PERFORMANCE AND COST EVALUATION: -

PARACHECK PF® TEST AND CLINICAL DIAGNOSIS ON THE

DEPLOYMENT OF ARTEMETHER-LUMEFANTRINE

IN LOW TO MODERATE MALARIA TRANSMISSION AREAS

TIGRAY, ETHIOPIA

A protocol study

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Master thesis in public health, 20 points

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TERMS AND ABBREVIATIONS

ACT, Artemisinin-based combination therapy
AMT, Annual mean temperature
ARI, Acute respiratory tract infection
BF, Blood films
CBIs, Community based interventions
CBMCP, Community-based malaria control programme
CBRHAs, Community based reproductive health agents
CCM, Country coordinating committee
CHWs, Community health workers
CJSC, Central joint steering committee
COI, Cost of illness
CQ, Chloroquine
CT, Combination therapy
DALYs, Disability adjusted life years
DDT, Dichlorodiphenyltrichloroethane
DSH, Demographic and health survey
EMVC, Environmental management for vector control
FDRE, Federal Democratic Republic of Ethiopia
FN, False negative
FP, False positive
GDP, Gross domestic product
GFATM, Global fund to fight AIDS, tuberculosis and malaria
GIS, Geographical information system
GNP, Gross national product
HDI, Human development index
HEP, Health extension programme
HEWs, Health extension workers
HMIS, Health management information system
HRP II, Histidine-rich protein II
HSDP, Health sector development programme
IEC, Information education and communication
IPTp, Intermittent preventive treatment for mothers
IRS, Indoor residual spraying
ITNs, Insecticide treated nets
LLIN, Long lasting insecticide treated nets
M&E, Monitoring and evaluation
Masl, Meter above sea level
Mbsl, Meter below sea level
MCP, Malaria control program
MCST, Malaria control support team
MDGs, Millennium development goals
MES, Malaria eradication service
MoH, Ministry of health
MOVBD, Malaria and other vector borne diseases
NGO, Non governmental organizations
NLF, National labour force survey
NPV, Negative predictive value
OPD, Outpatient department
P.f, Plasmodium falciparum
P.v, Plasmodium vivax
PCR, Polymerase chain reaction
PHCU, Primary health care unit
pLDH, Plasmodium lactate dehydrogenase
PPV, Positive predictive value
RBC, Red blood cells
RBM, Roll Back Malaria
RDT, Rapid diagnostic test
SDPRP, Sustainable development and poverty reduction programme
SP, Sulfadoxine-pyrimethamine
SSA, Sub-Saharan Africa
TB, Tuberculosis
TN, True negative
TP, True positive
TTBAs, Trained and traditional birth attendants
UNDP, United Nation Development Programme
UNICEF, United Nation Children Fund
WBC, White blood cells
WDP, Water dispersible powder
WHO, World Health Organization
WHO-CHOICE, World health organization-CHOosing Interventions that are Cost-Effective
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ABSTRACT

Ethiopia is one of the Sub Saharan Africa countries where malaria is an old and long standing disease. It is estimated that more than two thirds (51 million) of the population is at risk of malaria. The unstable nature of malaria makes the population non-immune and prone to epidemics. Ethiopia’s 50% population is at risk of malaria epidemic and this sets the country at the top of the list with a contribution of 26% to the global risk of malaria epidemic (Eve et al., 2004).

*P. falciparum* and *P. vivax* are the two dominant parasite species of which the former accounts for 60-70% of infections, and the later for the remainder. Almost all malaria deaths happen due to *P. falciparum* infection.

Early diagnosis and prompt treatment is the principal technical component of the national strategy to control malaria. However, one key challenge facing antimalarial treatment is achieving a balance among three essential, but at times competing, principles: ensuring prompt and effective treatment of malaria, ensuring that antimalarial drugs have a maximum useful therapeutic life and ensuring its cost effectiveness (WHO, 2001).

In order to ensure effective treatment Ethiopia has changed the first line treatment of uncomplicated plasmodium malaria to artemisinin-based combination therapy (ACT) with artemether-lumefantrine or Coartem®. A health extension programme has been recently launched with the objective of ensuring access. Accordingly, every tabia (sub district) will have one health post. At this level, malaria diagnosis is based on clinical assessment and/or results of rapid diagnostic test (RDTs).

Clinical diagnosis (suspected malaria case) of malaria is non-specific. As a result, antimalarials are being prescribed to patients who do not have malaria. The difficulty could be worsening with the expansion of primary health care where less trained health workers are expected to manage almost all uncomplicated malaria cases. Such *presumptive treatment* leads to major concerns of how we can make the highest “value
for money” and delaying the emergence of drug resistance. Paracheck pf\textsuperscript{®} test has been introduced with regards to the above apprehension. However, since it is adopted without any evaluation there are uncertainties on its accuracy and cost in local context.

Therefore, this research protocol is designed to evaluate cost and performance of paracheck pf\textsuperscript{®} test in the deployment of Coartem\textsuperscript{®} in comparison to clinical diagnosis of malaria from a health sector perspective in a low to moderate transmission where both \textit{P. falciparum} and \textit{P. vivax} are significant.

The study setting will be a routine heath service delivery at periphery level. The study subjects are consecutive suspected malaria cases who satisfy the inclusion criteria. Every subject identified in the out patient department will have a finger pricked blood sample for both paracheck pf\textsuperscript{®} test and blood film (thick and thin) tests.

The comparison of both alternatives will be done in terms of their performance and cost saving. Performance of the alternative diagnostic methods will be calculated vis-à-vis light microscopy. Costing will be limited only to direct cost of the initial treatment with a first-line drug prescribed and the test used from the provider’s perspective. The difference in the gross cost between the alternatives will give us the cost saving.

Furthermore, as malaria cost varies among seasons, epidemiological strata and age groups, we will asses the role of paracheck pf\textsuperscript{®} in reducing the consumption of Coartem\textsuperscript{®} (cost) at different situations. This will help to apply paracheck pf\textsuperscript{®} pf tests selectively to achieve highest value for money.

Generally, our research is expected to identify the more effective and cheapest way (improve technical efficiency) of treating malaria at the periphery level.

Key words: Clinical diagnosis, Coartem\textsuperscript{®}, Cost saving, Health extension programme, Paracheck pf\textsuperscript{®} test, Malaria, \textit{P. falciparum}, Suspected malaria case, Performance evaluation, Tigray.
1. BACK GROUND

1.1. GLOBAL MALARIA EPIDEMIOLOGY, BURDEN AND CONTROL STRATEGY

At present, about hundred countries in the world are considered malarious. The incidence of malaria is estimated to be 300-500 million clinical cases each year. Almost half of the malarious countries and about 90% of the global malaria incidence are occurring in Africa South of Sahara (Map1) where the disease exerts its heaviest toll. Malaria, mainly \textit{P. falciparum}, is estimated to kill between 1.5-2.7 million people in the world. Three thousand poor children, most of them living in Sub Saharan African (SSA), perish every single day which accounts for about 25% of all-cause mortality in this age group (WHO, 2000a).

Even though, malaria is curable and also a preventable disease, it is a disaster that people in affected countries lack access to prevention and treatment. The human toll is tragic, and the economic cost enormous. In endemic countries, malaria account for 25–40% of hospital admissions, up to 20-50% of outpatient visits and consumes 40% of public health expenditure (WHO,2005a). Malaria hinders the social and economic development of dozens of nations. In Africa alone, the total economic burden is estimated at US$ 12 billion annually leading to a slow down of the economic growth by 1.3% per year (RBM/WHO/UNICEF, 2005). It literally keeps poor people poor.

The number of people at risk has increased consistently from 0, 9 to 3 billion in the years 1900–2002. At the turn of the 21st century, it is estimated that 48% of the global populations are exposed to the risk of malaria, a situation that has deteriorated since the early 1990s and it’s substantially higher than the 40% widely cited (Simon et al., 2004).

Patterns of malaria transmission and disease vary markedly between regions and even within individual countries. This diversity results from variations between malaria parasites and mosquito vectors, ecological conditions that affect malaria transmission and socioeconomic factors, such as poverty and access to effective health care and prevention services.
To guide the battle against this deadly disease, current World Health Organization (WHO) strategies and policies on malaria control are focused in four main areas (WHO, 2005b):

- Preventive intervention strategies
- Access to prompt and effective treatment
- Prevention and control of malaria epidemics
- Strengthening local capacity and Monitoring and evaluation

The above strategies aim to achieve global targets from different angles. The WHO has declared the year 2000-2010 as a decade for malaria control. In line to this, a Roll Back Malaria (RBM) global partnership incepted in 2000 with the commitment of halving the world’s malaria burden by 2010 and again by 2015. The RBM partnership is also instrumental in bringing together partners to develop successful proposals to the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM) to meet the targets. In the
Abuja summit (WHO, 2005b; WHO, 2003d), in April 2000, African leaders also committed to ensure three principal interventions; access for treatment within 24 hours on the onset of fever, insecticide treated nets (ITNs) protection to those at risk of malaria, and access for intermittent preventive treatment (IPTp) for pregnant women, with at least 60% coverage each, by the end of 2005 so as to convene the global targets. The United Nations’ Millennium Development Goals (MDGs) according to sixth goal (target eight) also recognize malaria as a major factor underlining development and dedicated to halt and reverse its incidence by 2015 (WHO, 2005b; WHO, 2003c).

Even though recent developments in fighting malaria are considerable, they are still negligible with respect to the global burden of the disease. Malaria will therefore remain at the top of global priorities challenging the 21st century civilization. Among the many substantial challenges: (i) lack of practical and significant international and national commitment (ii) resistance of parasites and vector to commonly used anti-malarial drugs and insecticides; (iii) global warming (iv) breakdown of control programmes; (v) Complex emergencies; (vi) collapse of primary health services (vii) expansions of settlements and water development projects in low land area (viii) shortage of trained manpower, attrition and brain drain, and (ix) lack of resource (supplies and logistics) (RBM/WHO/UNICEF, 2005).

Ethiopia is one of the SSA countries where malaria is an old and long standing disease. Malaria situation is even worst in Ethiopia than most SSA countries where it often occurs in rampant epidemic that results in huge morbidity and high mortality. Furthermore the transmission of the disease generally occurs during the peak cultivating and harvesting period of the disease and has tremendous impact on productivity.

1.2. COUNTRY SITUATION ANALYSIS

1.2.1. GEOGRAPHY AND DEMOGRAPHY

Ethiopia is known as starting point of human being where the famous Australopithecus afarensis, a 3.7 million years old fossil was found. It is located in the Horn of Africa (Map 1) and it is one of the largest countries in SSA which covers an area of 1.14 million
square kilo meters (sq. km). It is a country with great geographical diversity. Its
topographical features range from the highest peak of Ras Dashen, 4,620 meters above
sea level (masl), down to the lowest and hottest point of the earth in the Afar, Danakil
depression, 110 meter below sea level (mbsl).

Ethiopia is the third populous country in Africa with a population of over 72 million
(projected from 1994 census with 2.9% population growth rate). The age structure of the
population shows a typical SSA pattern with 44% of the population being under the age
of 15 years and a large proportion (24%) of women being within the reproductive age
group (15–49 years) (WHO/AFRO, 2002). The National Demographic and Health Survey
(DHS) in 2000 stated that the total fertility rate was 5.9 children per woman during the
last five years. According to the 1999 National Labour Force Survey (NLFS) the overall
dependency ratio for the country was estimated at 102 dependants per 100 people in the
working age group (15–64 years) (WHO/AFRO, 2002).

1.2.2. POLITICS AND ADMINISTRATION
The country is a multi-ethnic society with approximately more than 80 nations,
nationalities and peoples contributing their own culture and language. The constitution of
the Federal Democratic Republic of Ethiopia (FDRE) established a federal system of
government with nine regional states and two city administrative councils that are further
divided in to Zones, Woredas (districts) and Kebeles (sub districts). The role of the
federal government is limited to directing the country’s fiscal, defense, and foreign affairs
and articulating economic and social policies. State governments are empowered to
design and operate region-specific programs and policies and are responsible for their
own legislative and administrative functions. This decentralized system follows the
transfer of resources, authority and accountability to regions, district and sub-district
levels so as to enhance priority identification, planning and decision-making at the level
where the problems occur.

1.2.3. SOCIO-ECONOMY
Ethiopian economy is agrarian and agriculture accounts for about 54% of the Gross
Domestic Product (GDP). The agriculture sector, which relies on traditional labour-
intensive technologies and is strongly rain-dependent, employs more than 80% of the population. The GDP grew at an annual average rate of 5.5% from 1992 to 1998, with sector growth rates of 3.4% for agriculture, 7.3% for industry and 7.7% for services. As per 2002 the public expenditure on health was 1.7% of the Gross National Product (GNP). The annual per capita income is almost US$ 100 (WHO/AFRO, 2002). Drought has become a chronic occurrence, affecting the country periodically since 1983. According to the 2002 United Nation Development Programme (UNDP) report, Ethiopia’s had a Human Development Index (HDI) of 0.359 (WHO/UNAIDS, 2005).

1.2.4. HEALTH POLICY AND ORGANIZATION
The health care delivery system was formerly highly centralized, with most service delivery taking place in urban centers whiles the remote and most in need rural majority had limited access to care. The Ethiopian health policy endorsed in 1993 commits to decentralize health service management and delivery system; promote prevention and promotion components of health care; equitable distribution of health services, etc (WHO/AFRO, 2002). The policy is founded on the recognition of the current health status (mentioned later). The regime decentralized health care administration to the local level is to keep the objective of community involvement and ownership in health matters.

The government has developed a twenty-year Health Sector Development Programme (HSDP) since 1997/98. The health sector follows a set of rolling five-year strategic plans to guide implementation of the national health policy. This policy is in turn part of Ethiopia’s Sustainable Development and Poverty Reduction Programme (SDPRP) as it gives appropriately high priority to primary and preventive health care (IDA/IMF, 2002). A Central Joint Steering Committee (CJSC) for health, with representatives from government ministries, multilateral and bilateral donors and Non Governmental Organizations (NGOs), guide implementation of the HSDP (WHO/AFRO, 2002; WHO/WR, 2004).

The main role of the Federal Ministry of Health is development of policy including guidelines; resource mobilization, capacity development activities and technical support to regions. Regional health bureaux are responsible to adapt policies and guidelines to
local situation, planning, monitoring and evaluation, resource mobilization and allocation, conduct operational research and providing technical assistance to districts. The districts are the implementers of the plan. Although the responsibility of the federal, regional and district levels are clearly defined, emphasis is also given to co-ordinate activities between the federal and those of the bureaux through joint meetings.

The health service is consisting of a four-tier system; the Primary Health Care Unit (PHCU), district hospital, zonal hospital and regional referral hospital. A PHCU is the grass-root level, which gives preventive and curative health services for an average of 25,000 people (Kahsu, 2002). It consist a health centre and five satellite health posts.

Since 2004, the government of Ethiopia has made a bold decision to strengthen and expand the PHCU by launching the Health Extension Programme (HEP). The Health Extension Program is designed to achieve significant basic health care coverage in the country over five years through the provision of a staffed health post to serve every 5000 people. This new community-based health care delivery system will improve access and equity in health care through a focus on sustained preventive health actions and increased health awareness.

Every health post is/will be staffed by two Health Extension Workers (HEWs), who are high school graduates with an extra of one year training course. The training program includes sixteen major packages such as i) building and maintaining healthful house, ii) construction, usage and maintenance of sanitary latrine, iii) food hygiene and safety measures, iv) personal hygiene, solid, and liquid waste management, v) water supply, safety and management, vi) maternal and child health, vii) family planning, viii) vaccination service, ix) nutrition, x) HIV/AIDS and TB prevention and control, xi) malaria prevention and control, xii) first aid, xiii) health education and promotion method, etc. Among the thousands health posts where the HEP is being put into practice, more than 5000 are expected in the rural malarious Kebeles.
1.2.5. HEALTH STATUS

Ethiopia has one of the poorest health statuses of low-income countries. As in many developing countries, Ethiopia's main health problems are communicable diseases (parasitic and infectious) and malnutrition. Physical and cultural problems isolated relatively large segments of the population from the modern sector. Wide spread poverty, the general low income level of the vast majority, and inadequate access to clean water, sanitation facilities, and health care are major contributors to the prevailing ill-health. Additionally, widespread illiteracy prevents the dissemination of information on modern health practices. A shortage of trained personnel and insufficient funding also hampers the equitable distribution of health services that has left predominant rural population without appropriate health care. Moreover, most health institutions are concerned with curative rather than preventive medicine.

Health indicators reflect high levels of morbidity and mortality. According to the 2001 World Population Data Sheet of the Population Reference Bureau and Ethiopia Science and Technology Commission (ESTC) policy paper, the average life expectancy at birth is 54 years (53 years for males and 55 years for females) (WHO, 2005c; ESTC, online). Infant mortality rate is estimated at 112 per thousand live births, while the under five-mortality rate is 187 per thousand live births. Maternal mortality is estimated at 500-700 deaths per 100,000 live births (THB, 2003). HIV/AIDS, malaria, tuberculosis (TB), diarrheal disease and acute respiratory tract infection (ARI) are among the top diseases. Malnutrition is prevalent particularly among children and mothers. Environmental health problems attributed to the occurrence of the great proportion of communicable diseases in the country. The health of children and mothers is affected by harmful traditional practices besides diseases.

As it will be described later malaria is a major public health problem in the country and therefore its control programme is prioritized within the HSDP and shared among its eight principal components.

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2The eight components include health services delivery and quality of care, health facility rehabilitation and expansion, human resource development, pharmaceutical supply and management, information, education
1.3. MALARIA EPIDEMIOLOGY AND BURDEN

1.3.1. MALARIA EPIDEMIOLOGY

Despite the long history of malaria eradication and control in the country since the 1950’s, the disease is still a major public health problem. It is estimated that about three-fourth of the land is malarious and more than two third (51 million) of the population is living in this area (Zein and Kloos, 1988).

As it is shown in Map 2 malaria is seasonal (unstable) and focal which depends largely on rainfall and altitude. September through November is the major transmission season following the main rains of June to August. A second transmission season occurs from March to April, following the short rains (belg) of January and February (WHO/RBM, 1999). Conducive conditions of temperature and relative humidity to both vector and extrinsic parasite development occur after the rains. In the Western part and in areas with permanent water bodies the transmission lasts more than six months.

The unstable nature of malaria makes the population non-immune and prone to epidemic and this also accounts to the fact that all malaria infection even with low-level parasitaemia is associated with clinical illness in all age groups. Recurrent outbreaks and epidemics associated with cyclical climatic variations frequently lead to significant morbidity and mortality. Ethiopia’s 50% population is at risk of malaria epidemic and this sets the country at the top of the list with a contribution of 26% to the global risk of malaria epidemic (Eve et al., 2004).

Generally, Ethiopia is classified into three major eco-epidemiological zones: kolla which is warm and lowland below 1500 meter above sea level (masl), weyna dega (temperate and midland between 1500-2400 masl and dega (cold and highland above 2400 masl). The annual mean temperature (AMT) ranges from +10 to +33 °C. The dega zone is malaria free since the AMT of below 15°C is too low to support the survival of the parasite and the development of the vector.

and communication (IEC), health sector management, health management and information system (HMIS), monitoring and evaluation( M&E) and operational research and health Care Financing.
Among the forty-two *Anopheles* species identified in Ethiopia the four malaria vectors *A. gambiae* s.l. (cytogenetically *A. arabiensis*), *A. pharoensis*, *A. funestus*, *A. nili* are widely distributed. *A. arabiensis* is the most important vector and is responsible for most epidemics in the country (Abose et al., 1998; Zein and Kloos, 1988).

*P. falciparum* and *P. vivax* are the two dominant parasite species of which the former accounts for 60-70% of infections, and the later for the remainder. In the hot and drier months from January to May *P. vivax* increases in proportion due to seasonal decrease in *P. falciparum* infection and relapse of *P. vivax* during times when enabling conditions for continued transmission are absent. In epidemic situations, *P. falciparum* is the dominant parasite specie and almost all malaria deaths happen due to infections by this species (WHO/RBM, 1999).
1.3.2. MALARIA BURDEN

In Ethiopia over five million episodes of malaria with 70,000 deaths are estimated to occur annually. The infection case fatality rate ranges from 17-35% (WHO/WR, 2004). In 2004, the disease was reported as the first cause of illness and death accounting for 15.5% of outpatient visits, 20.4% of admissions and 27% of deaths. The magnitude and periodicity of malaria epidemics in the country have also been on the rise in the past few years. Some 5.4 million cases of epidemic malaria cases were expected in 2005 transmission season (September-November) with 100,000 estimated deaths (WHO, 2005c).

Figure 1 illustrates the burden of malaria in the country. It should be taken into consideration that this does not reveal the actual malaria patients since data from health facility records do not reflect the real incidence of a disease in the population. Firstly, majority of the cases are managed at home. Secondly, the above figure is only part of those who visit health facilities as the health information system is too week to capture and to transfer complete information. Thirdly, it does not include those treated by community health workers (CHWs). Therefore, one can easily conclude that the above estimated annual malaria cases and mortality from malaria are highly conservative.

Figure 1. Malaria morbidity and slide positivity rate in Ethiopia, 1984-2001.

Since malaria occurs in all age groups, the social and economic consequences of the disease are sobering, with a large number of death, illness and debilitating productivity. The societal burden calculations based on institution data are likely to be underestimated. Even though reliable community-based information is limited; the magnitude of malaria burden can be appreciated from the few published studies available for review.

In malarious villages, Tembien and Tanqua Abrgele district, Tigray, northern Ethiopia, Cropper et al. (2004) reported the average number of workdays lost for an adult during a malaria episode was eighteen. On average, the cost of illness (direct and indirect cost) per episode was ranged from Ethiopian Birr\(^3\) 46 to 151 (8 to 24 USD) for adults, Birr 41 to 145 (7 to 23 USD) for teenagers, and Birr 23 to 78 (4 to 13 USD) for children. The average annual household cost of illness ranged from Birr 196 (31 USD) using high productivity assumptions to Birr 58 (9 USD) using low productivity assumptions. Mean household income was Birr 1,387 (220 USD) and median income is Birr 1,157 (183 USD).

In 1998 in a community-based cross-sectional study in Butajira district, central part of the country, 13.7% of householders were ill during a two-week recall period, and malaria accounted for 26% of illness during this period, and 9% of the deaths within the preceding two years. Overall, malaria was estimated to account for 10.4% of the total 59,125 Disability Adjusted Life Years (DALYs) lost per 100,000 populations (Abdulahi, 1998). In a study of subsistence farm households in western Ethiopia, malaria had statistically significant effect on total revenue, reducing average income by 24%-45%, depending on criteria used to define a malaria case (Abdulhamid, 1995).

1.3.3. MALARIA CONTROL PROGRAMME

As mentioned above, Ethiopia is one of the few African countries with a history of malaria control almost 50 years. The Malaria Eradication Service (MES) was established in 1959 and shifted to vertical Malaria Control Program (MCP) in 1971. In accordance to the Ministerial Conference in 1992 in Amsterdam (WHO, 1993) it was integrated and

\(^3\) 6.30 Birr was equivalent to US$1
decentralized with in the primary health care unit in 1993. After the RBM inception, a five years (2001-2005) strategic plan was prepared with the main objective of reducing the overall malaria burden by 25% by the end of 2005 as compared to the baseline level of 2000 in accordance to the Abuja summit. The national MCP is supported by a broad based partnership. A Malaria Control Support Team (MCST) is a strong partnership of co-ordination mechanism which comprises representatives from sectoral ministries, academic and research institutions. A Country Coordinating Committee (CCM) was also established as a result of requirements for the GFATM plan implementation and performance improvement (WHO/WR, 2004).

The national strategy focuses on three technical and four supportive strategic approaches, as advocated by RBM and WHO⁴:

- **Main strategies**
  - Early diagnosis and prompt treatment
  - Selective Vector control
  - Epidemic prevention and control

- **Supporting strategies**
  - Human resource development
  - Information education and communication (IEC)
  - Health management information system (HMIS) and Monitoring and Evaluation (M&E)
  - Operational research

The unique feature of early diagnosis and treatment of malaria in the country is aiming at radical cure, clearance of both symptoms and parasites. This strategy will take advantage from the current advancement in PHC expansion through HEP. All components of HEP are preventive except malaria that has both wings: preventive and case management.

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⁴ Malaria in pregnancy is among the main global strategies. However, the unstable nature of disease transmission and co-existence of *P.falciparum* and *P.vivax* in the country makes a special scenario and precludes the use of intermittent preventive treatment with sulfadoxine pyrimethamine (SP) as a malaria prevention tool during pregnancy.
The preventive aspects includes: distribution, re-impregnation and utilization of insecticide treated nets (ITNs), social mobilization for source reduction of mosquito breeding sites, indoor residual spray (IRS) of insecticides and health education.

In line with the provision of effective case management, early diagnosis and prompt treatment, *in-vivo* therapeutic efficacy assessment of SP (the then first line drug) and Coartem® (as candidate) for the treatment of uncomplicated falciparum malaria was conducted in 2004 in epidemiological representative sites in the country. The aggregated SP mean treatment failure was 35.9% (range 21.7-53.4%) which was far beyond the WHO cut off point and it was no more drug of choice to treat uncomplicated falciparum malaria (FMoH,2004). As the result, a new malaria diagnosis and treatment policy has been adopted. Accordingly, the first line treatment of uncomplicated plasmodium malaria has changed to Artemisinin-based combination therapy (ACT) with artemether-lumefantrine or Coartem® (Annex 1a).

The new policy recommends different diagnostic approaches based on the level of the health facilities. The most commonly used methods are clinical and confirmed diagnosis. The latter includes laboratory (microscopy) or rapid diagnostic test (RDTs). Laboratory based diagnostic facility is available at all levels of the health care delivery system except at health posts. At periphery health care system where microscope facility is not feasible due to the lack of infrastructure, supply and technicians, malaria diagnosis is based on clinical assessment and/or results of RDTs.

Clinical diagnosis is mainly based on the patient’s signs and symptoms. In a malarious area a patient with fever or history of fever with in the past two days (48 hours), or in non-malarious area a patient with fever or history of fever within the past two days and a history of travel to malarious area within the last two weeks is referred as clinical malaria, i.e. suspected malaria case. In both scenarios other obvious causes of fever should be ruled out (FMoH, 2004).
RDTs, made of plastic cassette, card or dipstick, capture parasite antigens in a drop of finger-prick blood on to bands of antibodies fixed to a strip of filter paper. As it is shown in Annex 3, when the test is positive, an indicator dye produces a visible colored line in addition to a second ‘control’ band. The tests are of three different antibodies to detect the following antigen in the parasite; Histidine-rich protein II (HRP II) specific to *P. falciparum*, Plasmodium lactate dehydrogenase (pLDH) specific to *P. falciparum*, *P. vivax* and pan-specific, and aldolase which is only pan-specific (WHO/AFRO/WPRO, 2005).

RDTs, using expert microscopy as the "gold standard" generally achieve a sensitivity and specificity of >95% in the detection of *P. falciparum* at density of 100 asexual parasites per µl blood and higher at higher parasite densities, which is probably similar to good field microscopy. Below the level of 100 parasites per µl blood, sensitivity decreases markedly (WHO, 2000b; WHO/AFRO/WPRO, 2005). Health workers with minimal skills specially form remote areas, can be trained in RDT techniques in periods varying from hours to a day.

The WHO recommendation for countries like Ethiopia where *P. falciparum* co-exists with non-falciparum infections is a combination tests detecting all species and distinguishing separately (WHO/AFRO/WPRO, 2005). Despite this, the country has selected paracheck pf® in cassette format (Annex 2a), that only detects *P. falciparum*.

Coartem® (administered 2 times a day for 3 days) is the first-line drug for treating all clinical malaria cases in clinical diagnosis and only for confirmed *P. falciparum* in paracheck pf® test. For all paracheck pf® negative cases with clinical signs and symptoms of malaria, it could be convincing to consider *P. vivax*. Even though Coartem® is active against blood stages of *P. vivax*, (but not against hypnozoites) Chloroquine (CQ) is still effective and cheap as a first line drug to treat *P. vivax* with/without of primaquine with prompt referral to the next higher level of health facility (FMoH, 2004).
2. RATIONALE AND AIM OF THE STUDY

As it will be described later it is globally confirmed that Coartem® is effective against the most resistant parasites in the world and so it should be effective everywhere (WHO, 2001). Therefore, efficacy is not a problem in deploying Coartem® as presumptive treatment with in the HEP. But, the policy change in the management of uncomplicated cases and the practical application in place are currently facing paradox due to the following facts.

1. The policy change is from a cheapest monotherapy which was widely used including the CHWs to the expensive ACT, Coartem®.
2. The epidemiological nature of malaria (non immune population) where the clinical algorithm almost equates fever to malaria and *P. vivax* is found in similar proportion to *P. falciparum*.
3. The PHC service expansion due to the HEP creates access to the remote majority population and also likely to increase the number of ‘presumptive treatment’.

Presumptive treatment based on clinical diagnosis (clinical algorithm) of malaria which is based on the patient's symptoms and on physical findings is notoriously difficult and extremely non-specific because the prominent clinical symptoms of malaria; fever, followed by chills, sweats, headaches, muscle pains, nausea, vomiting, and severe anemia overlap with those of other many diseases. As a result, antimalarials are being prescribed to patients who do not have malaria while some with malaria parasites might be left untreated. It is also unable to distinguish among the types of malaria. The difficulty could be worsening with the extreme expansion of PHC where less trained health workers (HEWs) are expecting to manage almost all uncomplicated malaria cases. In such case presumptive treatment (widespread deployment) leads to three major concerns.

1. The chief one being cost. The prescription of Coartem® which is more than 20-fold expensive than of the cost of the traditional mono therapies like CQ or SP to non malaria and non *P. falciparum* cases increasing the importance of minimizing the unnecessary drug use.
2. The second concern is the *P. falciparum* resistance that has been developed to nearly all traditional antimalarial drugs. It is highly likely that we risk to loss our most valuable artemisinin derivative antimalarial if we tend to use it irrationally, which is a potentially catastrophic event.

3. The third is misdiagnosed cases (malaria and non malaria) incur health sector and household loss including death.

These concerns are very critical in a country like Ethiopia where irrational (wide spread) use of drug is common. Amexo et al (2004) in their comparison of clinical malaria diagnosis versus microscopy confirmation among sixteen countries from Afro D, Afro E, South America, and Asia, showed that Ethiopia has the highest rate, 78%, (negative microscope/ total clinical malaria) where the mean is 61%. This is a strong indication for the need of definitive diagnostic.

The whole purpose of introducing Paracheck pf® test is in regard to the above apprehension. However, since it was adopted without any evaluation there are uncertainties on its accuracy and cost in the local context. The cost of the programme is dependent on the test accuracy (performance) which is unknown in the local context.

The above facts call for evidence based efficient and effective programme implementation.

Therefore, this protocol has two main purposes relevant to the national programme objectives and country priority. Firstly, it is to review the exiting global knowledge on accuracy of paracheck pf® test and clinical diagnosis and their relevant cost in the deployment of Coartem® with special emphasis to similar epidemiological characteristics like ours.

Secondly, it is to formulate a research proposal to evaluate the performance of paracheck pf® and clinical diagnosis with reference to microscopy as the golden standard and their role in the deployment of Coartem® at periphery health facilities.
3. LITERATURE REVIEW

In a first moment, the review was systematically sorted into four categories; i) coartem® efficacy and effectiveness, ii) paracheck pf® test accuracy iii) accuracy of the clinical diagnosis, and iv) cost-effectiveness of paracheck pf® test and clinical diagnosis in the deployment of Coartem®. Different databases such as PubMed, Medline, and WHO/RBM were assessed. The review was focused in the past ten years (since 1995), and only ten, four and five relevant articles were reviewed for the first, second and third categories, respectively. Some documents, guidelines and reports from national and regional were also helpful.

Whereas a number of studies have described the accuracy and cost effectiveness of paracheck pf® test in diagnosing *P. falciparum* compared to microscopy, accuracy of clinical diagnosis compared to microscopy and the effectiveness of coartem® compared to other drugs, to my knowledge evidence has not been available regarding the fourth category of (paracheck pf® test and clinical diagnosis in deploying Coartem®). In a similar way, Goodman et al (2000), in their work on ‘Economic Analysis of Malaria Control in Sub-Saharan Africa’, were able to identify one or two works on improving malaria diagnosis. Due to this limitation this review will strained to deal separately on performance of the individual interventions, the paracheck pf® test and clinical diagnosis, and the effectiveness of the drug (Coartem®).

3.1. ARTEMISININ-BASED COMBINATION THERAPY: COARTEM®

Early diagnosis and prompt treatment is the principal technical component of the global strategy to control malaria. The effectiveness of this intervention is highly dependent on antimalarial drugs, which should not only be safe and effective, but also available, affordable, acceptable and appropriate to the population at risk. The WHO explicitly recommended the use of ACT in order to provide effective treatment against malaria and to slow the spread of drug resistance (WHO, 2006).
Among the available ACTs, Coartem® is the only fixed-dose pre-qualified by the WHO. It is also efficacious, safe, tolerant, and highly recommended for the treatment of uncomplicated *P. falciparum* worldwide (Novartis international AG, 2005). It achieves cure rates of up to 95%, even in areas of multi-drug resistance. It is also reduces transmission (in areas with low or moderate malaria transmission) due to the effect of artemisinin derivatives on gametocyte carriage rate, this in turn may delay or slow the spread of drug resistance. No parasite resistance has been documented and its availability as a fixed-dose formulation compensates the impairment in adherence to the three day regimen (WHO, 2001).

Several studies proved it’s efficacious and cost effectiveness compared to other traditional drugs in the treatment of uncomplicated *P. falciparum*. In South Africa, Manguzi sub district, KwaZulu Natal province, where the intensity of malaria is similar to our local situation and *P. falciparum* accounts for the majority of infections, a study showed a decline in outpatient, inpatient and deaths, by 36%, 46% and 62% respectively between 2000 and 2002 after changing to coartem® as the first line drug. The study showed that though Coartem® is considerably ‘more expensive’ than SP, it improved the cure rate to 87% and reduced malaria transmission resulting in an estimated 201,065 US dollars cost saving in 2002 alone for the sub district (Muheki et al., 2004).

In another study Coleman et al (2004), in an incremental cost-effectiveness analysis, reported that ACTs is more than 95% likely to be cost-effective under most conditions, other than very low levels of initial resistance to SP and a five-year time frame.

At 95% coverage, the WHO-CHOICE (CHOosing Interventions that are Cost-Effective) has sorted ACT either individually or combined with other interventions as the most cost effective. The incremental cost per DALY averted for combinations of ACT+ ITNs, ACT +ITNs + IRS, ACT+ ITNs +IRS +IPTp, are US$56, US$118 and US$151 respectively. Any other combination is dominated (WHO, 2003a).

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5 Swissmedic, Swiss Agency for Therapeutic Products, Riamet ® Certificate number 54’594
Chantal et al (2005) have also demonstrated that high coverage with artemisinin based combination treatments was the most cost effective strategy for control of malaria in most countries in sub-Saharan. However, they also notice that treatment alone can achieve less than half the total benefit obtainable through a combination of interventions.

3.2. RAPID DIAGNOSTIC TEST (RDTs): PARACHECK PF®

Most of the studies reviewed regarding RDTs were not in relation to improve case management or drug prescription; rather they focused on comparing it with other types of RDTs. Singh and others have performed a number of paracheck pf® performance evaluations in different settings in central India. In one of their studies in Jabalpur district, where they evaluated the performance of paracheck pf® (Orchid Bio-Medical Systems, India) in the diagnosis of migrant and indigenous clinically suspected malaria patients using microscopy as the gold standard for *P. falciparum* infection they showed that among the migrants the test was highly sensitive (100%), but less specific (67%), with a positive predictive value (PPV) of 94% and a negative predictive value (NPV) of 100%. The accuracy of the test was 95% (Singh and Saxena, 2005a).

In a second study (Singh et al., 2002) to determine the lower limits of sensitivity and specificity of paracheck pf® in the diagnosis *P. falciparum* among asymptomatic children in remote villages of Mandla district, they found a sensitivity of 94% and a specificity of 89%. The positive and negative predictive values were 71% and 98%, respectively. The J-index was 0.83%. In a third study (Singh et al., 2005b) in two hospitals in the same district, they also showed that sensitivity and specificity of paracheck pf® for *P. falciparum*, was 93% and 84%, respectively, in placental parasitemia among pregnant women. The PPV and NPV were 50% and 99%, respectively. The corresponding result of paraHITf was 87.5%, 97%, 75.4% and 98.7%

In Vietnam, in a study to compare the sensitivity, specificity and post-treatment persistence of three commonly used rapid antigen detection methods, Huong et al.( 2002) demonstrated a sensitivity of 95.8%, 82.6% and 49.7% for paracheck pf®, ICT malaria P.f./P.v and OptiMAL, respectively. All were equally 100 % specific. In Africa, in a
study at the out-patient department of Mbarara Hospital, Uganda, to measure the overall performance of five HRP II sensitive RDTs for *P. falciparum* infection, in order to select the most appropriate test to be used in the field, Guthmann et al (2002) found that paracheck pf® was considered as the most appropriate for the use in the field, being sensitive (97%), moderately specific (88%), reliable (kappa coefficient = 0.97), easy to use and cheap (about US$ 0.5/test).

In the contrary, in a study to validate four type of rapid diagnostic tests, including paracheck pf® in field surveys in malaria-endemic areas of Palawan and Davao del Norte, Philippines, Belizario et al (2005) found a vary extreme result. Sensitivity was ranging from 4.8% to 20.6%, except for Diamed OptiMAL, which had sensitivities of 78.8% to 96.8% and all the specificities ranged from 18.2% to 100 % as compared to microscopy.

Despite the above results the manufacturer, Orchid Biomedical Systems, India, presumably under ideal conditions that paracheck pf® test compared to microscopy, can achieve a sensitivity of >99% and a specificity of 100% for detecting *P. falciparum* HRP II. The manufacturer also reports that the test remain stable for up to two years when stored at 4 to 30 degree Celsius (QAP/ WHO, online).

In summary, all reviewed studies except the one from Philippines recommended the use of paracheck pf® for the diagnosis of *P. falciparum* in area where it dominates the parasite poll. However, it should be borne mind that the accuracy of RDTs is dependent on the stability of the test (including shelf life, heat and humidity), transmission intensity (low, medium, high, seasonal), parasite prevalence in target population, setting of use (level health facility and health workers), parasite density and treatment history of patient, instruction follow up and correct reading and last but not least is the proper conditions at the time of manufacturing (Belizario et al., 2005).
3.3. CLINICAL MALARIA DIAGNOSIS

In many places, malaria diagnosis is solely based on the medical history and clinical examination of patients, since there is no trained staff and equipment available to confirm the presence of *Plasmodium* parasites. The etiology of fever is thus often notified as malaria. Numerous studies have shown that a reliable diagnosis of malaria cannot be done on clinical grounds only, even if algorithm scores are used. There is, therefore, a significant risk for mistreatment, either in excess or in lack (Amexo et al., 2004).

In Chad, at the level of primary care facilities in an urban Sahelian setting, in an area with seasonal transmission patterns like Ethiopia which occurs at the end of the rainy season, Othningué et al (2006) assessed the performance of clinical malaria diagnosis versus microscopy examinations. They showed that in 712 clinically malaria cases, 30% (211 slides) of clinically diagnosed cases were positive by thick film examination. Thus, false positive (no malaria parasite) cases constituted 70% (501 slides). In another hospital-based trial (Stephens et al., 1999) to compare the clinical diagnosis of malaria, microscopy, and a rapid diagnostic antigen (ParaSight-F), in North-west Thailand, the authors found that only 21.3% (64) were falciparum parasite positive among those 204 presumptively diagnosed as having malaria. This shows that 79.7% were presumptively mistreated for malaria.

Lepere et al (2004) also showed that due to the lack of emergency microscopic diagnosis, the presumptive antimalarial treatment rate was superior to 90% in isolated health centers in Mayotte, a French overseas territory in the Comoro Archipelago and they also demonstrated that after the introduction of RDT the rate was reduced to less than 3%.

Locally, in Tigray, Ethiopia in 1995-1996 a study was undertaken to determine the diagnostic performance of CHWs and health professionals at different levels. The nurses in the health station were 96% and 16% sensitive and specific, respectively (WHO/RBM, 1999). This indicates that 84% were treated wrongly for malaria but only 4% malaria cases were misdiagnosed. With clinical algorithm where fever equates malaria specificity overweighs sensitivity.
In conclusion, all the above reviewed studies were consistent in confirming that Coartem® is the most cost-effective treatment, when applied singly or in combination.

Though microscopy remains the gold standard for malaria diagnosis it is unaffordable and unfeasible in remote areas and therefore, all reviewed studies tried to search the cheapest and ease to use diagnostic tool which minimizes the number of patients who receive the wrong treatment. Paracheck pf® test demonstrated that it was the most sensitive and at least as equally as specific to other types of RDTs to provide on-site confirmation of uncomplicated \textit{falciparum} malaria.

Some of the studies have also mentioned the manufacturer cost of a test was cheap, but none of them dealt with either its total net benefit or its comparable economical advantage to other alternative kind of diagnosis. It was also shown that the accuracy of the test and its role was different from setting to setting dependent on several factors and one size does not fit all. The immense limitation of paracheck pf® is it’s being unable to detect malaria other than \textit{P. falciparum}.

Regarding the clinical diagnosis, all reviewed studies showed that at least 70% of presumptive malaria cases were misdiagnosed. This result leads to risks of side-effects, to the selection of resistant parasite strains due to drug pressure and to unnecessary cost for patients and/or health services. Conversely, regardless the high sensitivity of clinical diagnosis it is likely that few patients suffering from malaria may not treated, thereby risking progression to severe disease and death.
4. THE STUDY PROTOCOL

4.1 OBJECTIVES

4.1.1. GENERAL OBJECTIVES

- To evaluate the performance of paracheck pf® test and its role in minimizing cost in the deployment of artemether-lumefantrine (Coartem®) in comparison to clinical diagnosis of malaria from a health sector perspective in low to moderate transmission where both P. falciparum and P. vivax are significant.

4.1.2. SPECIFIC OBJECTIVES

- To determine performance capacity (accuracy) of paracheck pf® test as compared to the golden standard (microscopy) for diagnosis P. falciparum in a local situation.

- To measure the diagnostic capacity of clinical diagnosis of health workers in identifying malaria case at periphery health institutions as compared to microscopy.

- To assess cost and cost saving between the alternatives from the provider perspective.

- To identify environmental and operational factor affecting paracheck pf® performance and its utilization.

- To document the kind of symptoms and signs patients exhibit more frequently and to validate the existing clinical algorithm in comparison to microscopy results.
4.2. METHODS AND MATERIALS

4.2.1. THE STUDY AREA, POPULATION AND HEALTH SYSTEM

Tigray is the northern most national regional state of Ethiopia (Map 2 and 3) bordering Eritrea and Sudan and is located between latitude 12° and 15° north (THB, 2002/03). It is the origin of the famous Axumite kingdom which was one of the world’s four great powers along with China, Persia and Roma in the 300 BC. The region is divided into southern, western and northwestern lowland areas (700-1800 masl), eastern, central, and southern high land fringe areas (1800-2200 masl) and Eastern and southern high land (above 2200 masl) with 3935 masl of the Amba Alaje Mountain. The region covers 80,000 square kilometers (WHO/RBM, 1999).

Like the rest part of Ethiopia, the population is dominantly rural and engaged almost entirely in rainfall depended subsistence agriculture. The region is frequently famine attacked and drought. Population density ranges from 5 per sq. km in lowland areas to 120 per sq.km in the highlands. The 2004/05-projected population with a 3% growth rate per year is estimated to be 4,249,965. Under five year children, under 15 year adolescents and females constitute 17.7%, and 44.3% and 51% of the population, respectively (THB, 2002/03; WHO/RBM, 1999).

The health system in the region is organized as shown Figure 2. The principal objectives and activities are in line with the national policy. Maternal and child health, health promotion, environmental sanitation, epidemic control, improving health service quality and coverage, rehabilitation and expansion of health facilities, and human resource development are among the major programmes.

Since the new national health policy of 1993, health service coverage is improving (Figure 3). Construction of health facilities and internal accessories, training of health workers, and improving budgeting are the major progress in the last 12 years.
Figure 2. Organo-gram of Tigray Health Bureau.

Note: Under each department there are 2-5 divisions. DPC= Disease prevention and control, HR= Human resource, MOVBD= Malaria and other vector borne diseases, CBIs=Community based interventions. Health stations are expected to upgraded or degraded.
From 1990 to 1992 the number of health stations decreased because they were upgraded to health centres or degraded to health post.

Regardless of these endeavors, like elsewhere in the country the health care system in the region is still crippling, leaving much of the rural population without easy access even to the most peripheral health institutions. The improvement of the service coverage is mainly dependent of the community participation and ownership.

The role of the community in Tigray in expanding and strengthening health services has been very encouraging. The community participates in almost all health activities including identification of health problems, implementation of health interventions, and participation in the construction of health facilities either by contributing money or their labor. Community Health Workers (CHWs), Trained and Traditional Birth attendants (TTBAs and TBAs) and Community Based Reproductive Health Agents (CBRHAs) remain key partners in health development. As per 2002/03, 2,461 TBAs and 1,172 CHWs were active in the region (THB, 2003).
4.2.2. MALARIA: EPIDEMIOLOGY, BURDEN AND CONTROL

As in the rest of Ethiopia, malaria is seasonal and unstable with transmission ranges from hypoendemic to mesoendemic. Almost 65% of Tigray’s land is malarious and 56% of the population is at risk of malaria and outbreaks. Transmission occurs usually at altitudes below 2000 meters with lower frequency above this altitude. The transmission seasons are similar to the country with the belg rain limited to southern part of the region. The maximum and minimum AMT is +22 and +14 degree Celsius, respectively.

Malaria is challenging the socio economic development of the region. For instance, according 2001/2002 health profile of the region, malaria was the number one cause of death (19%), number one cause of admissions (15%), and number one cause of outpatient visits (15%) (THB, 2002/03). The last figure excludes febrile patients who were treated by trained CHWs at village level which accounts for 70% of malaria (febrile) cases. Malaria strikes during planting and harvesting seasons, cutting down productive capacity at a time when there is the greatest need for agricultural work force. The disease is also associated with loss of earnings in different ways, low school attendance, work load for health facilities, high treatment cost for the government and patients during complication.

To improve the service coverage and ensure early diagnosis and prompt treatment of malaria for the rural population, a community-based malaria control programme (CBMCP) supported by the WHO was introduced in 1992. In addition to early diagnosis and prompt treatment, the programme includes interventions such as environmental management for vector control (EMVC), distribution and re-impregnation of mosquito nets, use of a geographical information system (GIS) for area intervention stratification, and computer-based data management systems (WHO/RBM, 1999). The traditional indoor residual spraying (IRS) using dichlorodiphenyltrichloroethane (DDT) 75 % WDP or Malathion 50% WDP with systematic selection and appropriate targeting of epidemic prone localities is also a strong arm of the programme.

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6 Hypoendemic is an area with a spleen and/or parasite rate less than 10% in children 2-9 years-old and mesoendemic is ranging from11-50%.
Currently a total of 1020 volunteer CHWs are serving an estimated rural population of 1.8 million living in malarious areas in the region. Figure 4 shows CHWs free of charge treatment service and their reporting status. Currently this strong and well established CBMCP, especially its wing of early diagnosis and prompt treatment is likely to be compromised due the policy change as it is not easy to make available the new expensive drug at community level for presumptive treatment. The bureau is looking for ways if any to maintain the programme.

Figure 4. CHW treatment and reporting status, Tigray CBMCP, 2001/02-2003/04.

Insecticide treated nets (ITNS) are distributed in priority localities with at least one ITNs per house hold. Since 2002/03 until the end of 2005, 61% of the households at risk of malaria were expected to have at least one ITN. Each year the selective IRS operation protects in average 400,000-450,000 peoples from malaria (MOVBD, THB).

Despite these efforts, malaria remains a major health problem in the region. Parasite and vector resistance to drug and insecticide, and focal epidemics that may follow climatic changes have the potential to increase demand for malaria control services. There are also further strong reasons to keep malaria at top priority. Effort to address problems of recurrent drought and food insecurity including water conservation schemes at household
and community level, irrigated agriculture schemes, resettlement of population from the less fertile densely populated highland areas to the fertile but malarious lowlands and seasonal migration of labourers to areas of agricultural development are among the threats.

Mereb Leke is one of the districts in the region where this study will be will be carried. It is located at the tip north of the central zone of the region and it bordering the country with Eritrea (Map 3). As it is shown in Figure 5, the altitude ranges from 1300 to 2258 masl with a total area of 1,249 sq. km (MOVBD, THB). The district is divided in to three representative epidemiological strata; below 1500 masl (stratum I), 1501-2000 masl (stratum II) and above 2000 masl (stratum III). The district has nineteen sub districts (locally referred as ‘tabia’), eighteen of them are rural. Each tabia has four villages (referred as ‘kushet’). In each strata there are fifteen (four are in the town), fifty seven and four kushets, respectively.

Map 3. Map of Tigray regional national state and the study district, Mereb Leke.

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7 Tigray health profile, HMIS division. PPD, Tigray Health Bureau. Mekelle, Ethiopia.
Majority of the population estimated to be 95.5% live in kushet below 2000 masl. The land is dry, bushy, highly eroded, dissecting by numerous small valleys, making several hills like the majority part of Tigray.

Figure 5. GIS based altitudinal stratification of Kushet, masl, Mereb Leke district.

The population in 2005/06 is an estimated to be 135,106 (Ethiopian national census 1994, projected), which is administratively divided into 19 tabias and 76 villages. This expanding rural population is putting its agricultural land under ever greater pressure. The district is one of the most famines affected. Chronic food insecurity reflects a situation where more and more peasant families have farm holdings that do not provide a sustainable livelihood even when the weather is favorable.

Potential PHC service coverage as per 2003, with 10 km distance access to health post, was 65.8% and recently it is expected to increase for the fact that HEP is introducing and a newly constructed health centre in the district town has begun providing service. Like everywhere in the region, the district health service is supported by community participation. Forty-one CHWs were actively providing early diagnosis and prompt treatment using SP until the end of 2005 (MOVBD; THB). How ever, mentioned elsewhere above this component of the CBMCP has already started to be compromised. Nevertheless, the CHWs are still active in promoting distribution and proper use of ITNs,

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8 Data base, MOVBD dept, Tigray health bureau, Mekelle, Tigray.
mobilize people for EMVC and promote health education at their respective kushet. The district has shifted from IRS to ITNs in the mid of 2005.

Morbidity due to malaria constitutes a large part of the burden of disease in the district. For instance, in 2002/03 excluding the CHW service, malaria was not only the leading cause of morbidity but also accounted for 23.52% of all out patients. This figure may underestimate the actual level, as health services coverage is low and health seeking behaviour poor (THB, 2002/03). According to the database, department for the control of MOVBD, Tigray health bureau, the annual CHWs malaria treated cases of the district has grown from 14,993 (2002/03) to 25,395 (2003/04). Unfortunately there is no data on admission and case fatality as the district did not have inpatient service until early 2005. The last consecutive two years epidemic was regular. It is a one season transmission district after the big rains.

The reasons for selecting this district for the purpose of the study are mainly four. Firstly, it is one of the districts with great burden of malaria. Secondly, in recent years the district has been attacked by frequent malaria epidemics and drought. Thirdly, in most cases surveys and operational field studies had been focused on southern and western parts. Fourthly, it is epidemiological representative of a number of districts in the region and the country.
4.2.3. STUDY SUBJECTS AND STUDY DESIGN

The study setting will be a routine health service delivery. The study subjects are all suspected malaria cases\(^9\). Each study site team will comprise three health workers; two HEWs, from the specific health post, and a malaria microscopist. One of the HEWs, who work in the out patient department (OPD), will identify those suspected clinical malaria patients (history of fever is modified to 72 hours) and make clinical examination. According to the guideline the inclusion criteria will be;

- All age groups excluding pregnant mothers and children under 5Kg or three months old; (referral)
- Patients who had not been treated for \textit{P. falciparum} malaria in the last two weeks.

All the cases from the OPD will go to the second HEW and the microscopist to give blood for paracheck pf\(^6\) test and blood film (BF).

Since the measurement of performance of both alternative diagnoses is dependent on the microscope reading and quality of BF, microscopist will be assigned to prepare BF. The two HEWs in each post will turn their role of making clinical examination and paracheck pf\(^6\) test each other when half of the subjects allocated to the health post are recruited and this increases the number of HEWs who participating in the clinical diagnosis performance evaluation.

Every patient will be coded with a study number which will be equivalent to the institution code/patient number. This number should appear in all patient formats and in every slide and paracheck pf\(^6\). For example, the study number for a patient who enrolled in Arena health post which has a code of 21401 as 101\(^{st}\) is $= 21401/101$

Ethical clearance will be requested from the regional health bureau research ethical committee. Subjects or their families will be informed about the study and consent will be collected.

\(^9\) In a malarious area, it is a patient with fever or history of fever within the past two days (72 hours), whereas in a non-malarious area, a patient with fever or history of fever within the past two days and a history of travel to malarious area within the last two weeks with no any other identifiable cause of fever.
Since malaria is focal, varying from place to place and season to season, the cost incurred and the performance of the diagnoses of both clinical and RDT also vary from one to another setting and among health workers. In order to capture these variations the study will be stratified into the three strata and two transmission seasons.

Equal number of subjects, 33% of the total, will be recruited at each stratum. Among the health posts, one is located in stratum III, twelve are in stratum II (excluding the town) and five are in stratum I. To facilitate the evaluation of the clinical performance among sufficient number of health workers ten health post will be selected. All subjects in stratum III will be allocated only to one health post (the only existing at this stratum) while those in stratum II will be equally allocated to a randomly selected five (out of 12) health post and those in stratum I will be allocated equally to the four (out of 5) health post.

4.2.4. SAMPLE SIZE DETERMINATION

In order to capture both concerns of clinical and paracheck pf test® performance we use a common denominator, crude parasite rate of the district, to calculate sufficient sample size that could help us to draw a conclusion for both alternatives. The crude parasite rate in OPD during September-November is almost 35% with 60% of *p. falciparum*. The sample size will be then calculated using the formula;

\[
n = \frac{z^2pq \ast \text{DEEF}}{d^2}, \text{ Where,}
\]

- \(n\) = Sample size
- \(p\) = crude malaria parasite rate.
- \(q\) = \((1-p)\)
- \(\text{DEEF}\) = Design effect
- \(d\) = Degree of precision (the true value falls between lower and upper estimate)
- \(\alpha\) = acceptable margin of error- \(Z\) at 95% CI is 1.96
Therefore at 95% of confidence level with an absolute precision of five percentage (40-30%), and design effect of three (commonly used), the sample size is equal to \( n = Z^2 \times (P) \times (100-P) \times DEEF/d^2 \) which equal to \((1.96)^2 \times (35) \times (100-35) \times 3/5^2 \approx 1050\). In March-May the parasite rate decreases to 25% (30-20%), with increasing in \( P.vivax \) proportion and therefore, the sample size for this season will reduce to 865. Accordingly, in each stratum 350 and 289 cases will be enrolled in major and minor transmission, respectively.

Figure 6. Flow charts of malaria diagnosis and treatment where no microscope exists\(^{10}\).

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**Box 1.**
- Patient with fever or history of fever in the last 24 hours and lives in malarious area or has history of fever travel to malarious areas with in the last 15 days with out any other obvious fever cause.
- CQ= chloroquine
- Coartem is not recommended for children under 5 and pregnant women, and hence immediate referral.
- Treatment in referral case is to help the patient until he/she reaches referral site.

\(^{10}\) Adopted from the National malaria diagnosis and treatment guide line, Ministry of health Ethiopia, 2004.
4.2.5. CLINICAL DIAGNOSIS, PARACHECK PF TEST AND CASE MANAGEMENT

Baseline data of the subjects on demographics and clinical information including weight, axillary temperature, signs and symptoms related to current illness, chief complaint, and previous antimalarial intake within the past two weeks, duration of illness in days etc will be recorded using Annex 4, page 1 during the clinical examination and the outcomes in Annex 4, page 2.

Every subject will have a finger pricked blood sample for both paracheck pf® and a BF (thick and thin film) tests. Both tests will be done from one finger prick and BF will be taken after the paracheck pf® test is being set. The cassette should be labeled in permanent ink with the patient number; date, exact hour and minute of applying the test, and its result (Annex 2b). Test will be done strictly following the product instruction in Annex 3 (WHO, Job-Aid), read only within the time limit 15-20 minutes, and interpreted with out reference to the patient’s history. Test result including its intensity compared to the control line will be recorded in Annex 6.

A test will be considered valid if only the internal control line, red or pink appears. For each test, the test line intensity, which is dependent on parasite concentration, will be compared to the control line and will be graded using a 0 to 4 scales as follows;

- 0, negative, no test line;
- +1, positive test line, very faint but present;
- +2, positive test line, lighter than the control line, yet easily readable;
- +3, positive, strong test line, equal to the control line
- +4, positive, strong test line, more intense than the control line

If, a sample from a suspected case is with no control line or can’t be read clearly as negative or positive the test needs to repeated with a new test device since in most cases this happens due to insufficient specimen volume or incorrect procedural techniques. Such tests will be recorded differently.

Treatment will be guided by the national malaria diagnosis and treatment guideline following the decision chart in Figure 6. According to the decision tree a paracheck pf®
positive patient will be treated with a six dose regimen of Coartem®, shown in Annex 1a, according regimen in Annex 1c. Attention should be given to negative results as the test doesn’t detect malaria other than *P. falciparum*. A history of fever with no features of other severe diseases and the absence of an alternative explanation for the fever has been recommended to judge as malaria illness. In such case chloroquine is available and will be prescribed according to Annex 1d. In case of vomiting full dose will be repeated. The possibility of concomitant non malarial illness in positive results should also be considered. A full assessment of the patient is always needed.

4.2.6. THE GOLDEN STANDARD: MICROSCOPY REFERENCE

The recommended method and current gold standard used for the routine laboratory diagnosis of malaria is the microscopic examination of giemsa stained thin and thick BF. In this study three blinded qualified and experienced microscopists, one from district, another from the MOVBD and a third from regional laboratory will take the golden standard position and proceed according the ‘*WHO basic malaria microscopy guide*’.

Two slides, designate slide ‘A’ and its replicate slide ‘B’ will be prepared for each subject, each having both a thick and a thin blood smear. The paracheck pf® with its recording format (Annex 6) and the BFs will be sent to the district within 3-days. Care will be taken to avoid auto fixation and damage due to different hazards. Blood films should be dried evenly, protected from flies and dusts and stored front to back in the slide box.

The first two microscopists, will examine slide ‘A’ after (stained with Giemsa 3%) independently using X1000 (100 x oil-immersion objectives and a 10x ocular lens). The independent readings of slide ‘A’ will be compared for concordance in three areas: (i) agreement about the presence of asexual forms of *Plasmodium*, (ii) agreement about the species of *Plasmodium* if present, and (iii) agreement on the calculated level of parasitaemia. Parasitaemia will agree if the difference between them is within two fold. When all three conditions for concordance are met, the mean parasitemia value from the two independent readings will be recorded as the “true” parasite density.
When the results of both microscopists are discordant (discrepant) for any of the three criteria cited, the third senior microscopist, who has experience in research settings and quality control, will examine slides ‘A’ and its replicate ‘B’ following the same procedure of both microscopists. The cumulative findings of the third microscopist for the discordant readings will be then considered the “true” diagnostic outcome for the sample. Randomly 10% of the slides from both positive and negative results will be cross-checked for their congruence.

Negative will be declared after 200 microscopic fields read without finding a parasite. If a sample is found to be positive, the number of asexual parasites will be counted to determine the density against 200 or 500 white blood cells (WBC)⁴. In case of a positive slide with difficulty of species identification and parasite counting because of more numerous parasites than WBC, the counting will be done against 5000 RBC in the thin BF. Parasitaemia will be recorded per µL blood, assuming an average of 8000 WBC/ µL or 500,000 RBC/ µL (Wongsrichanalai et al., 1999).

The replicate slide ‘B’, besides validating discordant between first and second microscopist, it is also helpful if any damage in its pair. After reading slides need to be cleaned using toluene; packed in its previous pattern and stored properly for any doubt.

4.2.7. STANDARDIZATION AND QUALITY ASSURANCE
There are common ways in which qualities can be improved; training, equipment supervision and blinding.

Prior to the study, all HEWs will attend a theoretical training and practical exercise of how to perform paracheck pf® test, accurate filling of the record formats, and demonstrate proficiency in practice under supervision at a health centre. No refresher training on malaria clinical algorithm and no need of explaining the purpose of the study so as to measure the actual existing capacity in place. Emphasis will be given to follow a safe

⁴ If, after 200 WBCs, 10 or more asexual parasites are counting, then the total number of asexual parasites will be recorded. If parasites are fewer than 10 per 200 WBCs, then the microscopists will continue to examine the smear, counting asexual parasites and WBCs, until at least 500 WBCs counted.
code of practice when collecting and handling blood samples and disposing of contaminated materials. A special orientation focusing on the objective, procedures of the study and their responsibilities i.e. do’s and do not’s, will also given for the microscopists and the regional supervisor.

Supply quality is another issue. All microscopists are using identical microscope optics, clean and good quality slides (frosted). Giemsa stain quality is a very decisive element. Therefore, effort will be done to make available a certified product which will be tested prior the field work.

A supervisor will be assigned with term of reference including; monitoring the procedure, ensuring resource supply and quality in all study sites. He will be also in charge to take appropriate remedy actions if necessary. The microscopist, besides BF preparation is also responsible for tracking the changes in temperature, humidity and other factors (Annex-8), collecting used paracheck pf® including their results, and case recording forms on daily basis. Information on paracheck pf® storing will be collected from stores at different level; national, regional and district.

Blinding will be another concern. The clinical diagnosis is completely blind to the test result. The paracheck pf® test will also done without reference to the patient’s history and clinical information. All the microscopists will also be unaware of the clinical findings and paracheck pf® test results and also blind to each other.

Transportation of BFs and paracheck pf® devices from the field is also an important quality issue. Blood films will be wrapped in different packs by groups of ten, in the serial order that they are listed on the report form (Annex 6). The outside of each wrapped pack will be labelled with the study numbers of the first and last in the pack.

4.2.8. DATA MANAGEMENT AND VALIDATION
Format and questionnaires (in annexes) will be tested in pilot study to assess the capacity of capturing all necessary data. Then, they will transfer and coded to a database software
Epi-Info version 6.04 packages (Centers for Diseases Control, Atlanta, GA). The coding will be done in a way of avoiding unnecessary mistakes during the data entry (for example, nobody should have 31 February as a date of diagnosis). Data will be entered in duplicate and finally cross-checked. Once the data have entered, further cleaning to ensure that all data are valid and to look for any internal inconsistencies (such as a date of treatment being earlier than the subject's date of birth) and agreement between both data entry will be compulsory. In case of error all source documents including the labeling in the test cassette will be checked. Statistical analysis should only begin when the data set is as "clean" as possible.

4.3. THE COMPARISON: ANALYSIS AND INTERPRETATION

The analysis and interpretation will be categorized into; calculating performance, calculating costs and calculating diagnosis and treatment cost savings.

4.3.1. CALCULATING PERFORMANCE

Performance capacity of the alternative diagnostic approaches will be calculated vis-à-vis light microscopy as the gold standard.

Paracheck pf® does not able to detect malaria other than *P. falciparum*, hence its performance will be calculated only with the denominator of microscopic *P. falciparum* (*asexual ± sexual*) in the absence or presence of *P.vivax* (*asexual ± sexual*), i.e. *P.f ± P.v*. Whereas in case of the clinical diagnosis the denominator will be all confirmed malaria types regardless their species (*asexual ± sexual*). Mixed infections with *P. vivax* and *P. falciparum* will be are treated as *P. falciparum* infections for the purpose of analysis.

Performance capacity can be expressed through the descriptive statistics; sensitivity\(^{11}\), specificity\(^{12}\), positive\(^{13}\) and negative\(^{14}\) predictive values, accuracy rate\(^{15}\) at 95 % CI.

\(^{11}\) Sensitivity: The probability that an individual which is diseased is indeed tested as diseased as compared to “gold standard”.
\(^{12}\) Specificity: The probability that an individual which is not diseased is tested as not diseased as compared to “gold standard”.
\(^{13}\) PPV: The probability that a person is infected when a positive test result is observed.
\(^{14}\) NPV: The probability that a person is not infected when a negative test result is observed.
Briefly, sensitivity will be calculate as $TP/ (TP + FN)$, specificity as $TN/ (TN + FP)$, positive predictive value (PPV) as $TP/ (TP + FP)$, negative predictive value (NPV) as $TN/ (TN + FN)$, and accuracy as $(TP + TN)/\text{number of all tests}$, where $TP =$ true positive, $FN =$ false negative, $TN =$ true negative, and $FP =$ false positive. True positive is a suspected case with a microscope confirmed positive result and true negative is a confirmed negative. False positive and false negatives are suspected cases but with negative and positive confirmed results, respectively.

In connection to the performance evaluation other important results from the study will be explored. Crude and species specific slide positivity rate (prevalence of parasitaemia among febrile patients) will be determined. This is a helpful indicator for resource allocation and planning. False positives of the test due to gametocyte (not due to persistence of antigen since microscope does not allow this) will also be considered. It should be noted that both, gametocyte and persistence HRP II do neither cause illness nor require treatment with blood schizontocidal drugs. This ‘limitation’ of the test has economical implications and will be assessed.

Furthermore, the number of test negative patient shows the magnitude of management dilemma. Therefore, the result may open a room for discussion regarding a combination test that detects both species and non malaria cases.

In addition, $\chi^2$-test for trend and correlation will be used to analyze;

(i) If there is a positive correlation between sensitivity and specificity of both, the test and clinical examination with parasitemia level (not only small but also high) and patient age.

(ii) An association between the most common chief complaints with the type of malaria (Annex-4 part I).

(iii) If there is any variation in the paracheck pf test performance with temperature and humidity change (Annex 5)

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15 Accuracy: The number and proportions of all the observation which are classified correctly by the test. (Source: [http://home.clara.net/sisa/diaghlp.htm](http://home.clara.net/sisa/diaghlp.htm))
(iv) The dependency of test line strength in parasite density and to determine which score is best. The mean, the 25th and 75th percentile parasite density for each score will be calculated. We will also look how much (proportion) from each score are positive with microscope.

(v) If clinical examination sensitivity is dependent on the type of malaria and strata.

4.3.2. CALCULATING COSTS

Costing will be undertaken from the provider’s perspective at periphery health facilities. In such facilities malaria treatment has been free of charge for the last 14 years. It is obvious that the health sector expenditure does not only include the examination and the drug. There are also costs for building, furniture, salary of health personnel, supervision, training, health education, stationery, programme costs at different administrative levels outside the point of delivery of health care to beneficiaries including communication and others. From a practical point of view, these will be assumed to be fixed and similar in both cases and don’t bring any significant cost difference in the comparison of the alternatives. Moreover these costs are integrated with other services.

Therefore, comparison costing is related only with the direct cost of the initial treatment with a first-line drug prescribed and the test used. The cost of test and the drug includes not only the manufacturer’s costs but also transportation, storing, and local taxes. Artemether-lumefantrine is purchased through the negotiated cost price and only procures centrally according a special pricing agreement between WHO and Novartis Parma AG, the manufacturer of the drug, since 2001\(^6\). Paracheck pf\(^{®}\) kit including accessories (lancets, swabs, pipette) will be purchased separately from the manufacture at market price.

Data on cost (storage, taxation, airfreight and insurance) will be extracted from the original procurement document. The local cost of transportation and storage will be also collected from logistic, pharmacy, and finance divisions at the bureau. The accuracy of these data will be verified. Data on this matter will be collected by two independent

\(^{6}\) Novartis provides the drug at cost price (US$ 0.9 up to 2.4 per treatment course) for use in the public sector in malaria-endemic countries. Through the special price agreement WHO and UNICEF procure the drug at the agreed price for governments of malaria-endemic countries.
experts and an average cost of a dose per age-group and per test will be determined. There are four and eight age-groups in Coartem® and chloroquine treatment regimes, respectively. The final costing figures will reviewed by a third person. Data will be entered into software in respect to every treated case and analyzed in terms of both alternatives for different inquiries.

Table 1. Break down of cost of both alternatives and saving in cost.

<table>
<thead>
<tr>
<th></th>
<th>Expenditure cost, Eth. Birr (1US=8.6 birr)</th>
<th>Paracheck pf®</th>
<th>Clinical</th>
<th>Incremental cost</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Actual %</td>
<td>Actual %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1. Total cost of Coartem®</td>
<td></td>
<td>bΣT1 * X1</td>
<td>bΣC*X2</td>
<td>b-a</td>
</tr>
<tr>
<td>Consumed Coartem per age group( 4-groups, see annex 1a )</td>
<td>T1</td>
<td>C</td>
<td>C- T1</td>
<td></td>
</tr>
<tr>
<td>1.1. Manufacturer cost of Coartem®, including tax</td>
<td>b1</td>
<td>B2</td>
<td>B2-b1</td>
<td></td>
</tr>
<tr>
<td>1.2. Insurance, abroad airfreight, inland transport and store</td>
<td>c1</td>
<td>C2</td>
<td>C2-c1</td>
<td></td>
</tr>
<tr>
<td>1.3. UNICEF 6% service charge (Coartem is procured only through WHO or UNICEF)</td>
<td>d1</td>
<td>D2</td>
<td>D2-d1</td>
<td></td>
</tr>
<tr>
<td>Average cost per dose per age group</td>
<td>X1</td>
<td>X2</td>
<td>X1</td>
<td></td>
</tr>
<tr>
<td>2. Total cost of Chloroquine</td>
<td>ΣT2 * W</td>
<td>-</td>
<td>-ΣT2 * W</td>
<td></td>
</tr>
<tr>
<td>Consumed chloroquine per age group( 8-groups, see annex 1d )</td>
<td>T2</td>
<td>T2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.1. Chloroquine cost (local produced)</td>
<td>f1</td>
<td>-</td>
<td>-f1</td>
<td></td>
</tr>
<tr>
<td>2.2. Transport, store cost</td>
<td>g1</td>
<td>-</td>
<td>-g1</td>
<td></td>
</tr>
<tr>
<td>Average cost per dose per age group</td>
<td>W1</td>
<td>-</td>
<td>-W1</td>
<td></td>
</tr>
<tr>
<td>3. Total paracheck pf® test cost = 3.1+3.2+3.3</td>
<td>C*V</td>
<td>-</td>
<td>-C*V</td>
<td></td>
</tr>
<tr>
<td>Number of test kit used</td>
<td>C</td>
<td>-</td>
<td>-C</td>
<td></td>
</tr>
<tr>
<td>3.1. Manufacturer cost of paracheck pf® kit including tax</td>
<td>h1</td>
<td>-</td>
<td>-h1</td>
<td></td>
</tr>
<tr>
<td>3.2. Insurance, abroad airfreight, inland transport and store</td>
<td>j1</td>
<td>-</td>
<td>-j1</td>
<td></td>
</tr>
<tr>
<td>3.3. Gloves cost (locally produced)</td>
<td>k1</td>
<td>-</td>
<td>-k1</td>
<td></td>
</tr>
<tr>
<td>3.4. Transport, store cost</td>
<td>l1</td>
<td>-</td>
<td>-l1</td>
<td></td>
</tr>
<tr>
<td>Average cost per test</td>
<td>V</td>
<td>-</td>
<td>-V</td>
<td></td>
</tr>
<tr>
<td>4. others (average cost per case)</td>
<td>m1</td>
<td>m2</td>
<td>-(m2- m1)</td>
<td></td>
</tr>
<tr>
<td>Grand Total = (1+2+3+4)</td>
<td>Y1</td>
<td>Y2</td>
<td>-Y3</td>
<td></td>
</tr>
<tr>
<td>Save</td>
<td>Y2-Y1=Y3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

17 Dose and cost is increasing with age group, annex 1
In a previous section, we recommended to repeat a test with a new device if a sample from suspected case can’t be read clearly as negative or positive. This invalid test result has also to do with technical and economical implications and will be assed.

4.3.3. CALCULATING COST SAVINGS

From practical point of view, calculating cost saving will be done as shown in table 1. The estimation is based on the current Coartem® cost and anticipated use of diagnostic tests and anti-malarial therapies, Coartem® and chloroquine.

But, the question is, does the total cost for the paracheck pf test alternative outweighs the total cost of the present clinical diagnosis alternatives? As it is shown in Figure 6 all those diagnosed as suspected clinical malaria, (C), get Coartem®. Whereas in case of paracheck pf test® they all consume test cost (B plus repeated test ) and eventually divided into two groups; those positive for P. falciparum (T_1) and those negative but the health worker might believe the later cases are malaria other than P. falciparum. The number of the later will be calculated by subtracting the P.falciparum cases of the test from the total clinical malaria, C-T_1=T_2.

To calculate the gross cost we will use both figure 6 and table 1. In case of the clinical examination we simply multiple the clinical cases (Figure 6) in each age-group with its respective average cost (table 1) of Coartem® while in case of the test we need to sum up three different costs.; Cost of paracheck pf® corresponding to the total number of clinical malaria cases plus repeated tests , cost of Coartem® which is a product of positive cases in each age-group with its respective average cost of a dose, and the cost of chloroquine which is again the product of each age-group of non P. falciparum cases and the average cost of a dose. Finally the difference of the gross cost between the alternatives give us the cost saving.

Furthermore, as malaria cost varies among seasons, epidemiological strata and age groups, we will asses the role of paracheck pf® in reducing the consumption of Coartem®
(cost) at different situation. This help to apply paracheck pf® pf tests selectively to achieve highest value for money.

4.4.5. SENSITIVITY TEST AND UNCERTAINTY ANALYSES

It is often useful to report uncertainty around key parameters. For a decision-maker, the most important information is whether the results are robust to all possible sources of uncertainty around key parameters as a way of helping them to understand the sources of the overall uncertainty.

There is considerable uncertainty over the values of many of the key parameters of cost and performance variables, because true parameter values are varies with different scenario. This type of uncertainty is commonly handled by using point estimates for each variable, and then conducting a sensitivity analysis by varying these estimates to test the robustness of the conclusions of the analysis. This can take the form of a one-way sensitivity analysis, where one variable is varied at a time; multi-way sensitivity analysis, where several variables are varied together; or a max-min analysis, where all variables are given their extreme “optimistic” and “pessimistic” values to elicit a best and worst case scenario.

To see how the cost effectiveness varies with uncertainty we will do sensitivity test with certain key parameters.

1. Gloves are very important in protection of the HEWs from being contaminated. After certain time when the HEWs become experienced, improving techniques of pricking and taking blood, there is a possibility of withdrawing this item and reducing the cost.
2. It is also likely that with time the HEWs will improve their capacity of ruling out other febrile illnesses and improve their specificity. Therefore, we will try to make sensitivity analysis at 5% and 10% improvement of specificity.
3. Since Coartem® is delivered at cost price we only expect the cost reduction of paracheck pf®. Therefore we will do sensitivity test at 15 and 25% cost reduction.
4. Since the HEWs are aware that blood test is performing, their routine experience seems to be affected. This may lead to over or under clinical diagnosis according the health
worker personal ability and psychology make up. In order to catch this variation we will do 3% and 5% over and under clinical diagnosis sensitivity test.

5. METHODOLOGY CONSIDERATION

In our study few points deserve to be clear. First, the calculation of cost saving is limited to be a function of the specificity or PPV. It is also noteworthy that a test with good true specificity but low sensitivity is obvious seems ‘saving’ more antimalarial drugs at the spot. Sensitivity is a more serious issue, since false-negative results lead to other provider and patient cost and non treated malaria is potentially fatal.

Second, practically health sector cost saving due to the best alternative is not limited only to diagnosis and drug. In the absence of the interventions the work load is numerous and a numbers of cases may also develop complication and go through intensive treatment incurring additional cost and even death. For simplicity such expenses are excluding in our costing.

Third, the calculated cost in these comparative diagnostic approaches do not consider costs other than drug and the test

Therefore, our cost calculation does not show the actual unit net cost per benefit which would be definitely lower. Nevertheless, our objective of improving technical efficiency will not be compromised by the above limitations.

However, there is one major issue that can make difference. From theoretically point of view it is believed that RDTs improves compliance and treatment-seeking behavior. This in turn, improves cure rate and reduces transmission. It is also believed that treating ‘true cases’ decrease drug pressure by avoiding over treatment. If this holds true the epidemiological and economical advantage of RDT increases by far. These need prove and leads to a further research.
<table>
<thead>
<tr>
<th>No</th>
<th>Task</th>
<th>Activities</th>
<th>Activity Site</th>
<th>Focal Person</th>
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<th>Sep-07</th>
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<th>Dec-07</th>
<th>Feb-08</th>
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<tr>
<td>1</td>
<td>Preparatory</td>
<td>Ensuring study supplies</td>
<td>Region</td>
<td>Researcher</td>
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<td>Selection of health posts</td>
<td>District</td>
<td>Researcher</td>
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<td>Preparation of operational manual and reporting forms</td>
<td>Region</td>
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<td>2</td>
<td>Training</td>
<td>Training of health workers on the use of paracheck pf test</td>
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<td>Reading blood films</td>
<td>Health posts</td>
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<td>Data technicians</td>
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<td>Region</td>
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</tbody>
</table>
References


Annex 1a) Public sector: as long as Coartem® is commercially produced or distributed, Novartis will make it available to WHO at cost (product) price (ex-Basel):

Annex 1b) Private sector
**Annex 1c). Regimen of Artemether Lumefantrine**, a tablet containing 20 mg Artemether and 120 mg Lumefantrine per dose\(^9\).

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Age (years)</th>
<th>Number of tablets per dose Twice daily for 3 days</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Day 1 morning</td>
</tr>
<tr>
<td>5-14</td>
<td>3 months-2 years</td>
<td>1</td>
</tr>
<tr>
<td>15-24</td>
<td>3-7 years</td>
<td>2</td>
</tr>
<tr>
<td>25-34</td>
<td>8-10 years</td>
<td>3</td>
</tr>
<tr>
<td>35+</td>
<td>11+ years</td>
<td>4</td>
</tr>
</tbody>
</table>

**Annex 1d). Regime of Chloroquine.** Tablets of 150 mg base or syrup of 50 mg base per 5 ml. Total dosage of 25 mg per kg over 3 days (10 mg base per kg on days 1 and 2, 5 mg base per kg on day 3\(^9\)).

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>Age (years)</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 – 6</td>
<td>&lt;4 months Tablets Syrup</td>
<td>1/2 5 ml</td>
<td>1/4 5 ml</td>
<td>1/4 2.5 ml</td>
</tr>
<tr>
<td>7 – 10</td>
<td>4 – 11 months Tablets Syrup</td>
<td>1/2 7.5 ml</td>
<td>1/2 7.5 ml</td>
<td>1/2 5 ml</td>
</tr>
<tr>
<td>11 – 14</td>
<td>1 – 2 years Tablets Syrup</td>
<td>1 12.5 ml</td>
<td>1 12.5 ml</td>
<td>1/2 7.5 ml</td>
</tr>
<tr>
<td>15 – 18</td>
<td>3 – 4 years Tablets Syrup</td>
<td>1 15 ml</td>
<td>1 15 ml</td>
<td>1 15 ml</td>
</tr>
<tr>
<td>19 – 24</td>
<td>5 – 7 years Tablets Syrup</td>
<td>1 1/2 20 ml</td>
<td>1 1/2 20 ml</td>
<td>1 15 ml</td>
</tr>
<tr>
<td>25 – 35</td>
<td>8 – 10 years</td>
<td>2 ½ 20 ml</td>
<td>2 ½ 20 ml</td>
<td>1 15 ml</td>
</tr>
<tr>
<td>36 – 50</td>
<td>11 – 13 years</td>
<td>3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>50+</td>
<td>14+ years</td>
<td>4</td>
<td>4</td>
<td>2</td>
</tr>
</tbody>
</table>
Annex-2a: Paracheck pf Rapid One Step device for P. falciparum specific HRP 2 antigen in whole blood, Orchid Biomedical Systems (“cassette format”)  

QAP/WHO Field Report, Developing and Testing an RDT Job Aid

Annex-2b. Parts of a paracheck pf cassette and labeling.

18 http://www.wpro.who.int/rdt/link11.cfm, www.wpro.who.int/QAP, 2004
Annex 3: Materials and procedures for Paracheck pf® Test:
http://www.wpro.who.int/rdt/link11.cfm

Generic instructions for malaria rapid test cassette. Modify for specific product:

1. FIRST, read carefully the instructions on how to use the malaria test kit.
2. Next, open the package and look for the following:
   1) Desiccant
   2) Device
   3) Tube
3. Next, look at the expiry date at the back of the package. Use another package if expiry date has passed.
4. Collect:
   1) Alcohol
   2) Cotton
   3) Lancet
   4) Buffer
   5) Timer
5. Clean the patient's finger. The alcohol MUST be dry before pricking, or test may not work.
6. Prick the patient's finger to get just a very small amount of blood.
7. Barely touch the tip of the tube to the blood.
8. Immediately touch the tip of the tube with blood on the square hole marked “A”.
9. Put six (6) drops of buffer into the round hole marked “B”.
10. Read results exactly fifteen (15) minutes after adding buffer. Do not read the results before fifteen (15) minutes. Reading too early or too late can give false results.
11. HOW TO READ:
    - NEGATIVE (no falciparum malaria) - one pink line in window “C” at left.
    - POSITIVE (has falciparum) - one pink line in window “C” at left and one pink line in window “T” at right. It is positive even if second line is weak.
    - NO RESULT - no pink line in “C” or “T”. Repeat with new package.

Use new package and lancet for each patient.
Further information: www.wpro.who.int
Email: mal-rlt@wpro.who.int
WHO, QAP 2004
Annex 4: Patient history and clinical finding record form

Part I: Personal record

1. Health institution code……………………………………. 2. Date (dd/mm/yy) _____/____/____
3. Study (patient) number¹⁹ = HI code/ serial no. _____/____/____
4. Age of patient........................................ 5. Body temperature (Degree Celsius)......................
6. Sex of patient 1=male 2=female
7. Address; Tabia…………………………………….. Kushet…………………………
8. Duration of illness in DAYS (Since off set of fever) ....................................................................
9. Symptoms since the onset of fever (fill the table)......................................................................

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Yes</th>
<th>No</th>
<th>Don’t know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fever</td>
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<tr>
<td>Shivering</td>
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<tr>
<td>chills</td>
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<tr>
<td>sweating</td>
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<tr>
<td>Head ache</td>
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<tr>
<td>Vomiting</td>
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<td>Joint/back ache</td>
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<tr>
<td>Appetite loss</td>
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<tr>
<td>others</td>
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</table>

¹⁹ Coincide with slide or Paracheck pf number
Annex-5 Basic information on Paracheck pf® kits

Part I: Record before the study begins:

A. General description of Paracheck pf® kits used:

1. Manufacturer’s name and site (company name): ----------------------------------------
2. Manufacturing site (company site): --------------------------------------------------------
3. Batch number of the kit: --------------------------------------------------------------------
4. Date of manufacture: Month----------/Year---------------
5. Date of expiry: Month----------/Year---------------
7. Packaging type: 1. Packed individually-------- 2. Other (List) ---------------------------
   Inclusion to perform the test, consists,

B. Storing at different level

1.1. Duration of storage (days): ------------ 1.2. Temperature at storage: (°C) ------------
1.3. Humidity at storage --------------------- 1.4. Stored away from sunlight----------------

C. Technical matters

1. Readers are (is):
   1. One  2. multiple readers
2. Blood extraction: 1. Venous  2. Capillary
3. Blood transfer to strip:
   1. Using device provided by manufacturer 1. Yes 2. No
   2. If No, list what then-----------------------------------------------------------------
   3. Time taken to obtain reading per manufacturer guidelines (minutes), ------------
4. Result recording was applied on:
   4.2. Control window: 1. Yes 2. No
   4.1. Test window: 1. Yes 2. No
   4.3. Intensity: 1. Yes 2. No
Annex-5, Part II: Record at study site

A. For each study site (health post)
1. Local malaria situation:  1. Low  2. medium  3. High

B. For each test
1. Test number

2. Description of previous storage /transport conditions since manufacture:
2.1 State of packaging, if RDTs is damaged

3. Climatic conditions:
   3.1. Maximum local room temperature (°C):
   3.2. Maximum local room humidity:
   3.3. Workplace conditions:
      3.3.1. Facility was available:  1. Yes  2. No  3. Partial
      3.3.1. Enough lighting available for reading RDTs:  1. Yes  2. No

4. Description of technique used:
4.1. Time of strip package opening to time of use (minute):
4.2. Any significant/recurrent problems encountered in kit preparation including:
   4.2.1. Opening of packaging  1. Yes  2. No
   4.2.2. Obtaining blood  1. Yes  2. No
   4.2.3. Others (list)

4.3. Any variation from the exact RDT preparation technique detailed in the manufacturers insert.

4.4 other r comments

------------------------------------------------------------------------------------------------------------------
Annex 6: Paracheck pf® result registration form.

<table>
<thead>
<tr>
<th>Date (dd/mm/yy)</th>
<th>Patient name</th>
<th>Age (Mon Year)</th>
<th>Study number (slide or paracheck pf)</th>
<th>paracheck pf result</th>
<th>Anti malarial drugs given in tablet (CoA, CQ, PQ)</th>
<th>Referral</th>
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Name of Health worker _____________________________ signature________________ date_______/____/200___

20 The test result will be scored as 0 if no line is seen, 1 if a faint test line is visible, 2 if the test line is clear but its intensity was less than that of the control line, 3 if the test line intensity is equal to that of the control line, and 4 if it was greater than the intensity of the control line. If no control line discards.
## Annex 7: Microscope result recording form

<table>
<thead>
<tr>
<th>Date</th>
<th>Slide Number</th>
<th>Density of parasite[^1] per 200 or 500 WBCs</th>
<th>Comment(s) on slide quality</th>
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</thead>
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<tr>
<td></td>
<td></td>
<td>Pf Asexual</td>
<td>Pf Gametocyte</td>
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</table>

**Remark:** Write the result as follows: N=negative, PF= P.faliparum, Fg= PF gametocyte, F+g=PF and Fg, PV= P.vivax, & PP+PV= Fill all space provide

[^1]: Parasites per microliter = \( \frac{\text{Number of parasites} \times 8,000}{\text{Number of WBC’s}} \)