MALARIA TREATMENT IN ETHIOPIA: ANTIMALARIAL DRUG EFFICACY MONITORING SYSTEM AND USE OF EVIDENCE FOR POLICY

by

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DECLARATION

I declare that this thesis titled **"Malaria Treatment in Ethiopia: Antimalarial Drug Efficacy Monitoring System and Use of Evidence for Policy,"** is my own work and that all the sources that I have used or quoted have been indicated and acknowledged by means of complete references and that this work has not been submitted before for any other degree at any other institution.

18 July 2012

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SIGNATURE **DATE**

Ambachew Medhin Yohannes

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ABSTRACT

The purpose of this study was to describe the characteristics and findings of antimalarial drug efficacy studies conducted in Ethiopia and to use the findings to formulate recommendations for antimalarial drug efficacy monitoring and use of evidence to inform antimalarial treatment policy for the Ethiopian setting.

This study reviewed 44 antimalarial efficacy studies conducted in Ethiopia from 1974 to 2011. The analysis of results indicated that chloroquine as the first-line antimalarial drug for the treatment of malaria due to *Plasmodium falciparum* had a 22% therapeutic failure in 1985. Chloroquine was replaced with sulfadoxine-pyrimethamine in 1998, more than 12 years later, when its therapeutic failure had reached 65%. Sulfadoxine-pyrimethamine at the time of its introduction had a treatment failure of 7.7%; it was replaced after seven years in 2004 by artemether-lumefantrine; by then its treatment failure had reached 36%.

The WHO recommends the replacement of a first-line antimalarial drug when more than 10% of treatment failure is reported. The replacement drug should have a therapeutic efficacy of more than 95%; while the change itself should be completed within two years. The prolonged delay to replace failing antimalarial drugs in Ethiopia seems to have been influenced mainly by the lack of systematic antimalarial drug efficacy data collection and pragmatic use of the data and evidence gathered.

Almost eight years after its introduction, isolated studies show that the efficacy of artemether-lumefantrine has decreased from 99% in 2003 to around 96.3% in 2008. Though this decrease is not statistically significant (chi-square 1.5; P=0.22) and has not reached the threshold of 10%, it is plausible that its efficacy may drop further. This is mainly due to regulatory provisions in the country that allow marketing of oral artemisinin mono-therapies that are not recommended for malaria treatment, use of less effective antimalarial combination drugs in the neighboring countries and widespread drug quality problems.

The situation calls for and this study recommends the establishment of stringent drug efficacy monitoring and early warning system and alignment of the antimalarial drug regulatory practices with recommendations of the WHO.

KEY CONCEPTS

Malaria, antimalarial drug efficacy, monitoring, treatment policy and guideline change.

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- The University of South Africa (UNISA) Institutional Review Board for the ethical clearance of the study, the Ministry of Health of Ethiopia for making various reports and documents available, the researchers and communities in Ethiopia who participated in the antimalarial efficacy studies conducted in the country.

DEDICATION

In loving memory of my grandmother Almaz Adal

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LIST OF ABBREVIATIONS

ACT	Artemisinin-based Combination Therapy
AL	Artemether-lumefantrine
AP	Atovaquone -Proguanil
AS+AQ	Artesunate plus Amodiaquine
DALYs	Disability Adjusted Life Years
EANMAT	East African Network for Monitoring Antimalarial Treatment
HANMAT	Horn of African Network for Monitoring Antimalarial Treatment
HEW	Health Extension Worker
IPT	Intermittent Presumptive Therapy
ITN	Insecticide Treated Net
IRS	Indoor Residual Insecticide Spraying
NCBI	National Centre for Biotechnology Information
nmol	nano mole
OECD	Organization for Economic Cooperation and Development
Pfcrt	Plasmodium falciparum cytochrome transfer
P.m	*Plasmodium malariae*
PHC	Primary Health Care Unit
PCR	Polymerase Chain Reaction
RDTs	Rapid Diagnostic Tests
SADC	Southern Africa Economic Cooperation
SPSS	Statistical Package for Social Sciences
US	United States
USP	United States Pharmacopeia
WHO	World Health Organization

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CHAPTER 1

ORIENTATION TO THE STUDY

1.1 INTRODUCTION

The Federal Ministry of Health, Ethiopia (2006a:4) estimates that nearly 75% of the Ethiopian land where 68% of the population live is at risk of malaria. Adhanom, Deressa, Witten, Getachew and Seboxa (2006:556) explain that as a reflection of the diverse eco-climatic conditions in the country, the disease (malaria) transmission patterns shows seasonal and temporal variability often characterised by focal and cyclic epidemics of varying magnitude.

According to the Federal Ministry of Health, Ethiopia (2006b:35), malaria is on one of the leading health problems of public health concern and consistently reported as one of the leading causes of morbidity and mortality over the past years. In the years 2005/06, the Ministry of Health, Ethiopia (2006b:35) reports that malaria as the first cause of out-patient consultations accounting for 17.8% out-patient visits (1.23 million cases), second cause of admissions accounting for 14.1% admissions (45,975 admissions) and first cause of in-patient deaths accounting for 21.8% (1,434 deaths). Negash, Kebede, Medhin, Argaw, Babaniyi, Guintran and Delacollette (2005:186) also assert that the disease burden in-terms of morbidity and mortality are even higher during epidemics that occur in the main malaria transmission months from September to December that usually affect highland fringe areas where malaria transmission is seasonal.

In addition to direct health effects caused by malaria in Ethiopia, Paulander, Olsson, Lemma, Getachew and San Sebastian (2009:1) reported the negative impact of malaria in school attendance; while Deressa, Hailemariam and Ali (2007:1148) affirmed in a study conducted in selected villages in Ethiopia that malaria also reduces family income.

Malaria control in Ethiopia was started in 1959 in some high risk priority areas and in response to the recurrent malaria outbreaks and the wide-spread malaria epidemics that affected the highlands of Ethiopia in 1958 (Fountain, Najjar & Prince 1961:795).

Gebremariam and Teklehaimanot (1986:2) explained that the main malaria control intervention first introduced included treatment with chloroquine and the application of indoor residual insecticide spraying (IRS).

The current malaria control interventions in the country rely on malaria early diagnosis and treatment delivered through public and private health facilities, application of IRS in targeted malaria epidemic prone localities and distribution of Insecticide Treated Nets (ITNs) (Federal Ministry of Health, Ethiopia 2006a:13).

As the malaria transmission situation in Ethiopia is seasonal and unstable, the need to have a well-organised malaria diagnosis and treatment service is critical to preventing severe illness and death. However, the success of malaria treatment in Ethiopia as in many low-income settings has been challenged by to low access to health services. Beyond problems related to access and health service utilisation, the success of malaria treatment has also been seriously challenged due to the emerging problem of malaria parasite resistance to antimalarial drugs (Walsh 2012; Wellcome Trust 2012a).

The combined effects of low access to health service and the ever increasing incidence of resistance to antimalarial drugs need a coordinated effort to tackle them effectively. While increasing access to health services is mainly limited by the resources made available by the national government of Ethiopia and international donors, the monitoring of antimalarial drug efficacy and malaria parasites resistance to antimalarial drugs is mainly a responsibility of the National Health Service system.

Antimalarial drug efficacy monitoring and resistance monitoring in Ethiopia has been conducted by the Ministry of Health, Regional Health Bureaus, Academic and Research Institutions. However, antimalarial treatment guidelines changes introduced in the country in 1999 and 2004 were mainly based on findings of studies conducted by the Ministry of Health in Ethiopia. The objectives, findings and relevance of studies conducted by other entities and representativeness, timeliness and completeness of these studies in collecting data and information that can inform policy has never been fully assessed.

This study, therefore, aims to describe the characteristics and findings of the studies conducted in the Ethiopian setting from the date of the first study conducted in 1972

through 2011. The findings from the review are to be used to formulate recommendations and best practice guidelines to strengthen antimalarial drug efficacy monitoring systems and use of evidence to inform antimalarial drug policy and treatment guideline development for the Ethiopian setting.

1.2 BACKGROUND INFORMATION ABOUT THE RESEARCH PROBLEM

Abeku, De Vlas, Borsboo, Tadege, Gebreyesus, Gebreyohannes, Alamirew, Seifu, Nagelkerke and Habbema (2004:585) assert that large-scale malaria epidemics in Ethiopia have mostly been associated with a period of major climatic changes and discontinuation of malaria prevention and control activities. Population movement to and from endemic areas have also been indicated as a contributor to increased malaria incidence by Deressa, Ali and Berhane (2006:1).

The widespread malaria epidemics that occurred in Ethiopia in 1998 and 2003 have been coinciding with a period of confirmed low efficacy of the first-line antimalarial drug that has been in use. The malaria epidemics in 1998 coincided with the confirmed chloroquine resistance of 65% reported in the same year (WHO 2000:34). The 2003 malaria epidemics (Negash et al 2005:186) also coincided with the confirmed resistance of sulfadoxine-pyrimethamine of 36% (Jima, Tesfaye, Medhin, Kebede, Argaw & Babaniyi 2005a:391) around the same period of the epidemic.

While the impact of climatic factors on malaria epidemics and its use to predict epidemics has been described in a study conducted by Abeku, Oortmarssen, Borsboom, De Vlas and Habbema (2003:331), the contribution of diminishing efficacy of anti-malarial drugs to the occurrence of epidemics is also expected to contribute to increased malarial incidence and high prevalence of gametocytes (White 2008:1) that further contribute to increased malaria transmission.

The availability of effective antimalarial drugs is critical for malaria prevention and control. Therefore, understanding the representativeness, timeliness and completeness of antimalarial efficacy studies and the use of data collected from such studies to inform antimalarial treatment policy and treatment guideline development is highly relevant.

Findings of the efficacy of chloroquine for the treatment of uncomplicated *Plasmodium falciparum malaria* conducted in 18 study sites from 1997–1998 led to the decision to switch from chloroquine to sulfadoxine-pyrimethamine (WHO 2001:34). Findings of the efficacy study conducted on sulfadoxine-pyrimethamine in 10 study sites in 2003 led to the replacement of the drug by the ACT drug artemether-lumefantrine in July 2004 (Federal Ministry of Health, Ethiopia 2004a:1).

These relatively large multi-site studies were conducted in a time gap of nearly five years in 1998 and 2003. Apart from these major studies, all other studies that have been conducted in Ethiopia since the early 1970s were isolated studies carried using different study protocols.

The time interval between consecutive antimalarial drug efficacy studies conducted in Ethiopia, the number of sites and sample size considered, completeness of the information gathered and recommendations drawn from the studies have never been fully assessed and described. As a result of this, experiences from the previous studies that may help in providing valuable lessons for future studies and best practice approaches that can be adapted have not been identified. The research problem is, therefore, based on a practical challenge in antimalarial drug efficacy monitoring and use of evidence for policy and solving this problem is believed to have significant public health relevance for malaria control.

1.3 RESEARCH PROBLEM

Currently, there is no complete description and documentation on the antimalarial drug efficacy monitoring system and use of evidence to advice policy in Ethiopia. This gap coupled with the high risk of malaria epidemics in the country is likely to aggravate the malaria situation and hence increasing the malarial disease burden in the country.

Impact on the prevalence of severe disease and malaria related deaths largely depends on the availability of early diagnosis service and prompt treatment with safe and effective antimalarial drugs. The researcher's experience shows that the level of efficacy of antimalarial drugs declines through time and requires timely monitoring that can advise appropriate actions. To ensure the availability of effective, up-to-date antimalarial drug policy and treatment guidelines, therefore, understanding the practices in

antimalarial drug efficacy monitoring in Ethiopia is essential to guide evidence-based adoption of antimalarial drug policy and treatment guidelines that can effectively address the needs of the country.

1.4 AIM OF THE STUDY

1.4.1 Research purpose

The purpose of this study was to describe the characteristics and findings of antimalarial drug efficacy studies conducted in Ethiopia and to use the findings to formulate recommendations for antimalarial drug efficacy monitoring and use of evidence for policy and treatment guidelines development for the Ethiopian setting. Through this approach, data and findings from previous antimalarial drug efficacy studies were analysed; their strengths and weaknesses identified. The gaps observed in the completeness, timeliness and representativeness of the studies reviewed was used to formulate recommendations and best practice approaches for antimalarial drug efficacy monitoring.

The use of the recommendations and best practice approaches for antimalarial drug efficacy monitoring system and the use of data generated from such studies in informing antimalarial drug policy and treatment guidelines' development for the Ethiopian setting has also been stipulated.

1.4.2 Research objectives

The main objective of the study was to

- identify, describe and synthesise data and finding from previous antimalarial drug efficacy studies in terms of study representativeness, timeline and completeness of the studies conducted in Ethiopia
- identify strengths and weaknesses in the antimalarial drug efficacy studies and the antimalarial drug policy environment
- formulate recommendations and best practice approaches that can contribute to the improvement of antimalarial drug efficacy monitoring system and use of

evidence collected through such studies to inform antimalarial drug policy and treatment guideline development in Ethiopia

1.4.3 Research hypothesis

The researcher hypothesises that, regular antimalarial drug efficacy monitoring approaches and use of evidence for policy in Ethiopia has not been optimally synchronised to regularly update malaria treatment guidelines in Ethiopia. To prove the hypothesis, data and information from published and unpublished antimalarial drug efficacy studies was identified, described and analysed to formulate recommendations and best practice approaches in antimalarial drug efficacy monitoring.

1.5 SIGNIFICANCE OF THE STUDY

In the absence of a full understanding of the antimalarial drug efficacy trend and its monitoring system, the use of antimalarial drug efficacy data to inform antimalarial drug policy and guideline development would be challenging.

This study, therefore, aimed to provide significant information on antimalarial drug efficacy monitoring studies conducted in Ethiopia. The information collected from such studies conducted in Ethiopia from the early 1970s to 2011 was used to develop recommendations and best practice guidelines for antimalarial drug efficacy monitoring and use of data and information to advice policy and antimalarial treatment guidelines development.

The need to regularly assess the therapeutic efficacy of antimalarial drugs to ensure its continued parasitological and clinical efficacy is crucial for antimalarial treatment policy. However, the availability of complete and timely data on antimalarial drug efficacy in its own cannot guarantee timely decision on antimalarial treatment policy and treatment guideline change. Amin, Kangwana, Greenfield, Otieno, Akhwale and Snow (2007:1) confirms that in some settings, antimalarial treatment policy and guideline development can be seriously challenged by budgetary and health system issues.

Even when funding is available to support procurement of effective antimalarial drugs and to strengthen the health service delivery system, the use of the funding may not

align with the felt need. Attaran, Barnes, Curtis, D'Alessandro, Fanello, Galinski, Kokwaro, Looareesuwan, Makanga, Mutabingwa, Talisuna, Trape and Watkins (2004:237) criticise the obvious errors of scientific and medical judgment as one of the major risks in hindering the appropriate use of international donor fund in the fight against malaria. Financing institutions such as the World Bank has also been criticised for lack of impact on malaria in Africa as a result of their investment and Hopkin (2006:1096) explains how the World Banks defends such criticism.

Irrespective of the criticisms to donors, timely availability of representative and complete data on antimalarial drug efficacy remains the most critical to ensure timely review of the antimalarial drug policy. In 2003, when *Medicines Sans Frontier* (MSF) criticised the Ministry of Health of Ethiopia for using ineffective antimalarial drugs (The New York Times 2003), the Ministry was working to complete the then on-going antimalarial drug efficacy studies in a bid to obtain supportive evidence to inform decision.

The WHO (2009a:9) recommends an overall treatment failure of 10% or above to be used as a cut-off to introduce an effective antimalarial drug replacement. For treatment outcome to be determined, clinical and parasitological assessment should be conducted from 28 days for antimalarial drugs with elimination half-life of less than seven days. For antimalarial drugs with elimination half-life of more than seven days, a follow-up period of 42 days is recommended. Through this follow-up, treatment success is said to be achieved for patients who (a) have no parasitaemia on day 28 or day 42, irrespective of axillary temperature and (b) have no early treatment failure or late clinical and parasitological failure in the days before day 28 (WHO 2009a:6).

The lack of a locally up-to-date and sound antimalarial drug policy and evidence-based treatment guidelines can be serious hindrance to ensuring the provision of effective treatment services for malaria. Without ensuring effective antimalarial treatment services, the health and socio-economic consequences due to malaria can't be averted. This would in turn lead to further deterioration in the health and socio-economic well-being of the population in malaria endemic areas of the country where an estimated 68% or 50 million people live.

1.6 FOUNDATIONS OF THE STUDY

1.6.1 Research paradigm assumption

The positivist paradigm in research has ontological, epistemological, axiological, rhetoric and methodological assumptions that can be used to characterise the nature of the research (Polit & Beck 2008:13). The ontological assumption in the positivist research paradigm considers reality as an objective that can be measured and its epistemological assumptions reflect that the researcher is independent of the subject which is being researched. The axiological assumption in this study which refers to the values attached to the findings is one that doesn't attach special value for certain findings which may lead to a bias that can distort the objective findings.

The efficacy of antimalarial drugs is an objective reality that can be measured through experimental procedures and the timeliness, representativeness and completeness of such studies can be assessed using empirical measurements. The empirical measurements for timeliness are the time duration between two consecutive antimalarial efficacy studies. Study completeness refers to the number of variables recommended to be measured and the actual number measured and representativeness refers to the number of study sites and sample size compared to the recommended levels.

Based on Williams, Durrheim and Sheretta (2004:356) assertion on incomplete data as reported above, it follows that the collection of data and information on antimalarial drug efficacy at the right time with a complete set of data for the recommended variables related to antimalarial efficacy is a critical step in the process for antimalarial drug policy and treatment guideline development (WHO, Regional Office for Africa 2003:20).

Based on the concepts of representativeness, timeliness and completeness of antimalarial efficacy studies, this research theorises that the lack of representative, timely and complete data on antimalarial drug efficacy studies in Ethiopia has an implication on the success of malaria control in the country. This chapter, therefore, presents the theoretical framework description and its application in the context of the research conducted. Based on this background, the main foundations of quantitative

research of ontological, epistemological, axiological and rhetorical assumptions in relation to this research are described below.

1.6.2 Methodological assumptions

The methodological assumption in the positivist research paradigm describes the research process as deductive process that measures the cause and effect, with a defined category of outcome categories of the study set before the study. Based on the outcomes of the observations, generalisations leading to prediction, explanation, and understanding are made in an accurate and reliable way where validity and reliability of the findings are well tested.

The assessment of antimalarial efficacy and use of study findings to inform decision requires multi-disciplinary approach. Even in a resource limited setting, Hedt (2011:1) explains that the availability of a minimal expertise in clinical and laboratory assessment and basic infrastructure is essential. An antimalarial drug efficacy study team, therefore, should ideally ensure the participation of medical doctors, laboratory technical, pharmacist and epidemiologist at the right stage of the study design, data collection, analysis and report writing.

The effective conduct of antimalarial efficacy studies can ensure collection of data and information of high importance for antimalarial drug policy and treatment guideline development. However, delay in translating the study findings to inform policy can be another challenge. Mubyazi and Gonzalez-Block (2005:1) affirm that changing a national drug policy being a sensitive and time taking process, a systematic involvement of all main interested parties that includes policy makers, drug companies, health personnel, media and the general public is critical to ensure recognition of research findings and acceptance of recommendation formulated based on the study findings.

Various study techniques such as *in vivo, in vitro* and molecular methods may help detect trends in the efficacy of antimalarial drugs. All such studies should be representative, complete and timely in order to ensure use of their findings to inform antimalarial drug policy. Price, Dorswy, Ashley, Barnes, Baird, d'Alessandro, Guerin, Laufer, Naidoo, Nosten, Olliaro, Plowe, Ringwald, Sibley, Stepnieska and White (2007:1) indicate that a complete global database that includes the main determinants of clinical

response to antimalarial drugs with *in vitro*, molecular and pharmacokinetic parameters may help guide national drug policies. However, the WHO (2009a:9) recommends that national antimalarial drug policy changes to be based on data collected from representative sites. Accordingly the WHO (2009a:3) recommends the use of 4–8 sentinel study sites, depending on the size and malaria epidemiology of the country, and enrollment of statistically determined number of study subjects.

1.6.3 Rhetorical assumption

The rhetoric assumption in the positivist research paradigm describes that the research language used is clearly defined, formal and based on a set of definitions that are not personal but accepted quantitative words. In this research, the terms and definitions used in antimalarial drug efficacy studies are based on formal and standard definitions used by experts in the field.

This study uses the formal definitions of the variables measured and also uses standard dictionary definitions of representativeness, timeliness and completeness to determine if the variables measured met the desired level of attributes needed for antimalarial drug efficacy studies. The terms and concept and their definition is presented in section 1.7.

1.6.4 Theoretical framework description

The nature of a health research could be of an empirical or theoretical type. Empirical research which is mostly used in quantitative studies is based on an object of study with some aspects of reality and data is obtained through a systematic method of empirical observation. On the other hand, theoretical research which is mainly used in quantitative research focuses on problems and issues related to concepts, perspectives or theories of a given field of study or discipline and the research data consists of analysis and synthesis of theory.

A theory is a logical view that analytically explains the relationship of a phenomenon while theoretical framework in studies refers to the theoretical concept behind the research (Polit & Beck 2008:143; 768). Although the scope of use of theoretical frameworks may vary depending on the studies, research with well-articulated

theoretical framework can help obtain research findings that are meaningful and generalisable (Polit & Beck 2008:144).

The theoretical framework for this study consists of three components related to the factors that determine the quality and use of antimalarial efficacy studies. The factors identified as critical to the quality of antimalarial efficacy studies relate to representativeness, completeness and timeliness of the studies to inform antimalarial policy decision and development of antimalarial treatment guidelines.

Policy decision on antimalarial drugs or development of malaria treatment guidelines should ideally be based on complete set of information collected and used in a timely manner. Williams et al (2004:356) asserted that incomplete data and information with missing elements can delay the process to change of antimalarial drug policy and antimalarial treatment guideline development. Therefore, the collection of data and information on antimalarial drug efficacy at the right time with a complete set of data for the recommended variable related to antimalarial efficacy is a critical step in the process for antimalarial drug policy and treatment guideline development (WHO, Regional Office for Africa 2003:20).

1.6.5 Application of the theoretical framework

The three most important issues considered in this investigation are related to the representativeness, timeliness and completeness of antimalarial efficacy studies and their use to inform decision on antimalarial drug policy matters and development of guidelines. Delay in obtaining information on the efficacy of antimalarial drugs leads to delayed corrective action that can guarantee delivery of effective malaria treatment services. Moreover, if the data collected through such studies is not complete, the action that may be proposed and implemented based on incomplete and inadequate data may not be appropriate to addressing the antimalarial treatment needs of the population in need.

This research aimed to investigate the duration of the antimalarial efficacy studies conducted in the country, amount and completeness of the data collected and its appropriateness in reference to the standard 24 months recommended by the WHO (2009a:3).

For the purpose of this investigation, therefore, data from published and unpublished antimalarial drug efficacy studies was collected. The data collected was tested and scored for representativeness, timeliness and completeness taking the WHO set of recommendations as the standard and the information collected from this assessment is used to formulate recommendations and best practice approaches for the Ethiopia setting.

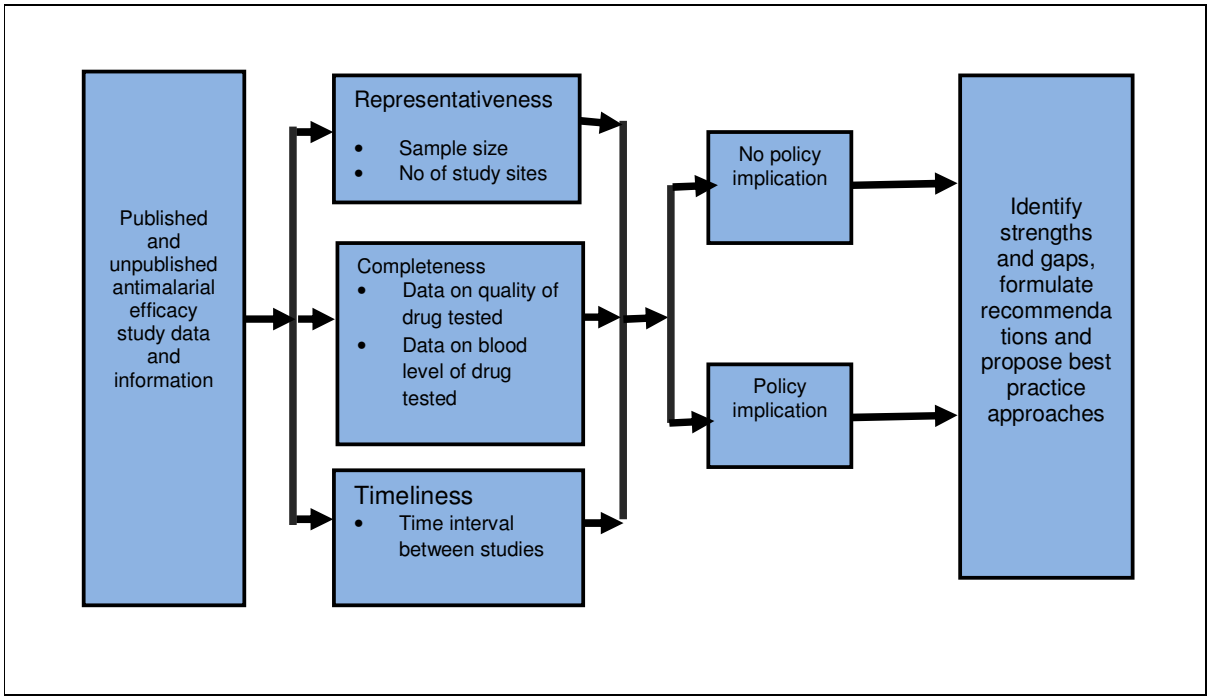

Figure 1.1 Schematic presentation of the theoretical framework

1.6.6 Justification for the proposed theoretical framework approach

1.6.6.1 The relevance of study representativeness, timeliness and completeness

The health and socio-economic impact of malaria can be alleviated when effective prevention and control interventions are applied at acceptably high levels of coverage. The WHO (2005a:60) indicates that malarial prevention and control interventions can provide better result in reducing the level of malaria when they are applied in an integrated approach.

Malaria treatment is one of the most life-saving interventions that need to be delivered to all population at risk of malaria. The effectiveness of malaria treatment interventions depend on prompt access to efficacious antimalarial drugs that are used appropriately as prescribed by a service provider. Even when promptly available, if the efficacy of the antimalarial drug in use is compromised, access to such drugs will not attain the desired treatment objective of complete parasitological and clinical cure.

Frosch, Venkatesan and Laufer (2011:1) explain that although chloroquine has been one of the most widely used antimalarial drug for the treatment of malaria in Sub-Saharan Africa, its continued use has been challenged due to parasite resistance. Resistance to the subsequently introduced replacement drug, sulfadoxine-pyrimethamine, was also relatively fast.

While addressing the main challenge of ensuring delivery of effective treatment for malaria requires introduction of an effective antimalarial drug options, some researchers recommend the need to strengthen other intervention. Lusingu and Von Seidleing (2008:253), for example, explain that the growing problem of drug resistance is driving the need to strengthen the existing interventions including the development of vaccines to augment the effect of the currently applied interventions.

However, to achieve the desired impact on malaria, the primary action should focus at ensuring the use of effective antimalarial drugs that are needed to save the lives of patients who are suffering and for whom other control interventions are not of immediate help. Therefore, a system for timely detection of decline in the efficacy of antimalarial drugs that eventually leads to full-blown resistance should be in place in order to ensure timely introduction of effective alternative antimalarial drugs.

The introduction of the new ACTs to overcome problems of malaria drug resistance and to ensure effective treatment for malaria has been praised for attaining the expected results. However, reports of emerging resistance to Artemisinin are yet again a new challenge which is threatening the effective use of the only effective ACTs available today (Mok, Imwong, Mackinnon, Sim, Ramadoss, Yi, Mayxay, Chotivanich, Liong, Russell, Socheat, Newton, Day, White, Preiser, Nosten, Fondorp & Bizdech 2011:391).

The WHO (2011a:7) reports that resistance to Artemisinin, which is one of the basic components of the ACTs antimalarial drugs, has been recently reported in the Thailand-Cambodian border which led to the launch of global plan to contain Artemisinin resistance. Anderson (2009:1) illustrates that, historically, the South-East Asian region has been the starting point of resistance to a number of antimalarial drugs and the emergence of resistance to Artemisinin in the same Geographic location may follow the same spreading pattern. This emerging problem is yet another challenge that calls for a stringent antimalarial drug efficacy monitoring system to be in place. In response to this growing concern, Noedl (2005:404) proposes methods on how to monitor and detect artemisinin resistance.

Vestergaard and Ringwald (2007:153) state that methods such as therapeutic efficacy tests, in vitro tests, and analyses of molecular markers can be used to monitor antimalarial drug resistance. However, Vestergaard and Ringwald (2007:153), stress that data obtained from therapeutic efficacy studies conducted based on the WHO recommended study protocols are the most important input to ensure timely updating of malaria treatment policies and guidelines. The use of data from such studies, therefore, should be representative, timely and must contain all the data and information needed.

To ensure scientifically correct, complete and timely conduct of antimalarial efficacy studies and to enable sound use of the data collected to inform decision, reviewing previous practices can help identify the strengths and weaknesses and lessons learned based on which future antimalarial drug efficacy approaches could be oriented. The theoretical framework outlined in this chapter, therefore, presents the description and application of the approaches used in previous studies so as to describe and identify gaps and shortcoming in order to formulate recommendations and best practice approaches for now and the future.

1.6.6.2 Disciplinary basis of antimalarial efficacy studies

The assessment of antimalarial efficacy and use of study findings to inform decision requires multi-disciplinary approach. Even in a resource limited setting, Hedt (2011:1) explains that the availability of a minimal expertise in clinical and laboratory assessment and basic infrastructure is essential. An antimalarial drug efficacy study team, therefore, should ideally ensure the participation of medical doctors, laboratory technical,

pharmacist and epidemiologist at the right stage of the study design, data collection, analysis and report writing.

The effective conduct of antimalarial efficacy studies can ensure collection of data and information of high importance for antimalarial drug policy and treatment guideline development. However, delay in translating the study findings to inform policy can be another challenge. Mubyazi and Gonzalez-Block (2005:1) affirm that changing a national drug policy being a sensitive and time taking process, a systematic involvement of all main interested parties that includes policy makers, drug companies, health personnel, media and the general public is critical to ensure recognition of research findings and acceptance of recommendation formulated based on the study findings.

Various study techniques such as in vivo, in vitro and molecular methods may help detect trends in the efficacy of antimalarial drugs. All such studies should be representative, complete and timely in order to ensure use of their findings to inform antimalarial drug policy. Price et al (2007:1) indicate that a complete global database that includes the main determinants of clinical response to antimalarial drugs with in vitro, molecular and pharmacokinetic parameters may help guide national drug policies. However, the WHO (2009a:9) recommends that national antimalarial drug policy changes to be based on data collected from representative sites. Accordingly the WHO (2009a:3) recommends the use of four to eight sentinel study sites, depending on the size and malaria epidemiology of the country, and enrollment of statistically determined number of study subjects.

1.6.6.3 Scope and measurement in antimalarial drug efficacy studies

The WHO (2009a:26) emphasises that the objective of antimalarial treatment is to achieve complete clinical and parasitological cure. In line with this objective, the scope of antimalarial efficacy studies is intended to inform national antimalarial policy based on parasitological and clinical response of patients to the antimalarial drug tested (WHO 2009a:42).

Antimalarial drug efficacy can be assessed using different methods that include *in vivo*, and *in vitro* assessment and analysis of molecular markers to map gene region that confer resistance to antimalarial drug. The use of one or the other method has its own

strength and weaknesses. Laufer (2009:59) recommends an integrated use of different methods to ensure rapid detection and characterisation of resistance, especially to the newly introduced class of antimalarial drugs, ACTs. Antimalarial drug efficacy studies can be conducted to assess the efficacy of drugs currently is use or new drugs that are in considered for introduction.

Röshammar (2009:27) explains the importance of characterisation of the pharmacodynamics of antimalarial drugs that refers to the association between drug levels at the site of action and its effect and pharmacokinetics data that refers to the pattern of absorption, distribution, metabolism, and elimination. The presence of parasites in blood samples of patients following administration of a full course of the antimalarial drug being evaluated may not necessarily reflect parasite resistance or treatment failure unless proof of availability of adequate blood levels of the antimalarial drug administered is demonstrated. Barnes, Lindegardh, Ogundahunsi, Olliaro, Plowe, Randrianarivelojosia, Gbotosho, Watkins, Sibley and White et al (2007:1) emphasise that pharmacokinetic and pharmacodynamics data of antimalarial drugs should be used in the assessment efficacy of antimalarial drugs more strictly.

In low income malaria endemic countries, ensuring the availability of all the required expertise and capacity for parasite genetic analysis and antimalarial drug pharmacokinetics may be challenging. As a result of this challenge, the timeliness and completeness of antimalarial drug efficacy studies to inform policy may be seriously challenged. Therefore, while building the required capacity in malaria endemic developing countries is the ultimate solution, Guerin, Bates and Sibley (2009:593) suggest that international support available from the World Wide and the WHO can be of help to overcome challenges in antimalarial drug efficacy studies in developing countries.

1.7 DEFINITIONS OF TERMS AND CONCEPTS

The key variables in this study are related to antimalarial drug efficacy, treatment failure and drug resistance. The conceptual definition and relevance of these variables to the study and the operational definition of the concepts in relation to the measuring instrument, method of test and decision criteria is presented below.

1.7.1 Antimalarial treatment policy

According to the WHO (1994) antimalarial treatment policy is "a set of recommendations and regulations concerning the availability and rational use of antimalarial drugs in a country. It should be part of the national drug policy and national malaria control policy and in line with overall national health policy".

1.7.2 Antimalarial treatment guideline

Antimalarial treatment guideline is a guide that provides global, evidence-based recommendations on the treatment of malaria (WHO 2010b:1).

1.7.3 Antimalarial drug efficacy

Antimalarial drug efficacy is defined as the ability of an antimalarial drug to clear clinical sign and symptoms and parasitaemia (Fidock, Rosenthal, Croft, Brun & Nwaka 2004:509). Antimalarial drug efficacy can be assessed by employing different methods such as *in vivo, in vitro* and molecular methods (WHO 2010a:15). In this study, the measuring instrument of antimalarial drug efficacy is based on data related to parasite detection through microscopy and PCR based methods and assessment of malaria clinical sign and symptoms. The efficacy of an antimalarial drug that needs to be introduced to replace a failing antimalarial drug should have a clinical and parasitological efficacy of 95% and above (WHO 2010b:9).

1.7.4 Therapeutic efficacy study

Therapeutic efficacy is defined as the clinical and parasitological efficacy of antimalarial drugs on *Plasmodium falciparum infections* through defined follow-up criteria (WHO 2010a:16). Operationally, therapeutic efficacy is measured using parasite density count in blood films and assessment of malaria clinical sign and symptoms assessed through physical and clinical assessment including measurement of actual body temperature and history of fever in the last 48 hours. The decision criteria for therapeutic efficacy are based on complete clearance of parasitemia and clinical sign and symptoms of the disease.

1.7.5 In vitro sensitivity assay

In vitro parasite sensitivity test is exposure of parasites in culture medium to antimalarial drugs with a range of varying strengths (WHO 2010a:16). In this study, in vitro parasite growth rates in the presence of different levels of concentration of the test antimalarial drug is collected. The decision criteria are based on the percentage of parasite growth and maturation from ring stage to schizont stage. High percentage growth to a schizont stage of the parasite indicates that the amount of test drug in the respective test well was tolerated by the parasite.

1.7.6 Molecular markers

Polymorphic genes that are responsible for modifying the response of the parasite to a given antimalarial drug can be used as markers or indicator for resistance (WHO 2010a:16). Genetic markers are analysed through Polymerase Chain Reaction (PCR) and enzyme digestion of the parasite dioxyribose nucleic acid regions containing the genes of interest (WHO 2008:1).

1.7.7 Drug concentration

Drug concentration is an estimate of the concentration of the active chemical component and metabolite of an antimalarial drug in whole blood, plasma or serum (WHO 2010a:16). In this study, data on drug concentration in whole blood or serum determined using high performance liquid chromatography method (Debrus, Lebrun, Kindenge, Lecomte, Ceccato, Caliaro, Mbay, Boulanger, Marini, Rozet & Hubert 2011:5205) or other methods (WHO 2011j:11) reported in the studies is analysed. The decision criteria are based on the amount of drug metabolite detected in the blood sample. The presence of parasites in the blood sample with drug concentration above the minimum effective concentration for the specific antimalarial drug is an indicator for parasite resistance.

1.7.8 Treatment failure

The WHO (2010a:9) defines antimalarial treatment failure "as inability to clear malarial parasitaemia or resolve clinical-l symptoms despite administration of an antimalarial medicine." Treatment failure could be due factors related to the incorrect dosage, lack of patient compliance to the prescribed quantity and duration of treatment, poor drug quality, low drug absorption and interaction with a another drug concomitantly administered, rapid elimination due to poor metabolism of the drug.

In this study, treatment failure data is collected based on confirmed detection of parasites in the blood of the patient accompanied by the presence of malaria clinical sign and symptoms is compared. The decision criteria for treatment failure, therefore, are the presence of parasitemia and clinical sign and symptoms of malaria following completion of a full course of treatment.

1.7.9 Drug resistance

According to the WHO (2010a:9) antimalarial drug resistance is defined as "the ability of malaria parasite strain to survive and/or to multiply despite the administration and absorption of an antimalarial drug medicine given in doses equal to or higher than those usually recommended but within the tolerance of the subject, provided that drug exposure at the site of action is adequate." Resistance to antimalarial drugs arise as a result of genetic changes such as random gene mutations and/or gene intensification that can show reduced susceptibility and the continued selection and proliferation of such strains in the parasite population.

In this study, drug resistance is measured based on data collected from the studies reviewed to determine the presence of parasitemia and malaria clinical sign and symptoms in the patients assessed. The decision criteria of drug resistance are based on the presence of parasite development in the presence of the recommended amount of drug and require confirmation of parasitemia and determination of blood concentration of the drug and its metabolite.

1.7.10 Representativeness

Representativeness is defined as serving as a typical or characteristic example (Merriam-Webster Incorporated Online Dictionary 2011). Due to the logistic and resource requirements and the need to collect representative data in a short period of time, studies on antimalarial drug efficacy may not be conducted in all parts of a country, region or district. To avoid the unnecessary challenge of trying to reach everywhere, statistical methods such as sampling are used to focus the study only on a manageable but representative sample.

The findings from such sample on the level of antimalarial drug efficacy can then be used to make inference about the rest of the Geographic area, which the sample represents. In the absence of representative sampling, the study findings and conclusion that may be derived, therefore, would also not be representative and may be misleading. In this study, representativeness is measured based on assessment of the antimalarial efficacy studies coverage in terms of statistically acceptable minimum sample size of 50 subjects per site and use of four to eight study sites.

1.7.11 Timeliness

Timeliness is defined as appropriate or adapted to the time or the occasion (Merriam-Webster Incorporated Online Dictionary 2011). Monitoring the efficacy of antimalarial drugs at regular and appropriate time interval and use of the evidence to guide policy is an important aspect of antimalarial efficacy study. Studies of irregular interval may fail to detect trends of an imminent or potential health threat.

Delays in making use of evidence from such studies to update or change a health service policy or guideline also contributes to further deterioration in the quality of treatment that may result in more health problems. In this study, timeliness is measured based on the time lapse between two consecutive antimalarial efficacy studies. A time lapse of two years between two consecutive studies is considered to have the desired timeliness (WHO 2009a:3).

1.7.12 Completeness

Completeness is defined as having all the necessary parts, elements and steps (Merriam-Webster Incorporated Online Dictionary 2011). This is usually assessed on a case-by-case audit of the variables included and reported by a study compared to the recommended or ideal list of variables that are expected to be included in a study. In this study, completeness is measured based on the availability of data on quality of the antimalarial drug tested and pharmacokinetic data that show presence of adequate concentration of test drug in blood sample of the patients. The decision criteria are based on the availability of these two key measures and a study is deemed in complete if it lacks one or both of the required data variables.

1.8 RESEARCH DESIGN AND METHODS

The research design used for this study was a descriptive epidemiological analytical study design based mainly on data extracted from published and unpublished reports and other relevant sources. To compare treatment failure and/or drug resistance levels from different studies, statistical comparison of proportions and means with the corresponding 95% confidence intervals and P-values reported by the original studies was used. For the comparison of time lapse between studies, duration in years was calculated by taking in to consideration the years during which time the studies were conducted.

The data collection method mainly involved search for published scientific articles from scientific journal available electronically and on printed copies. Other relevant reports and information was also searched through internet based search using Google Scholar, scientific publication repository of the National Centre for Biotechnology Information (NCBI) and by consulting websites of relevant institutions. A detailed description of the research design and method used in the study is presented in chapter 3 and highlights of the main components are presented in the following sections.

1.8.1 Study sample and population

The study sample and population was the same as what was considered and analysed in the studies conducted from 1972 to 2011. With the exception of two antimalarial

efficacy studies conducted in the capital city of Addis Ababa, where local malaria transmission is rarely reported, most of the studies were conducted in malaria endemic areas where malaria transmission occurs. The subjects who were involved in the antimalarial efficacy study conducted in Addis Abeba were residents or short-time visitors to malarious localities in other parts of the country and most of the locations are towns along the frontier with Kenya and the Sudan.

1.8.2 Data collection and analysis approach and the instrument

Country data on antimalarial drug efficacy studies was collected from available published and unpublished records and was entered in Microsoft Excel based spread sheet developed for this purpose for further analysis. The list of variables on which data collection was based and the data collection tool for the different type of studies is presented in Annexure B. The data collected was further analysed to determine representativeness, timeliness and completeness based on a scoring method developed for the purpose.

1.9 ETHICAL CONSIDERATIONS

This study was mainly based on analysis of study findings extracted from antimalarial drug efficacy studies conducted in Ethiopia. Due to the study approach applied, the study didn't involve in-person participation of patients, biological sampling or interview with patients and other informants or laboratory based experimentation or use of laboratory animals. The study also didn’t involve the use of raw secondary data from the original studies that could have required permission from the originators.

Data and information that were collected from included published and unpublished documents and web based resources have been acknowledged and included in the citation and list of bibliography.

1.10 SCOPE OF THE STUDY

The study was based on retrospective review of published and unpublished antimalarial drug efficacy study reports and other relevant web based resources. Published and unpublished reports on antimalarial drug efficacy studies conducted in Ethiopia are

available and fairly complete. The study, therefore, was not seriously challenged by lack of data and information from previous studies.

The scope of the study is limited to the analysis of past studies and drawing conclusion and recommendation for future on antimalarial drug efficacy studies and use of evidence for policy and guideline development. However, testing the feasibility and appropriateness of the recommendation and best practice guideline proposed by this study for the Ethiopian setting was beyond the scope of the research objective.

Therefore, the recommendations and best practice guideline proposed, although have been justified for soundness and feasibility of application, will need to be tested and this is considered as the main limitation of the study.

1.11 STRUCTURE OF THE THESIS

This thesis is presented in five chapters, organised in the following order:

Chapter 1: Orientation of the study, covering the background information about the research problem, definitions of key terms and concept, statement of the research problem, aim of the study, significance of the study, foundations of the study, research design and method, scope of the study and the structure of the thesis.

Chapter 2: Literature review, covering the malaria situation in Ethiopia, malaria prevention and control activities, the role of malaria diagnosis and treatment, efficacy profile antimalarial drugs used in the country and the region, drug regulatory practices and malaria diagnosis and treatment policy issues.

Chapter 3: Research design and methods, including sample and study population characteristics, ethical consideration, data collection approach and method and data analysis.

Chapter 4: Analysis, presentation and description of the research findings. In this section results of the antimalarial drug efficacy studies reviewed and the use of the data collected from these studies in the context of the WHO recommendations is reviewed. A

summary of the antimalarial drug policy in other countries including explanation on the commonalities and differences is also presented in context.

Chapter 5: Conclusions and recommendations including best practice approaches for antimalarial drug efficacy monitoring and use of antimalarial drug efficacy data to inform policy for the Ethiopian setting.

1.12 CONCLUSION

The main aim of the study was to describe the characteristics and findings of antimalarial drug efficacy studies conducted in Ethiopia and to use the findings to formulate recommendations for antimalarial drug efficacy monitoring and use of evidence for policy and treatment guidelines development for the Ethiopian setting. The approach allowed to fully describe the antimalarial drug efficacy studies conducted in Ethiopia and to draw recommendations and best practice approach for antimalarial drug efficacy monitoring for now and the future.

The study involved mainly search of data and information from published and unpublished printed reports obtained from national workshops on antimalarial drug efficacy studies convened by the Federal Ministry of Health of Ethiopia. The scope of the study was mainly influenced by the amount of past and current information available. Based on the data currently collected during the study, there was a great deal of information and obtaining data and information collected by the studies was possible.

The conclusions and recommendation drawn from this study and the best practice guideline proposed are expected to provide technically sound approaches on the way forward. However, the recommendations on best practice approaches proposed by this study, although based on sound justification, will need to be tested and the proposed approaches are expected to motivate other investigators and the health authorities to pursue the idea further. The next chapter will address the theoretical framework of the study with further description on the relevance of timeliness, representativeness and completeness of antimalarial drug efficacy studies for antimalarial drug policy and treatment guidelines development.

In the following chapter 2, detailed literature review is presented. The literature review covers epidemiology of malaria and history of malaria control in Ethiopia. In addition to the basic information on malaria distribution, its socio-economic impact and prevention and prevention and control efforts in the country, description on the drug policy in general and antimalarial drug efficacy monitoring and use of findings from such studies for policy is presented.

The literature review also covers information on the distribution of malaria in other endemic countries and the commonalities and differences in malaria diagnosis and treatment approaches provided in these countries. The literature search has also attempted to cover issues related to health care financing, price of antimalarial drugs and availability of antimalarial drugs in the private and public sectors.

The overall strategy of the literature search focused on the importance of antimalarial drug resistance monitoring and practices on the use of evidence for policy at international level and in the geographic region where Ethiopia is located. The next chapter will address the findings of the relevant literature reviewed.

CHAPTER 2

LITERATURE REVIEW

2.1 INTRODUCTION

The literature review section in this chapter presents background information on the epidemiological and eco-climatic factors that determine distribution of malaria in Ethiopia. A description of the malaria situation in the neighbouring countries and commonalities and difference in the malaria diagnosis and treatment approaches including policy on the prevention of malaria during pregnancy is presented.

The chapter also presents information on the type of antimalarial drugs included in the national drug list of Ethiopia and profile of efficacy of the antimalarial drugs used as first-line treatment against the disease. Health service delivery and access to antimalarial drugs being one of the major factors that can determine the success of a malaria control program in a given setting, issues related to access to antimalarial drugs through public and the private sector including quality and price of antimalarial drugs and financing for antimalarial drugs is presented.

Due to the different factors that influence antimalarial drug policy and development of treatment guidelines, literature reviewed in this study has been broadened to cover aspects that directly or indirectly influence access to antimalarial drugs and development of antimalarial treatment policy.

2.2 BACKGROUND

The appropriateness of an antimalarial drug policy and antimalarial treatment guidelines developed based on these policies can be affected by a number of factors. The WHO (2001:25) illustrates that antimalarial policy on which treatment guidelines are based is a set recommendations and regulations related to the availability and appropriate use of antimalarial drugs in the country for which the policy is needed. The WHO (2001:33) also asserts that antimalarial drug policy development is a dynamic process which is

based on the disease epidemiology, transmission, drug resistance patterns and socio-economic and political contexts.

Therefore, issues related to the quality of the antimalarial drugs, their efficacy profile, registration status in the national formulary and essential drug list, supply chain management system, price, availability and access by end users can influence the scope of an antimalarial drug policy and the antimalarial treatment guideline (WHO 2007a).

Findings of the literature review presented in this chapter, therefore, provide a detailed description of the different factor listed above that have direct and indirect influence on antimalarial drug policy and treatment guideline in Ethiopia in the context of the Geographic region of the Horn of Africa.

2.3 ECO-CLIMATIC FEATURES OF ETHIOPIA

The diverse topography of the country with altitude ranges from 110 meter below sea level in the Danakil depression in north-eastern Ethiopia to 4620 meters above sea level in northern mountains ranges renders high eco-climatic variability. As a result, Ethiopia has three distinct eco-climatic zones. These include the hot lowland region of altitude below 1000 meters, the mid-land region with altitude of 1,001–1,500 meters and the highland region with altitude of above 1,500 meters above sea level. The mean annual temperature in Ethiopia in the three eco-climatic zones of the low-land, mid-land and high-land areas range from 10–16°C, 16–29°C and 23–33°C, respectively (Federal Ministry of Health, Ethiopia 2006a:7).

The Federal Ministry of Health, Ethiopia (2006a:7) reports show that Ethiopia has two rainy seasons but generally erratic that makes the country prone to periodic drought, loss of agricultural production and disease epidemic of which malaria is the most common. Adhanom et al (2006:556) describe that, as a result of the diverse eco-climatic conditions, malaria in Ethiopia is generally seasonal and unstable and its seasonality and intensity is often determined by rain in the low-land area and temperature in the high-land and highland fringe areas.

As described above the eco-climatic features in Ethiopia have significant influence on the distribution and seasonality of malaria. Cognisant of this phenomenon, malaria diagnosis and treatment services in Ethiopia need to target priority areas depending on the level of endemicity of malaria. For an effective malaria treatment service to be implemented in all areas where the service is needed, understanding the efficacy profile of the antimalarial drugs is critical. Talisuna, Okello, Erhart, Coosemans and Alessandro (2007:170) confirm that malaria transmission intensity as an important factor for the spread of drug resistant falciparum malaria. Therefore, understanding the malaria transmission intensity and the factors that influence malaria transmission intensity is of importance in identifying areas where antimalarial drug efficacy studies should be conducted.

2.4 SOCIO-ECONOMIC CONDITIONS IN ETHIOPIA

According to the third population and housing census conducted in 2007 by the Population Census Commission, Federal Democratic Republic of Ethiopia (2008:83), the Ethiopian population was 73.9 million with an average household size of 4.7 persons per household. An estimated 85% of the population live in rural areas and 23.2% of the population densely live in 9% of the highland area while nearly 50 per cent of the arid and semi-desert plains in the peripheries of the country are sparsely populated (Federal Ministry of Health, Ethiopia 2006a:8).

The socio-economic conditions in Ethiopia are one of the lowest in the world. The report of the Ministry of Finance of Ethiopia (Ministry of Finance and Economic Development 2006:55) indicates that the average per capita income in the country which is US$100 or US$720 in purchasing power parity terms in 2010 leaves an estimated 39% of the population under extreme poverty with income of less than US$1.25 per day.

The United Kingdom Department for International Development (2011:1) report indicates that poverty in Ethiopia is still high with more than 30 million people living in poverty. Although the level of poverty is high, access to primary education in Ethiopia has been increasing significantly over the past few years.

The Ministry of Education (2010:10) estimates that primary school enrolment has increased from 61.6% in 2001/2002 to 79.8% in 2004/2005. However, literacy rate in

the general population, although it has increased from 18% in 1995/1996 to 31% in 2004/05 is still very low. With the increasing government allocation of budget for the education sector from 13.8% in 2000/2001 to 19% in 2004/2005 (Ministry of Education 2005:10), further positive development in the sector is anticipated. The improved level of education is also expected to improve health awareness and Paulander et al (2009:1) report that increasing level of literacy in Ethiopia can positively influence knowledge, attitude and practice on malaria prevention and treatment.

2.5 HEALTH STATUS IN ETHIOPIA

The WHO (1948) defines health as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity". The definition asserts social well-being as one of the essential needs for every human being to enjoy good health. Whitehead and Dahlgren (1991:1059) illustrate that social well-being relies on the level access to food, shelter, education, employment and security among other necessities for everyday human life.

The Commission on Social Determinants for Health (2008:12) affirms that socio-economic development in rich countries is supported by publicly financed infrastructure while low-income countries do not have the financial resources to support services such as health care in an equitable manner to the population in need. The level of economic development of a country, its equitable distribution among the population and the political will to implement healthy social policies is, therefore, basic for good health standards to prevail.

As a result of the economic disparities between the low and high-income countries, the health status of the population in different countries shows variability. To measure the health status of populations, the WHO (2004) applies the disability-adjusted life year which is defined as the number of life years lost due to premature death, illness and disability from a health risks. Based on the disability adjusted life years (DALYs) estimated by the WHO (2004), the leading global health risks that have the highest contribution to the DALYs are underweight, unsafe sex, alcohol use and unsafe water, sanitation and hygiene. These leading causes of disability mainly affect populations in low-income countries, especially in the regions of South-East Asia and sub-Saharan Africa.

The Federal Ministry of Health, Ethiopia (2005:4) asserts that as a result of the low socio-economic conditions in the country; the health status of the population is one of the lowest in Africa. According to the Federal Ministry of Health, Ethiopia (2005:4), an estimated 60-80% of the health problems in the country are due to communicable diseases and nutritional deficiencies. The WHO (2004) estimates a DALYs of 47,528 per 100,000 population for Ethiopia, which is one of the highest in the world. The highest DALYs of 82,443 per 100,000 are estimated for Sierra Leon while the lowest of 9803 DALYs per 100,000 population is estimated for Iceland and Kuwait.

Although the health status of nations can be compared based on DALYs, the actual assessment of progress towards improved health conditions is measured through a selected set of indicators. The WHO (2004) uses infant and child mortality, maternal mortality and life expectancy as some of the most important health indicators. According to the WHO estimates (2004), Ethiopia has one of the lowest life expectancy at birth of 54 years, high maternal mortality ratio of 470 per 100,000 live births and infant and children less than five year of age mortality of 63 and 106 per 1000 live births, respectively.

The WHO (2004) estimates show low infant, child and maternal mortality rates and high life expectancy in high income countries compared to low-income countries. Infant mortality rate as low as 2 per 1000 live births was estimated for Finland, Iceland, Japan, Luxembourg, Singapore Slovenia and Sweden while as high as 174 deaths per 1000 live births was estimated for Sierra Leon. Similarly, mortality of children under five years of age is lower in high income countries such as Finland and Iceland with 2 deaths per 1000 live births compared to the highest of 209 deaths per 100 live births in Chad.

Malaria is prevalent mainly in the hot tropical region of the world and Africa is the most affected continent due to its location in the tropics. The WHO (2011a:ix) estimates 216 million malaria episodes and 655,000 malaria deaths in 2010 of which 81% of the cases and 91% were in Africa with approximately 86% of the global malaria deaths occurring in children under 5 years of age. The DALYs discounted due to malaria in Africa is also one of the highest in the world. The WHO (2004) estimates DALYs lost due to malaria in Africa to range from 1 in Mauritius to 8,212 in Niger per 100,000 population while that of Ethiopia is 2347.

The Roll Back Malaria Partnership (2007:4) affirms that the reason for the high malaria morbidity and mortality in Africa to be partly due to the high level of decline in the efficacy of the most widely available and affordable antimalarial drugs such as chloroquine and sulfadoxine-pyrimethamine due to lack of access to effective alternative antimalarial drugs. To impact on the morbidity and mortality caused due to malaria, the Roll Back Malaria Partnership (2011:51) calls for improved access and high coverage with safe and effective drugs for malaria treatment and prevention interventions to the populations at risk of malaria. `

2.6 HEALTH CARE DELIVERY SYSTEM IN ETHIOPIA

The Federal Ministry of Health, Ethiopia (2005:2) implements health service delivery organised with a four tier system that includes Primary Health Care Unit (PHC), health centres, zone and regional hospitals. A PHC which has one health centre and five health posts is designed to serve 25,000 people, while a district and a zone hospital are intended to serve 250,000 and 1 million people, respectively.

To ensure reach and equitable health service to the vast majority of the rural population, the Federal Ministry of Health, Ethiopia (2005:1) implements the Health Service Extension Program (HSEP). The HSEP program was launched in 2003 has completed its plan of training and deployment of 30,000 female Health Extension Workers (HEWs) assigned in a ratio of 2 HEWs per 5,000 inhabitants. The primary task of the HEWs is to provide promotive and preventive health care services and diagnosis and treatment for acute illnesses such as malaria.

As a result of implementation of the HSEP, the Federal Ministry of Health, Ethiopia (2006a:4) estimates a significant increase in the health service coverage from 76.9% to 100%. The health service coverage which is expressed in percentage is calculated based on the number of inhabitants living within 5 kilometres radius from the most peripheral health facility. Based on this calculation, the Federal Ministry of Health, Ethiopia (2010a:21) reports an increase in the potential health service coverage from 45% in 1996/97 to 64% in 2003/4 and the overall goal was to attain universal primary health service coverage by the end of 2008.

The Federal Ministry of Health, Ethiopia (2006b:4) had a plan to achieve a significant increase in the ratio of medical doctors to population from 1:42,706 in 2006 to 1:14,662 by the end of the year 2010. Despite the relative increase in the health service coverage and ratio of health workers to the population, the Federal Ministry of Health, Ethiopia (2006b:4) report confirms that the out-patient health service utilisation per capita still remains as low as 0.32.

The cause of the low health services utilisation in Ethiopia is believed to be due to a number of factors related to the limitation of access and consumer awareness. Fantahun and Degu (2003:141) report that problems of accessibility, illiteracy and assumption by service users that modern health institutions are not helpful for certain diseases contributes to the low health service utilisation in some parts of the country.

Consumer user fees for health services provided in Ethiopia do not seem to have negative influence on health service utilisation. El-Saharty, Kebede, Dubusho, and Siadat (2009:35) report that the user fee introduced in Ethiopia 50 years ago used to help recover the service cost. However, with the introduction of user fee exemptions based on proof of inability to pay, health service user fee in Ethiopia remained only symbolic.

To better understand the health service delivery system in Ethiopia, a comparison of the system with the system in developed countries and low-income developing countries that have similar socio-economic level of development as Ethiopia may be important. Doorslaer, Masseria and the Economic Cooperation and Development (OECD) Health Equity Research Group Members (2004:6) report that income related health inequalities in the Organization for Economic Cooperation and Development member countries where the rich are more likely to access specialist medical service than the poor exist to a larger extent in countries such as Portugal, Finland and Ireland.

The main reason for the disparity in health service utilisation in the OECD countries is more related to the income of the individuals and ability to pay for health services than the overall country budget allocated for health services. Squires (2011:2) for example, reports the health care spending in the United States of America in 2008 was US$7,538 per capita which is more than double of the median per capita expenditure in the rest of

OECD countries. However, access to health services in the United States is pro-rich and less equitable compared to the rest of the OECD countries.

Carmen, Proctor and Smith (2011:1) explain decline in median household income, increase in poverty rate and increase in the number of people without health insurance to be the main contributors for the inequitable access to health services in the United States of America. Confirming this assertion, report of the Centres for Disease Control and Prevention (2011:35) indicates that the number of people without health insurance in the United States was estimated to reach 52 million by the end of 2010 which is likely to further impose a negative impact on access to health services.

The impact of user fee on individuals and families in low income and developing countries could also be a factor for low service utilisation. Lagard and Palmer (2011:34) suggest that reducing or removing user fees increases the utilisation of certain healthcare services while it may have unintended consequences on utilisation of preventive services and service quality.

The WHO (2011c:128) estimates government expenditure on health as per cent of total expenditure in Ethiopia to be at 51.9% while the private expenditure share is 48.1%. There is a relatively similar pattern of share between the public and private expenditure for health in many African countries while the share of the private expenditure is higher in Kenya and South Africa which is 63.7% and 60.3%, respectively.

In low income malaria endemic countries where the level of poverty is relatively higher, user fees for malaria diagnosis and treatment services may limit access to service. Alba, Hetzel, Goodman, Dillip, Liana, Mshinda and Lengeler (2010:1) reports that non-adherence to user fee exemptions in the public health sector in Tanzania to be associated with low utilisation of the most effective ACT drugs such as AL. To overcome the lack of access to affordable effective antimalarial medicines, the Roll Back Malaria Partnership (2007: xi) calls for mechanism to ensure affordability and increase access to ACTs.

The Carter Centre (2010:3) asserts that malaria diagnosis and treatment service and ITNs are provided in Ethiopia free of charge. Although malaria diagnosis and treatment services are provide free of charge, Deressa, Chibsa and Olana (2003:9) report that

distance to malaria control laboratories and household workload have been shown to cause delay in seeking early diagnosis and treatment by patients in the Eastern Shoa zone of Ethiopia. Therefore, the need to ensure wider access of services closer to the population through the Health Extension Program in Ethiopia is expected to improve access to malaria diagnosis and treatment services.

2.7 MALARIA IN ETHIOPIA

In this section, description of the malaria distribution and transmission pattern, disease burden and malaria prevention and control interventions applied reduce the impact of the disease on the socio-economic conditions in Ethiopia is presented.

2.7.1 Malaria distribution and transmission pattern in Ethiopia

Malaria in Ethiopia is generally prevalent in areas below 2000 meters above sea level. However, Negash et al (2005:186) in a study conducted in 50 malaria epidemics affected districts in 2004 indicated malaria transmission at altitude ranges as high as 2,400 meters above sea level. The dominant malaria parasite species are *Plasmodium falciparum* and *Plasmodium vivax* accounting for approximately 60% and 40% of the total malaria cases, respectively while *Plasmodium malariae* is rarely reported, and *Plasmodium ovale* is not prevalent (Federal Ministry of Health, Ethiopia 2006a:3).

Armstrong and Mathews (1981:299) confirm that the prevalence of *Plasmodium vivax* in the Ethiopia population is associated with high frequency of the duffy positive blood types and Collins and Jeffery (2005:570) report that *Plasmodium ovale* is more prevalent in the western part of Africa where the duffy-negative blood type is dominant. The main malaria vector in Ethiopia is *Anopheles arabiensis* and *Anopheles pharoensis, Anopheles funestus* and *Anopheles nili* have been reported as secondary vectors in some parts of the country (Ribeiro, Seulu, Abose, Kidane & Teklehaimanot 1996:299).

The main malaria transmission season in Ethiopia is generally from September to December following the major rainy season from June to September and a shorter transmission season also occurs from February to March following the short rainy season from April to May. Following the bimodal rainfall pattern, the major malaria transmission season occurs in all parts of the country situated below 2000 meters of

altitude while the shorter transmission season is mainly limited to the Eastern part of the county (Federal Ministry of Health, Ethiopia 2005:2).

Based on the eco-climatic factors related to altitude, annual rainfall and mean monthly temperatures, the Federal Ministry of Health, Ethiopia (2005:2) stratifies the malaria transmission pattern in Ethiopia in to seven different transmission regions as shown in Figure 2.1.

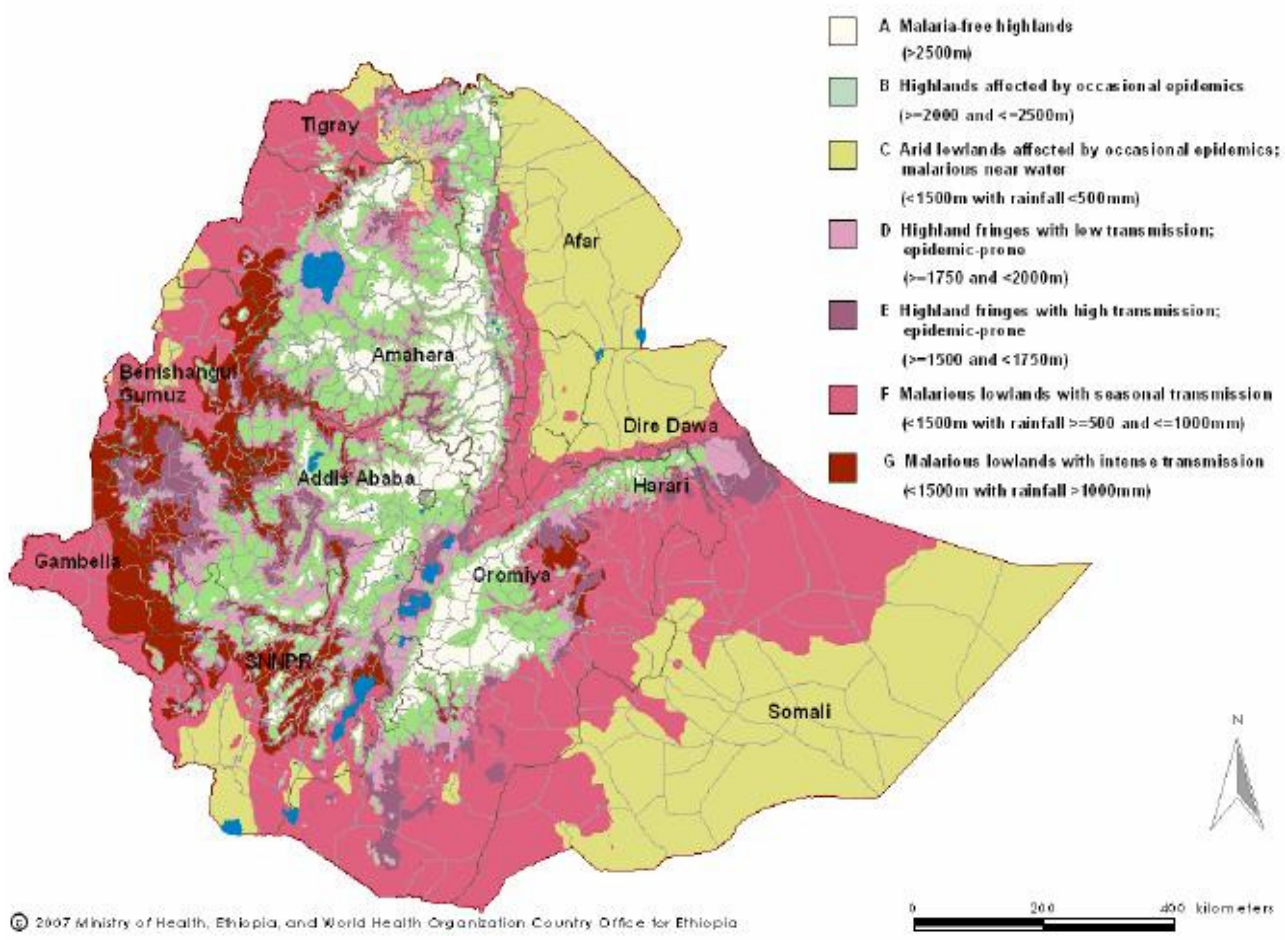

Figure 2.1 Distribution of malaria in Ethiopia

(Federal Ministry of Health, Ethiopia 2006a:2)

Knowledge of the malaria distribution seasonality and relative prevalence of the malaria parasite species is of high importance in antimalarial drug efficacy study planning and site selections. However, although the malaria transmission map shown in figure 2.1 provides the different malaria transmissions patterns in the country, it provides no specific information on the reported relative prevalence of the malaria parasite by area.

The *Plasmodium falciparum* risk map developed based on estimates by Hay, Guerra, Gething, Patil, Tatem, Abdisalan, Noor, Kabaria, Manh, Elyazar, Brooker, Smith, Moyeed and Snow (2009) shown in figure 2.2 indicates a more specific distribution pattern of *Plasmodium falciparum malaria* which is the main parasite species of interest in antimalarial drug efficacy studies due to the ability of the parasite to developing resistance to different antimalarial drugs. This map also lacks information on the seasonal distribution of *Plasmodium vivax* malaria infections.

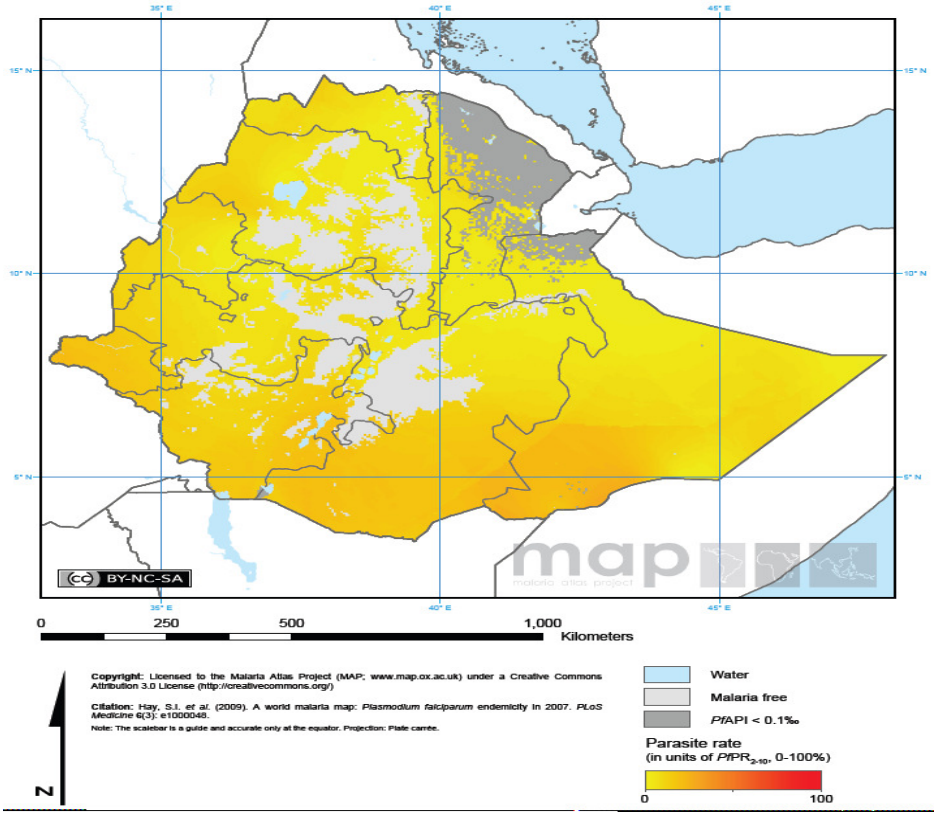

Figure 2.2 Spatial distribution of plasmodium falciparum malaria endemicity in Ethiopia

(Hay et al 2009:1)

2.7.2 Malaria disease burden in Ethiopia

As a reflection of the unstable and seasonal nature of malaria transmission in Ethiopia, parasite prevalence rates show variability depending on the season. Alemayehu, Ghebreyesus, Bosman, Witten and Teklehaimanot (1998:259) report that parasite rates varying from 3–10% during high transmission season months and 0–3% during low transmission confirmed in a community based survey conducted in the northern part of

Ethiopia. Shargie, Gebre, Ngondi, Graves, Mosher, Emerson, Ejigsemahu, Endeshaw, Olana, WeldeMeskel, Teferra, Tadesse, Tilahun, Yohannes and Richards (2008:1) also report that in a community malaria parasite prevalence survey conducted in the regions of Oromiya and Southern Nations, parasite rates of 0.9% and 5.4%, respectively were detected.

In the 2007 malaria indicator survey conducted during the major malaria transmission season in a selected representative sites across the country, Jima, Getachew, Bilak, Steketee, Emerson, Graves, Gebre, Reithinger, Hwang and the Ethiopia Malaria Indicator Survey Working Group (2010:1) report an overall malaria parasite rate confirmed by microscopy of 1% (95% CI 0.5–1.5). Of the 7,167 individuals of all ages included in the survey, the relative rates of the malaria parasite rate by species were 0.7% for *Plasmodium falciparum and* 0.3% *Plasmodium vivax.*

Abeku et al (2003:331) affirm that malaria epidemic risk in Ethiopia shows geographical and temporal variability as a result of altitudinal and weather variations. Deressa et al (2006:1) also highlight that in areas where malaria transmission is known to occur, imported malaria due to population movement to and from malaria endemic lowland areas is common. Negash et al (2005:186) also confirm that malaria deaths are much higher during malaria epidemic season, and that death rates decrease during the non-epidemic season indicating the instability of the risk and the lack of protective immunity in the population.

According to the Federal Ministry of Health, Ethiopia (2006a:5) the annual number of malaria cases reported by health facilities in Ethiopia in the period from 2001–2005 was 9.4 million (range 8.4–11.5) while the annual average number of microscopically confirmed malaria cases was 487,984 (range 392,419–591,442). However, due to the limited access of health services in the Ethiopian setting, the annual number of malaria cases reported through health facilities is not expected to be representative of the overall burden of malaria in the community.

Considering fever based estimates of annual number of malaria cases in Ethiopia, Teklehaimanot, Singer, Spielman, Tozan, Schapira (2005:98) estimate that the number of malaria cases that are likely to occur annually in the period from 2005 to 2015 is as high as 13.7 million. Apart from the high disease burden especially during epidemics as

observed in the most recent epidemic in 2003 that caused more than 2 million cases and over 3,000 deaths in just four months in 211 districts (Negash et al 2005:186), the Federal Ministry of Health, Ethiopia (2006a:12) indicates that the DALYs lost due to malaria annually is estimated at 30%.

2.7.3 Malaria control in Ethiopia

The WHO (2005b:30) recommends provision of early diagnosis and treatment for patients and prevention using Indoor Residual Insecticide Spraying (IRS), Insecticide Treated Nets (ITNs) and Intermittent Presumptive Therapy (IPT) for the prevention of malaria during pregnancy. Although services for early diagnosis and prompt treatment of malaria is mandatory for all areas where malaria is endemic, the application of IRS, distribution of ITNs and IPT seems not to be uniformly applied in all malaria endemic countries.

In Ethiopia, the Federal Ministry of Health, Ethiopia (2006a:4) implements provision of early diagnosis and treatment for malaria and vector control through the use of Indoor IRS and ITNs while IPT is not applied. The study finding on the burden of malaria during pregnancy in Ethiopia by Newman, Hailemariam, Jima, Degifie, Kebede, Rietveld, Nahlen, Barnwell, Steketee and Parise (2003:1765) indicating the need for further evidence on the effectiveness of IPT supports the Federal Ministry of Health decision not to apply IPT in Ethiopia.

In other parts of Africa such as the Southern Africa Economic Cooperation (SADC) region, all malaria prevention and control interventions are applied in the 11 member countries of the region. The continuation of application of some intervention seems to relate with some technical and managerial problems associated to its application. The use of IPT for the prevention of malaria during pregnancy, for example, is partly challenged by the spreading resistance to sulfadoxine-pyrimethamine, the recommended drug for IPT. Vinetz (2010:755) explains that the increasing level of resistant to sulfadoxine-pyrimethamine makes the intervention less effective. This trend may eventually lead to the discontinuation of the intervention unless an effective replacement drug is identified.

The application of Indoor Insecticide Spraying (IRS) has not also been uniform in all endemic countries in Africa. Sadasivaiah, Tozan and Breman (2007:249) asserts that although IRS achieved significant reduction on malaria transmission during the malaria eradication era, the introduction of ITNs in some countries has been associated with reduced application of IRS.

For a significant impact on malaria transmission, the WHO (2005b:36) recommends an integrated application of malaria vector control interventions. The integrated vector control approach that can impact on malaria transmission can also benefit the malaria diagnosis and treatment intervention as it helps reduce the number of new malaria cases.

2.7.3.1 Malaria control program objectives in Ethiopia

Malaria control activities in Ethiopia first started as a pilot project in 1955 which was then scaled-up to national eradication program in the 1960's. In 1969 the 22nd World Health Assembly (WHO 1973:66) decides to apply malaria control activities in areas where malaria eradication was not feasible in the near future based on socio-economic and epidemiological factors. The WHO (2011d) explains that the malaria eradication program in Ethiopia was then re-organised in to vertical Malaria and Other Vector-Borne Disease Control Program that operated from 1976 to 1993 and then integrated in to the general health service system introduced in 1993.

The Federal Ministry of Health, Ethiopia (2006a:20) malaria prevention and control national strategic plan in Ethiopia aims to achieve a 50% reduction in malaria morbidity and mortality by 2010 as compared to the 2005 levels. The plan includes malaria diagnosis and treatment service as one of the major interventions that will be applied during the implementation period for the strategic plan. This intervention is of significant relevance to malaria control in Ethiopia as protective immunity to malarial disease in the population is low and all age groups are at risk the disease.

Alamirew and Equbazghi (1998:69) confirm that asymptomatic parasitaemia as is the case in other hyperendemic African countries where protective immunity against malaria in the adult population is well developed is not common in Ethiopia. This epidemiological characteristic of the disease in the country, therefore, makes malaria

diagnosis and treatment a top priority intervention. To ensure effective treatment for malaria, the availability of safe, effective, affordable, and accessible anti-malarial drugs is one of the major pre-requisites. In this context, therefore, further details on the malaria diagnosis and treatment service in Ethiopia are presented in the following sections.

2.7.3.2 Malaria diagnosis in Ethiopia

Laboratory based malaria diagnosis services in Ethiopia are available only in hospitals and health centres. However, Tegbaru, Meless, Kassu, Tesema, Gezahegn, Tamene, Hailu, Birhanu and Messele (2004:43) report that shortage of essential equipment and laboratory supplies as one of the major and chronic problems that has been limiting the reach of the service to the population in need. Shortage of trained laboratory technicians is also a major problem that has been limiting expansion of the service.

The Federal Ministry of Health, Ethiopia (2005:69) reports that the total number of laboratory technicians deployed by the end of 2010 was 4,200 and the ratio of laboratory technicians to population of 1 to 7,600 population reflects the low level of access to the service.

As a result of the limited availability and access to laboratory diagnostic services, malaria diagnosis at the most peripheral health facilities such as the health posts is done predominantly based on clinical sign and symptoms while Rapid Diagnostic Tests (RDTs) are used rarely when available. The Federal Ministry of Health, Ethiopia (2004a:7) indicates that, in health centres and hospitals, malaria diagnosis is based on clinical history of mainly fever or history of fever in the last 48 hours and parasitological confirmation of cases using microscopy based diagnosis while in most peripheral health facilities such as health posts, diagnosis based on clinical sign and symptom is the main approach.

The Federal Ministry of Health, Ethiopia (2005:4) introduces the use of RDTs in 2004 mainly for use in areas where microscopy based diagnosis is not available. However, access to diagnosis with RDTs has not been widely available in the following years. The WHO (2010c:186) estimates that about 108,324 malaria RDTs were used in Ethiopia in 2009 alone while the number of tests procured and used prior to 2009 is not known.

Most of the RDTs used in Ethiopia were tests that detect *Plasmodium falciparum only*. The use of single species RDTs in a setting where *Plasmodium falciparum and Plasmodium vivax* co-exist in considerably comparable proportions may not be an appropriate choice for malaria treatment to be based on. In an effort to collect evidence that can be used to guide RDT product selection and procurement decisions, Ashton, Kefyalew, Tesfaye, Counihan, Yadeta, Cundill, Reithinger and Kolaczinski (2010:1), compare three different multi-species RDTs, namely: CareStart®, ParaScreen® and ICT Combo® and reported that the brand CareStart had high sensitivity and specificity for diagnosis of both *Plasmodium falciparum* and *Plasmodium vivax*. Due to the availability of a wide range of malaria RDTs, WHO (2009b:3) advises national programs to use the test results provided by its product testing program to make their product selection and procurement decisions for RDTs.

The cost of RDTs varies by type and selecting the right test with a reasonable cost is of high importance. Lemma, San Sebastian, Löfgren and Barnebas (2011:1) report that for malaria diagnosis in the health posts in rural areas, the use of parascreen pan/pf based tests are a preferable option in terms of cost and quality.

2.7.3.3 Malaria treatment and antimalarial drugs in Ethiopia

Chloroquine, primaquine and quinine were the most popular antimalarial drugs that have been in use for malaria treatment in Ethiopia in the period pre-1998 (table 2.1). The Federal Ministry of Health, Ethiopia (2004a:7) recommends the use of quinine tablets and injection for the treatment of severe malaria. The WHO (2000:34) reports that the detection of widespread treatment failure to chloroquine by *Plasmodium falciparum in* 1997–1998 in Ethiopia led to the introduction of sulfadoxine-pyrimethamine for the treatment of *Plasmodium falciparum* malaria, while chloroquine remained in use for the treatment of *Plasmodium vivax.*

The first edition of the malaria diagnosis and treatment guideline in Ethiopia was revised in 2004 following report by Jima et al (2005a:391) high level of (35.6%) treatment failure of sulfadoxine-pyrimethamine for the treatment of uncomplicated *Plasmodium falciparum malaria.* This led the Federal Ministry of Health, Ethiopia (2004a:18) to introduce artemether-lumefantrine for the treatment of falciparum malaria while

chloroquine and Quinine remained to be is use for the treatment of *Plasmodium vivax* malaria and severe malaria, respectively. While changing the first-line antimalarial drugs based on the efficacy study reports, the Federal Ministry of Health, Ethiopia (2004a:13) decides to introduce mefloquine for prophylactic use and Artemether injection for the pre-referral treatment of cases with severe malaria based on recommendations of the WHO.

The national malaria diagnosis and treatment guidelines provide instructions for dose regimen of antimalarial drugs based on age and body weight (Federal Ministry of Health, Ethiopia 2004:57). Personal experience shows that drug dose regimen is based on age-group based treatment regimen than dose regimen based on an actually measured body weight. The treatment of malaria in special population groups such as pregnant mothers and infants with body weight of less than five kilogram differs from the rest of the population. The Federal Ministry of Health, Ethiopia (2004a:13) recommends the use of quinine for the treatment of malaria in children under five kilograms of body weight and pregnant women. The administration of quinine for the treatment of malaria requires careful management due to the adverse effects the drug may cause. Achan, Talisuna, Erhart, Yeka, Tibenderana, Baliraine, Rosenthal and D'Alessandro (2011:1) confirm that despite the long history of use of quinine for the treatment of malaria, its continued use is challenged by poor tolerance by patients, low compliance and its complex dose regimen.

A comparative efficacy study on artesunate injection versus quinine intravenous conducted by Dondorp, Fanello, Hendriksen, Gomes, Seni, Chaganlal, Bojang, Olaosebikan, Anunobi, Maitland, Kivaya, Agbenyega, Nguah, Evans, Gesase, Kahabuka, Mtove, Nadjm, Deen, Mwanga-Amumpaire, Nansumba, Karema, Umulisa, Uwimana, Mokuolu, Adedoyin, Johnson, Tshefu, Onyamboko, Sakulthaew, Ngum, Silamut, Stepniewska, Woodrow, Bethell, Wills, Oneko, Peto, Von Seidlein, Day, White and the AQUAMAT Group (2010:1647) for the treatment of severe malaria in children conducted between 2005–2010 in 11 African countries proved the superior level of efficacy, safety and ease of administration of artesunate injection compared to quinine.

Comparative safety and efficacy study on the use of rectal artemisinin versus quinine Intravenous by Biruk, Makonnen and Bjorkman (1999:154) in Ethiopia also showed rectal artesunate to provide better parasite and fever clearance and recovery of patients

from comma. Based on available evidence, the WHO (2011e:37) now recommends the use of artesunate administered by intravenous or intramuscular route for the treatment of severe malaria replacing quinine. The study evidence showed that, artesunate was significantly better than quinine in reducing the risk of death from severe malaria and hypoglycemia.

Table 2.1 Malaria diagnosis and first-line anti-malaria drugs used in Ethiopia

Facility level	Pre-1998		1998–2004		2004 to present	
	Diagnosis	**Treatment**	**Diagnosis**	**Treatment**	**Diagnosis**	**Treatment**
Health post	Clinical	Chloroquine (CQ)	Clinical	CQ and Sulfadoxine-Pyrimethamine (SP) combined	Clinical and Rapid Diagnostic Tests (RDTs) when available	▪ Artemether-Lumefantrine (AL)-
Health Centre	Clinical and microscopy based	▪ CQ for *Plasmodium falciparum* infection ▪ CQ plus PQ for *Plasmodium vivax* infection	Clinical and microscopy based	▪ CQ and sulfadoxine-pyrimethamine combined for clinical cases ▪ CQ for *Plasmodium vivax* and ▪ SP for *Plasmodium falciparum*	Clinical and Rapid Diagnostic Tests (RDTs) or microscopy when available	▪ AL – for *Plasmodium falciparum* cases ▪ CQ - for *Plasmodium vivax*
Hospital	Parasito-logical confirmation by microscopy	▪ CQ for *Plasmodium falciparum* infection ▪ CQ plus PQ for *Plasmodium vivax* infection ▪ Quinine (QN) for severe cases	Parasito-logical confirmation by microscopy	▪ CQ for *Plasmodium vivax* ▪ SP for *Plasmodium falciparum* ▪ Quinine (QN) for severe cases	Parasito-logical confirmation by microscopy	▪ AL – for *Plasmodium falciparum* cases ▪ CQ – for *Plasmodium vivax* ▪ QN for severe cases

(Ministry of Health1999:28; Federal Ministry of Health, Ethiopia 2004a:7)

2.7.3.4 Malaria prevention and treatment during pregnancy

Desai, Kuile, Nosten, McGready, Asamoa, Brabin and Newman (2007:93) affirm that malariaas one of the major contributors to anaemia and low birth weight during pregnancy in areas with high malaria transmission. To prevent the consequences of malaria during pregnancy, the WHO (2007b:1) recommends the administration of IPT with sulfadoxine-pyrimethamine in areas with high malaria transmission where the risk of malaria in pregnancy is greatest.

Based on annual incidence of malaria, the WHO (2011a:82), classifies areas with annual malaria incidence of 1 or more per 1,000 population as high transmission areas. Based on this classification, most countries in Sub-Saharan Africa fall in to this category, with the exception of countries such as Ethiopia where transmission is seasonal and epidemic type and a few other countries such as South Africa where malaria is prevalent in limited parts of the country and Lesotho and Mauritius where malaria transmission is non-existent. Following the recommendation and the need to reach the beneficiaries in rural settings where access to health services is limited, Mbonye, Bygbjerg and Magnussen (2008:22) report that IPT delivery though community-based approaches as instrumental in expanding access to the service.

Malaria transmission in Ethiopia is seasonal and the population that live in high transmission areas with annual incidence of 1 or more malaria cases per 1,000 population is around 1% while the vast majority of 66% of the population lives in areas with annual incidence of less than 1 malaria case per 1000 population (WHO 2010c:117). As a result of the variable malaria transmission pattern, the effect of malaria during pregnancy shows variability. In a cross-sectional study conducted in four sites in Ethiopia, Newman et al (2003:1765) report placental parasitaemia of 6.5% (12/185) in two study sites with relatively stable malaria transmission compared to 2.5% (21/833) is two other sites with unstable malaria transmission.

The risk of low-birth weight was higher in the unstable transmission area (Relative Risk, 3.9; p=0.01) compared to the stable transmission area (Relative Risk, 2.7; p=0.04) while the risk of stillbirth was seven folds higher in the stable transmission sites. Newman et al (2003:1765) also reported that the level of *Plasmodium vivax* detected in the study

site with unstable or seasonal malarial transmission was an additional risk that might have contributed to the relatively higher risk of low-birth weight.

Based on the highly seasonal pattern of malaria transmission in Ethiopia and the lack of evidence to support the application of IPT with sulfadoxine-pyrimethamine, the intervention was not recommended and has not been applied in Ethiopia (Federal Ministry of Health, Ethiopia 2006a:4).

2.7.4 Drug regulatory services in Ethiopia

The Food, Medicine and Healthcare Administration and Control Authority of Ethiopia is the sole agency responsible for the quality control of food, medicines and health service. According to the Ethiopian Food, Medicine and Healthcare Administration and Control Authority of Ethiopia (2010a), 13 drug and medical product manufacturers, 3,228 registered drug retail outlets that include pharmacies, drug shops and rural drug vendors operate in Ethiopia.

According the Federal Negarit Gazeta of the Federal Democratic Republic of Ethiopia (2010:1), monitoring and ensuring the safety, efficacy, quality and proper use of medicines is one of the major responsibilities of the institution. An estimated 4,000 medical products are registered in the country and most of the products are imported from abroad. To ensure quality assurance of locally produced and imported medical products, the Ethiopian Food, Medicine and Healthcare Administration and Control Authority of Ethiopia (2010a) operates a central drug quality control laboratory. The laboratory has technical capacity and equipment to conduct quality testing on only 346 medical products.

Mohammed (2008:7) indicates that most of the 300 essential drugs listed, only 90 drugs are locally produced while the bulk of the remaining products are imported from abroad. The basic antimalarial drugs chloroquine and sulfadoxine-pyrimethamine are locally produced while the no ACTs are produced locally. Mohammed (2008:6) also reports that of the 17 local manufacturing plants registered in the country, none have international certification for Good Manufacturing Practice (GMP) while six of these manufacturing plants are GMP certified by the local regulatory authority. Drug quality problems pose multifaceted public health problems in developing countries, especially

Africa (Wellcome Trust 2012b) and solving the problem requires coordinated approach (Newton, Green & Fernández 2010:99).

Newton, Amin, Bird, Passmore, Dukes, Tomson, Simons, Bate, Guerin and White (2011) call for an international treaty under the umbrella of the WHO as an important step to strengthen the effort to control the counterfeit and substandard medical products. Durrheim and Williams (2005:178) emphasises that without a strict control of the quality of drugs, monitoring the efficacy of the drugs alone can't ensure good quality treatment service. Onwujekwe, Kaur, Dike, Shu, Uzochukwu, Hanson, Okoye and Okonkwo (2009:22) calls for legal measures to ensure stringent control on stockpiling and circulating poor quality drugs and for countries who manufacture and export medical products to apply strict quality and standard assurance checks (United Nations Office on Drugs and Crime 2012).

2.7.4.1 Ethiopian formulary of essential drugs list (EDL)

The most recent Ethiopian national drug formulary was revised in 2007 by the Drug Administration and Control Authority of Ethiopia (2007: vi). The Drug policy in Ethiopia first developed by the Transitional Government of Ethiopia (1993:1) envisages the availability of a regularly updated list of essential medicines that can address the priority health care needs of the population. The identification and selection of medicines is based on epidemiological needs and the proven safety, efficacy, quality, price and ease of use of the products for the patients.

The main purpose of the Essential Medicines List in Ethiopia is to guide all those involved in health services delivery in the selection, procurement, production, distribution and storage of medicines. According to the Food, Medicine and Healthcare Administration and Control Authority of Ethiopia (2010c:v), preparation process of the list involves a technical working group of the authority composed of an internist, a nurse and a pharmacist who prepare the initial working draft of the list. The draft version is then further enriched through a national consultative workshop with participants from various areas and specialties in medicine. Participants of the workshop also include delegates from medical schools, relevant professional associations, Regional Health Bureau, and departments of the Ministry of Health, pharmaceutical manufacturers and importers, government hospitals and other related organisations.

Based on the additional input and recommendations from the national workshop, the revised list of Essential Medicines is reviewed and finalised by the National Drug Advisory Committee. During the revision process, medicines of proven quality formulated with a single compound are prioritised for inclusion in to the list. Fixed dose formulations are selected only when they have proven advantage over single compound presentations and the issues of safety, efficacy, adherence and ability to combat drug resistance.

The essential drug list presents products in their generic and international non-proprietary names according to their pharmaco-therapeutic areas. Once the essential drug list is disseminated, a mechanism to collect views and opinions though email and telephone system is made available for patients and prescribers to give their feedback on the list (Food, Medicine and Healthcare Administration and Control Authority of Ethiopia 2010c: xi).

2.7.4.2 Antimalarial drugs in the essential drug list

The Food, Medicine and Healthcare Administration and Control Authority of Ethiopia (2010b:49) indicate that the 6th edition of the essential medicines for Ethiopia published in 2010 as the current list in use. The previous editions were published in 1985, 1987, 2004, 2007 and 2010. The number of years between the versions is not uniform and it is not clear as to what the reasons could have been. The antimalarial medicines included in the national essential drug list have been changing in accordance with the changing pattern of efficacy of the antimalarial drugs and their recommended use for the treatment of malaria.

Table 2.2 below summarises the antimalarial drugs included in the sixth edition of the national drug list for Ethiopia (Food, Medicine and Healthcare Administration and Control Authority 2010b:49). The latest list includes oral Artemisinin monotherapies that are not recommended by the WHO (2010b:1).

Table 2.2 Anti-malarial drugs included in the Ethiopia National essential drug list

No	Product	Presentation
1	Alpha, Beta Arteether	Injection, 150 mg/2ml
2	Artemether Oral Suspension,	40 mg/0.5 ml, 80 mg/ml; Injection, 20 mg/ml, 40 mg/ml, 80 mg/ml; Suppository, 40 mg
3	Artesunate	Tablet, 100 mg, 200 mg; Injection, 60 mg/vial
4	Artemether +Lumefantrine	Tablet and dispersible, 20 mg artemether+120 mg lumefantrine
5	Chloroquine Phosphate	Tablet, 250 mg, 500 mg (equivalent to 150 mg, 300 mg base) Syrup, 50 mg base/5 ml; Injection, 50 mg/ml (equivalent to 40 mg/ml base)
6	Dihydroartemisinin	Tablet, 60 mg
7	Dihydroartemisinin + Piperaquine	Tablet, 40 mg + 320 mg 50 Phosphate
8	Mefloquine Hydrochloride	Tablet, 250 mg
9	Primaquine Phosphate	Tablet, 7.5 mg base, 15mg base
10	Quinine Dihydrochloride	Injection, 300 mg/ml in 1 ml ampoule Tablet, 300 mg, 600 mg
11	Proguanil Hydrochloride	Tablet, 100 mg
12	Sulfadoxine +Pyrimethamine	Injection, 500 mg sulfadoxine +25 mg pyrimethamine in 2.5 ml ampoule; Tablet, 500 mg sulfadoxine +25 mg pyrimethamine

(Food, Medicine and Healthcare Administration and Control Authority 2010b:49)

The list of antimalarial drugs in the Ethiopian National essential drug list includes products such as Artemisinin and dihydroartemisinin oral formulations. However, the revised WHO malaria treatment guideline recommends the use of ACTs. The use of artemisinin oral mono-therapies has been identified as a major risk to artemisinin resistance. To minimise the risk of resistance to artemisinin, the WHO (2007a:2) endorses to ban the use of oral artemisinin mono-therapies at its 60th Assembly.

2.7.4.3 Access to antimalarial drugs through the public and private sectors in Ethiopia

The Federal Ministry of Health, Ethiopia (2007:3) reports that 10,744 government owned health facilities and 2,153 private sector health facilities operate in the country. A large majority (92%) of the government owned health facilities are peripheral health posts health facilities that provide mainly primary level of care. The health facilities in the private sector are licensed and supervised by the Ministry of Health. The main source of medical supply for the private sector is through the 17 government and private owned importers and manufacturers registered in the country.

Regular information on the availability of essential medicines in the public and private sector is not usually available. Carasso, Lagarde, Tesfaye and Palmer (2009:1394) survey report shows that, most essential medicines were available in private health facilities and dispensaries with the exception of the newly introduced antimalarial drug, artemether-lumefantrine. Carasso et al (2009:1394) also report that although essential medicines were available at the time of the survey in both the public and private sector facilities surveyed, prices of medicines was more than twice in the private out-lets compared to prices in the budget pharmacies operating in the public sector.

The limited availability of the first-line antimalarial ACT drug in the private sector (Carasso et al 2009:1394) shows that the market penetration of the ACT drug artemether-lumefantrine which was first introduced in July 2004 was quite slow and this is likely to have a significant impact on the success of malaria treatment in Ethiopia.

2.7.4.4 Drug supply chain management, availability and stock-outs

A Federal Ministry of Health and WHO (2010:3) survey finding affirms that availability of the necessary structure and mechanisms required to implement the National Drug Program was "more or less in place" within the health sector of the country. However, the survey finding identifies lack of appropriate stock control system in 60% of the health facilities surveyed as the major problem of the pharmaceutical supply management system in health facilities.

Daniel and Hailu (2009:10) also reported medical and laboratory supply chain and stock management related problems in a survey conducted involving 19 hospitals, 31 health centres, 27 health posts, 33 private drug outlets, nine Regional Health Offices, 18 zone health offices, 29 district health offices and 44 laboratories. The major problems identified include antimalarial drug stock-out in health facilities for a period of 1–2 months, low stock of paediatric antimalarial drugs, significant problems in monitoring expiry dates of antimalarial and anti-tuberculosis drugs.

In addition to the technical problems, administrative challenges such as lack of adequate coverage of training on the management of the new antimalarial drugs, limited availability of the new antimalarial treatment guideline, absence of stock control cards and lack of adequate storage and shelving facilities were identified as some of the major

gaps in the drug management system. The combined effect of these shortcomings can pose serious challenges on the quality and coverage with malaria diagnosis and treatment services in the country.

2.7.4.5 Quality of antimalarial drugs

Drug registration in Ethiopia is required by law both for the purpose of production, and importation. The Food, Medicine and Healthcare Administration and Control Authority (2008:1), specifies the requirements for the application and registration of new medical products. The accepted pharmacopeia includes the United States Pharmacopeia (USP), British, European pharmacopeia and other applicable Ethiopian standards as relevant. The quality testing of antimalarial drugs is conducted as per the methods described in the pharmacopeia relevant to the product.

There are no local reports that provide regular information on the quality of antimalarial drugs that are being sold in the country. Such drug quality activities are sometime done by international institutions such as the WHO. The WHO (2011f:52) reports no drug quality problems in 102 antimalarial drug samples collected from four different parts of the country. The sample included 47 artemether-lumefantrine and 55 sulfadoxine-pyrimethamine tables collected from different batches traced in the public and private drug outlets.

Although quality of the sampled antimalarial drugs was confirmed to have the required properties for quality, nearly 41% of the samples collected were not products registered in the country. The fact that a significant proportion of the antimalarial drugs were not registered was identified as a major concern as the lack of such regulatory measures can be vulnerable to the entry of poor quality drugs. Smine and Bempong (2009:6) confirms that the US President's Malaria Initiative (2011) is providing training and capacity building support in collaboration with the USP. Technical support in the area of drug quality control is expected to improve the local capacity.

2.7.4.6 Financing and cost of antimalarial drugs

The Federal Ministry of Health, Ethiopia (2005:111) reports that although the budget for health care services has been increasing over the years. However, the overall health expenditure per capita in Ethiopia remains below the US$12 average for Sub-Saharan Africa. The funding for health care services in the country is provided both through the public and the private sectors.

The Federal Ministry of Health, Ethiopia (2005:112) explains that an estimated 49% of the funding which accounts for US$2.77 of the health expenditure per capita in the public sector is covered from internal and external sources. Private health service utilisation including out-of-pocket spending represents 36% which represents US$ 1.96 per capita. The contribution of the private sector and non-governmental organizations is 5% and 10%, respectively.

Barnett and Tefera (2010:4**)** report that health facilities charge separately for every type of service provided including registration, consultation, laboratory investigation and inpatient, treatment and other services. As reported by Barnett and Tefera (2010:4) fees for drug prescriptions are usually equal to the purchasing price or sometimes above with additional cost ranging from 20–40 percent for imported drugs and 5–10 percent for local manufactured drugs.

Asfaw and Braun (2005:241) report that market reform actions and expansion of the private sector health service has been associated with considerable increase in prices for health care services and price of drugs. In an effort to protect the health needs of households with low income, fee adjustment and exemptions are wide used in Ethiopia. Barnett and Tefera (2010:4) cite that the waiver and exemption system usually lacked appropriate targeting and coverage and fee waivers are partial leaving much of the cost for drugs and laboratory service left to be covered by the patient.

The Health Sector Development Plan (HSDP III) adopted by the Federal Ministry of Health, Ethiopia (2005:29) for the period from 2005–2010 plans to increase health service user-fees to improve its share for the overall health spending. The Federal Ministry of Health, Ethiopia (2010:30) also aims to introduce a health insurance scheme. However, Save the Children UK (2005) contests that the approach may impoverish poor

families as they will be forced to sell assets they have in order to meet the required fees for the health service they need. According to a sources cited in Barnett and Tefera (2010:4) the Federal Ministry of Health of Ethiopia has now developed a plan to introduce a nationwide health insurance scheme in the near future.

The overall situation of service delivery in Ethiopia is compounded by lack of equitable access and high level of poverty which deters the population from accessing available health services. The high cost of drugs and the inability of the community to afford for malaria diagnosis and treatment services may lead to the use of other cheap but in effective medications such as chloroquine and sulfadoxine-pyrimethamine. In the absence of an equitable access to health services, malaria diagnosis and treatment services in Ethiopia may face a serious challenge.

2.8 PROFILE OF THERAPEUTIC EFFICACY OF ANTI-MALARIAL DRUGS

Gebremariam and Teklehaimanot (1986:1) report that chloroquine in Ethiopia was the most popular, safe, effective and affordable antimalarial drug that has been in use for the treatment of all forms of malaria for more than three decades. Although Dennis, Doberstyn, Sissay and Tesfai (1974:241) report the tolerance of Ethiopian *Plasmodium falciparum* parasite strains to a single dose of treatment with chloroquine at 10 mg per kilogram of body weight, *Plasmodium falciparum* resistance to standard regiment of chloroquine at 25 mg/kg has never been reported in Ethiopia until the mid-1980s. Armstrong, Asfaha and Palmer (1976:5) also report no recrudescent cases of *Plasmodium falciparum in* a study conducted on 150 patients in four malarious villages in the central and western Ethiopia over a follow-up period of 6 to 11 following treatment with chloroquine at a dose of 25 mg/kg.

Following reports of increasing complaints on slow response to treatment with chloroquine and reports on *Plasmodium falciparum resistance* to chloroquine in neighbouring East African countries of Kenya and Sudan, a study to assess the efficacy of chloroquine for the treatment of *Plasmodium falciparum was* first conducted by Gebremariam and Teklehaimanot (1986:1) following the WHO study protocol with a follow-up period of 7 and 28 days. In this study conducted in 1983–1984, Gebremariam and Teklehaimanot (1986:1) report that no resistant cases were detected in a total of

159 and 133 *Plasmodium falciparum* patients treated with 25 mg/kg of chloroquine administered over a period of three days and followed for 7 and 28 days, respectively.

Teklehaimanot (1986:127) reports the first cases of chloroquine resistant falciparum malaria cases in a follow-up conducted on 28 patients who visited or resided in areas bordering Kenya, Somalia and Sudan. Assefa (1997:209) also reports another chloroquine resistant *Plasmodium falciparum case* in a staff member of the Ethiopia National Research Institute of Health who visited the town of Gambella situated in the malaria endemic area in Western Ethiopia bordering the Sudan in 1997.

Although the initial reported chloroquine resistant *Plasmodium falciparum* cases were few in number and restricted to areas bordering other countries, report of chloroquine resistant cases started to increase in number and Geographic distribution. Alene and Bennett (1996:810) report that out of the 39,824 patients diagnosed and treated with chloroquine for *Plasmodium falciparum* in 36 malaria case detection and treatment posts run by the national malaria control program between August 1989 to July 1991, around 4% returned back to the posts within two weeks after treatment with complaints of no health improvement. Of the returning patients, 87% were confirmed as treatment failure cases and treated with sulfadoxine-pyrimethamine (Fansidar®).

The increasing risk of *Plasmodium falciparum* resistance and the growing concern over its efficacy to achieve the intended cure rate, the national malaria control program decided to conduct a nationwide representative study. The WHO (2001:34) reports that the first nationwide study on the efficacy of chloroquine for the treatment of *Plasmodium falciparum* was conducted in 18 sites by the Ministry of Health in the period from 1997–1998. According to the WHO (2001:34), an overall chloroquine treatment failure of 65% was detected and the finding led to the decision of introducing sulfadoxine-pyrimethamine (Fansidar®) in 1998 to replace the failing chloroquine as the first-line antimalarial drug for the treatment of uncomplicated *Plasmodium falciparum.*

The WHO (2001:34) report also shows that at the time of introduction of sulfadoxine-pyrimethamine (Fansidar®), its baseline level of efficacy observed in four study sites was 92.3%. However, in a study conducted in 2002, nearly four years after the introduction of sulfadoxine-pyrimethamine, Kassa, Mekonnen, Wolde-Micheal,

Mohamed and Bulcha (2005:167) report a higher treatment failure rate of 12.7% in one study site in Central Ethiopia.

Following these observations and the growing concern and complaints of patients and health care providers, a nationwide study on the therapeutic efficacy of sulfadoxine-pyrimethamine (Fansidar®) was conducted in 10 sentinel sites from October to December in 2003. At the end of the study, Jima et al (2005a:391) report a mean treatment failure rate of 36% (range 20–54%) which is much higher than the treatment failure detected by Kassa et al (2005b:167).

Cognisant of the high treatment failure rates of sulfadoxine-pyrimethamine and expert advice and locally confirmed safety and efficacy of artemether-lumefantrine (Coartem®) for the treatment of uncomplicated falciparum malaria by Jima, Tesfaye, Medhin, Kebede, Argaw and Babaniyi (2005b:387), the Federal Ministry of Health, Ethiopia (2004a:8) decides to introduce the ACT, AL, as a first-line drug for the treatment of *Plasmodium falciparum* malaria in July 2004 while the use of chloroquine for the treatment of vivax malaria was recommended to continue.

The efficacy of chloroquine for the treatment of *Plasmodium vivax* malaria has never been widely evaluated in the Ethiopian setting. Tulu, Webber, Schellenberg and Bradley (1996:556) report the first chloroquine resistant *Plasmodium vivax* malaria cases in Debrezeit, Central Ethiopia with an overall treatment failure of 2%. Yeshiwondim, Tekle, Dengela, Yohannes and Teklehaimanot (2010:105) also report treatment failure of 2.9% and 0.74% after treatment *Plasmodium vivax* cases with chloroquine alone and combined administration of chloroquine plus primaquine, respectively.

In later similar studies conducted in Debrezeit and Nazareth, Yohannes, Teklehaimanot, Bergqvist and Ringwald (2011:137) confirm *Plasmodium vivax* resistance to chloroquine of 4.8% and Teka, Petros, Yamuah, Tesfaye, Ibrahim, Elhassan, Muchohi, Kokwaro, Aseffa, Engers (2008:1) also report *Plasmodium vivax* chloroquine resistance of 3.5%. In a most recent study, Ketema, Bacha, Birhanu and Petros (2009:1) report an even higher treatment failure rate of 7% in a study site located in the western part of Ethiopia.

Despite the growing levels of chloroquine treatment failure and confirmed *Plasmodium vivax* resistance to chloroquine, the Federal Ministry of Health, Ethiopia (2004a:7)

recommends the continued use of chloroquine for the treatment *Plasmodium vivax* malaria as the reported level of treatment failure is localised and generally less than 10%.

2.9 ANTI-MALARIAL TREATMENT POLICY CHANGES IN ETHIOPIA

The Ministry of Health (1999:1) develops the first edition of the malaria diagnosis and treatment guideline in 1998 following the change from chloroquine to sulfadoxine-pyrimethamine as the first-line drug for the treatment of *Plasmodium falciparum malaria*. Prior to the first edition of the malaria diagnosis and treatment guideline, all malaria prevention and control technical guidelines including malaria diagnosis and treatment was bound in a single document. From experience the book known to the malaria control program personnel as the "green book" was the main guideline for malaria prevention and control activities.

The WHO (2000:34) asserts that malaria diagnosis and treatment guideline change process in Ethiopia involved a broad-based discussions and consultations with various stakeholders. Revision of the malaria diagnosis and treatment guideline in Ethiopia in 2004 was initiated after evidence of treatment failure of the drugs in use was confirmed.

The Federal Ministry of Health, Ethiopia (2004a:2) confirms that, antimalarial drug efficacy study results are presented to a national workshop for discussion and recommendation. In line with approach, a national workshop attended by experts from the Ministry of Health, academic and research Institutions, referral hospitals, Regional Health Bureaus, drug regulatory authority, the private sector, non-governmental organizations and United Nations (UN) agencies such as the WHO and UNICEF was convened in May 2004 (2004b:4).

The decision involved consideration of the findings of the antimalarial efficacy study, recommendations by international organisations such as the WHO and suitability of the recommended replacement medicine for use in the local setting. Upon agreement, the guidelines were revised by a selected group of experts from the Ministry of Health, academic institutions and referral hospitals.

The original versions of the malaria diagnosis and treatment guidelines for health workers in Ethiopia were prepared in English. From personal experience, translation to other official languages such as Amharic was partly done by the Federal Ministry of Health. The regional health offices also translate the guideline in to other official languages such as Oromiffa and Tigrigna. In Tigray region where the researcher worked, the guideline translated in to Tigrigna were pre-tested and re-checked for consistency with the original versions and their technical quality was double checked before printing and distribution.

2.10 MALARIA DIAGNOSIS AND TREATMENT PRACTICES IN OTHER COUNTRIES: COMMONALITIES AND DIFFERENCES

According to the WHO (2010c:185), malaria treatment in the horn of African region is mainly based on clinical diagnosis while microscopy and rapid diagnostic test (RDT) based diagnosis and treatment is relatively widely implemented in Djibouti, Eritrea and Ethiopia (table 2.3).

Table 2.3 Trends in health facility malaria cases and deaths in the Horn of Africa, 2005–2009

Country	Population at risk of malaria in 2009 in millions and per cent at risk	Diagnosis	Number of cases by year				
			2005	2006	2007	2008	2009
Djibouti	0.43 (50)	Suspected malaria	3,969	6,457	7,945	6,305	7,120
		Plasmodium falciparum	413	1,796	210	119	-
		Plasmodium vivax	-	-	-	-	-
		other malaria	-	-	-	-	-
		Deaths	-	29	1	-	0
Eritrea	3.6 (71)	Suspected malaria	64,056	49,703	80,428	62,449	77,946
		Plasmodium falciparum	7,506	5,750	3,006	1,519	3,358
		Plasmodium vivax	1,567	791	6,508	2,832	3,244
		other malaria	-	-	0	0	0
		Deaths	49	47	42	19	23
Ethiopia	55.5 (67)	Suspected malaria	4,727,209	3,375,994	2,844,963	3,060,407	4,335,001
		Plasmodium falciparum	374,335	293,326	269,514	274,657	594,751
		Plasmodium vivax	158,658	149,020	171,710	173,300	287,114
		other malaria	-	-	-	-	0
		Deaths	1,086	1,357	991	1,169	1,121
Kenya	30.2 (76)	Suspected malaria	9,181,224	8,926,058	9,610,691	-	8,123,689
		Plasmodium falciparum	-	-	-	839,904	-
		Plasmodium vivax	-	-	-	-	-
		other malaria	-	-	-	-	-
		Deaths	44,328	40,079	-	-	-
North Sudan	33.4 (100)	Suspected malaria	2,515,693	2,117,514	4,597,254	4,555,054	4,440,882
		Plasmodium falciparum	-	-	-	-	-
		Plasmodium vivax	-	-	-	-	-
		other malaria	-	-	-	-	-
		Deaths	1,789	1,193	1,254	1,125	1,142
South Sudan	8.9 (100)	Suspected malaria	337,582	116,473	101,008	136,492	325,634
		Plasmodium falciparum	-	-	-	-	-
		Plasmodium vivax	-	-	-	-	-
		other malaria	-	-	-	-	-
		Deaths	-	-	-	263	254

(WHO 2011a:194)

The malaria diagnosis approaches in the region lacks uniformity and uses a mix of clinical and confirmed diagnostic approaches using microscopy and RDTs. The coverage of microscopy or RDT based diagnosis in 2009 in the region showed high variability ranging from 30% in North Sudan to 55% in Eritrea while data on percentage of confirmed malaria is not reported for Kenya and South Sudan. The overall percentage of confirmed malaria cases showed remarkable increase in Djibouti, Ethiopia and North Sudan diagnostic percentage of confirmed malaria cases in Eritrea has been declining (table 2.4).

Table 2.4 Annual trends of malaria cases in the Horn of Africa countries, 2005–2009

Country	Diagnosis	Annual number of cases				
		2005	2006	2007	2008	2009
Djibouti	Probable and confirmed	2,469	6,457	4,694	3,528	7,120
	% Confirmed malaria	16.7	27.8	4.5	3.4	37.7
Eritrea	Probable and confirmed	24,192	10,148	19,568	10,572	21,298
	% Confirmed malaria	37.5	64.5	79.5	82.9	55.2
Ethiopia	Probable and confirmed	3,901,957	3,038,565	2,557,152	2,532,645	3,043,203
	% Confirmed malaria	13.8	14.7	17.7	18.1	34.1
Kenya	Probable and confirmed	9,181,224	8,926,058	9,610,691	839,904	8,123,689
	% Confirmed malaria	No data (ND)	ND	ND	ND	ND
N. Sudan	Probable and confirmed	2,515,693	2,117,514	3,040,181	3,073,996	2,361,188
	% Confirmed malaria	25.0	34.1	22.6	18.5	30.1
S. Sudan	Probable and confirmed	337,582	116,473	101,008	71,948	325,634
	% Confirmed malaria	No data	ND	ND	ND	ND

(WHO 2010a:185)

The types of antimalarial drugs used in the countries of the region vary. The ACT drug artemether-lumefantrine is used as the first-line antimalarial drug in Kenya and Ethiopia while the rest of the countries still use combination drugs with partner drugs such as amodiaquine and sulfadoxine-pyrimethamine that are long known to have low level of efficacy against *Plasmodium falciparum* parasites in Ethiopia (WHO 2001:34).

The use of artemisinin derivatives such as artesunate in combination with failing drugs such as amodiaquine and sulfadoxine-pyrimethamine bears a risk of exposing artesunate that may lead to development of resistance by *Plasmodium falciparum*

(Nosten & White 2007:181). The drug of choice for the treatment of *Plasmodium vivax* malaria, chloroquine and primaquine is uniform across all countries of the region. However, primaquine, which is essential to fully eliminating *Plasmodium vivax parasites that may cause relapses,* is not included in the Kenya list of antimalarial drugs probably due to the low level of *Plasmodium vivax* malaria in the country (table 2.5).

IPT for the prevention of malaria during pregnancy is with sulfadoxine-pyrimethamine is applied in Kenya, North Sudan, South Sudan and Somalia while the intervention is not implemented in Djibouti, Eritrea and Ethiopia.

Table 2.5 Antimalarial drugs used for the treatment of malaria in the Horn of Africa countries

Country	Type of antimalarial drugs used by diagnosis				
	Unconfirmed clinical malaria	**Uncomplicated confirmed malaria**	**Confirmed sever malaria**	**IPT**[8]	**Treatment for *Plasmodium vivax***
Djibouti	AS[1]+SP[2]	AS+SP	QN[6]	NA[9]	CQ plus PQ for 14 days
Eritrea	CQ[3]+SP	AS+AQ	QN	No	CQ+PQ
Ethiopia	AL[4]	AL	QN	No	CQ
Kenya	AL	AL	QN	SP	None
Somalia	AS+SP	AS+SP	QN	SP	CQ+PQ for 14 days
North Sudan	AS+SP	AS+SP	AM[7] or QN	SP	CQ+PQ for 14 days
South Sudan	AS+AQ[5]	AS+AQ	QN	SP	CQ+PQ for 14 days

Key: 1= Artesunate; 2= sulfadoxine-pyrimethamine; 3= chloroquine; 4= artemether-lumefantrine; 5=amodiaquine; 6=quinine; 7=artemether; 8= Intermittent presumptive therapy; 9=Not applied.

(WHO 2010a:168)

2.11 CONCLUSION

The literature search and review findings indicate that malaria is one of the leading public health problems in Ethiopia. Although there has been on-going effort to prevent malaria in Ethiopia, the socio-economic level of development was not supportive to carry the resource intensive malaria prevention and control activities in the country.

The spread of treatment failure and resistance to a number of antimalarial drugs mainly by Plasmodium falciparum has been posing serious problems in the effort to ensure effective malaria treatment services. Efforts to monitor the efficacy of antimalarial drugs and timely action to introduce more effective antimalarial treatment have been challenged by lack of coordinated system and monitoring protocol.

The antimalarial drug quality regulatory and quality control monitoring system in the country also needs systematised approach to ensure availability, marketing and use of antimalarial drug of good quality. The literature search findings also indicate that malaria in Ethiopia being mainly of epidemic nature, population in rural areas where the health system coverage is low are the most affected. Access to health services is not affected only by low coverage, but also by users fees which most of the population can't afford due to the low level of household income in the population.

The WHO (2001:23) provides a list of recommended of antimalarial drug combination therapies based on their efficacy and irrespective of cost to be considered when selection replacement drugs. Before the selection of the alternative antimalarial drugs, the antimalarial drug changing process needs to be based on evidence on the efficacy of the antimalarial drug currently in use. Plow (2005:55) asserts the suitability of the in vivo antimalarial drug efficacy testing for on-going efficacy monitoring while emphasises the importance of using longitudinal studies focused on incidence on uncomplicated malaria as the best source of information on which antimalarial treatment policy change should be based on.

However, such approaches may not be focused on the main issue that matter which is efficacy of the antimalarial drug current in use. To guide the discussion and decision-making process for antimalarial drug policies, a set of minimum criteria set by the WHO (2001:25) is more practical.

Currently, the first-line antimalarial drug for the treatment of uncomplicated malaria in Ethiopia is AL. At the time of its introduction in 2004, baseline efficacy of the drug was 99% (Jima et al 2005b:387). However, Kebede, Woyessa, Urga, Messelle and Jima (2010:246) report that wider access to the new antimalarial drug access is still a major problem due to its cost and recommends the participation of various stakeholders to ensure adequate supply and distribution of the ACT drug.

Moreover, treatment based on confirmed diagnosis in Ethiopia is low and most of the treatment is provided based on clinical sign and symptom. D'Alessandro and Buttiens (2001:845) explain that the use of antimalarial drugs based on clinical diagnosis only results in the over utilisation of the antimalarial drugs and is known to facilitate the selection of resistant strains through drug pressure.

Historically, resistance to chloroquine was first reported in South East Asia (Hasting 2004:512). Trape, Pison, Spiegel, Enel and Rogier (2002:224) affirm that In the 1980s and 1990s, significant increase of malaria related mortality ranging from 2 to 5.5% detected in many African countries has been shown to have been associated with decreasing efficacy of the then widely used antimalarial drug chloroquine.

In the Ethiopian context the risk that will contribute to the development of resistance to artemether lumefantrine is high due to the marketing of artemisinin oral monotherapies that are not recommended by the WHO and the use of less effective artemisinin based combination drugs in the neighbouring countries. This situation calls for speedy revitalisation of the antimalarial monitoring system and alignment of the drug regulatory and quality control approaches in line with international standards.

With these major findings in the background, the next section, chapter 3 presents the research design and method designed to conduct the study at depth. In chapter 4, the specific data search, collection and analysis approaches are presented in details. The research design and methods provides detailed study specific scoring for representativeness, timeliness and completeness of the antimalarial efficacy studies conducted in Ethiopia and the relevance and use of evidence collected from the studies to inform antimalarial drug policy and antimalarial treatment guideline updating.

CHAPTER 3

RESEARCH DESIGN AND METHODS

3.1 INTRODUCTION

The study was designed to extract and analyse data from antimalarial drug efficacy studies conducted in Ethiopia. The variable collected and analysed in the study varied depending on the antimalarial drug efficacy study method employed, the malaria parasite species subjected and the antimalarial drug tested. The nature of the data collected and analysed, therefore, was the main aspect of the study that determined the data collection method and format employed and the design selected. Accordingly, data collection was done using different formats for the vivo, in vitro and molecular studies, separately.

A description of the study design and approaches used in the original anti-malarial drug efficacy studies conducted in the country from which the data was extracted is also presented. In the following sections, further details on the research design, methodology, study population, data variables, collection and analysis method and ethical considerations relevant to the study are presented.

3.2 RESEARCH DESIGN

The study design applied is this research was the epidemiological analytical study approach based on analysis of data collected from various antimalarial efficacy studies conducted in Ethiopia in the period from 1974 to 2011. The data collected was analysed to describe the occurrence of events related to antimalarial drug efficacy failure and resistance, its public health significance and implication and the policy related actions that were taken as a result of the findings.

The study approach used in the original studies analysed in this research included observational, case-control and comparative study designs. In the in vivo method of studies, observational studies, subjects who met inclusion criteria were enrolled and observed for a pre-defined follow-up period of 7, 14 or 28 days after treatment with the

test drug. At the end of the follow-up period treatment outcomes classified based on the parasitological and clinical observations were determined and recorded. In the *in vitro* experimental studies, parasite growth in culture medium containing different concentration levels of the test drug was used. Genetic analysis of parasite sample collected from blood sample of patients with treatment failure was conducted to analyse polymorphic gene regions associated with resistance to the antimalarial drug being tested taking the gene markers of the same locus from parasites sensitive to the drug being used as a comparator.

The epidemiological descriptive study design was identified as the most appropriate method for the study. The main reason for the selection of this method was to ensure appropriate handling of the variables measured in the source studies that were not uniformly the same. The use of meta-analytical study design approach was not preferred due to the different types of study designs applied in the original antimalarial drug efficacy studies conducted in the country and the diverse variables measured in each of the studies which do not permit merging of the data for pooled analysis.

The epidemiological study design can be used to evaluate health interventions and to assess the level of delivery and impact of health programs. Martine (2006:98) states that data can be extracted from existing information or through data collected using epidemiological study design. Cullinan (2006:47) describes that study designs such as systematic review for research methodological description and meta-analysis for generating quantitative data and inference based on data pooled from separate studies are effective when the variables are amenable to pooling. However, these approaches were not considered appropriate for this study as the study design and data points collected in the original studies varied and the time gaps between some of the studies was considerably long.

Moreover, the studies employed different lengths of follow-up duration, tested different antimalarial drugs and parasite species and were conducted in different areas where the malaria transmission situation is identical. Therefore, to ensure maintaining the specific characteristics of the studies, applying the descriptive epidemiological study method was preferred. To critically assess previous practices on antimalarial drug efficacy studies and to learn from the gaps and shortcoming in in order to improve the

use of current evidence for policy, therefore, the application of epidemiological descriptive study approaches could provide practical use.

3.3 RESEARCH METHOD

3.3.1 Sampling

3.3.1.1 Study population

The population included in the original studies reviewed in this research included predominantly residents in places where active malaria transmission occurs. In some isolated cases, antimalarial efficacy studies were also conducted in areas where malaria transmission does not normally occur, such as the capital Addis Ababa, in patients who contracted the infection elsewhere.

In the studies conducted between the years from 1996 to 2002, a study protocol for the *in vivo* assessment of the therapeutic efficacy of antimalarial drugs for the treatment on uncomplicated *Plasmodium falciparum* infections developed by the WHO (1996:2) was used. This protocol was mainly developed for the assessment of antimalarial drug efficacy in areas with intense malaria transmission and primarily recommends the enrolment of patients aged 6 to 59 months who meet the clinical and parasitological criteria for inclusion in the study (WHO 1996:7).

Enrolment of children less than five years of age is generally recommended for the evaluation of the efficacy of antimalarial drugs as this age group is the most vulnerable to severe malaria and have low level of protective immunity (WHO 2003:7). However, in case of lack of adequate number of subjects in this age group who can meet the criteria for inclusion, children above five years of age and adults who can meet inclusion criteria (WHO 1996:6) were included in the studies. Therefore, meeting the inclusion criteria was more determining and the reliance of age limits was not strictly delineated.

Malaria in Ethiopia is seasonal and of epidemic type characterised by low transmission (Adhanom et al 2006:556). In areas where malaria transmission is low, the WHO (2003:33) recommends the enrolment of children above five years of age and adults. Based on this provision, the study population enrolled in most of the studies conducted

in Ethiopia involved children above five years of age and adults who met the specific clinical and parasitological criteria for enrolment in the study, with the exception of infants under six months of age and pregnant women. Infants and pregnant women were not included in the studies reasons related to their biological state that makes them vulnerable to malarial infection that requires prompt and highest level possible care.

The Ethiopian Science and Technology Commission (2005:7) guideline for health research ethics enforces compliance to the WHO and International Conference on Harmonization guidelines for good clinical practice. Accordingly, the antimalarial drug efficacy study protocol developed by the WHO was selected in line with the Ethiopian guidelines for health research ethics.

3.3.1.2 Sampling

This study aimed to achieve complete review of all available published and unpublished antimalarial drug efficacy studies conducted in Ethiopia. Accordingly, the approach was to achieve full coverage of review of all available documents and publication without a specific need for sampling. Although total coverage of all studies was considered in this study, describing the sampling approach employed in the original studies is of relevance.

The sample size determination approaches used in the original studies was not well explained in most of the studies while some studies had a clear sampling approach and sample size determination. The major nationwide studies conducted in Ethiopia in the late 1990s involved the Double Lot Quality Assurance sampling that allows minimum sample size without compromising statistical precision (WHO 1996:16).

In most of the recent studies conducted in the 2000s, sample size determination based relevant statistical assumptions and approaches were employed. For example, to detect treatment failure of 20% in the population with 10 percentage point precision at 95% confidence interval and study power of 80, a sample size of 73 subjects including a contingency of 20% for loss and withdrawal was considered. Irrespective of such statistical sampling approaches, the WHO (2003:46) study protocol for antimalarial drug efficacy tests recommends a minimum of sample size of 50 as adequate to generate evidence required to support antimalarial drug policy decisions.

3.3.1.3 Ethical issues related to sampling

The sample selection in the original antimalarial drug efficacy studies was based on enrolment of patients who met the inclusion criteria. Once the inclusion criteria were met, patients were informed of the objectives of the study and requested to express their consent verbally or in writing on whether they wished to participate in the study.

To ensure protection of safety of patients, investigators in the reviewed studies indicated that patients who had clinical conditions that require further medical attention and support were referred to the nearest health facility for further care. For patients whom, during the follow-up period, had confirmed treatment failure or resistance to the antimalarial drug being tested, rescue treatment with other effective antimalarial medicines was placed.

The sampling considered in this study, aimed to ensure review of all available study publications and documents on antimalarial drug efficacy studies conducted in Ethiopia. Therefore, no study was excluded on any ground or no study was preferred than the other. Therefore, by ensuring review of all available antimalarial drug efficacy studies conducted in Ethiopia, the sampling followed ethically correct approach of all-inclusiveness.

3.3.2 Data collection

3.3.2.1 Data collection approach and method

The study didn't involve the use of raw secondary data that could have required permission from the originators. Data from the published and unpublished studies was extracted and entered in to a Microsoft Excel (Microsoft Corporation 2009) based data collection form. As the studies involved different methods that included *in vivo*, *in vitro* and genetic analysis methods, the variables measured in each of the studies were not uniform. Although collection of the data from the studies related to the findings, conclusions and recommendations was relatively manageable, the relevance of findings and recommendation and the follow-up action that will be taken was mostly unavailable or loosely mentioned in the publications and reports.

The data collection was done through internet based search using Internet Explorer version 8 (Microsoft Corporation 2009). Library search for periodicals, mainly at the WHO library in Geneva was done to access early publications and reports for which electronic versions were not available. The internet based search mainly relied on search engines such as the Google Scholar (2011), NCBI (2009), the University of South Africa library online services (University of South Africa 2011).

The main search words used included a combination of the following key words: *Ethiopia, malaria, treatment policy, antimalarial drugs, treatment failure, resistance, efficacy, Plasmodium falciparum, and Plasmodium vivax.* For specific search on articles whose authors were known, the name of the author together with the key search words was used. For country specific information on health service system in general and malaria prevention and control services in particular, drug regulatory issues and other relevant health and socio-economic information, specific web-sites of the organisation run by the government of Ethiopia and other non-governmental and United Nations organizations' web sites were consulted.

To ensure review of the antimalarial drug efficacy and treatment policy in Ethiopia in light of the regional context, antimalarial drug policies and antimalarial drug efficacy monitoring system in the neighbouring Horn of African countries, namely: Eritrea, Djibouti, Kenya, Somalia and Sudan was conducted. The main data search approach used was websites based mainly the WHO and country specific scientific publications and reports. In addition to the internet based search on websites of institutions such as the WHO, publications and reports of regional antimalarial treatment monitoring networks of the East African Network for Monitoring Antimalarial Treatment (EANMAT) and the Horn of African Network for Monitoring Antimalarial Treatment (HANMAT) were consulted.

The search for publications started in November 2010 and 420 articles and reports were obtained of which relevant data and information was cited from 231 published and unpublished reports and web based resources. In additions to the publication and reports, text books relevant to the study subject have been consulted and referenced as appropriate.

3.3.2.2 Development and testing of the data collection instrument

The data collection tool used to capture data from the published and unpublished studies was developed using Microsoft Excel (Microsoft Corporation 2003). The tool was designed to suit collection of the variables measured in each of the studies. Although no special field testing was necessary to test the data collection format, its appropriateness has been assessed during the course of the data collection.

Through this process, the data collection format was regularly revised to suit the purpose based on actual experience obtained during its use. Depending on the type of the antimalarial drug study method, separate data entry and analysis sheets were used for the in vitro, in vivo and genetic methods of study for each parasite species studied and the antimalarial drug tested.

3.3.2.3 Characteristics of the data collection instrument

The data collection instrument used in this study was specifically constructed for the purpose of the study based on the type of variables in the original studies that were targeted for collection and analysis. A total of 30 data variables were collected (Annexure B).

Depending on the type of the study technique such as in vivo, in vitro and molecular methods and the type of parasite and antimalarial drugs assessed, all the 45 data variables were not uniformly applicable to all and varied accordingly. The characteristics of the data collection formats are, therefore, mainly distinguished by the type of variables each format captures. Based on this approach, a total of 10 different data collection sections were developed and used. The data collection tool included the following section:

a) *in vivo* therapeutic efficacy assessment of chloroquine for the treatment of *Plasmodium falciparum* malaria (for published studies)
b) *in vivo* therapeutic efficacy assessment of chloroquine for the treatment of *Plasmodium falciparum* malaria (for unpublished reports)
c) *in vitro Plasmodium falciparum* sensitivity test to chloroquine

d) molecular marker analysis on *Plasmodium falciparum* and *Plasmodium vivax* to analyse genetic markers related to resistance to AL, Quinine and Atovaquone proguanil
e) *in vivo* therapeutic efficacy assessment of amodiaquine for the treatment of *Plasmodium falciparum* malaria
f) *in vivo* therapeutic efficacy assessment of sulfadoxine-pyrimethamine for the treatment of *Plasmodium falciparum* malaria
g) *in vivo* therapeutic efficacy assessment of chloroquine for the treatment of *Plasmodium vivax* malaria
h) *in vivo* therapeutic efficacy assessment of chloroquine plus primaquine for the treatment of *Plasmodium vivax* malaria
i) *in vivo* therapeutic efficacy assessment of artemether-lumefantrine for the treatment of *Plasmodium falciparum* malaria
j) *in vivo* therapeutic efficacy assessment of artemether-lumefantrine for the treatment of *Plasmodium vivax* malaria

3.3.2.4 Data collection process

The data collection process first involved search for published and unpublished antimalarial efficacy studies from as early period available until 2011. Copies of the articles were saved electronically and in printed versions. Once the search was completed, the articles and reports were classified based on the method of the study employed, the malaria parasite studied and the antimalarial drug evaluated.

Following grouping of the studies, data variables available in the reports were extracted and entered into the relevant data collection format developed on Microsoft Excel (2003).

3.3.2.5 Ethical considerations related to data collection

The data collection and analysis was based on data extracted from published and unpublished reports. In the data collection and analysis and interpretation, confidentiality was maintained by strictly ensuring the collection and analysis of data without making any reference to individuals or their identity. In the selection of the studies for analysis, fairness was ensured by including findings from all antimalarial

drug efficacy studies conducted in the country. There was no any study excluded from being considered in the analysis for any reason whatsoever and the findings of each of the studies were fairly and equally reflected in the study without any sentiment of judgment.

The researcher has also verified from the reports if the investigators and subjects enrolled in the original studies had adhered to standard ethical practices. In all the studies reviewed, researchers confirmed that patient enrolment and participation in the studies was fully voluntary and based on informed consent and the required ethical clearance was obtained from relevant institutional and national authorities prior to the conducting the studies. With the exception of a three studies, most of studies ensured verbal consent and didn't use consent forms.

The investigator asserts that the principal pillars of health research ethics (Pilot & Beck 2008:167) that refer to non-maleficence, beneficence, respect for autonomy, and justice were adhered to by the researchers who conducted the original studies. This is confirmed from the reports which confirmed attainment of ethical clearance by responsible institutional or national authorities, informed consent of participants and the rescue interventions placed in order to provide the necessary medical support to ensure safety of patients. This study obtained ethical clearance by the University of South Africa Ethics Committee (Annexure A).

3.3.3 Data analysis

The statistical tests applied in the original studies included proportion of treatment failure and Kaplan Meier survival analysis with 95% confidence intervals and significance level of 0.05. In some studies that involved comparison of two different antimalarial drugs, a case-control approach of study design was applied and analysis outcomes presented in terms or proportion of treatment success or failure with the corresponding 95% confidence intervals at significance level of 0.05.

In the analysis, comparison of the proportion of treatment failures reported by each study and the level of significance of the treatment failure detected was compared for each of the studies. Based on the comparison, the approaches used in the studies have been assessed.

A Microsoft Excel (Microsoft Office Excel 2003) based data entry and analysis was applied to calculate proportions, mean, median and range using the therapeutic efficacy data collected from the relevant studies. Statistical test such as comparison of proportions and determining the corresponding 95% CI (confidence interval) and P-values was also calculated for study findings that required comparison. For the purpose of statistical analysis, Statistical Package for Social Sciences (SPSS) version 10 (SPSS Inc 2007) and MedCalc version 11.6 statistical software for biomedical research (MedCalc Software 1993-2011) were used as necessary.

The main variables analysed include treatment failure rates through comparison of proportions of treatment failure. This comparison was used to test for significance of difference between study findings for which comparison was needed. Assessment related to the time duration between antimalarial drug efficacy studies was also one of the variables considered to determine the extent of timeliness and regularity of the studies. The time lapse between antimalarial drug treatment efficacy study reports that led to antimalarial drug policy and treatment guideline change and activities related to antimalarial drug efficacy monitoring in the interim period was also one of the most important features assessed.

The main aim of this study was to assess the representativeness, timeliness and completeness of antimalarial drug efficacy studies to inform policy decision. Based on this a conventional numeric scoring was used to grade the representativeness, timeliness, completeness and adequacy of the studies to inform policy decision based on the scoring described below (table 3.1).

Table 3.1 Antimalarial drug efficacy study representativeness, timeliness and completeness scoring

Measure	Score	Attribute
Representativeness	0	Sample size below 50 and number of study sites below four and study subjects pre-selected
	1	Meets the minimum sample size of 50 or more and more than 4 study sites and study subjects selected on presentation
	2	Meets both the minimum sample size and number study sites and subject selection approach
Completeness	0	No blood film examination re-check, no drug quality analysis and no blood level of drug administered determined
	1	Only one of the three tasks met
	2	Only two of the three tasks met
	3	All the three tasks completed
Timeliness	0	Study conducted after two years from the date of publication of the preceding study
	1	Study conducted within two years from the date of publication of the preceding study
Study adequacy to inform policy	Yes or No	Yes = Study achieved a score of above 60%, No = Study achieved a total score of 60% of less

3.4 INTERNAL VALIDITY AND EXTERNAL VALIDITY OF THE STUDY

Polit and Beck (2008:295) defines internal validity as the extents of certainty of the effect of interventions on the outcomes while external validity is the applicability of the research findings in the real world beyond the controlled research setting.

The sampling approach used in this study aims to ensure review of all published and unpublished studies on antimalarial drug efficacy conducted in Ethiopia. The fact that all available sources are covered in the study ensures that the highest possible sample size was considered for the study. Therefore, the risk of having findings and conclusions that are based on unrepresentative sample is minimal.

The conclusions derived from this study being exhaustive in covering all published and unpublished studies has enabled to avoid errors that might have arisen from low sampling. The data collection tool used to extract the data also picks all the relevant variable data points that are used to measure the level of antimalarial treatment failure. Therefore, appropriate approach and data collection and analysis has been used to measure the main outcome variables of this study that are related to representativeness, timelines and completeness of antimalarial drug efficacy studies in Ethiopia.

Based on the findings on representativeness, timeliness and completeness of antimalarial drugs conducted in Ethiopia, it was also possible to assess if this was adequate to inform antimalarial treatment policy decisions and development of malaria treatment guidelines that appropriate to the Ethiopian setting. The specific issues related to sampling, study power and precision of the instruments used in the original studies was critically reviewed and presented in the chapter 5 that covers the study findings.

3.5 CONCLUSION

The research method and design presented in this chapter provided detailed description and justification on the type of design applied and components of the research method. In the research method section, specific description on the study population, sampling, data collection instrument and its characteristics and data analysis was covered.

In this chapter, ethical issues at the stage of sampling and data analysis have been described asserting that the standard followed was driven to meet high ethical standards. A detailed description on the internal and external validity of the research was also presented with a specific explanation on how this was achieved in the study.

In the following chapter 4, analysis, description and presentation of the research findings is presented based on the data collection and analysis approaches explained in chapter 4. The relevance of the research findings in terms of representativeness, completeness and timeliness and completeness of antimalarial drug efficacy studies in Ethiopia and its relevance to informing antimalarial treatment policy and guideline development is also one of the main elements presented in chapter 4.

CHAPTER 4

ANALYSIS, PRESENTATION AND DESCRIPTION OF THE RESEARCH FINDINGS

4.1 INTRODUCTION

The research design and method in chapter 3 presented the approaches applied in the data collection and analysis. In chapter 4, the research findings are presented with the relevant analysis and description of the findings in relation to antimalarial drug efficacy studies representativeness, completeness and timeliness and its implication and adequacy to inform antimalarial drug policy and malaria treatment guidelines in Ethiopia.

The type of data collected from the antimalarial efficacy studies conducted in Ethiopia varied depending on the study method applied, the antimalarial drug tested and the parasite species subjected. In addition to these differences, the antimalarial drug efficacy assessment protocols and the specific study approaches employed by the researchers have not been uniform.

As a result of such differences, which in most cases are quite unambiguous, the data collection and analysis approach has been tailored to suit the design of the studies and findings have been grouped accordingly to the category they fall into. Based on this approach the study findings from *in vivo, in vitro* and molecular studies by type of antimalarial drug evaluated and the malaria parasite species subjected and the duration of the study and findings reported have been complied and analysed.

While the broader approach was to critically review finding from all studies, the main focus of the analysis was on *in vivo* antimalarial drug efficacy studies as this method is the recommended data collection approach to guide antimalarial treatment policy decisions (WHO 2009a:9). The modelling approach to antimalarial treatment policy change based on financial implication of antimalarial treatment policy change proposed by Yeung Pongtavornpinyo, Hasting, Mills and White (2004:179), seem to focus more

on the budgetary implication of treatment policy change than the public health problem that need to be addressed.

The strengths and gaps in antimalarial drug efficacy monitoring and the use of evidence for policy and guideline development has been critically assessed in order to draw recommendations and best practice approaches for the Ethiopian setting. The data collection and analysis has also taken in to considerations antimalarial drug monitoring practices in the neighbouring countries where the malaria transmission epidemiology shows some similarity.

The common pattern of seasonal malaria transmission in the Horn of African countries and the similar profile of parasite response to antimalarial drugs indicated in the WHO (2005a:103) envisages a harmonised approach to defining and applying the antimalarial treatment options. In this chapter, findings and analysis of the study is presented in relevant sections grouped according to their focus and outlines the strength and gaps of the studies conducted and their implications to influencing antimalarial treatment policy decision making and updating antimalarial treatment guidelines in Ethiopia.

4.2 DATA MANAGMENT AND ANALYSIS

4.2.1 Data collection and analysis approach

The data extracted from published and unpublished studies was entered and analysed using a Microsoft Excel based data management tool that has ten different sections suitable for the different types of the study approaches used.

The data collected included values for a total of 30 variables of which 15 variables that are of high relevance to the study objectives were selected for in-depth analysis. The variables collected included data related to study area and population, test drug type and batch, expiry date, study findings, duration to dissemination of the study findings and its implication to antimalarial drug policy and treatment guideline change.

The number of variables collected and analysed do not apply for all types of studies. In vivo therapeutic efficacy studies, for example, have more data variables compared to

the *in vitro* parasite sensitivity assessment studies to antimalarial drugs and molecular methods of analysis.

The overall data collection and analysis was designed to provide summary measure that can be used to assess the representativeness, timeliness and completeness of the studies conducted in Ethiopia. A detailed list of the variables and summary measures considered during the analysis is presented in Annexure B. The main measures used during the analysis include the following:

a) Study design
   - i Study protocol for the setting
   - ii Samples size
   - iii Parasite species studied
   - iv Antimalarial drugs tested
   - v Number of study sites
   - vi Duration of patient follow-up

b) Test drug
   - i Quality analysis of the antimalarial drug tested for active ingredient
   - ii Blood level of drug and its metabolite at the date of confirmed treatment failure

c) Study quality control
   - i Slide examination result cross-checking by a second

d) Study outcomes / in vivo therapeutic efficacy studies
   - i Total number of subjects who completed the study
   - ii Per cent total treatment failure
   - iii Per cent treatment failure (*Plasmodium vivax*)

e) Study findings and policy implication
   i Number of years lapsed since the immediate previous similar antimalarial drug efficacy study
   ii Implication of the findings on antimalarial drug policy and treatment guidelines
   iii Changes introduced as a result of the study findings

4.2.2 Detailed review and data analysis to determine adequacy of the studies

Study reports from published and unpublished sources have been individually reviewed to determine completeness, timeliness, representativeness and policy actions taken as a result of the study finding and recommendations. Analysis of the studies to estimate the representativeness, timeliness and completeness was done based on a numeric score attained by each of the studies and a scoring approach presented in table 4.1. Based on this assessment and scoring, the adequacy of the studies to informing antimalarial drug policy decision in Ethiopia is presented in section 4.6.

4.3 RESEARCH RESULTS

4.3.1 Overview of antimalarial drug studies conducted in Ethiopia

Published and unpublished reports reviewed through this research show that the first antimalarial drug testing in Ethiopia was conducted in 1974 by Dennis et al (1974:241). In the period from 1974 to 2011, a total of 28 published and unpublished documents on 44 antimalarial efficacy studies involving 5,949 study subjects in 159 study sites across the country have been conducted. Of these, 26 of the reports on 39 studies (89%) were published in peer-reviewed journals while 2 reports on 5 (11%) studies conducted by the Federal Ministry of Health in 1997–1998, the findings of which led to the treatment policy in 1998 were not published in peer reviewed journals.

The studies were conducted to assess the efficacy of nine different antimalarial drugs which the majority of 24 (55%) were on chloroquine, 8 (18%) on sulfadoxine-pyrimethamine and 6 (14%) on AL. Most of the studies (80%, n=35) were conducted to assess the efficacy of five different antimalarial drugs used as first second-line antimalarial drugs for *Plasmodium falciparum* malaria while the remaining 9 (20%) studies were conducted to assess four different antimalarial drugs for the treatment of *Plasmodium vivax* infections.

The antimalarial drug assessment technique involved in vitro methods in 4 (9%) of the studies and in vivo and genetic analysis methods in 34 (77%) and 6 (14%) of the remaining studies, respectively. Most of the in vivo studies (69%, n=20) conducted involved a period of follow-up of seven or 14 days while the remaining (41%, n=14) in vivo studies involved a follow-up period of 28 days. A summary of the studies conducted in Ethiopia is presented in table 4.1.

Table 4.1 Summary of antimalarial drug studies conducted in Ethiopia, 1972–2011

Test Drug, Parasite	Study protocol	Studies	Sites	Sample	Outcome	Year
Chloroquine, *Plasmodium falciparum*	In vitro	4	7	130	0--70%[a]	1974–1985
	Genetic analysis	1	1	69	78.3--95.7[b]	2006
	In vivo 7 days	1	55	*2015*	0—100[c]	1980–1996
	In vivo 14 days	1	24	837	47.7--73.6[c]	1998
	In vivo 28 days	2	12	213	0--22.4[c]	1985
Sulfadoxine-pyrimethamine *Plasmodium falciparum*	In vitro	-	-	-	-	-
	Genetic analysis	1	1	69	81.2-82.6 [a]	2006
	In vivo 7 days	2	2	12	0--1.3[b]	1993–1996
	In vivo 14 days	3	9	369	5.6--21.1[c]	1998–2002
	In vivo 28 days	1	11	523	33.5 [c]	2003
Artemether-lumefantrine *Plasmodium falciparum*	In vitro	-	-	-	-	-
	Genetic analysis r	1	1	35	0	2010
	In vivo 7 days	-	-	-	-	-
	In vivo 14 days	1	2	105	0	2006
	In vivo 28 days	2	5	294	0.9--6.7[c]	2003–2010
Quinine *Plasmodium falciparum*	In vitro	-	-	-	-	-
	Genetic analysis	1	1	30	0	2010
	In vivo 7 days	-	-	-	-	-
	In vivo 14 days	-	-	-	-	-
	In vivo 28 days	-	-	-	-	-
Atovaquone-proguanil *Plasmodium falciparum*	In vitro	-	-	-	-	-
	Genetic analysis	1	1	32	0	2010
	In vivo 7 days	-	-	-	-	-
	In vivo 14 days	-	-	-	-	-
	In vivo 28 days	-	-	-	-	-
Chloroquine *Plasmodium vivax*	In vitro	-	-	-	-	-
	Genetic analysis	-	-	-	-	-
	In vivo 7 days	1	1	255	2	1997
	In vivo 14 days	5	7	298	3.6--8.8[c]	2008–2011
	In vivo 28 days					
Sulfadoxine-pyrimethamine *Plasmodium vivax*	In vitro	-	-	-	-	-
	Genetic analysis	1	1	31	3.2-6.5	2010
	In vivo 7 days	-	-	-	-	-
	In vivo 14 days	-	-	-	-	-
	In vivo 28 days	-	-	-	-	-

Key for outcome

a= per cent parasite growth in culture medium with chloroquine of greater than 1.5 nmol
b= per cent samples with one or more gene polymorphic regions that conform resistance
a= per cent of treatment failure cases

4.4 CHARACTERISTICS OF THE STUDIES

4.4.1 Sample characteristics

The review included all published and unpublished studies available with no specific need for sampling. The review being all inclusive, the presentation and analysis of the findings and the conclusion that can be drawn based on the analysis is expected to representative. The characteristics of the studies reviewed can be best described based on the objective of the assessment, method of study applied, sample size considered and implication of the study finding.

In general, the studies reviewed involved sample size ranging from 1 to 1,706. The study referred to as having a sample size of 1 was a case report by Assefa (1987:209). Most studies did not present a detailed sampling approach and statistical assumption the sampling was based on. Although this can be a reasonable generalisation of the sampling characteristics of the antimalarial efficacy studies conducted in Ethiopia, the specific details of the sampling approach is presented under the specific study in the following sections.

4.4.2 Study subjects

Detailed methodological description of the antimalarial drug studies conducted in Ethiopia presented that, the studies were conducted on patients who met the inclusion criteria for the study and who consented voluntarily to take part in the study. In all studies, infants below six months of age and pregnant women were not included because of their biological vulnerability to malarial infection.

Of the total 49 studies reviewed, 4 (8%) studies conducted in 36 (22%) of the study sites involved participation of 1,039 (15%) children from the age of 6 to 59 months. The remaining 44 (92%) studies in 129 study sites involving 5,830 (85%) study subjects were conducted in subjects in the five years of age and above category. In any of the studies, there was no specific mention of the highest age limit for study eligibility. The main groups that were strictly excluded were infants and pregnant women while inclusion of all other subjects was mainly based on meeting the specific inclusion criteria for the study.

4.4.3 Study site distribution

The antimalarial efficacy studies conducted in Ethiopia were predominantly in malaria endemic localities. The only two studies exception to this are those conducted by Dennis et al (1974:241) and Teklehaimanot (1986:127) that were conducted in the capital Addis Ababa where malaria transmission does not normally occur.

A total of 41 subjects aged between 5–44 years and 98 subjects aged between 14 to 58 years were enrolled in the studies conducted by Dennis et al (1974:241) and Teklehaimanot (1986:127) respectively. Based on the travel history recorded at the time of enrolment in the study, none declared permanent residence in malarious localities but temporary visits and stays in malarious localities bordering the Sudan and Kenya.

A total of 10 studies (54%) were conducted involving only one study site while 15 (35%) studies involved 2 to 7 study sites with the remaining 4 studies involving 11 to 36 sites. The WHO recommends the use of 4–8 study sites depending on the size of the country and the malaria transmission epidemiology for a study to be representative.

4.4.3 Study protocols

The antimalarial drug efficacy study protocols used in Ethiopia are the protocols developed by the WHO updated in 1967 and 1972 which was further revised in 1996, 2001 and 2009, in a bid to address the appropriateness of the study protocols with the evolving pattern of efficacy of antimalarial drugs and drug resistance malaria endemic countries (WHO 2010a:15).

As a reflection of the evolution of the antimalarial drug efficacy monitoring protocol, antimalarial drug efficacy study protocols used in Ethiopia employed follow-up period of 7-days, 14-days and 28 days (Table 4.1). The appropriateness and adequacy of the follow-up duration and the advantages and disadvantages are presented in section 4.5 of this chapter.

4.5 DETAILED REVIEW OF THE ANTIMALARIAL DRUG STUDIES

4.5.1 Early studies on sensitivity of *Plasmodium falciparum to* chloroquine

Early studies conducted in Ethiopia provided information on the sensitivity of *Plasmodium falciparum* to single dose of chloroquine administered at 10 mg/kg, Since then a number of studies have been conducted.

The objective and set-up of the studies, however, has never been fully described in the context of its implication to antimalarial treatment policy in Ethiopia. In this section, therefore, the studies conducted beginning from the early 1970s, which marks the starting of studies on the sensitivity of Ethiopian *Plasmodium falciparum strains* to antimalarial drugs is described and assessed.

4.5.1.1 In vitro studies

The first published study on the sensitivity of *Plasmodium falciparum* to chloroquine was conducted *in vitro* by Palmer, Townley, Yigzaw and Armstrong (1976:10) in the period from 1971–1972. The study involved 82 patients diagnosed for *Plasmodium falciparum* in three field stations of the United States Naval Medical Research Unit 5 (NAMRU 5) located in central and western parts of Ethiopia.

The testing involved exposure and evaluation of parasite development *in vitro* in test vials containing 0.5, 0.75 and 1 nmol (nano mole) of chloroquine. Of the 82 parasite samples, 21 (25.6%) parasite samples showed continued growth and development in test vials containing 0.5 nmol of chloroquine while no growth was observed in the 0.75 and 1.0 nmol drug containing test vials. In this study no simultaneous *in vivo* evaluation of the therapeutic efficacy of chloroquine was conducted.

4.5.1.2 In vivo and in vitro simultaneous Plasmodium falciparum sensitivity studies to chloroquine

Dennis et al (1974:241) conducted a study involving simultaneous *in vivo* and *in vitro* evaluation of *Plasmodium falciparum* sensitivity to chloroquine at the NAMRU-3 hospital in Addis Ababa, Ethiopia. The individuals involved in the study were presumed to have encountered the infection in other malarious parts of the country as the study site, Addis Ababa, is a predominantly malaria free highland area. The primary aim of the study was to describe and define the clinical significance of *in vitro* sensitivity study findings.

The in vivo follow up was done over a period of 28 days following treatment of subjects with confirmed *Plasmodium falciparum* mono-infection with 10 mg/kg single dose of chloroquine. The in vitro test involved exposure of the test parasite, *Plasmodium falciparum*, to drug concentrations of 0.5, 0.75 and 1.0 nmol of chloroquine. The findings of the study presented in table 4.2 showed 11 recrudescent cases over the 28-day follow-up and in vitro tolerance in 9 (37.5%) cases in test medium with 0.5 nmol and 5 (20.8%) in the 1.0 nmol test vials.

This finding clearly showed an increase in the number of chloroquine tolerant strains as parasite growth in the 1.0 nmol chloroquine concentration was not detected in the previous study by Palmer et al (1976:10). The conclusion drawn from the study was that, sensitivity of Ethiopian *Plasmodium falciparum* strain was between the sensitive Ugandan strain and the resistant Malayan strain indicating a relatively higher tolerance of the Ethiopian strain to chloroquine in the African region.

Table 4.2 ***In vivo*** **and** ***in vitro Plasmodium falciparum*** **sensitivity study to chloroquine in Ethiopia, 1972**

Details	Drug Evaluation Method	
	In vivo	***In vitro***
No. of study sites	1	1
No. of patients enrolled	41	24
Study protocol	*In vivo* 28-days test	Rickemann *in vitro* test
Test dosage	10 mg/kg single dose	0.5; 0.75 & 1 nmol
Outcome	11 recrudescent cases	9 (37.5%) cases at 0.5 nmol, & 5 (20.8%) cases at 1 nmol

(Dennis et al 1974:241)

4.5.1.3 Second in vivo Plasmodium falciparum sensitivity test to single dose chloroquine

A second *in vivo* test on the sensitivity of *Plasmodium falciparum* to 10 mg/kg single dose chloroquine was conducted by Armstrong, Asfaha and Palmer (1976:10) in a field setting. A total of 150 patients were recruited for the study in three endemic sites located in Arbaminch, Abela and Gambella in the Southern and Western parts of Ethiopia. After a follow-up period of 6 to 11 days, the team reported no recrudescent cases but sited the limitations of the study related to the logistic difficulty that hindered from completing a 28 days follow and assessment of treatment outcome.

Compared to the previous studies, this study adopted a limited period of follow-up that does not allow complete evaluation of the efficacy of the antimalarial drug tested and the results from the finding were not supportive to take any action.

4.5.1.4 Studies conducted in the early 1980s

For nearly eight years from the study by Armstrong et al (1976:5), no chloroquine sensitivity studies were conducted. Following this long period, Gebremariam, Abdullahi and Mebrate (1982:1) conducted i*n vivo* chloroquine efficacy study in Nazareth town, Central Ethiopia. In this study, a total of 21 subjects were enrolled for *in vivo* evaluation of *Plasmodium falciparum* response to 25 mg/kg of chloroquine administered over three

days and 14 isolates were subjected *in vitro* to chloroquine concentration levels ranging from 0.25 to 3 nmol.

The findings at the end of the study summarised in table 4.3 showed no early treatment failure cases of the RI and RII type while parasite growth was recorded in 7 (50%) cases in test vials containing 0.5 nmol chloroquine; 2 (14.3%) cases in 0.75 nmol and 1 (7%) case in 1.0 nmol. These finding led the investigators to conclude that the study findings were similar with the results of earlier studies reported by Dennis et al (1974:241) and Armstrong et al (1975:5) but called for more extensive and detailed study to be conducted.

Comparing the results from this study and the results reported by Dennis et al (1974:241), there was no significant difference in the proportion of growth inhibition both at 0.5 nmol (z score 0.75; P=0.4515) and 1.0 nmol concentrations (z score 1.1; p=0.2642).

Table 4.3 *Plasmodium falciparum in vitro* sensitivity test to chloroquine in Ethiopia in 1980

Details	Drug evaluation method	
	In vivo	***In vitro***
No of study sites	1	1
No of patients enrolled	21	14
Study protocol	*In vivo* 7-days test	Rickemann *in vitro* test
Test dosage	25 mg/kg over 3 days	0.25 to 3.0 nmol
Outcome	No recrudescent cases	7 (50%) cases at 0.5 nmol, 2 (14.3%) case 0.75 nmol 1 case (7%) at 1.0 nmol

(Gebremariam et al 1982:1)

In a subsequent study, Gebremariam and Teklehaimanot (1986:1) evaluate *Plasmodium falciparum* sensitivity to full course of 25 mg/kg of chloroquine in 11 study sites from 1983 to 1984. The study involved *in vivo* therapeutic efficacy evaluation of chloroquine in 139 patients for seven days and 115 patients for 28 days and no recrudescent or treatment failure cases were detected in both groups.

This led the researchers to conclude that the sample size and sampling area covered was sufficiently representative and *Plasmodium falciparum* is still sensitive to chloroquine despite the continued use of the drug in the country for the past 25 years preceding the study.

However, in view of the reported chloroquine resistant malaria cases in the neighbouring country Kenya and of the extensive population movements across the common borders and non-inclusiveness of these sites in the current study, Gebremariam and Teklehaimanot (1986:1) recommend conducting chloroquine sensitivity study in these locations as necessary.

4.5.1.5 First report of Plasmodium falciparum resistance to chloroquine

The first chloroquine resistant *Plasmodium falciparum* cases were reported by Teklehaimanot (1986:127) in a study conducted on 98 subjects with confirmed *Plasmodium falciparum malaria*. The subjects declared travel to malarious areas while the study was conducted at the National Malaria Control Laboratory located in the capital Addis Ababa which is a predominantly malaria free area.

In the 28-days follow-up period after treatment with standard dose of chloroquine at 25 mg/kg administered over three days, parasitaemia persisted in 22 (22.4%) of the cases. *In vitro* testing of blood samples from 10 of the patients with chloroquine resistant parasites detected during the study also showed parasite growth in test vials containing more than 1.5 nmol of chloroquine which is believed to be the maximum growth inhibitory concentration for sensitive strains.

There were no other major studies covering wider sample size, area or follow-up duration of up to 28 days for nearly seven years since the first confirmed report of chloroquine resistance by Teklehaimanot (1986:127). In 1993, Wezam (1993:271) reports no recrudescent or treatment failure *Plasmodium falciparum* cases in a 7-day *in vivo* assessment of 23 patients treated with standard course of chloroquine and 24 patients treated with sulfadoxine-pyrimethamine.

After three years from the study conducted by Wezam (1993:271) and Tulu et al (1996:556) report 86% (n=29) recrudescent *Plasmodium falciparum* and 2% (n=255)

Plasmodium vivax cases following completion of a 7-day *in vivo* follow-up after treatment with standard course of chloroquine in the study site of Debrezeit 40 km east of the capital, Addis Ababa. In this same study, Tulu et al (1996:556), *Plasmodium falciparum* sensitivity to single dose standard dose of sulfadoxine-pyrimethamine was also assessed in 80 subjects and 1 (1.3%) recrudescent case was reported. In concluding, Tulu et al (1996:556) highlight the need further studies in other Geographic regions of the country to evaluate the sensitivity of *Plasmodium falciparum* to chloroquine while the response of *Plasmodium vivax* to chloroquine and *Plasmodium falciparum* to sulfadoxine-pyrimethamine was considered as effective.

4.5.1.6 Malaria case detection and treatment posts report

The increasing reports of chloroquine resistant *Plasmodium falciparum* cases led the National Malaria and Other Vector-Borne Diseases Control Program to introduce a follow-up procedure to confirm treatment outcomes in malaria patients treated in the laboratories managed by the programme.

The procedure introduced in August 1989 and implemented by 36 malaria case detection and treatment posts across the country involved daily supervised administration of chloroquine to *Plasmodium falciparum infected* patients and blood examination for three consecutive days to monitor parasite clearance. Further follow-up was done in all *Plasmodium falciparum* cases who return to the laboratory with clinical symptoms within two weeks from the preceding visit and treatment.

Through this procedure, cases that didn't show parasite density reduction on day-3 of the follow-up to less than 25% compared to the parasite density on day-zero on which treatment was started and those with parasites on day-7 were considered as treatment failure cases and treated with sulfadoxine-pyrimethamine. Alene and Bennett (1996:810) analyse data collected through the new follow-up procedure from August 1989 to July 1991 and confirm that of the 39, 824 *Plasmodium falciparum* patients detected, 1,706 (4.3%) patients returned to the treatment posts with malaria clinical symptoms within 15 days from the preceding treatment.

The 1,706 returning patients were again treated with chloroquine under direct observation and their blood examined for four consecutive days. On the fourth follow-up

day, 1,488 (87.2) cases had parasite densities of more than 25% compared to the parasite density on day-zero and were parasitemic on day-7 as well. All these cases were considered as treatment failure cases and subsequently treated with sulfadoxine-pyrimethamine.

4.5.1.7 Multi-site supervised 28-days in vivo chloroquine efficacy assessment studies

Although a number of studies reported confirmed indicative trends in the declining sensitivity of *Plasmodium falciparum* to chloroquine, the findings were not widely representative enough to inform decision making on the continued use or need to replace the drug.

According to unpublished reports of the Ministry of Health (1998a:3) most of the antimalarial drug efficacy studies conducted in Ethiopia didn't have sample size that can allow statistically acceptable conclusions. Moreover, the proportion of drop-outs from the studies was unacceptably high and the studies were not representative of the diverse eco-epidemiological setting in Ethiopia that influences malaria transmission in the country.

The lack of use of uniform study protocols being one of the major problems in the previous studies, the Ministry of Health conducted chloroquine efficacy studies for the treatment of uncomplicated *Plasmodium falciparum* malaria in 15 representative sites shown in figure 4.1 following the study protocol developed by the WHO (1996:3).

The WHO (1996:3) describes that the study protocol was primarily developed for antimalarial drug efficacy assessment in areas with intense malaria transmission involving children less than five years of age. However, due to the seasonal and unstable nature of malaria transmission in Ethiopia, the Ministry of Health (1998a:4) decides to conduct a study both in children under five years and in older children and adults. Accordingly, a study involving 527 children aged 5 to 59 months in 14 study sites and 298 patients aged five years and above were conducted in the period from October 1996 to April 1998.

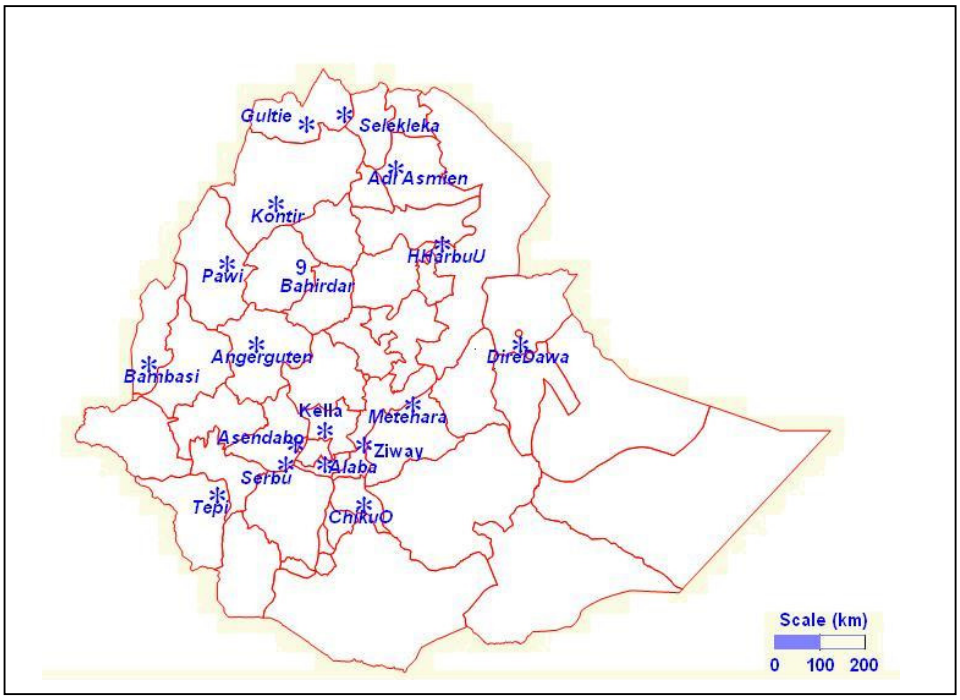

Figure 4.1 Distribution of anti-malarial drug efficacy study sites, 1996–1998

(Federal Ministry of Health 2002)

At the end of the study, the overall chloroquine treatment failure in children under five years of age detected in 14 study sites was 68.7% (95 CI, 64.5 to 72.8) (table 4.4). The levels of treatment failure varied by site from 0% in Bambasi, North-Western Ethiopia, to 100% in Harbu, Northern Ethiopia. Although there was no specific explanation for the low treatment failure in the study site of Bambasi, the sample size of 16 patients was small compared to the other sites ranging from 2 to 65 patients.

Table 4.4 Therapeutic efficacy of chloroquine on uncomplicated *Plasmodium falciparum* in children under five years of age, Ethiopia, 1996–1998

No	Study site	Subjects		Treatment outcome		Treatment failure	
		Enrolled	Follow-up completed (%)	Adequate clinical response	Treatment failure	Per cent	95% CI
1	Harbu	45	42 (93.3)	0	42	100.0	-
2	Chuko	26	17 (65.4)	1	16	94.1	82.9–105.3
3	Serbo	36	27 (75.0)	3	24	88.9	77.0–100.7
4	Bahirdar	50	44 (88.0)	5	39	88.6	79.2–97.9
5	Alaba	23	18 (78.3)	3	15	83.3	66.0–00.5
6	Tepi	24	21 (87.5)	4	17	81.0	64.2–97.7
7	Zeway	50	48 (96.0)	11	37	77.1	65.2–88.9
8	Metehara	38	36 (94.7)	11	25	69.4	54.3–84.4
9	Pawi	36	35 (97.2)	11	24	68.6	53.2–83.9
10	Dire Dawa	48	47 (97.9)	15	32	68.1	54.7–81.4
11	Selekleka	65	57 (87.7)	20	37	64.9	52.5–77.2
12	Angerguten	44	40 (90.9)	15	25	62.5	47.5–77.5
13	Kella	26	26 (100)	11	15	57.7	38.7–76.6
14	Bambasi	16	15 (93.8)	15	0	0	-
Total		**527**	**473 (89.8)**	**124**	**325**	**68.7**	**64.5–72.8**

(Ministry of Health 1998b:4)

The follow-up and data analysis on therapeutic efficacy assessment in patients aged five years and above was done separately. Accordingly, a total of 107 subjects of above five years of age were enrolled in four study sites (table 4.5). At the end of the follow-up period of 28 days, an overall treatment failure of 47.7% (95% Confidence Interval (CI), 23.8 to 41.5%) was detected. The level of treatment failure reported varied by site ranging from 32.7% in the study site of Kontir to 75% in the study site of Asendabo.

Table 4.5 Therapeutic efficacy of chloroquine for uncomplicated *Plasmodium falciparum* malaria in children above five years and adults, 1997–1998, Ethiopia

No		Subjects		Treatment outcome		Treatment failure	
		Enrolled	Follow-up completed (%)	Adequate clinical response	Treatment failure	Per cent	95% CI
1	Asendabo	25	24 (96.0)	6	18	75.0	57.6–92.3
2	Gulti	20	18 (90.0)	8	10	55.6	32.6–78.5
3	Adi Asmien	17	16 (94.1)	9	7	43.8	19.4–68.1
4	Kontir	51	49 (96.1)	33	16	32.7	19.5–45.8
Total		**113**	**107 (94.7)**	**56**	**33**	**47.7**	**23.8–41.5**

(Ministry of Health 1998b:4)

According to the Ministry of Health (1998a:22) unpublished report the chloroquine efficacy study assessment findings were disseminated in a national workshop convened by the Ministry of Health in Nazareth, Ethiopia, 21–25 July 1998 (Ministry of Health 1998b:5). The workshop participants questioned the representativeness of the study as most of the sites were in urban areas and recruiting study subjects attending health facilities could increase the risk of bias of selecting cases that might have been infected with drug resistant parasite strains.

This led to the recommendation of conducting additional studies in other sites. Accordingly, the Ministry of Health (1998a:10) reports that in six rural study sites, a total of 257 children under five years diagnosed with *Plasmodium falciparum* were followed for 28 days after treatment with chloroquine. At the end of the study, an overall treatment failure of 63.4% (95% CI, 57.5 to 69.3%) was reported. The level of treatment failure varied from 12.5% in Bambasi to 88.2% in Alaba (table 4.6). The sample size included in the Bambasi site was more than double compared to the previous study sample size of 16 patients and treatment failure of 12.5% which was significantly different that the 0% level reported in the previous study.

Table 4.6 Therapeutic efficacy of chloroquine for uncomplicated *Plasmodium falciparum* malaria in children under five years of age in remote villages, 1998, Ethiopia

No	Study site	Subjects		Treatment outcome		Treatment failure	
		Enrolled	Follow-up completed (%)	Adequate clinical response	Treatment failure	Per cent	95% CI
1	Alaba	60	51 (85.0)	5	45	88.2	79.4–97.1
2	Harbu	41	35 (85.4)	8	27	77.1	63.2–91.0
3	Bahirdar	55	48 (87.3)	12	36	75.0	62.8–87.3
4	Zeway	59	56 (94.9)	16	40	71.4	59.6–83.2
5	Gambella	50	35 (70.0)	24	11	31.4	16.0–46.8
6	Bambasi	33	32 (97.0)	28	4	12.5	1.0–24.0
	Total	**298**	**257 (86.2)**	**93**	**163**	**63.4**	**57.5–69.3**

(Ministry of Health 1998a:13)

4.5.1.8 Therapeutic efficacy of alternative antimalarial drugs

Based on the recommendation of the national workshop, the Ministry of Health (1998b:2) also conducts baseline efficacy studies on sulfadoxine-pyrimethamine and amodiaquine as the potential candidate to replace the failing chloroquine, studies were conducted in seven sites for each drug in 1998.

Five of the seven study sites where assessment of the efficacy of sulfadoxine-pyrimethamine was conducted were the same sites used for the study on chloroquine efficacy. Of the 224 subjects recruited for the study in the seven sites, 206 (92.0%) completed the follow-up and an overall treatment failure rate of 5.3% (95% CI 2.2 to 8.4) was detected (table 4.7).

The Ministry of Health (1998b:6) reports that despite the wide use of sulfadoxine-pyrimethamine as a second-line treatment for malaria in Ethiopia since the late 1980s, the level of treatment failure detected in the study conducted in 1998 was acceptably low at 5.3% (95% CI 2.2 to 8.4). This finding was supportive of the possible decision of introducing the drug as the first-line treatment.

Table 4.7 Therapeutic efficacy of sulfadoxine-pyrimethamine on uncomplicated *Plasmodium falciparum* malaria in children under 5 years of age, Ethiopia, 1998

No	Study site	Subjects		Treatment outcome		Treatment failure	
		Enrolled	Follow-up completed (%)	Adequate clinical response	Treatment failure	Per cent	95% CI
1	Chuko	30	23 (76.7)	14	9	39.1	19.2–59.0
2	Metehara	60	60 (100)	60	0	0.0	0
3	Kella	23	21 (91.3)	20	1	4.8	-4.3–13.9
4	Merti Jeju	29	25 (86.2)	24	1	4.0	-3.7–11.7
5	Harbu	27	23 (85.2)	23	0	0	0
6	Sille	12	12 (100)	12	0	0	0
7	Zeway	43	42 (97.7)	42	0	0	0
Total		**224**	**206 (92.0)**	**195**	**11**	**5.3**	**2.2–8.4**

(Ministry of Health 1998b:6)

On the other hand the therapeutic efficacy of amodiaquine for the treatment of uncomplicated *Plasmodium falciparum* malaria in seven sites was unacceptably high.

Of the 227 subjects who completed the 28-day follow-up, a mean treatment failure of 21.1% (95% CI, 15.8 to 26.4) was detected (table 4.8). The treatment failure levels varied by site with the lowest of 6.3% (95% CI, -5.6 to 18.2) in the study site of Harbu and 66.7% (95% CI, 42.9 to 90.6) in the study site of Asendabo. The treatment failure of chloroquine in the study site of Bambasi was 22.9% (95% CI, 11.0 to 34.8%) which was higher than the chloroquine treatment failure of 12.5% reported in the same study site in 1997.

Table 4.8 Therapeutic efficacy of amodiaquine on uncomplicated *Plasmodium falciparum* cases in children under five years of age, Ethiopia, 1998

No	Study site	Subjects		Treatment outcome		Treatment failure	
		Enrolled	Follow-up completed (%)	Adequate clinical response	Treatment failure	Per cent	95% CI
1	Asendabo	16	15 (93.8)	5	10	66.7	42.9–90.6
2	Zeway	28	24 (85.7)	13	11	45.8	25.9–65.7
3	Bambasi	50	48 (96.0)	37	11	22.9	11.0–34.8
4	Gultie	42	37 (88.1)	30	7	18.9	6.3–31.5
5	Kontir	48	41 (85.4)	36	5	12.2	2.2–22.2
6	Bahirdar	49	46 (93.9)	43	3	6.5	-0.6–13.6
7	Harbu	18	16 (88.9)	15	1	6.3	-5.6–18.2
	Total	**251**	**227 (90.4)**	**179**	**48**	**21.1**	**15.8–26.4**

(Ministry of Health 1998b:5)

4.5.1.9 Monitoring efficacy of sulfadoxine-pyrimethamine after its introduction as a first line antimalarial drug

Although there is no documented evidence on the first date of entry and use of sulfadoxine-pyrimethamine for the treatment of malaria in Ethiopia, from personal experience while working in the program, large-scale use of the drug for malaria treatment was practiced since 1986 mainly for mass treatment of tens of thousands of highlanders from the northern part of the country who were re-settled then in to malaria endemic regions in the Western and North-Western parts of Ethiopia.

Olliaro (2001:207) explains the mechanism of resistance to sulfadoxine-pyrimethamine being due to mutation in the dihydrofolate reductase and dihydropteroate synthetase coding genes of *Plasmodium falciparum* which are the target enzymes of the drug. Gatton, Martin and Cheng (2004:2116) illustrate that mass use of the drug has been

shown to increase drug pressure that enhances selection of resistant strains. Although there are no studies on the effect of mass use of the sulfadoxine-pyrimethamine in the Ethiopian setting, the uncontrolled use of the drug in settlement villages was likely to have contributed to increasing drug pressure and selection of sulfadoxine-pyrimethamine resistant *Plasmodium falciparum strains*.

Most of the studies conducted on the efficacy of sulfadoxine-pyrimethamine after its introduction as the first-line drug in 1998 were isolated studies conducted by individual researchers and research institutions. As presented in table 4.9, from 2004 to 2005, a total of four studies were known to have been conducted but published in 2005 after the nationwide treatment guideline change was introduced. In these studies, Degefa (2004:35) reports sulfadoxine-pyrimethamine treatment failure of 2.6% in the study site of Alamata, northern Ethiopia, Kassa et al (2005:167) report 12.3% treatment failure in Metehara, Central Ethiopia and Worku et al (2005:1) 45.3% in Jima, western Ethiopia.

Table 4.9 Therapeutic efficacy of sulfadoxine-pyrimethamine (SP) for the treatment of *Plasmodium falciparum* malaria, Ethiopia

Details	Studies reviewed		
	Degefa et al (2004:35)	**Kassa et al (2005:167)**	**Worku et al (2005:11)**
Study site location (#)	Alamata, Northern Ethiopia (1)	Metehara, Central Ethiopia (1)	Jimma, Western Ethiopia (1)
Study dates	Sep. to Nov. 2001	Oct. to Nov. 2002	Oct. 2003
Year of publication	2004	2005	2005
No. of patients enrolled	41	57	86
Study protocol	14-day follow-up WHO 1996 protocol	14-day follow-up WHO 1996 protocol	14-day follow-up WHO 1996 protocol
Test drug dosage	As per national guideline	As per national guideline	As per national guideline
% Treatment Failure	2.6	12.3	45.3
Recommendation	Findings suggest that sulfadoxine-pyrimethamine is effective and its use can continue	The Ministry of Health should search for economically feasible replacement to SP.	SP may no longer be considered adequate for treating *Plasmodium falciparum* in the study area

(Degefa 2004:35; Kassa et al 2005:167; Worku, Girma & Shiferaw 2005:11)

With the exception of the studies conducted in these isolated sites (table 4.9), there was no regular monitoring of the efficacy of sulfadoxine-pyrimethamine until 2003 and since the last multi-site study in 1998. Following the heavy rains after a prolonged period of drought in Negash et al (2005:186) report a major malaria epidemic in 2003 that affected more than 2000 villages causing over 3 million malaria cases and 3,663 malaria death.

Cognisant of the possible effect of the reduced efficacy of sulfadoxine-pyrimethamine and the disruption of malaria vector control activities as some of the major contributors to the major epidemics, the Ministry of Health decided to conduct nationwide efficacy study on sulfadoxine-pyrimethamine in the same sentinel sites where previous major antimalarial efficacy studies were conducted. At the end of the study conducted between September-December 2003 in 11 study sites, Jima et al (2005:391) report treatment failure of 35.9% (95% CI 31.8 to 40.3) in a 14-days follow-up completed on 474 patients (table 4.10).

Table 4.10 Therapeutic efficacy of sulfadoxine-pyrimethamine for uncomplicated *Plasmodium falciparum* malaria, in vivo 28-day test results, Ethiopia October–December 2003

No	Study site	Subjects		Treatment outcome		Treatment failure	
		Enrolled	Follow-up completed (%)	Adequate clinical response	Treatment failure	Per cent	95% CI
1	Zuway	66	56 (84.8)	8	48	85.7	76.5–94.9
2	Metehara	61	44 (72.1)	8	36	81.8	70.4–93.2
3	Awassa	57	49 (86.0)	9	39	79.6	68.2–90.9
4	Angergutin	72	42 (58.3)	10	32	76.2	63.3–89.1
5	Pawe	43	35 (81.4)	9	26	74.3	59.8–88.8
6	Serbo	65	45 (69.2)	13	32	71.1	57.9–84.3
7	Selekleka	55	45 (81.8)	14	31	68.9	55.4–82.4
8	Alaba	53	47 (88.7)	15	32	68.1	54.8–81.4
9	Bambasi	59	10 (16.9)	4	6	60.0	29.6–90.4
10	Harbu	59	49 (3.1)	20	29	59.2	45.4–73.0
11	Bahirdar	67	53 (79.1)	25	28	52.8	39.4–66.2
	Total	**657**	**474 (72.1)**	**135**	**339**	**71.5**	**67.4–75.6**

(Jima et al 2005a:391)

Due to the growing concern and a number of reports of high level of *Plasmodium falciparum* resistance to the most commonly and widely used antimalarial drugs such as chloroquine and sulfadoxine-pyrimethamine, the WHO (2001:18) recommends the use

of ACTs. In addition to the high cure rate of cases treated with ACTs, the drugs were also effective for the treatment of multi-drug resistant malaria parasites and effect on gametocytes which contribute to reducing malaria transmission (Tangpukdee, Krudsood, Srivilairit, Phophak, Chonsawat, Yanpanich, Kano & Wilairatana 2008:65).

Expecting a high treatment failure rate of sulfadoxine-pyrimethamine and recalling the earlier evidence of high treatment failure of amodiaquine, artemether-lumefantrine was considered the best option that can be introduced as the first-line antimalarial drug for the treatment of *Plasmodium falciparum replacing* sulfadoxine-pyrimethamine.

Accordingly, along the evaluation of efficacy of sulfadoxine-pyrimethamine, base-line efficacy study on artemether-lumefantrine for the treatment of uncomplicated falciparum malaria was conducted in four study sites in advance. Jima et al (2005b:387) reports treatment success of 99.1% in a follow-up period of 28-days on 213 *Plasmodium falciparum* patients treated with the ACT drug artemether-lumefantrine in four study sites (table 4.11).

Table 4.11 Baseline study on the efficacy of Artemether-Lumefantrine on uncomplicated *Plasmodium falciparum* malaria in Ethiopia

No	Study site	Subjects		Treatment outcome		Treatment failure	
		Enrolled	Follow-up completed (%)	Adequate clinical response	Treatment failure	Per cent	95% CI
1	Assendabo	60	59 (98.3)	57	2	3.4	-1.2–8.0
2	Alamata	39	36 (92.3)	36	0	0	0
3	Humera	64	62 (96.9)	62	0	0	0
4	Nazareth	56	56 (100)	56	0	0	0
Total		**219**	**213 (97.3)**	**211**	**2**	**0.94**	**-0.4–2.2**

(Jima et al 2005b:387)

4.5.2 Recent antimalarial drug efficacy study findings

The new malaria diagnosis and treatment guideline with artemether-lumefantrine for uncomplicated *Plasmodium falciparum* malaria was introduced nationwide in July 2004. At the start of implementation of the new guideline, the emphasis was on ensuring adequate supply of artemether-lumefantrine to replace the stock of the obsolete

antimalarial drug sulfadoxine-pyrimethamine. This was not achieved until the end of 2005 by which time a huge supply of artemether-lumefantrine procured through the support of the Global Fund, the WHO and UNICEF started to enter the country. In the following sections, studies conducted after the newly introduced antimalarial treatment guideline was introduced are presented.

4.5.2.1 In vivo therapeutic efficacy studies on Plasmodium falciparum 2006–2010

Since the introduction of the new malaria treatment guideline in Ethiopia in 2004, four studies were conducted in the period from 2006 to 2010. Despite the World Health Organisation recommendation of a follow-up period for clinical and parasitological assessment of 28 days, the study by Seboxa, Mao, Pinchouk, Anbessie, Alemu and Diro (2010:285) assessing the efficacy of artemether-lumefantrine in one arm and artesunate plus sulfadoxine-pyrimethamine on the other was done only for 14-days. Through the 14-day follow-up, no treatment failure cases were detected. Although conducting a 14-day test can provide useful information (WHO 2003:16), continuing the follow-up until day-28 is critical to check for late treatment failures especially when no early treatment failure have been detected. Data from such short duration follow-ups, therefore, may not generate the required type and amount of information.

Kefyalew, Animut, Tamene, Jima, Hailemariam and Legesse (2009:129) report no treatment failure with artemether-lumefantrine in 102 *Plasmodium falciparum* patients followed for 28 days in the study site of Alaba, Southern Ethiopia. However, Assefa, Kassa, Tadese, Mohamed, Animut, Mengesha (2010:1) report artemether-lumefantrine treatment failure of 6.7% in a study conducted from November 2007 to January 2008 involving 90 *Plasmodium falciparum* diagnosed patients in Kersa, western Ethiopia.

Compared to the baseline efficacy study conducted in 2004 that reported a 0.9% treatment failure in a 28-day follow-up by Jima et al (2005b:387), the treatment failure reported by Assefa et al (2010:1) has shown a significant increase (P=0.0004) that warrant for a more representative study and follow-up through a multi-site monitoring.

Table 4.12 ***In vivo*** **therapeutic efficacy study of artemether-lumefantrine on** ***Plasmodium falciparum***

Details	Studies reviewed			
	Seboxa et al (2010:285)	**Seboxa et al (2010:285)**	**Kefyalew et al (2009:129)**	**Assefa et al (2010:1)**
Study site location (#)	Assendabo and Dimtu, Western Ethiopia (1)	Deneba, Western Ethiopia (1)	Alaba, Souther Ethiopia (1)	Kersa, Western Ethiopia (1)
Study dates	28 November to 26 December 2006	28 November to 26 December 2006	October December 2007	November 2007 to January 2008
No. of patients enrolled	99	35	102	90
Study protocol	WHO 2001 (14-day follow-up)	WHO 2001 (14-day follow-up)	WHO 2003 (28-day follow-up)	WHO 2003 (28-day follow-up)
Test drug dosage	Artemether-Lumefantrine	Artesunate plus sulfadoxine-pyrimethamine	Artemether-Lumefantrine	Artemether-Lumefantrine
% Treatment Failure	0	0	0	6.7%
Conclusion	Both artemether-lumefantrine and Artesunate plus Sulfadoxine-pyrimethamine are effective	Both artemether-lumefantrine & Artesunate plus Sulfadoxine-pyrimethamine are effective	AL has excellent level of efficacy	AL is still effective but more follow-up is needed

(Seboxa et al 2010:285; Kefyalew et al 2009:129; Assefa et al 2010:1)

4.5.2.2 In vivo therapeutic efficacy studies on Plasmodium vivax 2009 – 2010

The first report of chloroquine treatment failure on *Plasmodium vivax* malaria of 2% was reported by Tulu et al (1996:556) in a 7-day follow-up study conducted in Debrezeit, Central Ethiopia. The reported treatment failure cases were not confirmed with PCR based detection of parasite DNA, considered diagnosis which is believed to be the gold standard. Moreover, the blood level of the drug administered and its metabolite, desethychloroquine, was not measured to confirm if parasite persistence in the treatment failure cases was happening despite the presence of the minimum inhibitory concentration of the drugs in blood which is >100 ng/mL of whole blood (Baird, Leksana, Masbar, Fryauff, Sutanihardja, Suradi, Wignall & Hoffman 1997:621).

Following the first report of treatment failure of chloroquine for the treatment of *Plasmodium vivax* reported by Tulu et al (1996:556) and Yeshiwondim et al (2010:105) reported PCR corrected *Plasmodium vivax* treatment failure of 2.9% after treatment with chloroquine and 0.74% after treatment with chloroquine plus primaquine in the same and areas adjacent area to the town of Debrezeit in a study completed in 2003.

In later similar studies conducted in Debrezeit and Nazareth in 2005 by Yohannes et al (2011:137) and in Debrezeit alone in 2006 by Teka et al (2008:1) PCR corrected and chloroquine blood level verified resistance to chloroquine of 4.8% and 3.5%, respectively was reported. In other locations, chloroquine treatment failure on *Plasmodium vivax* of 3.8% in Serbo, Western Ethiopia (Ketema et al 2009:1) and 13.8% in Halaba, Southern Ethiopia (Ketema, Getahun & Bacha 2011:1) were reported. In both reports, PCR confirmation of the treatment failure cases and determination of chloroquine and desethylchloroquine blood level concentration was not reported indicating that there was no confirmation if the treatment failure cases were due to *Plasmodium vivax* resistance to chloroquine.

Table 4.13 ***In vivo*** **therapeutic efficacy study of chloroquine, chloroquine plus primaquine and artemether-lumefantrine on** ***Plasmodium vivax***

Details	Studies reviewed						
	Yeshiwondim et al 2010	**Yeshiwondim et al 2010**	**Yohannes et al 2011**	**Yohannes et al 2011**	**Teka et al 2008**	**Ketema et al 2009**	**Ketema et al 2011**
Study site location (#)	Debrezeit and Nazareth, Central Ethiopia	Debrezeit and Nazareth, Central Ethiopia	Debrezeit and Nazareth, Central Ethiopia	Debrezeit and Nazareth, Central Ethiopia	Debrezeit, Central Ethiopia (1)	Serbo, South Western Ethiopia (1)	Alaba, Southern Ethiopia (1)
Study dates	Jan to Aug 2003	Jan to Aug 2003	Oct 2004 to May 2005	Oct 2004 to May 2005	Jun to Aug 2006	Oct 2007 to Jan 2008	Jan to Feb 2009
Test drug	Chloroquine plus primaquine	Chloroquine	Chloroquine	Artemether-lumefantrine	Chloroquine	Chloroquine	Chloroquine
Study protocol	WHO 28-day test	WHO 28-day test	WHO 28-day test	WHO 28-day test	WHO 28-day test	WHO 28-day test	WHO 28-day test
No. of patients enrolled	136	141	57	75	83	78	80
% Treatment Failure	0.75	5.8	8.8	25.3	4.8	3.8	13.8
Conclusion	emergence of resistance/treatment failure to chloroquine plus primaquine in *Plasmodium vivax* confirmed	emergence of resistance/treatment failure to chloroquine *Plasmodium vivax* confirmed	Chloroquine resistant *Plasmodium vivax* confirmed	Artemether-lumefantrine may not be effective for the treatment of *Plasmodium vivax*	Chloroquine-resistant *Plasmodium vivax* parasites are emerging in Debrezeit, Ethiopia	Chloroquine resistant *Plasmodium vivax* strains in Serbo town confirmed	Chloroquine treatment failure increasing from earlier levels

(Yeshiwondim et al 2010:105; Yohannes et al 2011:137; Teka et al 2008:1; Ketema, Bacha, Birhanu & Petros 2009:1; Ketema et al 2011:1)

4.5.2.3 Genetic analysis based antimalarial drug efficacy studies

Genetic analysis based determination of polymorphic genes associated with antimalarial drug resistance was one of the study methods implemented in one site in Southern Ethiopia. In this study, the prevalence of polymorphic genes of *Plasmodium falciparum* and *Plasmodium vivax* associated with resistance to chloroquine and sulfadoxine-pyrimethamine showed high prevalence of polymorphic genes associated with resistance to the drugs (Schunk, Kumma, Miranda, Osman, Roewer, Alano, Löscher, Bienzle & Mockenhaupt 2006:1).

Although it is of interest from scientific information point of view, the study did not elucidate the potential benefit of the findings from such study in a situation where both drugs are not recommended anymore for the treatment of *Plasmodium falciparum* malaria in Ethiopia. Moreover, the investigators didn't provide justification on the desire and objective of conducting genetic analysis on *Plasmodium vivax* dihydrofolate reductase (dhfr) and dihydropteroate genes conforming to polymorphic genes that predict resistance to sulfadoxine-pyrimethamine when the drug is actually not recommended for the treatment of *Plasmodium vivax* malaria in the national guideline.

Table 4.14 Parasite genetic analysis and prevalence of genes associated with resistance to chloroquine and sulfadoxine-pyrimethamine, Dilla, Southern Ethiopia, 2006

Details	Test drug and parasites		
	Plasmodium falciparum		*Plasmodium vivax*
	Chloroquine	Sulfadoxine-pyrimethamine	Sulfadoxine-pyrimethamine
Study site (#)	Dilla, Southern Ethiopia (1)	Dilla, Southern Ethiopia (1)	Dilla, Southern Ethiopia (1)
Subjects enrolled	66	66	31
Recrudescent cases (28-day follow-up)	No information	No information	No information
Polymorphic Genes analysed			
Pfmdr[1]	56	-	
Pfcrt76[2]	69	-	
dhfr[3]	-	60	29
dhps[4]	-	59	23

(Schunk et al 2006:1)

Key: 1=multi-drug resistant; 2=Plasmodium falciparum cytochrome76; 3=Plasmodium falciparum dyhydrofolate reductase; 4=Plasmodium falciparum dihydropteroate synthetase

Another genetic analysis based study conducted on *Plasmodium falciparum* and polymorphic genes associated with resistance to quinine, artemether-lumefantrine and atovaquone-proguanil was conducted by Eshetu, Berens-Riha, Fekadu, Tadesse, Gürkov, Hölscher, Löscher and Miranda (2010:1) in Jimma, Western Ethiopia. In this study, *in vivo* treatment failure rates with quinine, artemether-lumefantrine and atovaquone-proguanil of 8.6%, 0% and 6.3%, respectively was detected. Following confirmation of *in vivo* treatment failure, genetic analysis of polymorphic genes that are associated with resistance to the drugs tested was conducted and showed high number of the cases being due to parasites with mutations that confer resistance (table 4.14).

Table 4.15 *Plasmodium falciparum* genetic analysis and prevalence of genes associated with resistance to Quinine, Artemether-lumefantrine and Atovaquone-proguanil, Jimma, Western Ethiopia, 2010

Details	Test drugs		
	Quinine	Artemether-Lumefantrine	Atovaquone-proguanil
Source			
Study site (#)	Jima, Western Ethiopia (1)	Jima, Western Ethiopia (1)	Jima, Western Ethiopia (1)
Subjects enrolled	35	30	32
Recrudescent cases (28-day follow-up)	4	0	2
Polymorphic Genes analysed			
Pfdhfr[1]	-	-	1
Pfdhps[2]	-		2
Pfmdr186Y[3]	3	0	-
Pfserca[4]	-	0	-
Pfcytb[5]	-	-	0

(Eshetu et al 2010:1)

Key: 1=Plasmodium falciparum dyhydrofolate reductase; 2=Plasmodium falciparum dihydropteroate synthetase; 3=Plasmodium falciparum multi-drug resistant 186Y; 4=Plasmodium falciparum sarco/endoplasmic reticulum calcium-ATPase; 5=Plasmodium falciparum cytochrome b

4.6 REPRESENTATIVENESS, TIMELINESS AND COMPLETENESS OF THE STUDIES AND THEIR ADEQUECY TO INFORM ANTIMALARIAL POLICY IN ETHIOPIA

The adequacy of antimalarial drug studies conducted in Ethiopia in terms of their representativeness, timeliness and completeness to inform antimalarial drug policy and development of treatment guidelines in Ethiopia are the main parameters assessed. The data collected and analysed provided important findings that can inform the representativeness, timeline and completeness of the studies.

In order to ensure simplistic and systematic approach to assess the representativeness, timeliness and completeness of the studies, a numeric scoring based assessment was used. All measures being of equal importance, equal weight was considered for study representativeness, completeness and timeliness. Based on this, the following scoring approach was applied.

4.6.1 Study representativeness

Representativeness, is defined as serving as a typical or characteristic example, (Merriam-Webster Incorporated Online Dictionary 2011). Due to the logistic and resource requirements and the need to collect representative data in a short period of time, studies on antimalarial drug efficacy may not be conducted in all parts of a country, region or district. To avoid the unnecessary challenge of trying to reach everywhere, statistical methods such as sampling are used to conduct the study only on a manageable but representative sample.

The findings from such sample on the level of antimalarial drug efficacy can then be used to make inference about the rest of the Geographic area, which the sample represents. In the absence of representative sampling, the study findings and conclusion that may be derived therefore would not be representative and may be misleading. Operationally, representativeness is determined based on the statistical approaches that can ensure appropriate sampling and random selection of samples and allocation of samples to study sites. The decision criteria used to ensure representativeness is based on statistical tests on sample size determination and randomisation.

Study representativeness has been estimated based on the statistical adequacy of the sample size considered in the study and the number of study sites involved. For a study to be representative, the WHO recommends a sampling approach based on an assumption of 50% treatment failure if the rate of treatment failure in the study area is not known. Regardless of the rate of treatment failure, the WHO (2009a:5) recommends that follow-up on a minimum of 50 subjects each be completed in at least 4–8 selected representative sites. Based on this, studies have been scored based on a scale of 0 to 2 presented in table 4.1 in the research design and method section.

4.6.2 Study completeness

Completeness is defined as having all the necessary parts, elements and steps (Merriam-Webster Incorporated Online Dictionary 2011) has been of high relevance to antimalarial efficacy studies. The antimalarial drug studies conducted in Ethiopia, although were following a specific study protocol, most of the studies failed to report on the quality of the antimalarial drug tested and the pharmacokinetic information of the drugs tested at the time of the confirmed treatment failure.

Pre-testing the quality of the antimalarial drug used in antimalarial efficacy studies for product quality is critical. This is particularly of high importance in light of the high prevalence of counterfeit and poor quality drugs in the markets of malaria endemic countries. Bate, Coticelli, Tren and Attaran (2008:1) confirm that an estimated 35% of antimalarial drugs sampled from six African countries to have failed quality standards. In the absence of proof of quality of the antimalarial drug tested, asserting that the observed treatment failure was due parasite resistance would not be possible.

Determining the amount of the antimalarial drug and its metabolite in the blood of patients with presumed treatment failure is also critical information. Study completeness was scored based the availability of confirmed results that are critical is resolving doubts about the conclusion derived from the findings. For a certain level of treatment failure or treatment success to be declared beyond doubt, the following three criteria are proposed as mandatory a) examination of blood films by two different readers and analysis that excludes discordant results b) the antimalarial drug was tested for quality and content of its active ingredient and c) the blood level of the drug tested and its metabolite was above the minimum effective concentration at the time of the confirmed

treatment failure. Based on this, study completeness was scored on a scale of 0 to 3 as presented in table 4.16 and table 4.17.

4.6.3 Study timeliness

Timeliness is defined as appropriate or adapted to the times or the occasion (Merriam-Webster Incorporated Online Dictionary 2011). Monitoring the efficacy of antimalarial drugs at regular and appropriate time interval and use of the evidence to guide policy is an important aspect of studies. Studies of irregular interval fail to detect trends of an imminent or potential threat to the efficacy of antimalarial drugs. Delays in making use of evidence from such studies to update or change antimalarial drug policy or guideline also contributes to further deterioration of the health service resulting in more health problems. Operationally, timelines is measure by calculating the time laps between two similar studies as compared to the recommended time laps. The decision criteria are based on the calculated time laps and durations that are equal to the recommended duration are said to have the desired timeliness while durations less or over the recommended duration are not.

The WHO (2009a:3) recommends regular assessment of the efficacy of antimalarial drugs of every two years. Studies conducted within two years from the preceding study would be considered timely compared to studies conducted after more than two years from the previous study. The scoring developed to rate the representativeness, completeness and timeliness of antimalarial efficacy studies is summarised in table 4.16. Based on this scoring method, a study that fulfils all the scores without missing any of the elements is considered as adequate to inform antimalarial policy decision. Based on approach, the score for each of the antimalarial drug studies conducted in Ethiopia is presented in tables table 4.16 and table 4.17.

Based on the scoring proposed for each of the main parameters assessed, a study that fulfils all the scores (100%) without missing any element is considered as adequate to inform antimalarial policy decision and treatment guideline updating. However, considering the lack of local capability in the Ethiopian setting to conduct PCR based confirmation of malarial infection and drug quality and blood level concentration determination in the early days, a score of 60% of above was arbitrarily set as a cut-off for adequacy.

Table 4.16 *In vivo* therapeutic efficacy study on *Plasmodium falciparum* and adequacy score of studies

No	Author	No of study sites	Sample size	Method and follow-up duration	Test drug	Outcome	Score of adequacy				Adequacy to inform policy	Recommended action
							Rep	Com	Tim	% Total Score		
1	Dennis et al 1974	1	41	*In vivo*, 28 days	CQ*	26.8	0	0	1	16.7	No	Further study
2	Dennis et al 1974	1	24	*In vivo*, *in vitro*	CQ	0[a]	0	0	1	16.7	No	Further study
3	Armstrong et al 1976	4	99	*In vivo*, 6-11 days	CQ	0	1	0	1	16.7	No	Further study
4	Gebremariam et al 1982	1	21	*In vivo*, 7 days	CQ	0	0	0	0	0.0	No	Further study
5	Gebremariam et al 1986	11	136	*In vivo*, 7 days	CQ	0	2	0	0	33.3	No	Further study
6	Gebremariam et al 1986	11	115	*In vivo*, 28 days	CQ	0	2	0	0	33.3	No	Further study
7	Teklehaimanot et al 1985	1	98	*In vivo*, 28 days	CQ	22.4	1	0	1	33.3	No	Further study
8	Wezam 1993	1	23	*In vivo*, 7 days	CQ	0	0	0	0	0.0	No	Further study
9	Alene and Bennett 1996	36	1706	*In vivo*, 7 days	CQ	87.2	1	0	0	16.7	No	Further study and need to consider alternatives antimalarial drug
10	Tulu et al 1996	1	29	*In vivo*, 7 days	CQ	86.2	0	1	0	16.7	No	Further study
11	Assefa 19897	1	1	*In vivo*, 7 day	CQ	100	0	0	1	16.7	No	Further study
12	Ministry of Health 1998a	14	473	*In vivo*, 14 days	CQ	73.6	2	1	0	50.0	Yes	Treatment policy change
13	Ministry of Health 1998a	6	257	*In vivo*,14 days	CQ	63.4	2	1	0	50.0	Yes	Treatment policy change
14	Ministry of Health 1998b	4	107	*In vivo*,14 days	CQ	47.7	2	1	0	50.0	Yes	Treatment policy change
15	Wezam 1993	1	24	*In vivo*, 7 days	SP	0	0	1	0	16.7	No	Further study
16	Tulu et al 1996	1	80	*In vivo*, 7 days	SP	1.3	1	1	0	33.3	No	Further study
17	Ministry of Health 1998b	7	232	*In vivo*,14 days	SP	5.6	2	1	0	50.0	Yes	Treatment policy change
18	Degefa 2004	1	77	*In vivo*,14 days	SP	2.6	1	1	0	33.3	No	Further study
19	Kassa et al 2005	1	60	*In vivo*,14 days	SP	21.1	1	0	1	33.3	No	Further study
20	Jima et al 2005[a]	11	523	*In vivo*,28 days	SP	33.5	2	1	1	66.7	Yes	Treatment policy change
21	Jima et al 2005b	4	213	*In vivo*,28 days	AL	0.9	2	1	1	66.7	Yes	Treatment policy change
22	Seboxa et al 2010	2	105	*In vivo*,14 days	AL	0	1	1	0	33.3	No	Further study
23	Assefa et al 2010	1	81	*In vivo,28 days*	AL	6.7	1	0	0	16.7	No	Further study

Key for outcome: a=per cent parasite growth in culture medium with chloroquine of greater than 1.5 nmol
b=per cent samples with one or more gene polymorphic regions that conform resistance
a=per cent of treatment failure cases Rep.=representativeness
Com.= completeness; Tim.= timeliness

Table 4.17 *In vivo* therapeutic efficacy study on *Plasmodium vivax* and adequacy score of studies

No	Author, Year	No. of study sites	Sample size	Protocol	Test drug	Outcome	Score				Adequacy to inform policy	Recommended actual
							Rep	Comp	Time	Total		
1	Tulu et al 1996	1	255	*In vivo*, 7 days	CQ	2	1	1	1	50.0	No	Further study
2	Yeshiwondim et al 2010	2	145	*In vivo*, 28 days	CQ	5.76	1	1	0	33.3	No	Further study
3	Yeshiwondim et al 2010	2	136	*In vivo*, 28 days	CQ + PQ	0.75	1	1	0	33.3	No	Further study and co-administration of Primaquine
4	Teka et al 2008	1	83	*In vivo*, 28 days	CQ	4.8	1	3	0	66.7	Yes	Further study and co-administration of Primaquine
5	Ketema et al 2009	1	78	*In vivo, 28 days*	CQ	3.6	1	1	1	50.0	No	
6	Yohannes et al 2011	2	75	*In vivo, 28 days*	AL	25.3	1	2	1	66.7	Yes	Strengthen diagnosis to minimize the chance of clinical malarial cases due to *Plasmodium vivax* with AL
7	Yohannes et al 2011	2	57	*In vivo, 28 days*	CQ	8.8	1	2	1	66.7	Yes	Further study and co-administration of Primaquine
8	Ketema et al 2011	1	80	*In vivo, 28 day*	CQ	6.7	1	0	1	33.3	No	Further study

Key for outcome

a=per cent parasite growth in culture medium with chloroquine concentration of greater than 1.5 nmol
b=per cent samples with one or more gene polymorphic regions that conform resistance
a=per cent of treatment failure cases

4.7 ANTIMALARIAL DRUG POLICY AND TREATMENT GUIDELINES CHANGE PROCESS

4.7.1 Use of antimalarial drug efficacy data for policy

Following the recommendation by Bloland, Kazembe, Oloo, Himonga, Baratand Ruebush (1998:543), clinical failure of 25% after treatment with chloroquine within a follow-up period of 14 days was considered a high level of failure that should warrant change in the treatment policy. Based on this cut-off point and specific methodological approach the 1996 WHO (1996:17) study protocol for the *in vivo* assessment of antimalarial drugs was developed. However, the protocol was mainly intended for areas with intense malaria transmission and study subjects of under five years of age and no methodological approaches for the assessment of antimalarial drug efficacy in low to moderate malaria transmission settings where all ages are equally affected by malaria was included.

The therapeutic efficacy data used to change from chloroquine to sulfadoxine-pyrimethamine in Ethiopia in 1998, for example was collected using the protocol developed based on the WHO (1996:3). However, the Ministry of Health decided to also collect chloroquine efficacy data from the age group of five and above, who are the most affected in the Ethiopian setting. Irrespective of the recommendation of the WHO (1996:3), the decision to broaden the scope of the protocol to include all age groups was a locally sound decision based on the malaria transmission pattern that affects all age groups.

Following a practical field experience in using the WHO 1996 protocol the WHO has been revising the protocol for the assessment of antimalarial drug efficacy to fit all malaria endemicity settings, types of antimalarial drugs tested, age group of study subjects involved, duration of follow-up and classification of treatment outcomes (WHO 2010:15).

The overall treatment failure cut-off level to decide whether to change a failing first-line antimalarial drug of 25% was lowered to 10% over a follow-up period of 28 to 42 days depending on the type of antimalarial drug tested and the malaria parasite subjected

(WHO 2009:5). The antimalarial treatment policy change effected in Ethiopia 2004 was based on the 25% treatment failure cut off (Jima et al 2005a:391).

4.7.2 Studies' results dissemination and policy change process

In the Ethiopian context dissemination of therapeutic efficacy studies conducted at national level under the leadership of the Ministry of health was done through a national workshop (WHO 2001:34). Participants of the national workshop include Regional Health Bureaus, academic and research institutions, referral hospitals, UN agencies, civil societies and non-governmental organizations.

The dissemination process and implementation of the new antimalarial drug treatment guidelines introduced both in 1998 and 2004 were never assessed and the lessons learned have not been documented.

The major preparatory issues that determine success of a new malaria treatment guideline described by the WHO (2001:38) include:

a) resources required by the health sector and the community seeking treatment
b) human and technical resources and health care infrastructure capacity to implement the policy
c) awareness-raising, health promotion and information dissemination to ensure smooth implementation
d) education and training of health workers in public, private and community sectors
e) drug supply, distribution, price regulation and quality assurance
f) monitoring and evaluation of the policy and its impact

In an effort to assess the pace of introduction of the new malaria treatment guideline developed in 2004 and to identify implementation challenges such as those described by Bosman and Mendis (2007:193), a full assessment at national, regional, district and health facility level is essential. The most challenging issues in the implementation of new antimalarial treatment guidelines is also related to the quantification and procurement of the amount of antimalarial drug needed. Therefore, although the eventual aims is to ensure availability of good quality drugs to all who need them (Coll-Seck, Van Erps & Halil 2008), the exercise of need estimation must to be well

developed (Kindermans, Vandenbergh, Vreeke, Olliaro & D'Altilia 2007:91) in order to secure appropriate quantities of antimalarial drugs.

4.7.3 Antimalarial drug efficacy monitoring and the use of evidence for policy in Horn of Africa Region

The EANMAT comprising national programs and research institution in Kenya, Tanzania, Uganda, Tanzania, Burundi and Rwanda was established to bring complementary skills of malaria researchers and to provide technical support in malaria treatment issues in the region (East African Network for Monitoring Antimalarial Treatment [EANMAT] 2001:891).

East African Network for Monitoring Antimalarial Treatment [EANMAT] (2003:860) reported that due to increasing levels of chloroquine resistance, Kenya, Uganda, Tanzania, Zanzibar, Rwanda and Burundi changed their first-line antimalarial drug in a window period of three years from 1998 to 2001. Most countries changed their first-line antimalarial drug to sulfadoxine-pyrimethamine or chloroquine plus sulfadoxine-pyrimethamine while Burundi and Zanzibar introduced amodiaquine plus artesunate.

EANMAT's eventual aims being to gear approaches towards a single antimalarial treatment policy in light of the uniform nature of malaria epidemiology in the region, the network focused on assessing the efficacy of Sulfadoxine-pyrimethamine and amodiaquine which are the major components of the new combination therapy approach. Accordingly, to the data collected from the countries, clinical response with sulfadoxine-pyrimethamine showed a slight decline from 88.8% (range: 86.9 to 90.3) in three study sites conducted before the year 2000 to 83.8 (range; 71.8 to 93.8) in six studies conducted after the year 2000. The efficacy of amodiaquine on the other hand was 93.5% in two study sites conducted before 2000 and 95.2% after 2000. The relatively comparable level of efficacy of the antimalarial drugs has been indicative of a possibility of adopting similar treatment policy in the region.

A similar antimalarial drug resistance monitoring sub-regional network was also established by the horn of African countries that comprises, Djibouti, Eritrea, Ethiopia, Somalia, Sudan and Yemen. The HANMAT was formally established in 2004 (WHO, East Mediterranean Regional Office 2004). The network aims to share antimalarial drug

efficacy data information in the countries that can influence policy decision. Although there are no publications released, this network has been convening annual meeting to share country level report on antimalarial drug efficacy monitoring activities.

In general, although regional antimalarial treatment monitoring networks have been instrumental in collecting and disseminating country specific data and information on antimalarial treatment, the main policy decision and process seems to be governed by more of an internal process than a regional effort. The activities of some of the regional networks have been declining. However, continued effort to coordinate information sharing harmonisation of antimalarial drug resistance and monitoring approaches is still supported by some of the member countries (Ministry of Health of Rwanda 2011).

4.8 CONCLUSIONS

Plasmodium falciparum resistance to chloroquine was first reported in the Thailand-Cambodian Border by Harinasuta et al (1965:657) in 1965 while *Plasmodium vivax* resistance to chloroquine was reported by Schuurkamp, Spicer, Kereu, Bulungol and Rieckmann (1992:192) in Papua New Guinea nearly 27 years later. The first chloroquine resistant *Plasmodium falciparum* in Ethiopia was reported in 1986 (Teklehaimanot 1986:127). Although such reports were communicated, the technical approach on how to conduct systematic representative assessment of resistance to antimalarial drugs and the decision making process whether to replace an existing antimalarial drug has not been clearly defined until the late 1990s.

The first country to replace chloroquine was Thailand in 1973 while its use in Africa continued until the early 1990s. Although chloroquine resistant *Plasmodium falciparum* was first reported in cases encountered in Kenya (Fogh, Jepsen & Effersoe 1979:228) the first country in Africa that replaced chloroquine with a combination of chloroquine plus sulfadoxine-pyrimethamine at national level was Malawi in 1993 (Talisuna et al 2004:253).

After the start of implantations of the new malaria treatment guideline, antimalarial drug efficacy studies in Ethiopia have been conducted on a range of antimalarial drugs used for the treatment of *Plasmodium falciparum and Plasmodium vivax*. The antimalarial drug efficacy test protocols used in the earlier studies were not uniform and this was

creating problems in aggregating data collected from different studies. With a more complete protocol for the therapeutic efficacy assessment of antimalarial drugs developed by the WHO (2003:5), hopes were high that all such studies will follow the same protocol and that findings from such studies can be used for meta-analysis. However, what was observed in practice was not as expected.

In Ethiopia and Kenya for example, despite the first reports of chloroquine resistant malaria cases in the mid-1980s and 1970, respectively and the significant amount of data collected afterwards, the decision to replace the filing drug chloroquine with sulfadoxine-pyrimethamine was reached in the late 1990s in Kenya and Ethiopia (WHO 2000:13).

CHAPTER 5

CONCLUSIONS AND RECOMMENDATIONS

5.1 INTRODUCTION

The development of antimalarial drug policy should be based on evidence on antimalarial drug efficacy data and evidence collected in the local setting, recommendations by national health authorities and the WHO as the lead normative agency on health matters. Ogbonna and Uneke (2008:621) explain that the lack of effective national anti-malarial policies in many African countries and the high cost of ACTs, low drug quality and under-resourced health care delivery systems among others as the major obstacles to the implementation of effective malaria treatment approaches.

Kramer, Dickinson, Anderson, Fowler, Miranda, Mutero, Saterson and Wiener (2009:133) report that the development of an appropriate policy based on evidence has been shown to have significant effect in improving malaria program management. Hasting, Korenromp, Bloland (2007:739) recommend that regularly updating malaria treatment policy based on combined evidence from *in vitro* parasite sensitivity studies and parasitological and clinical antimalarial efficacy studies as a scientifically sound approach that should be implemented in malaria endemic countries in order to ensure implementation of effective malaria treatment services.

Based on the strengths and weaknesses in antimalarial drug efficacy monitoring and the use of evidence to inform antimalarial drug policy in Ethiopia, therefore, the following recommendations relevant to the antimalarial efficacy study protocols in general and the Ethiopian need in particular is presented.

5.2 CONCLUSIONS ON THE RESEARCH FINDINGS AND RECOMMENDATIONS

The antimalarial drug efficacy studies conducted in Ethiopia over the last 37 years (1974–2011) have had significant contribution to the scientific knowledge on the efficacy of antimalarial drugs in the country. However, most of the studies recommended the need for additional studies to be conducted further as the findings were not conclusive

and generalisable and substantive enough to initiate or indicate an antimalarial policy or change in treatment guidelines.

Of the 44 studies conducted in the period from 1972 to 2011, only findings from four studies had direct impact on the antimalarial drug policy and malaria diagnosis and treatment guidelines in the country. Therefore, for antimalarial drug efficacy studies to have relevance in influencing antimalarial drug policy and treatment guideline development, adequate representativeness, timeliness and completeness and closer collaboration with the institutions that have institutional mandate in leading antimalarial treatment policy and treatment guideline changes is critical.

For an effective collaboration and coordination to happen, identifying the specific components of the antimalarial drug efficacy monitoring and use of evidence for policy is essential. The following section, therefore, clarifies the areas that require specific attention and the actions that need to be in place.

5.2.1 Antimalarial drug efficacy studies' protocols

As indicated in section 4.4.3, the development and dissemination of antimalarial drug efficacy study protocols by the WHO appears to have been time taking. A study protocol that can be used in both in high transmission areas and areas with low to moderate transmission was made available only in 2003 (WHO 2003:16). For countries like Ethiopia where malaria transmission is seasonal and unstable, applying the correct study protocol is of critical importance. The lack of such protocols might have been delaying timely action and application of locally appropriate antimalarial drug policy and treatment guidelines.

Beyond assessing the efficacy of antimalarial drugs, the availability of quality replacement drugs in adequate quantities and affordable prices is also another critical issue that can influence the pace at which treatment policies are introduced. Therefore, beyond the task of timely developing tools to determine the level of efficacy of antimalarial drugs, countries that need to change their antimalarial treatment guideline should be provided a hands-on technical support by relevant international institutions such as WHO and other local partners.

Through this process, data collection and use of data for decision making and rapid introduction of the newly recommended antimalarial drugs can be properly managed through the support of international and local partners.

5.2.2 Appraisal of antimalarial drug efficacy proposals

The use of an appraisal process for antimalarial drug efficacy studies in Ethiopia can be a good mechanism to check and confirm the appropriateness of the study, its aims and the scientific and operational data and information it can generate. Therefore, appraisal of study proposals along the ethical review process would advantageous.

The ethical clearance for antimalarial drug efficacy studies in Ethiopia passes through institutional or national review process conducted by the Ethiopian Science and Technology Commission (2005:10). Although the process involves assessment of the ethical aspects of the study, the process usually doesn't focus on the merits of the study and on the opinions of the relevant responsible institution on the potential advantages of the study for the health services improvement in the country.

Therefore, a letter of recommendation from the Ministry of Health on the significance of the study and a possible future use of the study findings can pave the way for the Ministry of Health to engage in seeking important data and information from such studies for timely use.

Therefore, the ethical clearance issuing authority should assume the responsibility of confirming that the studies planned have public health importance by addressing potential or actual knowledge and information gap in the efficacy of antimalarial drugs used in the country.

5.2.3 The use of antimalarial efficacy studies' findings and treatment guidelines changes

Studies on antimalarial drug efficacy should ideally contribute to the existing scientific knowledge and also be of use to inform local policy issues and guide to determine appropriate treatment guidelines and policy decisions. Malaria treatment policy changes in Ethiopia have been preceded by reports of antimalarial efficacy studies. However, the

timing of the studies was usually late and the results happen to emerge after a significant problem of widespread antimalarial drug resistance has occurred. According to the WHO (2010a:5), malaria treatment policy change initiation should be considered when the treatment failure rate with a given antimalarial drug exceeds beyond 10%.

As presented in section 4.3 of the results section, the use of antimalarial drug efficacy study findings are usually delayed due to lack of appropriate consultation mechanisms that can lead a process of consensus building on how best to use the findings. Williams et al (2004:356) assert that even after determining the level of treatment failures in a given country or area, convening the right forum to review the results and agree on the change process has been challenging.

According to Williams et al (2004:356), the factors that influence antimalarial treatment policy change include political climate cost, treatment seeking behaviour of the population, replacement drug selection related to safety efficacy cost availability, procurement and distribution system and lead-time to policy change among others.

Therefore, the value and use of antimalarial drug efficacy study findings can be very much influenced by the other preconditions stated above and meeting these preconditions is equally important to having the antimalarial drug efficacy data.

5.2.4 Sentinel antimalarial efficacy studies

The selection of sentinel antimalarial drug efficacy monitoring approach in Ethiopia has been used in two of the nation-wide studies conducted in 1997–98 by the Federal Ministry of Health and Jima et al in 2003. All the other isolated studies were conducted mostly in other locations. The use of such sentinel monitoring sites can enable compare findings over-time in the same location and avoids the risk of other confounding effect that may arise from the site changes and the local malarial epidemiology in the new study sites.

The *in vitro* test kits developed by the WHO (2001:6) for different antimalarial drugs are also useful tools to provide baseline information on parasite sensitivity to antimalarial drugs. Therefore, when conditions permit, use of such test kits to determine baseline

parasite sensitivity data to antimalarial drugs and monitoring over time should be used every year in order to advice decision on whether to conduct in vivo therapeutic efficacy studies.

In addition to the *in vitro* malaria parasite sensitivity studies to selected antimalarial drugs of interest for the country, routine in vivo therapeutic efficacy study on the first line antimalarial drug currently in use in the country should be conducted based on the WHO study protocol every two years (WHO 2009a:3).

5.2.5 Selection and effective use of antimalarial drugs

According to WHO (2010b:15), the recommended ACTs for the treatment of malaria include artemether-lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine and artesunate plus sulfadoxine-pyrimethamine. The efficacy of the combination of these drugs is dependent on the efficacy of each of the partner drugs (Guerin et al 2009).

Reports on the declining efficacy of sulfadoxine-pyrimethamine (SP) for the treatment of *Plasmodium falciparum* has been documented from studies conducted in Djibouti and Somalia (Abdel-Hameed 2003) and Sudan (A-Elbasit, Elbashir, Khalil, Alifrangis & Giha 2006:604). Therefore, the use artesunate plus amodiaquine combination in these countries is basically conflicting with the WHO recommendations. The use of such ineffective combinations is likely to expose the Artemisinin component of the antimalarial drug to risk of development of resistance by the malaria parasites, especially *Plasmodium falciparum* parasites.

Malaria in younger people and in patients with high initial temperature and high parasitaemia has been shown to have strong association with treatment failure and higher probability of worsening anaemia in cases treated with chloroquine (Hamer, MacLeod, Addo-Yobo, Duggan, Estrella, Fawzi, Konde-Lule, Mwanakasale, Premji, Sempertegui, Ssengooba, Yeboah-Antwi & Simon 2003:422). The use of such indicators, however, cannot replace the need to conduct regular antimalarial efficacy studies.

The treatment of malaria based on confirmed diagnosis is a very important tool to prevent irrational use of antimalarial drugs that may contribute to building drug pressure that may lead to the selection and spread of antimalarial drug resistant parasites. The WHO (2012b:6) recommends treatment of malaria based on confirmed parasitological diagnosis. As can be seen from table 2.4, the coverage of malaria diagnosis services in Ethiopia and most of the neighbouring countries has been increasing over the last few years with the exception of Kenya and South Sudan where there is no data to show the trends of increased used of malaria diagnostic services.

Although the coverage of confirmed diagnosis for malaria using microscopy or RDTs)has been increasing over the years, treatment of most of the malaria cases in Ethiopia and the neighbouring countries is still largely based diagnosis using clinical sign and symptoms. Eritrea is an exception in this case. While the coverage of diagnostic services in most of the other countries is increasing, malaria diagnostic services in Eritrea seems to show some level of decline.

Fever or history of fever in the last 48 hours which is the main clinical sign used to diagnose malaria can occur due to many other infectious diseases. Moreover, clinically distinguishing the cause of fever is always challenging (Cunha & Cunha 2008:194-199). Treatment of malaria based on clinical signs and symptoms therefore can result in misdiagnosis and over/under-treatment and irrational use of antimalarial drugs (Amexo, Tolhurst, Barnish & Bates 2004:1896). Misdiagnosis has been shown to slow down learning and use of new health technologies for diagnosis (Adhvaryu 2011:1).

5.3 RECOMMENDATONS FOR ANTIMALARIAL DRUG EFICACY MONITORING AND USE OF EVIDENCE FOR POLICY IN ETHIOPIA

5.3.1 A model for an antimalarial drug efficacy monitoring system

The study protocol recommended by WHO should be used as the main standard guideline for the assessment of efficacy of antimalarial drugs that aim to inform antimalarial drug policy and treatment guideline development and updating. The current WHO (2009a:1) antimalarial drug efficacy study protocol clearly states the need to ensure quality of test drugs and patient follow-up schedule. With regard to the quality of test drugs and patient follow-up, the following should be critically adhered:

a) The quality of the test drug should be confirmed not only based on the quality analysis report provided by the manufacturer but also by an independent laboratory. This will also detect any quality deterioration that might have occurred during manufacturing, transportation and storage of the drug.

b) Whenever possible, patients involved in antimalarial drug efficacy studies should be followed in an in-patient setting and all treatment doses should be supervised. In situations where this is not feasible, study subjects should be provided with and strongly advised to use insecticide treated bed nets at home to prevent possible re-infection.

c) Study participants should also be asked to confirm that they have taken the prescribed amount of drug at the right time and that they also confirm if there was vomiting or diarrhoea during the course of the treatment. Depending on the frequency and pattern of the vomiting or diarrhoea episodes, the clinician should determine if the subject should continue in the study.

d) In the absence of adequate sample size of study subjects, a statistically sound approach should be used to determine if data from different sites could be aggregated or the study could be continued over an extended period. In either case, the approach should be cleared from being a potential or actual source of bias.

e) For all cases enrolled, blood samples should be taken for microscopy and PCR based detection of parasites. In the absence of PCR based confirmation, blood slides from study subjects should be prepared in duplicates for simultaneous reading by two microscopists. In case of a discordant result, the examiners should demonstrate presence or absence of parasitaemia to the second examiner. The jointly agreed result should be binding.

5.3.1.1 Organisation and management of antimalarial efficacy studies

The study team should be supplied with all the necessary laboratory material, stationary, sanitary supplies, waste disposal containers and the agreed payment right at the start of the study. Transport should be arranged for the trained study team and their study material to ensure safe arrival of all the necessary items to the point of the study site. A list of the materials required for antimalarial drug efficacy studies in presented in Annexure F.

5.3.1.2 Coordination with development partners and timeframe of activities

The study should be organised and planned as a joint venture of the Ministry of Health and the Regional Health Offices together with the National Pharmaceutical Regulatory Authority, relevant Research and Academic Institutions, International organisation such as WHO and UNICEF, funding agencies and health care workers in the study health facilities.

Through a joint consultation with these institutions, a small technical group composed of democratically selected experts should be formed to carry management responsibility of the study. The technical group should prepare a study proposal, implementation plan, mobilise fund and selection and training of study teams from each of the study sites.

To prevent discontinuation of study due to problems faced by study team members, the study team that should be trained for each site should be double of the minimum number required. Training of the study teams should be conducted in an actual health facility setting and all procedures of the study protocol should be covered through both theoretical and practical training. Once preparation for the study is completed, the team should organise start of the study, conduct follow-up supervision, data quality validation, data entry, analysis and report writing as per the time frame. An example of time frame that can guide local planning is presented in Annexure D.

5.3.1.3 Supervision and reporting

Members who participated in the training will perform the study. However, to ensure adherence to the study protocol and for the direct inspection of blood film preparation, slide reading and parasite density estimation, all study sites should be visited on weekly basis by supervisors trained for the task.

The team will have to submit detailed written report, all record forms, and all study slides properly wrapped and labelled to the study coordinator(s). Data analysis and writing of the report should be completed by the technical working group. Once a final version of the report and recommendations are prepared, this should be submitted to an independent expert group for review and clearance. Following the clearance process, the following actions need to be coordinated by the Federal Ministry of Health:

a) The Ministry of Health and the participating partners to organise a national workshop to disseminate the findings and agree on a plan to implement the recommendations.
b) The national workshop to nominate responsible institutions at national and regional level that will be guide the overall implementation of the new recommendation.
c) The national team together with the regional teams should prepare an overall implementation plan of the recommendation together with a detailed plan needed for guideline revision, health workers training, procurement and supply chain management of the new product needed and preparation and mobilisation of the required budget.
d) The national team should coordinate with the regional teams to regularly assess implementation status of the recommendation and progress towards the achievements by the due dates. Any challenge and obstacles in implementing the plan should be immediately notified to the Ministry of Health for action.

The overall implementation plan of any new recommendation for malaria treatment should be planned for completion within 12 to 18 months in order to prevent unnecessary delay in ensuring rapid access to effective antimalarial drugs. In the event of lack of funding to fully implement the new recommendation, the national and regional teams should have a fully endorsed alternative exit plan to address immediate malaria treatment issues.

5.4 BEST PRACTICE APPROACHES FOR ANTIMALARIAL DRUG EFFICACY MONITORING FOR ETHIOPIA

5.4.1 Establishment of antimalarial drug efficacy early warning system

The emergence of resistance to antimalarial drugs is a gradual process and starts with signs related to delayed parasite clearance. Sowunmi, Adewoye, Gbotsho, Happi, Sijuade, Folarin, Okuboyejo and Michael (2010:1) report that the causes for delayed resistance are multifaceted and are not attributed to a single cause. Early indications of delayed parasite clearance is a reliable early indicators that can be used to initiate

closer follow-up of patients treated with such antimalarial drugs to ensure that the required efficacy pattern of the antimalarial drug in use is continuing as expected.

According to White (1999:739), delayed parasite clearance is defined as occurrence of parasite in blood sample two days after the start of treatment. However, as parasite clearance time may vary according to the blood level and concentration of the antimalarial drug as well, Flegg, Guerin, White Stepniewska (2011:1) recommends that setting cut-off points to determine delay need to be based on local studies. In addition to the overall delay in parasite clearance time, Barnes, Little, Mabuza, Mngomezulu, Govere, Durrheim, Roper, Watkins and White (2008:1605) and Dondorp, Nosten, Yi, Das, Phae, Tarning, Lwin, Ariey, Hanpithakpong, Lee, Ringwald, Silamut, Imwong, Chotivanich, Lim, Herdman, Yeung, Singhasivanon, Day, Lindegardh, Socheat and White (2009:455) also report that parasite gametocytemia increases with increasing level of delayed clearance or parasite resistance.

The practice of early detection of delayed treatment response, reporting of such cases and further follow-up in the Ethiopian setting is not part of the antimalarial efficacy monitoring approach in Ethiopia. Therefore, given the advantage of such early detection of delayed response as a precursor for further closer follow-up, the following early monitoring approaches for early warning and reporting of delayed treatment response are proposed.

5.4.1.1 Health facility based early warning system

Health facilities providing malaria diagnosis and treatment services to patients on routine basis should keep detailed patient records to allow compilation of the required information. One of the main patient records worth including in medical records is travel history and overnighting in to another area over the last two weeks. The two weeks cut-off is based on the incubation period of malaria parasites which differs by the type of malaria parasite species which generally from 7 to 30 days (Centres for Disease Prevention and Control 2010).

The main activities that need to be implemented by the health facilities in order to ensure the early warning system include the following:

a) Record details of patients returning to the health facility with malaria clinical sign and symptoms within 15 days of the initial treatment for malaria administered based on microscopic examination of RDT, The patient specific record should include:
   - Name, sex and age and measured body weight
   - Residential address
   - Patient confirmation that all the antimalarial drug doses prescribed for a recent malarial illness were taken as instructed and there was no vomiting or diarrhoea
   - Travel during the last two weeks

b) Conduct parasitological examination to determine malarial infection and retain blood films with positive findings.

c) The use of RDTs to determine malarial infection for the purpose of the early warning system may not be reliable as parasite antigens that can be detected by the RDTs are known to persist up to two weeks after the parasite was eliminated following treatment (Kyabayinze, Tibenderana, Odong, Rwakimari & Counihan 2008:221). Therefore, although the use of RDTs is recommended to track resistant malaria parasites (Houzé, Boly, Le Bras, Deloron & Faucher 2009:211) its use should be cautious.

d) The health facility should also monitor clustering by village of such patients returning to health facilities within two weeks after treatment to identify localities where most of the cases are coming.

e) Compile and submit quarterly report on returning patients to the district health office.

5.4.1.2 District health offices-based early warning system

a) Identify pattern of patients returning with clinical sign and symptoms of malaria within two weeks after the initial treatment by time and location.

b) Ensure regular supply of second-line antimalarial drugs to health facilities in areas where the frequency of returning patients is higher.

c) Identify areas and request the Regional Health Bureau to assign experts to determine the need to investigate the pattern of response of the parasites to standard regimen on antimalarial drugs and determine if there is unexpected delayed response. Delayed response to antimalarial treatment is defined as

persistence of parasitaemia and clinical symptoms two days after treatment with an antimalarial drug (Sowunmi et al 2010:1).

d) Record parasite species and laboratory examination parasitological diagnosis malaria cases treated with the recommended antimalarial drug and who return to the facility with clinical sign and symptoms of malaria within two-weeks of the initial treatment.

5.4.1.3 Regional and national level early warning system

The Regional Health Bureau and Federal Ministry of Health at national level are responsible for the identification of areas where increasing frequency of returning patients are reported from. In this regard the health authorities at these levels should put in place measures for the following actions:

a) Identify and select area with high frequency of returning patients for further follow-up study.
b) Conduct parasite clearance rate assessment studies following full course of treatment and identify area with high frequency of patients whose parasite clearance took three or more days.
c) Investigate other possible reasons that contribute to delayed response to treatment such as quality the antimalarial drug administered and compliance of patients to prescribed treatment regimens.
d) Review pattern and concentration of returning patients and determine the need for a full antimalarial drug efficacy study.
e) Consider drug resistance containment actions in areas where delayed response to Artemisinin or resistance have been confirmed.
f) Ensure availability of second-line antimalarial drugs that can be used to treat patients and to contain spread of resistance.
g) Conduct full-scale representative and complete antimalarial efficacy study every two years in selected sites by ensuring timeliness, completeness and representativeness of the studies as per the most up-to-date study protocol recommended by the WHO.
h) For some isolated case studies to determine the susceptibility of the *Plasmodium falciparum* parasites to artemisinin, considering applying the methods used by Stepniewska, Ashley, Lee, Anstey, Barnes, Binh, D'Alessandro, Day, De Vries,

Dorsey, Guthmann, Mayxay, Newton, Olliaro, Osorio, Price, Rowland, Smithuis, Taylor, Nosten and White (2010:570) could be advantageous.

5.5 POLICY AND REGULATORY ISSUES

5.5.1 Antimalarial drug policy issues

The use of oral Artemisinin mono-therapies is likely to contribute to increasing prevalence of resistant strains to Artemisinin. The use of Artemisinin oral mono-therapy therefore may put at risk other ACT drugs containing artemisinin and its derivatives to be exposed to development of resistance by malaria parasites, especially *Plasmodium falciparum.* In this regard, therefore, at national level the following policy and regulatory measures should be in place.

a) The Ministry of Health and Drug regulatory authorities at national level should enforce ban of local manufacturing, importation or marketing of oral Artemisinin mono-therapies.
b) The national essential drug list should not include antimalarial drugs that are not recommended by WHO.
c) For additional products that need to be included in to the national drug list, inclusion should be ensured with supporting recommendation from normative agencies such as WHO.

To ensure importation of antimalarial medicines of proven quality and to prevent circulation of substandard, counterfeit or fake formulations, drug quality inspection at point of entry should be enforced.

5.5.2 Appropriate policy and guidelines implementation

Access to prompt and effective treatment for malaria will remain one of the main interventions for malaria prevention and control in Ethiopia. The success of this intervention will depend not only on the availability a malaria diagnosis and treatment guideline but also on ensuring the efficacy and safety of the medicines recommended for use in the country.

Ensuring efficacy of antimalarial drugs in use in the country involves regular monitoring. The regular monitoring of efficacy of antimalarial drugs and the use of the study findings to inform policy should be based on internationally recommended approaches endorsed by internationally mandated organisations such as the WHO and other in-country regulatory and normative guidelines.

In all cases, the antimalarial drug efficacy monitoring should be tailored to fit the local needs. To ensure this, the following best-practice approach is recommended based on the existing WHO's guideline and the findings from this study.

Antimalarial drug efficacy monitoring studies is Ethiopia have contributed significant amount of information on the pattern of sensitivity of the parasites and efficacy of the antimalarial drugs used in the country. However, the research question of some of the studies, justification for the method used, implementation of the studies and strength of the findings has not mostly been adequate requiring for more extensive and representative study.

From the Ethiopian context, the findings from isolated antimalarial efficacy studies have not been adequately used to inform policy due to the methodological disparities, lack of timeliness, representativeness and completeness of the data and information collected through the studies. Williams et al (2004:356) described a number of actions that need to be taken in order for evidence on antimalarial drug efficacy to be effectively used for antimalarial drug policy development and its implementations. Based on the actions proposed by Williams et al (2004:356), the antimalarial drug efficacy monitoring and use of evidence for policy change in Ethiopia can be said to have attempted to ensure all the necessary actions.

However, most of the actions taken in Ethiopia seem to have been driven by disease epidemic imposed need to change the first-line antimalarial drug. As a result, implementation of the new antimalarial drug policy and treatment guideline change has not been well coordinated and implemented in a reasonably short period of time.

Therefore, to ensure timely and smooth introduction of antimalarial drug policy and treatment guideline change, the following actions are proposed:

a) Raise the issues and inform stakeholders that treatment policy change might be needed based on the evidence collected.
b) Confirm the data that raise concern and present data to appropriate audience in a clear manner.
c) Strengthen consensus building among stakeholders emphasising that a change may be required by clearly presenting the evidence.
d) Promote for the necessary change to take place and be implemented at the same time.
e) Identify replacement antimalarial drugs, options of introducing the change and possible alternatives.
f) Develop policy document and specific directions on the change process and time line for implementation.
g) Ensure completion of timely preparatory activities. These include:
   - revise and print the new guideline including in local languages for all levels of health workers
   - prepare training plan and conduct the training
   - advice local manufacturers and importers to manage stocks of the old antimalarial drugs that may not be needed any more

5.6 CONTRIBUTIONS OF THE STUDY

The study has attempted to map the pattern of antimalarial drug efficacy monitoring studies and their contribution to the wealth of scientific information and use of the evidence for policy in the Ethiopian context. This has enabled identify the strengths and weakness of the previous antimalarial drug efficacy studies so that such future studies will have better design, conduct and dissemination of results and assessing the potential policy implication of the findings and alerting authorities of the possible actions required.

Through this study effort has also been made to obtain the overall and specific picture of the antimalarial drug efficacy studies conducted in Ethiopia over a period of 39 years. Although the contribution of the studies to the overall scientific knowledge is remarkable, the use of the findings has been seriously hampered by methodological disparities and lack of timeliness, completeness and representativeness and coordination with the decision making bodies such as the Ministry of Health.

Therefore, apart from conducting and publishing antimalarial drug efficacy studies, creating a mechanism to ensure use of the data to inform decision or identify next steps needs to be strengthened. To assist the overall management of antimalarial drug efficacy monitoring system and use of evidence for policy in Ethiopia, the best practice approaches and recommendations proposed are believed to be of significant importance to malaria treatment and monitoring of antimalarial drug efficacy in Ethiopia.

5.7 LIMITATIONS OF THE STUDY

The study employed an approach that allows reviewing and document findings of antimalarial efficacy studies conducted in Ethiopia and to assess their contribution to inform policy. The methodological approach and the data collection method used were appropriate for the study. However, ensuring a complete review of all available publications requires exhaustive search including work of individual researchers whose report was not published or shared in any form. Attaining this would have required identifying and interview with lead in-country experts. Although this can be seen as a potential methodological limitation, the researcher believes that, important study reports have been available.

The status of implementation of a new antimalarial drug policy and treatment guidelines depends on its appropriate implementation. This also contributes to ensuring an appropriate system to continue further monitoring of efficacy of antimalarial drugs. In this case, the lack of on ground assessment and reports on the assessment of implementation of the new antimalarial treatment policy is also a major limitation of the study.

The limitations identified in this study have no significant implication on the way forward. Therefore, implementing the recommendations and best practice approaches proposed in this report to strengthen antimalarial drug resistance early warning and monitoring system can significantly contribute to the improvement of malaria treatment in Ethiopia which contributes towards reducing malaria related illness and death and this contributes to improved public health and socio-economic development in the country.

5.8 CONCLUDING REMARKS

An estimated 54 million people in Ethiopia live in areas at risk of malaria and the disease poses significant public health and socio economic problems. *Plasmodium falciparum* malaria which causes nearly all the malaria related deaths is also the parasite species that developed resistance to different antimalarial drugs.

The success in malaria prevention and control in Ethiopia will continue to depend on the availability of safe, effective, affordable and accessible antimalarial drugs. Although public health service to prevent lack and delay in accessing prompt diagnosis and effective treatment services is improving through international support and national efforts, the issue of retaining the useful life of existing antimalarial drugs will depend on their rational use and advances to develop new effective antimalarial drugs.

To date the development of resistance to antimalarial drugs is more rapid than the scientific and industrial advance to develop new effective antimalarial drugs. Currently there are ten antimalarial molecules globally that are completing phase IIb/III clinical trial (Medicines for Malaria Venture [MMV] 2012). These molecules are expected to enter the market in few years provided that the clinical trial findings are supportive and acceptable. On the other hand, the efficacy of the currently available and widely used ACT drugs is at risk of losing its useful life due to the development of resistance to the artemisinin component of the combination drug.

Artemisinin resistance first started in localised foci in the Thai-Cambodia border and is now expanding to wider geographic areas (WHO 2010d). Although resistance to artemisinin has not yet been reported in Africa, the early symptoms of declining responsiveness have been confirmed in Kenya by Borrmann, Sasi, Mwai, Bashraheil, Abdallah, Muriithi, Frühauf, Schaub, Pfeil, Peshu Hanpithakpong, Rippert, Juma, Tsofa, Mosobo, Lowe, Osier, Fegan, Lindegårdh, Nzila, Peshu, Mackinnon and Marsh (2011:1). To strengthen antimalarial drug efficacy monitoring system and use of evidence for policy and planning will remain as the most important tool. The WHO (2010d) advises malaria endemic countries to establish a strong system for antimalarial drug efficacy monitoring system in order to timely detect problems and ensure placement of corrective actions.

For antimalarial drug efficacy monitoring study to be of use to develop relevant policies and treatment guidelines, data collected through these studies should be representative, timely and complete beyond any doubt. Failure to obtain high level of quality of the evidence on antimalarial drugs and the decision that may need to be taken may not attract full support from all stakeholders and this can cause delay in taking actions of public health relevance.

Beyond the regular monitoring of the efficacy of antimalarial drugs, policy and regulatory environment that support the judicious use of existing antimalarial drugs should be enforced. These includes a) inclusion in the National essential drug list of antimalarial drug formulations that are recommended by the WHO and local evidence supported by the national health and regulatory authorities b) monitoring of quality and ascertaining prequalification status of antimalarial drugs authorised for marketing and c) ensure appropriate use of antimalarial drugs based on confirmed diagnosis and limit use of antimalarial drugs based on sign and symptoms.

Antimalarial drug efficacy monitoring should be conducted on regular basis of every two years as recommended by the WHO. However, a routine system to monitor early indications of delayed response to antimalarial treatment and resistance should be gathered from selected early warning spots. The evidence gathered from these early warning spots should be used to guide selection of regular spots for a full antimalarial drug efficacy study.

In conclusion, the recommendations and best practice approaches proposed in this report are sound both from scientific and international recommendation point of view and the local setting. Therefore, as a way forward, the researcher will work to present findings and recommendations of this study to relevant audience in Ethiopia.

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Annexure A

Study ethical clearance

Annexure B – Study ethical clearance

UNISA university of south africa

UNIVERSITY OF SOUTH AFRICA
Health Studies Research & Ethics Committee
(HSREC)
College of Human Sciences

CLEARANCE CERTIFICATE

Date of meeting: 19 April 2010 Project No: **44678037**

Project Title: **Malaria Treatment in Ethiopia: Anti-malaria drug efficacy monitoring system and use of evidence for policy**

Researcher: **A Yohannes**

Supervisor/Promoter: **Prof LI Zungu**

Joint Supervisor/Joint Promoter: **Dr NG Malangu**

Department: **Health Studies**

Degree: **D Litt Et Phil**

DECISION OF COMMITTEE

Approved [√] **Conditionally Approved** [ ]

Date: 19 April 2010

Prof ON Makhubela-Nkondo
RESEARCH COORDINATOR: DEPARTMENT OF HEALTH STUDIES

Prof MC Bezuidenhout
ACADEMIC CHAIRPERSON: DEPARTMENT OF HEALTH STUDIES

PLEASE QUOTE THE PROJECT NUMBER IN ALL ENQUIRES

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Annexure B

Data variables and analysis

Annexure C – Data variables and analysis

Data category	Variable	Data collected	Analysis
Study Ares and population	Locality, region	Number of sites	– Total number of study sites – Existence of the risk of malaria infection in the study site
	Per cent population at risk of malaria	Total and population at risk of malaria	
Test drug	Generic name	Name	– Confirmation of expiry date of the test drug at the time of the time of use, – Quality analysis of the drug for active ingredient
	Batch	Number	
	Manufacturer, supplier	Name	
	Expiry date	Date	
	Quality analysis for active ingredient	Pass, fail	
Study design	Study population age group	Under five years or five years and above	– Appropriateness of the study protocol for the setting – Adequacy of the samples size – Random or purposive – In-patient or outpatient – Parasite species studied – Types of antimalarial drugs tested – Appropriateness of drug dosage in milligram per kilogram body weight
	Study protocol	Name	
	Sampling assumptions	Description	
	Calculated sample size	Number	
	Patient allocation approach	Name	
	Patient follow-up arrangement	Name	
	Test parasites	Name	
	Test drug	Name	
	Drug dosage	dosage	

Annexure B – Data variables and analysis (continued)

Data category	Variable	Data collected	Analysis
Study quality control	Urine test for drug prior to treatment	Number	– Per cent with positive urine test – Per cent with drug concentration above the minimum effective concentration – Per cent slide examination result concurrence between two readers – Per cent microscopy examination results confirmed by PRC – Per cent treatment failure cases with drug or metabolite concentration above the minimum effective concentration
	Drug concentration in blood samples at the time of treatment failure	Number	
	Blood film result quality control	Total or random	
	PCR confirmation of microscopy based examination results	Number	
	Drug concentration in blood samples at the time of treatment failure	Number	
Study outcome – in vivo studies	Follow-up outcome	Number	– Total enrolled – Per cent who completed follow-up – Per cent loss and withdrawals – Per cent adequate clinical response – Per cent adequate clinical and parasitological response – Per cent early treatment failure – Per cent late treatment failure – Per cent total treatment failure – Per cent treatment failure – Per cent treatment success (*Plasmodium vivax*) – Per cent treatment failure (*Plasmodium vivax*)

Annexure B – Data variables and analysis (continued)

Data Category	Variable	Data collected	Analysis
Study outcome in vitro studies	Schizont maturation at 0.025 nmol	Number	– Per cent schizont maturation at various drug concentrations (0.25, 0.5, 0.75 and 1.0 nmol) in vitro studies
Study outcomes - Molecular studies	Genetic analysis for polymorphic genes conforming with resistance	Number	– Per cent parasite samples with polymorphic genes conforming resistance
Publication	Study period	Year	– Number of years that lapsed from completion of the study to communication of the findings – Number of years lapsed from completion of study to dissemination of results
	Year of publication	Year	
	Duration to publication	Year	
Policy implication	Study timelines	Year	– Number of years from the first report – Extent of missing information – Number of years needed to introduce revised malaria treatment guideline
	Study completeness	Name	
	Treatment policy change and updating treatment guidelines	Year	

Annexure C

Chronological list of antimalarial drug sensitivity and efficacy studies in Ethiopia

Annexure C – Chronological list of antimalarial drug sensitivity and efficacy studies in Ethiopia

No	Year	Author	No. of study sites	Sample size	Subjects age group (years)	Method and follow-up duration	Test drug	Test parasite	% Treatment failure
1	1974	Dennis et al	1	41	5 & above	*In vivo*, 28 days	Chloroquine	*Plasmodium falciparum*	26.8
2	1974	Dennis et al	1	24	5 & above	*In vivo*, *in vitro*	Chloroquine	*Plasmodium falciparum*	0[a]
3	1976	Palmer et al	3	82	5 & above	*in vitro*	Chloroquine	*Plasmodium falciparum*	0[a]
4	1976	Armstrong et al	4	99	2—55	*In vivo*, 6-11 days	Chloroquine	*Plasmodium falciparum*	0
5	1980	Gebremariam et al	1	21	above 5	*In vivo*, 7 days	Chloroquine	*Plasmodium falciparum*	0
6	1980	Gebremariam et al	1	14	above 5	*in vitro*	Chloroquine	*Plasmodium falciparum*	0[a]
7	1984	Gebremariam et al	11	136	1 to70	*In vivo*, 7 days	Chloroquine	*Plasmodium falciparum*	0
8	1984	Gebremariam et al	11	115	1 to 60	*In vivo*, 28 days	Chloroquine	*Plasmodium falciparum*	0
9	1985	Teklehaimanot et al	1	98	above 14	*In vivo*, 28 days	Chloroquine	*Plasmodium falciparum*	22.4
10	1985	Teklehaimanot et al	2	10	above 14	*in vitro*	Chloroquine	*Plasmodium falciparum*	70[a]
11	1993	Wezam	1	23	All ages	*In vivo*, 7 days	Chloroquine	*Plasmodium falciparum*	0
12	1993	Wezam	1	24	All ages	*In vivo*, 7 days	SP	*Plasmodium falciparum*	0
13	1996	*Alene*	36	1706	1 to 80	*In vivo*, 7 days	Chloroquine	*Plasmodium falciparum*	87.2
14	1996	Tulu et al	1	29	1 to 76	*In vivo*, 7 days	Chloroquine	*Plasmodium falciparum*	86.2
15	1996	Tulu et al	1	80	1 to 76	*In vivo*, 7 days	SP	*Plasmodium falciparum*	1.3
16	1997	Tulu et a.	1	255	1 to 76	*In vivo*, 7 days	Chloroquine	*Plasmodium vivax*	2
17	1997	Assefa	1	1	25	*In vivo*, 7 day	Chloroquine	*Plasmodium falciparum*	100

No	Year	Author	No. of study sites	Sample size	Subjects age group (years)	Method and follow-up duration	Test drug	Test parasite	% Treatment failure
18	1998a	MOH	14	473	Under five	*In vivo*, 14 days	Chloroquine	*Plasmodium falciparum*	73.6
19	1998a	MOH	6	257	Five and above	*In vivo*, 14 days	Chloroquine	*Plasmodium falciparum*	63.4
20	1998b	MOH	4	107	Under five	*In vivo*, 14 days	Chloroquine	*Plasmodium falciparum*	47.7
21	1998b	MOH	7	227	Under five	*In vivo*, 14 days	Amodiaquine	*Plasmodium falciparum*	21.1
22	1998b	MOH	7	232	Under five	*In vivo*, 14 days	SP	*Plasmodium falciparum*	5.6
23	2001	Degefa	1	77	Above 6 months	*In vivo*, 14 days	SP	*Plasmodium falciparum*	2.6
24	2002	Kassa et al	1	59	1 to 7	*In vivo*, 14 days	Mefloquine	*Plasmodium falciparum*	0
25	2002	Kassa et al	1	60	1 to 8	*In vivo*, 14 days	SP	*Plasmodium falciparum*	21.1
26	2003	Yeshiwondim et al	2	145	4 to 65	*In vivo*,28 days	Chloroquine (CQ)	*Plasmodium vivax*	5.76
27	2003	Yeshiwondim et al	2	136	4 to 60	*In vivo*, 28 days	CQ + primaquine	*Plasmodium vivax*	0.75
28	2003	Jima et al	11	523	$\geq$ 6 months	*In vivo*, 28 days	SP	*Plasmodium falciparum*	33.5
29	2003	Jima et al	4	213	$\geq$ 6 months	*In vivo*, 28 days	AL	*Plasmodium falciparum*	0.9
30	2006	Teka et al	1	83	8 mo. to 52 yrs.	*In vivo*, 28 days	chloroquine	*Plasmodium vivax*	4.8
31	2006	Seboxa et al	2	105	2 to 35	*In vivo*, 14 days	AL	*Plasmodium falciparum*	0
32	2006	Seboxa et al	1	36	2 to 35	*In vivo*, 14 days	Artesunate + SP	*Plasmodium falciparum*	0
33	2006	Schunk et al	1	69	All ages	molecular	Chloroquine	*Plasmodium falciparum*	78.3--95.7[b]
34	2006	Schunk et al	1	69	All ages	molecular	SP	*Plasmodium falciparum*	81.2--82.6[b]
35	2006	Schunk et al	1	31	All ages	molecular	SP	*Plasmodium vivax*	3.2--6.5[b]

No	Year	Author	No. of study sites	Sample size	Subjects age group (years)	Method and follow-up duration	Test drug	Test parasite	% Treatment failure
36	2007	Kefyalew	1	102	1 to 50	28 days	AL	*Plasmodium falciparum*	0
37	2008	Ketema et al	1	78	9 mo. to 42 yrs.	*In vivo*, 28 days	chloroquine	*Plasmodium vivax*	82.6
38	2010	Eshetu et al	1	35	All ages	molecular	AL	*Plasmodium falciparum*	0[b]
39	2010	Eshetu et al	1	30	All ages	molecular	Quinine	*Plasmodium falciparum*	0[b]
40	2010	Eshetu et al	1	32	All ages	molecular	AP	*Plasmodium falciparum*	3.1--6.3[b]
41	2010	Assefa et al	1	81	1 to 30yrs	*In vivo*, 28 days	AL	*Plasmodium falciparum*	6.7
42	2011	Yohannes et al	2	75	Above 1 year	*In vivo*, 28 days	AL	*Plasmodium vivax*	25.3
43	2011	Yohannes et al	2	57	Above 1 year	*In vivo*, 28 days	Chloroquine	*Plasmodium vivax*	8.8
44	2011	Ketema et al	1	80	9 mo. to 52 yrs.	*In vivo*, 28 day	Chloroquine	*Plasmodium vivax*	6.7

Annexure D

Antimalarial efficacy study implementation time frame

Annexure D – Antimalarial efficacy study implementation time frame

No	Activity	July	August	September	October	November	December	January	February	March	April
1	Preparation and endorsement of study proposal										
2	Test drug analysis and mobilizing test materials and fund										
3	Training of study team										
4	Actual study period										
5	Data entry and cleaning										
6	Data analysis and report writing										
7	Dissemination of result (workshop)										

Annexure E

Proposed study team training

Annexure E – Proposed study team training

Day	Duration	Topic
1	1 hour	Back ground and objectives of the Therapeutic efficacy study and site & time selection
	2 hour	Fundamental components of the WHO antimalarial efficacy study protocol
	2 hour	Patient examination, inclusion & exclusion criteria, Enrolment & follow-up procedures
	3 hour	Blood film preparation, staining, examination and recording results and materials required for the test
2	4 hours	Practical session for laboratory technicians • blood slide preparation, staining, examination, • Parasite count and density estimation • Recording keeping
	4 hours	Practical session for medical doctors • Patient screening, • Blood film result and parasite count, Inclusion and exclusion criteria, • Adherence to study protocol inclusion and exclusion criteria of patients,
Day 3	6 hours	Actual practical in health facility

Annexure F

Study materials required

Annexure F – Study materials required

Laboratory ware and Cleaning materials			
NO.	**ITEM**	**UNIT**	**Quantity Per Study Site**
1	Graduated cylinder	500 ml	2
2	Graduated cylinder	100 ml	2
3	Graduated cylinder	10 ml	2
4	Staining rack and dish	Large set	2
5	Rinsing trough	Each	2
6	Timer	Each	2
7	Drying rack	Each	4
8	Slide tray	Each	4
9	Slide box	100 slides	2
10	Compound microscope	Each	2
11	Weighing scale	Each	2
12	Digital Thermometer	Each	4
13	Plastic dropper for immersion oil	Each	4
14	Towel	Each	2
15	Detergent	Pack	2
16	Hand Soap	Each	2
17	Soft Paper	Roll	2
18	Distilled Water	Container of 5L	5
19	Blue ink pen	Each	4
20	Red ink pen	Each	4
21	Pencil	Each	4
22	Carbon paper	Box of 100	1
23	Folders	Each	4
24	Rubber Band	Box	2

Laboratory Materials			
NO.	**ITEM**	**UNIT**	**Quantity Per Study Site**
1	Latex gloves	Box of 50 pair	4
2	Frosted slides	Box of 50	40
3	Lancets	Box of 500	4
4	Cotton	25 gm roll	4
5	Alcohol	1 litre bottle	2
6	Methanol	1 litre	1
7	Giemsa stock solution	Litre	1
8	Buffer tablets	Bottle of 100	4
9	pH indicator	Roll	1
10	Xylene	Litre	0.5
11	Microscope lens cleaning tissue	Pad	2
12	Immersion oil	250 ml bottle	1
13	Test drug	Treatment courses	150
14	Rescue treatment	Treatment courses	150
16	Other supportive treatment (e.g. antipain)	Treatment course	150

Stationary			
NO.	**ITEM**	**UNIT**	**Quantity Per Study Site**
1	Blood film slip	Sheet	100
2	Registration forms	Pad	2
3	Case record forms	Each	300
4	Enrolled form	Each	50
5	Follow-up forms	Each	400
6	Referral forms	Each	100
7	Study manual	Each	1
8	Location form	Each	400
9	Malaria diagnosis bench aids	Each	1

Annexure G

World Health Organization recommended methods for surveillance of antimalarial drug efficacy

Annexure G – WHO recommended methods for surveillance of antimalarial drug efficacy

Available from http://whqlibdoc.who.int/publications/2009/9789241597531_eng.pdf

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