL or quinine) under each diagnosis strategy (see section 5.4). The unit costs per drugs are those described in table 4.6 (in the methods section). Thus, the total cost per false positive (TCFP) can be summarised by equation 1:

$$TCFP = FP \times \sum_{d=1}^{4} prob_{d} \times UnitCostTretament_{d} \qquad (1)$$

Where,

TCFP = Total cost of false positives

FP = Number of false positives

$Prob^{d}$ = The probability of treating a positive case with drug 'd '

$UnitCostTretament_{d}$ = Unit cost of drug 'd'

The mean cost per false positive per each diagnostic method was:

CFP (Clinical) = 0.0339*0 + 0.3401*0.18 + 0.6096*2.45 + 0.0164*0.84 = 1.57

CFP (microscopy) = 0.0195*0 + 0.3579*0.18 + 0.5784*2.45 + 0.0441*0.84 = 1.52

CFP (RDTs) = 0.0059*0 + 0.2129*0.18 + 0.7564*2.45 + 0.0248*0.84 = 1.91

Similarly the cost of false negatives was estimated using the probabilities of treating a case found negative with antimalarials as follows:

CFN (Clinical) = 0.5676*0 + 0.1675*0.18 + 0.2509*2.45 + 0.0141*0.84 = 0.66

CFN (microscopy) = 0.0728*0 + 0.5398*0.18 + 0.3771*2.45 + 0.1013*0.84 = 1.11

CFN (RDTs) = 0.1533*0 + 0.4321*0.18 + 0.3666*2.45 + 0.0480*0.84 = 1.02

Although the cost of non-antimalarial drugs would have been most appropriate to indicate the cost of false negatives, as stated earlier, the prescription of non-antimalarials drugs was not recorded. On the other hand, as demonstrated earlier even cases found negative were given antimalarials. In this case then it is expected that even if some cases were missed at diagnosis, treatment was given to them.

The total cost of false positives per month was highest in the clinical strategy and lowest in the RDT strategy as shown in table 5.13 below. These results are influenced by unit cost and number of false positive per strategy (which in turn depend upon utilisation). That is why the expected cost per person diagnosed is also included for comparison (see last column table 5.13). The unit cost per false positive visit was highest in the clinical strategy (USD 1.17) and lowest in the RDT strategy (USD 0.16).

Table 5.13 Cost of False Positives and False Negatives by Diagnostic Strategy (USD)

	Number (a)	Probability of this diagnosis (b)	Unit Cost/ person with this diagnosis	Cost 8-Month (a)x(c)	Cost per month	Expected cost per visit (b)x(c)
False positives						
Clinical	4875	0.75	1.57	7654	957	1.17
Microscopy	1972	0.19	1.52	2997	375	0.29
RDT	546	0.08	1.91	1043	130	0.16
False negatives						
Clinical	93	0.014	0.66	61	8	0.01
Microscopy	185	0.018	1.11	205	26	0.02
RDT	58	0.01	1.02	59	7	0.01

The cost of false negatives was almost similar among the three strategies as shown in table 5.13 above. This is because false negatives are mostly treated with SP. However, the overall cost of false positive (misdiagnosis) for the 8 months period (in 12 facilities) was estimated to be USD 11, 694. Nevertheless, in other contexts, where health workers treat based on the diagnostic result, it would be important to evaluate the other (non-malaria) costs of false negatives.

5.7 Unit Costs, Cost Effectiveness and Incremental Cost-effectiveness Ratios

In order to give a comprehensive overview of the cost and outcomes, various unit costs were calculated per strategy. This is mainly due to the fact that, as demonstrated in section 5.5, the actual treatment costs are not in line with the malaria test results. Therefore, the cost per case diagnosed (total cost of diagnosis/visits) was estimated using the total cost while excluding treatment costs. Then later, when estimating the cost per case correctly diagnosed, treatment costs were included in the total costs. In order to show the difference between treating all (as observed in the study) and treating only cases that are found positive by the diagnostic strategy, the treatment costs were split into treatment costs 'All' (d) and treatment costs 'only positive treated' (e). Thus the treatment costs, total costs and ACER was calculated separately for these two treatment scenarios.

Table 5.14 below shows the costs and cost effectiveness ratios for the three strategies. The average cost per patient undergoing malaria diagnosis was found to be lowest in the clinical strategy (USD 2.7). The cost of microscopy was three times the cost of clinical diagnosis and twice the cost of the RDT strategy per patient diagnosed.

Table 5.14 Costs and Cost-Effectiveness Ratios

	Clinical	Microscopy	RDT
a.Visits	6520	10460	6685
Diagnosis Costs			
b. Cost of Diagnosis (prior treatment)	17,864	86,103	31,508
c. Cost/patient diagnosed (b/a)	***2.7***	***8.2***	***4.7***
Treatment Costs			
d. Treatment costs (All treated)*	9,422	12,708	7,918
e. Treatment costs (Only positive treated)**	9,429	5,590	3,226
Total Costs			
f. Total cost (b+d)*	27,286	98,811	39,426
g. Total cost (b +e)**	27,293	91,693	34,734
h.Cost/patient diagnosed and treated (f/a)*	4.2	9.4	5.9
i.Cost/patient diagnosed and treated (g/a)**	4.2	8.8	5.2
Total Effectiveness			
j. Number of cases correctly diagnosed	1598	8303	6082
k. Proportion of cases correctly diagnosed (j/a)	0.25	0.79	0.91
Average Cost Effectiveness Ratios (ACER)			
l. Total cost/cases correctly diagnosed (f/j)*	***17.1***	***11.9***	***6.5***
m. Total cost/cases correctly diagnosed (g/j)**	***17.1***	***11.0***	***5.7***

* Scenario treating all as observed in the study
** Scenario where only cases found positive are treated

The potential savings on treatment if only cases found positive are treated were zero for clinical, 56% for microscopy and 59% for RDT strategy respectively. This shows that using clinical diagnosis may not lead to cost savings on treatment, while using RDT result for treatment prescription has the potential to maximise savings on antimalarial drugs.

As mentioned earlier, the effectiveness measure for each diagnostic strategy was defined as the number of cases correctly diagnosed (true positives+ true negatives) and the proportion of cases correctly diagnosed ([true positives+ true negatives]/ visits). This distinction was done to estimate ACER (where the number of cases are needed) and ICER (where the proportion is needed). Clinical diagnosis was least effective (0.25) while RDT was the most effective (0.91) at correctly diagnosing cases as shown in table 5.14 above.

The average cost per patient diagnosed and treated was highest in the microscopy strategy (USD 9.4) and lowest in the clinical strategy (USD 4.2) (see row h). However, the cost per patient diagnosed and treated is higher under current treatment practices (row h) than in a scenario where only found positives were treated (row i), except for clinical diagnosis were it is the same. Note that in this scenario, the difference between clinical and RDTs diagnosis was just above one dollar per visit.

The ACER per case correctly diagnosed was highest in the clinical strategy, followed by microscopy and least in the RDT strategy. As expected, considering the two situations described above (treatment as observed and treatment if only found positives are treated), the ACER under the observed treatment pattern (row l) was higher than when only cases found positive are treated (row m), again except for the clinical strategy.

Incremental analysis among the strategies was conducted in order to evaluate the additional cost of increasing cases correctly diagnosed. The changes in costs and effectiveness were calculated for moving from the least cost effective (clinical) to either microscopy or RDT. Given the differences in the number of patients seen by each strategy, cost and effect have been estimated per patient. Hence, as shown in table 5.15 below, the clinical strategy was used as baseline.

Thus, when considering only diagnoses costs, the incremental cost required per additional case correctly diagnosed was found to be lower for RDT (USD 3) than microscopy (USD 10). In other words, microscopy should be eliminated by extended dominance (Karlsson

and Johannesson 1999). Now when considering the incremental cost per additional case correctly diagnosed and treated, which was considered as the baseline ICER results (*), values reduced from USD 3 to USD 2.6 for RDT and from USD 10.2 to USD 9.6 for microscopy as shown in table 5.15 below. These decreases are due to the fact that, in comparison to clinical diagnosis, treatment patterns with RDTs and Microscopy generates some savings on antimalarials.

Table 5.15 Incremental Cost-Effectiveness Ratios

Incremental Cost Effectiveness Ratios	Clinical	Microscopy	RDT
Cost/patient diagnosed (USD)	***2.7***	***8.2***	***4.7***
Effectiveness per case diagnosed	0.25	0.79	0.91
Moving from clinical to either microscopy or RDTs			
Incremental costs (USD)	-	5.5	2.0
Incremental effects	-	0.54	0.66
ICER		10.2	3.0
Cost/patient diagnosed and treated (USD)*	***4.2***	***9.4***	***5.9***
Effectiveness per case diagnosed	0.25	0.79	0.91
Moving from clinical to either microscopy or RDTs			
Incremental costs (USD)	-	5.2	1.7
Incremental effects	-	0.54	0.66
ICER (USD)		**9.6**	**2.6**

5.8 The Potential Annual Impact of Scaling up RDTs in the Four Districts

RDTs were found most cost effective strategy with USD 6.5 per case correctly diagnosed and an incremental cost of USD 3 over clinical strategy per additional case correctly diagnosed. On the other hand microscopy was dominated by RDTs (as this was more expensive and less effective than RDTs). These results suggest that if one strategy (different to clinical diagnoses) is to be scaled up to the rest of the facilities this should be RDTs diagnosis. Thus, the cost of implementing this intervention was estimated in the four districts under study. The facilities in these districts already have basic infrastructure and human resource needed to implement the RDT for malaria diagnosis. Therefore the incremental cost of this strategy against clinical diagnosis was used to

measure and value the total additional resources required to implement RDT based on the existing establishments in each facility.

The main assumption in the estimation of the costs of scaling up the RDT strategy is that this will be used for malaria diagnosis in all the first level health facilities that exist in the district involved in the study (the lowest level of health care in Zambia). Thus, the few microscopy services available could be used for the diagnosis of other diseases. This is justified by the fact that the existing microscopy services are scarce and available only in main referral centres (inequitably distributed). Further, where these services are available, clinicians still do not necessarily prescribe antimalarials based on the microscopy results partly due to the lengthy period that it takes to get the laboratory results. Since the goal is to provide prompt and effective case management, RDT provide a faster, simpler, more practical and (as demonstrated here) more cost-effective way of diagnose malaria in first level health facilities. It should be noted that specialised microscopy services would still be available at the higher levels of health care.

The expected proportion of malaria related visits were estimated from the malaria utilisation rates in the respective district (see table 5.2). The incremental cost of the diagnostic strategy (USD 1.7) was used based on the incremental costs of diagnosis and treatment for the RDT strategy in relation to the clinical strategy (see table 5.15).

Another cost of rolling out the RDT strategy include, one-week training programme for front line health workers to cater for theoretical and practical knowledge on the use of RDTs for malaria diagnosis. This training should put a special emphasis on encouraging treatment prescriptions practices in line with the diagnostic results. At least four participants (2 nurses, 1 clinical officer, 1 EHT and 1 CHW/CDE) per health facility would be trained (83 health facilities in total). All these cadres from each of the facilities in the study districts would be invited to participate in the training at one central level place. These trained workers would then in turn orient their fellow workers at their respective facilities. The cost of training includes cost of materials, per diems and accommodation of participants. Facilitation costs of trainers were also included. The cost

of such training was annualised at 5% for a period of five years to get an equivalent annual cost of USD 23, 487. Thus assuming that the knowledge gathered through the training will last 5 years. Table 5.16 below illustrates the potential costs of scaling up RDTs in the four districts.

Table 5.16 Annual Cost of Scaling up RDTs in Four Districts (in USD)

District	Catchment Population	Utilisation Rates (malaria)	Expected Visits (malaria 8 month)	Unit Cost	Cost for a 8 months period	Cost/ Month	Annual Cost
Diagnostic Costs							
Chongwe	157664	0.24	37839	1.7	64,326.3	8,040.8	96,489.5
Chingola	196685	0.09	17702	1.7	30,093.4	3,761.7	45,140.1
Kabwe	196829	0.17	33461	1.7	56,883.7	7,110.5	85,325.6
Kalomo	181379	0.23	41717	1.7	70,918.9	8,864.9	106,378.4
Sub Total	732557		130,719		222,222.3	27,777.8	333,333.5
Training (AEC)							23,487.0
TOTAL							**356,820.5**

AEC= Annual Equivalent Cost

As shown in table 5.16 above, the annual scale up costs for RDTs in the four districts would be USD 356,820.5 leading to about 129,412 (0.66 x 196,079) additional cases correctly diagnosed per year. Out the total cost of scaling up the RDT strategy in the facilities, training accounted for 7%. The actual costs however would depend on availability of key personnel. Further, the average costs reported here are likely to change with changes in expected visits. The incremental cost per case correctly diagnosed and treated was found to be USD 2.6, however, deploying RDTs entails start up costs related to training. Thus the average incremental cost per case correctly diagnosed in the scale up would be around USD 2.8.

5.9 Sensitivity Analysis

One-way sensitivity analysis was conducted on various parameters in order to evaluate how changes in assumptions affect the average and incremental cost effectiveness ratios for each diagnostic test. The discount rates of 0%, 3% and 6% were used in order to allow for comparison with other studies. The cost of RDT and AL might increase or decrease due to variations in demand and exchange rates. Hence, the use of lower and higher estimates than the baseline values. The other estimates for sensitivity analysis include test accuracy, allocation factor and sensitivity of clinical diagnosis. Personnel costs usually increase over time; hence a 10% increase in the cost of salaries was used as sensitivity value. Variations in the accuracy of clinical diagnosis were conducted as best case scenario at 40% while a lower accuracy for RDT at 80% was tested as worse case scenario. The summary results of the sensitivity analysis are contained in table 5.17.

As shown in table 5.17 below, undiscounted capital costs lead to a higher unit cost of diagnosis and consequently a higher ACER for all the three strategies. However, the degree of increase in costs depended on the proportion of capital costs found among the strategies being compared. For example, the ACER for microscopy changed by 30% while that for RDT strategy increased only by 18% (The proportion of capital costs was 10% and 2% for microscopy and RDT respectively). However, RDT remained with lower cost per case correctly diagnosed. The ICER for RDT reduced by 12% (less by USD 0.3) while that for microscopy increased by 51% (USD 4.9) when capital costs were left undiscounted.

The impact of changing the discounting rate on the ACER was similar between clinical and microscopy strategies. When a lower discount rate was applied (3%), there was a USD 0.10 decline in the ACER of both the clinical and microscopy strategies. However the ACER for the RDT strategy did not change with varying discount rates. This may be attributed to the observation that RDTs facilities had the lowest proportion of capital costs (2%) than either clinical (4%) or microscopy (10%) facilities. However, among all the three strategies, varying the discount rates did not impact on the unit cost per case

correctly diagnosed and treated. The incremental cost per case correctly diagnosed did not change much in the RDT strategy because the proportion of capital costs was too low to cause meaningful impact.

Table 5.17 Sensitivity Analysis Variables and Results

Variable	Baseline	Sensitivity value	ACER Clinical	ACER Microscopy	ACER RDT	ICER Microscopy	ICER RDT
Baseline results*			**17.1**	**11.9**	**6.5**	**9.6**	**2.6**
Discount rate	5%	0%	22.3	17.0	7.7	14.5	2.3
Discount rate	5%	3%	17.0	11.8	6.5	9.5	2.6
Discount rate	5%	6%	17.1	11.9	6.5	9.6	2.6
RDT cost	USD 1.5	USD 0.5	17.1	11.9	5.4	9.6	1.1
RDT cost	USD 1.5	USD 2.00	17.1	11.9	7.1	9.6	3.5
AL cost	USD 2.45	USD 1.5	15.4	11.4	6.1	9.7	2.8
AL cost	USD 2.45	USD 3.5	19.5	12.4	7.0	9.3	2.4
Sensitivity clinical	100%, 90%	80%	20.4	11.9	6.5	8.1	1.4
Personnel costs	-	10% increase	18.2	12.6	6.7	10.2	2.6
Clinical Accuracy	25%	40%	10.5	11.9	6.5	13.3	3.3
RDT accuracy	91%	80%	17.1	11.9	7.4	9.6	3.1
Malaria allocation factor	-	10%	21.5	14.5	8.4	11.7	3.6
Malaria allocation factor	-	-10%	13.1	9.4	4.7	8.0	1.7

*Baseline values for ACER and ICER refer to the scenario when all patients are diagnosed and treated as observed in the study as shown in table 5.14 and 5.15 respectively.

When the cost of RDT was reduced to USD 0.5 per unit, the cost per case correctly diagnosed and treated by RDT reduced by 17% (in USD 1.0). On the contrary, if the cost of RDT rises to USD 2, the average cost per case correctly diagnosed and treated would increase by 9% (in USD 0.50). The incremental cost per case diagnosed with RDT

reduced to USD 1.1 for the lower costs and increased to USD 3.5 when the RDT costs were increased. However, despite the changes in the unit cost, the RDT still dominates over the microscopy and clinical strategies.

Variations in the cost of AL showed that at lower costs (USD1.5), the average cost per case correctly diagnosed reduced by 11% (USD 1.88) for clinical, 5% (USD 0.4) for RDT and least of all 4% (USD 0.5) for microscopy. The opposite patterns were observed for increasing costs of AL to USD 3.5, where the increase in the ACER was found to be 14% for clinical and 4% for both microscopy and RDT respectively. The largest impact was on clinical diagnosis because AL was used more for both cases found negative and positive whereas RDT and microscopy were likely to use AL more in the cases found positive than those found negative. The incremental cost per case correctly diagnosed and treated by microscopy and RDT increased by 1% and 8% respectively when drug costs were reduced to USD 1.5. However, increasing drug costs to USD 3.5 resulted in a 3% and 5% increase in the ICER for microscopy and RDT respectively.

If the *sensitivity* (true positives/total positives) of clinical diagnosis reduces to about 80%, it was observed that this would increase the average cost per case correctly diagnosed and treated by clinical strategy by 19% (USD 3.3). This is because at such low sensitivity, the number (and proportion) of cases correctly diagnosed reduces. This leads to a lower incremental cost of correctly diagnosing and treating cases by microscopy (USD 8.1) and RDT (USD 1.4). This is important especially for low malaria transmission areas where the sensitivity of clinical diagnosis is expected to be lower than in high transmission areas (Muhe et al 1999).

Any increase in personnel costs would increase the ACER of all the three strategies. But the impact was less in the RDT strategy (3%) than either clinical (5%) or microscopy (6%). This is because the proportion of personnel costs out of the total costs were 51%, 65% and 83% for RDT, microscopy and clinical respectively. The increase in personnel costs did not impact on the ICER of RDTs against clinical diagnosis, but increased the ICER for microscopy by USD 0.6 when compared to baseline.

If a training programme on clinical diagnoses were implemented, so that clinical diagnosis accuracy increases up to about 40%, this would reduce the average cost per case correctly diagnosed by 39% (USD 6.6). This would make clinical diagnosis to have a lower ACER than microscopy (at USD 10.50 versus USD 11.9 for microscopy). However, RDTs would still be the most cost effective intervention. Nevertheless, the feasibility of improving clinical accuracy to this level is not easily attainable.

Assuming a lower accuracy of RDT diagnosis of 80%, (which could be argued due to poor training or quality assurance issues in current practise), would increase the average cost per case correctly diagnosed by RDT from USD 6.5 to USD 7.4. This also led to a 19% increase in the incremental cost per case correctly diagnosed. Nevertheless, the RDT was still more cost effective.

Variations in the malaria allocation factor on shared resources (mainly personnel) had demonstrable impact in the same direction on all the three strategies. Increasing the allocation factor by 10 units (x +10%) showed that the average cost per case correctly diagnosed increased by 26%, 22% and 29% for clinical, microscopy and RDT respectively. Conversely, reductions in the allocation factor reduced the ACER by similar proportions. The larger impact was on RDT and lowest in the microscopy. This is because in microscopy, laboratory related costs had a different allocation factor from other costs. Increasing the allocation factor increased the incremental cost of diagnosis to USD 11.7 (22% higher) for microscopy and USD 3.6 (38% higher) for RDT.

Overall, the parameters that had the strongest effect on reducing RDT efficiency against the alternatives were increases in RDT and AL costs, reducing accuracy of the RDT, an increase in the malaria allocation factor (malaria visits as a proportion of all OPD visits and increasing personnel costs. On the other hand, the parameters that improve even more the position of RDT were lower unit costs of RDT and AL and reduced malaria allocation factor.

CHAPTER SIX

6.0 DISCUSSION

This study has demonstrated the role of economic evaluation in malaria control. The cost effectiveness analysis of three available diagnosis methods for malaria (clinical, microscopy and RDTs) was conducted. The study was based on lower level health facilities in four districts in Zambia. Data on malaria visits, diagnosis strategies and treatment characteristics in the actual facility setting was used on, as is basis. Cost effectiveness was conducted from a providers' perspective. Effectiveness data was used from field evaluations on the ability of each strategy to correctly diagnose malaria related visits (accuracy).

The cases correctly diagnosed were estimated based on the '2x2' table by applying the sensitivity of each test to the observed results so as to obtain true positives, false positives, false negatives and true negatives. Thus the number of cases correctly diagnosed was the sum of true positives and true negatives, while the proportion of true diagnoses out of all visits was referred to as the accuracy. The cost associated to malaria misdiagnosis was estimated in terms of the number of false positives and false negatives.

The cost per patient diagnosed was least in the clinical and highest in the microscopy strategies. Clinical diagnosis was found to have the lowest diagnostic accuracy than either microscopy or RDT. Both groups of patients, found positives and negatives were being treated with an antimalarial, however, cases found negative received a cheaper drug in comparison to the cases found positive. The cost of correctly diagnosing cases was cheaper for RDT and highest in the clinical strategy. Changes in parameters and assumptions did not affect these results. RDTs remained the most cost effective strategy at correctly diagnosing cases for all tests performed, although increases and decreases in the average cost effectiveness ratio were observed in same cases.

These findings are discussed in detail in the following sections. Other available studies relevant to cost effectiveness of malaria diagnosis were explored for any relationship to this study. The strengths and limitations of the study are outlined and policy recommendations suggested.

6.1 Mean Cost per Patient Visit

The findings in this study have shown that personnel costs are the major cost component for malaria diagnosis in all the facilities under study. However, personnel costs in relation to total costs by strategy accounted for 83%, 65% and 51% for clinical, microscopy and RDTs respectively. Differences in the level of staffing in these facilities had a demonstrable impact on the unit cost per malaria patient visit. Overhead costs per patient visit were higher for the microscopy strategy than clinical and RDT strategies. This is much expected because microscopy services need extra utilities (water and electricity) apart from laboratory supplies while the RDT strategy needs extra recurrent costs for RDT and other supplies. On the other hand, laboratory related capital costs were unique to microscopy diagnosis alone (up to 1% of total costs of malaria diagnosis).

As expected, clinical diagnosis was found to be cheaper per patient visit. This may be attributed to the lower resources required to implement this strategy. The unit cost for clinical diagnosis (USD 2.7) was three times lower than microscopy and almost two times lower than the cost of RDT diagnosis per patient. This is because RDT and microscopy require additional resources in order to confirm the presence of malaria infection. The unit cost per visit for clinical diagnosis of malaria did not vary much with setting, utilisation and underlying prevalence. The main source of variation was the personnel and overhead costs. Costs related to the diagnostic technology as a proportion of all malaria costs were higher in RDT sites than in microscopy sites. This may have implications for long-term sustainability of funding to implement RDTs.

Clinical diagnosis of malaria was cheapest in the rural areas and most expensive in the urban areas. This may generally be attributed to the variations in the facility utilisation

rates between the two settings. This clear distinction in cost levels per patient diagnosed was not observed in the microscopy sites whose cost depended on resources as mentioned in the paragraph above. The cost was USD 2.18 for the most rural district (Kalomo) and USD 4.14 for the urban district (Chingola). The RDT strategy also showed a higher cost per patient diagnosed in the urban districts than in the rural districts. The lowest cost per patient was USD 4.30 in Chongwe (rural) and the highest being USD 6.89 in urban Chingola for the RDT strategy. Among the three strategies, the highest cost of diagnosis per patient was found in rural Chongwe district (USD 12.1 - microscopy). Malaria diagnosis was least expensive in rural Kalomo district (USD 1.6 – clinical).

The differences in the personnel costs were related to the qualifications of the health worker at each facility. Some facilities had less professional health workers than needed hence resorted to hiring CDEs whose salaries were very low. This tended to reduce the cost per patient because personnel costs accounted for the highest proportion of the total costs. Urban health facilities had more health workers than rural facilities hence seemingly increasing the cost per patient diagnosed.

6.2 Treatment Characteristics

One major treatment feature was that, the diagnostic test result did not seem to influence the decision to either treat or not treat with an antimalarial. It was found that almost 87% of all facility visits were prescribed antimalarials regardless of the malaria test result. Thus antimalarials were given as much to cases found negative as the cases found positive.

However, an interesting observation was that the test result influenced the type of antimalarial, which was prescribed to a patient. Given that the diagnostic strategies were not 100% accurate, health workers seem to be faced with two important decisions: Saving costs by treating only those found positive or reducing the risk of false negatives and its consequent complications by also treating the cases found negative. It is clear from the study that health workers were more inclined to favour the latter than the

former. However, even in such a situation, there was a systematic pattern of attempting to rationalise antimalarial use by prescribing a cheaper antimalarial to those who were less likely to have malaria (those found negative). Those cases that were more likely to have malaria (found positive) had a higher chance of being prescribed AL. Based on these observations; this study does not fully support the proposition that malaria diagnostic techniques do not guide treatment decision.

This study demonstrated that there are cost savings (although moderate) on treatment associated to a specific diagnostic test. This in spite of the treatment patterns behaviour discussed above. Clinical diagnosis had the higher rate of cost on treatment per visit at USD 1.44 while RDT had the lower USD1.18. Moreover, assuming a situation where a diagnostic test result could strongly influence the decision to prescribe or not an antimalarial, microscopy and RDT diagnosis would have the potential of saving 56% and 59% respectively on antimalarials. This applies to the scenario that only cases found positive are treated. It was also demonstrated (given the observed diagnoses results) that clinical diagnosis does not offer any potential savings on drugs costs. The differences in the levels of potential savings are mainly attributed to the variations in the accuracy of microscopy and RDT, and the observed treatment patterns.

In Malawi, Jonkman et al (1995) found that using microscopy could lead to about USD14, 000 savings on drugs annually in one hospital. In the Zambian context, it would be interesting to find out if the prescription trends found in the facilities (in this study) are similar in hospitals. This would provide an idea of the potential savings in antimalarials at that level of care.

The ability of the available test in transforming a low pre-test malaria probability into a higher post-test probability is also important in treatment decision-making. The post-test probability for a positive result on RDT (70%) was high enough to allow the clinicians to confidently treat a positive case. This would go a long way in improving treatment decision-making when compared with clinical (17%) and microscopy (53%). The post-test probability of a microscopy test was moderate. A low or moderate post-test

probability (like the one observed in microscopy and clinical) makes treatment decision more difficult and most likely would lead to treating even the cases found negative.

6.3 Cost of False Positives for Each Diagnostic Strategy

The effectiveness of a diagnostic test is measured by the ability of the test to reduce misdiagnosis. A good diagnostic test should differentiate the positive cases from the negative cases. This is important in helping to decide who should receive treatment for the disease in question.

The cost of false positives is the result of the diagnostic inaccuracy together with treatment prescription behaviour. False positives arise when the test strategy has low specificity. The clinical strategy was found to have the highest number and proportion of false positives and consequently a high cost of treating them. The proportion of false positives was lowest in the RDT strategy (see table 5.3 to 5.5). Consequently, the average cost on false positives per visit was highest for clinical diagnosis at USD 1.17, followed by microscopy USD 0.29 and least of all in the RDT strategy at USD 0.16. Similarly, the highest cost of false positives per month was found in the clinical strategy (USD 957) while microscopy amounted to USD 375 and RDT USD 130 per month. It is important to state that the cost of false positives could have been higher if only AL had been used for malaria treatment.

As reported in the literature (Amexo et al 2004), here clinical diagnosis is likely to lead to unnecessary treatments and consequently increase drug costs. The proportion of false positives was as high as 74% in the clinical diagnosis strategy. These findings are consistent with earlier reports that clinical diagnosis of malaria is responsible for overestimation of disease burden (Stephens et al 1999) and increase in drug expenditure (Amexo et al 2004). Further, in Thailand, the rate of false positives due to clinical diagnosis was found to be 68%, a figure similar to the estimates found in this study in Zambia. However, lower levels of false positives have been reported elsewhere. In Tanzania, 30% false positive malaria diagnoses were found (Tarimo et al 2001) and 43%

in Uganda (Guthman et al 2002). Another study in Zambia, conducted during the peak malaria transmission season found that 49.3% cases clinically diagnosed were false positives (Ndhlovu et al 2004).

Apart from the obvious effect on costs, irrational drug use may lead to stock outs of antimalarials at a time when they are most needed. The potential negative health effects this may have, cannot be underestimated. Furthermore, the increase in drug pressure in the population could increase the probability of drug resistance to ACTs developing early (Laxminarayan 2004, Bjorkman 2002).

Microscopy diagnosis reported up to 18% false positives under routine conditions in this study. This is also explained by the fact that routine microscopy is less accurate than the *gold standard* expert microscopy. It is therefore important to observe here that in terms of reducing false positives (and in turn expenditure on unnecessary drugs) RDTs were more effective than microscopy and much more than clinical diagnosis. The RDTs' proportion of false positives was found to be lowest among the three strategies (8%). These findings are within the range of about 10% false positives expected on HRP-2 based RDT (Shiff et al 1993).

The cost of false positives could not be estimated in its true measure because the cost of non-antimalarial drugs was not consistently recorded. Thus it was not possible to estimate the cost of other drugs (non-anitmalarials).

6.4 Cost of False Negatives for Each Diagnostic Method

The proportion of false negatives was 1.1%, 1.8% and 0.9% for clinical microscopy and RDT strategy respectively. False negatives have been said to be responsible for prolonged illness (Amexo et al 2004). This becomes more costly for both the health system and even more so for the patient. In terms of the health system, extra costs arise from repeated visits leading to more diagnostic and treatment costs. If hospitalised, the

cost of patient management escalated due to inpatient costs of managing severe malaria. Thus a diagnostic strategy, which produces less false negatives, is preferred.

Since most cases found negative were treated with SP, false negatives may be at risk of poor health outcomes. This is because SP has lower efficacy than AL (Chanda et al 2004) and so patients treated with SP may have a higher probability of returning to health facilities for further management. As clinical outcome was not the scope of this study we could not estimate such costs. A potential question for future research would be to assess cost effectiveness of diagnostic strategies for malaria using clinical outcome as effectiveness measure. Clinical outcome would be influenced not only by the test accuracy but also by the prompt and adequate treatment provided.

Nonetheless, in this study, it was common practice for health workers to treat all fevers with antimalarials, including cases found negative for malaria. This helped to indirectly treat even the false negatives, which were missed at the point of diagnosis. Further, since almost all negatives received antimalarial treatment, the cost of treating false negatives with an antimalarial was not considered as a cost of misdiagnosis.

6.5 Effectiveness of Diagnostic Tests

Out of a total of 23 600 malaria suspected visits, 48% were found positive across the three strategies. However, the proportion of cases found positive was 89%, 37% and 26% for clinical, microscopy and RDTs respectively. The overall proportion of cases correctly diagnosed was highest in the RDT strategy (91%), followed by microscopy (79%) and least of all in the clinical strategy (25%). This is mainly due to the variations in the sensitivity and specificity of each of these tests under routine clinic conditions. When both the sensitivity and specificity are high, then the accuracy (proportion of cases correctly diagnosed) is expected to be high. For example, even though clinical diagnosis might have had a high sensitivity (as much as 100% in some facilities, the specificity was too low (below 20%) hence leading to a reduction in true negatives.

The cases correctly diagnosed were selected as outcome measures because retrospective data was collected among patients who were not actively followed up. This made it difficult to use a final outcome measure such as cases successfully treated after correct diagnosis. Thus within the realm of this study, it was not possible to estimate the link between correctly diagnosing a patient and the final clinical outcome. Such would be essential in assessing the true usefulness of the test. This is a potential area for further research.

6.6 Cost Effectiveness of the Diagnostic Strategies

The RDT was found to be cheaper at correctly diagnosing malaria (USD 6.5) than microscopy (USD 11.9) and clinical (USD 17.1) in routine outpatient clinics. This study is the first in Zambia to demonstrate the cost effectiveness of malaria diagnosis in the era of ACTs as treatment for uncomplicated malaria. In different epidemiological settings and variable contexts, the clinical diagnosis of malaria was not a cost effective strategy for malaria diagnosis in Zambian districts if cases correctly diagnosed were to be maximised. The cost implication of using clinical malaria diagnosis is exacerbated by the high cost of antimalarials being used. For example, the average cost of treatment per person visit was USD 1.44, USD 1.21 and USD 1.18 for clinical, microscopy and RDTs respectively. This showed that using RDT was likely to lead to lower costs of drugs per patient visit than clinical and microscopy.

The rate of false positives was too high in the clinical strategy (in comparison with the other 2 methods) and may play a role in deteriorating health status of the population who are misdiagnosed. These patients are administered with antimalarials when they should in fact be receiving the correct treatment for their true illness. This is even more relevant when prevalence is expected to be low. In the study the lowest and highest prevalence were 10.6% in Kabwe district and 26.3% in Kalomo district respectively. Thus the level of prior prevalence (around 20% on average) and the high proportion of cases found positive (89%) demonstrated the limited ability of clinical diagnosis to correctly diagnose cases.

Microscopy malaria diagnosis in the peripheral health centres was less effective than expected (as compared by its assumed sensitivity). This may be largely due to the poor performance by laboratory personnel in these facilities. These findings challenge the notion that microscopy is the gold standard for malaria diagnosis (Moody 2002, WHO 2000c). Microscopy is only gold standard when performed by expert microscopists (Hanscheid 2003).

A study conducted by Rolland et al (2006) in a hypothetical epidemic situation found the cost per true malaria case detected by RDT was USD 19.87 while for clinical diagnosis it was USD 18.4 at 25% prevalence. Estimations at 50% and 75% prevalence level found RDTs to be less cost effective. Rolland et al used a hypothetical epidemic situation and a different outcome measure hence making comparisons with this study difficult.

In a study by Buolombai et al (2003) in Thailand the cost effectiveness of microscopy was compared to two types of RDTs (OptiMAL and ICT) from a societal perspective. The study was conducted between April to October 2000 in remote non-microscope areas of Thailand. Microscopy was found to cost more per true *falciparum* positive case detected than the two RDTs (446.75 Baht vs 282.40 Baht and 343.56 Baht). At an exchange rate of about 37.56 Baht = 1USD, this may be equivalent to about USD 11.90 for microscopy, USD 7.52 for OptiMAL and USD 9.15 for ICT. Since this study is comparable in terms of using a longer data collection period and actual malaria setting (except for the costing perspective), the findings may be more comparable to the Zambian situation than the Rolland et al study. However, none of these studies compared all the three interventions as conducted in this study.

Thus when assessing the cost effectiveness of malaria diagnosis, differences in methodologies, and patient population characteristics are very important and need to be explored more. Additionally, this study found that health workers might have a role to play in modifying the potential effectiveness of a test through their actual practice when diagnosing malaria. Hence future research should explore these areas and the extent to which they act as a confounding factor.

The clinical strategy, which is the natural comparator for any other diagnostic method on malaria, was found to be less effective. Thus this strategy was used as baseline for incremental analysis, against which microscopy and RDT were evaluated. In incremental analysis, the cost per additional case correctly diagnosed was found to be 70% (USD 7) lower for RDT than microscopy. Thus demonstrate that it is more likely that policy makers would opt to implement RDTs since they require less additional resources but also yield more correct diagnoses than microscopy, holding all other factors constant. Othnigue and colleagues have stated that,

"At this stage and as the equipment and the necessary technical skills for microscopy-based examination maybe difficult to scale up in the short run, rapid diagnostic tests based on the detection of Plasmodium antigens may be the most efficient approach to appropriately manage malaria as well as non-malaria cases." (Othnigue et al 2006).

6.7 Cost of Implementing RDTs in Four Districts

Since RDTs were found to be the most cost effective strategy, cost estimation was performed for scaling up RDTs to all the four districts in which the study took place. The incremental approach to scale up was used, based on the assumption that the available resources would allow for the roll out of RDTs in the lower level facilities. Of the total costs of scale up, RDTs accounted for a larger proportion (66%) while the remainder was for personnel costs and training.

Thus RDTs themselves accounted for the larger proportion of implementing RDT strategy in the four districts. This is important because the cost of RDTs varies with the quantities used. Thus if this strategy is implemented in areas of higher prevalence and utilisation rates than the ones observed in this study, the cost of RDT would proportionally increase.

The availability of RDTs on the market may determine the extent of scaling up this strategy. However, it has been reported that the increased demand for non-microscopic malaria confirmatory tests has led to more participation in producing RDTs to suit

various species of *Plasmodia* (WHO 2000c). The resultant competition among suppliers would lead to reduction unit costs of RDTs and thus a lower incremental cost per case correctly diagnosed.

The costs of supportive supervision and monitoring may be reduced if the RDT programme were integrated within other programmes. This would allow for savings as opposed to a vertical programme. About USD 356,821 is needed annually in order to scale up RDTs in the four district of the study. This would have an effect of 129,412 additional cases correctly diagnosed.

The health centres in which RDTs were being used were more under staffed than microscopy facilities. However, there are fewer lower level facilities, which are as well staffed as microscopy centres. Thus the cost of delivering RDTs based on the under staffed facilities is representative of the actual human resource constraints in lower level facilities in Zambia. Nevertheless it remains to be established whether the seemingly efficiency (lower cost per output) in these facilities do not lead to concerns related to quality of health care. This is because in these facilities, due to the human resource crisis, untrained CHWs and CDEs are part of the staff that attends to patients. This may compromise the quality of health care delivered. However, this was not established under the scope of this study and remains an area for further research.

6.8 Sensitivity Analysis

None of the parameters used in the sensitivity analysis changed the position of the RDT as the most cost effective strategy at correctly diagnosing malaria. However, some parameters increased the costs of cases correctly diagnosed, while others reduced the costs of case correctly diagnosed.

Undiscounted capital costs led to an increase in the unit cost of diagnosis. The increase was higher in the microscopy (50%), followed by clinical (48%) and least in the RDT (23%) strategies respectively. These variations in the impact of undiscounted costs is

attributed to differences in the proportion of capital costs which were, 10%, 4% and 2% for microscopy, clinical and RDT strategies in that order. However, changes in the discount rates at 3% and 6% showed small variations in the cost effectiveness ratio. This was because the proportion of capital costs was lower than other cost components such as personnel. More variations were observed in microscopy than clinical and RDTs. This is attributed to the observation that microscopy had the highest proportion of capital costs.

Variations in the unit cost of RDTs would impact on the cost of correctly diagnosing cases. Should market prices reduce, this will definitely render the RDT strategy to be more technically efficient than either microscopy or clinical (as shown in table 5.17). However, increases in the unit cost of RDT will increase both the average cost per case correctly diagnosed and the incremental cost of correctly diagnosing cases by 9% and 35% respectively. Thus price changes in the cost of an RDT will affect the amount of resources needed to implement this strategy.

Cost of ACTs in the future may be expected to be lower than they are today, however, the countries' unstable exchange rates could lead to prices increasing or decreasing. Changes in the cost of AL would have a higher impact on clinical diagnosis, followed by RDTs and least in microscopy strategy. This is assuming that treatment patterns remain as observed in each strategy. A higher cost of AL increased the ACER of clinical diagnosis by 14%, RDT 8% and lowest in microscopy at 4%. Clinical diagnosis was more affected by changes in treatment cost because of higher rates of cases found positive and hence increased costs of drugs per visit.

Advocating for lower costs of RDTs and ACT treatment is thus necessary so as to reduce the incremental cost of providing malaria diagnosis and treatment. This might help to encourage policy makers to adopt the new but more effective technologies in malaria control.

The accuracy of a diagnostic test determines the resultant cost per case correctly diagnosed. Unfortunately, clinical diagnosis was consistently less effective at correctly

diagnosing malaria cases. When the accuracy was assumed at 40%, the ACER was USD 10.50. However, even at this plausible higher estimate, RDTs and microscopy were cheaper at correctly diagnosing cases. This showed that even though clinical diagnosis is widely practised, it is a very inefficient way of increasing cases correctly diagnosed.

A 10% increase in personnel costs increased the cost per case correctly diagnosed by 5% in clinical, 6% in microscopy and 3% in RDT. Microscopy was most affected because these sites had more personnel than any other sites (with the exception of rural Namwianga). This also shows that the unit cost of malaria diagnosis observed in this study may be related to the low staffing levels in most of the facilities. In areas where human resource capacity is higher, the cost of malaria diagnosis and treatment should be expected to be higher than that observed in this study.

The malaria OPD equivalent (malaria related visit as proportion of all visits) was used as a major allocation factor for shared costs. Any increase in the allocation factor was seen to increase the ACER for all the three strategies. When the allocation factor was increased in ten perceptual points, the ACER increased more on RDT (29%) than clinical (26%) and microscopy (22%). Similar proportions of reduction were observed when for a decrease of ten perceptual points in the allocation factor. Thus if malaria OPD visits increase, the malaria share of the total facility costs would increase. It must be noticed here that in practice the allocation factor is correlated with other study parameters such as prevalence. Therefore this apparently high impact of the allocation needs to be treated with caution as it can be reduced when adjusting for a higher prevalence rate.

In view of the changes in assumptions and parameters discussed above, RDTs are more cost effective at correctly diagnosing malaria cases than microscopy and clinical diagnosis. All changes in assumptions and parameters only impacted the cost of the strategy but not the ranking of effectiveness in relation to other strategies.

6.9 Strengths and Limitations of the Study

6.9.1 Strengths

A major strength of this study is that it was conducted within the actual malaria context using field-based data in a malarious population. This helped to incorporate actual practice unlike experimental studies, which may not apply to routine practice. Most studies, which have been conducted, based on hypothetical patient populations and settings miss the dynamics observed in this study. Even if such data is useful, but the application of the findings to a true set up may be limited.

The observation period was long enough to account for seasonal variations. The study was carried out over 8 months between March and November 2005. This allowed capturing both the high and low malaria transmission seasons. Malaria transmission in Zambia varies by season and this affects the expected patient visits and the prevalence of malaria at OPD.

Furthermore, the study used a very large sample size of about 23 600 participants, 12 facilities and four districts. The study districts had variable confirmed malaria prevalence ranging from 10.5% to 26%. Both rural and urban facilities were captured for each strategy. Thus the settings of the sample encompasses geographical and malaria epidemiology variations. These variations in the study sites offer an understanding into how facility utilisation, staffing levels, capital endowment and other capacities affect the cost of malaria diagnosis.

The costing of the facilities was comprehensive as all the inputs required for malaria diagnosis were estimated in each facility. Costs were categorised into personnel, capital and overheads. This was measured according to the way they were used whether it is diagnostic technique related costs, patient screening or treatment. A discount rate of 5% was used to get the annual equivalent cost for capital items.

The study also looked at all the possible outcomes of a diagnostic test as opposed to just focussing on the positive malaria cases. Thus the outcome measure considered both the true positive and true negatives, as these were the correct diagnoses while false positive and false negatives were misdiagnoses.

The ability to conduct sensitivity analysis on variables used in the estimations of costs and effects provided insights into how the study findings would change across other settings and contexts. This not only helped to show the robustness of the results but also showed how costs of malaria diagnosis may vary depending on the prevailing situation in an area being considered.

The ICER for scaling up RDTs can be considered conservative as similar prescription practices were assumed, however if training proves to be effective at reducing over treatment with antimalarials, the incremental cost of rolling out the strategy should be lower.

6.9.2 Limitations

One of the main limitations of the study is that the outcome measure used in the analysis is an intermediate one. Thus it has been assumed that cases correctly diagnosed may be linked to improved final outcome (recovery from disease). However, the link between correctly diagnosing a case, an optimal clinical management of the patient and a satisfactory health outcome (after treatment) may be difficult to prove, without a close patient follow up. It was not possible within the context of this study to assess the differences in patient outcome after malaria diagnosis. This is an area for further research.

The true cost of misdiagnosis in relation to other illnesses could not be fully documented as data on non-malaria prescriptions was not documented in the facilities.

The use of facility registers may raise concerns with the reliability of the data due to potential errors in the data recording at facility level. However, the use of a three level supervision system (facility, district and national level) during the entire 8 months ensured completeness and consistency in the data collection process.

Another limitation of the study arose from difficulties in defining the sensitivity of clinical diagnosis, as this can be very subjective. Further, clinical diagnosis does not allow for assessing the extent of missing patients who ideally should be suspected to have clinical malaria. Nevertheless, other studies conducted elsewhere, have shown similar sensitivity values as the estimates found in this study (Hozhabri et al 2002, Tarimo et al 2001).

In a study of this nature, gold standards (against which diagnostic results are measured) are impractical and potentially very expensive. Therefore the study relies on the assumptions on the sensitivity of different diagnostics techniques and prior prevalence of the districts sampled. Additionally, a strict inclusion criterion was applied to available studies to obtain estimates, which are similar to the Zambian setting. However, even though the best available estimates were used, there will always be some uncertainty about the selection of these values.

The study facilities were not randomly assigned a diagnostic technique; hence differences in unit costs were not necessarily explained by differences in diagnostic strategies. That is why detailed tables were prepared and diagnostic and non-diagnostic costs were calculated separately. Nonetheless, the selected study sites were representative of the dynamics of the lower level facilities found in Zambia in terms of size, staffing levels and resource availability.

Treatment practices (such as giving antimalarials to all patients) contribute to conceal the true cost-effectiveness values. On the other hand however, the study allows identifying a potential roll out challenge in this sense, which would have not come out if CEA had been assessed in a theoretical setting.

CHAPTER SEVEN

7.0 CONCLUSION AND RECOMMENDATIONS

7.1 Conclusion

Among the available strategies for malaria diagnosis in Zambia, clinical diagnosis was the cheapest per patient visit at USD 2.7; microscopy was highest at USD 8.2 while RDT was at USD 4.7 per patient visit. However, considering the proportion of cases correctly diagnosed as the effectiveness indicator, clinical diagnosis was less effective at 25%, followed by microscopy at 79% and the highest cases correctly diagnosed were by RDT at 91%. Thus, even if the clinical strategy was costing less per patient diagnosed, it was found to be less effective at correctly diagnosing cases. A positive result with clinical diagnosis was a poor indicator of malaria infection (17%), moderate for microscopy (50%) and better for RDT (73%). This demonstrates that microscopy diagnosis of malaria under routine conditions may not be the gold standard.

A lower accuracy of a diagnostic test resulted into a high proportion of false positives. The average rate of false positives was highest in the clinical strategy at 75%, 19% for microscopy and 8% for RDT. Consequently the cost of false positives per month was USD 957 for clinical, USD 375 for microscopy and USD 130 for RDT strategy.

It was estimated that the proportion of false negatives out of total visits was highest in the microscopy strategy (1.8%), followed by clinical at 1.4% and lowest in the RDT at 1%. False negative are not desirable in malaria diagnosis as such cases can easily develop severe malaria, which may be fatal.

This study has shown that RDTs are the most cost effective method at correctly diagnosing malaria in lower level health facilities in Zambia when compared to clinical and microscopy strategies. This is relevant if cases correctly diagnosed are expected to influence the clinical management and health outcomes of patients visiting these clinics.

The cost per case correctly diagnosed was USD 17.1 for clinical, USD 11.9 for microscopy and USD 6.5 for RDT from a providers' perspective. The incremental cost per case correctly diagnosed and treated was USD 2.6 for RDT compared to USD 9.6 for microscopy. Thus RDT would be much cheaper to scale up than microscopy. The findings were robust to changes in assumptions and parameters. The annual incremental cost of scaling up RDTs in the four districts involved in this research was estimated at about USD 356, 821.

The cost of treatment per patient visit was lower for RDT (USD 1.18) than either microscopy (USD 1.21) or clinical (USD 1.44). This lower cost of treatment when using RDT shows that potentially RDT could lead to reductions on treatm0ent costs. However, the amount of cost savings in drugs was limited by the treatment practices (both cases found positive and found negative were treated with an antimalarial). Noteworthy is the observation that both the ACER and ICER were lower for the scenario where the test is assumed to direct the decision to treat only cases found positive by microscopy and RDT strategies. This was however not true for clinical diagnosis.

These findings could be relevant for transferability to low-income countries where malaria is endemic, AL is being used for first line treatment of malaria and diagnostic services are not readily available.

7.2 Recommendations

This study has endeavoured to illustrate various issues related to malaria diagnosis in the context of cost effectiveness. However, cost effectiveness of diagnoses alone may not be enough if other components of malaria case management are not addressed. Furthermore, there is need for more field-based evidence in the area of malaria diagnosis to encompass both quantitative and qualitative techniques. The following recommendations are suggested:

- Improving malaria diagnosis can no longer be focussed on laboratory microscopy, but other non-microscopic methods such as RDTs should be explored.

- Microscopy should not be considered a gold standard for routine malaria diagnosis in lower level health facilities. This is because under daily practice in health centres, malaria microscopy had lower accuracy than it is purported to have.

- Undertaking qualitative studies to understand why health workers opt to treat most negative cases despite the test showing a negative result. This is especially important because for an RDT, the same person performs the test is the one who also prescribes treatment.

- Further research on the difference in health outcomes observed among the cases diagnosed clinically, microscopically or by RDT should be undertaken. This would contribute to the evaluation of the health impact of false positives and false negatives.

- An economic evaluation from a societal perspective would help to derive benefits to the patient when malaria is correctly diagnosed.

- The competency of malaria microscopists needs to be evaluated and judged against fully trained laboratory technologists. This will help to understand whether cost saving through lower personnel costs is worth the compromise on quality of laboratory results.

- The link between cases correctly diagnosed and final health improvement should be explored by follow up studies.

REFERENCES

Amexo, M., Tolhurst, R., Barnish, G. and Bates, J. 2004. Malaria misdiagnosis: effects on the poor and vulnerable. *Lancet* **364**:1896-1898.

Bailey, W. 1998. Latest developments in the laboratory diagnosis of malaria. *Afr Health* **20**(4):16-18.

Barat, L., Chipipa, J., Kolczak, M., Sukwa, T. 1999. Does the availability of blood slide microscopy for malaria at health centres improve the management of persons with fever in Zambia? *Am J Trop Med Hyg* **60**(6): 1024-1030.

Bell, D., Go, R., Miguel, C., Walker, J., Cacal, L., Saul, A. 2001. Diagnosis of malaria in a remote area of the Philippines: comparison of techniques and their acceptance by health workers and the community. *Bull World Health Organ* **79**(10):933-941.

Bhatia, M. R., Fox-Rushby, J. and Mills, A. 2004. Cost-effectiveness of malaria control interventions when malaria mortality is low: insecticide-treated nets versus in-house residual spraying in India. *Soc Sci Med* **59**(3): 525-39.

Bjorkman, A. 2002. Malaria associated anaemia, drug resistance and antimalarial combination therapy. *Int J Parasitol* **32**:1637-1643.

Bjorkman, A. and Bhattarai, A. 2005. Public health impact of drug resistant *Plasmodium falciparum* malaria. *Acta Tropica* **94**:163-169.

Bloland, P.B., Kazembe, P.N., Oloo, A.J., Himoonga, B., Barat, L.M., Ruebush, T.K. 1998. Chloroquine in Africa: critical assesment and recommendations for monitoring and evaluating chloroquine therapy efficacy in Sub-Saharan Africa. *Trop Med Int Health* **3**:543-552.

Bojang, K.A., Obaro, S., Morrison, L.A., Greenwood, B.M. 2000. A prospective evaluation of a clinical algorithm for the diagnosis of malaria in Gambian children. *Trop Med Int Health* **4**:231-236.

Bossert, T., Chitah, M.B., Bowser, D. 2003. Decentralization in Zambia: resource allocation and district performance. *Health Policy and Planning*; **18**(4):357-369.

Breman, J. G., Alilio, M. S., Mills, A. 2004. Conquering the intolerable burden of malaria: what's new, what's needed: a summary. *Am J trop Med Hyg* **71**(2 suppl):1-15.

Briggs, A. 2001, *Handling uncertainty in economic evaluation and presenting the results*,in Drummond M, McGuire, A., (eds), Economic evaluation in health care: merging theory with practice, Oxford University Press, Oxford.

Bualombai, P., Prajakwong, S., Aussawatheerakul, N., Congpoung, K., Sudathip, S., Thimasarn, K. Sirichaisinthop, J., Indaratna, K., Kidson, C. and Srisuphanand M. 2003. Determining cost-effectiveness and cost component of three malaria diagnostic models being used in remote non-microscope areas. *Southeast Asian J trop Med Public Health* **34**(2): 322-33

Cairns, J. 1994, Valuing health benefits, *Econometrics and Health Economics* **3**: 221-229.

Central Board of Health. 1998. *Designing and Operating Cost Sharing Schemes for Health Care: Guidelines for Districts and Regions*. Lusaka, Zambia.

Central Board of Health. 2002. *Health Institutions in Zambia. A Listing of Health Facilities According to Levels and Location for 2002*.Lusaka, Zambia.

Central Board of Health. 2003. *Annual Health Statistics Bulletin*. Lusaka, Zambia.

Central Statistcis Office. 2003. *Living Conditions Monitoring Survey 2002-2003*. Lusaka, Zambia.

Chanda P, Sikaala C, Kapelwa W, Nkunika S, MacDonald M, Thea DM, MacLeod WB, Sipilanyambe N, Hamer DH. 2004b. Decreasing efficacy of sulphadoxine-pyrimethamine (SP) in Zambian children. *53rd Annual Meeting of the Society of Tropical Medicine and Hygiene, 7-11 November 2004, Miami, FL. Abstract 708.*

Chanda P, Sikaala CH, Kapelwa W, Moonga H, Njunju E, Macdonald M, Thea D, Hamer DH, Sipilanyambe N. 2004a. Assesment of the therapeutic efficacy of

artemether-lumefantrine (Coartem®) and sulphadoxine-pyrimethamine (SP)-artesunate in Zambian children. *53rd Annual Meeting of the Society of Tropical Medicine and Hygiene, 7 – 11 November 2004, Miami, FL. Abstract 213.*

Chandramohan, D., Carneiro, I., Kavishwar, A., Brugha, R., Desai, V., Greenwood, B.2001. A clinical algorithm for the diagnosis of malaria: results of an evaluation in an area of low endemicity. *Trop Med Int Health* **6**(7);505-510.

Chandramohan, D., Jaffar, S., Greenwood, B. 2002. Use of clinical algorithms for diagnosing malaria. *Trop Med Int Health* **7**(1):45-52.

Colin, O., Purnomo, M., Sutamihardja, A., Tang, D., Kain, K.C. 2002. Impact of microscopy error on estimation of effectiveness in malaria prevention trials. *J Inf Dis* **186**:540-546.

Creese, A. and Parker, D. 1994. *Cost analysis in primary health care. A training manual for programme managers*. World Health Organisation, Geneva. Switzerland.

De Savigny, D. and Binka, F. 2004. Monitoring future impact of malaria in Sub-Saharan Africa. *Am J Trop Med Hyg* **71** (2 suppl):224-231.

Drummond M. Output measurement for resource-allocation decisions in health care. In: McGuire A, Fenn P, Mayhew K, eds. *Providing health care. The economics of alternative systems of finance and delivery.* Oxford: Oxford University Press , 1991.

Drummond, M. 1992. Cost-effectiveness guidelines for reimbursement of pharmaceuticals: is economic evaluation ready for its enhanced status? *Health Economics* **1**:85-92.

Drummond, M., Stoddart, G., Torrance, G. 1987, *Methods for the economic evaluation of health care programmes*, Oxford University Press, Oxford.

Evans, B., D and Hurley, F., S. 1995. The application of economic evaluation techniques in the health sector: the state of the art. *Journal of International Development* **7**(3):503-524.

Fagan, T.J. 1995. Nomogram for Bayes's Theorem. *N Engl J Med* **1975**:293:257

Fernando, S.D., Karunaweera, N.D., Fernando, W.P., Attanayake, N., Wickremasinghe, A.R. 2004. A cost analysis of the use of the rapid, whole-blood, immumochromatographic P.f/P.v assay for the diagnosis of Plasmodium vivax malaria in a rural area of Sri Lanka. *Ann trop Med Parasitol* **98**(1): 5-13.

Foster, S. and Phillips, M. 1998. Economics and its contribution to the fight against malaria. *Ann Trop Med Parasitol* **92**(4):391-398.

Goodman, C. A. and Mills, A. J. 1999. The evidence base on the cost-effectiveness of malaria control measures in Africa. *Health Policy and Planning* **14**(4): 301-312.

Goodman, C.A., Coleman, P.G., Mills, A. 2001. Economic evaluation: changing the first line drug for malaria treatment – cost effectiveness analysis with highly uncertain inter-temporal trade-offs. *Health Econ.* **10**: 731–749.

Goodman, C.A., Coleman, P.G., Mills, A. J. 1999. Cost-effectiveness of malaria control in sub-Saharan Africa. *The Lancet* **354**:378-385.

Gove, S. 1997. Integrated management of childhood illness by out-patients health workers: technical basis and overview. *Bull World Health Organ* **75**(Suppl.1):7-24.

Greenwood, B.M., Bojang, K., Whitty, C., et al. 2005. Malaria. *Lancet* **365**:1487- 1488.

Grimes, D.A. and Schulz, K.F. 2002. Uses and abuses of screening tests. *The Lancet* **359**:881-884.

Guerin, P. J., Olliaro, P. Nosten, F., Druilhe, P., Laxminaravan, R., Binka, F., Kilama, W. L., Ford, N. and White, N. J. 2002. Malaria: current status of control, diagnosis, treatment, and a proposed agenda for research and development. *Lancet Infect Dis.* **2**(9): 564-73.

Guthman, J.P., Ruiz, A., Priotto, G., Kiguli, J., Bonte, L., Legros, D. 2002. Validity, reliability and ease of use in th field of five rapid tests for the diagnosis of *Plasmodium falciparum* malaria in Uganda. *Trans R Soc Trop Med Hyg* **96**(3):254-257.

Hanson, K., Goodman, C., Lines, J., Meek, S., Bradley, D., Mills, A. 2004. *The Economics of Malaria Control Interventions*. Global Forum for Health Research. Geneva.

Hozhabri, S., Luby, S.P., Rahbar, M.H., Akhtar, S. 2002. Clinical diagnosis of *plasmodium falciparum* among children with history of fever, Sindh, Pakistan. *Int J Infect Dis* **6**(3):233-235.

Hutubessy, R., Chisholm, D., Edejer, T.T., WHO-CHOICE. 2003. Generalised cost-effectiveness analysis for national-level priority-setting in the health sector. *BioMed Central. Cost Effectiveness and Resource Allocation* **1**:8. Available at: http://www.resource-allocation.com/content/1/1/8.

Jha, P., Bangoura, O., Ranson, K. 1998. The cost-effectiveness of forty health interventions in Guinea. *Health Policy Plan* **13**(3):249-262.

Johns, B., Baltussen, R., Hutubessy, R. 2002. Programme costs in the economic evaluation of health interventions. Accessed 10th March 2006, available at http://www.resource-allocation.com/content/1/1/1.

Jonkman, A., Chibwe, R. A., Khoromana, C. O., Liabunya, U. L., Chaponda, M. E., Kandiero, G.E., Molyneux, M. E., Taylor, T.E. 1995. Cost-saving through microscopy-based versus presumptive diagnosis of malaria in adult outpatients in Malawi. *Bulletin of the World Health Organization* **73** (2): 223-227.

Kamolratanakul, P., Butraporn, P., Prasittisuk, M., Prasittisuk, C., Indaratna, K. 2001. Cost-effectiveness of lambdacyhalothrin-treated mosquito nets in comparison to DDT spraying for malaria control in western Thailand. *Am J Trop Med Hyg* **65**(4):279-284.

Karlsson, G. and Johannesson, M. 1999. The decision rules of cost effectiveness analysis. In Mollarkey, F. (Eds). Economic Evaluation in Health care, Adis International Limited, Hong Kong.

Korenromp, E. L., Miller, J., Cibulskis. R. E., Cham, k. M., Alnwick, D., Dye. C. 2003. Monitoring mosquito net coverage for malaria control in Africa:possession vs. use by children under five years. *Trop Med Int Health* **8**(8):693-703.

Laxminarayan, R. 2004. Act now or later? Economics of malaria resistance .*Am J Trop Med Hyg* **71** (Suppl 2): 187-195.

Lee, S. H., Kara, U.A., Koay, E., Lee, M. A., Lam, S. and Teo, D. 2002. New strategies for the diagnosis and screening of malaria. *Int J Hematol* **Suppl 1**: 291-3.

Lubanga, R.G., Norman, S., Ewbank, D., Karamagi, C. 1997. Maternal diagnosis and treatment of childrens' fever in an endemic malaria zone of Uganda: implications for the malaria control programme. *Acta Tropica* **68**(1):53-64.

Luce, B. R. and Elixhauser, A. 1990. Estimating costs in the economic evaluation of medical technologies. *International Journal of Technology Assessment in Health Care* **6**:57-75.

Luxemburger, C., Nosten, F., Kyle, D. E., Kiricharoen, L., Chongsuphajaisidhi, T., White, N. J. 1998. Clnical features cannot predict a diagnosis of malariaor differentiate the infecting species in children living in an area of low transmission. *Trans R Soc Trop Med Hyg* **92**: 45-49.

Luxemburger, C., Nosten, F., Kyle, D.E., Kiricharoen, L., Chongsuphajaisiddhi, T., White, N.J. 1998. Clinical features cannot predict a diagnosis of malaria or differentiate the infecting species in children living in an area of low transmission. *Trans R Soc trop Med Hyg* **92(1)**:45-49.

Marsh, K. 1998. Malaria disaster in Africa. *Lancet* **352**: 924.

Mendiratta, D.K., Bhutada, K., Narang, R., Narang, P. 2006. Evaluation of different methods for diagnosis of P. falciparum malaria. *Brief Communications* **1**(24):49-51.

Milne, L.M., Kyi, M.S., Chiodini, P.L., Warhurst, D.C. 1994. Accuracy of routine laboratory diagnosis of malaria in the United Kingdom. *J Clin Pathol* **27**:142-149.

Ministry of Health. *2005. National Health Strategic Plan 2006-2011. Ministry of Health Lusaka. Zambia.*

Ministry of Health. *National 10-Year Human Resource Plan for the Public Sector. 1st Edition, January 2001*. Lusaka, Zambia.

Moody, A. 2002. Rapid diagnostic tests for malaria parasites. *Clin Microbiol Rev* **15**(1):66-78.

Mudondo, C., Chanda, P., Ndhlovu, M., Wamulume, P. 2005. *Artemisini-based combination therapy: From policy change to implementation*. Country Report. Accessed 20th November 2005, Available at http://www.who.int.

Muhe, L., Oljira, B., Degefu, H., Enquesellasie, F., Weber, M.W. 1999. Clinical algorithm for malaria during low and high transmission seasons. *Arch Dis Child.* 81(3):**216-220.**

Muheki, C., McIntyre, D., Barnes, K. I. 2004. Artemisinin-based combination therapy reduces expenditure on malaria treatment in KwaZulu Natal, South Africa. *Trop Med Int Health* **9**(9):959-966.

Mwangi, T.W., Mohammed, M., Dayo, H., Snow, R.W. and Marsh, K. 2005. Clinical algorithms for malaria diagnosis lack utility among peplum of different age groups. *Trop Med Int Health* **10**(6):530-536.

National Malaria Control Centre. 2000. *Malaria Situation Analysis*. NMCC/CBOH. Lusaka, Zambia.

National Malaria Control Centre. 2001. *Roll Back Malaria Baseline Survey*. National Malaria Control Program. Zambia.

National Malaria Control Centre. 2003. *Drug Policy Implementation Plan*. Lusaka, Zambia.

National Malaria Control Centre. 2004a. *Post Spray Workshop Summary Report* (30th March to 2nd April 2004). Lusaka.

National Malaria Control Centre. 2004b. *Insecticide Treated Mosquito Nets: Guidelines for Implementation and Monitoring*. Central Board of Health, Lusaka.

National Malaria Control Centre. 2004c. *Guidelines for the Diagnosis and Treatment of Malaria in Zambia*. Central Board of Health. Lusaka.

National Malaria Control Centre. 2005. *Outcomes Monitoring Report 2005*. NMCC, Lusaka, Zambia.

National Malaria Control Centre. *Roll Back Malaria Strategic Plan 2001-2005*. 2001. Central Board of Health, Zambia.

Ndhlovu, M., Dejan, Z., Nawa, S. 2004. *Final Report: Evaluation of Outpatient Malaria Case Management in Four Areas of Different Malaria Ecologies in Zambia*. Central Board of Health/Ministry of Health, Lusaka, Zambia, Unpublished.

Omari, A., Preston, C., Garner, P. 2002. Artemether-lumefantrine for treating uncomplicated falciparum malaria. *Cochrane Database of Systematic Reviews* **2**: 2002.

Othnigue, N., Wyss, K., Tanner, M., Genton, B. 2006. Urban malaria in the Sahel: prevalence and seasonality of presumptive malaria and parasitaemia at primary care level in Chad. *Trop Med Int Hlth* **11**(2):204-210.

Palmer, C.J., Lindo, J.F., Klaskala, W.I., Quesada, J.A., Kaminsky, R., et al. 1998. Evaluation of the OptiMAL test for rapid diagnosis of *Plasmodium vivax* and *Plasmodium falciparum* malaria. *J Clin Microbiol* **36**(1):203-206.

Palmer, S. and Torgerson, D. 1999. Economic notes: definitions of efficiency. *BMJ* **318**:1136-1136.

Phillips, M. and Phillips-Howard, P. A. 1996. Economic implications of resistance to antimalarial drugs. *Pharmacoeconomics* **10**(3):225-238.

Rajab, J.A., Withaka, P.M., Orinda, D.A., Scott, C.S. 2005. Analysis of cost and effectiveness of pre transfusion screening of donor blood and antimalarial prophylaxis for recipients. *East Afr Med J* **82**(11):565-571.

Rolland, E., Checchi, F., Pinoges, L., Balkan, S., Guthman, J., Guerin, P.J. 2006. Operational response to malaria epidemics: are rapid diagnostic tests cost-effective?. *Trop Med Int Health* **11**(4):398-408.

Sachs, J., D. Macroeconomics and health: investing in health for economic development. Report of the Commission on Macroeconomics and Health. Geneva, World Health Organisation, December 2001. Accessed 6 March 2006 available at: http://www3.who.int/whosis/cmh/cmh_report/e/pdf/001-004.pdf

Schmid, G., P. 1995. Understanding the essentials of economic evaluation. *Journal of Acquired Immune Deficiency Syndromes and Human Retrovirology* **10**(Suppl 4):S6-S13.

Snow, R. W., Eckert, E., Teklehaimanot, *A.* 2003. Estimating the needs for artemisinin-based combination therapy for malaria case-management in Africa. *Trends in Parasitology* **19**(8):363-369.

Stephens, J. K., Phanart, K., Rooney, W., Barnish, G. 1999. A comparison of three malaria diagnostic tests under field conditions in North-West Thailand. *Southeast Asian Trop Med Public Health* **30**(4):625-630.

Tarimo, D.S., Minjas, J.N., Bygbjerg, I.C. 2001. Malaria diagnosis and treatment under the strategy of the integrated management of childhood illness (IMCI): relevance of laboratory support from the rapid immunochromatographic tests of ICT Malaria P.f/P.v and OptiMal. *Ann Trop Med Parasitol* **95**(5):437-444.

Utzinger, J., Tozan, Y., Doumani, F., Singer, B. H. 2002. The economic pay off of integrated malaria control in the Zambian Copperbelt between 1930 and 1950. *Trop Med Int Health* **8**:657-677.

World Health Organisation Statistics Information System, (n.d.). Retrieved 18th September 2005, from http://www.who.int/nha/country/ZMB.xls.

World Health Organisation Statistics Information System. (n.d) Accessed 20/02/2006 from http://www.who.int/nha/country/en/

World Health Organisation. 2000c. *New Perspectives in Malaria Diagnosis. Report on a Joint WHO/USAID Informal Consulation, 25-27 October 1999.*Geneva. WHO/RBM/2000.14.

World Health Organization. *Roll back malaria: facts on artemisinin-based combination therapies.* Geneva: WHO; 2005. Available: www.rbm.who.int/cmc_upload/0/000/015/364/RBMInfosheet_9.htm (accessed 2005 Dec 8).

World Health Organization. *World Malaria Report 2005.* Geneva, Switzerland. WHO/HTM/MAL/2005.1102.

World Health Organization.2000a. *WHO Expert Committee on Malaria. Twentieth Report*, Geneva, World Health Organisation, 2000. (WHO Technical Report Series, No. 892).

World Health Organization.2000b. *The African Summit on Roll Back Malaria, Abuja, April 25, 2000.* Geneva, Switzerland, World Health Organization. Roll Back Malaria.

Yeung, S., Wirichada, P., Hastings, I. M., Mills, A. J., White, N. J. 2004. Antimalarial drug resitance, artemisinin-based combination therapy, and the contribution of modelling to elucidating policy choices. *Am J Trop Med Hyg* **71**(2 suppl):179-186.

Zambia Malaria Foundation.n.d Accessed 12 April 2006. Available at: http://www.malaria.org.zm/treatment.hml

Zambia RBM News. 2004. *Newsletter of the Partnership to Roll Back Malaria in Zambia*. Volume 1, Issue 2.

Zambia. 2002. .*Demographic Health Survey 2001/2002*. Central Statistical Office. Lusaka.

Appendix I. Data Collection Tools

Cost and cost-effectiveness analysis of the available strategies for diagnosing malaria in outpatient clinics in Zambia.

1. Facility Characteristics

Health Facility:_____ Date:_____

District:_____

District catchment population:_____

Number of health centres in district:_____

Month being transcribed :_____

Malaria OPD attendance:_____ All disease OPD attendance:_____

2. Cost Data

1. Capital Costs (List)	Quantity/ Cost	Life span
1.1 Diagnostic related		
1.2 Medical consultation related		
1.3 Pharmacy related		
2. Personnel Costs		
Staff cadre	Time spent on malaria related care	Salary plus fringe benefits per month
Clinical Officer		
Nurse		
Lab Technician		
EHT		
CDE		
Other (specify)		
3. Supplies as used by each cadre;eg reagents, etc	Cost	Quantities/Month

4. Over heads		
Administration		
Electricity		
Water		
Communication		
Cleaning		
Storage	Area occupied	cost
Reagents cupboard		
RDTs storage, etc		

3.0 Malaria Facility Data

Month	Diagnostic Strategy	Under Five Years Status			5 Years and above Status		
		+ ve	-ve	Treatment	+ve	-ve	Treatment
February							
March							
April							
May							
June							
July							
August							
September							
October							
November							
Total							

+ve = Declared malaria positive
-ve = Declared malaria negative

Annualization factors

Expected useful life in years	Discount rate 1%	2%	3%	4%	5%	6%	7%	8%	9%	10%	11%	12%	13%	14%	15%	16%	17%	18%	19%	20%
1	0.990	0.980	0.971	0.962	0.952	0.943	0.935	0.926	0.917	0.909	0.901	0.893	0.885	0.877	0.870	0.862	0.855	0.847	0.840	0.833
2	1.970	1.942	1.913	1.886	1.859	1.833	1.808	1.783	1.759	1.736	1.713	1.690	1.668	1.647	1.626	1.605	1.585	1.566	1.547	1.528
3	2.941	2.884	2.829	2.775	2.723	2.673	2.624	2.577	2.531	2.487	2.444	2.402	2.361	2.322	2.283	2.246	2.210	2.174	2.140	2.106
4	3.902	3.808	3.717	3.630	3.546	3.465	3.387	3.312	3.240	3.170	3.102	3.037	2.974	2.914	2.855	2.798	2.743	2.690	2.639	2.589
5	4.853	4.713	4.580	4.452	4.329	4.212	4.100	3.993	3.890	3.791	3.696	3.605	3.517	3.433	3.352	3.274	3.199	3.127	3.058	2.991
6	5.795	5.601	5.417	5.242	5.076	4.917	4.767	4.623	4.486	4.355	4.231	4.111	3.998	3.889	3.784	3.685	3.589	3.498	3.410	3.326
7	6.728	6.472	6.230	6.002	5.786	5.582	5.389	5.206	5.033	4.868	4.712	4.564	4.423	4.288	4.160	4.039	3.922	3.812	3.706	3.605
8	7.652	7.325	7.020	6.733	6.463	6.210	5.971	5.747	5.535	5.335	5.146	4.968	4.799	4.639	4.487	4.344	4.207	4.078	3.954	3.837
9	8.566	8.162	7.876	7.435	7.108	6.802	6.515	6.247	5.995	5.759	5.537	5.328	5.132	4.946	4.772	4.607	4.451	4.303	4.163	4.031
10	9.471	8.983	8.530	8.111	7.722	7.360	7.024	6.710	6.418	6.145	5.889	5.650	5.426	5.216	5.019	4.833	4.659	4.494	4.339	4.192
11	10.368	9.787	9.253	8.760	8.306	7.887	7.499	7.139	6.805	6.495	6.207	5.938	5.687	5.453	5.234	5.029	4.836	4.656	4.486	4.327
12	11.255	10.575	9.954	9.385	8.863	8.384	7.943	7.536	7.161	6.814	6.492	6.194	5.918	5.660	5.421	5.197	4.988	4.793	4.611	4.439
13	12.134	11.348	10.635	9.986	9.394	8.853	8.358	7.904	7.487	7.103	6.750	6.424	6.122	5.842	5.583	5.342	5.118	4.910	4.715	4.533
14	13.004	12.106	11.296	10.563	9.899	9.295	8.745	8.244	7.786	7.367	6.982	6.628	6.302	6.002	5.724	5.468	5.229	5.008	4.802	4.611
15	13.865	12.849	11.938	11.118	10.380	9.712	9.108	8.559	8.061	7.606	7.191	6.811	6.462	6.142	5.847	5.575	5.324	5.092	4.876	4.675
16	14.718	13.578	12.561	11.652	10.838	10.106	9.447	8.851	8.313	7.824	7.379	6.974	6.604	6.265	5.954	5.668	5.405	5.162	4.938	4.730
17	15.562	14.292	13.166	12.166	11.274	10.477	9.763	9.122	8.544	8.022	7.549	7.120	6.729	6.373	6.047	5.749	5.475	5.222	4.990	4.775
18	16.398	14.992	13.754	12.659	11.690	10.828	10.059	9.372	8.756	8.201	7.702	7.250	6.840	6.467	6.128	5.818	5.534	5.273	5.033	4.812
19	17.226	15.678	14.324	13.134	12.085	11.158	10.336	9.604	8.950	8.365	7.839	7.366	6.938	6.550	6.198	5.877	5.584	5.316	5.070	4.843
20	18.046	16.351	14.877	13.590	12.462	11.470	10.594	9.818	9.129	8.514	7.963	7.469	7.025	6.623	6.259	5.929	5.628	5.353	5.101	4.870
21	18.857	17.011	15.415	14.029	12.821	11.764	10.836	10.017	9.292	8.649	8.075	7.562	7.102	6.687	6.312	5.973	5.665	5.384	5.127	4.891
22	19.660	17.658	15.937	14.451	13.163	12.042	11.061	10.201	9.442	8.772	8.176	7.645	7.170	6.743	6.539	6.011	5.696	5.410	5.149	4.909
23	20.456	18.292	16.444	14.857	13.489	12.303	11.272	10.371	9.580	8.883	8.266	7.718	7.239	6.792	6.399	6.044	5.723	5.432	5.167	4.925
24	21.243	18.914	16.936	15.247	13.799	12.550	11.469	10.529	9.707	8.985	8.348	7.784	7.283	6.835	6.434	6.073	5.746	5.451	5.182	4.937
25	22.023	19.523	17.413	15.622	14.094	12.783	11.654	10.675	9.823	9.077	8.422	7.843	7.330	6.873	6.464	6.097	5.766	5.467	5.195	4.948
26	22.795	20.121	17.877	15.983	14.375	13.003	11.826	10.810	9.929	9.161	8.488	7.896	7.372	6.906	6.491	6.118	5.783	5.480	5.206	4.956
27	23.560	20.707	18.327	16.330	14.643	13.211	11.987	10.935	10.027	9.237	8.548	7.943	7.409	6.935	6.514	6.136	5.798	5.492	5.215	4.964
28	24.316	21.281	18.764	16.663	14.898	13.406	12.137	11.051	10.116	9.307	8.602	7.984	7.441	6.961	6.534	6.152	5.810	5.502	5.223	4.970
29	25.066	21.844	19.188	16.984	15.141	13.591	12.278	11.158	10.198	9.370	8.650	8.022	7.470	6.983	6.551	6.166	5.820	5.510	5.229	4.975
30	25.808	22.396	19.600	17.292	15.372	13.765	12.409	11.258	10.274	9.427	8.694	8.055	7.496	7.003	6.566	6.177	5.829	5.517	5.235	4.979

Response to Reviewers' Comments on Dissertation

1. Response to Dr C Goodman's Comments

Comments:

Literature review – In parts this reads as a summary of studies one-by-one, each with its own paragraph e.g. pages 22-25, 28-29, 33-36. A literature review should aim to do more than this. It should synthesise studies, showing where they are in agreement, and where they are not. This would have been facilitated by grouping studies by e.g. area, main malaria species, type of test etc. and describing general findings across studies, rather than the details of each one.

Response:

The sections have been reviewed and studies combined where necessary for the above-mentioned pages.

Comment:

Parasite prevalence assumptions - I think the prevalence you refer to on page 57 refers to the % of the community parasite positive. One would expect prevalence to be significantly higher among the sub-population presenting with fever. For example, in Tanzania the parasite prevalence of those presenting with fever at facilities was

Response:

Parasite prevalence assumptions: Although no change was made on the values used, details of why these data applies to facility-based malaria suspected cases were added in page 55 paragraph 3.

Comment:

Definition of Clinical Diagnosis – you need to clarify how this was done. Normally all fevers are considered "suspected malaria" and therefore clinically diagnosed. In which case you wouldn't expect some of the suspected malarias to be found negative by clinical diagnosis (Table 5.1 – in one facility – Kabwe – this is particularly high). Can you clarify for Table 5.1 what the denominator is for % found negative and how clinical diagnosis was conducted.

Response: Clarification of the definition of clinical diagnosis was emphasised in page 44 paragraph 2.

Accuracy and consistency of results.

Comment:

- Fig 5.1 – total negative for clinical stated as 1702, but from Table 5.1 is 691. Similarly for most cells in table.

Response:

Fig 5.1 Total diagnosed clinically negative overall is more because some patients had more than one test performed such first the clinical diagnosis was done and thereafter microscopy was performed. However, the diagnostic test assigned to each facility was given dominance. Text and figures were amended to be consistent with table **5.1**, therefore changes were done in pages 60 and figure 5.1

Comment:

- Page 72, para 1 – 74% seems wrong, surely 977/5829 = 17%. Similarly for 1%, and for 19% in para 2

Response: Page 72: revised as suggested.

Comment:

- Page 85 – you appear to be using 2.45 as AL cost, but in Table 4.6 you give the average AL cost as 1.65.

Response: Page 85: Corrected on page 61. USD 2.45 cost of antimalarials used (included storage and distribution costs). 1.65 was weighted average per dose before distribution and storage costs and should not have appeared in the table. **Corrections have been made.**

Comment:

- Page 85 – the proportions getting QN with microscopy appear to have been reversed between the positives and negatives ie. Should be 0.1013 for false positives (although it is difficult to read from Fig 5.11, so maybe I'm mistaken)

Response: Page 85; No changes because proportion getting QN with microscopy is correct as presented.

Comment:

- Page 87, Table 5.14 – line e for clinical of 9,380 does not seem to match 9,429 from Table 5.10. Similarly line j of 1552 and 6081 do not seem to match Table 5.6. In rows l and m denominator should be j not h.

Response: Page 87: verified and corrections made

Comment:

- Page 89, para 1 – you state these results are for "only positives treated" but they seem to match those for all treated in Table 5.14.
- Page 89, Table 5.15 – where do the incremental costs 4.6 and 1.1 come from – they don't seem to be derived from the cost/patient diagnosed and treated row.

Response: Page 89, Table 5.14 figures and Table 5.15 , Table 5.6 corrections made and changes in ACER for clinical made to USD 17.1 as shown in table 5.14 and revised where applicable in the text.

Comment:

- Page 93, Table 5.17 – why do you use as your baseline the results excluding drug costs? Surely it would be more appropriate to include drugs as well?

Response: Page 93, Table 5.17 the baseline results for ACER have drug costs included, please refer to Table 5.14 row f and g. However for ICER, the unit cost of diagnosis and treatment have been used also.

Comment:

Clarify which findings are based on data and which on assumptions – you frequently make comments about diagnostic accuracy results e.g. Page 73, para 1, you state the diagnostic accuracy of microscopy in different facilities. This is only the *assumed* accuracy based on your assumptions about sensitivity which you assumed to be constant across facilities. In reality, average sensitivity may have been different, and sensitivity may have varied across facilities. I would start these sentences with a

Response: Clarification on findings referring data or assumptions. An opening sentence has been inserted on page 71 to ensure that the reader is reminded on how cases correctly diagnosed (and hence accuracy) was calculated based on available literature on sensitivity for each diagnostic test as showed in table 4.6.

Comment:

Comparing costs and cost-effectiveness across diagnostic groups – by using the cost data from each group of facilities in your CEA you effectively assume that all the differences in cost between the groups can be attributed to the diagnostic method used. If you had a large and representative sample of facilities, allocated randomly to diagnostic method, this might be fair. In your case it is not, as it appears that e.g. microscopy was practiced in bigger facilities, with more qualified health workers, and as you note, utilisation varied. One needs to think in terms of "what would be the costs of introducing microscopy in the RDT and clinical facilities and vice versa. In comparing cost-effectiveness I therefore think it would be more appropriate to include only the costs specifically related to diagnosis, and to use an average across all facilities for the non-diagnostic costs. (you refer to Diagnosis costs in the analysis e.g. Table 5.14, but I think you mean all non-drug costs i.e. including consultation etc).

Response: Issue pointed out in discussion (weaknesses):

Comment:

Costs of false positives and false negatives – I would have thought the appropriate analysis here would be to consider the cost of treating false positives *compared* to what they would have cost if they had been diagnosed accurately, and similarly for false negatives. This would be the "cost associated to malaria misdiagnosis" you refer to on page 96, para 2 (NB false negatives would actually have cost more if diagnosed appropriately).

Response: Costs of false positives and false negatives. The primary objective of these calculations was to estimate the wastage on drugs due to wrong diagnosis. Thus, the ideal was to estimate the extent of otherwise "avoidable" expenditure on treatment. With this argument antimalarials given to false positives are relevant to consider as well as other drugs (non-malaria) given to false negatives patients. Unfortunately the latter information was not available and therefore this is recognised as part of the limitations (**inserted on page 111**).

Comment:

Scope of Costs included – it is inconsistent to include a different scope of costs in the CEA and the scale up estimates (training and supervision included only in the latter). You could only do this if you could argue that these additional costs would not vary across diagnostic method. If these activities are required for implementation, and vary across methods, they should be included in the CEA costs.

Response: Changed as suggested. The M&E and supervision costs were excluded from the cost analysis, only trainbing costs were maintained.

Comment:

Data reliability – you rely heavily on data from facility registers – these are notoriously incomplete and inaccurate – do you have a feel for how reliable they were in this setting?

Response: Data Reliability. Normally, facility registers are considered unreliable. However, in the context of the study, measures were put in place to assure data quality as described in the methods section. However, the issue has been **added to limitation on page 111**.

Comment:

Limitations section – this is rather thin. Could be added to using some of the points above!

Response: Other limitations have been identified as shown on page 109-110

Comment:

Table 2.1 – what does "% for every 25 births" mean?

Response: Table 2.1 . Low birth weight occurrence **clarified on page 10**.

Comment:

Table 2.1 and Fig 2.1 – how is malaria prevalence defined in the table – does this mean the prevalence of parasitaemia in the community? How are malaria cases defined in the figure – is this outpatient diagnoses? It's important to be specific about this as malaria is not the same as parasitaemia and (as you are clearly aware) malaria diagnoses are not all malaria. Similarly you need to define malaria incidence in Table 4.1, and prevalence in Table 4.6

Response: Malaria prevalence clarified. HMIS report include both confirmed and unconfirmed cases. Figure2.1 malaria cases defined in the footnote. Table 4.1 and 4.6 clarifications on definitions made.

Comment:

Page 22, para 3 – "Fever in the past 3 days" does not imply fever beginning at least 3 days ago. Therefore a patient starting a fever today would still qualify as fever in the past 3 days.

Response: Page 22. Noted.

Comment:

Page 36, para 4 – Goodman et al date is incorrect.

Response: Page 36. Citation corrected to Goodman et al 1999.

Comment:

Page 37, para 4 – specify that you mean IPTp i.e. in pregnancy, rather than in infants or children.

Response: Page 37. IPT in pregnancy inserted.

Comment:

Page 38, para 2 – you attribute some of good CEA results for malaria treatment to the fact that treatment can also reduce transmission. However these preventive benefits are actually very rarely included in CEAs of treatment, and so won't account for the good results cited.

Response: Page 38. Reduced transmission and thus lowers the malaria allocation factor leading to a lower cost effectiveness ratio. No changes made.

Comment:

Page 42, para 2 – definition of allocative efficiency. It's a bit misleading defining this as looking at distributive patterns as it doesn't matter who receives the benefits. The key point is that it considers the allocation of resources across different interventions.

Response: Page 42. Revised as suggested.

Comment:

Page 46, para 3, define CDE

Response: Page 46. CDE=Commissioned Daily Employee.

Comment:

Figure 4.1, third row, would be better labelled "suspected malaria" than "malaria confirmation". Also unclear why you have "wastage of drugs" under "don't give antimalarial".

Response: Figure 4.1 Corrections made

Comment:

Page 54 – does Table 4.4 and text refer to initial suspected malaria or confirmed diagnoses? It's unclear whether the data are comparable across facilities, or influenced by the diagnostic strategy used.

Response: Page 54. Table 4.4 refers to all malaria related visits (regardless of whether they come out positive or negative) reported at each facility regardless of diagnostic test method used.

Comment:

Page 56 – what do you mean by a Bayesian Model? I don't see any use of Bayesian statistical methods in this study... (similarly page 71)

Response: Page 56. 2 x 2 Table used instead of Bayesian Model. However, the calculations used in the 2 x 2 originate from the Bayesian Theory not Bayesian Statistics.

Comment:

Page 56 – sensitivity for clinical diagnosis – you argue that 100% sensitivity can be assumed if all suspected malaria visits were classified as positive for malaria. However, you have no way of knowing if other true malaria cases never even got included in the suspected malaria group and were therefore false negatives. You have no way of assessing this, but it would be worth mentioning as a limitation.

Response: Revised. The limitation aspect has been included.

Comment:

Page 63, para 1 – by saying "Of these" you imply 47.46% of the 12,267 referred to in the previous sentence, which is not what you mean.

Response: Page 63. Correct text inserted.

Comment:

Page 64, para 3 – you attribute the lower malaria-related visits in certain facilities to use of IRS – it could presumably also reflect underlying differences in disease patterns e.g. due to urban location.

Response: Page 64. Noted and added as possible explanation for the observations.

Comment:

Page 65, Table 5.2 – specify time period for data. I think you mean rate of visits per population rather than % malaria visits. This is normally presented as a rate per 1000 population, so for first row would be 78.

Response: Page 65. Time period clarified and inserted in the table title.

Comment:

Page 66, para 1 – the cases do not start reducing in Sep.

Response: Page 66. Clarified and corrected.

Comment:

Page 78, para 3 – you are excluding rather than controlling for the extra costs.

Response: Page 78. Revised by inserting correct word, 'excluding'.
Comment:

Page 83, line 7 – do you mean "higher than both microscopy and clinical diagnosis"?

Response: Page 83: Corrected as suggested.

Comment:

Page 84, para 3, line7 – should refer to Table 4.6?

Response: Page 84. corrected.

Comment:

Page 88, para 2 – check references to rows in Table 5.14 – don't seem to be correct.

Response: Page 88. reviewed and corrected.
Comment:

Page 90, para 1, line 7/8 – on what basis do you argue that clinicians did not follow microscopy results because of the delay? You also find they don't follow RDT results, which are quicker.

Page 90, para 3 – do all health facilities really have this full complement of staff? If not, training costs will be lower.

Response: sentence clarified on page 89 paragraph to include... *partly*
Response: Clarified in text on page 89.

Comment:

Page 94, line 2 – RDT strategy does not dominate clinical. Similarly page 95, para 1 & 2.

Response: Page 94. Clarification inserted.

Comment:

Page 104, para 2 – is it possible to recalculate your results to make them comparable to Rolland et al.?

Response: Page 104. Methods used by Rolland et al differ from the ones used in this study, including the scenario (he used an epidemic situation and different outcome measure). No changes were made to avoid misinterpretation.

Comment:

Page 104, para 3 – Buolombai et al ref is not in bibliography.

Response: Page 104. Buolombai et al ref inserted.

Comment:

Page 112, para 3 – why are the results only relevant where microscopy is not available – surely you have shown that RDTs would be better even if microscopy were available?

Response: Page 112. *microscopy* changed to *diagnostic* services for better understanding. The case for Zambia was what do we implement in areas where there is no microscopy already.

Comment:

There are at least 50 typos in the thesis – I suggest a final proof read before re-submission.

Response: Detected typos corrected and proof reading performed by author and a second person.

2. Response to Charlotte M Zikusooka Comments

Comment:

1. Pg 3: Reference is made to 2001 data and the candidate uses the word 'currently'.

Response: Pg 3. Currently deleted.

Comment:

2. Pg 18, 26, 36: Whenever an author is quoted (with exact words in a quotation marks), the reference must have a page number.

Response: Pg 18, 26, page numbers for quotations inserted. Page 36, quotation rephrased.

Comment:

3. Pg 37: Whenever a 'Personal Communication' reference is used, both the names of the person and their designation have to be indicated.

Response: Page 37. Name of person in personal communication indicated.

Comment:

4. Pg 41 Table 3.3. I think more studies have been conducted on specificity and sensitivity of microscopy and RDTs. Hence more studies should be included for those categories. The candidate should make references to the following:

Response: No changes: Page 41, Table 3.3 the studies included in this table have a specific inclusion criteria and specific tests so that only the results applicable to the Zambian situation were used.

Comment:

5. Pg 45: The discussion on economic evaluation methods is somewhat disjointed. E.g. in para 1, the candidate moves from 'discounting' to 'ICER' to 'sensitivity analysis' all in the same paragraph.

Response: No changes: Page 45. The paragraph is a closing summary of the entire major steps in economic evaluation hence all concepts in one paragraph.

Comment:

6. Pg 54: Are the cases presented in Table 4.4 CONFIRMED malaria cases?

Response: Footnote inserted: Page 54. Table 4.4 refers to all malaria related visits (confirmed and unconfirmed) in the facilities for the entire 2005 as per district information systems.

Comment:

7. Pg 57: What is the basis for methods used in calculating health outcomes (i.e. False positive, True positives, False Negatives and True Negatives). Are these methods used elsewhere in other literature? There is no reference made to such literature.

Response: Page 57. The outcome measure in this case is based on screening methodology, which is in turn drawn from Bayesian theory. In other literature it is referred to as accuracy (true positives + true negatives). Please refer to articles in literature review.

Comment:

8. Pg 67-70: What are the reasons for variations noted on Figures 5.5 and 5.7? Why is Kawama different from other study sites? The candidate should explore possible reasons for such differences.

Response: Page 67-70. Kawama is located in an area where indoor residual spraying was conducted hence likely to record less malaria parasite positivity.

Comment:

9. It is not clear whether the results presented under the classifications of True positives, False positives, etc... (pg 72 – 72) are calculated on the basis of the formula presented on page 57 or whether it is reported based on the results from the "gold standard" (i.e. expert microscopy).

Response: Page 72. Formula for true positives, false positives, etc. refers to page 57 in the methods section. Opening statement in the section 5.2 also clarifies the source of calculations.

Comment:

10. What does "prior prevalence" mean?

Response: Prior prevalence- underlying parasite prevalence in the district as obtained from specialised surveys. Also defined in page 57 as "pre-test probability"

Comment:

11. Pg 72-73: Explain the differences noted in different study areas. E.g. in Table 5.5 why is the accuracy of RDTs in Chalimbama different from that in other study sites?

Response: Page 72 – 73. Plausible reasons for variations added.

Comment:

12. Pg 76-77: Similarly, explain the variations in 'cost per visit'. E.g. see Table 5.8

Response: Page 76-77 Variations in cost explained under discussion section on page 97-98.

Comment:

13. In GENERAL: the results could be better discussed. The current discussion of results is only descriptive.

Response: Discussion reviewed and figures verified.

Comment:

5. Pg 87: Table 5.14 on rows 'l' and 'm', the formula should be f/j and g/j respectively.

Response: Page 87. Rows l and m formula corrected.

Detectable grammatical errors and spellings revised.