

**THE PREVALENCE OF MALARIA IN
MEFLOQUINE HYDROCHLORIDE - MEFLIAM®
USERS DURING THE DEPLOYMENT OF
MILITARY FORCES IN BURUNDI, EAST
AFRICA**

By

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DECLARATION

I, Eldrian Basson, declare that this study: *The prevalence of malaria in Mefloquine Hydrochloride-Mefliam® users during the deployment of military forces in Burundi, East Africa*, represents my original work and has not been submitted for any degree or diploma to any tertiary institution, including universities. Where references have been made and quoted, they are duly acknowledged in the text.

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Date

ABSTRACT

Malaria and the mosquito that induces the disease in humans have hounded the military for decades. Malaria represents one of the most important infectious disease threats to deployed military forces. Malaria in soldiers has a serious economic impact, both in terms of lost productivity and treatment cost for the state. A contingent of South African National Defence Force members has been deployed in Burundi since November 2001, as part of a peacekeeping mission. At the time of the study no information was available regarding the prevalence of malaria among military personnel during deployments in Burundi and East Africa.

In Africa, the saying is that malaria is the disease of poverty and a cause of poverty. To combat malaria, it is of vital importance that the recommended medication be taken exactly as prescribed and that the course is completed. However, one of the greatest challenges facing the African continent in the present fight against malaria is drug resistance. The discovery of *Mefloquine* and the subsequent development of suitable drugs, have been intimately associated with military imperatives, contingencies and requirements. Since World War II, the development of *Chloroquine*-resistant *falciparum* malaria has driven the search for new drugs. *Mefloquine*, developed by the Walter Reed Army Institute of Research in the United States, was first shown effective as a prophylaxis and treatment of resistant *falciparum* malaria in the 1970's.

To obtain data, questionnaires were administered to SANDF soldiers deployed in Burundi, East Africa. The total size of the population under investigation was 336 with a final sample size of 111 respondents. The sample was selected by using simple random sampling. The questionnaire aimed to determine the perception of respondents regarding the malaria threat, their compliance with taking the medication, and their experiencing of possible side-effects which might occur due to the chemoprophylaxis and the prophylactic efficacy of Mefliam®.

The fact that, of the 111 people who used Mefliam®, only four presented with any malaria symptoms, is an indicator that Mefliam® is an effective option as an antimalarial drug to be used in East Africa and Burundi.

The results of this study will be used by the personnel of the South African National Defence Force (SANDF) and other military forces deployed in East Africa. It is envisaged that the results will be used by military policy- and decision-makers as a control programme and by others involved in the control of malaria. The findings and recommendations should also be of interest to anyone visiting the area

ABSTRAK

Malaria en die muskiet is al dekades lank 'n uitdaging vir die internasionale militêre gemeenskap. Malaria verteenwoordig een van die grootste bedreigings as oordraagbare siekte vir militêre magte tydens ontplooiings. Soldate geïnfekteer met malaria het 'n ernstige ekonomiese impak in terme van verlies in produktiwiteit en mediese kostes vir die onderskeie regerings. 'n Kontingent soldate van die Suid Afrikaanse Nasionale Weermag is sedert November 2001 in Burundi ontplooi, as deel van 'n vredesmissie. Geen inligting aangaande die voorkoms van malaria by militêre personeel tydens ontplooiings in Burundi en Oos-Afrika is beskikbaar nie.

Malaria word as die siekte van armes beskou en terselfder tyd is dit ook die oorsaak van armoede. Dit is van kardinale belang dat die voorgeskrewe medikasie presies gebruik word soos voorgeskryf, en dat die kurses voltooi moet word. Een van die grootste uitdagings, aangaande die bekamping van malaria, is die malaria muskiet se groeiende weerstandigheid teen die antimalaria medikasie. Die ontdekking van *Mefloquine* en die ontwikkeling van anti-malaria medikasies is grootliks deur militêre behoeftes gedryf. Sedert die Tweede Wêreld Oorlog het die weerstandigheid van muskiete teen *Chloroquine* die soeke na nuwe antimalaria medikasie genoodsaak. *Mefloquine*, ontwikkel deur die Walter Reed Navorsings Sentrum in die Verenigde State, het in die 1970's bewys dat dit effektief is vir gebruik as profalaksis en behandeling van weerstandige *falciparum* malaria.

Vraelyste is aan SANW soldate wat in Burundi, Oos Afrika, ontplooi is uitgedeel. Die grootte van die populasie was 336 lede en die finale moniterings groep was 111 individue. Die groep is deur middel van die eenvoudige lukrake metode gekies. Die vraelyste het ten doel gehad om die persepsie van die gebruiker ten opsigte van die malaria bedreiging te toets, die gebruiker se onderworpenheid aan die gereelde gebruik van die medikasie te bepaal, potensiële nuwe effekte wat mag presenteer as gevolg van die gebruik van die chemoprolaksis te identifiseer en die effektiwiteit van Mefliam® te bepaal.

Die feit dat 111 persone Mefliam® gebruik het, en net vier persone malaria simptome getoon het, is 'n goeie aanduiding dat Mefliam® 'n ideale opsie is as antimalaria medikasie in Oos-Afrika en Burundi.

Die resultate van hierdie studie sal beskikbaar wees vir die gebruik van personeel van die Suid Afrikaanse Nasionale Weermag (SANW) en ander magte wat in die toekoms in Burundi, Oos Afrika ontplooi kan word. Die resultate kan deur ander weermagte gebruik word as kontrole programme en deur ander beleidmakers en gesagstrukture in die beheer van malaria. Hierdie inligting sal ook van belang wees vir enige persoon wat die gebied besoek.

This study is dedicated to my late father
who instilled in me my love and passion for
nature and who stimulated my inquisitive mind.

*We must be prepared to meet malaria by training as strict and earnest
as that against enemy troops. We must be as practiced in our weapons
against it as we are with a rifle.*

(Field Marshal Viscount Sir Archibald Wavell)

Quemadmodum vivas, quandiu vivas

As long as you live, keep learning how to live

(Seneca)

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DEFINITION OF TERMS

- Airport malaria:** malaria caused by infected “jet–setting” mosquitoes that travel on international flights and spread the disease (Lusina, 2000:75-76).
- Services:** different divisions within a national defence force, namely Army, Air Force, Navy and Military Health Services (Fourie, 2003:personal communication).
- Chemoprophylaxis:** antimalarial drugs taken orally or intravenously to prevent malaria infection or used as a therapeutic medication to treat the symptoms of the disease, malaria (Maharaj, 2004:personal communication; Barnes, 2005:personal communication).
- Clinical testing:** tests of antimalarial drugs on humans with induced malaria in a controlled environment (Hlolongwane, 2002:personal communication; Maharaj, 2004:personal communication).
- Congenital:** “present, belong to one” (Hornby, 1985:179).
- Essential medicines:** Essential medicines are those drugs that satisfy the priority health care needs of the population. They are selected with due regard to public health relevance, evidence on efficacy and safety and comparative cost-effectiveness. Essential medicines are intended to be available within the context of functioning health systems at all times in adequate amounts, in the appropriate dosage forms and with assured quality and adequate information at a price the individual and the community can afford (ACT: The way forward for treating malaria, 2001:1).

Idiopathic:	disease or condition without a cure (Hlolongwane, 2002: personal communication; Barnes, 2005:personal communication).
Induced malaria:	“malaria acquired through artificial means e.g. blood transfusion or of shared syringes” (Macarthur, Levin, Mungai, Roberts, Bloland, Kachur, Newman, Steketee and Parise, 2001:28).
Monotherapies:	a single drug used as a stand-alone treatment (Hlolongwane:personal communication, 2002; Maharaj: personal communication, 2004).
Paroxysm:	“sudden attack or outburst” (Hornby, 1985:611).
Pathogenesis:	“the production or development of a disease” (Brusher and Joers, 1997:CD ROM).
Prophylaxis:	“preventive treatment of disease” (Hornby, 1985:671).
Relapsing Malaria:	“renewed manifestations (i.e. clinical symptoms and/or parasitemia) of malarial infection that are separated from previous manifestations of the same infection by an interval greater than the usual periodicity of the paroxysms” (MacArthur <i>et al.</i> , 2001:28).
Teratogenicity:	“an agent as a chemical or disease that causes malformation of a fetus” (Brusher and Joers, 1997:CD ROM).

ABBREVIATIONS

ACT:	<i>Artemisinin</i> -based Combination Therapies
DDT:	Dichlorodiphenyltrichloroethane
DEET:	Diethylmetatoluamide
DoD:	Department of Defence
DoD GEIS:	The Global Emerging Infections Surveillance and Response Systems
EPI:	Expanded Programme on Immunisation
EU:	European Union
GIS:	Geographic Information Systems
IDE:	Intervention Development and Implementation Research
ITN:	Insecticide-Treated Nets
MAL:	World Health Organisation Malaria Control Department
MARA:	Mapping Malaria Risk in Africa
MIM:	Multilateral Initiative on Malaria
MIT:	Intermittent treatment with antimalarials
MMV:	Medicines for Malaria Venture (MMV)
MRU:	Medical Research Unit
MR4:	Malaria Research and Reference Reagent Resource Centre
MSF:	Medecins Sans Frontieres
NIAID:	National Institute of Allergy and Infectious Diseases
RBM:	Roll Back Malaria
SANDF:	South African National Defence Force
SCAT:	Sub-Committee for Chemoprophylaxis and Therapy
SN:	The abbreviation for the Latin <i>secundum naturam</i> , which means “According to Nature”
STR:	The Basic and Strategic Research
TB:	Tuberculosis
TDR:	Programme for Research and Training in Tropical Diseases
UNICEF:	United Nations Children’s Fund
US:	United States of America
USAMRU:	United States of America’s Medical Research Unit
WHO:	World Health Organisation

WHOPES: WHO Pesticide Evaluation Scheme
WR: Chemical Compounds that were designed by the WRAIR
®: Registered Brandname of a Product

CHAPTER 1

1. THE PROBLEM AND ITS SETTING

1.1 INTRODUCTION

Malaria-bearing mosquitoes have hounded the military for decades. Some instances were recorded in ancient Macedonia, where Alexander's army was crippled by malaria. In the 12th century malaria was known as "marsh fever" (Borza, 1987:1).

When peacekeeping military forces are deployed, malaria represents one of the principal threats of infectious disease. The majority of military personnel from developed countries are not immune to malaria, and are therefore potentially at risk of being infected and of contracting clinical malaria. This is especially true for forces which are deployed on the African continent in countries with a high endemic status and where drug resistant malaria is widespread (Sanchez, Bendet, Grogl, Lima, Pang, Guimaraes, Guedes, Milhous, Green & Todd, 2000:275). It is estimated that malaria was the major cause of mortality among British troops stationed in West Africa in 1940-1945, accounting for attack rates of 30 to 83 cases per 10 000 members per year (Sanchez *et al.*, 2000:275-276).

Long-term chemoprophylaxis issued to United States soldiers was found to be suboptimal. Long-term chemoprophylaxis with *Mefloquine* (250 mg weekly), or *Doxycycline* (100 mg daily), of United States (US) soldiers deployed to Somalia for "Operation Restore Hope" in 1992-1993, was found to be inferior in a cross section assessment year. In 1993, a total of 48 malaria cases was reported among these soldiers while in Somalia, mostly due to *Plasmodium falciparum*, and an additional 79 cases were detected after the soldiers had returned home (Smart, Heppner, Magill, Gasser & Oster, 1993:889-890).

Long-term chemoprophylaxis has also been found to be only 91% effective among United Nations peacekeeping forces deployed in Cambodia in 1993 (Hopperus Buma, Van Thiel & Lobel, 1996:1506). Alternative agents, such as *Doxycycline* taken daily, *Chloroquine*, or *Proguanil* (200 mg) prophylactics, used among French

soldiers in Gabon and the Central African Republic, have also been found not to be effective (Sanchez *et al.*, 2000:275,277). Failure of *Mefloquine* prophylactics due to poor compliance and/or substandard doses has been documented in Southeast Asia, East Africa, West Africa and more recently in Somalia (Sanchez *et al.*, 2000:275-276). Malaria in soldiers has a serious economic impact in terms of loss due to reduction of productivity and treatment cost for the state (Robert, 2001:67-73).

Since November 2001, a contingent of South African National Defence Force (SANDF) members are deployed in Burundi, as part of a peace keeping mission. This operation is South Africa's contribution to maintain peace in the country during the transition from the Tutsi to the Hutu-ruled democratic government. Burundi is situated in Eastern Africa, three degrees south of the equator. The country's equatorial climate, with its annual rainfall of above 1200 mm, is conducive to the living and breeding of the *Anopheles* mosquito. *Plasmodium falciparum* is the most common mosquito species found in eastern Africa and it is therefore responsible for most malaria infections (Miambu, Ndayiragijje, Le Bas & Chaperon, 1993:399-401).

Data for the study were collected from SA soldiers during their deployment in Burundi from February to July 2002. As the Red Cross and United Nations offices in Bujumbura could provide only limited information regarding the effectiveness of Mefliam® among soldiers in Burundi and eastern Africa, it was deemed of vital importance to conduct this study.

1.2 THE PROBLEM STATEMENT

Mefloquine Hydrochloride- Mefliam® has been used for the treatment of malaria infection amongst military forces deployed in Burundi, East Africa. However, the chemoprophylactic efficacy and usability of this drug have never been determined in that country.

1.3 THE IMPORTANCE OF THE STUDY

The incidence of malaria causes concern in eastern Africa, as well as South Africa and many other areas in the world. Current information on drug-resistant malaria in the tropical and subtropical regions of Africa is limited. Although endemic malaria no longer occurs in many temperate zone countries and well-developed areas of tropical countries in Africa, the disease is still a major cause of ill health in many parts of the tropics and subtropics where socio-economic development is deficient. Current information on foci of drug-resistant malaria in the tropical and subtropical regions of Africa is insufficient and unreliable, and it is therefore necessary to establish the efficacy of *Mefloquine Hydrochloride* (brand name - Mefliam®) as a malaria resistant drug (Gasasira, Dorsey, Nzarubara, Staedke, Nassali, Rosenthal & Kanya, 2003:127-132; Kindermans, 2002:1).

For South African soldiers deployed in a hostile, foreign country, it is important to be combat ready and alert at all times. The working conditions, the location of the area, as well as the living conditions in open canvas tents are conducive to the malaria risk (Sub-Committee for Chemoprophylaxis and Therapy (SCAT) of the Malaria Advisory Committee, 2003:10-14).

Drug resistant malaria has become one of the most important problems in malaria control. In some situations, resistance *in vivo* has been reported for all antimalarial drugs, except for *Artemisinin* and its derivatives. Cross-resistance exists among *Mefloquine*, *Quinine* and *Chloroquine* (World Health Organisation, 1993:18). Multidrug resistance necessitates the use of alternative drugs that may be expensive and difficult to administrate, and may often have side-effects (WHO, 1993:22).

The British Army policy for malaria chemoprophylaxis for military exercises in central Kenya recommended *Chloroquine* 300 mg weekly and *Proguanil* 200 mg daily. This policy was reassessed following seven cases of malaria sustained among 150 soldiers during an exercise in 1992 (Miller, Byers, Whiteoak & Warrell, 1994:119). Although compliance with chemoprophylaxis was not directly assessed, the policy was changed to simplify the regimen to *Mefloquine* 250 mg weekly.

The British Army policy change was interesting, considering the experience of the Dutch military forces, who did not favour *Mefloquine*. Three battalions (\pm 600 troops per battalion) of Dutch marines using *Mefloquine* chemoprophylaxis suffered *falciparum* malaria infections during their deployment in Cambodia during 1992–1993 (Hopperus Buma *et al.*, 1996:1506-1509). Although the Dutch were operating in areas of potential endemic *Mefloquine*-resistant *falciparum* malaria, compliance with medication was only 86%, and 30% of the marines reported adverse side-effects to the drug (Hopperus Buma *et al.*, 1996:1506-1509).

More information regarding the use of *Mefloquine* under military operational conditions arose from military peace keeping operations in East Africa. Between December 1992 and May 1993, 9000 US troops were deployed in Somalia, of which 48 were reported as casualties of malaria (Wallace, Sharp, Smoak, Iriye, Rozmajzl, Thornton, Batchelor, Magill, Lobel, Longer & Burans, 1996:49-55). A risk factor identified was non-compliance with chemoprophylaxis (*Mefloquine*). *Mefloquine* effectiveness in the region was not comprehensive, as five casualties diagnosed with malaria were found to have had suppressive serum *Mefloquine* levels. One year after the commencement of the operation, the US military had 112 cases of imported malaria (Newton, Schnepf, Kennedy, O'Hara, Wallace, Ohl, Oldfield, Sharp, Smoak, Defraites, Magill, Welde, Klamerus & Longfield, 1993:1; Robert, 2001:69-76). During interviews, more than half of these subjects reported compliance with chemoprophylaxis; however, half of the group interviewed had been prescribed inadequate doses of *Mefloquine* (Newton *et al.*, 1993:1; Robert, 2001:70-76).

Members of the Italian military forces operating in Somalia were less infected. The Italian army suffered only 18 casualties from malaria among 1600 soldiers deployed. They used *Chloroquine* 300 mg weekly and *Proguanil* 200 mg daily (Peragallo, Sabatinelli and Majori, Cali & Sarnicola, 1997:343-346). Compared with the British experience in Kenya, these were pleasing results (Miller *et al.*, 1994:119-123). However, the combination of *Chloroquine* with *Proguanil* began to fail the Italian forces, as they sustained 100 malaria casualties in the first three months of 1992 when 4800 peacekeepers were deployed to Mozambique. They responded with a similar change in chemoprophylaxis policy to the British, employing

Mefloquine 250 mg weekly. This contributed to limiting the subsequent malaria casualties to 19 in the last two months of the operation (Peragallo *et al.*, 1997:343-346). A subsequent review of these two operations, collectively involving 5120 Italian soldiers used *Mefloquine* chemoprophylaxis as an anti-malarial drug, found it easier to comply with. It was not associated with a greater discontinuation rate than *Chloroquine* and *Proguanil* chemoprophylaxis (Peragallo, Sabatinelli & Sarnicola, 1999:73-77).

Brazilian peacekeepers deployed in Angola used *Mefloquine* for malaria chemoprophylaxis. Brazilian peacekeepers deployed to Angola for six months in 1995 to 1996 used *Mefloquine* 250 mg weekly for malaria chemoprophylaxis (Sanchez *et al.*, 2000:275,282). Despite this regimen, 78 of the 439 personnel contracted clinical malaria. An investigation was conducted in collaboration with US military health investigators. The conclusion was that a more updated, more effective chemoprophylactic agent was required for military forces, despite the finding that poor and erratic compliance was the major risk factor for contracting malaria (Ohr, Richie, Widjaja, Shanks, Fitriadi, Fryauff, Handschin, Tang, Sandjaja, Tjitra, Hadiarso, Watt & Wignall, 1997:963-965). Results of a study in that regard would be used as a guideline in planning malaria management for future military forces.

This begged the question whether a more efficacious chemoprophylactic drug for the prevention of malaria in Burundi, eastern Africa was needed. This study aimed to shed a clearer perspective on the question.

CHAPTER 2

2. REVIEW OF RELATED LITERATURE

2.1 INTRODUCTION

A mere bite from the *Anopheles* mosquito is where it all starts! Malaria is a sickness caused by a malaria-carrying organism that enters the bloodstream. Malaria is a life-threatening disease responsible for killing over one million humans per year. On average world-wide, over 300 million clinical cases of malaria are reported per year; this is five times more than Measles, Leprosy, Tuberculosis and Acquired Immune Deficiency Syndrome (AIDS) (Du Toit, 2003:23).

In Africa the saying is that malaria is a sickness of poverty and a main reason for poverty. Compared to healthy families, malaria affected families are able to yield only 40% of their harvest, signifying the link between malaria and poverty (Du Toit, 2003:23-26). The direct cost of the disease in Africa is estimated to exceed two billion US dollar per year. It is believed that malaria could be controlled with a budget of a tenth of that amount (Du Toit, 2003:25).

Minimising the risk of contracting the disease is possible. Antimalarial prophylactic drugs fight the parasites in the red blood cells and prevent the spread of malaria in the human body. However, it is important to take the recommended medication as prescribed and that the regimen is completed (Du Toit, 2003:23-24; Kouznetsov & Beales, 1996:32,38). Failing to complete the course may leave an insufficient drug level in the blood, allowing parasites to multiply and causing the disease to develop (Du Toit, 2003:24; Kouznetsov & Beales, 1996:37-38).

Malaria parasites have, however, become progressively more resistant to one drug after another (Du Toit, 2003:23-26; WHO, 1995:31). Many insecticides are no longer effective against the mosquitoes that carry the disease-causing organisms (Du Toit, 2003:23,25; WHO, 1995:20-22). Experience has shown that a thorough understanding of the malaria problem and risk, knowledge of the vector, the human host and the environment are prerequisites for effective planning and targeting of vector control interventions (WHO Technical Report, 1993:18).

2.2 WHAT IS MALARIA?

Briggs (1998:41-42) explains that malaria is a potentially fatal parasitic disease transmitted by mosquitoes. In the early days it was believed that *mal aria* (bad air) originated from fetid marshes. In 1880 *Plasmodium*, a single cell parasite, was discovered by scientists who identified it as the real cause of malaria. It was later discovered that the female *Anopheles* mosquito parasite is responsible for the transmission of the parasite from person to person through her bite (Briggs, 1998:41-42; Gubler, 2001:1-5).

Currently, roughly 40% of the world's population, mostly those from the poorest countries, are at risk of contracting the disease (What is Malaria, 2003:1). Malaria was once more extensive internationally, but it was effectively eliminated from many regions during the middle of the 20th century. Today malaria is found mainly throughout the tropical and sub-tropical areas (Curtis, 1996:1; What is Malaria, 2003:1).

There are four types of malaria found in humans. The four types are *Plasmodium vivax*, *P. malariae*, *P. ovale* and *P. falciparum*. *Plasmodium vivax* and *P. falciparum* are the most widespread and *P. falciparum* the most fatal type of malaria infection. In Africa largely south of the Sahara, *Plasmodium falciparum* malaria is most common, accounting for the extremely high mortality on the continent. There are concerned indications of the spread of *P. falciparum* malaria into new regions of the world and its reappearance in areas where it was eliminated some time ago (Benenson, 1990:267-269; Heymann, 2004:325-326). According to Richard (1974:23), De Meillon established that, of the twenty *Anopheles* mosquito types, only two types, *A. fenustus* and *A. gambiae*, are malaria carriers.

2.3 LIFE CYCLE AND SYMPTOMS

The malaria parasite enters the human host when an infected *Anopheles* mosquito takes a blood meal. Inside the human host, the parasite undergoes a series of changes as part of its complex life cycle. The various stages allow plasmodia to evade the immune system, infect the liver and red blood cells and finally develop

into a form that is able to infect a mosquito again when it bites an infected person. Inside the mosquito, the parasite matures until it reaches the sexual stage where it can again infect a human host when the mosquito takes her next blood meal, usually between 10 to 14 days later (Leech, Sande & Root, 1988:287).

Adams (2006:1) explains that once injected into the bloodstream, the malaria parasite travels through the blood circulation system until it reaches the liver, which it occupies. Within the liver cells the parasite can dwell for weeks or even months. This is the silent period of the disease. During this stage no symptoms are present and the liver cells are protecting the parasites from any antimalarial drugs the individual might be taking. The parasites then start replicating, filling the invaded cells to bursting point with new individuals. Ensuing release from the liver cells frees billions of the organisms into the blood. Each parasite attacks a red blood cell, enters it and again replicates.

Malaria symptoms appear approximately nine to 14 days after the infectious mosquito bite. This varies with the different *plasmodium* species. Typically, malaria produces fever, headache, vomiting and other flu-like symptoms. If drugs are not available for treatment or the parasites are resistant to them, the infection can progress rapidly to become life threatening. Malaria can kill by infecting and destroying red blood cells (anaemia) and by clogging the capillaries that carry blood to the brain (cerebral malaria) or other vital organs (Heelan & Ingersoll, 2002:125-126). Ruptured red blood cells, the oxygen delivering pigment of blood cells, also discharge haemoglobin into the plasma. This is then broken down in the body to a compound called urobilinogen, which is released in the urine, and can without difficulty be detected by a dipstick urine test (LaMar, 2000:51-52). The damage and invasion of red cells can be substantial. As blood filters of the body, the kidneys may be challenged with an unexpected surge of cellular debris, which blocks and harms the kidney's vascular and tubular system. Kidney failure may occur. The clustered platelets and debris may congest and block the capillary networks in the brain, leading to cerebral malaria with convulsions, confusion, coma and even resulting in death (LaMar, 2000:52,56).

Until now the reproduction of the parasites has been asexual. Each organism simply divided and replicated itself exponentially during the attack of the red blood

cells. For the infection to spread to other individuals, a sexual phase is required. A number of parasites now change into males and females. When a different *Anopheles* mosquito bites an infected person and drinks the blood filled with parasites, the male and female parasites merge within the mosquito. The asexual form of the parasite dies. After the merger, a cyst develops within which large numbers of new parasites develop, which then pass through to the mosquito's salivary glands, creating the environment for the additional spreading of malaria (Perlin & Cohen, 2002:11; Sub-Committee for Chemoprophylaxis and Therapy (SCAT) of the Malaria Advisory Committee, 2003:8-9).

Humans must be cautious of any flu-like symptoms. If any influenza-like illness or fever occurs within one week of entering, or six months from leaving a malaria area, a medical practitioner must be informed regarding the exposure to the disease. A blood test must then be done. A fatal misdiagnosis can be avoided and the symptoms must be regarded as possible malaria until proven otherwise. It can present as a sore throat, headache, body aches, fatigue or nausea and diarrhoea and then deteriorate with rapidity into serious illness. The presence of anaemia, a low platelet count and increased amounts of urobilinogen in the urine during a urine test must make a person even more suspicious of malaria (LaMar, 2000:55; Perlin & Cohen, 2002:23).

Positive identification of malaria sometimes requires repeated blood testing. During an attack of fever and rigors, the parasites are often seen within red blood cells on a blood smear under a microscope. The microscopic absence of visible parasites does not exclude the presence of the disease (Perlin & Cohen, 2002:23). Very sensitive antibody tests are also available and these may need to be repeated up to four times, as it often takes time for antibodies to reach detectable levels (Perlin & Cohen, 2002:23; SCAT, 2003:8-9).

Although scientists are intensifying the search for malaria control, an effective vaccine has still not been found (What is Malaria, 2003:1). Science still has no magic answer for malaria, and many doubt that a single solution will ever exist. Nevertheless, effective low-cost strategies are available for its treatment, prevention and control, and the Roll Back Malaria (RBM) global partnership is

promoting these strategies in Africa and other malaria-endemic regions of the world.

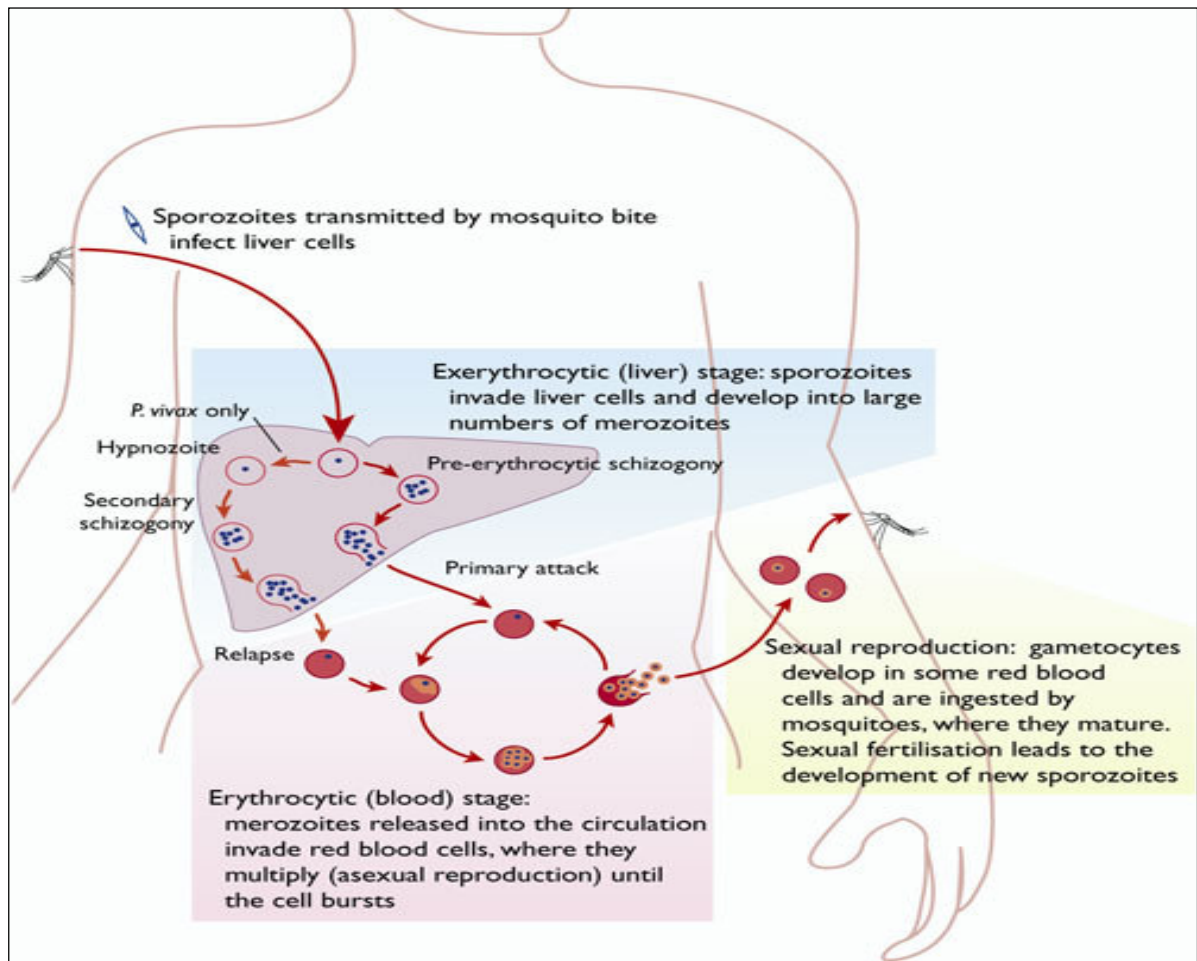


Figure 2.1: The simplified life cycle of the *Plasmodium* parasites infecting humans, as illustrated by Kitchener (2003:36).

2.4 EPIDEMIC PREDICTION AND RESPONSE

Epidemics occur when malaria attacks populations with little or no immunity. In situations like these, people of all age groups are at risk of severe illness or death. Epidemics of *Plasmodium falciparum* malaria, the most severe form of malaria, can be devastating if not controlled. The populations that are mostly at risk of malaria are those people living in highlands, arid and desert-fringe zones, as well as those staying in areas where successful control measures have not been properly managed and maintained (De Savigny & Binka, 2004:225-227; Epidemic Prediction and Response, 2001:1). Factors that may stimulate a malaria epidemic are divided into two categories namely

- natural (climatic changes, natural disasters); and
- man-made (conflicts and wars, agricultural projects, dams, mining, logging and failure to apply control measures) (Epidemic Prediction and Response, 2001:1; SCAT, 2003:11):

These factors make the breeding and living environment of the mosquitoes more suitable to transmit malaria. Factors such as human conflicts, as in Burundi, produce massive population movements that expose non-immune populations to the malaria parasite (Epidemic Prediction and Response, 2001:1; Grover-Kopec, Kawano, Klaver, Blumenthal, Ceccato & Connor, 2005:1).

Malaria epidemics usually occur in populations not normally exposed to malaria. It also occurs in populations that are, due to the climatic conditions of the specific region, only exposed for a short period of the year (Epidemic Prediction and Response, 2001:1; Grover-Kopec *et al.*, 2005:1). Local health officials are not able to predict, detect or control such epidemics in time, resulting in severe outbreaks and high mortality rates. When control measures are eventually taken, they are often too late (Epidemic Prediction and Response, 2001:1; Grover-Kopec *et al.*, 2005:1).

The outbreak of malaria is predictable to a large extent. Prediction is based on a combination of socio-economic, meteorological information and local epidemiological knowledge. Epidemics caused by man can be predicted and anticipated with considerable precision, for example during development projects such as irrigation projects, and the construction of fish ponds and dams. Multidisciplinary actions at the planning stages can help prevent such epidemics from occurring (Epidemic Prediction and Response, 2001:1). In contrast, it is difficult to anticipate a malaria epidemic arising from natural causes. However, such epidemics tend to reoccur, and it is important to learn from past experiences. The World Health Organisation (WHO) has supported retrospective analysis of malaria epidemics in several African countries. The finding builds evidence for practical guidelines on malaria epidemic prevention and control and early detection of such epidemics in Africa (Epidemic Prediction and Response, 2001:1; WHO, 1995:29-30).

Forecasting and early warning of possible future epidemics can reinforce local preparedness. Forecasting and early warning can also allow authorities and communities to use cost effective and emergency control plans to prevent excessive mortality rates (Epidemic Prediction and Response, 2001:1).

2.5 TRANSMISSION AND PATHOGENESIS

The *Anopheles* mosquito is the primary vector for malaria. Heelan and Ingersoll (2002:118) state that the number and species of mosquitoes present in an area, as well as the climate and geography, determines the risk of being infected. In many malaria endemic countries, transmission coincides with the wet season when there is increased agricultural activity and mosquitoes thrive. Movement of people caused by political instability, deforestation and irrigation, climatic events and environmental changes brought on by urbanisation have all contributed to the increased prevalence of malaria. An increase in international travel has raised the incidence of imported cases of malaria and brought about the phenomenon of “airport malaria” (Heelan & Ingersoll, 2002:121; SCAT, 2003:10). Due to this phenomenon, international airport workers at no apparent risk have contracted malaria from the bite of an imported infected mosquito. Benenson (1990:263) and Heymann (2004:326) report cases where patients became infected following a blood transfusion, after sharing contaminated hypodermic needles or through congenital transmission.

Untreated *Plasmodium vivax* attacks may last for weeks and relapses are common. Heelan and Ingersoll (2002:120) articulate in their study that untreated *Plasmodium vivax* attacks may last three weeks to two months; relapses are common and may persist for five to eight years. The first attack of *Plasmodium ovale* lasts from two to three weeks and often ends with spontaneous recovery. Relapse is possible, but seldom occurs after one year. Initial infection with *Plasmodium falciparum* lasts from three weeks to as long as twenty-four weeks. The patient may recover completely or maintain a low-grade parasitemia, which results in a series of reoccurrences over the next two decades. An untreated case of *Plasmodium falciparum* normally has a duration of two to three weeks, but may be marked by a variety of complications such as a coma or even death. Reoccurrence may occur,

but is seldom seen after a year. Complications of malarial infection, particularly *Plasmodium falciparum*, are in general caused by the blocking of capillaries by cell debris and/or parasitised red blood cells. In the case where the central nervous system is affected, it may cause cortical blindness, severe headaches, strokes and eventually death. Renal complications may also be life threatening if left untreated. (Heelan & Ingersoll, 2002:125-126; Heymann, 2004:336). Certain genetic conditions occur that cause changes to the red blood cells, resulting in some degree of natural immunity against malaria (Benenson, 1990:262-263).

2.6 INTERNATIONAL MANAGEMENT OF MALARIA INFECTION

2.6.1 The role of the World Health Organisation (WHO) and other international organisations

Malaria was declared a global priority. The worsening malaria situation in many parts of the world led the World Health Assembly, in resolution WHA 42.30 (1989), to declare malaria control a global priority and to request the Director General of the WHO to put in all possible efforts to mobilise appropriate human, scientific and financial resources to this end. They agreed to improve the use of existing resources to make malaria control an essential component of health and national development and to involve communities as partners in control (WHO Technical Report, 1993:2-3). In its support for collaborative studies on how best to assist malaria control programmes in planning and funding control projects, the WHO has emphasised the need to evaluate the susceptibility of *P. falciparum* to operationally use drugs and to determine the efficacy and safety of alternative therapeutic regimens as a basis for developing national policies on antimalarial drugs (World Health Organisation, 1992:87-88).

The International Federation of Red Cross and Red Crescent Societies is the largest global humanitarian organisation. This international organisation has an extensive network in 178 countries. Red Cross and Red Crescent volunteers are in the forefront in efforts to manage and eradicate malaria. With more than 100 million volunteers internationally (including two million in Africa), the Red Cross and Red Crescent are able to reach the individuals most vulnerable to malaria.

Furthermore, the African Red Cross and Red Crescent Health Initiative 2010, involving epidemiological experts, national societies, government ministries of health, the WHO and other international agencies, combine all the major role-players in the fight against malaria to guarantee a synchronised and cohesive endeavour (Health and Community Care, 2003:1).

2.7 THE INCIDENCE OF MALARIA IN AFRICA

Malaria epidemics in Africa are caused by certain primary factors. These factors include rapidly spreading resistance to antimalarial drugs, climatic changes and population movements (Nchinda, 1998:398; SCAT, 2003:11).

According to the latest statistics available in the media in November 2006, malaria was ranked third among major infectious disease threats in Africa after pneumococcal acute respiratory infections and TB (Medilinks, 2006:1; Nchinda, 1998:398). Malaria cases in Africa account for approximately 90% of malaria cases in the world. Between 1994 and 1996, malaria outbreaks in 14 countries of sub-Saharan Africa caused an unacceptably high number of deaths, many in regions previously free of the disease. Adolescents and young adults are now dying of severe forms of malaria (Nchinda, 1998:398). Factors favouring the spread of malaria include:

- resistance of parasite to drugs;
- conflicts forcing mass migration of people to or from infected areas;
- migration of non-immune people to infected areas for agricultural reasons, and
- changing rainfall patterns favouring mosquito breeding sites (Grover-Kopec *et al.* 2005:1; Medilinks, 2006:1; Nchinda, 1998:398).

In 1999 malaria was Africa's leading cause of under-five mortality (20%) and constituted approximately 10% of the continent's overall disease burden. It accounted for 40% of public health expenditure, 30-50% of inpatient admissions and up to 50% of outpatient visits in areas with high malaria transmission (The World Health Report, 1999:52).

There is a variety of reasons why the African continent bears an overwhelming share of the malaria burden internationally. The biggest percentage of malaria cases in Africa south of the Sahara is due to the *P. falciparum* organism, the most critical and acute form of the disease. This part of the continent is where the most efficient, and therefore fatal, species of the mosquitoes that transmit malaria is found. In addition, most of the countries on the African continent do not have the infrastructure and assets necessary to organise sustainable programmes against the disease (Africa Malaria Report, 2003:1; Malaria in Africa, 2001:1).

Internationally malaria has huge economic influence on people and regional business. Annual economic growth in countries with high malaria transmission has historically been lower than in countries without malaria. Economists believe that malaria is responsible for a growth penalty of up to 1,3 percent per year in some countries on the African continent (Health and Community Care, 2003:1; Sachs & Malaney, 2002:680-685; World Malaria Report, 2005:1).

When compounded over the years, this penalty leads to substantial differences in Gross Domestic Product (GDP) between countries with and without malaria and severely restrains the economic growth of the entire region. Malaria also has a direct impact on Africa's human resources. Not only does malaria result in loss of life and lost productivity due to illness and premature death, but malaria also hampers children's schooling and social development through both absenteeism and permanent neurological and other damage associated with severe episodes of the disease (Health and Community Care, 2003:1; Hotez, Molyneux, Fenwick, Otteson, Sachs & Sachs, 2006:1; The World Health Report, 1999:59-60).

One of the primary challenges in the fight against malaria is drug resistance. Throughout Africa (particularly in the southern and eastern parts of the continent) resistance to *Chloroquine*, the cheapest and most widely used antimalarial, is common. In eastern and southern Africa the resistance to *Sulfadoxine-Pyrimethamine* (SP), often seen as the first and least expensive alternative to *Chloroquine*, is also increasing. As a result, many countries have to change their current treatment policies and use drugs that are more expensive, including the combination of drugs, which will hopefully slow down the development of

antimalarial drug resistance (Huff, 2003:1; Malaria in Africa, 2001:1; Shepard, Ettling, Brinkmann & Sauerborn, 1997:1-3).

Political commitment by African leaders for action on malaria was given a boost. This was initiated by the founding of the Roll Back Malaria (RBM) global partnership in 1998. During 2000 African heads of state and their representatives met in Abuja, Nigeria, to translate RBM's goal of halving the malaria burden by 2010 into solid political action. The Abuja Declaration, signed in April 2000, endorsed a strategy to tackle the problem of malaria across the African continent (Health and Community Care, 2003:1; Malaria in Africa, 2001:1).

Progress made since Abuja includes reduction or elimination of taxes and tariffs on insecticide-treated nets (ITNs), promoting their use. The Country Strategic Plans (CSPs) were established by more than half of the malaria-endemic African countries, representing almost half the population at risk, to achieve the RBM goal and the targets set in Abuja. Country Strategic Plans are all based on the four technical elements of RBM and the management thereof. They are prompt access to effective treatment, promotion of ITNs and improved vector control and prevention and management of malaria in pregnancy. These elements aim to improve the prevention of and response to malaria epidemics and malaria in complex emergencies (Malaria in Africa, 2001:1; Epidemic Prediction and Response, 2001:1).

Local partnerships around the world are working together to develop their resources to implement their CSPs using continuous health sector reforms. Interaction between other initiatives such as Integrated Management of Childhood Illness (IMCI) and Making Pregnancy Safer (MPS) is used to improve access to key interventions. Country Strategic Plans have been successful in developing new strategies for malaria control. However, considering the resources needed until 2010, only 20% of the required funds will be made available by the local governments. International countries are looking to a selection of sources to ensure sustainable financing of their efforts. These include funding from the national treasury and donors, as well as the exploration of new opportunities

through debt relief schemes and the newly formed Global Fund to fight AIDS, TB and Malaria (Huff, 2003:1; Malaria in Africa, 2001:1).

2.8 MALARIA AND CONFLICT IN AFRICA

In 2003, 90% of all malaria mortalities occurred in Africa, south of the Sahara. In the order of 30% of Africa's malaria fatalities are found in countries experiencing acute, chronic or post-conflict complex emergency situations. It is estimated that over 200 million people in Africa are living in countries either directly or indirectly affected by complex emergencies (RBM and Complex Emergencies, 2004:1).

“Malaria deaths during complex emergencies usually far exceed those caused by the conflict at the root of the emergency itself” (RBM and Complex Emergencies, 2004:1). The chaos that follows war or civil unrest can destroy health systems, cut food supplies and expose people to multiple infections. Insecurity and poor living conditions in temporary camps and war-affected towns increase both people’s vulnerability to disease and the chances of vector and waterborne disease transmission. The collapse of medical infrastructure and facilities makes it difficult to address even basic health care needs (Africa Malaria Report, 2003:1; RBM and Complex Emergencies, 2004:1).

Implementing partners, mainly Non-Governmental Organisations (NGOs), UN agencies and the donor community are helping to select and implement best practices according to WHO guidelines and standards. Technical support is provided to enhance partner capacity to respond quickly and effectively to emergency situations (Epidemic Prediction and Response, 2001:1; WHO, 1999:55-60).

2.9 INCIDENCE OF MALARIA IN BURUNDI AND NEIGHBOURING COUNTRIES

“Malaria is now even affecting the highland areas of Burundi” (February 2003). According to a human rights organisation operating in Burundi, the number of

malaria cases increased from 200 000 in 1984 to 3 million in 2002 (International Activity Report, 2002:1; Malaria: the leading cause of death in Burundi, 2003:1). "Malaria, which for years plagued only the low-lying parts of Burundi, has now surfaced in the highlands, and constitutes the leading cause of death in the country", said health officials (Malaria: the leading cause of death in Burundi, 2003:1).

A spokesperson from Iteka, a Burundi human rights organisation, said that malaria patients accounted for 50 percent of individuals seeking medical care and assistance. Between 30 and 50 percent of patients admitted to hospital was suffering from malaria (Malaria: the leading cause of death in Burundi, 2003:1). Iteka quoted the leader of the national project to fight vitamin deficiencies, Dr Ndaruhutse, as saying malaria was impeding development, because those struck down by it spent long periods away from their workplaces. Iteka said that the worst affected parts in the country were Gitega and Ngozi, according to the statistics for 2002-2003 (Malaria: the leading cause of death in Burundi, 2003:1).

However, Iteka stated that the battle against malaria in Burundi was won, by means of the drug, Co-artem. Iteka recalled, however, that when it had first been introduced into the market, there had been some resistance by the general public due to its high price, and it had not been approved by the health ministry in Burundi (Malaria: the leading cause of death in Burundi, 2003:1). Iteka quoted the Director General of the health ministry, Dr Rirangira, as saying that the ministries of agriculture and livestock, education, environment, public health, interior, as well as NGOs, all needed to be involved in the effort to triumph over the disease. Since November 2002 an increase of malaria cases, especially in the provinces of Ngozi and Gitega has occurred. In Ngozi the number of malaria patients quickly rose from 16 000 in September to 34 000 in November, and over 48 000 in December 2002 (Malaria: the leading cause of death in Burundi, 2003:1).

The highland populations had little or no acquired immunity, making them extremely susceptible to the disease. The drug policy change adopted by the Burundi government in 2003 has proven to be a success. With funding from the European Commission's Humanitarian Aid Office (ECHO), and technical

assistance from UNICEF, the government of Burundi is hopeful that malaria can be controlled (Menon-Broker, 2005:1). Control of the disease includes both prevention and treatment. Prevention and the use of insecticide-treated bed nets remain priorities (Menon-Broker, 2005:1).

New drug therapies are a key element of the rolling back malaria plan. According to an ECHO representative, studies proved that the new generation drugs – the Artemisinin Combination treatment (ACTs) – are more effective (Menon-Broker, 2005:1). In Burundi, the state is subsidizing the cost of the new drugs and UNICEF is also working to increase the supply of the safe, effective and affordable ACTs, spending 1.6 million US dollars in 2002 for this purpose (Menon-Broker, 2005:1).

The United States of America's Medical Research Unit (USAMRU) in Kenya, East Africa, is a special foreign unit. This unit is a satellite of the Walter Reed Army Institute of Research (WRAIR). USAMRU is affiliated with the Kenya Medical Research Institute (KEMRI). It was established on a temporary basis in 1969 at the invitation of the government of Kenya to study trypanosomiasis. The success of this venture led to the establishment of a permanent unit in 1973. During that time research was intensively conducted on malaria in the central and eastern parts of Africa (United States Army Medical Research Unit – Kenya. 2003:1).

USAMRU in Kenya comprises of three main facilities. These facilities include a central laboratory in Nairobi and field laboratories at Kisian, on Lake Victoria, in western Kenya, and at Kericho, in the tea plantations of the highlands. The Nairobi facility is situated within the KEMRI main campus. Situated on the same premises are the Center of Disease Control and Prevention (CDC), the Japanese International Cooperative Agency (JICA) and the Wellcome Trust. Capabilities of these units include malaria and leishmanial parasite culture and *in vitro* malaria and enteric drug sensitivity testing (United States Army Medical Research Unit – Kenya, 2003:1).

Field testing of malaria drugs and vaccines is done routinely. Large-scale epidemiological studies on malaria are also done throughout the year. Infectious disease activities include extensive regional monitoring for drug resistance in

malaria. Accomplishments over the past include the establishment of the first *in vitro* malaria drug sensitivity laboratory in equatorial Africa and the investigations of high altitude and urban malaria in Africa (United States Army Medical Research Unit – Kenya. 2003:1).

2.10 MALARIA AND INTERNATIONAL MILITARY FORCES

2.10.1 The army's war against malaria: partnership in drug research since World War II

Malaria crippled allied forces in the early stages of World War II. The disease produced one and a half million American casualties during that time and influenced the capabilities of American-friendly forces as well. By January 1943, malaria had, on average, infected every allied service member deployed in the southwest Pacific four times. These conditions made the control and treatment of malaria an urgent priority of the US Army's medical establishment (Bennett, 2006:1-4).

US Army members suffered from several types of malaria. *Plasmodium vivax* and *P. falciparum* were the most common. Bouts of chills, fever and sweating caused soldiers to be out of action for a week or longer (Bennett, 2006:3-5; Hart & Hardenberg, 1963:531). *Plasmodium vivax* debilitates its victims, making them liable to secondary infections that could be fatal. This type of malaria was not a primary cause of death among these soldiers. It was *Falciparum* malaria that, if left untreated, could lead to death. The most pressing question for the United States Army was therefore the development of a prophylactic drug or a cure for malaria (Bennett, 2006:37-39; Hart & Hardenberg, 1963:531).

During World War II, military and civilian scientists assisted the armed forces in combating malaria. These alliances produced a number of malaria studies and numerous new or improved remedies, some of which tested superior to traditional antimalarial drugs. These co-operative efforts improved chemotherapy for the prevention and treatment of malaria after years of neglect in the development of

prophylactic drugs (Bennett, 2006:29-39). Between World War I and World War II, the Malaria Commission of the League of Nations and the International Health Division of the Rockefeller Foundation undertook antimalarial campaigns. These organisations acquired knowledge and skills that would later benefit the military. The Malarial Commission regarded antimalarial drugs as the main line of defence against malaria, whereas the Rockefeller Foundation, which soon came to dominate the war on malaria, favoured destroying the *Anopheles* mosquito which transmitted the illness. The World War II programme involved both approaches, but it soon became apparent that the attempts to control malaria through the killing of the *Anopheles* mosquito were probably hopeless during combat situations. Thus, the main attack on malaria had to come through the development of drugs (Harrison, 1978:183-186). War stimulated the scientific community to create organisations to help the armed forces control malaria (Harrison, 1978:186).

During the first years of the war, research concentrated on the search for more effective antimalarial prophylaxis. Scientific trials with *Atabrine*, a German synthetic drug which became the preferred operational drug after Japan had cut off the source of *Quinine* (an alkaloid of *cinchona* bark), were conducted. No better antimalarial drug had been found by April 1943, but scientists had proved that *Atabrine* had the pharmaceutical properties that could prevent and cure *falciparum* malaria and that the drug was immeasurably superior to *Quinine*. Military forces worldwide quickly adopted *Atabrine* that had the clinical trials, improved regimens of therapy and suppression. Scientists in the Second World War were stimulated to obtain more information in a single year about *Atabrine* than had been published in the media in the decade before the war (Bennett, 2006:9-10; Condon-Rall, 1994:2).

The scientific community intensified their research when no drugs, including *Atabrine*, were found to cure of *vivax* malaria. Controlled military operational field studies and studies within military hospitals would partly solve this challenge. A board comprising military and civilian members was establishment to provide close association and cooperation between military field trials and civilian laboratories. By doing this, the second challenge would be solved (Condon-Rall, 1994:2; Sweeney, Blackburn & Rieckmann, 2004:187-189).

The Board for the Co-ordination of Malarial Studies recommended limited trials in keeping with protocol when advances in chemotherapy warranted clinical testing (tests of antimalarial drugs on humans with induced malaria in a controlled environment such as a clinic or medical institution). The board also proposed to the scientists involved to conduct operational field tests on humans in malaria regions without malarial drugs passed during clinical trials. Although *Atabrine*, when properly administered, could suppress malaria and actually cure *falciparum* malaria, military senior management was concerned about returning soldiers infected with *vivax* malaria which could not be cured by *Atabrine*. As soon as these soldiers returned home, they would develop full-blown symptoms of malaria after they had stopped taking their daily dosages of antimalarial drugs (Bennett, 2006:9-18; Condon-Rall, 1994:3).

In 1944 military and civilian research became more integrated. In February 1944 the Surgeon General of the US Army assigned 12 military doctors to civilian research centres to investigate and do laboratory experiments on malaria. The army could now focus on the research of new drugs. This was possible, because operational experience had proven the efficacy of *Atabrine* for routine suppression and treatment. Malaria was only considered a problem when soldiers became lax about taking the *Atabrine* prophylaxis and the wearing of protective clothing (Bennett, 2006:11-33).

During the first half of the Second World War, experiments on malaria parasites were done by civilian laboratories using more than 600 new drugs. These compounds were used in clinical testing for trials on humans. From the middle of the war to June 1946 another 8000 new drugs were produced by affiliated drug companies (Condon-Rall, 1994:3-4; Sweeney, Blackburn & Rieckmann, 2004:187-189).

Scientists also tried a second approach, looking for a curative agent that had different chemotherapeutic characteristics than *Atabrine* and *Quinine* (Condon-Rall, 1994:1-9). The new suppressive compounds were a member of a pharmacological chain, named the *4-aminoquinolines*, which were closely interrelated to *Plasmocin* (a tradename for *Pamaquine*, a slightly toxic antimalarial) (Condon-Rall, 1994:4-5; Russell, 1963:1-7). Researchers screened approximately 200 of these drugs for

antimalarial properties. More or less ten of these drugs were tested on human beings. Two of these drugs (SN-6911 and SN-7618) that were German synthetic drugs, were researched more extensively. By June of 1944, *Bisulphate* had undergone clinical testing in military and public health services and passed the compulsory research investigation. The drug's antimalarial activities were compared quantitatively with a standard antimalarial drug such as *Quinine*, *Atabrine* or *Plasmocin* (Condon-Rall, 1994:4; Elslager, Tendick & Werbel, 1948:93-95).

Another potentially suppressive antimalarial drug was *Chloroquine*. After a long-term chronic toxicity study performed on volunteers, scientists compared the effectiveness, toxicity and administrative advantages of weekly or biweekly dosages against the required daily doses of *Atabrine* (Condon-Rall, 1994:3-4; Russell, 1963: 4-10). By April of 1945 the operational trials with *Atabrine* were completed, and the army and navy's feedback was that of little toxicity and more rapid disappearance of fever and parasitemia. In addition, the clinical management of an acute malaria attack with *Chloroquine* resulted in a longer period between relapses than with *Atabrine* compound drugs. Brigadier Fairley, Director of Medicine for the Australian Army Medical Corps and a noted malariologist, forwarded similar data from Australia and added that *Chloroquine* as well as *Atabrine* cured and suppressed *falciparum* malaria.

The US Military Medical Services continued to investigate promising antimalarial drugs after Japan had surrendered in September 1945. Researchers conducted clinical trials of *Chloroquine* in the Philippines, India and in US Military hospitals. The Army School of Malariology was founded in 1944 to provide field studies and training under tropical conditions (Mullins, 1974:178-193). During its trials with *Bisulphate*, *Chloroquine* and *Oxychloroquine*, the US Navy found that all of the experimental compounds were less toxic than *Atabrine* (Condon-Rall, 1994:4-6; Shannon, Earle, Brodie, Taggart and Berliner, 1944:307–330). In 1946, after World War II, medical researchers and scientists agreed on the superiority of *Chloroquine* over *Atabrine*. The administration of the former drug once weekly had positive results in effective suppression. As compared to the usual five to seven day treatment with *Atabrine*, it caused an immediate termination of the clinical

symptoms of *vivax* malaria between 24 to 48 hours. The same regimen also cured *falciparum* malaria when consumed for one or two days. Furthermore, it did not cause any gastrointestinal disturbances or skin stains. After various analyses of *Bisulphate* and *Oxychloroquine*, scientists made similar claims regarding these compounds (Condon-Rall, 1994:4-6; Elslager *et al.*, 1948:94-97).

Scientists studied another series of suppressive compounds, the *Quinoline methanols*. This chemical was closely related to *Quinine* in animals, but they never reached the stage of testing it on humans. Some new curative compounds in a series called *8-aminoquinolines*, that were related to the British drug, *Pamaquine*, were tested in prisons before the war, but not in military deployed installations (Russell, 1963:4-10; Shannon, 1946:712-716).

Although smaller and less organised than the American and Australian programmes, the British research efforts were impressive. Scientists in England studied the clinical characteristics of malaria and conducted curative trials on the British Isles and West Africa, comparing *Plasmocin* which they called *Pamaquine* with *Quinine* and *Atabrine* (which the British called *Mepacrine*). The final conclusion by the study group was that *Plasmocin* reduced relapse rates (Condon-Rall, 1994:5; Jones, Craige, Alving, Whorton, Pullman & Eichelberger, 1948:6-9).

The American government made a request to the research groups not to reveal the composition of this drug to commercial companies (Condon-Rall, 1994:5-7). In 1942 the new drug *Penicillin*, which had been discovered by a British company was patented by American manufacturers due to the fact that British companies seemed uninterested in the patent. In fact Florey appealed to American manufacturers to get involved, since it was against ethical medical principles for British companies to patent medical research results for profit (Condon-Rall, 1994:5-7).

Before the Board for the Co-ordination of Malarial Studies was finally adjourned, they suggested the prompt publication of information on *Chloroquine*. *Chloroquine* had proven superior to *Quinine* and *Atabrine*. The Board also published informative literature advising the public and military community regarding dosage

schedules and therapeutic use of *Atabrine* and *Chloroquine* for returning soldiers. In October 1947, the British military adopted *Chloroquine* as the drug of choice for malaria suppression and treatment as recommended by the Board.

The research and collaboration worldwide to fight malaria that was stimulated by World War II advanced our knowledge of the disease and our ability to prevent and control it. This collaboration enhanced the therapeutic management of malaria by the development of new drugs that proved superior to *Atabrine* (Condon-Rall, 1994:7-9; Jones *et al.*, 1948:8-11).

The armed forces were satisfied with the results, although no cure was found. Years of neglect in the development of antimalarial drugs had now given way to the development of favourable new drugs and better management of the disease (Condon-Rall, 1994:7-9).

2.10.2 Malaria in the armed forces of Thailand

Malaria was a significant threat to the military forces of Thailand (RTA). The highest threats occurred on Thailand's Burmese and Cambodian borders. With the RTA units that deployed to the Tak province in 1995, one out of four patients seen by the medical personnel monthly suffered from malaria. Due to ever increasing drug resistances, sustained research and development of more effective drugs, vaccines and repellents were required (Malaria is a Significant Military Threat, 1999:1; Saito, 1998:3).

Saito (1998:3) of the Cambodia Daily reported that malaria sickened 60 % of military patients in the Thai Defence Force. Approximately 60 % of in-patients at military health centres are suffered from the disease, according to a report from the health department of the Ministry of Defence in Thailand (Saito, 1998:3).

According to the annual review of the Ministry of Defence, malaria was one of the highest causes of death of all government soldiers in 1997 (Saito, 1998:3). Officials from the National Malaria Centre in Thailand said that a lack of malaria

medicine and bed nets, combined with inadequate medical knowledge concerning treatment of the disease, contributed to the high statistics (Saito, 1998:3).

A total of 11 142 confirmed cases of malaria was reported in 1996 and 19 166 confirmed cases were reported in military hospitals in 1997. Of the confirmed cases in 1997, 284 people died (Saito, 1998:3). The report also attributed the high incidence of malaria to the increased movement of military forces in areas of high malaria transmission. Military operations along the Thai borders exposed military members to some of the world's most drug resistant strains of malaria (Huff, 2003:1; Saito, 1998:3).

Some strains of malaria in the north-western regions of Cambodia were found to be resistant to *Chloroquine* and *Mefloquine*. Malaria statistics from the National Malaria Centre in Thailand has increased by 60% from 1996 to 1998 (Bussaratid, Wilairatana, Krudsood, Silachamroon, Walsh and Looreesuwan, 2002:5-7; Saito, 1998:3).

Officials, however, reported that the severity of cases had not increased and that the increase in cases could be attributed to improved reporting conditions. Military health centres did not include their statistics in the national malaria reports. Increased movement of civilians into former Khmer Rouge regions in the north-western part of the country and continued displacement of refugees from fighting along the Thai borders contributed to the higher number of cases (Bussaratid *et al.*, 2002:3-12; Saito, 1998:3).

The National Malaria Centre planned to continue future training sessions on malaria treatment for medical personnel at military hospitals. Doctors and medical personnel at military hospitals would receive continuous training (Miller, Wongsrichanalai, Buathong, McDaniel, Walsh, Knirsch & Ohrt. 2005.1; Saito, 1998:3).

2.10.3 Malaria in the American armed forces

Health organisations estimate that between 2,5 million and 5 million people died of AIDS in the first fifteen years since the pandemic started. However the same time, malaria killed nearly 50 million people worldwide (Driessen, 2005:1; Gillert, 2003:1-2). Captain Hoffman, Navy doctor and director of the malaria programme at the Naval Medical Research Institute argues that, due to global climatic changes the occurrence of malaria could double in the next fifty years (Driessen, 2005:3-7; Gillert, 2003:1-2).

According to Gillert (2003:1-2), Hoffman stated that this could be a challenge for the military. Hoffman added, "In every US military campaign this century we lost more casualties to malaria than bullets". This was seconded in the US Army malaria and military online fact sheet "Malaria and the Military" (2004:1). During World War II and the Vietnam War, whole divisions ceased to be effective combat units due to malaria. Six of the last seven United States military deployments were to malarial regions of the world, with Bosnia the exception. During "Operation Restore Hope" in Somalia, malaria was the number one cause of casualties. Currently, members deployed in malarial areas take antimalarial prophylaxis to avoid infection. USA soldiers take either *Mefloquine* weekly or *Doxycycline* daily. In 2003 the US Navy was testing a third drug, *Primaquine*, which would also be taken daily (Baird, Fryauff & Hoffman, 2003:1659-1667; Gillert, 2003:1-2).

However, according to Hoffman in Gillert (2003:1-2) and SCAT (2003:14) drugs are not always hundred percent effective. He adds that researchers are discovering more and more strains of drug-resistant malaria. If malaria is not treated properly, or if the medication does not work effectively, victims may develop kidney, liver or lung problems. The most serious complication affects the brain. Patients become disoriented, delirious and often comatose during the advanced stage. Gillert (2003:1-2) refers to Hoffman as saying that it is not unusual, however, for malaria sufferers to hallucinate within seven days of becoming ill, but then to fully recover. According to Hoffman, because of the high costs and human misery, medical researchers rank malaria as the top priority for new and better drugs and, ultimately, vaccination. Since malaria also severely impacts on military combat

readiness, the US Department of Defence leads the development effort of the fight against malaria and the parasites causing the disease (Gillert, 2003:1-2).

The concern internationally is the fact that nobody has ever manufactured a vaccine against a complex parasite like malaria. These micro-organisms develop multiple stages of life and when inside the human host the organisms live near a blood source in the liver, as well as inside and outside cells in the blood stream. They exist at a different stage in the body of the mosquitoes (Gillert, 2003:1-2; Malaria, 2006:1).

To be completely optimal, the vaccination must attack the parasite at all stages of its life cycle. “Developing this vaccine requires a whole new type of technology, which we’re at the forefront of, but it takes time. We have made enormous progress and should field a vaccine in five to ten years” (Gillert, 2003:1-2). Other international agencies, including the World Health Organisation and National Institutes of Health Centers for Disease Control, try to find a malaria vaccination as well, but their objective is different from that of the US Department of Defence (US DoD). “They are interested in preventing death from malaria, and their first objective is sub-Saharan Africa” (Gillert, 2003:1-2). The US DoD, on the other hand, wants a vaccine that would protect people from ever falling ill with malaria. According to Gillert (2003:1-2), Hoffman predicted the development of a vaccine that would last for about a year.

“Eventually, we would like a vaccine that would be life-long. However, it has to offer lifelong protection against infection, which is far different from lifelong protection against disease. If we can make children in Africa not die from malaria that will be an amazing contribution, because it will wipe out millions of deaths a year. But that’s not good enough for the US Department of Defence, because, to sustain operational capability, military people cannot afford to get malaria at all”.

Epidemiologists from the US Army recommended that *Permethrin* be used on civilian clothes of members during deployments. *Permethrin* is an insect repellent

applied to clothes. They agree that much of the exposure to malaria among military personnel may occur while the members are wearing civilian clothing. It is noted that *Permethrin* is commercially available and there is no reason it cannot be applied to civilian garments and bedding (Bradley and Bannister, 2003:184-199). In the United States Army there were 40 confirmed cases of malaria in 1997. The number of patients increased to 41 in 1998, and until October 1999, 56 cases had been reported. Most of the cases (82%) during 1998 and 1999 were troops from the different units in the United States of America Defence Force deployed to South Korea.

2.10.3.1 Malaria among US military personnel returning from Somalia (1993)

In late December 1992 US military personnel were first deployed to Somalia as part of "Operation Restore Hope". In the first four months until April 1993, malaria was diagnosed in 48 members who presented with symptoms of the illness while in Somalia. Additionally, from late June 1993, 83 military members were diagnosed with malaria following their return from Somalia. This significant number of cases has underlined the concerns regarding malaria prophylaxis, the need for proper diagnostic tools and treatment of malaria in military personnel and the approximate risk for infection (Newton *et al.*, 1993:1; Robert, 2001:67-76).

Mefloquine was one of the medications used for malaria prevention (Robert, 2001:67-76). The use of prophylaxis was not supervised after arrival in the United States and compliance was reportedly low (Newton *et al.*, 1993:1; Robert, 2001:73-76).

2.10.3.2 Malaria among active duty soldiers in the US Army (2001-2002)

In the US Army, soldiers operate and train in many areas of the world where malaria is endemic. In 2001, malaria was conducted by 52 US soldiers in the demilitarised zone in Korea. Thirty-three of the patients were hospitalised and one died of the infection. Seventeen cases of malaria infections were reported in Africa. Nearly all of the malaria cases of African origin were due to *Plasmodium*

falciparum. There were more *P. falciparum* induced malaria cases in 2001 than in any year since 1995 (Lum, 2002:2-4).

In the United States Military, many soldiers are permanently assigned to malaria endemic regions. In addition, many soldiers are exposed to the malaria risk during operations and training internationally (Fact Sheet: Malaria and the Military, 2004:1; Lum, 2003:2-3;).

During 2002, 57 soldiers were diagnosed and treated with malaria. Thirty-six soldiers were diagnosed with *Plasmodium vivax* malaria; 80% were white and more than half of the cases were younger than 25 years of age. There was one report of malaria in a female soldier (Lum, 2003:2-3).

In 2002, malaria was identified among US Army soldiers at more than 20 different locations worldwide. More than two-thirds of all cases were diagnosed at medical care facilities remote from locations where malaria is endemic (Lum, 2003:2-3).

Nearly 40 US Army personnel returning home from Afghanistan in 2002 may have contracted malaria because of inadequate use of preventative measures. Conflict and war have had a long partnership with malarial epidemics. Transporting of military personnel, disruptions in health care infrastructure and exposure of individuals with nominal or no immunity bring about an increased risk of contracting malaria (Kotwal, Wenzel, Sterling, Porter, Jordan & Petruccelli, 2005:212-214).

US Army soldiers deployed in endemic regions are directed to consume antimalarial chemoprophylaxis and to use personal protection methods, including minimising exposed skin through proper wear of the uniform and use of bed nets, impregnating uniforms and bed nets with *Permethrin*, and regularly applying topical insect repellent (Kotwal *et al.*, 2005:213-216; Robert, 2001:69-76).

An anonymous post-deployment survey of 72 % (521/725) of the force, indicated a compliance rate of 52 % for weekly chemoprophylaxis, 41 % for post deployment chemoprophylaxis, 31 % for both weekly and terminal chemoprophylaxis, 82 % for

treating uniforms with *Permethrin*, and 29 % for regular application of insect repellent (Kotwal *et al.*, 2005:212-213; Robert, 2001:70-75).

“A major cause of malaria prophylaxis failure is patient non-adherence to prescribed treatment. Providing continuous education about the need to comply with prophylaxis medication and having leaders directly observe therapy and enforce personal protective measures may help safeguard soldiers from vector-borne disease” (Kotwal *et al.*, 2005:212).

2.10.3.3 Malaria among marines in the US Army

United States Navy medical personnel are still investigating an incredibly high rate of malaria among United States Army marines and navy personnel. These members were in Liberia during 2003 on a peacekeeping mission (Rhem, 2003:1; Smith & Hooper, 2004:1-10).

Forty-four military members were evacuated from their United States navy ships off the West African shore to hospitals in Germany and the United States. Medical doctors and personnel from the National Naval Medical Centre in Bethesda have confirmed that 13 cases were due to the bite of the *P. falciparum* mosquito (Rhem, 2003:1; Smith & Hooper, 2004:1-10). There were several questions regarding this aspect. Healthcare workers investigated three possibilities:

- the type of malaria had become resistant to the drug taken by the marines;
- the members did not take the prophylactic medicine correctly; or
- the drug had expired, or there was a default in the manufacturing process.

Medical officials said that all members going ashore changed to another antimalarial drug in case of resistance. Five of the cases were serious, including two patients who contracted cerebral malaria, but all of them were expected to recover (More US Marines contract Malaria, 2003:1; Rhem, 2003:1).

According to medical officials, the marines and United States navy personnel started taking the antimalarial drug, *Mefloquine*, in late June or early July 2003 in a

regimen that required troops to start using the medication two weeks in advance of a deployment, then to take the drug once a week thereafter for a month until the troops were out of the malarial area for a month. The defence force members were also issued with a mosquito repellent cream containing *DEET* and a mosquito net per person (Rhem, 2003:1; Smith & Hooper, 2004:1-10).

The 40 marines and three United States Army naval officers who fell ill went ashore in Liberia. They operated from an airport outside the capital Monrovia for about 10 days. Other United States Army soldiers went back and forth from the ships to land, sometimes for as little as a couple of hours at a time (Rhem, 2003:1; Smith & Hooper, 2004:1-10). Ten more US military personnel serving as part of the peacekeeping mission in Liberia were showing symptoms of malaria. US military officials stated that another ten military members had been evacuated. This followed the evacuation of 46 other United States Army naval members to Germany and Bethesda for treatment against malaria (More US Marines contract Malaria, 2003:1; Sirleaf, 2003:1). The members formed part of a quick reaction force sent to the Liberian capital to assist in the peacekeeping mission in the war-torn country. The troops were ashore from 15 August to 26 August 2003 before they returned to the Iwo Jima. The two thousand military members, most of whom did not go ashore, had been issued with proper prophylaxis to avoid malaria. The US Army military members were issued the antimalarial drug *Mefloquine* three weeks before arriving in Liberia, and were instructed to take the *Mefloquine* tablets once a week (Rhem, 2003:1; Smith & Hooper, 2004:1-10). These members were also instructed to take the medication while in the area and three weeks after leaving Liberia. United States military officials articulated that the troops who contracted the disease were probably exposed while they were ashore (More US Marines contract Malaria, 2003:1; Rhem, 2003:1).

2.10.4 Malaria in the Canadian forces

Sixteen confirmed malaria cases and four unconfirmed cases were reported in the Canadian Forces during 1993. Among the 16 confirmed cases, one member contracted malaria while on an official visit to Central Africa. The infection was the result of a bite from the *P. falciparum* mosquito. The other 15 cases all occurred in

military members sent to Honduras during the hurricane Mitch relief effort. All 15 developed malaria as a result of the bite of the *P. vivax* mosquito, six to twelve months after returning. The military members did not use prophylaxis (Malaria Surveillance in the DoD and Canadian Forces, 2002:1).

2.10.4.1 Canadian military malarial prophylaxis under scrutiny

According to Desautels, Auditor-General of the Canadian government, the 900 Canadian military members deployed in Somalia in 1992 and 1993, failed to follow proper safety protocols in administering antimalarial drugs (Kondro, 1999:1507; Report of the Somalia commission of inquiry, 1997:1). Desautels reported that in giving *Mefloquine* to soldiers during a clinical trial, the Department of National Defence failed to “consistently keep essential records or follow required procedures to fulfil its obligation as a participant in the clinical study of an unlicensed drug”, while the Health Department of Canada lacked adequate oversight procedures to ensure that the trial were being properly managed and conducted, (Kondro, 1999:1507; Report of the Somalia commission of inquiry, 1997:1). Although licensed in Canada, *Mefloquine* was associated with side-effects such as hallucinations and depression. Soldiers on the mission in Somalia blamed the drug as being partly responsible for the excessive force used by military members, leading to the death of a Somali teenager (Kondro, 1999:1507; Report of the Somalia commission of inquiry, 1997:1).

The problem is not that the soldiers were not given the drug. They had to be protected against malaria. According to Kondro (1999:1507), what concerned Desautels was the manner in which it was done. He added that the antimalarial drugs were obtained through a clinical trial, but were given to soldiers without following the required measures to monitor the effects and to keep track of the drugs’ distribution. In response to the report of the Department of National Defence of Canada, Desautels said that *Mefloquine* achieved the desired effect of preventing malaria, and that it was internationally acknowledged as having “an established record of safety and efficacy” (Kondro, 1999:1507; Veterans Affairs, 2006:1).

2.11 MALARIA CONTROL IN THE SOUTH AFRICAN NATIONAL DEFENCE FORCE (SANDF)

2.11.1 The prevention and control of malaria in the SANDF during external deployments

2.11.1.1 Control of the *Anopheles* mosquito

When SANDF members are deployed internationally, environmental health officers plan malaria-spraying programmes according to epidemiological tendencies. The Fertilisers, Farm Feeds, Agricultural Remedies and Stock Remedies Act, Act 36 of 1947 (South African Government) is used as the legislative guideline. All international laws, regulations and South African Bureau of Standards (SABS) codes pertaining to malaria are adhered to. The policies of the county in which the SANDF are deployed are respected and wide consultation with different local state departments, local authorities and non-governmental organisations (NGOs) is part of the modus operandi. The pest control operators of the South African Military Health Services (SAMHS) are only allowed to execute malaria control actions within the boundaries of the SANDF premises in the deployed country and/or authorised locations (Malaria policy for the SANDF, 1996:1).

It is the responsibility of the officer commanding to ensure that the unit is sprayed to ensure vector control. The management and administration of malaria control actions of structures and buildings in endemic areas are the responsibility of the environmental health officer and take place according to predetermined pest control programmes. The environmental health officer is responsible for the determination of malaria control actions by assessing the active ingredient of the pesticides used. An example of factors influencing the type of pesticide used is the texture of the surface on which the poison will be applied, the humidity and the temperature (Malaria policy for the SANDF, 1996:1).

Regular spraying with *Pyrethroid*-based insecticides forms part of the vector control programme to prevent malaria. These programmes have been extremely effective in areas of no resistance (Curtis, 1996:3-5).

2.11.1.2 Prophylaxis policy and administration

Although the Armed Forces of South Africa have been deployed in malaria endemic regions for decades, their deployment to Burundi in 2001 was the first formal deployment of SANDF soldiers to East Africa. After 1994, no chemoprophylaxis and treatment of malaria policy was available until May 2003 when the current policy was drafted. According to SAMHS Order SG/12/2003, *Mefloquine* and *Doxycycline* are the prophylactic treatment of choice for external deployments (Chemoprophylaxis and Treatment of Malaria, 2003:2).

The SAMHS head quarters, in consultation with the Director Medicine and Director Pharmacy, determines the appropriate treatment regime and malaria prophylaxis. The provision of the antimalarial drugs to SANDF members deployed in malaria areas is the responsibility of the SAMHS, while the responsibility for their use rests with the individual. The officers commanding of the respective units are responsible to inform the military health centre of any changes in their malaria prophylaxis register. This enables proper planning with regard to the ordering and issuing of prophylactic medication. It is the responsibility of the officer commanding of the local military medical centre to ensure that the environmental health officer gives counselling on malaria prophylaxis and prevention to the newly arrived members. The military health centre is responsible for preparing the malaria prophylaxis in quantity according to a register (Malaria policy for the SANDF, 1996:1).

The malaria medication will be supplied weekly, as per the guidelines of the manufacturers. The malaria medication will be supplied, against signature, to the unit officer commanding or a delegated person for issue to members. The following information must be provided in writing to the local Military Health Centre:

- area where the members will be deployed;
- date when the prophylaxis is required;
- expected time of deployment; and
- number of members involved.

The person in charge must issue the malaria medication to the deployed members according to a register. Counselling must accompany the issuance of the prophylaxis. The members will be informed about the importance of starting the course on time, as well as the importance of finishing the medication as stipulated. The possible side-effects of the medication will also be highlighted (Malaria policy for the SANDF, 1996:1).

In the case of *Mefloquine* (Mefliam®), military members will be supplied with a minimum of four weeks' medication before leaving for the endemic deployment area. Persons visiting the areas of deployment are responsible for obtaining their own prophylaxis from the nearest military health centre. It is advised that malaria prophylaxis registers contain the following information:

- amount of medication provided;
- any known side-effects;
- date on which member received counselling;
- date when malaria medication was issued;
- whether the member received any repellent;
- personal particulars of the member;
- signature of the member; and
- the type of medication provided (Malaria policy for the SANDF, 1996:1).

The malaria prophylaxis register should be archived for audit purposes. It is the responsibility of the officer commanding of the military health centre to provide trained individuals to issue malaria medication, identify possible side-effects and to provide informal counselling and education to the users. The control of the registers is the responsibility of the environmental health officer. Registers must be supplied to the military health centre on a monthly routine for control purposes and to provide the opportunity for the information to be captured on the patient management system (Malaria policy for the SANDF, 1996:1).

2.11.1.3 Preventative measures

Prevention and proper application of the following measures have the potential to reduce the incidence of malaria in endemic regions:

- Build camps and pitch tents away from marshy areas and water bodies that are potential larval breeding sites.
- Make provision for the optimum drainage of rain and household water near accommodation.
- Install gauze screens in front of doors and windows of tents and temporary accommodation.
- Apply larvicides to standing water that cannot be drained near temporary accommodation.
- Apply long acting insecticides onto interior walls of tents and/or temporary accommodation.
- Repellents. As with prophylaxis, the use of repellents is the responsibility of the individual. The issuing of repellents during external deployments areas is done against signature in the relevant register as soon as the member arrives in the country of deployment. Members on *ad hoc* visits in the deployed region will receive the repellent together with their malaria prophylaxis.
- Mosquito nets. It is the responsibility of each officer commanding in the endemic malaria area to ensure that each person entering his/her unit is issued with a proper mosquito net (Malaria policy for the SANDF, 1996:1).

2.11.1.4 Active surveillance

Active surveillance is the process of early identification of personnel exposed to malaria vectors. This process provides proactive action eliminating a substantial amount of active malaria vectors due to early intervention at low costs. Where possible, members deployed in endemic malaria areas will undergo pre-deployment screening. This pre-deployment screening will be in the form of rapid blood tests, and thereafter at a frequency established by the surgeon general, depending on the malaria status of the region with a positive blood smear as part of early intervention. Active surveillance is the responsibility of the environmental health officer (Malaria policy for the SANDF, 1996:1).

2.11.1.5 Information

The member should be informed that the symptoms of malaria might be mild. The member should suspect malaria if they experience unexplained fever or other symptoms such as persistent headaches, muscular aching and weakness, vomiting or/and diarrhoea. The soldier has to be informed that medical help should be sought promptly if malaria is suspected. Self-care should be taken only if prompt medical care is not available, and such medical advice should still be sought as soon as possible after self-treatment (Malaria policy for the SANDF, 1996:1).

2.11.1.6 Urine testing

Random urine testing will be done per unit deployed in an endemic area on a weekly basis. Non-compliance will be specifically followed up (Malaria policy for the SANDF, 1996:1).

2.11.1.7 Notification of malaria cases

All malaria cases must be notified and investigated. These notifications will give indication of the effectiveness of the malaria prevention programme (Malaria policy for the SANDF, 1996:1).

2.12 GLOBAL TREATMENT AND CONTROL MEASURES

2.12.1 Global treatment measures

The treatment of malaria has become a challenge due to the sheer nature and tenacity of both the parasite and the *anopheles* mosquito (Heelan & Ingersoll, 2002:125-126; SCAT, 2003:6-9). Prior to World War I, only *Quinine*, a derivative of the bark of the *cinchona* tree, was available for antimalarial treatment (Heelan & Ingersoll, 2002:125-126; White, 1996:1122-1123). Between World War I and World War II, several synthetic drugs were developed, of which *Chloroquine* became the drug of choice (Heelan & Ingersoll, 2002:125-126). The use of standard antimalarial drugs and incomplete courses was directly responsible for

drug resistant strains, particularly *Plasmodium falciparum*. After years of using antimalarial chemicals in endemic areas, the *anopheles* vector has also developed resistance to the most common insecticides (Heelan & Ingersoll, 2002:125-126; TDR: Strategic Direction Malaria, 2002:1).

Ideally, malarial treatment should destroy all forms of the parasite. The medication must kill all from sporozoite to gametocyte, without being toxic to the user (Heelan & Ingersoll, 2002:125-126; Heymann, 2004:325-326). Unfortunately each of the available chemotherapeutic agents acts on specific morphologic stages of the malarial life cycle. Combination drug therapy may be required to prevent relapse or recrudescence. Current treatment regimes generally include some form of *Quinine* or *Quinine* derivative. *Chloroquinine* is the least toxic drug that effectively eliminates non-resistant forms of the parasite in areas of the world where resistant strains of *P. falciparum* and *P. vivax* predominate, and *Mefloquine* or *Quinine* may be the drug of choice. Managing infections of *P. vivax* or *P. ovale* may require long term treatment with *Primaquine*, which is known to eliminate hypnozoites from the liver and prevent “true relapse” (Heelan & Ingersoll, 2002:125-126; Heymann, 2004:326).

2.12.2 Global control measures

2.12.2.1 Malaria control

“Malaria control is the business of everybody, and everyone should contribute” (Malaria in Africa, 2003:1; WHO, 1993:1). It requires the joint venture of community members and the involvement of those engaged in education, the environment in general, water supply, sanitation and community development in particular. The discerning use of protection methods, including vector control, is proving to be more cost-effective and sustainable and insecticide-impregnated mosquito nets are increasingly being used (Malaria in Africa, 2003:1; Robert, 2001:68-76).

2.12.2.2 Multilateral initiative

In January 1997, funding groups from the private and public sector joined efforts and the Multilateral Initiative on Malaria (MIM) aimed at malaria control in Africa was founded. It was an African-led project to strengthen research capabilities, particularly for improving antimalarial drug policies, reducing morbidity and death, and conducting epidemiological and vector studies, as well as other operational research. The main research components to be funded were antimalarial drug policy, chemotherapy, epidemiology, pathogenesis, insects (vectors), health systems and social science (Malaria in Africa, 2003:1; WHO, 1999:54-62).

2.12.2.3 Role of the Red Cross/Red Crescent (RC/RC)

The Red Cross/Red Crescent is often on the vanguard of caring and addressing the health problems of internally displaced people and refugees. Experience has shown that malaria is one of the most important health problems confronting these populations. Thus, in partnership with other role-players and by applying the abovementioned interventions, the RC/RC plays a leading role in the control and prevention of malaria during natural and man-made disasters, as well as in complex emergency settings. Where possible, efforts made in the prevention and treatment of malaria will also be blended into pre-existing programmes. The Red Cross/Red Crescent will collaborate closely with international or national ministries of health and fill identified gaps to complement governments' efforts to contain malaria (Health and Community Care, 2003:1). The Red Cross/ Red Crescent is also involved in the following missions throughout the world:

- advocacy;
- village or community volunteers may play a part in fever surveillance in order to counsel caretakers in appropriate behaviour;
- RC/RC and branches may wish to supply insecticide-impregnated mosquito nets as a service to the community and generate money from the sale of nets and from their periodic re-impregnation every 6-12 months. In some countries, the production of nets has become a small home-based industry providing employment and income; and

- RC/RC village or community volunteers can serve to motivate the residents in the acquisition and appropriate use of insecticide-treated bednets (Malaria in Africa, 2003:1).

2.13 DISEASE PREVENTION

The key to the control of malaria is long-term mosquito abatement and human treatment and prophylaxis. In addition, effective chemoprophylaxis should be taken wherever and whenever the risk of malaria exceeds the probability of experiencing an adverse reaction to the chemoprophylaxis. The risk of contracting malaria is determined by the intensity of transmission in the area and the season of visit, as well as the duration of stay, type of accommodation and type of activities between dusk and dawn (SCAT, 2003:6). Elimination of standing water and mosquito breeding sites and the correct use of environmental insecticides should drastically reduce the vector population. Early diagnosis and treatment of existing cases is also fundamental to the breaking of the human-mosquito-human cycle (Robert, 2001:69-76; WHO, 1993:19-20).

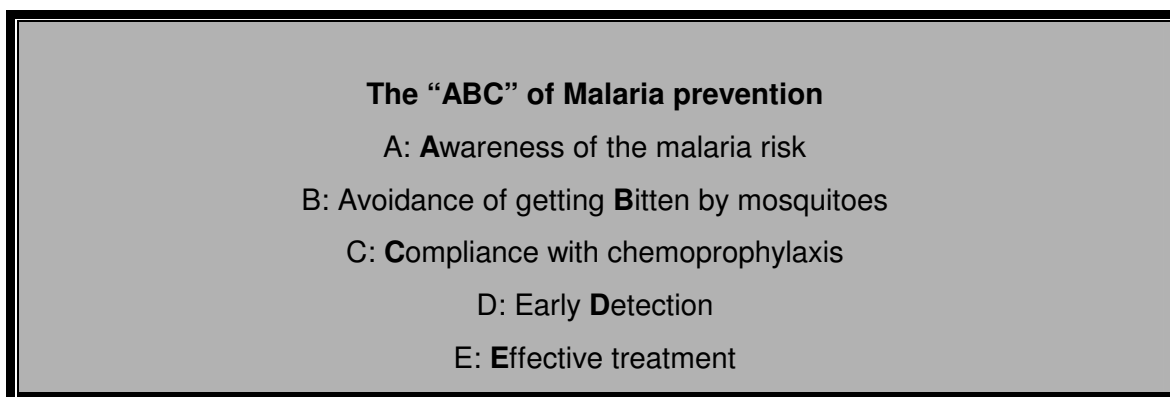


Figure 2.2: The “ABC” of malaria prevention (SCAT, 2003:6)

2.13.1 Active approaches for malaria prevention

2.13.1.1 Procedures to prevent mosquito bites

The following procedures are recommended:

- Spray an insect repellent containing *diethyltoluamide*, for example *Tabard®*, onto exposed skin, as well as your clothing at dusk every day.
- Wear long- sleeved shirts, long pants and socks after dusk.

- The mosquito is a night feeder and the thin skin over exposed ankles and wrists is a favoured site for feeding.
- Burn insecticide coils in sleeping quarters at night.
- Move around when outdoors at night; mosquitoes prefer static prey.
- Ensure that there are mosquito screens on all doors and windows. Spray an insecticide inside living quarters every evening to eliminate indoor mosquitoes.
- Sleep under *Pyrethroid* insecticide impregnated mosquito nets tucked under the mattress.
- A ceiling fan is effective. Mosquitoes do not have the flight power to penetrate the downdraft of the fan.
- Build houses and villages away from marshy areas and water bodies, which are potential breeding sites. The adult mosquitoes are carried by the wind but few are found 1-2 km from their original larval site.
- Make provision for optimal drainage of rainwater and household water near residential areas.
- Where standing water exists near houses and cannot be drained, larvicides should be applied (Banck, 2004:1; Robert, 2001:70-76; SCAT, 2003:13).

Ultrasound buzzers and Vitamin B supplements do not deter mosquitoes from biting. The abovementioned procedures may seem to be troublesome, but compared to the situation when malaria is diagnosed and admission to a hospital becomes an emergency, these precautions are minor (Chen, Wilson and Schlagenhauf, 2006:2234-2244).

2.13.1.2 Preventative therapy

Resistant *Plasmodium falciparum* parasites are no longer inhibited by *Chloroquine* alone (Anderson & Roper, 2005:269-277). There are two other antimalarial prophylactic groups that prove active against resistant malarial strains. These are *Mefloquine*, for example *Laruim®*, *Mefliam®* and *Doxycycline* (Anderson & Roper, 2005:269-277). Strict adherence to the recommended doses and schedules of the prophylactic drugs selected is necessary for effective protection against malaria.

- Antimalarial tablets are to be taken on the same day and more or less the same time each week.
- Tablets are to be taken after you have had a meal or while eating something.
- The recommended doses should be taken one to two weeks before travelling, throughout the stay and for four weeks after leaving the malarious area.
- Drug allergies and other contra-indications for the use of drugs to prevent malaria should be recorded.
- Complete the full course (CDC/NCID Brochure Publication, 1995:3-4; SCAT, 2003:15).

2.13.1.3 Malaria chemoprophylaxis and the use of vaccines

Malaria chemoprophylaxis should not be used with oral typhoid vaccine due to the possible inactivation of the immunisation. The immunisation should be completed three days before taking *Mefloquine* (Griffin, 1999:25-43, WHO, 2001:3-6). Rabies vaccine should not be used concurrently with malaria chemoprophylaxis. If intradermal Human Diploid Cell Vaccine (HDCV) must be used, *Mefloquine* should not be given concomitantly. Where possible, rabies immunisation should be given one to two months before starting the malaria chemoprophylaxis (Stockley, 1994:145-149).

2.14 MALARIA TREATMENT

2.14.1 Strategic direction for research, disease burden and epidemiological trends

Malaria is a public health problem in more than 90 countries, inhabited by 2.4 billion people. Best estimates for 2005 describe the annual global burden of malaria as 1.1 million to 2.7 million deaths, 300-500 million cases and 44 million disability adjusted life years (Teklehaimanot, Singer, Spielman, Tozan & Schapira, 2005:13-19; Podger, 2002:1). Malaria has many manifestations and its impact varies depending on the epidemiological setting. More than 90 percent of the disease burden is to be found south of the Sahara dessert, and roughly all fatalities (due to *P. falciparum*) occur on the African continent (TDR: Strategic Direction Malaria, 2002:1; Teklehaimanot *et al.*, 2005:13-19). The remaining fatalities due to malaria

worldwide, are spread between the Indian sub-continent, Southeast Asia, Oceania, and the Americas. Following *P. falciparum*, *P. vivax* is the next most significant malaria carrying mosquito. About 80 million humans are suffering from the disease annually, with approximately 15 % on the African continent and 85 % outside Africa (Teklehaimanot *et al.*, 2005:13-19).

The malaria burden differs according to age and gender. Adults have reduced risks due to their ability to develop a degree of immunity to the disease as a result of continuous exposure. Outside Africa, where continuous exposure does not occur, the disease burden extends into adulthood. Pregnant women in Africa are at high risk, and are the major adult risk group in Africa. The malaria burden associated with pregnancy has an additional impact due to the effect on the health of the foetus (Rowe, Rowe, Snow, Korenromp, Armstrong, Schellenberg, Stein, Nahlen, Bryce, Black & Steketee, 2006:6-20; Sachs & Malaney, 2002:680-685).

There is a strong economic and humanitarian dimension to the disease. The poor people and marginalised communities, such as ethnic minorities and people displaced as a result of civil unrest, are at greatest risk of malaria (Njau, Goodman, Kachur, Palmer, Khatib, Abdulla, Mills & Bloland, 2006:299-306; TDR: Strategic Direction Malaria. 2002:1; Teklehaimanot *et al.*, 2005:19). Tendencies over the last three decades point to a deteriorating state of affairs if effective action is not taken. These tendencies include the following:

- an increase in epidemic malaria;
- a rising trend in mortality over the last few decades, including in sub-Saharan Africa;
- an increase in drug-resistant *P. falciparum* malaria;
- the re-emergence of *P. vivax* malaria in countries where it has been eradicated, for example Central Asia; and
- an increase in imported malaria in the developed world, for example the United States of America and the British Isles. (TDR: Strategic Direction Malaria, 2002:1; Teklehaimanot *et al.*, 2005:22-39).

2.14.1.1 Control strategy

The Roll Back Malaria (RBM) strategy emphasises the following aspects:

- early diagnosis and the timely, effective treatment of malaria patients;
- prevention through the use of insecticide-treated products and other vector control measures including larviciding, residual indoor spraying and environmental management;
- prevention of malaria during pregnancy (insecticide-treated bednets and intermittent treatment);
- prevention, early detection and rapid response to epidemics (through preparedness, monitoring, surveillance, and timeous action);
- strategies, methodologies, development of new tools and improvement in distribution of existing tools through research and development; and
- co-ordinated planning and action through establishing partnerships that utilise an optimal range of measures adapted to local conditions (TDR: Strategic Direction Malaria, 2002:1).

Emphasising each aspect is the recognition that it needs to be related to broader initiatives involving education programmes, public health sector development, partnerships (public–public and public–private) and capacity building (TDR: Strategic Direction Malaria, 2002:1; Teklehaimanot *et al.*, 2005:27-39). However, a package of interventions to decrease the bulk of the malaria burden is not affordable in very low-income countries (Sachs & Malaney, 2002:680-685).

2.14.1.2 Challenges for disease control

The burden of malaria persists for numerous reasons. Among them is failure to achieve sufficient coverage with and reduced costing of existing tools such as insecticide-treated bednets and drugs, and there is user ignorance on usage of these products. This is the consequence of supplying information and reasonably priced control tools closer to the community, particularly at peripheral levels of the health care system. Connecting the methodologies and tools related to malaria control and management into a logical, incorporated approach is exceedingly challenging (TDR: Strategic Direction Malaria, 2002:1; Teklehaimanot *et al.*,

2005:59-70). Associated with these constraints, is the lack and failure of financial and human assets to effectively predict, detect, monitor and respond quickly and purposefully to malaria outbreaks. These outbreaks are often tied to complex emergency situations with failure to detect early rises in drug resistance, and subsequent proactive steps to revise drug policies accordingly. The diminishing effectiveness of current existing tools (e.g. surfacing of drug resistance, predominantly to *Sulphadoxine-Pyrimethamine* and *Chloroquine*, resistance to third and fourth line antimalarials in Southeast Asia, and resistance to insecticides, including *Pyrethroids*) is a challenge that demands unambiguous national drug/insecticide policies and consistent regional strategies. These policies and strategies are not always clear or in place, and the strategic execution of the current existing tools is neither optimal nor adequate (Mulligan, Mandike, Palmer, Williams, Abdulla, Bloland & Mills, 2006:453-459; TDR: Strategic Direction Malaria, 2002:1; Teklehaimanot *et al.*, 2005:82-86).

Highly cost-effective new tools are required urgently. These tools are required to replace and supplement the existing ones. Too little energy has been spent on translating scientific data into sensible solutions (tools) and rolling it out into the communities. Tools such as diagnostics that are tailored and packaged for easy use, methodologies for rapid detection of disease outbreaks, monitoring of drug and insecticide resistance and inexpensive drugs are required. The need to launch affordable new treatments due to the increase in drug resistance is particularly important. A reasonably priced vaccine is also anticipated (TDR: Strategic Direction Malaria, 2002:1; Teklehaimanot *et al.*, 2005:82-86). Poor intersectoral and interdepartmental collaboration, inadequate international resources and systems, including a lack of private sector engagement, all play major parts in the persistence of the disease. These trends should be viewed within the context of extreme poverty and an environment in which factors external to biomedical science and public health systems have an impact, e.g. development projects, war, social unrest and weather (Sachs & Malaney, 2002:680-685; Mulligan *et al.*, 2006:452-457).

2.14.1.3 Research needed to address these constraints

In order to improve execution of current malaria control tools, health care delivery strategies must reach the underprivileged and neglected populations. This may involve the formal and non-formal sectors of the international economy, the public and private sectors, and even businesses that are not directly involved in the health sector (Sama, Owusu-Agyei, Felger, Dietz & Smith, 2006:13-21; TDR: Strategic Direction Malaria, 2002:1; Teklehaimanot *et al.*, 2005:88-92).

Better awareness needs to be fostered to do research on social promotion. Attention must also be paid to health education and the development of information and communication methods to develop the understanding of control tools, strategies and interventions at personal, community and systems level. New studies have confirmed the impact of communal marketing on achieving larger allocation of public health goods (e.g. insecticide-impregnated bednets). Nonetheless, these strategies need to be united in resourceful ways with strategies that endeavour to achieve more impartial distribution of the products among the underprivileged, through subsidies or better pricing. Overall, there has been a less than optimal attempt in developing valuable financing policies and strategies. These policies and strategies would remove the affordability barriers to accessing major interventions by the underprivileged and would also be suitable to governments, multilateral organisations and donors (Mulligan *et al.*, 2006:453-458; TDR: Strategic Direction Malaria, 2002:1).

New drugs are needed with qualities that enhance applicability, user-friendliness prolonged existence, acceptance and affordability to the consumer. Other needs include an effective vaccine and new methods of disease control and vector control. There is a demand to adapt fundamental, molecular data on resistance development and monitoring potential into useful tools for field studies. Additionally, molecular-based tests and superior *in vitro* tests for drug resistance could be very useful (Reyburn, Ruanda, Mwerinde & Drakeley, 2006:4; Sachs & Malaney, 2002:680-685; TDR: Strategic Direction Malaria, 2002:1).

An evidence-based information system, to support decision-making, is required in order to better surveillance and information management. This system will improve the efficiency and rationale of malaria control and management. This will allow timely detection of malaria epidemics, increased speed of response to epidemics and identification of resistance to drugs and insecticides as early as possible, enabling relevant and timely policy response. Although some new surveillance tools and strategies are now being assessed, e.g. Mapping Malaria Risk in Africa (MARA), rapid diagnostic kits, improved linkage to a widely accessible information base and studies into the best way to utilise this information, would be valuable. Technical strategies, policies and methods to counter resistance to antimalarial drugs and insecticides need to be developed (Reyburn *et al.*, 2006:4; TDR: Strategic Direction Malaria, 2002:1). Research is needed to identify and confirm indicators to measure the impact of combined antimalarial interventions. Evaluation and monitoring of the impact of control activities and strategies, as well as constant review and modification of strategies to achieve maximum impact, should be an integral component of disease control (Riley, Wahl, Perkins & Schofield, 2006:37-47; Sachs & Malaney, 2002:680-685).

2.14.1.4 Continuous research on malaria

In the Programme for Research and Training in Tropical Diseases (TDR) there is increased emphasis on economic, social and behavioural research, including a better application in social and economic stratification of the malaria risk. Research is in progress on new methods for monitoring public health sector financing methods such as 'sector-wide approaches' (SWAps), tracking of assets to definite diseases within SWAps and evaluating the impact of decentralisation of the health system on specific health outcomes. Investigations into better policies and planning to allocate funds (e.g. SWAps), and improved monetary policies for health care for the underprivileged, are also currently on track (Riley *et al.*, 2006:40-49; TDR: Strategic Direction Malaria, 2002:1; Teklehaimanot *et al.*, 2005:22-27).

Innovative knowledge regarding malaria epidemiology and typical risks is being collected by various agencies (e.g. United States National Institutes of Health (NIH), Wellcome Trust and United States Centers for Disease Control and

Prevention as primary information on drug resistance and vector control. Related research is being sponsored by individuals and scientific companies to spawn fresh information in clinical research, microbiology of malaria parasites pathogenesis and immunology, epidemiology, molecular entomology and disease transmission. There is extensive scope for strategic planning and research linking basic knowledge to the development of new tools and disease management (Dike, Onwujekwe, Ojukwu, Ikeme, Uzochukwu & Shu, 2006:37-53; TDR: Strategic Direction Malaria, 2002:1).

Research on new methods to apply existing control tools is endorsed by the Special Programme for Research and Training in Tropical Disease (TDR). An example is the research done on intermittent treatment with antimalarials (MIT) on babies that can prevent malarial anaemia, a primary cause of morbidity and mortality in patients. New applications for impregnated bednets for pregnant mothers, and the value of MIT with *Sulphadoxine-Pyrimethamine* (SP) were identified during studies in Kenya. Research is also in progress with new formulations and new presentations of drugs available at present, that will better access to malaria control tools in the communities where they are needed (TDR: Strategic Direction Malaria, 2002:1; Teklehaimanot *et al.*, 2005:59-70). Mounting effort is being directed worldwide at the development of new and improved tools and methodologies for malaria control links to public private partnerships, for example Medicines for Malaria Venture (MMV). The prospect of involving industry in partnership for the development of new pesticides is being addressed in an initiative led by the WHO Pesticide Evaluation Scheme (WHOPES). New and improved strategies and surveillance tools are being assessed, for example rapid diagnostic kits and MARA (TDR: Strategic Direction Malaria, 2002:1; Teklehaimanot *et al.*, 2005:72-79).

Projects to assist with policy development occur at a functioning level. Although some research is aimed at policies with specific tools in mind, more integrated research efforts are needed. Efforts are being directed towards how best to inform those responsible for policies and how best to initiate policy changes, taking into consideration new tools as and when they become available. Research is in progress on development of consistent drug policies for malaria treatment and

strategy development to prolong the shelf life of antimalarial drugs. The first chapter of a plan to demonstrate the worth of combination drug therapy over monotherapy for better efficacy has been finalised. This TDR-RBM initiative has been vital in the first steps during the development of policy changes regarding combination drugs as first-line malaria therapy in Africa (Njau *et al.*, 2006:303-313; TDR: Strategic Direction Malaria, 2002:1; Teklehaimanot *et al.*, 2005:81-86). The Multilateral Initiative on Malaria in Africa (MIM) has given the progress in research links between disease specific programmes, health systems and policy programmes a major boost. This initiative finances a number of key projects in Africa and a number of agencies participate in it, including the TDR (TDR: Strategic Direction Malaria, 2002:1). The objective of reducing malaria can in due course only be achieved through local capacity to complete the research, put into practice successful malaria control programmes and expand policy frameworks for control. Schemes sponsored by the Rockefeller Foundation offer generic methods, and some MIM projects also use this approach. Building research capacity can be primarily achieved through lucrative cooperation between endemic malaria countries (TDR: Strategic Direction Malaria, 2002:1; Teklehaimanot *et al.*, 2005:59-70).

International malaria-specific research capacity building tended to direct its focus on Africa. Nevertheless, TDR has widespread projects in Thailand with a dedicated malaria component. Projects to reinforce good practices potential have also had vital spin-offs for malaria, as has the setting up of initiatives such as health care practitioners' assistance to the EU for the launch of the African Malaria Vaccine Testing Network (AMVTN) (TDR: Strategic Direction Malaria, 2002:1; Teklehaimanot *et al.*, 2005:81-86).

The need for ongoing research regarding Malaria Information Systems (MIS) is outlined in five categories, namely:

- Mapping malaria incidence/prevalence. This system is a basic application and involves mapping the incidence/prevalence of malaria over a specific geographic area. The focus is on examining past trends as well as present situations and does not include any statistical analysis, with the possible exception of correlating malaria incidence/prevalence with population in

order to calculate populations at risk (Kleinschmidt, Bagayoko, Clarke, Craig & Le Seuer, 2000:355-361; Gething, Noor, Gikandi, Ogara, Hay, Nixon, Snow & Atkinson, 2006:271-277). The goal of these studies will be to see if any obvious patterns exist.

- Mapping of relationships between malaria incidence/prevalence and other potentially related variables (Hightower, Ombok, Otieno, Odhiambo, Oloo, Lal, Nahlen & Hawley, 1998:266-272; Gething *et al.*, 2006:271-277). The goal of this study is to see if any relationship exist between malaria incidence/prevalence and other variables including: temperature, rainfall, land use, land cover, breeding sites, control programmes, climate changes, population movements and demographics.
- Using innovative methods for the collection of data (Bergquist, 2001:13-20 Schroder, 2006:23-36). Data collection is one of the major limitations of using Geographic Information Systems (GIS). GIS is mostly used for aerial photography and satellite imagery.
- Modelling malaria risk (Snow, Craig, Deichmann & Le Seuer, 1999:99-104; Tatem, Hay & Rogers, 2006:6242-6247). This system is future orientated and focuses on predicting future areas of malaria risk. This malaria risk models typically use many of the same variables discussed above.
- General commentary and reviews of GIS use in malaria control and research (Tanser & Le Seuer, 2002:4).

According to Basu (2002:59-65), some of the challenges of malaria control in poor countries are the production and distribution of malaria vaccine and the control of mosquitoes that harbor the malaria parasite. As stated, the development of a malaria vaccine is indeed likely although it will take years to produce because of both biological obstacles and insufficient research support. The destitution of such a vaccine will require that wealthy countries promise a market to pharmaceutical companies who have traditionally failed to investigate diseases affecting the poorest of nations. The analysis indicated that both endogenous programmes in malarial regions and molecular approaches to parasite control will provide pragmatic solutions to the malaria problem. The successful control of malaria will require sustained support from the wealthy nations, without whom vaccine development and vector control programmes are likely to fail (Basu, 2002:65-75).

Genetic approaches to controlling the transmission of mosquito-borne diseases are being developed to augment the chemical control practices, by means of insecticides, and environmental manipulation methods. Progress has been made in research that seeks to develop antipathogen or antivector effector genes and methods for genetically manipulating host vector strains. Future challenges include discovering a method of spreading antiparasite genes through mosquito populations, determining the threshold levels below which parasites intensities of infection must be held, and defining the circumstances in which genetic control strategies would be employed in the field (James, 2002:1317).

2.15 THE WAY FORWARD FOR TREATING MALARIA

The growth of drug-resistant malaria means that the drugs available to communities are losing their effectiveness (ACT: The way forward for treating malaria, 2001:1; Anderson & Roper, 2005:269-278; WHO, 1999:55-61). Supporting research into affordable alternatives through initiatives such as the Medicines for Malaria Venture (MMV) is an important component of the RBM strategy (Medicines for Malaria Venture (MMV), 2005:1).

Recent evidence indicates that the number of deaths due to malaria in Africa has begun to increase, and that this is attributed to failing medicines and medicines of poor quality (Anderson & Roper, 2005:277-280; Basco, 2004:245-250; WHO, 1999:52-60). Surveys indicate that due to high levels of resistance to the drugs in use, a high percentage of money spent on antimalarial medicines is being used to pay for inappropriate treatments (Anderson & Roper, 2005:269-280 ; Basco, 2004:245-250). On the other hand, research has shown that access to effective antimalarial treatment can significantly reduce child mortality and the frequency of severe malaria. These findings highlight the need for greater efforts on malaria control, combining improved access to effective treatment with preventive measures such as insecticide-treated nets (ITNs) (Tami, Mbatia, Nathan, Mponda, Lengeler & Schellenberg, 2006:1-9; What is Malaria, 2003:1; WHO,1999:55-57).

Bednets must not only be seen as a tool to protect the sleeper underneath the bednet. The net can and must also be used as a baited trap (Curtis, 1996:3-6;

Curtis, 2005:50-51). Spraying residual insecticide on bednets is a very effective tool in managing mosquitoes, because the insects are attracted to the person underneath the net by the carbon dioxide, body odour and heat emitted by the sleeper (Maharaj, 2004:personal communication). The net therefore acts as a baited trap. In comparison with spraying temporary accommodation such as military tents, the amount of insecticide needed to treat the bednets is much less (Curtis, 1996:3-6; Curtis, 2005:50-51). Netting is a more favourable substrate for a residual insecticide than the non-absorbent and smooth surface of a military tent (Curtis, 1996:3-6). In addition, mosquitoes come in contact with the bednets in their search for a human blood meal, while normal residual spraying presupposes that the insect will sit and rest on the surface inside the tent before or after feeding, which is not the habit of the *Anopheles* mosquito (Curtis, 1996:4-7; Curtis, 2005:50-51).

Antimalarial drugs, when used as monotherapies, are rapidly losing their effectiveness. In some places, malaria is resistant to all affordable first-line therapies. Moreover, few new affordable drugs are being developed to replace those being lost due to resistance. This is largely because malaria, being a disease of the poor, resulted in the research-based pharmaceutical industry not considering the malaria drug markets as a lucrative investment opportunity (Millennium Project, 2006:1; Ridley, 2001:1).

Monitoring the extent and spread of drug resistance is an important aspect of containment. Resistance to a drug does not necessarily extend uniformly across a country, and there may be pockets within regions where resistance prevails or where the drug is still effective. However, too often victims of malaria and health care providers do not know if the malaria they are facing is drug-resistant or not. Areas of drug resistance therefore have to be identified and, where appropriate, alternative drugs have to be recommended and made available. In order to make this possible, the WHO is supporting countries to map drug resistance, and recommends that countries begin the transition to an effective new treatment when or before levels of resistance to the drugs begin to exceed healthy levels (Kakkilaya & Chakrapani, 2006:1; Killer Number One: The Fight Against Malaria, 2005:1).

The next step is to line up strategies to contain the spread of resistance. Experience has shown that when two or more drugs with different biochemical targets in the malaria parasite are used in combination, the development of resistance to both drugs can be delayed. Drug combinations containing *Artemisinin* derivatives have the highest therapeutic efficacy and the greatest potential to delay the onset of resistance. Because *Artemisinin*-based combination therapies (ACTs) comprise two medicines which work in different ways, it is thought unlikely that the malaria parasite, which has rapidly developed resistance to other, single treatments, would evolve to resist these medicine combinations. In many African countries, more than three-quarters of all malaria cases are first treated at home with antimalarial drugs purchased from small local shops or from travelling vendors. The RBM partnership is working to provide simple regimes of new, effective drugs and to train mothers, caregivers, shopkeepers and community workers to correctly diagnose malaria and provide early and appropriate treatment near or in the home (Malaria, 2002:1; Medicines for Malaria Venture (MMV), 2006:1).

Even at cost price, many countries will not be able to afford the new recommended treatments from their national budgets, nor will they be able to treat sick people from their own resources. There is, therefore, a critical need to address worldwide support for the financing and pricing of ACTs, and to amplify efforts to develop new, affordable antimalarial drugs, preferably with simplified treatment regimes to encourage compliance (ACT: The way forward for treating malaria, 2001:1). A very positive development is that the Board of the Global Fund to Fight AIDS, TB and Malaria (GFATM) has approved funding proposals from malaria endemic countries to roll back malaria, and to use ACTs. Following their first-cycle awards to support ACT deployment in Zambia and Zanzibar, an increasing number of proposals from countries in Africa has been approved in subsequent funding cycles to implement ACT-based treatment policies. As a result, GFATM awards for the procurement of ACTs in African countries have increased exponentially. This trend, if continued, offers much hope (ACT: Facts On, 2005:1). In the 1920's Michael Kremmer, senior fellow in Economic Studies at the Brookings Institute in Washington, made the following statement (Kayle, 1999:2):

“The critical problem is finding the money for malaria research, development and distribution. There is simply not enough money in malaria, as drug companies know. Since the mosquito can transmit the disease only in warm temperatures, the disease is highly concentrated in tropical climates. But people in the tropics are overwhelmingly poor and in no position to pay for antimalarial prophylaxis and so drug companies have little incentive to fund research. In short, the 2,4 billion people in the tropics who are vulnerable to malaria provoke remarkable little research effort”.

As case in point is that malaria research is carried out mainly in government research institutes all suffering from limited budget resources. Worldwide malaria research amounts to \$84 million annually, or perhaps \$42 per malaria fatality. This expenditure is tiny compared to what is spent on diseases affecting richer and more temperate areas. Most current information on research funding for asthma was about \$800 million or \$500 per fatality in 1999 (Kremer, 1999:1).

Ironically, the very phenomenon that is leading to Africa’s increased malaria cases may actually save the continent. Global warming is taking malaria to the rich. The increase in the average temperature during winters and summers in the northern hemisphere is making it more tolerable for the *Anopheles* mosquito to live and breed. The World Health Organisation has reported that Europe has experienced a tenfold increase in malaria during 1997 to 1999. In 1999, 200 000 cases of malaria were reported in Europe (Okenu,1999:1)

While the chemoprophylactic options against *Chloroquine* resistant malaria is far from ideal, the situation is improving with the licensing of *Doxycycline* and *Atovaquane/Proguanil* for this purpose. The regiments still suffer from the following limitations: inadequate protection, unpleasant side-effects, high cost, inadequate trials or experience the need for prolonged continuation of drug after leaving malarious area, and frequent dosing. There is hope for the future with new drugs

under trial either alone or in combination. Malaria vaccines remain a hope for the distant future, but for the present we are dependent on reducing the risk of being bitten by mosquitoes and available medicines for chemoprophylaxis (Bradley & Bannister, 2003:180-199; Flanagan, Buckley-Sharp, Doherty & Whitty, 2006:233-237).

2.16 THE DEVELOPMENT OF *MEFLOQUINE* AS AN ANTIMALARIAL AGENT

The discovery of *Mefloquine* and its subsequent development has been closely associated with military imperatives, contingencies and requirements. The following discusses military experience with *Mefloquine* in an attempt to generate a perspective for future policy.

2.16.1 *Mefloquine* as an antimalarial agent

The healing properties of the bark of the cinchona tree, chewed or made into a mixture, were probably known by the Inca tribe long before it first attracted European attention. In 1630, the wife of the Viceroy of Peru, Countess Cinchon, was reputedly given a concoction of tree bark by Juan Lopez, a Jesuit, for the treatment of an ague (Burba, 1999:1-3; Kitchener, 2003:34-38). When the Countess recovered, she distributed, in her beneficence, the recipe to the poor of Peru for treatment of the illness. From the year 1641 the bark was officially exported to Spain. Malaria was identified as being endemic in the Iberian peninsula and southern Europe during that period, and the new treatment was gradually accepted by the people for the treatment of ague (Burba, 1999:1-3; Kitchener, 2003:34-38).

James Lind, a surgeon, described the specific pharmaceutical applications of the powdered bark in 1760's. The drug was listed in the London Pharmacopoeia by 1677, and Lind specifically described the applications in an attempt to reduce the indiscriminate use that had developed. During 1820, two scientists, Pelletier and Caventou, isolated *Quinine* and *Cinchonine*. This allowed accurate dose

prescribing of the alkaloid content in the bark (Caventou, Pelletier and Quinine, 2001:1, Kitchener, 2003:34-38).

In 1865 the next milestone in the development of antimalarial drugs was achieved. In this year seeds were extracted from trees in the Bolivian Andes and covertly sent to London. These seeds were purchased by the Dutch consul for plantations in Java. In doing that the production of cinchona alkaloids was diversified and that made the potential control of the ague in military and trade missions to the East Indies much more uncomplicated (White, 1996:1122-1123). The first synthetic antimalarial drugs were developed in 1926. The development was done through clinical trials by German pharmaceutical companies (*8-aminoquinolines* and *Pamaquine*). After the development of *8-aminoquinolines* and *Pamaquine*, *Primaquine* and the *4-aminoquinolines* followed, which later led to *Sontoquine* and *Chloroquine* (Method of Treating Malaria, 1981:1).

By December 1941, Japan had conquered the Indonesian archipelago and Malaya. By Japan gaining control of most of the cinchona plantations, the country had monopolized the supply of *Quinine* to the rest of the world (White, 1996:1122-1123). Due to that, the supply of *Quinine* to the Western Alliance was marginalised. During the following campaign of British and Australian forces in Burma and New Guinea, non-battle casualties were crippling. Subsequently, the Australian Army responded to this experience by founding the Medical Research Unit (MRU) under the command of colonel Fairley (Kitchener, 2003:34-38; Stockton & Clayton, 2001:1).

The MRU was predominantly triumphant in the research they conducted with *Atabrine* (*Mepacrine*) for operational use in New Guinea. The present Army Malaria Institute was born out of the MRU. Military events and the increasing non-battle casualties were a huge catalizer in stimulating research and development regarding antimalarial agents (Kitchener, 2003:34-38). Following the success of *Mepacrine*, the United States, by means of the Walter Reed Army Institute of Research (WRAIR), increased their development efforts on *Chloroquine* (Alving, 1954:209-218) and continued the research into prolonging the antimalarial effects of the cinchona alkaloids (Garnham, 1984:1305-13108; Kitchener, 2003:34-38).

Numerous allied nations became occupied after the Second World War in wars taking place in South-East Asia. Again, these nations sustained great numbers of non-battle casualties from malaria. During that period, it was discovered that *Cinchonine* and *Quinine* were evidently metabolised by oxidation at the 2-position of the cinchona side-chain (Kitchener, 2003:34-38).

About 120 different compounds were manufactured at Walter Reed Army Institute of Research (WRAIR) after the end of the Second World War. An early compound (WR30090) was taken to field trials, on behalf of the class *2-phenyl-4-Quinoline Methanol*, which is part of the second generation of *Quinoline Methanols* from the cinchona alkaloids and *Quinine* (Pharmacology of Current Malaria Chemotherapy, 1999:1). The above mentioned drugs, which were in the class of blood schizonticides, developed by WRAIR, were useful as suppressive chemoprophylaxis applied in the treatment of non-relapsing (non-*vivax*) malaria. Unfortunately, these compounds have no effect against the pre-erythrocytic hepatic stage of any of the plasmodial species. As a result, they do not provide any true causal prophylaxis against malaria. Another concern is that the drug is also inactive against the liver hypnozoites of *Plasmodium vivax* and therefore does not inhibit relapses of *vivax* malaria (Adak, Valecha & Sharma, 2001:891-894).

The research into and discovery of *P. falciparum* malaria resistant to *Chloroquine* stimulated the research into blood schizonticidal agents to replace *Quinine*, and particularly *Chloroquine* (Baird, 2004:4075-4083). The appearance of *Chloroquine*-resistant *falciparum* malaria in countries of military concern to the United States in South America and South-East Asia coincided with the intensification of preclinical trials with WR30090 (White, 1996:1122-1123). In early clinical trials, the *falciparum* malaria parasite tolerated WR30090, with moderate and high resistance to *Chloroquine* (Martin, Arnold & Clyde, 1973:214-219).

Consequently, WR30090 was used in Thailand for treatment trials against known *Chloroquine*-resistant *falciparum* malaria. Although the drug was effective against malaria, it produced serious neurological and gastrointestinal side-effects in patients, and was thus problematic to use (Clyde, McCarthy, Robert & Miller, 1973:220-223). As a result of these findings, WRAIR developed WR142490 (*Mefloquine*). In 1974

Rieckmann, Trenholme & Williams first published studies regarding the efficacy of *Mefloquine* as a prophylactic agent against *falciparum* malaria (Rieckmann, Trenholme & Williams, 1974:375-377) and the following year they wrote a paper on the treatment of malaria with *Mefloquine* (Trenholme, Williams & Desjardins, 1975:792-794). In 1976 Clyde and colleagues published their findings regarding the suppressive activity of *Mefloquine* against sporozoite-induced infection in humans (Clyde, McCarthy, Miller & Hornick, 1976:384-386). Following the necessary research, it was found that *Mefloquine* was effective against all known resistant strains of *falciparum* malaria (Kitchener, 2003:34-38). In the decade after these initial pre-registration trials, it was still evident in future field trials that *Mefloquine* was effective in areas of known *Chloroquine*-resistant *falciparum* malaria. Pre-registration trials were done in Africa, South-East Asia, China and South America, which including children with complicated malaria (Chongsuphajaisiddhi, Sabchareon & Chantavanich, 1987:223-226). Trials also indicated corresponding efficacy with *Chloroquine* in managing a *vivax* malaria patient (Alcantara, Uylangco, Sangalang & Cross, 1985:534-538). During the time of *Mefloquine*'s general availability in 1985, clinical evidence of parasites resistant to the drug began to appear in the Australasian region (Hoffman, Rustama & Dimpudus, 1985:1039-1040). Due to increasing resistance of antimalarial drugs on the African continent and India, strategies to "protect" the new drugs, for example *Mefloquine*, were recommended in an attempt to slow down the development of resistance (Peters, 1985:705-715). The use of combination drugs such as *Mefloquine* with *Sulfadoxine* and *Pyrimethamine* (MSP) was one strategy recommended for delaying the development of resistance to antimalarial drugs. Although initial use of MSP did not produce any visible benefits (Hoffman *et al.*, 1985:1039-1040), the combination did become the chosen therapeutic option on the Asian and African continents, in areas of known or suspected *Mefloquine* resistance (Guo, Arnold & Fu, 1988:538-540).

2.16.2 Current recommended use of *Mefloquine*

The suggested regimen for malaria prophylaxis with *Mefloquine* is 250 mg weekly, starting three weeks prior to exposure. For treatment, the dose of *Mefloquine* varies from 15 mg base/kg in semi-immune patients to 25 mg base/kg in non-immune patients (White, 1996:1122-1123). The Australian Defence Force follows a split-

dose regimen of 15 mg/kg given in three doses (750 mg, followed by 500 mg six hours later, then 250 mg a further six hours later) to ease unpleasant side-effects (Kitchener, 2003:34-38).

2.17 INFORMATION ON MEFLOQUINE HYDROCHLORIDE

2.17.1 Brandname: Mefliam® (Package Insert: Annexure B)

Mefloquine is a *Quinoline Methanol* derivative, structurally related to *Quinine*. *Mefloquine* is a blood schizontozide with effects on the asexual blood forms of the malarial pathogens that affect humans. It is also active against the gametocytes of *P. vivax*, although the mechanisms of action are unknown. *Mefloquine* has no effect on the hepatic stage of malaria parasites, and strains of *Plasmodium falciparum* resistant to *Mefloquine* have been reported. Cross-resistance between *Halofantrine* and *Mefloquine* has been observed, and resistance to *Mefloquine*, as well as to any other antimalarial drug, may occur in any endemic area. Resistance patterns occur and vary from region to region and with time (Mefliam® package insert, 2002:1).

2.17.2 Pharmacokinetics

The maximum plasma concentration after a single oral dose is reached in 6 to 24 hours (average 17 hours). This achieved plasma concentration in nanograms per millilitre is roughly equivalent to the dose in milligrams. In optimal circumstances with weekly doses of 250 mg, a maximum plasma concentration of 1000 mg/ml has been recorded. *Mefloquine* is 98% bound to plasma proteins and has a large apparent volume of distribution (13.5–29.1l/kg). The main metabolite of *Mefloquine* 2, 8-Bistrifluoromethyl-4-Quinoline carboxylic acid is inactive against *P. falciparum*. It appears that *Mefloquine* is mainly excreted into bile and faeces and that the elimination half-life of *Mefloquine* is three weeks. After a single dose in healthy adults, it was between 12–37 days on average (Mefliam® package insert, 2002:1).

2.17.3 Contra-indications

Mefloquine is contra-indicated in children under five kilograms in body mass. It is also contra-indicated with pregnancy, lactation, a history of epilepsy or psychiatric disturbances and impaired liver or kidney functioning. The drug is excreted in breast milk and if it must be taken, breast feeding should be discontinued (Mefliam® package insert, 2002:1).

Special care should be taken when scuba diving, piloting an aircraft and driving heavy machines, as dizziness and vertigo have been reported. Other side-effects include psychiatric disturbances, convulsions, cardiac abnormalities and gastrointestinal problems, such as diarrhoea and vomiting. *Mefloquine* must not be used for longer than three months consecutively (Mefliam® package insert, 2002:2). Drug interactions include an increased risk of convulsions when *Quinine* is used if malaria does occur. A potentially fatal conduction disorder of the heart is possible if *Halfan* is used when malaria does occur, or if taken with some medications for high blood pressure blockers and calcium channel antagonists, antihistamines and antidepressants (Mefliam® package insert, 2002:2).

It is recommended that the dosage for adults and children over 45 kilograms be one 250 mg tablet once a week, starting one week prior to entering a malaria area and continuing for four weeks after leaving the area. The tablet should be taken after a meal, preferably after supper. A doctor's prescription is required (Mefliam® package insert, 2002:3).

Preventative medication for people entering a malaria area is absolutely essential (Bradley & Bannister, 2003:180-199). Mefliam® tablets are indicated for prophylaxis of *Plasmodium falciparum* malaria in the regions where *P. falciparum* strains resistant to 4-aminoquinolines (e.g. *Chloroquine*) occur.

2.17.4 Dosage and directions for use

As seen in 2.16, 2.18 and 2.19, history has shown that substantial sickness will occur among military forces if the use of the correct type and dosage of preventative medicines is delayed.

Table 2.1: Weekly recommended doses of Mefliam® as malaria prophylaxis

Body weight	Weekly dose for prophylaxis
Up to 19 kg	¼ tablet (82.5 mg)
20 – 30 kg	½ tablet (125 mg)
31 –45 kg	¾ tablet (187.5 mg)
>45 kg	1 tablet (250 mg)

(Mefliam® package insert, 2002:3)

2.18 THE MILITARY EXPERIENCE OF *MEFLOQUINE* MALARIA CHEMOPROPHYLAXIS

The development of synthetic antimalarial drugs was given a vital start in the Second World War when Japan captured the world's core supplies of *Quinine* in Java. *Chloroquine* and *Mepacrine* were the primary agents developed at that time (Cotton, 2005:1).

Since World War II, the development of *Chloroquine*-resistant *falciparum* malaria has driven the hunt for new drugs. *Mefloquine*, developed by the Walter Reed Army Institute of Research in the United States, was first proven to be effective for prophylaxis and treatment of resistant *falciparum* malaria in the 1970's (Laruim Label update, 2002:1-8).

Mefloquine concentrates on the blood stages of the *Plasmodium* life cycle after the discharge of merozoites from the liver. It does not have tissue schizonticidal activity, and so does not heal those forms of malaria retained in the advanced liver stages (hypnozoites). It does not take action against the sexual stages taken up by the mosquito in the life cycle, and therefore does not block transmission.

Mefloquine is associated with neuropsychiatric and gastrointestinal unfavourable reactions, but no more so than other antimalarial drugs. Dosage regimens for *Mefloquine* prophylaxis are simpler than those for other comparably efficient antimalarial drug regimens (Department of Health and Human Services, 2006:1).

2.19 MILITARY USE OF MEFLOQUINE

During the British military exercises in central Kenya, the British Army policy for malaria chemoprophylaxis, recommended *Chloroquine* 300 mg weekly and *Proguanil* 200 mg daily. Following seven cases of malaria sustained among only 150 soldiers during an exercise in 1992, the policy was reassessed (Miller *et al.*, 1994:119-123). Even though compliance with chemoprophylaxis was not officially monitored, the policy was changed to *Mefloquine* 250 mg weekly (Miller *et al.*, 1994:119-123). The policy change of the British Army in favour of *Mefloquine* was interesting in that the experience of the Dutch military did not favor *Mefloquine*. During their deployment to Cambodia during 1992–1993, three battalions (\pm 600 troops/battalion) of Dutch marines that used *Mefloquine* chemoprophylaxis contracted *falciparum* malaria (Hopperus Buma *et al.*, 1996:1506-1509). Even though the Dutch soldiers were deployed in regions where *Mefloquine*-resistant *falciparum* malaria was potentially endemic, compliance was only 86%, and 30% of the marines reported unpleasant side-effects. The Dutch nevertheless concluded that *Mefloquine* was “well tolerated”, though not entirely effective, after comprehensive supervision of the final group, (Jaspers *et al.*, 1996:230-234).

For the British Army, Croft pointed out in his studies that *Mefloquine* toxicity was equivalent to that of other brands of chemoprophylaxis currently in use (Croft, 1995:191). In later studies by Croft, he demonstrated that less than one in 6000 soldiers deployed in Kenya had the symptoms of neuropsychiatric side-effects (Croft & World, 1996:326). The findings of his studies showed that operational British soldiers did not report any more side-effects from *Mefloquine* than from the combination of *Chloroquine* and *Proguanil* (Croft, Clayton & World, 1997:199-203). During subsequent military peacekeeping operations in East Africa, more information arose concerning the use of *Mefloquine* under operational conditions.

Between December 1992 and May 1993, 48 troops, out of a group of 9000 contracted malaria whilst deployed to Somalia (Wallace *et al.*, 1996:49). *Mefloquine* effectiveness in the region was incomplete. On interview, more than half of these subjects reported compliance with chemoprophylaxis; however, half of the group interviewed had been prescribed inadequate doses of *Doxycycline* or *Mefloquine* (Robert, 2001:73-76; Newton *et al.*, 1993:1).

Members of the Italian military force operating in Somalia were less infected. Only 18 members contracting malaria were using *Chloroquine* 300 mg weekly and *Proguanil* 200 mg daily among 11 600 soldiers deployed (Peragallo *et al.*, 1997:343-346). In the light of the British experience in Kenya, these results were positive (Miller *et al.*, 1994:119-123). Nevertheless, in 1992 the combination drugs of *Chloroquine* with *Proguanil* began to fail the Italian forces, as they sustained 100 malaria casualties in the first three months of deploying 4800 peacekeepers to Mozambique. Their response was to use *Mefloquine* 250 mg weekly, the same as prescribed by the British chemoprophylaxis policy. Due to this decision the subsequent malaria casualties were limited to 19 in the last two months of the operation (Peragallo *et al.*, 1997:343-346). In the subsequent review of the two operations, collectively involving 5120 Italian soldiers, *Mefloquine* chemoprophylaxis was identified as the drug easier to comply with, and no greater discontinuation rate than *Chloroquine* and *Proguanil* chemoprophylaxis was recognised (Peragallo *et al.*, 1999:73-77).

Brazilian peacekeepers were deployed to Angola for six months in 1995–1996. They used *Mefloquine* 250 mg weekly for malaria chemoprophylaxis (Sanchez *et al.*, 2000:275-282). Notwithstanding this regimen, 78 of the 439 soldiers contracted clinical malaria. Due to this outbreak of malaria, an investigation was conducted in partnership with the US military. The findings of this investigation were that a more efficacious chemoprophylactic drug was needed for military forces deployed in endemic malaria areas (Sanchez *et al.*, 2000:275-282).

In another international operation supported by the US Army, non-immune Indonesian soldiers were deployed to Irian, Java. These soldiers were originally from non-malaria endemic regions of Indonesia and were provided with *Mefloquine*

250 mg weekly, *Doxycycline* placebo, *Doxycycline* 100 mg daily and *Mefloquine* placebo or only placebo tablets for the first three months of posting (Ohrt *et al.*, 1997:966-969). The regimen of *Mefloquine* chemoprophylaxis proved itself to be effective and the minimum side-effects were reported. This result was similar to the finding of earlier studies by the US AFRIMS group, who did their study with the Royal Thai Marines on the Thai-Cambodia border. The findings of the study were that *Mefloquine* was well tolerated and compliance readily achieved (91%) (Suriyamongkol, Timsaad & Shanks, 1991:515-518).

The Australian military experience with *Mefloquine* was limited. *Doxycycline* 100 mg daily was the main chemoprophylaxis regimen since replacing *Chloroquine* and *Maloprim* in the early 1990s. After the increasing failure of this combination regimen under field conditions in Papua, New Guinea, it was changed to *Doxycycline* 50 mg daily with *Chloroquine* 300 mg weekly (Rieckmann, Yeo & Davis, 1993:446-449). Various combinations of chemoprophylaxis were considered and tested, including *Mefloquine* 250 mg weekly, which was found completely effective in protecting a small group of soldiers against *falciparum* malaria. Without using *Primaquine* terminal prophylaxis to address liver stages of the parasite, *vivax* malaria occurred on return to Australia. *Mefloquine* was established as the first alternative to *Doxycycline* 100 mg daily for short-term exposures in malaria endemic areas (Edstein, Nasveld & Rieckmann, 2001:12-16). It was used in this capacity for those intolerant to *Doxycycline* during Australian deployments to Cambodia and Somalia and exercises in Papua New Guinea, although numbers of personnel using this regimen were very small (Shanks, Roessler, Edstein & Rieckmann, 1995:443-445).

CHAPTER 3

3. METHODOLOGY AND INTERPRETATION OF DATA

3.1 OVERVIEW

The previous two chapters focused on the origin, history and incidence of malaria in the armed forces of the world, and on the importance of studying malaria as a global problem. The review of the literature also focused mainly on the incidence of malaria in soldiers deployed to Eastern Africa.

As South African troops were deployed in East Africa as a peacekeeping force in Burundi, the threat of malaria infection was imminent. This study therefore aimed to explore South African National Defence Force (SANDF) members' attitudes to, and compliance with anti-malaria medication. This sample group of this study was soldiers. All the members that filled in the questionnaires were in their second last month of their deployment of six months. Various factors influencing malaria were highlighted.

The sample group comprised SANDF members who were in their second last month of a deployment period in Burundi of six months. Data were collected using a questionnaire, which respondents completed voluntarily. Questions highlighted various aspects of malaria as it would affect the SANDF members under investigation. This chapter outlines the methodology used to approach the research process in order to investigate the issues in question. The questionnaire design, sample selection and size, administration of data capturing and the data collection procedures are explained. The limitations, as well as the criteria for admissibility of the data are identified.

3.2 THE DESIGN OF THE STUDY

It is envisaged that the results of this study will be used by the personnel of the SANDF and other military forces deployed in East Africa. The findings could be

used by military forces designing a control programme, as well as by others involved in the control of malaria, such as policy and decision makers.

Burundi is a country with enormous tourism potential. When a democracy is achieved in the country and peaceful settlement is found among the warring rebel groups, this country will be a true paradise for tourists. The Tanganyika Lake and the lush equatorial forests make this area a potential popular tourist attraction (Briggs 1998:202). Unfortunately, the malaria mosquito is endemic to this area, and it is important that the results of the study be made available to tourists to establish which chemoprophylactic regime would be most suitable to use. This should also be of interest to anyone else whose activities may have an impact on the malaria situation or its control in that region.

3.3 THE AIM OF THE STUDY

The aim of the study was to investigate the prevalence of malaria in the users of *Mefloquine Hydrochloride* – Mefliam®. This drug was administered to soldiers stationed in Burundi, East Africa.

The results of this study could also be expoliated to the local population. It was argued that, if *Mefloquine* is the drug of choice and proves to be effective during military deployments to Burundi, it could be presumed that the *Plasmodium* organism in that area was not resistant to *Mefloquine*. *Mefloquine* would thus be regarded as an effective malaria management tool and hence as a therapeutic and preventative drug.

The information gathered in this study would aid the armed forces of the world. This information would help in selecting the most effective antimalarial prophylaxis to use during extended deployments to Burundi. The results of this study would show the efficacy of *Mefloquine Hydrochloride* - Mefliam® as an antimalarial drug. This would determine if the use of this drug would reduce the risk of malaria infection among military force members deployed in Burundi.

The results of the study could also be helpful to international travellers visiting that part of the continent. The fact that hundred and eleven (111) people used Mefliam® and only four members presented with any malaria symptoms, is a good indicator that Mefliam® is a good option as an antimalarial drug in Burundi.

3.4 SAMPLE SELECTION

The target population was South African National Defence Force soldiers deployed in Bujumbura, Burundi, for more than hundred days. Based on the advice of Mr C.K.M. Makgadi (MA, Research Psychology), the sample size was determined. The total size of the group/population was 336 members and the sample group size (chosen portion) was 111 members. Of the 336 members, 11 (3.29%) were females.

The demographics of the different race groups were:

- 229 (68.37%) Black;
- 70 (20.84%) Coloured;
- 33 (9.87%) Caucasian; and
- 4 (0.91%) Asian.

The figures above indicate that the race groups, as well as the gender groups were represented according to percentage representativity in the research study. The research group (111) represented 33.04% of the total group.

No control group was established, as ethical and moral guidelines prohibiting people from entering an endemic malaria area without access to proper antimalarial prophylaxis.

The questionnaire design, sample selection, administration of data capturing and data collection procedures are identified.

The sample was determined by means of simple random sampling. This method was used to ensure that every member of the accessible population had an equal chance to be included in the sample (Leedy, 1989:140). The lottery method was used by allocating a number to the name of each member of the population. These

were put into a container. The container was then shaken and names were randomly drawn from the container until the required number of names had been selected (Lues, 2003:39). The exploratory research method was used to gain insight into the group involved. Using the social survey method, a questionnaire was designed and administered to each voluntary respondent (Lues, 2003:45). Before responding, each participant gave his/her informed written consent. The responses to the questionnaire were analysed, interpreted and ordered.

3.5 DATA COLLECTION

The first objective was to identify the persons using Mefliam®. The information required was identified by means of the questionnaires (Annexure A) using the descriptive survey method (Leedy, 1989:140). The study was of an explanatory, descriptive nature and the survey mode of observation was used in the form of questions contained in the questionnaire.

The first part of the questionnaire distributed to the soldiers determined their ethnic background. The respondents were required to supply the research team with the name of the antimalarial prophylaxis used.

This information enabled the research team to detect what kind of prophylaxis each respondent was using at the time of the investigation. The alternative drugs used were Mefliam® and *Doxycycline*. The airforce pilots and two female respondents used *Doxycycline*. The female respondents probably used *Doxycycline* due to the side-effects of Mefliam® indicated in the Mefliam® package insert (2002:2).

3.6 QUESTIONNAIRES

Questionnaires were administrated to the selected soldiers of the SANDF deployed in Burundi, East Africa. The questionnaire aimed to determine the following:

- perception of the user regarding the malaria threat;
 - compliance with taking the medication;
 - possible side-effects which may have occurred due to the chemoprophylaxis;
- and

- the prophylactic efficacy of Mefliam®.

Each respondent gave their written consent. The questionnaire was compiled in English, which is the language medium of the South African National Defence Force.

3.7 QUESTIONNAIRE FORMULATION

3.7.1 Objectives

Guidelines for the design of the questionnaire used were obtained from the following sources:

- Makgadi (personal communication, 2002); and
- Hlongwane (personal communication, 2002)

The questionnaire was developed to determine respondents' views on sickness and health, this specific knowledge of malaria, and their compliance with anti-malarial regimens.

Questionnaires were then constructed in five broad analytical categories addressing demographic and personal data, knowledge of anti-malarial medication, and knowledge and beliefs about and practices with regards to malaria. The questionnaire (Annexure A) was designed to attain the following objectives:

3.7.2 Independent variables (zero control variables)

Section one of the questionnaire obtain socio-demographic information regarding the users of Mefliam®:

- Age
- Services (occupational class)
- Home Language
- Home Province
- Gender
- Race

3.7.3 Dependent variables

The second category in section two of the questionnaire, involved experiences, perceptions, beliefs and views on malaria and anti-malarial prophylaxis.

The third category in section three of the questionnaire, involved the respondents' knowledge regarding Mefliam®.

The fourth category involved the treatment regimen. Questions explored respondents' perceptions regarding the convenience of the drug use, the necessary behaviour change, as well as the reactions to and perceptions regarding the medication. As a qualitative rather than empirical study, the content validity of the questionnaire was developed not through pilot studies, but by refinement and sharpening of the questions during the pre-testing phase that took shape in the form of personal interviews. The people involved in the interviews were randomly chosen from the same group of people that were used in the actual study.

3.7.4 Breakdown of sections

In order to achieve the objectives listed in section 3.7.1, a structured questionnaire (Annexure A) consisting of 5 sections was designed.

SECTION I

Socio-demographic data collected

Questions 1.1 to 1.6

SECTION II

Information on the knowledge of malaria and the use of anti-malarial prophylaxis before, during and after deployment in endemic malaria areas.

Questions 2.1 to 2.6

SECTION III

Information regarding the anti-malarial prophylaxis in use and feedback concerning the use or experience of the drug.

Questions 3.1 to 3.6

SECTION IV

The users' personal experience with the drug.

Question attempted to determine whether the user contracted malaria while using the drug.

Question 4.1 to 4.5

SECTION V

Any concerns or problems about the anti-malarial drug in use were offered by the respondents' in this section.

Question 5

3.8 ADMINISTRATION OF DATA CAPTURING

The questionnaires were all handed out to the respondents while in the deployment area. The questionnaires were administered to eight groups of 15 SANDF soldiers over the course of 2 days. The questionnaires were gathered immediately after completion.

The front page of the questionnaire explained the importance of the study and requested their co-operation (Annexure A). The respondents were informed of the confidential nature of their responses to the questionnaire. The questionnaires were completed in the presence of the researcher. There were no time constraints in completing the questionnaires.

Questionnaires were used for the following reasons:

- A questionnaire is one of the strongest measuring tools (Lues, 2003:49).
- Due to the fact that the respondents were all military personnel, they were geographically fairly easily accessible.

3.9 SAMPLE REALISATION

Questionnaires were handed to 120 participants. As eight of the sample group used *Doxycycline*, and would therefore not conform with the aim of the study, they were not included. The other 112 respondents used Mefliam®. One of the questionnaires was not completed. The return rate for the questionnaires was 100%. Hundred and eleven (92.5%) of the initial 120 questionnaires were relevant to the study.

3.10 ANALYSIS OF THE DATA

Data were entered onto a Microsoft Excel spreadsheet and analysed using the SAS Statistical Programme. The confidence interval and Wilson reliance interval (score method) were utilised as statistical guidance tools.

Confidence interval (CI)

p = proportion of positive responses

n = individuals

r = characteristics of interest

z = 1,96 for a 95 percent confidence interval

begin value; top value = $[p - z\sqrt{p(1-p)}; p + z\sqrt{p(1-p)}]$

n = 111

r = 4

$p = r/n = 4/111 = 0,036 = 3,6\%$

CI of population: $p \pm z\sqrt{p(1-p)}/n$

Wilson reliance interval (score method)

$A = 2r + z^2$; $B = z\sqrt{z^2 + 4r(1-r/n)}$; $C = 2(n + z^2)$

CI = $[(A-B)/C; (A+B)/C]$

Detailed reporting and interpretation of the data are presented in Chapter 4.

3.11 POSSIBLE LIMITATIONS

The study took place in a military environment. Some of the respondents could have been intimidated by the more senior ranks of the members who handed out the questionnaires, and could have responded by stating what they wanted their seniors to hear, and not the actual truth.

To eliminate this possibility of intimidation as far as possible, the members were referred to the medical confidentiality of the document when completed, and the legal implications of information leaking out. Before the questionnaires were eventually handed out, the members were also briefed by senior management regarding the confidentiality of the process, and their co-operation was asked.

3.12 SUMMARY OF CHAPTER 3

This chapter outlined the procedures followed in obtaining the data using the simple random sampling and lottery method. Every member of the accessible population had an equal chance to be included in the sample (Leedy 1989:140). The survey research study used observation (questionnaires) to obtain the data. The methodology used to obtain the data was discussed. The process included an examination of the sample selection, administration of the data capturing, questionnaire formulation, determining criteria for the admissibility of the data and the interpretation of the data. The limitations of the survey were discussed.

CHAPTER 4

4. RESULTS

4.1 OVERVIEW

The method of data collection was discussed in the previous chapter. In this chapter the results of the processed data are tabulated, interpreted and evaluated. Only relevant results that emerged are dealt with. The following results are reported:

- perceptions of malaria threat;
- awareness of preventative methods to avoid contracting malaria;
- malaria history of members;
- perceptions of malaria and the use of anti-malarial prophylaxis during deployment;
- knowledge of the anti-malarial drugs which were used at the time of the study;
- the importance of taking the anti-malarial prophylaxis; and
- ascertaining whether the users of Mefliam® contracted malaria during their deployment in Burundi.

4.2 RESULTS

4.2.1 Gender of respondents and malaria infection

Due to the hostile nature of the area in which the SANDF soldiers are deployed, and the fact that Burundi is a Muslim country, only a few females were part of the contingency. Although the study aimed to get maximum participation from the female group, only six of the eight women participated in the study (Table 4.1).

Table 4.1: Gender of respondents (n = 111)

Male	Female
% (n)	% (n)
94.6% (105)	5.4% (6)

According to the study 3,8% (4) of the males contracted malaria, and none of the females contracted malaria during the same period.

Both males and females were exposed to the anti-malarial active drug found in *Mefliam®*, yet the males, and not females contracted malaria. This begged the question why females appeared to be more immune to malarial infection than men. One possible explanation could be that the *Anopheles* mosquito is attracted to, or repelled by, particular odours. The main olfactory cue for attracting mosquitoes is carbon dioxide (CO₂) (Maharaj, 2004:personal communication; Robert, 2001:69-74). Carbon dioxide is acting as an attractant, and orientation towards the source of CO₂ is due to the optomotor anemotaxis (Hutchinson, 2004:1). The attraction to a host may be relatively fixed as with *Anopheles gambiae*, which is highly attracted to human host odours (Hutchinson, 2004:1). For example the *Anopheles arabiensis* mosquito will reduce the number of blood meals taken from humans when the amount of livestock in the district has increased (Hutchinson, 2004:1). Researchers combined CO₂ with 1-octen-3-ol (octenol) and found it to attract some *Anopheles* species (Hutchinson, 2004:1). Hutchinson (2004:1) reported that octenol is identified as an odour specific to mammalian origin. However deodorants and other perfumed products associated with females specifically are thought to interfere with the chemoreceptors on the antennae of the mosquito and disturb the perception of carbon dioxide and octenol identification (Maharaj, 2004:personal communication). It could thus be assumed that, because females are normally known to use more deodorants and other perfumed products than their male colleagues, they will be less attractive to the *Anopheles* mosquito

4.2.2 Age of respondents and malaria infection

Age is an important variable when taking malaria prophylaxis. The ages of the respondents were determined and categorised (see Table 4.2). As can be seen from Table 4.2, most of the respondents (107) were in the 20 to 30 and 31 to 40 years age categories.

Table 4.2: Age of respondents (n = 111)

20 – 30	31 – 40	41 – 50	50+
% (n)	% (n)	% (n)	% (n)
40.5% (45)	55.9% (62)	2.7% (3)	0.9% (1)

The study showed that one person from the 20 to 30 age group contracted malaria and three members from the 31 to 40 group contracted malaria, while none from the two older age groups contracted malaria.

A possible reason for this could be that, in the younger age groups, people tend to be more egocentric and nonchalant concerning the taking of the prophylaxis (Hlolongwane, 2002:personal communication, Makgadi, 2002:personal communication). Members had been informed that the Mefliam® tablets should not be taken with alcohol, so they would rather take a few beers and postpone the taking of the drugs than using them as prescribed (Makgadi, 2002:personal communication). It could be assumed that, this practice resulted in the members forgetting to take the anti-malarial medication.

The members of the fifty years and older age group are not exempt from risk in a malarial area, and they should be routinely monitored for fluctuations in their blood pressure and educated accordingly. A potentially fatal conduction disorder of the heart may occur if *Halfan* is used when malaria is contracted, or if taken with some medications for high blood pressure blockers and calcium channel antagonists, antihistamines and anti-depressants (Mefliam® package insert, 2002:3). Other side-effects include psychiatric disturbances, convulsions, cardiac abnormalities and gastrointestinal problems, such as diarrhoea and vomiting. There also might be different pharmacokinetic parameters for persons older than 50 years. Caution is advised in renal compromised patients and inpatients with compromised hepatic functions (Mefliam® package insert, 2002:1).

The aim of the following statistics was to determine if there was a correlation between the respective age groups and the possibility of contracting malaria.

Age Group: 20-30

p = proportion of positive responses

n = individuals

r = characteristics of interest

z = 1,96 for a 95 percent confidence interval

begin value; top value = $[p - z\sqrt{p(1-p)}; p + z\sqrt{p(1-p)}]$

$p = r/n = 1/45 = 0,022 = 2,2\%$

CI of population: $p \pm z\sqrt{p(1-p)}/n$

$= 0,022 \pm 1,96\sqrt{[(0,022)(0,78)]/45}$

$= 0,022 \pm 1,96\sqrt{0,172/45}$

$= 0,022 \pm 1,96\sqrt{0,00381}$

$= 0,022 \pm 1,96 \cdot 0,0618$

$= 0,022 \pm 0,121$

CI = [-0,099; 0,143]

Because the lower limit of the interval is less than zero, a false indication can be experienced regarding the probability that a member of this age group is likely to contract malaria. According to a level of confidence of 95% the parameter of the population will lie between these two limits, but can not be negative, therefore a more reliable test is necessary. For this purpose, the Wilson reliance interval was used.

Wilson reliance interval (score method)

$A = 2r+z^2$; $B = z\sqrt{[z^2+4r(1-r/n)]}$; $C = 2(n+z^2)$

$CI = [(A-B)/C; (A+B)/C]$

$A = 2r+z^2 = 2(1) + (1,96)^2 = 2 + 3,842 = \mathbf{5,842}$

$B = z\sqrt{[z^2+4r(1-r/n)]} = 1,96\sqrt{[1,96^2+4(1)(1-0,022)]} = 1,96\sqrt{[3,842+4(0,978)]}$

$B = 1,96\sqrt{[3,842+4(0,978)]} = 1,96\sqrt{7,754} = 1,96 \cdot 2,785 = \mathbf{5,458}$

$C = 2(45 + 1,96^2) = 2(48,842) = \mathbf{97,684}$

$CI = (5,842-5,458)/97,684; (5,842+5,458)/97,684$

$CI = 0,384/97,684; 11,3/97,684$

CI = [0,0393; 0,116]

According to this statistical method there is a 95% certainty that when a population (age group 20-30) is using *Mefloquine*, the chance of getting malaria will be

between 0,0393 and 0,116. In other words, an individual in this age group has a 3,9% to 11,6% chance of contracting malaria when he/she is using *Mefloquine* (Mefliam®).

Age Group: 31-40

$$p = r/n = 3/62 = 0,048 = 4,8\%$$

Making use of the Wilson reliance interval (score method):

$$A = 2r + z^2; B = z\sqrt{z^2 + 4r(1-r/n)}; C = 2(n + z^2)$$

$$CI = [(A-B)/C; (A+B)/C]$$

$$A = 2r + z^2 = 2(1) + (1,96)^2 = 2 + 3,842 = \mathbf{5,842}$$

$$B = z\sqrt{z^2 + 4r(1-r/n)} = 1,96\sqrt{1,96^2 + 4(1)(1-0,048)} = 1,96\sqrt{3,842 + 4(0,952)}$$

$$B = 1,96\sqrt{3,842 + 4(0,952)} = 1,96\sqrt{7,65} = 1,96 \cdot 2,766 = \mathbf{5,421}$$

$$C = 2(62 + 1,96^2) = 2(65,842) = \mathbf{131,684}$$

$$CI = (5,842 - 5,421)/131,684; (5,842 + 5,421)/131,684$$

$$CI = 0,421/131,684; 11,263/131,684$$

$$\mathbf{CI = [0,003; 0,086]}$$

According to this statistical method there is a 95% certainty that when a person in this age group (31-40) is using *Mefloquine*, he/she has a 0,3% to 8,6% chance of contracting malaria when using *Mefloquine* (Mefliam®).

4.2.3 Race of respondents and malaria infection

The race of the respondents was determined and categorised as shown in Figure 4.1.

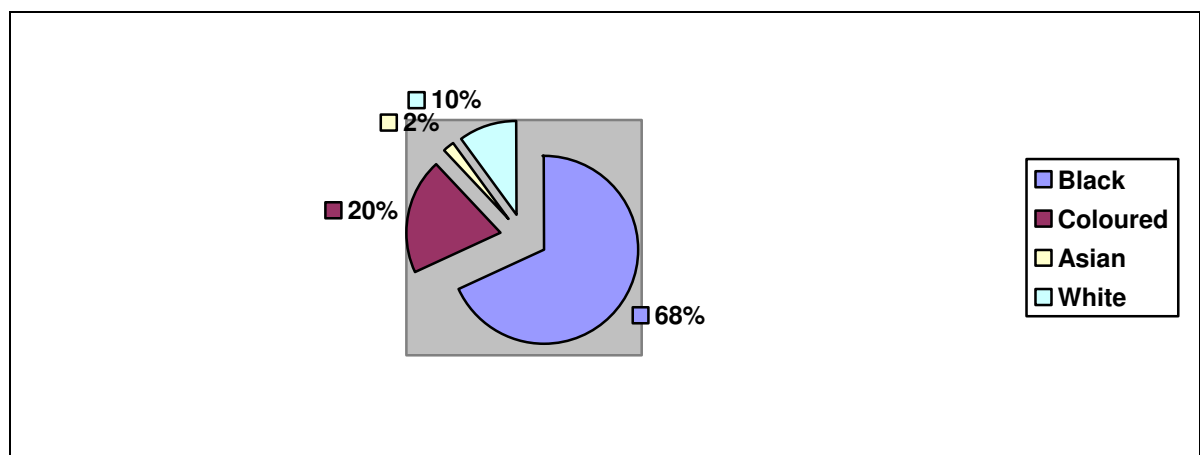


Figure 4.1: Race of respondents (n = 111)

In this section the emphases will fall on the behaviour of the mosquito and the stimuli (e.g. skin colour) attracting it to the host.

African populations have traditional perceptions concerning disease prevention, treatment and management. Some diseases are considered suitable for management by western medicines, while other diseases are considered the exclusive domain of local traditional health practitioners. The decision to use western medicine for an illness is often considered as a last resort (Nchinda, 1998:398). There is no medical evidence to support the use of homeopathic preparations for the prevention or treatment of malaria (Barnes, 2005:personal communication; SCAT, 2003:15).

The study showed that one of 11 white persons contracted malaria, while three of 76 black members contracted malaria. all these respondents had used *Mefloquine*.

In an attempt to determine if there was a correlation between the respective race groups and the possibility of contracting malaria, the following statistical analysis was applied:

Black

Confidence interval (CI)

$$p = r/n = 3/76 = 0,039 = 3,9\%$$

$$\text{CI} = [-0,0045; 0,083]$$

Because the lower limit of the interval is less than zero, a false indication can be experienced regarding the probability that a member of this race group is likely to contract malaria, thus the Wilson reliance interval were used. The Wilson reliance interval indicated a confidence interval (CI) of [0,026; 0,128]. According to this statistical method, there is a 95% certainty that when a population (black) is using *Mefloquine*, the chance of getting malaria will be between 0,026 and 0,128 (2,6% to 12,8%) when using *Mefloquine* (Mefliam®).

White

$$p = r/n = 1/11 = 0,091 = 9,1\%$$

The Wilson reliance interval indicates a confidence interval (CI) of [0,0162; 0,377]. There is a 95% certainty when using this specific statistical method that a population (whites) using *Mefloquine* will have a 1,6% to 37,7% chance of contracting malaria when using *Mefloquine* (Mefliam®).

Although the compound eye of the mosquito has less resolving power than that of most mammals, the aperture allows better vision in the dark (Hutchinson, 2004:1). The eye of a mosquito performs a number of functions. It detects movement, colours, shapes and edges of objects (Hutchinson, 2004:1). Some of the first studies by Bellamy and Reeves in 1952, reported the importance of visual cues in traps for mosquitoes. They used three transparent lard traps. The traps were placed in a line about one metre apart. The one in the middle was baited with CO₂ released via a hidden pipe. This trap caught the least mosquitoes. The two unbaited traps were made visible by placing twigs and leaves around them or by sticking black tape in criss cross patterns across them. This experiment showed that mosquitoes followed the CO₂ plume upwind, but then visual cues led them to the unbaited traps. This proves that visual stimuli would lead a mosquito to fly towards a prominent object when lacking an odour plume (Hutchinson, 2004:1). Although the *Anopheles* mosquito prefers to rest on dark surfaces (Maharaj, 2004:personal communication), mosquitoes are visually stimulated by objects that are in contrast with the background (Hutchinson, 2004:1). Since the *Anopheles* mosquito feeds exclusively during the night, especially at dusk and dawn, lighter skins would be perceived as contrasting on the black background of the night, and would therefore attract the *Anopheles* mosquito.

4.2.4 Home province of respondents and the risk of malaria

As seen from Figure 4.2, most of the respondents were from Eastern Cape (58), Gauteng (15) and Western Cape (11). Only a few members were from the traditionally malaria-plagued provinces of KwaZulu-Natal, Mpumalanga and Limpopo. This is important because the province of origin may have an influence on the respondents' knowledge and attitude towards the control of malaria, as well as on their potential natural immunity against malaria. The four persons who

contracted malaria were all from different provinces: Eastern Cape, Gauteng, Mpumalanga and the Free State respectively.

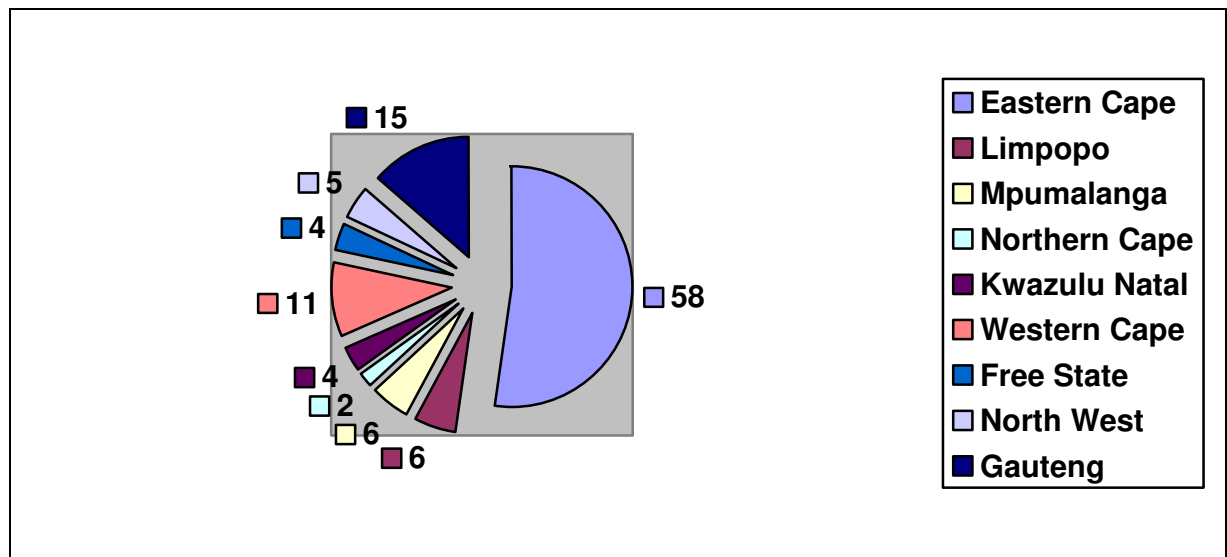


Figure 4.2: Home province of respondents (n = 111)

Malaria normally occurs in the low altitude areas (1000 metres above sea level) in South Africa, for example the Limpopo Province, Mpumalanga and the north-eastern parts of KwaZulu-Natal. Occasionally limited focal transmission may develop in the North-West Province and Northern Cape along the Molopo and Orange Rivers. Infections are seldom contracted outside the malarious areas and are then possibly as a consequence of the importation of infected mosquitoes by aircraft or other transport (South Africa, 2002:2). Members from endemic malaria areas are generally well informed about the disease. They know the seriousness of the taking of prophylaxis and the protection against being bitten. They have seen the symptoms of the disease and know the suffering that is involved. The people who are living in areas of endemic malaria sometimes have a naturally acquired immunity against the *Plasmodium* mosquito in that area. Soldiers from such areas will have a resistance to that specific strain of *Plasmodium* if they would move into an area where that specific *Plasmodium* is endemic (Anthony Conway, Cox-Singh, Matusop, Ratnam, Shamsul & Singh, 2005:1558-1564. People who have grown up in endemic malaria areas and who may have developed immunity, will lose this immunity within a year of being out of the malaria area (Walker, Williams & Raeside, 2000:11-14). These individuals must take the necessary precautions when re-entering a malaria area.

People who are living at high altitude, where the *Anopheles* mosquito cannot survive and transmission is absent, are not exposed to malaria (Nchinda, 1998:398; SCAT, 2003:11). In industrialised parts of the country where the disease does not exist, for example in big cities, people are more susceptible to malaria and should be monitored accordingly.

Military personnel who are living close to international airports are susceptible to possible “airport malaria”. This illness is due to mosquitoes that are arriving in the country from endemic areas (Lusina, 2000:75-76; SCAT, 2003:10). A person might be sickening from malaria after he/she was deployed internationally.

Frequent armed conflicts and civil unrest in areas forced large populations to settle under difficult conditions. These areas are sometimes high in malaria transmission. Military personnel that are working and/or living under these conditions are very susceptible to malaria (Health and Community Care, 2003:1; Nchinda, 1998:398).

Areas with changing rainfall patterns, as well as those involved in water development projects, are high malaria risk areas. Water development projects include projects such as new dams, canals and irrigation schemes that create new mosquito breeding sites. Soldiers that are living or working in such areas must be even more cautious regarding the transmission of malaria (Epidemic Prediction and Response, 2001:1, SCAT, 2003:11).

The following statistics were used to determine if there is a correlation between the respective provinces of origin and the possibility of contracting malaria.

Eastern Cape

$$p = r/n = 1/58 = 0,017 = 1,7\%$$

The Wilson reliance interval indicates a confidence interval (CI) of [0,003; 0,091]. With a 95% certainty, it was determined that members from the Eastern Cape who use *Mefloquine*, will have a 0,3% to 9,1% chance of contracting malaria when using *Mefloquine* (Mefliam®).

Free State

$$p = r/n = 1/4 = 0,25 = 25,0\%$$

With this group the Wilson reliance interval indicates a confidence interval (CI) of [0,046; 0,699]. There is a 95% certainty that when members from the Free State use *Mefloquine*, their chances of contracting malaria will be between 0,046 and 0,699. In other words, an individual from this area has a 4,6% to 69,9% chance of contracting malaria when he/she is using *Mefloquine* (Mefliam®).

Gauteng

$$p = r/n = 1/15 = 0,066 = 6,6\%$$

Individuals from Gauteng have a 3,7% to 27,3% chance of contracting malaria when using *Mefloquine* (Mefliam®).

Mpumalanga

$$p = r/n = 1/2 = 0,5 = 50,0\%$$

This study showed that one of the two members who came from Mpumalanga, contracted malaria within the first four months of deployment to Burundi. Although this sample figure is in proportion of the whole sample group it is highly coincidental that 50% of the members of Mpumalanga, contracted malaria. Although Mpumalanga is an endemic malaria region, the member who contracted malaria had no previous history of malaria.

$$CI = [-0,193; 1,193]$$

4.2.5 Home language of respondents and the risk of malaria

Although the population had as many as ten home languages (Table 4.3), they all used English to communicate internally. Thus nobody could use language as a reason for not being informed regarding the proper precautionary use of anti-malarial prophylaxis and personal protection against mosquitoes.

Table 4.3: Home language of respondents (n = 111)

Afrikaans	English	Xhosa	Zulu	Sotho	Thwana
% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
28.8% (32)	3.6% (4)	39.6% (44)	6.3% (7)	7.2% (8)	8.1% (9)
Swazi	Ndebele	Shangaan	Venda		
% (n)	% (n)	% (n)	% (n)		
1.8% (2)	2.7% (3)	0.9% (1)	0.9% (1)		

4.2.6 Different armed services in the SANDF and the risk of malaria

The service or unit where the member is working is an important variable during the deployment in an endemic malaria area. This is also an indication of the level of exposure to malaria and the chemoprophylaxis that should be taken. The services in which the respondents were working were determined, and are presented in Table 4.4.

Table 4.4: Armed services (n = 111)

Army	Medical and Health Services (SAMHS)	Airforce (SAAF)	Navy	Military Police (MPA)
% (n)	% (n)	% (n)	% (n)	% (n)
70.3% (78)	3.6% (4)	9.0% (10)	3.6% (4)	4.5% (5)
Signal Unit (CMI)	Engineers	Logistics		
% (n)	% (n)	% (n)		
1.8% (2)	3.6% (4)	3.6% (4)		

Logistics, transportation and other support units scattered in the deployment area are not always part of the communication lines and disciplinary structures. This makes the compliance with the antimarial regimen of these members more of a challenge.

Engineering units are involved in construction projects in tropical conditions with the building of roads, sewerage works, networks, water pumps and pipelines. These members are sometimes compelled to overnight in tropical conditions with constant rains, living in wet and humid conditions. These conditions are the optimal breeding ground for mosquitoes, and therefore these individuals are at great risk of contracting malaria (SCAT, 2003:9).

Military Police members work in shifts. These personnel are working at night and are more exposed to the bites of the *Anopheles* mosquito (WHO, 2002:9-17). They are working in and around artificial light, which attracts mosquitoes (Hutchinson, 2004:1).

Kitchen personnel are part of the logistical services. These members often work during the dark hours of the day between dusk and dawn. This is the time of day when members are the most exposed to the bites of the *Anopheles* mosquito (SCAT, 2003:10; Wood, 1993:67-68). Around the kitchens in temporary military bases stagnant water, due to the constant cleaning of the facility, and kitchen sewerage water as part of the normal processes in the kitchen facilities, is usually found. This stagnant water attracts mosquitoes for breeding purposes. Mosquitoes need relatively clean water to lay their eggs (Curtis, 1996:1; SCAT, 2003:9). Constant pest control and mosquito control in and around these facilities is crucial.

Army guards patrol the area during the night or stand guard at entrances. Due to the high temperatures at night in the area, it is uncomfortable to wear long sleeve shirts, and therefore skin is exposed for the mosquitoes to feed on. The stationary and roaming guards must constantly be reminded to take precautions to prevent mosquito bites. The guards must be issued with the prescribed repellents.

Health care workers (SAMHS) are potentially exposed to the plasmodium organisms by means of a needle stick. This is called "induced malaria" (MacArthur *et al.*, 2001:28). The medical personnel were on duty 24 hours a day, in two shifts. The personnel working in the evening, were therefore exposed to mosquitoes for the entire night.

Military personnel that are involved in tasks requiring fine co-ordination and spatial discrimination such as scuba diving (Navy), piloting an aircraft (SAAF) and those driving heavy machines (Engineers) are discouraged to use Mefliam®, as dizziness and vertigo have been reported as side-effects (Notices to Readers' Change of Dosing Regimen for Malaria Prophylaxis with *Mefloquine*, 1991:1; SCAT, 2003:15).

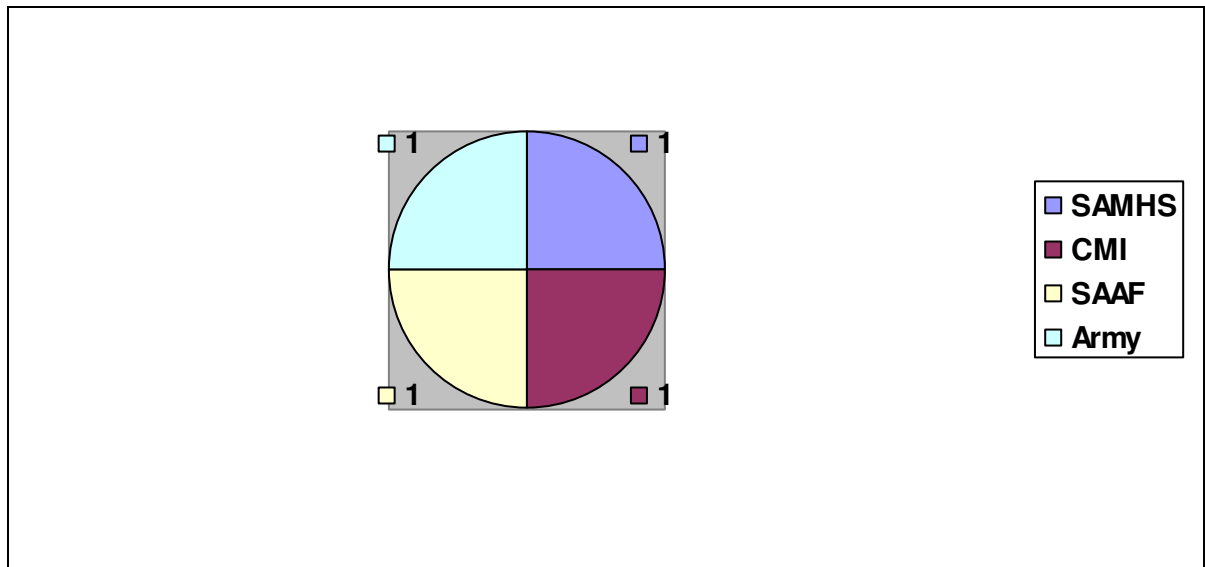


Figure 4.3: Persons from different services contracting malaria (n = 4)

This study showed that one out of 78 **Army** members that used the *Mefloquine* (Mefliam®) tablets contracted malaria within the first four months of deployment to Burundi.

Confidence interval (CI)

$$0,0128 + 1,96\sqrt{[(0,0128)(0,9872)]/78}$$

CI = [- 0,0121; 0,0377]

As the lower limit of the interval is less than zero, a false indication can therefore be experienced regarding the probability that a member of the Army is likely to contract malaria. According to a level of confidence of 95%, the parameter of the population will lie between these two limits, but can not be negative, therefore a more reliable test is necessary.

Wilson reliance interval (score method)

$$A = 2r+z^2; B = z\sqrt{[z^2+4r(1-r/n)]}; C = 2(n+z^2)$$

$$CI = [(A-B)/C; (A+B)/C]$$

$$CI = [0,0099; 0,0615]$$

There is a 95% certainty that when a member of the Army is using *Mefloquine*, the chance of getting malaria when exposed to the specific climatic and environmental variables this force is operating in is 0,9% to 6,2%, when using *Mefloquine* (Mefliam®).

This study showed that one out of 10 Airforce (**SAAF**) members that used the *Mefloquine* (Mefliam®) tablets contracted malaria during the same period deployed to Burundi.

$$p = r/n = 1/10 = 0,1 = 10,0\%$$

$$CI = [-0,086; 0,286]$$

The Wilson reliance interval indicates a confidence interval (CI) of [0,0171; 0,405]. An individual in this specific service of the SANDF, that is exposed to the specific climatic and environmental variables this force is operating in, has a 1,7% to 40,5% chance of contracting malaria when using *Mefloquine* (Mefliam®).

This study showed that one out of 4 Health Service (**SAMHS**) members that used the *Mefloquine* (Mefliam®) tablets contracted malaria.

$$p = r/n = 1/4 = 0,25 = 25,0\%$$

$$CI = [-0,174; 0,674]$$

The individual working in this circumstances will have a 4,6% to 69,9% chance of contracting malaria when using *Mefloquine* (Mefliam®) during this specific deployment.

This study showed that one out of two Information Services (**CMI**) members that used the *Mefloquine* (Mefliam®) tablets contracted malaria within the first four months of deployment to Burundi. Although two CMI members are in proportion of the whole sample group, it is highly coincidental that 50% of all the respondents

whose questionnaires were received back from CMI, contracted malaria. The function of this grouping is primarily administrative, and therefore office bound. Statistical feedback is thus of minimal value.

$$p = r/n = 1/2 = 0,5 = 50,0\%$$

$$CI = [-0,193; 1,193]$$

According to the confidence interval (CI) test, the lower limit of the interval is less than zero and the upper limit is above one. According to a level of confidence of 95%, the parameter of the population will lie between these two limits, but can not be negative or above one.

4.2.7 The respondents' knowledge of methods to prevent malaria

This question served to evaluate the effectiveness of pre-deployment education. Health seeking behaviour, perceptions of malaria, treatments and decision making for health care at unit level are crucial to malaria control. Such education must be accompanied by improved awareness of the importance of seeking appropriate treatment and complying with recommended regimens of anti-malarial prophylaxis. The small percentage of "no" answers (Table 4.5) indicates that the pre-deployment educational programme had a positive impact on the awareness and knowledge of the members.

Table 4.5: The respondents' knowledge of methods to prevent malaria (n = 111)

Yes	No
% (n)	% (n)
87.4% (97)	12.6% (14)

All four persons who had contracted malaria had, according to the study, a good knowledge of methods to prevent malaria.

4.2.8 History of malaria infections among respondents

The members (6) who reported positively (yes) to the question knew the symptoms of malaria. They realised that the disease is accompanied by much suffering and may also realised the severity of the disease and would take the necessary precaution to prevent becoming a victim.

The members who submitted a positive “yes” answer to this question also had to be identified as possible future patients of rebound malaria. These soldiers might develop rebound malaria during the deployment phase, and by having the information of these personnel on hand, they could be treated accordingly. This proactive management of rebound malaria patients will also prevent any doubt in the effectiveness of the current anti-malarial regimen. All of the six (6) members who had a previous history of malaria infections answered positively to questions 2.4 to 2.6 and 3.6 (Annexure A). Most of the respondents (105) had no history of malaria infections and they would be the primary target group to educate, and to confirm that they understand malaria and the severity of the disease.

None of the four members who contracted malaria had a history of previous malaria infections.

4.2.9 The consumption of malaria tablets while the respondents were deployed in a malaria area

The perceptions regarding malaria and the current malaria medication consumed, were tested and are reported in this section.

The primary purpose of the process was to establish the reasons for not taking the anti-malarial tablets and to try and change the perception of the person. With this question the effectiveness of pre-deployment education could be evaluated, and shortfalls could be identified. This was also a tool to evaluate the effectiveness of malaria administration and the distribution plan of the malaria prophylaxis to the military personnel during deployment. Discipline and supervision regarding the taking of the prophylaxis could be revisited in future programmes.

The result of this question indicates that all the respondents (111) consumed the chemoprophylaxis while deployed in the malaria area. Thus the education, procedures and policies regarding the use of the drug seem to be effective. The four members who contracted malaria, had all consumed their malaria tablets while they were deployed in a malaria area.

4.2.10 The taking of malaria tablets before the respondents’ deployment in a malaria area

In this section the pre-deployment education and malaria management programme regarding effective malaria administration and the distribution of the anti-malarial medication to the military personnel will be evaluated.

Table 4.6: The taking of malaria tablets before the respondents’ deployment in a malaria area (n = 111)

Yes	No
% (n)	% (n)
96.4% (108)	2.7% (3)

It is evident from the small number of “no” answers in Table 4.6, that the distribution programme of the malaria tablets was successful. The members who were on Mefliam® had to commence the regimen one week prior to entering the malaria area (Mefliam® package insert, 2002:4).

All four persons who contracted malaria, stated in the questionnaire that they had taken malaria tablets before their deployment to a malaria area.

4.2.11 The maintenance of the malaria regimen while the respondents were deployed in a malaria area

Abovementioned is an important variable associated with the respondents’ use of the malaria prophylaxis. The answers of the respondents were determined and categorised. All the respondents stated that they had maintained the anti-malaria regimen while they were deployed in the malaria area. It was also evident from the

study that the four persons who contracted malaria maintained the anti-malaria regimen while they were deployed in the malaria area.

The taking of the tablets should become part of the unit routine. For example, taking the anti-malarial tablets could form part of a social activity or get-together where each member is issued with his/her tablets and must drink it under informal supervision. This activity would serve as a vehicle to reinforce the reason why prophylaxis medication is being used, with senior unit members leading by example. The social activity also serve as a motivation to drink the tablets on time, as part of a routine. Such practice will be part of the vertical malaria management programme, which will fit into the holistic malaria management programme.

4.2.12 The respondents' knowledge regarding the brandname of the malaria tablets they used

Of the 120 respondents who participated in the study, 111 (92.5%) indicated that they were using *Mefliam®*. Eight (7.5%) respondents used *Doxycycline*, therefore they were excluded from the research project.

The data therefore revealed that respondents were informed about the brand name of their medication. However, as only the two names were given as options in the questionnaire, it is possible that some respondents could have guessed.

4.2.13 Side-effects experienced by the respondents when taking the malaria tablets

In response to question 3.2, the symptoms listed in Table 4.7 were identified by the military members deployed to Burundi, East Africa, as possible side-effects of *Mefliam®*. Eleven persons experienced some sort of problem when taking the malaria tablets. None of the four persons who contracted malaria stated any problems while taking the medication. The following table highlights the problems experienced by the respondents when taking the malaria tablets.

Table 4.7: Side-effects experienced by the respondents when taking the malaria tablets (n=11)

Abdominal cramps	Sensitive skin	Diarrhoea	Bad taste *	Nausea	Headache	Perfuse sweating
% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
9.1% (1)	9.1% (1)	18.2% (2)	9.1% (1)	27.3% (3)	18.2% (2)	9.1% (1)

* Chronic bad taste in mouth

All the above symptoms were possible symptoms listed in the manufacturers' package insert. A factor that could have influenced the sensation of side-effects could be the poor quality of the water the people had to drink. Gastrointestinal diseases might have contributed to the symptoms of diarrhoea and nausea (Benenson, 1990:267; Heymann, 2004:161; Hlolongwane, 2002:personal communication). This might explain the response to the "Diarrhoea" and "Nausea" categories. Headache is also a primary symptom of dehydration that is associated with gastrointestinal disease (Hlolongwane, 2002:personal communication).

However as only 11 of the sample of 111 experienced side-effects (9.9%), it could be argued that these military force members showed acceptable tolerance to Mefliam®.

Side-effects in humans as listed in the manufacturers' package insert were the following:

- Abdominal pains
- Aggression
- Agitation
- AV Block
- Hair loss
- Confusion
- Hallucinations
- Convulsion
- Psychological changes
- Decrease of platelets
- Erythema
- Depression
- Anxiety
- Transient elevation of transaminases
- Dizziness or disturbed sense of balance
- Nausea
- Transient cardiac conduction
- Leucopenia or leucocytosis

- Psychosis
- Headaches
- Myalgia
- Loss of appetite
- Panic attacks
- Restlessness
- Feeling of weakness
- Visual disturbances
- Forgetfulness
- Irregular pulse
- Extrasystoles
- Paranoia
- Emotional instability
- Palpitations
- Bradycardia
- Psychiatric reactions
- Vomiting
- Rash or puritis
- Urticaria alterations
- Paraesthesia

According to the manufacturer's instructions, if signs of unexplained anxiety, depression, restlessness or confusion are evident, the medication should be stopped immediately. The rate of serious adverse side-effects is in the order of 1:10 000 for Mefliam®. *Mefloquine* appears to cause more disabling neuropsychiatric symptoms in clinical trials done. Adverse side-effects associated with *Mefloquine* include insomnia, strange dreams, mood changes, headaches, diarrhoea and nausea. These would usually be experienced within the first three weeks of medication. These side-effects do not become worse in subsequent weeks of use (Lobel & Kozarsky, 1997:1767-1771; Peragallo, *et al.*, 1999:73-77). If the side-effects are not experienced during the first use of *Mefloquine*, the side-effects are unlikely to appear during subsequent use for prophylaxis. To forestall these side-effects, it is suggested, when *Mefloquine* is taken for the first time, that chemoprophylaxis should commence three weeks before exposure to malaria. This is to enable the member to make a timeous change to another drug, should side-effects occur (Bradley & Bannister, 2003:180-199; Bradley & Warhurst, 1997:138-152; WHO, 2002:9-17). Side-effects can develop as early as the first week of use and more than 75 percent of the adverse reactions are apparent by the third dose. In most cases symptoms resolved within three weeks of stopping the drug, but there are a very small number of reports of symptoms persisting for months and even years (Phillips-Howard & Ter Kuile, 1995:370-383).

4.2.14 The attitude of the respondents towards the consumption of the malaria tablets

The perception of the respondents regarding the anti-malarial tablets was assessed in this section. Due to the extreme bitterness of the tablets and the uncomfortable side-effects, it is understandable that some of the users (22) did not like to use the tablets. Two individuals out of the 111 respondents were uncertain. One of these was also diagnosed with malaria during the deployment.

With a continuous education programme, the perception of the members must be formed that despite the bad taste and the possible side-effects of the tablets, it is still a privilege to have such effective chemoprophylaxis available to protect them against malaria.

4.2.15 Indicate where the malaria tablets were obtained

By making use of the questionnaires, an indication was obtained regarding the place or person where the malaria tablets were obtained from.

Table 4.8: Indicate where the malaria tablets were obtained from (n = 111)

Sickbay	Platoon Commander	Unit	Myself
% (n)	% (n)	% (n)	% (n)
74.7% (83)	16.2% (18)	8.1% (9)	0.9% (1)

Although nearly 75 percent of the respondents received their tablets directly from the sickbay, it is not the most ideal scenario. The commanding officer of the unit or a delegated person should receive/collect the tablets by means of the completing of a register, against signature. The respondent who answered “myself” received the complete regimen of malaria tablets before they left for Burundi. According to the four persons that contracted malaria, they all received their medication from the sickbay.

4.2.16 Problems that could be experienced if the respondent did not use the malaria tablets

Question 3.5 aimed to test the knowledge of the members regarding malaria. It was also of use to evaluate the impact of the pre-deployment education and information programmes.

Table 4.9: Problems that could be experienced if the respondents did not use the malaria tablets (n = 111)

Malaria	Malaise	Fever	Die	Loss of water	Yellow fever	Pneumonia
% (n)	% (n)	% (n)	% (n)	% (n)	% (n)	% (n)
70.3% (77)	2.7% (3)	15.3% (17)	1.8% (2)	0.9% (1)	1.8% (2)	0.9% (1)
Tiredness	Don't know	Vomiting	No appetite	No problem		
% (n)	% (n)	% (n)	% (n)	% (n)		
0.9% (1)	2.7% (3)	0.9% (1)	0.9% (1)	1.8% (2)		

The mindset must be cemented into military personnel that, should they not use the anti-malarial medication issued to them, they could be infected with malaria. The members must be informed about the symptoms and seriousness of the disease and knowledge of malaria must be instilled in them. This must serve as a motivation for the military personnel to get into the routine of using the prophylaxis medication.

The fact that only 70.3% of the persons knew that they could contract malaria if they did not drink their anti-malarial drugs presents a negative reflection on the effectivity of the educational tools used to empower the members. The soldiers were all taking their chemoprophylaxis, as discussed in a previous section, but according to this result they were not sure why they actually had to use the drugs.

According to the study, all four persons who contracted malaria were aware of the fact that they could contract malaria if they did not use the malaria tablets.

The females were less informed than the males about the reason for taking the tablets. Five of the six females stated that nothing would happen if they did not use the malaria tablets, and one said that a person could contract yellow fever by not drinking the tablets. The feedback regarding this question outlines a weak point in the educational process, and it should be revisited and rectified. It should be investigated why specifically the female group was so misinformed.

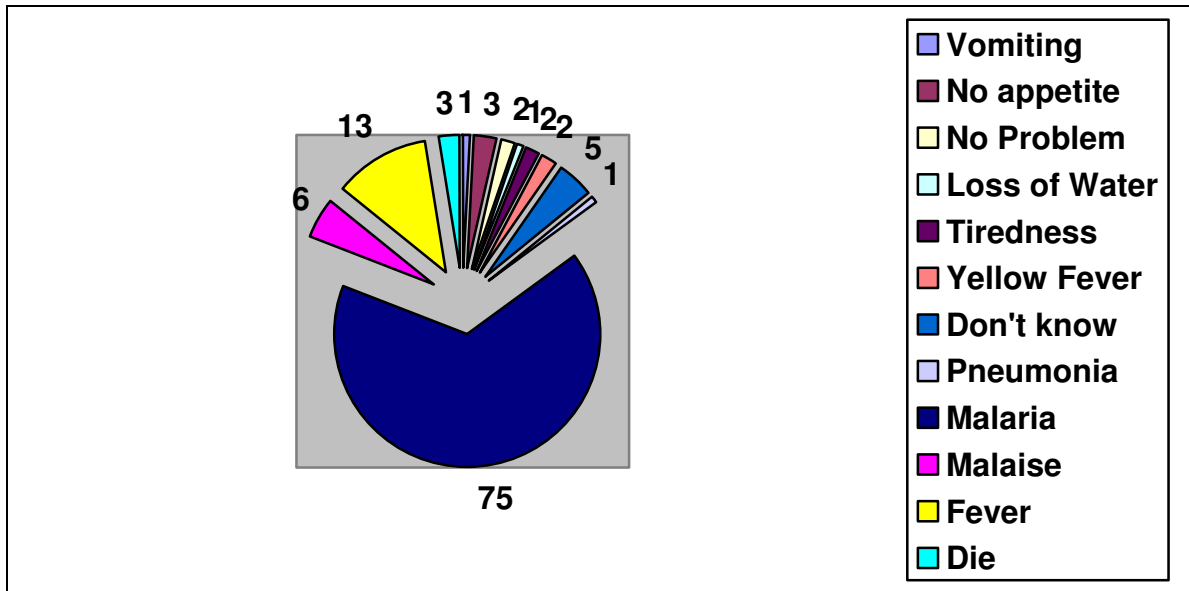


Figure 4.4: Knowledge about problems that could be experienced if the respondent did not use the malaria tablets (n = 111)

4.2.17 The respondents' awareness of continuing the regimen for four weeks after leaving the malaria area

Nine (8,1%) of the respondents were not willing to drink the anti-malarial medication after deployment, or did not know that they were supposed to drink it for four weeks after leaving the deployment area. Experience has taught that once military members have left the malarial deployment area, it is very difficult to keep to the routine. This is understandable, since they have to adjust to a new routine or take leave. There is then often no support group to motivate and remind them to drink the anti-malarial medication. The members must be informed of the necessity to continue using the anti-malarial medication. The members must be informed of and understand the pharmacokinetics of the prophylaxis medication that they are using or are going to use. Members should be educated that although

they are out of the “danger” area, they can still contract malaria after four weeks of leaving the malarial area, due to the extended lifecycle of the *Plasmodium* organism. Exposure may have been on the last day of the stay, the incubation period may be variable and current chemoprophylaxis may only be effective once the parasites enter the red blood cells. Members need to be well motivated and educated to ensure the highest possible level of compliance (SCAT, 2003:15). One of the four persons who contracted malaria was not aware of the fact that it was expected of him to continue with the malaria medication for four weeks after leaving the malaria area.

4.2.18 The motivation of the respondents to use the malaria tablets

The respondents were asked the reasons why they took the tablets. Ninety percent of the respondents acknowledged that Mefliam® kept them healthy. It is the aim of the malaria education and information programme to instil the mentality in the military personnel that it is for a member’s own benefit to use the anti-malarial medication, and to use it correctly. This mentality will prevent members from becoming malaria victims.

Table 4.10: The motivation of respondents to use the malaria tablets (n = 111)

It is important to keep me healthy	It is expected of me to do so	I am forced to	It is the rule
% (n)	% (n)	% (n)	% (n)
90.1% (100)	6.3% (7)	1.8% (2)	1.8% (2)

The fact that the malaria tablets would keep them healthy was the primary motivation why all four persons who contracted malaria, had used it.

4.2.19 Symptoms/feelings related to the taking of the malaria tablets

The survey indicated that 92 persons did not have any negative symptoms or feelings related to the consumption of the drugs. The 19 that had symptoms, presented with typical side-effects as listed in the manufacturer’s package insert.

4.2.20 The time of day respondents normally took their malaria tablets

The feedback from the respondents was that seventy two percent (72%) of the members took the tablets after their meals.

Table 4.11: The time of day respondents normally took their malaria tablets
(n = 111)

At night before I go to sleep	After lunch	After breakfast	When I get the chance
% (n)	% (n)	% (n)	% (n)
18.9% (21)	42.3% (47)	29.7% (33).	9.1% (10)

These results are an indication that the majority of the respondents used the prophylaxis medication in a routine of some sort.

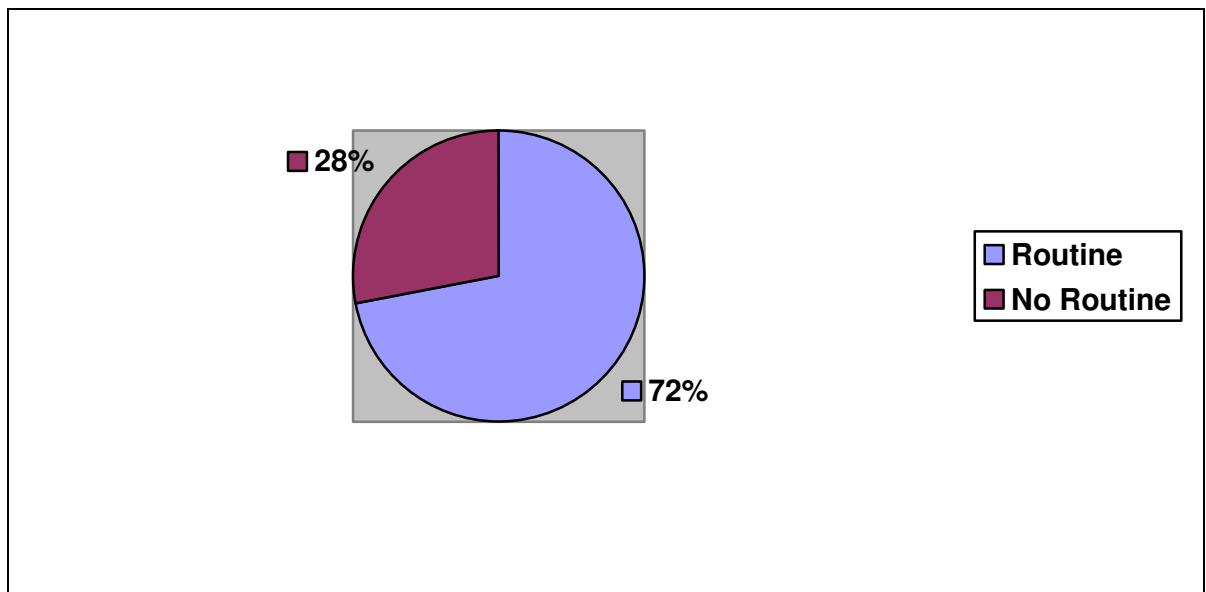


Figure 4.5: The consumption of the chemoprophylaxis by the respondents

The member can therefore associate a certain event (e.g. Saturday supper) with the use of the Mefliam® tablets. The member remembers that after supper on Saturdays, he/she has to take the anti-malarial tablets. For members who are suffering from side-effects, it is a good idea to drink the Mefliam® before they go to sleep (personal observation). This practice will alleviate most of the side-effects

that might be experienced. According to the Mefliam® package insert, the Mefliam® tablets should be taken after a meal with plenty of fluids.

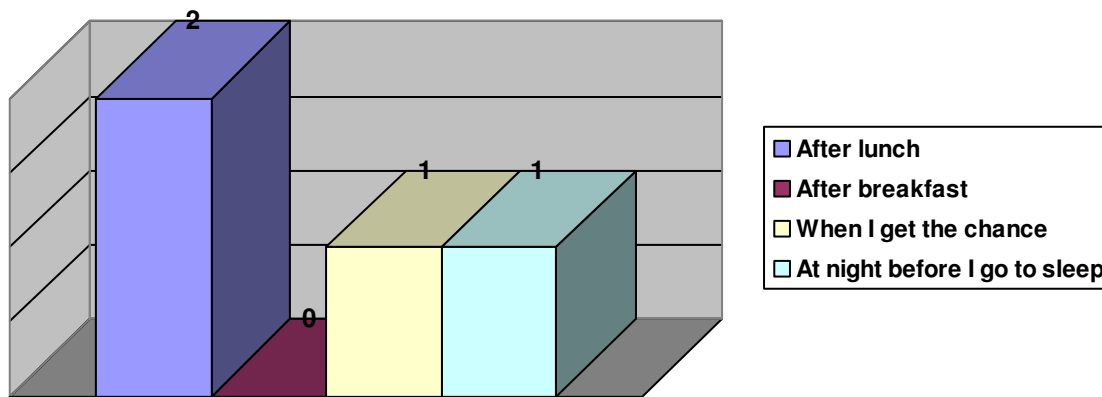


Figure 4.6: The time of day the persons that contracted malaria normally took their malaria tablets (n = 4)

4.2.21 The perception of the respondents regarding the taste of the malaria tablets

When answering the questionnaires, it was interesting that nearly 47 percent (52) of the respondents stated that the Mefliam® tablets were tasteless. They are considered very fortunate, because the Mefliam® tablets are generally considered to be extremely bitter. This statement can probably be accounted to the fact that persons are advised to swallow the tablets whole, due to the awful taste. Some persons had the unpleasant experience of tasting the Mefliam® tablets when the tablets got stuck in their mouths or throat when swallowing. The sensory perception of “sour” and “sweet” by some of the members is interesting.

Table 4.12: The perception of the respondents regarding the taste of the malaria tablets (n = 111)

Tasteless	Sour	Sweet	Bitter
% (n)	% (n)	% (n)	% (n)
46.8% (52)	9.9% (11)	0.9% (1)	42.3% (47)

Three of the persons who contracted malaria regarded the taste of the malaria tablets to be “tasteless” while one perceived it as “bitter”.

4.2.22 The number of persons who contracted malaria during the deployment in Burundi

This was the primary question of the questionnaire. This question directly determined the effectiveness of Mefliam® in Burundi, East Africa. Hundred-and-seven respondents answered “no” to that specific question four months into the deployment. However four members had contracted malaria.

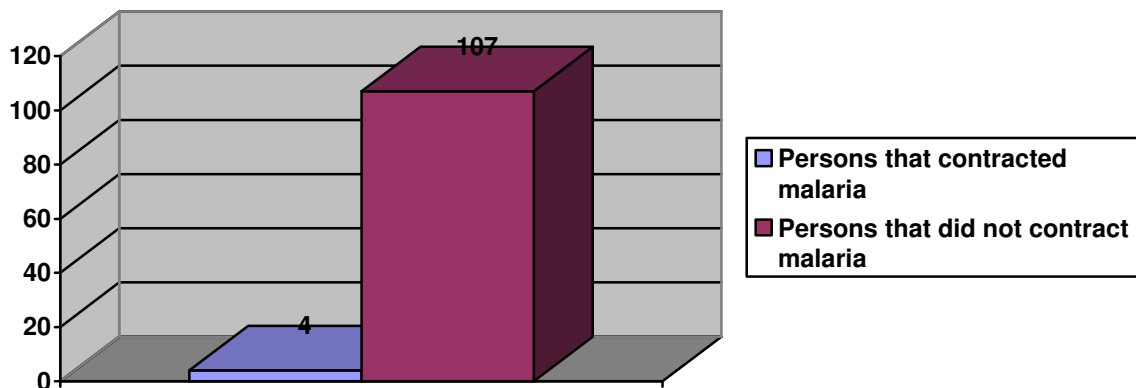


Figure 4.7: The number of persons who contracted malaria during the deployment in Burundi (n = 111)

According to clinical trials done in Kenya, East Africa, *Mefloquine* had a 95% prophylactic efficacy (Meuhlberger, Jelinek, Schlipkoeter, von Sonnenbeurg & Nothdurft, 1998:357-363). Barnes (2005:personal communication) and Talmut (2005:personal communication) claimed a 95% prophylactic efficacy of *Mefloquine* internationally. *Mefloquine* had a 100% prophylactic efficacy in a double-blind, placebo controlled trial with 204 Indonesian soldiers, who used the drug for 13 weeks. (Ohrt *et al.*, 1997:963-967). The evidence from a number of large trials on the African continent indicated a prophylactic efficacy of over 90% (Steffen, Fuchs, Schildknecht, Naef, Funk & Schlagenhauf, 1993:1299-1303).

4.2.23 Any concerns or problems regarding the malaria tablets that were not listed in the questionnaire

Cognisance should be taken of individual problems and concerns regarding the consumption of Mefliam® in the compilation the final education programme. Table

4.13 thus provides important information to educators when they emphasise the topic of possible side-effects.

Table 4.13: Concerns or problems about the malaria tablets that were not listed in the questionnaire (n = 111)

Concerns/Problems	Number of respondents	%
None	94	83.8
Sweating	2	1.8
Affect females	3	2.7
Not with liquor intake	2	1.8
Emotional side-effects	4	3.6
Sex life	1	0.9
Expose family to malaria	1	0.9
After-taste	1	0.9
Big appetite	2	1.8
Continue taking tablets after leaving Burundi	1	0.9

One of the four persons who contracted malaria was concerned or had a problem with the after taste of the tablets, while one of the females had a concern regarding the affect it might be having on females.

4.3 SUMMARY OF CHAPTER 4

It is evident from the results that all the respondents who were issued with Mefliam® tablets were using them, although some members were identified who did not take the Mefliam® tablets before arriving in Burundi. All the respondents, except one who did not fill in the answer, maintained their Mefliam® regimen while being deployed in Burundi. It was revealed that respondents did not realise that they were supposed to continue using the Mefliam® tablets for four weeks after the deployment. Four respondents were diagnosed with malaria from the period of arriving in Burundi to the time they completed the questionnaire. This period comprised a minimum of hundred days.

Thus four out of 111 persons who used the *Mefloquine* (Mefliam®) tablets contracted malaria within the first four months of deployment to Burundi. The following is a statistical summary of the findings.

The value of this section lies in the statistical determination of *Mefloquine* as an effective antimalarial prophylaxis. The confidence interval and Wilson reliance interval (score method) were be utilised as statistical guidance tools.

Confidence interval (CI)

$$p = r/n = 4/111 = 0,036 = 3,6\%$$

$$\text{CI of population: } p \pm z\sqrt{[p(1-p)]/n}$$

$$= 0,036 \pm 1,96\sqrt{[(0,036)(0,964)]/111}$$

$$= 0,036 \pm 1,96\sqrt{[0,0347/111]}$$

$$= 0,036 \pm 1,96\sqrt{0,000313}$$

$$= 0,036 \pm 1,96 \cdot 0,0177$$

$$= 0,036 \pm 0,0347$$

$$\text{CI} = [0,0708; 0,0012]$$

Because (p) is so small, this was regarded as a false indication can be experienced regarding the prophylactic efficacy of the drug. A more reliable test was thus necessary. For this purpose, the Wilson reliance interval was used.

Wilson reliance interval (score method)

$$A = 2r+z^2 = 2(4) + (1,96)^2 = 8 + 3,842 = \mathbf{11,842}$$

$$B = z\sqrt{[z^2+4r(1-r/n)]} = 1,96\sqrt{[1,96^2+4(4)(1-0,036)]} = 1,96\sqrt{[3,842+16(0,964)]}$$

$$B = 1,96\sqrt{[3,842+16(0,964)]} = 1,96\sqrt{19,266} = 1,96 \cdot 4,389 = \mathbf{8,603}$$

$$C = 2(111 + 1,96^2) = 2(114,842) = \mathbf{229,683}$$

$$\text{CI} = [(11,842-8,603)/229,683; 11,842+8,603)/229,683]$$

$$\text{CI} = 3,239/229,683; 20,445/229,683$$

$$\text{CI} = [0,0141; 0,0890]$$

According to this statistical evaluation, there is a 95% certainty that when a population is using *Mefloquine*, the chance of getting malaria will be between

0,0141 and 0,0890. In other words, an individual has a 1,4% to 8,9% chance of contracting malaria when he/she is using *Mefloquine* (Mefliam®).

Using the score method, the confidence interval out of a population of 336 is 4,7 to 29,9 members. The results of the study indicate that the prevalence of malaria in the users of *Mefloquine Hydrochloride* was 3,6% with a 95% Wilson reliance interval of 1,4%; 8,9% (Altman, Machin, Bryant and Gardner, 2000:9-11). According to the study, *Mefloquine* (Mefliam®) had a high prophylactic efficacy in Burundi, East Africa. This result is in line with international tendencies and standards.

CHAPTER 5

5. DISCUSSION AND RECOMMENDATIONS

5.1 DISCUSSION

The purpose of the study was to investigate the prevalence of malaria in *Mefloquine hydrochloride* - Mefliam® users. This research was executed during the deployment of military forces in Burundi, East Africa, in 2002.

According to studies done by Colonel Robert DeFreitas of the Medical Corps of the US Army during 2003, relapsing malaria is the primary military medical problem of malaria cases worldwide. *Falciparum* malaria is the greatest threat to the lives of soldiers in the military due to drug resistance (DeFreitas, 2003:1-12). Complications can present very rapidly and the drug resistance can present as an epidemic. One conclusion is that antimalarial prophylaxis courses are either not taken or are ineffective.

The type of military mission also plays a role in the malaria health threats. Most malaria exposure and least compliance with drug regimens occur during combat operations (DeFreitas, 2003:1-12). During combat operations soldiers are living and sleeping in tents or in the open. Soldiers have to work during night (dusk and dawn) when mosquitoes are most active (Wood, 1993:67-68). Soldiers are working under pressure and there is sometimes little opportunity to take the antimalarial chemoprophylaxis.

During non-violent operations such as peacekeeping operations or humanitarian assistance, low or absent threat of hostile action may permit more emphasis on disease and non-battle injury threats. It should therefore be the opportunity for military forces during such times to actively evaluate their malaria programme, to do rectifications, educate and train the soldiers and medical personnel, and to conduct research regarding antimalarial and therapeutic drugs. During repeated insertions and extractions and the short exposures in malarious areas, members are reluctant to take the antimalarial drugs, due to initial side-effects and the fact that, when they start using it, they have to use it for four weeks after the last

possible exposure such as in the case of the users of Mefliam®. This is a particular concern for people deployed for less than two weeks at a time, or those persons having to go to the area with short intervals, for instance every four weeks. That means that the person has to use the *Mefloquine* chemoprophylaxis for a long time, although he/she is not permanently exposed during that time. This scenario necessitates a different antimalarial drug regimen or more intense research for the quest of the ideal drug.

Military members vary greatly in their need for and response to prophylaxis. The regular infantry troops are normally more disciplined with a stricter disciplinary structure. They are normally a bigger group and are living and working in the same areas for what could lead to better control and observation. It is therefore easier to manage each member's compliance with the antimalarial prophylaxis.

Logistics, transportation and other support units scattered in the deployment area are not always part of the communication lines and the disciplinary structures, which renders their compliance with the antimalarial regimen of these members more of a challenge.

Engineering units are involved in construction projects in tropical conditions with the building of roads, sewerage works and networks, water pumps and pipelines. These members are sometimes compelled to overnight in tropical conditions conducive to mosquito breeding.

In some instances older, experienced military members often believe themselves to be above the need to take antimalarial medication. The non-compliance with taking antimalarial drugs may create a reputation of legendary status among soldiers, fame or infamy, regardless of the merit of such actions.

Military pilots and scuba divers are using *Doxycycline* due to the possible side-effects of Mefliam®. No reliable studies have been done on the effectiveness of *Doxycycline* in certain parts of the world, and until such research is done, or by experience with the drug, its effectiveness could be in doubt (Ohrt *et al.*, 1997:965-972).

Leadership and command emphasis regarding malaria prevention is crucial in achieving compliance among military members. According to the study, 75.7% of the soldiers received their medication from the medical personnel. The antimalarial drugs should be distributed to the respective commanding officers, and they should in turn distribute them to the leaders of the different sections. The structured and organised way in which the drugs are managed should emphasise the importance of achieving compliance with a drug-taking routine among the soldiers. If the section leaders are issuing out and controlling the use of the drugs, it will form part of the weekly routine. This behaviour will be associated with a disciplined structure and negative conduct will be sanctioned. Awareness education must form part of the pre-deployment training. This will determine:

- how the troops perceive the malaria threat; and
- whether military members have practised taking antimalarial medication in the past.

In a studies by DeFreitas (2003:1-12), he observes that the longer the mission, the greater the malaria risk. The cumulative risk of contracting malaria is proportional to the length of stay in an endemic malaria area. A stay of three months carries a risk six times higher than a two week visit (Bradley & Warhurst, 1997: 138-152). This is especially true for relapsing malaria. DeFreitas completed a range of studies on the optimum duration of military deployments, and one of his conclusions was that long deployments almost always resulted in chemoprophylaxis compliance failure. This was due to the fact that command emphasis evaporated, the perception of disease waned and side-effects might persist. He found compliance of only 40% after five months among soldiers using the daily medication regime. Long deployments ensured that the military members got exposed during the high malaria transmission season. The highest transmission typically followed the rainy season.

Troops may be lulled into non-compliance if they do not notice other members becoming sick during the low transmission seasons. Geographical distribution of malaria complicates the threat assessment. Soldiers living in drier areas are a bad influence on other soldiers when they do not use their antimalarial medication regularly. Due to the low presence of malaria mosquitoes in those areas, they do

not contract malaria. In return, soldiers working near stagnant water sources perceive the threat as over-exaggerated and start to fall in the groove of non-compliance, with the expected consequences.

Soldiers generally do not like to take pills (DeFreitas, 2003:1-12). A single episode of vomiting and/or dizziness will stop some soldiers from taking the antimalarial chemoprophylaxis again.

5.2 THE OPTIMAL ANTIMALARIAL REGIMEN

To choose the optimal antimalarial regimen, the following should be taken into consideration:

- A short course of antimalarial medication that would result in several weeks of protection would be highly desirable. *Tafenoquine* for 3 days protects for 10 weeks (Queguiner & Engers, 2001:149-151; Walsh, Eamsila, Sasiprapha, Sangkharomya, Khaewsathien, Supakalin, Tang, Jarasrumgsichol, Cherdchu, Edstein, Rieckmann & Brewer, 2004:1456-1463).
- The taking of daily medication without supervision is not successful. Daily *Doxycycline* requires supervision.
- Weekly regimens are generally superior to daily regimens.
- Antimalarial chemoprophylaxis with a longer half-life allows missed doses to be made up.
- Antimalarial chemoprophylaxis with a longer half-life keeps the intravenous and intracellular chemoprophylactic levels high to prevent the build-up of resistance among malaria plasmodiums.
- Commands should create a routine of the consumption of antimalarial drugs among all the deployed military members in a malarious area, for example once weekly "Malaria Monday". This routine will lead to more streamlined supervision.
- Simpler is better.
- A single drug is a necessity; two drugs are easily confused or forgotten.
- Antimalarial medication administered before deployment for short exposures is highly desirable. During short exposures/visits to malarious areas, people tend to easily forget to take the drugs, because they are not part of the unit routine.

- Consistent malaria policy among military personnel is essential.
- The ultimate malaria prophylaxis would be a *single dose* of medication or immunisation administered during basic training that is 100% efficacious against malaria worldwide, without any adverse effects.
- *Mefloquine* is contra-indicated with pregnancy. In pregnant women malaria poses a particular risk to the health of the mother and the foetus, increasing the risk of maternal death, neonatal death, miscarriage and stillbirth. Pregnant women should if possible, avoid malaria areas. Pregnant women should take every precaution to prevent mosquito bites and, where applicable the appropriate anti-malarial drugs should be taken (South Africa, 2002:5; SCAT, 2003:20).

5.3 RECOMMENDATIONS

The motto of the war against malaria is to stay one step ahead. It is also important to learn more about our common malaria parasite enemy and to develop the means to combat it. We must also learn from our experiences of current and previous military deployments. Problems regarding compliance with and intolerability towards the medication should be documented, while a surveillance programme should also support this feedback. With a surveillance network in place, there will be a better understanding of the clinical relevance of antimalarial drug resistance.

It is critical that education regarding the proper use of chemoprophylaxis forms part of the pre-deployment training of soldiers. The members must be informed regarding the possible build-up of resistance of the malaria parasite against antimalarial drugs if the medication is not used correctly. As part of the malaria education programme, the military personnel should practise taking malaria medications.

Military personnels' perceptions should also be tested regarding possible side-effects and allergic reactions. A herd mentality could easily develop among soldiers during deployment as a result of bad experiences with the medication. If a

member does not use the drugs at all or not according to the prescribed method, other soldiers may follow the example, and soon an entire group may be involved.

The gathering of these data will also allow health care providers to manage patients more effectively. Medical planners can effectively select the best possible drug regimens for different geographic areas. Critical to patient management and triage, is a prompt and accurate diagnosis. The ability to rapidly diagnose malaria in remote military healthcare echelons will help healthcare professionals treat malaria patients sooner.

After extensive studies and research coordinated by the Director of Pharmacy (SAMHS) between 1997 and 2002, it was decided that *Mefloquine* would be used as a drug of choice during deployments for a period of six months, after which all deployed members would have to leave the deployment area (Chemoprophylaxis and Treatment of Malaria, 2003:2; Venter:personal communication). According to Mefliam® package insert (2002:3), *Mefloquine* has in the past been administered to individuals for periods longer than one year. If the drug is used for a prolonged period (longer than three months), periodic monitoring, including liver function, should be performed (Mefliam® package insert, 2002:3). This practise is thought to contribute to the development of resistant strains of *P falciparum*. Mefliam® is not a long term prophylaxis (Mefliam® package insert, 2002:3). A register should be kept of military personnel who have taken the Mefliam® prophylaxis for more than three (3) months consecutively. The current study was conducted four months into the deployment period. However investigations into the monitoring of long-term exposure were beyond the scope of the study. Future studies should take cognisance of this deficiency.

Further research regarding drug resistance is required. It is necessary to initiate monitoring of drug resistance in Africa, using standardised methods. Drug efficacy studies using *in vivo* methods have been standardised by the World Health Organisation. Management guidelines should be developed concerning when and under which conditions to change the treatment regimen for different levels of resistance. Development and field testing of new malaria drugs are required to replace present drugs when resistance makes them unusable. The emergence of

multi-drug resistant malaria will continue to confound the drug development of antimalarial drugs. The medical community must have a better understanding of the mechanics of drug resistance. Resistance to *Mefloquine* has been documented in East Africa and sporadic cases are occurring in West Africa. As these and other reports of drug resistance continue to evolve, the need for a replacement drug for weekly prophylaxis will continue to escalate. *Halofantrine* was developed as a back-up drug for *Mefloquine* in a collaboration effort between the US Army and SmithKline Beecham. However, its usefulness is limited by possible cross-resistance with *Mefloquine*, cardiac toxicity and poor absorption.

The military should document the clinical relevance of drug resistance. They should also examine the potential for spread of resistance in the field. There is mutual agreement that the critical methodology and approach required to describe antimalarial drug resistance requires well documented clinical studies with adequate follow up, confirmation that adequate drug levels were reached in the users of antimalarial prophylaxis and that the drugs were used regularly. Mapping malaria transmission intensity and resistance using geographic positioning systems has to be developed for the mapping of malaria across the continent. This process will have the potential for predicting potential malaria epidemics and monitoring control. Results of these studies in other international armies have facilitated documentation of clinically relevant resistance to *Mefloquine*, *Halofantrine*, *Chloroquine*, *Proguanil* plus *Dapsone* and *Atovaquone* (Queguiner & Engers, 2001:149-151). These and other data will help guide the selection of the next generation of prophylactic drugs.

Future directions must focus on basic and applied research for a better understanding of the modes of actions. Future directions should also concentrate on the mechanisms of resistance to these drugs. The synthesis and design of new drugs would hopefully result in the development of safe and effective drugs that circumvent the malaria parasite's elusive mechanics of drug resistance. Multiple drug resistance in *falciparum* malaria will continue to pose problems for targeting the blood stages of malaria (Queguiner & Engers, 2001:149-151).

There must be an increased emphasis on developing drugs with true causal prophylactic properties. An increased emphasis on developing drugs with radical curative properties before blood stages emerge and cause clinical disease must also be clear. The solution for the current malaria problem is to establish a critical mass of investigators, collaborators and clinical centers that are focused and committed to document and evaluate malaria resistance, examine the potential for spread of resistance in the field and the discovering and development of new medication.

Military research on malaria in Africa is a serious requirement. Collaborations with other defense forces for information on clinical trials and drug resistance surveillance are pivotal for future drug selection and malaria management. No other private or government organisations will adopt this process, due to the limited monitoring possibilities. Should this endeavour not be successful, we cannot expect to protect deployed soldiers who will be scattered on missions in diverse geographic locations all over the world against malaria.

An important fact that emerged from the study is the emergence of the role of females in the military. Cognisance should be taken of the risk sexually active females take when using Mefliam®, as *Mefloquine* is contra-indicated with pregnancy.

5.4 CONCLUSION

Malaria is an important social, economic and developmental health problem affecting military members, their families and their communities. The best chance to successfully combat the disease will require collaboration between those who control the disease and the researchers. The eradication of malaria is placed on a strong research base, international collaboration and sustained governmental support.

Mefloquine is closely aligned with military needs. This biodefence agent addresses the operationally relevant malaria species, *P. falciparum*, and drug-resistant phenotypes of this species. It has an operationally suitable frequency of dose.

The shortcomings of *Mefloquine* have been the adverse event profile on the background of military use, particularly neuropsychiatric events and limitations in suppressive management of *vivax* malaria. In terms of a biodefence system, these are not critical, as they are reasonably predictable and manageable. While chemoprophylaxis remains the cornerstone of malaria casualty control, attention will need to be paid to compliance. With comparable attention to tailoring *Mefloquine* use, as that paid to appropriate uniform fit or weapon allocation, most service personnel will be well protected with *Mefloquine* during military operations in malarious areas. This is in line with findings by Jaspers *et al* (1996:230-234).

This fact must prompt researchers and health personnel to double all efforts to find a solution that will protect 100% of all military personnel against the risk of contracting malaria when deployed in malaria endemic areas.

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ANNEXURE A:

CONFIDENTIAL (When completed)

Dear Participant,

This questionnaire is aimed at finding out the effectiveness of the malaria tablets we are currently using in Burundi. The information that you provide will be important in the helping the other deployments to this area in the future and a possible masters degree. Your opinion is of great importance and will be taken into account in this study

Please answer the questions as honest as possible. All the information that you provide as strictly confidential and will not revealed in such a manner as to disclose your identity. Also the biographical information asked in this questionnaire will only be used for the purpose of analysis.

Your involvement and honest participation is greatly appreciated!

CONSENT FOR THE COMPLETING THE EVALUATION SCHEDULE FOR SANDF MEMBERS DEPLOYING IN EAST AFRICA (BURUNDI)

Full names and surname

.....

Hereby consent to be assessed during the above-mentioned programme by Eldrian Basson (98110414 PF) Environmental Health Practitioner.

I further consent to the anonymous use of these results for research purposes. Also, to provide information in an honest and truthful manner to the best of my knowledge and feelings when asked during the programme.

I declare that the above-mentioned information provided by myself is correct and the information provided during the programme will be accurate and correct to the best of my knowledge.

Signed at

Date

.....

Member's signature

CONFIDENTIAL (When completed)

QUESTIONNAIRE

QUESTION	OPTIONS						
1.1	Gender						
	1.	2.					
	Male	Female					
	105	6					
1.2	Age						
	1.	2.	3.	4.			
	20 – 30	31 – 40	41 – 50	50+			
	45	62	3	1			
1.3	Race						
	1.	2.	3.	4.			
	Black	Coloured	Asian	White			
	76	22	2	11			
1.4	Home Province						
	1.	2.	3.	4.	5.	6.	7.
	Eastern Cape	Limpopo	Mpumalanga	Northern Cape	KwaZulu Natal	Western Cape	Gauteng
	58	7	6	2	4	11	14
	8.	9.					
	Free State	North West					
	3	6					
1.5	Home Language						
	1.	2.	3.	4.	5.	6.	7.
	Afrikaans	English	Xhosa	Zulu	Sotho	Thwana	Venda
	32	4	44	7	8	9	1
	8.	9.	10.				
	Swazi	Ndebele	Shangaan				
	2	3	1				
1.6	Arms of service						
	1	2	3	4	5		
	Army	SAMHS	SAAF	NAVY	MPA		
	78	4	10	4	5		
	CMI	Engineers	Logistics				
	2	4	4				

QUESTIONNAIRE

QUESTION	OPTIONS						
2.1	Have you ever seen someone suffering from malaria?						
	1	2	3				
	Yes	No	Uncertain				
	35	75	1				
2.2	Are you aware of any preventative methods for malaria?						
	1	2					
	Yes	No					
	97	14					
2.3	Did you ever suffer from malaria?						
	1	2					
	Yes	No					
	6	105					
2.4	When you are deployed in a malaria area, do you take the malaria tablets?						
	1	2					
	Yes	No					
	111	0					
2.5	When you are deploying in a malaria area, do you take the malaria tablets before arriving at the area?						
	1	2					
	Yes	No					
	108	3					
2.6	When deployed in malaria area, do you maintain the taking of the malaria tablets?						
	1	2	3				
	Yes	No	Not answered				
	110	0	1				

QUESTIONNAIRE

QUESTION	OPTIONS						
3.1	What is the name of the malaria tablets that you use?						
	1.	2.	3				
	Mefliam®	<i>Doxycycline</i>	Non responsive				
	111	8	1				
3.2	Did you experience any problems about the malaria tablets that you are using?						
	1	2					
	Yes	No					
	11	100					
3.2.1	If your answer is yes, elaborate your answer:						
	1	2	3	4	5	6	7
	Abdominal cramps	Sensitive skin	Diarrhoea	Bad taste	Nauseous	Headache	Perfuse sweating
	1	1	2	1	3	2	1
3.3	Do you enjoy the malaria tablets?						
	1	2					
	Yes	No	Uncertain				
	87	22	2				
3.4	How do you obtain the malaria tablets?						
	1	2	3	4			
	Sickbay	Platoon Commander	Unit	Myself			
	83	18	9	1			
3.5	What problems do you think you can experience if you don't use the malaria tablets? (e.g. Flu)						
	1	2	3	4	5	6	7
	Malaria	Malaise	Fever	Die	Loss of water	Yellow fever	Pneumonia
	78	3	17	2	1	2	1
	8	9	10	11	12		
	Tiredness	Don't know	Vomiting	No appetite	No problem		
	1	3	1	1	2		
3.6	When you complete the deployment, will you continue using these tablets for four weeks being at home?						
	1	2					
	Yes	No					
	102	9					

QUESTIONNAIRE

QUESTION	OPTIONS						
4.1	I take the malaria tablets because...						
	1.	2.	3	4			
	It's important to keep me healthy	It's expected of me to do so	I'm forced to	It's the rule			
	100	7	2	2			
4.2	When I'm taking the tablets, I'm feeling...						
	1	2	3	4			
	OK	Nauseous	Headache	Sleepless			
	92	11	6	2			
4.3	I normally taking my malaria tablets...						
	1	2	3	4			
	At night before I go to sleep	After lunch	After breakfast	When I get a change			
	21	47	33	10			
4.4	I find the malaria tablets to be...						
	1	2	3	4			
	Tasteless	Sour	Sweet	Bitter			
	52	11	1	47			
4.5	Did you get malaria during the current deployment in Burundi?						
	1	2					
	Yes	No					
	4	107					
5.	Please list any concerns or problems about the malaria tablets that were not listed in the questionnaire?						
	1	2	3	4	5	6	7
	None	Sweating	Affect females	Not with liquor intake	Emotional side-effects	Sex life	Expose family to malaria
	94	2	3	2	4	1	1
	8	9	10				
	After taste	Big appetite	Continue taken tablets after leaving Burundi				
	1	2	1				

MEFLIAM TABLETS

SCHEDULING STATUS

Schedule 4

PROPRIETARY NAME

(and dosage form):

MEFLIAM TABLETS

COMPOSITION

Each tablet contains **mefloquine** hydrochloride 274 mg equivalent to mefloquine 250 mg.

PHARMACOLOGICAL CLASSIFICATION:

A: 20.2.6 Medicines against protozoa

PHARMACOLOGICAL ACTION:

Mefloquine is a quinoline methanol derivative, structurally related to quinine. Mefloquine is a blood schizontozide with effects on the asexual blood forms of the malarial pathogens that affect humans (*Plasmodium falciparum*, *P. vivax*). It is also active against the gametocytes of *P. vivax*. Its mechanism of action is unknown. Mefloquine has no effect on the hepatic stage of malaria parasites. Strains of *P. falciparum* resistant to mefloquine have been reported.

Cross-resistance between halofantrine and mefloquine has been observed. Resistance to mefloquine as well as to any other antimalarial may occur in any endemic area. Mefloquine resistance has been described. Resistance patterns occur and vary from region to region and with time.

Pharmacokinetics: The maximum plasma concentration after a single oral dose is reached in 6 to 24 hours (average 17 hours). The achieved plasma concentration in nanograms per millilitre is roughly equivalent to the dose in milligrams. In steady state with weekly doses of 250 mg, maximum plasma concentration of 1 000 ng/mL have been recorded. Mefloquine is 98% bound to plasma proteins. Mefloquine has a large apparent volume of distribution (13,5-29,1 L/kg). The main metabolite of mefloquine, 2,8-bistrifluoromethyl-4-quinoline carboxylic acid, is inactive against *P. falciparum*. It appears that mefloquine is mainly excreted into bile and faeces. The elimination half-life of mefloquine is three weeks. After a single dose in healthy adults it was between 12-37 days on average.

INDICATIONS:

MEFLIAM tablets are indicated for prophylaxis of *Plasmodium falciparum* malaria, in regions where *P. falciparum* strains resistant to 4-aminoquinolines (e.g. chloroquine) occur. MEFLIAM may be effective against malaria parasites resistant to proguanil, pyrimethamine-sulfonamide combinations.

CONTRA-INDICATIONS:

MEFLIAM is contra-indicated in the following:

- Patients with known hypersensitivity to mefloquine or related compounds (e.g. quinine and quinidine).
- Patients with depression or a past history of depression, generalized anxiety disorder, psychosis, including schizophrenia or other psychiatric disturbances.
- Patients with a history of convulsions.
- Children of body weight less than 5 kg.
- Patients with impaired renal or hepatic function.
- The safety in pregnancy and lactation has not been established.

WARNINGS:

Mefloquine may cause psychiatric symptoms in some patients, ranging from anxiety, paranoia and depression to more serious hallucinations and psychotic behaviour. In some instances, these symptoms have continued long after mefloquine was stopped, according to reports. Rare cases of suicide and suicidal ideation have been reported, although no causal relationship with mefloquine has been confirmed. To minimize the chances of these adverse events, mefloquine should be avoided in patients with depression or a past history of depression, generalized anxiety disorder, psychosis, including schizophrenia or other psychiatric disturbances.

If psychiatric symptoms such as unexplained anxiety, depression, restlessness or confusion are evident during mefloquine prophylaxis, the medicine must be discontinued and alternative prophylaxis instituted, as these could be prodromal to a more serious neuropsychiatric event.

Quinine and quinidine which are commonly required for the treatment of severe malaria, are contra-indicated when MEFLIAM prophylaxis has been used.

- Concomitant administration of mefloquine and other related compounds (quinine, quinidine and chloroquine) may produce ECG abnormalities and increase the risk of convulsions.
- As teratogenicity has been shown in animal studies, reliable contraception is recommended whilst taking MEFLIAM tablets and for three months after the last dose. Data in human exposure during the first trimester are insufficient to conclude safety in pregnancy.
- Mefloquine is excreted into breast milk and therefore if it must be taken, breast feeding should be discontinued.
- Mefloquine has been administered for longer than 1 year. If administered for a prolonged period (longer than 3 months), periodic monitoring, including liver function tests, should be performed. Although the retinal abnormalities seen with long-term chloroquine use in humans, have not been found with mefloquine, dose-related ocular lesions have been observed in rats after long-term use of mefloquine at 12.5 mg/kg/day (3-4 x human prophylactic dosage) or higher. Periodic ophthalmic examinations are therefore also recommended.
- Caution is advised in patients who have cardiac conduction diseases because asymptomatic sinus bradycardia and other conduction abnormalities have been reported.
- Caution must be exercised during driving, piloting aircraft, scuba diving, and operating machines as dizziness, disturbed sense of balance or neuropsychiatric reactions have been reported whilst taking MEFLIAM and for three weeks afterwards.
- Mefloquine and halofantrine used simultaneously may lead to a potentially fatal prolongation of the QTC interval.
- MEFLIAM may cause toxic encephalopathy of unknown etiology during prophylaxis.
- There is no evidence that dose adjustment is required for patients with renal impairment. However, since the clinical evidence is limited, MEFLIAM should be used with caution in these patients.
- Mefloquine prophylaxis should not exceed three months as long term prophylaxis is thought to contribute to the development of resistant strains of *P. falciparum*.
- Resistance to mefloquine has been documented in some areas.
- If flu-like symptoms develop in patients who have been in a malaria area they should inform their doctors accordingly.

Additional preventative measures: As preventative medication with all antimalarials is not 100% effective, the following measures to prevent mosquitoes from biting should be taken to reduce the risk of contracting malaria:

- I. visiting endemic areas during the dry season or in years when rainfall is low;
- II. high risk persons should avoid malaria areas altogether, (high risk persons include babies and young children less than 5 years of age, pregnancy, immunocompromised individuals such as those on long term steroids, cancer patients, chemotherapy. AIDS patients and those who have had their spleen removed.);
- III. not going outside between dusk and dawn, when mosquitoes are most active;
- IV. applying insect repellent to exposed skin and clothes;
- V. wearing long sleeves and long trousers at night;
- VI. using mosquito nets, screens, coils and pads.

DOSAGE AND DIRECTIONS FOR USE:

The following weekly doses of MEFLIAM are recommended:

Body weight:	Weekly dose for prophylaxis:
Up to 19 kg	1/4 tablet (62,5 mg)
20-30 kg	1/2 tablet (125 mg)
31-45 kg	3/4 tablet (187,5 mg)
>45 kg	1 tablet (250 mg)

Experience with MEFLIAM in infants less than 3 months old or weighing less than 5 kg does not exist.

The first dose should be taken one week before arrival in an endemic area and subsequent weekly doses should be taken on the same day of each week. Prophylaxis should be continued for four weeks after leaving the malarial area, and should not exceed 3 months' duration. The tablets should be taken after food with plenty of fluids.

SIDE-EFFECTS AND SPECIAL PRECAUTIONS:

Side-effects: Dizziness or disturbed sense of balance, nausea, vomiting, loose stools or diarrhoea, abdominal pain and loss of appetite. Less frequent reactions reported include headache, somnolence and sleep disorders (insomnia, abnormal dreams), myalgia, feeling of weakness, visual disturbances, palpitations, bradycardia, irregular pulse and extrasystoles, AV-block, hair loss, rash or pruritus, urticaria, convulsions, psychological changes, transient elevation of transaminases, leucopenia or leucocytosis and decrease of platelets. Erythema multiforme and Stevens-Johnson syndrome have been reported. Transient cardiac conduction alterations and paraesthesia have been observed in patients taking mefloquine. These adverse events can be observed several weeks after the last dose has been taken.

Psychiatric reactions, sometimes disabling and prolonged, have been reported in association with mefloquine. These include aggression, agitation, anxiety, confusion, convulsions, depression, emotional instability, encephalopathy, forgetfulness, hallucinations, sensory and motor neuropathies (including ataxia, paraesthesia and tremor), panic attacks, paranoia, psychosis and restlessness. Rare cases of suicidal ideation and suicide have been reported, although no causal relationship with mefloquine has been established.

Special precautions:

Caution is advised in renal compromised patients, in compromised hepatic function and in elderly patients as there may be different pharmacokinetic parameters for these groups.

If signs of unexplained anxiety, depression, restlessness or confusion are evident, the medication must be stopped as these could be prodromal symptoms of a more serious neuropsychiatric event.

Interactions:

Concurrent use of beta-blockers, calcium channel blocking agents, quinidine or quinine with MEFLIAM tablets may result in sinus bradycardia, prolonged QT intervals or cardiac arrest; the risk of seizures may also be increased with quinine; concurrent use should be avoided; if concurrent use is necessary, close monitoring of patient response is recommended; in addition, patients should be advised to take mefloquine at least 12 hours after the last dose of quinidine or quinine.

Mefloquine and halofantrine used simultaneously may lead to a potentially fatal prolongation of the QTC interval.

Mefloquine may lower serum concentrations of anticonvulsants (e.g. valproic acid, carbamazepine, phenobarbital or phenytoin) and cause loss of seizure control; monitoring of these anticonvulsant serum concentrations is recommended and dosage adjustments may be necessary during and after therapy with mefloquine.

The concurrent use of the oral typhoid vaccine with mefloquine may decrease the effectiveness of the oral typhoid vaccine; doses of the two medications should be separated by 7 to 10 days. It must be remembered that the first dose of MEFLIAM should be taken one week before entering the malaria area.

Patients who are taking anticoagulants and oral antidiabetic agents should be monitored and have the relevant parameters checked before taking these with mefloquine as it is not known if there are any interactions.

KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

In the event of an overdose with mefloquine, the symptoms would be those specified under "Side-effects and special precautions" but more pronounced. There is no known specific antidote for an overdose, treatment should include standard gastric decontamination procedures and routine symptomatic and supportive treatments. Cardiac function, neurological and psychiatric status should be monitored for at least 24 hours.

IDENTIFICATION:

Flat, white, circular uncoated tablets with bevelled edges. One side has a cross breakline and the other side is plain.

PRESENTATION:

MEFLIAM Tablets are available in blister packs of 6 and 8 tablets.

STORAGE INSTRUCTIONS;

Store below 25°C. Keep out of reach of children.

Protect from moisture.

REGISTRATION NUMBER:

31/20.2.6/0502

NAME AND BUSINESS ADDRESS OF APPLICANT:

Cipla Medpro (Pty) Limited
Rosen Heights, Pasita Street, Rosen Park, Bellville, 7530

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