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## PREFACE

Malaria is a potentially fatal disease that can be prevented in the majority of cases by taking appropriate precautions. These guidelines, produced by the National Department of Health, provide detailed approaches to the options available for preventing malaria transmission in South Africa.

The objective of these guidelines is to provide health care practitioners with information on the most appropriate interventions for people who enter into malaria affected areas in South Africa. These guidelines incorporate the World Health Organization's guidelines for the prevention of malaria.

These guidelines include information on non-drug measures to prevent mosquito bites, determining whether chemoprophylaxis is indicated, selecting the most appropriate chemoprophylaxis to use, including the interactions between malaria chemoprophylaxis and other drug treatments and the benefits and risks of alternative chemoprophylactic agents. A map of malaria risk in South Africa and detailed tables on antimalarial drug dosages have also been included.

I trust that these guidelines will be useful to all health care practitioners, and I thank all those involved in their development.



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Ms B Hogan, MP  
Minister of Health

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Mr TD Mseleku  
Director-General Department of Health

## 1. EXECUTIVE SUMMARY

Malaria poses a risk to travellers to, and residents in, malaria areas. Stringent non-drug measures should be taken to avoid mosquito bites throughout the year, even in areas of low malaria transmission intensity. In addition, effective chemoprophylaxis should be taken whenever and wherever the risks of acquiring malaria exceed the probability of experiencing a serious adverse reaction to the chemoprophylaxis. The risk of acquiring malaria is determined by the intensity of malaria transmission in the area and season of visit, as well as the length of stay, type of accommodation, and likely activities between dusk and dawn.

The choice of chemoprophylaxis is determined by local antimalarial drug resistance patterns and patient factors including, co-morbid disease, drug interactions and activities. Mefloquine or atovaquone - proguanil or doxycycline are currently the recommended prophylactic agents.

Patients should be made aware that malaria should be urgently excluded with ANY febrile illness occurring within 1 week to 3 months after visiting a malaria area, regardless of whether or not chemoprophylaxis was taken or mosquitoes were seen. Early effective treatment is essential to prevent progression to potentially fatal severe malaria.

### **Disclaimer**

*This material is intended for use by healthcare professionals. It has been compiled from information currently available, and although the greatest care has been taken, the Department of Health and its Malaria Advisory Group do not accept responsibility for errors or omissions. The guidelines for prevention of malaria may change over time as parasite resistance patterns change. Policy may therefore need to be revised. Readers are referred to the reference articles for further information and should exercise their own professional judgement in confirming and interpreting the findings presented in the publication. These guidelines were issued in 2009 by the National Department of Health, and replace all previous guidelines.*

## 2. INTRODUCTION

Malaria is a common and life-threatening disease in many tropical and subtropical countries.<sup>1</sup> In some tropical districts in Africa, over half of the residents may be infected with malaria. It is estimated that more than a million African children die of malaria each year. Malaria control operations have substantially reduced the risk of malaria in some countries. In South Africa, malaria was originally endemic in the low-lying northern and eastern districts. However, control measures introduced since 1930 have reduced malaria transmission significantly, and the risk of malaria is now comparatively low and seasonal.

Malaria prevention includes measures taken both against mosquito vectors and against the malaria parasite. These include vector control programmes managed by government health authorities, personal protection measures to avoid mosquito bites and the use of chemoprophylaxis. Due to the development of drug resistant parasites, drug side effects and contraindications, the control of vector mosquitoes and avoidance of their bites have become increasingly important.

Parasite resistance to antimalarials used for chemoprophylaxis and treatment has increased significantly over time. Resistance to chloroquine and sulfadoxine-pyrimethamine (in certain areas for treatment<sup>2</sup>) has become so widespread that these drugs can no longer be used as monotherapy<sup>3,4</sup>. This has necessitated changes in chemoprophylaxis and treatment policies in South Africa. Multidrug resistance further limits the availability of effective antimalarials for travellers internationally.

These guidelines are for use by medical personnel and contain information on malaria transmission, the life cycle of the parasite, advice on the avoidance of mosquito bites and the use of antimalarial chemoprophylaxis.

### 2.1 Distribution of malaria

Malaria occurs mainly in tropical developing countries in sub-Saharan Africa, Central and South America, Asia and Oceania. Through effective malaria control measures, malaria transmission has been limited to the north-eastern part of South Africa, mainly in the low altitude (below 1000m) areas of Limpopo, Mpumalanga and Northern KwaZuluNatal<sup>10</sup>. (See page 30 - map of malaria risk areas in South Africa.) Limited focal transmission may occasionally occur in the North West and Northern Cape provinces along the Molopo and Orange rivers. Malaria is distinctly seasonal in South Africa, with the highest risk being during the wet summer months (September to May)<sup>5</sup>.

### 2.2 Malaria – the disease

Malaria is transmitted to humans by the bite of an infected female *Anopheles* mosquito. Human malaria is a parasitic infection/disease caused by four species of the *Plasmodium* parasite:

- *Plasmodium falciparum* (*P. falciparum*)
- *Plasmodium malariae* (*P. malariae*)
- *Plasmodium ovale* (*P. ovale*)
- *Plasmodium vivax* (*P. vivax*)

In Sub-Saharan Africa over 90% of human malaria infections are due to *P. falciparum*. *Plasmodium falciparum* is the only species associated with severe morbidity and mortality<sup>6,8</sup>. The other three species cause milder illness, however infections with *P. ovale* and *P. vivax* may relapse months later if appropriate treatment is not provided. Mixed infections involving more than one species may also occur.

The life cycle of the malaria parasite involves two hosts (Figure 1). During a blood meal, a malaria-infected female *Anopheles* mosquito inoculates sporozoites into the human host. Sporozoites infect liver cells and mature into schizonts, which rupture and release merozoites into the blood stream where they infect red cells.

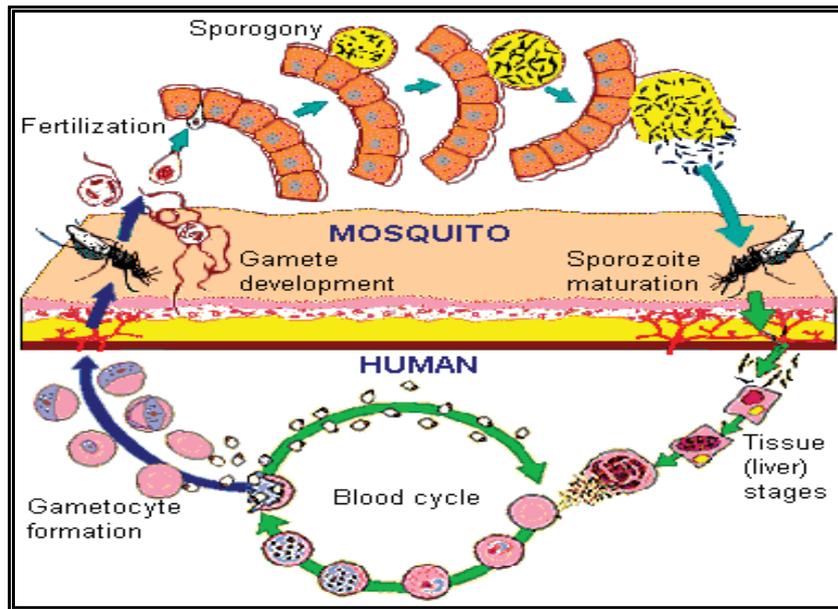


Figure 1: Life cycle of malaria parasites in human and mosquito  
[http://www.malaria.org.za/Malaria\\_Risk/General\\_Information/general\\_information.html](http://www.malaria.org.za/Malaria_Risk/General_Information/general_information.html)

In *P. vivax* and *P. ovale* malaria infections, a dormant stage [hypnozoites] can persist in the liver and cause relapses by invading the bloodstream months, or even years later. After this initial replication in the liver (exo-erythrocytic schizogony), the parasites undergo asexual multiplication in the erythrocytes (erythrocytic schizogony). The ring stage trophozoites mature into schizonts, which rupture, releasing merozoites. Some parasites differentiate into sexual erythrocytic stages (gametocytes). Erythrocytic schizogony is responsible for the clinical manifestations of the disease.

Some parasites differentiate into sexual erythrocytic stages (gametocytes). The gametocytes in the blood do not cause symptoms and may persist for several weeks after successful treatment of the acute illness<sup>8</sup>. This is the stage of the parasite's lifecycle responsible for continued malaria transmission and spread of drug resistance. The *Anopheles* mosquito ingests the male (microgametocytes) and female (macrogametocytes) gametocytes during a blood meal. The parasites' multiplication in the mosquito is known as sporogony. The resulting sporozoites make their way to the mosquito's salivary glands from where inoculation into a new human host perpetuates the malaria life cycle.

Following infection during a mosquito blood meal, there is an asymptomatic incubation period of approximately 7 to 30 days during which the parasites develop in the liver and multiply in the blood. This period can be prolonged in patients taking chemoprophylaxis (or some antibiotics). Reproduction in the blood is extremely rapid and destruction of red blood cells soon induces disease symptoms. Without treatment, the illness may progress rapidly, especially in high-risk groups (non immunes, pregnant women, young children, splenectomised and immunocompromised patients). Following appropriate treatment, *P. falciparum* and *P. malariae* infections are normally completely cured. However, hypnozoites (the dormant stage) in the liver may be responsible for relapses of *P. ovale* and *P. vivax* infection, presenting 2 – 3 months or more after treatment of the asexual stages of the original infection<sup>8</sup>. A two-week course of primaquine is needed to ensure a radical cure (eradication of this latent liver stage).

### 2.3 Malaria - The Mosquito Vector

Mosquitoes are scientifically classified by their appearance into groups (families). One of these, the *Anopheline* family, includes all of the species responsible for transmitting malaria. At least three species have been shown to transmit malaria in Southern Africa.

Mosquitoes have four distinct stages in their life cycle: egg, larva, pupa and adult. The duration of the larval stage and lifespan of the adult mosquito is strongly influenced by temperature. The average optimum temperature for the development of mosquitoes is around 25-27°C. The development can be completely arrested at 10°C or over 40°C

when a high mortality may occur. With ideal hot conditions the larval stage may be as short as 4 – 7 days and adults may survive for 3 – 4 weeks. Water is essential for the larval stage. This explains why malaria transmission increases in the warm, wet months (September to May) in South Africa.

### Features of Anopheline mosquitoes:

- They are relatively small; about 8 mm long with dark-spotted or dappled wings.
- Their posture when resting or feeding is distinctive – head down, body at an angle and hind legs raised. This is in contrast with the horizontal position maintained by most other mosquito species.
- They fly more quietly and bite more subtly than other mosquitoes.
- They generally prefer clean water for the development of their larval stages in contrast to the dirty water found in drains, tins and rubbish preferred by the *Culicine* family. Individual *Anopheline* species differ in their preferences – *Anopheles arabiensis* (*An. arabiensis*) larvae are commonly found in small sunlit water collections e.g. hoof prints, small sandy pools, while *Anopheles funestus* (*An. funestus*) larvae are found in deep-shaded clean water.
- Adult *An. arabiensis* rest both indoors and outdoors, while *An. funestus* and *Anopheles gambiae* (*An. gambiae*) favour resting indoors. This results in residual household spraying being more effective in the control of the latter species.
- The adults are carried by wind but few are found further than 1 – 2 km from their larval site. Adults may rest inside motor vehicles, trains, or aircraft, and be transported for considerable distances. In this way infected mosquitoes have been responsible for local transmission of malaria infections in non-malaria areas particularly near airports and major truck stopovers.
- The adult female *Anopheles* mosquitoes require protein from blood meals for their eggs to mature. They generally feed between sunset and dawn<sup>1,6</sup>. Personal protective measures to prevent mosquito bites need to be ensured at this time.
- *Anopheles* prefer to feed near ground level and feed selectively on the lower leg rather than arms or upper body, thus it is especially important that insect repellent is applied to the lower leg and foot when in the sitting or standing position.

## 3. PREVENTION OF MALARIA

Malaria is a life-threatening disease that poses a major health risk for residents and travellers to malaria areas. Appropriate advice and use of drugs and, most importantly, non-drug prophylactic measures can prevent persons from contracting the disease.

This chapter will address the five key components of preventing malaria morbidity and mortality (Summary Box 1)

### SUMMARY BOX 1

#### The “ABC” of Malaria prevention

A: Awareness and assessment of malaria risk

B: Avoidance of mosquito Bites

C: Compliance with Chemoprophylaxis, when indicated

D: Early Detection of malaria

E: Effective treatment

#### 3.1 Awareness And Assessment of Malaria Risk

A number of factors must be taken into consideration prior to entering an area in which malaria is prevalent.<sup>9</sup> These factors determine the likelihood of a traveller acquiring malaria, or of progression to severe and complicated malaria, and thus should aid a healthcare provider in determining whether chemoprophylaxis is needed (and which regime is recommended), in addition to stringent non-drug measures.

The first step in deciding on appropriate prophylactic measures is to confirm that the area to be visited is indeed

a malaria area. Accurately identifying malaria transmission areas is difficult. Within countries and even within regions in those countries, there are often malaria risk areas and other areas that may be free from malaria. Malaria risk areas are not static and may change with time, depending on factors such as rainfall and migration of infected individuals. Detailed and up-to-date information should be sought through information centres or credible websites. (refer page 32)

The risk of malaria transmission varies greatly according to the specific destinations within a defined geographic area. While the risk of malaria is much less at altitudes above 1500 metres, disease can occur in hot climates at altitudes of up to 3000 metres<sup>1,9</sup>.

Malaria transmission is seasonal in South Africa with increased risk during wet summer months (September to May). Travellers should ideally visit malaria areas when malaria transmission is minimal, usually during winter or the dry season.

Pregnant women, children under the age of five years, and immunocompromised patients should avoid high-risk malaria areas if at all possible<sup>10</sup>.

Personal protection against mosquito bites remains essential in malaria prevention, and should be used throughout the year by all residents in, and visitors to, malaria risk areas. Malaria transmission occurs primarily between dusk and dawn because of the nocturnal feeding habits of mosquitoes and precautions during these hours are most important<sup>1,6</sup>.

### **FACTORS DETERMINING MALARIA RISK**

- The malaria risk in the area being visited
- The length of stay in the area
- The time of year (in areas of seasonal malaria transmission)
- The inclusion of an overnight stay (as transmission occurs between dusk and dawn)
- The intensity of transmission and prevalence of drug resistant malaria in the area
- High risk groups [non-immunes, pregnant and breast-feeding women, young children, comorbid disease, splenectomised and immunocompromised patients(including those with HIV and AIDS, taking corticosteroids or on chemotherapy)]
- Comorbid disease and concurrent medications
- The type of accommodation (e.g. air conditioned rooms, camping)
- Mode of travel (e.g. backpacking, motoring, flying)
- Whether the destination is rural or urban
- Any outdoor activities between dusk and dawn.
- Access to medical care

### **3.2 Mosquito Avoidance**

Due to increasing development of parasite resistance to drugs, non-compliance and other factors, no antimalarial drug used for prophylaxis is 100% effective. This, together with the inconvenience of taking continual chemoprophylaxis if living in malaria endemic areas, means that special emphasis should always be placed on the importance of preventing contact with mosquitoes.

Avoiding mosquito bites is at least as important as using chemoprophylactic medicines. Measures that reduce contact with mosquitoes have the advantage that they are less toxic than chemoprophylactic drugs and that their effectiveness does not depend on the drug sensitivity of the parasite.

#### **3.2.1 Preventive Measures For Residents In Malaria Areas**

For residents of malaria risk areas mosquito preventive measures are the primary focus. The following measures can reduce mosquito exposure:

- Residents are encouraged to allow for the interior walls of their houses to be sprayed annually with

effective non-toxic long-acting insecticides. Indoor residual spraying (IRS) is the mainstay of malaria vector mosquito control in South Africa. IRS relies on the fact that most malaria parasite carrying mosquitoes enter houses during the night to feed on the occupants and rest on the walls or roofs prior to and/or after feeding. If the wall or roof is treated with an effective residual insecticide, the mosquito will pick up a lethal dose as it rests. The actual surfaces to be sprayed include the interior surfaces of walls and roofs, the interior and exterior surfaces of doors and windows, and the underside of roof eaves. The provincial malaria control programme normally provides this service in malaria areas of South Africa.

- Build houses and villages away from marshy areas and water bodies, which are potential larval breeding sites.
- Make provision for optimum drainage of rainwater and household water near houses.
- Where standing water exists near habitations and cannot be drained, larvicides should be applied.
- Install gauze screens in front of outside doors and on windows of houses.



Figure 2: Insecticide Residual Spraying in South Africa

### 3.2.2 Additional Preventive Measures For Residents and Visitors to Malaria Areas

These measures include:

- Remain indoors between dusk and dawn as much as possible
- Long (preferably light-coloured) clothing should be worn to minimize the amount of exposed skin.
- Mosquito repellents containing DEET (N,N-diethyl-3-methylbenzamide), are especially useful for protection during outdoor activities. They should be applied to exposed skin surfaces and repeated after 4 – 6 hours according to the manufacturers' instructions. Repellents should not be sprayed on the face nor applied to lips or eyelids, and the dosage should not be exceeded, especially for small children. In infants and young children, insect repellents should be applied to the skin sparingly for a number of reasons, including the relatively large body surface area compared to the body weight in this age group. The American Academy of Paediatrics advocates that DEET-containing insect repellents used for children should contain 30% of the active ingredient, should be applied sparingly and should not be used for children under the age of 2 months.<sup>76</sup> Citronella oil is the most effective and most commonly found plant extract, however, even in its pure form, it is less active than DEET and it is also shorter acting than most DEET-based products. It must be reapplied every 40-90 minutes for continued efficacy.<sup>13, 14, 15</sup>
- Using knockdown insecticidal sprays, vaporization mats, mosquito coils etc. to eliminate mosquitoes that have gained entry to a dwelling
- Insecticide - treated bed nets are useful in preventing mosquito bites and can also kill mosquitoes, further reducing malaria risk. One insecticide treatment should last for a minimum of one malaria

season, unless the nets are repeatedly washed. Re-treatment kits, usually using a pyrethroid type of insecticide are widely available but manufacturer's directions should be carefully followed, as the solution is toxic. Longer lasting insecticide impregnated mosquito nets are now available and remain effective for up to three years. Nets should not be damaged and must be tucked in. Baby cots and prams may be covered with mosquito netting for protection against mosquitoes.

- Ceiling fans and air conditioners are also effective in disturbing mosquito feeding.

#### PRECAUTIONS THAT SHOULD BE TAKEN TO MINIMISE INSECTICIDE PROBLEMS:

- Apply repellent sparingly to exposed skin or clothing<sup>11</sup>.
- Repeat applications at intervals according to the duration of action of the particular repellent<sup>14</sup>.
- Re-apply more frequently after bathing, showering, sweating, etc<sup>14,17</sup>.
- Avoid contact with the eyes, mucous membranes and broken skin<sup>14,15</sup>.
- Do not inhale or ingest<sup>11</sup>.
- Avoid applying high concentrations of the products to the skin, particularly in children<sup>11</sup>.
- Avoid applying repellents to the hands of young children, as these are likely to have contact with the eyes and mouth<sup>11</sup>.
- Avoid using plant extracts if prone to allergy<sup>14</sup>.
- People with sensitive skin should avoid lotions and gels. These often contain alcohol<sup>14</sup>.
- If a suspected reaction to insect-repellent occurs, wash treated skin and seek immediate medical attention<sup>11</sup>.
- STOP using DEET and obtain immediate medical advice if a change in behaviour is noticed<sup>14</sup>.
- Read the entire repellent label before use and use only as directed.
- Note that DEET can opacify spectacles, binoculars and other plastics<sup>14,15</sup>.
- Keep repellents out of the reach of children.

#### **SUMMARY BOX 2**

##### **PERSONAL PROTECTION MEASURES TO PREVENT MOSQUITO BITES**

- Remain indoors between dusk and dawn
- Wear long-sleeved clothing, long trousers and socks when going out at night
- Cover doorways and windows with screens, but if not available, windows and doors should be closed at night.
- Apply a DEET-containing insect repellent to exposed skin; repeat as recommended on the container label. Avoid eyelids, lips, sun burnt or damaged skin, do not spray on the face and do not overdose young children.
- Use mosquito mats, impregnated with an insecticide (heated electrically or by a non-electric lamp), or burn mosquito coils in living and sleeping areas during the night.
- Use a mosquito-proof bed net over the bed, with edges tucked in.
- Ensure that the net is not torn and that there are no mosquitoes inside. Protection will be increased by periodically treating the net with an insecticide registered for this purpose, e.g. a pyrethroid.
- Spray inside the house with an aerosol insecticide (for flying insects) at dusk, especially the bedrooms, after closing the windows.
- Ceiling fans and air conditioners are very effective.
- Treat clothes with an insecticide registered for this purpose, e.g. a pyrethroid.

### 3.3 Use Of Antimalarial Agents For Chemoprophylaxis

#### 3.3.1 Indications For Chemoprophylaxis

If an individual is travelling to a malaria area, it is important to determine whether he or she requires chemoprophylaxis, or whether adequate protection can be provided by the regular use of personal protection measures as discussed above.

The decision as to whether chemoprophylaxis is necessary is complex. It depends on the areas to be visited (see map) and the risk that the traveller has of being exposed to mosquitoes and of developing malaria. The greater the traveller's risk of contracting malaria and developing complications, the greater the need for chemoprophylaxis. People at highest risk of developing severe malaria complications include the elderly, babies and young children (< 5 years), pregnant women and immunocompromised individuals (e.g. patients living with HIV and AIDS, those who have had a splenectomy, and patients receiving long-term steroids or chemotherapy).

When deciding on the need for chemoprophylaxis, it must be remembered that all medicines have adverse effects and that the risk of developing a serious adverse effect must be weighed against the risk of developing malaria. No chemoprophylaxis is 100% effective. However, disease in those taking chemoprophylaxis is likely to be milder or less rapidly progressive even if the parasites exhibit a degree of drug resistance<sup>17</sup>. The most reliable way of preventing malaria is to avoid mosquito bites.

#### 3.3.2 Choosing Appropriate Chemoprophylaxis

It is not advisable to make blanket recommendations for malaria prophylaxis. The choice of suitable prophylaxis should be tailored to the individual. All travellers to malaria areas should be advised to use non-drug measures. Whether chemoprophylaxis is necessary or not, depends on the traveller's risk of exposure to infected mosquitoes and therefore the risk of developing malaria.

There are currently three effective chemoprophylactic options available in South Africa (see Summary Box 3).

### SUMMARY BOX 3

#### RECOMMENDED PROPHYLACTIC REGIMENS

One of the following regimens is currently recommended for use in South Africa:

- **Mefloquine. (Weekly).** Start at least one week before entering a malaria area, take weekly while there and for **FOUR** weeks after leaving the malaria area<sup>1</sup>.
  - **Doxycycline. (Daily).** Start one day before entering a malaria area, take daily while there and for **FOUR** weeks after leaving the malaria area<sup>1</sup>.
  - **Atovaquone - proguanil. (daily).** Start one to two days before entering malaria area, take daily while there and for **SEVEN** days after leaving the area.<sup>63</sup>
- See table 3 for a comparison of the benefits and risks of these prophylactic regimens.

Chemoprophylaxis may refer to absolute prevention of infection (i.e. causal prophylaxis) or to suppression of parasitaemia and its symptoms (i.e. suppressive or clinical prophylaxis). Drugs, which act on the erythrocytic stages of the parasite (i.e. once the parasite has invaded the red blood cells) are known as blood schizonticides and are suppressive prophylactics. These medicines suppress the disease by destroying the asexual parasites. Examples of blood schizonticides include doxycycline and mefloquine. If prophylaxis is continued until there are no more parasites entering the blood, then a suppressive cure is achieved. In *P. falciparum* infections, this is estimated to occur up to one month after the last infective bite.

Causal prophylaxis is provided by tissue schizonticides, which destroy the exo-erythrocytic forms of the parasite. Proguanil acts on the pre-erythrocytic intra-hepatic forms of the parasite but alone it is not enough to completely prevent malaria. The combination of atovaquone and proguanil may be classed as a causal prophylactic.

In order to choose a safe and appropriate prophylactic agent for a person travelling to a malaria area, various clinical and drug-related factors need to be taken into account (See Table 1).

- Pregnancy or planning a pregnancy shortly after the trip
- Breast-feeding
- Age
- Pre-existing medical conditions such as psoriasis, epilepsy, diabetes, renal impairment, cardiac complications or psychiatric problems
- Other medication being taken (including prescription, over-the-counter and complementary or traditional medicines)
- Activities requiring fine co-ordination and spatial discrimination, e.g. piloting, scuba-diving
- Length of visit to the area  
The cumulative risk of contracting malaria is proportional to the length of stay in a malaria area. A visit of 3 months carries a risk six times greater than a 2-week visit<sup>18</sup>. Long-term safety of some chemoprophylactic drugs has not been evaluated.
- The level of compliance expected with each of the options.

### 3.3.3 Measures to ensure effective and safe use Of Chemoprophylaxis:

- Chemoprophylaxis needs to be used in addition to, and not instead of, personal protection measures.
- Dosing schedules for children should be based on body weight;
- Anti-malarials (particularly doxycycline and atovaquone-proguanil) should be taken with food and adequate fluids;
- **Patients need to be well educated and motivated to ensure the highest possible level of compliance.**
- All antimalarials should be started before entering a malaria area (1- 2 days before for doxycycline and atovaquone-proguanil; 1-2 weeks before for mefloquine).
- Antimalarials should be taken with unfailing regularity for the duration of exposure and for the correct duration after leaving the malaria area (4 weeks for mefloquine and doxycycline, and 7 days for atovaquone proguanil).
- Antimalarials taken weekly must be taken on the same day each week.
- Antimalarials taken daily must be taken at the same time each day.
- All currently available effective chemoprophylaxis options require a medical prescription for purchase.
- **There is no scientific evidence to support use of complementary, alternative and homeopathic preparations for the prevention (or treatment) of malaria.**

### 3.3.4 Efficacy and adverse reactions of recommended Prophylactic regimens

In terms of protective efficacy, mefloquine, doxycycline and atovaquone-proguanil are considered comparable at around 90%, but the best quality evidence is available for mefloquine<sup>64</sup>. The advantages and disadvantages of each of the recommended chemoprophylactic options are summarised in Table 3. A high percentage of travellers who take malaria chemoprophylaxis will report side effects, the majority of which are mild and self-limiting. Atovaquone-proguanil reportedly has less severe reactions than the other options.<sup>64</sup>

#### Mefloquine:

Mefloquine is the most thoroughly documented option for long-term prophylaxis and is therefore the best option for those requiring prophylaxis for more than 6 months, if tolerated.<sup>66</sup>

Mefloquine is active against *P. falciparum* parasites including those that are resistant to chloroquine and sulfadoxine-pyrimethamine and against the other three *Plasmodium* species that affect humans<sup>8</sup>. Weekly dosing should encourage compliance. It is recommended for use for up to 12 months but has been safely used for more than 2 years<sup>25</sup>.

Adverse effects associated with mefloquine include insomnia, strange dreams, mood changes, nausea, diarrhoea and headache. These would usually be experienced within the first three weeks of medication and do not become worse in subsequent weeks of use<sup>18,22,23,24,26</sup>. If they are not experienced during the first use of mefloquine they

are unlikely to appear during subsequent use for prophylaxis. Severe neuropsychiatric reactions (psychosis, convulsions) are infrequent with prophylactic doses and occur in approximately 1/10 000 to 1/13 000 persons<sup>23</sup>. The frequency of mild neuropsychiatric effects is probably much higher<sup>24</sup>. These are more common in women.<sup>64</sup>

These side effects may be sufficiently severe for the individual to discontinue prophylaxis. To forestall this event it is suggested that when mefloquine is to be taken for the first time that prophylaxis should commence three weeks before exposure to malaria to enable a change to be made timeously to another drug should side effects occur<sup>1,17</sup>.

Rare cases of suicidal ideation and suicide have been reported, though no relationship to mefloquine has been confirmed.

There is inadequate experience of the safety of mefloquine taken during the first three months of pregnancy. It should not be used during this time but in the event of a pregnancy, available safety data does not support termination<sup>27,28</sup>. The WHO guidelines state that mefloquine is safe to use in breastfeeding.<sup>1</sup>

Mefloquine may cause spatial disorientation and lack of fine coordination and should not be used where fine coordination is required, e.g. for pilots, or those contemplating underwater diving<sup>1,29</sup>.

### **Doxycycline:**

Doxycycline is effective against all four species of human malaria parasites and has comparable efficacy to mefloquine<sup>8</sup> and is taken daily starting one day before entering the malaria area and continuing daily while in the area, and daily for 4 weeks after leaving the area.

This drug affects bone formation during early life and should not be given during pregnancy, breast-feeding and the first eight years of life. Adverse effects include gastrointestinal symptoms and *Candida* infection of the gut and vagina and may be severe enough to discontinue prophylaxis. Severe skin sensitivity to sunburn may develop. Excessive exposure should be avoided and the use of sunscreen preparations is advised. Other rare symptoms include dizziness, headache and blurred vision<sup>1,17,23</sup>.

There is limited experience with long-term use of prophylactic doses for more than 4-6 months<sup>1,17,23</sup>.

### **Atovaquone – Proguanil:**

Atovaquone-proguanil has the best safety profile and because of compliance is better choice for short-term travellers<sup>66</sup>.

Atovaquone-proguanil appears to have a relatively mild adverse event profile, with nausea being the most common symptom. It has no adverse psychomotor effects on aircrew.<sup>64</sup>

This combination should be taken at least one day before exposure, continued daily during exposure and for seven days after the last exposure to malaria<sup>1</sup>. Atovaquone-proguanil is a causal prophylactic and acts on the liver stage, hence the reason for the shorter regimen<sup>30</sup>. This shortened regimen is expected to significantly improve compliance. Lack of safety data preclude its use during pregnancy, breast-feeding or for children under 11 kg<sup>1</sup>. There is presently a paucity of data regarding the use of atovaquone-proguanil in patients with co-morbid disease, but it should be used with caution in patients with renal failure. Side effects include gastrointestinal symptoms. As it is a relatively new antimalarial, efficacy data in non-immunes is limited. However, available data on efficacy would support its use for chemoprophylaxis.

### 3.3.5 Alternatives not recommended for Prophylaxis

Artemisinin-derivatives and their combinations:

The artemisinin derivatives are pivotal for the treatment of malaria and so should be strictly protected for this indication and never used (alone or in combination or as herbal or complementary medicines) for the prevention of malaria. This is strongly recommended by the World Health Organization in order to delay the development of resistance. Furthermore, their very short elimination half-lives makes them ineffective for prophylaxis.

#### Dapsone-pyrimethamine:

This combination is still used in some parts of the world, but in general its use is no longer recommended. There is widespread resistance to antifolate agents and it is also associated with a high incidence of agranulocytosis<sup>35</sup>. Agranulocytosis has been reported in approximately 1 in 2000-5000 courses<sup>36</sup>.

#### Chloroquine plus Proguanil:

This combination is no longer effective as high-level chloroquine resistance is prevalent in almost all malaria transmission areas. Proguanil is no longer available in South Africa.

#### Alternative medicines:

There is no scientific evidence to support use of complementary, alternative and homeopathic preparations for the prevention (or treatment) of malaria.

### 3.3.6 Patient-Specific Prescribing Problems

#### Patients being treated with rifampicin:

There is no ideal option. It is most important however to take prophylaxis. All 3 options can interact with rifampicin. The safest is probably doxycycline as the interaction appears to only occur in slow metabolisers.

#### Changing from one chemoprophylactic to another:

If it is necessary to change from one antimalarial agent to another the following is recommended:

Patients changing from mefloquine to doxycycline may do so without a washout period. There is currently no information on changing from atovaquone-proguanil to doxycycline or vice versa and changing from doxycycline or atovaquone-proguanil to mefloquine less than a week before entering the malaria area is inadvisable.

Changing from mefloquine to atovaquone-proguanil once in the malaria area is also inadvisable because of the different sites of action.

#### People taking doxycycline for acne:

One of the many drugs used to manage acne is oral doxycycline. For malaria prophylaxis, doxycycline is administered as a single daily dose of 100mg, starting one to two days before entering the area, taken daily while in the area and continuing for four weeks after leaving the area<sup>1</sup>. A person who is already taking doxycycline for acne need only ensure that the daily dose of doxycycline is equivalent to that recommended for malaria chemoprophylaxis.

If a patient is taking another tetracycline, such as minocycline, for acne, an option is to replace it with doxycycline in the recommended doses for malaria chemoprophylaxis. There is insufficient data to support the use of minocycline for malaria prophylaxis, and there is a possibility of an increase in adverse reactions at the dose that would be required.

## People with epilepsy:

Selecting a chemoprophylactic agent for an epileptic patient is problematic. Some of the agents have been reported to cause convulsions and others may interact with anti-epileptic medication. Epileptic patients must use non-drug measures diligently to protect themselves against mosquito bites. They must also be warned about the possible risks of taking chemoprophylactic agents and of contracting malaria to allow them to make an informed decision.

### Mefloquine:

Mefloquine is contraindicated for malaria prophylaxis in patients with a history of convulsions<sup>29</sup>. Several case reports of first-time seizures in patients taking mefloquine in prophylactic doses have been reported<sup>44,45</sup>.

There have also been reports of mefloquine reducing the half-life and lowering the blood levels of the anticonvulsant, sodium valproate.

### Doxycycline:

Doxycycline does not affect epilepsy, but may interact with some of the anti-convulsants. Carbamazepine, phenytoin and barbiturates may shorten the half-life of doxycycline by up to 50%, thus potentially compromising its therapeutic efficacy. The degree to which the levels are affected is not clear and an exact recommendation cannot be made because there is limited experience with an increased prophylactic dose. Increasing the doxycycline dose may also result in increased incidence of side-effects<sup>17,45,46</sup>.

In summary, epileptic patients not taking carbamazepine, phenytoin or barbiturates can safely use doxycycline as prophylaxis. Patients taking carbamazepine, phenytoin and/or barbiturates must be made aware of the fact that the normal dose of doxycycline may not provide adequate protection and increasing the dose may result in an increased risk of side-effects.

### Atovaquone-proguanil:

The guidelines for malaria prevention in travellers from the United Kingdom recommends this combination as being suitable for people suffering from epilepsy who require malaria prophylaxis.<sup>64</sup>

Although there is currently insufficient published information on its use in epilepsy, epilepsy is not listed as a contraindication or precaution.

#### Recommendations:

Doxycycline is an option for epileptics with the above proviso.

Atovaquone-proguanil has also been used.

## Prophylaxis during pregnancy:

**Pregnant women should avoid travelling to malaria endemic areas<sup>1</sup>.** There is no prophylactic regimen that provides total protection against malaria, and malaria poses a significant risk to the health of both the mother and foetus. Malaria increases the risk of stillbirth, miscarriage, neonatal death and maternal death<sup>1</sup>. Pregnant women are also more likely to suffer from severe malaria than non-pregnant women. This is especially true of the *primigravidae*. The mechanism is unclear but may be related to cellular immune function suppression, the greatest risk being spontaneous abortion<sup>47</sup>.

If travel to a malaria area is unavoidable, both meticulous non-drug measures and chemoprophylaxis are essential.

### Mefloquine:

Although the manufacturers contraindicate the use of mefloquine in pregnancy, the World Health Organisation and others recommend that mefloquine may be considered for chemoprophylaxis in women in their second or third trimester of pregnancy when visiting high-risk chloroquine-resistant *P. falciparum* areas. Cumulative evidence from clinical trials and reports of inadvertent use of mefloquine during pregnancy do not suggest an association with adverse foetal outcomes<sup>17,28,45</sup>.

The use of mefloquine in the second and third trimester has not been linked with increased congenital malformations<sup>26,45</sup>. Recent literature also suggests that the use of mefloquine may be considered for chemoprophylaxis in women during their first trimester of pregnancy when visiting very high-risk chloroquine-resistant *P. falciparum* areas<sup>23</sup>. Further studies are however needed due to concerns about a possible increase in the occurrence of spontaneous abortion after use in the first trimester<sup>23</sup>.

#### Doxycycline:

Doxycycline is contraindicated during pregnancy. Tetracyclines are human teratogens and have been associated with inhibition of skeletal development, foetal bone growth and teeth dysplasia and discoloration<sup>45</sup>. Inadvertent exposure to doxycycline during pregnancy may not necessarily warrant therapeutic abortion<sup>47</sup>.

#### Atovaquone – proguanil:

The safety of atovaquone and proguanil hydrochloride when administered concurrently for use in human pregnancy has not been established and the potential risk is unknown.<sup>63</sup>

#### **Recommendations:**

If it is absolutely necessary for a pregnant person to enter a malarious area, mefloquine, depending on the stage of pregnancy and the risk of malaria in the specific area, is recommended. In all cases the use of very strict non-drug measures is advised. Pregnant women must be informed of the high risk to both themselves and their unborn baby, and told to seek medical attention immediately if any malaria symptoms occur.

#### **Breastfeeding mothers:**

Infants should not be taken to malarious areas, as they are at a significantly higher risk of developing severe malaria<sup>28</sup>. If it is absolutely necessary for them to enter a malarious area then breast-fed as well as bottle-fed babies must receive the full recommended paediatric doses of appropriate antimalarials. The amount of antimalarial agent excreted into breast milk is insufficient to provide adequate protection against malaria in the infant<sup>45</sup>.

#### Mefloquine:

Mefloquine is contraindicated in breastfeeding mothers by the manufacturers<sup>29,49</sup>, but the WHO guidelines state that it is safe to use<sup>1</sup>. Approximately 4% of a single 250mg mefloquine dose has been shown to be recovered from the milk. Although these amounts are not considered harmful to the nursing infant, long-term effects of the drug via breast milk have not been studied<sup>48,50</sup>. The levels reached in the infant are insufficient to provide adequate protection against malaria<sup>48</sup>.

#### Doxycycline:

Doxycycline is excreted into breast milk in low concentrations and may have adverse effects on the breastfeeding infant<sup>48</sup>. However, the American Academy of Paediatrics considers tetracycline to be compatible with breast feeding<sup>48</sup>. The length of exposure to doxycycline in breast milk is a potential hazard to the infant.

#### Atovaquone – proguanil:

Safety has not been established and it is therefore not recommended.<sup>1,65</sup>

#### **Recommendations:**

The World Health Organization recommends mefloquine for breastfeeding mothers travelling to chloroquine-resistant malarial areas<sup>1</sup>. In addition, breast-fed babies should receive the full recommended paediatric doses of the appropriate antimalarials.

#### **People involved in activities requiring fine co-ordination and spatial discrimination:**

#### Mefloquine

Mefloquine can cause dizziness, disturbed sense of balance and neuropsychiatric reactions during and up to three weeks after its use. Caution must therefore be exercised when driving and operating machines while taking this drug<sup>29</sup>.

The WHO recommends that piloting of aircraft and deep-sea diving should be avoided while taking mefloquine<sup>1</sup>. Although the latest studies do not seem to show significant effects of mefloquine on fine motor co-ordination, it seems prudent to exercise caution when used in persons operating machines, driving, deep-sea diving or flying<sup>28</sup>. (The drug may cause sleep disturbances, which in the long term, may affect co-ordination).

#### Atovaquone-proguanil

Atovaquone has no adverse psychomotor effects on aircrew.<sup>64</sup> Based on the pharmacology of atovaquone and proguanil, a detrimental effect on driving and operating machinery is not expected.<sup>63</sup>

#### **Recommendation:**

Doxycycline or atovaquone - proguanil may be considered as prophylactic options.

#### **People with psychiatric problems:**

Going on holiday and having a change of scenery may be particularly beneficial for the stressed and/or depressed individual. However, careful consideration must be paid to choosing appropriate prophylaxis for those with mental illness of any kind.

#### Mefloquine:

Mefloquine has been reported to cause serious neuropsychiatric symptoms in approximately 1 in 10 000 users. Symptoms can develop as early as the first week of use and more than 75% of the adverse reactions are apparent by the third dose. In most cases, symptoms resolve within three weeks of stopping the drug, but there are reports of symptoms persisting for some months and even years in a very small number of cases<sup>51</sup>. Reported side effects include depression, anxiety, acute psychotic episodes, subtle mood changes, insomnia, strange dreams, and depersonalisation. Mefloquine is therefore contraindicated in individuals with a present or prior history of any central nervous system (CNS) disorder<sup>29</sup>.

#### Atovaquone – proguanil:

Although there is no specific information relating to the use of atovaquone – proguanil in individuals with a CNS disorder, the side effect profile does not indicate that there would be a problem.<sup>1,63</sup>

#### Doxycycline:

Doxycycline may occasionally cause dizziness, headache, blurred vision and nausea, but psychiatric adverse effects are extremely rare.

#### **Recommendation:**

Doxycycline and atovaquone-proguanil are the safest options for patients with psychiatric symptoms who require malaria prophylaxis<sup>51,64</sup>

#### **Malaria chemoprophylaxis in children:**

Children are at special risk as they can become seriously ill with malaria very rapidly. Babies and young children under the age of five years should not be taken into malaria areas unless it is absolutely essential. Children must be protected against mosquito bites at all times and mosquito nets must be used to cover bedding. It is advisable to keep babies under mosquito nets as much as possible between dusk and dawn<sup>28</sup>.

#### Mefloquine:

Mefloquine can be used in children over 3 months of age or weighing over 5kg; the dose is based on the weight of the child<sup>29,45</sup>.

#### Doxycycline:

Doxycycline should not be used for prophylaxis in children under 8 years of age because of the risk of staining permanent teeth and inhibiting bone growth.

### Atovaquone-proguanil:

This combination is not recommended for children under 11kgs in weight due to lack of data.<sup>1</sup>

Antimalarial drugs must be kept out of reach of children, preferably stored in childproof containers.

When a child develops a febrile illness either whilst in a malaria area or after having left the area, medical help must be sought immediately. The symptoms of malaria in children may not be typical and therefore malaria should always be suspected. In infants, malaria should even be suspected in non-febrile illness<sup>28</sup>.

### **People already on chloroquine therapy:**

#### Mefloquine

Mefloquine should not be taken concurrently with chloroquine because of the danger of toxic cardiac or CNS reactions<sup>52</sup>.

#### Doxycycline

Doxycycline is an option for these patients entering chloroquine-resistant areas.

### Atovaquone-proguanil:

There is no documented interaction between atovaquone and chloroquine, and although proguanil and chloroquine can increase the incidence of mouth ulcers, they were previously used together. There is therefore no reason why atovaquone-proguanil cannot be used in patients already on chloroquine therapy.

### **Long-term chemotherapy for people traveling for extended periods**

As with all recommendations, the advice for travellers requiring long-term chemoprophylaxis must be individualised according to their specific circumstances. The risk of contracting malaria is roughly proportional to the length of stay in a malaria area. The longer the stay therefore, the more important it is to use a highly effective chemoprophylactic regimen.<sup>64</sup>

The restriction on long-term use of any of the regimens is based on lack of data rather than by any evidence of new toxicity problems from long-term use.<sup>64</sup>

Most adverse events from the use of antimalarials tend to occur shortly after the first few doses, and the incidence of late-onset events is very low.<sup>64</sup>

#### Mefloquine

The Centre for Disease Control (CDC), Atlanta, USA has recommended that mefloquine can be used for long-term malaria chemoprophylaxis<sup>53</sup>. The Advisory Committee on Malaria Prevention (ACMP) for UK travellers, considers that, in the absence of problems in the short term, mefloquine can be used for up to 3 years<sup>64</sup>. Long-term use of mefloquine does not appear to be related to increased side effects.

#### Doxycycline

Experience with doxycycline use for periods exceeding six months is limited<sup>1,17,23</sup>, but evidence suggests that it may be used safely for periods of up to 2 years. There is no evidence of harm in long-term use.<sup>65</sup> It should however ideally be used by individuals who will be exposed to malaria for short periods of time<sup>53</sup>.

### Atovaquone-proguanil:

Although both components have been used individually on a long-term basis, there is limited data concerning long-term use of atovaquone-proguanil<sup>65</sup>. In South Africa, this combination is registered without a restriction on the length of the course.<sup>63</sup>

People who have grown up in an endemic malaria area and who may have developed immunity, will lose this immunity within a year or so of being out of the malaria area<sup>52</sup>. These individuals must take the necessary precautions when re-entering or visiting a malaria area.

## Patients on anticoagulant therapy

**Patients on anticoagulant therapy should avoid traveling to malaria areas where chemoprophylaxis is indicated.** Malaria chemoprophylaxis is very difficult in these patients, especially as monitoring of International Normalised Ratio (INR) is particularly challenging when traveling in malaria endemic areas. Both bleeding and clotting, which can occur when trying to regulate the INR, can be very dangerous. Thus, the use of strict non-drug measures in those traveling to low risk malaria areas should be vigorously encouraged and visits during the high risk malaria season or high risk malaria areas actively discouraged. If travel to those areas is essential, patients should be fully informed both of the potentially life threatening risks of malaria and of potential of chemoprophylaxis to interfere with their anticoagulation, which may increase their risk of bleeding or clotting. Mefloquine is the only chemoprophylaxis option that can be considered in these patient, as both doxycycline and atovaquone-proguanil may potentiate the effect of oral anticoagulants. However, there is insufficient data on the safety of mefloquine in these patients so this prophylaxis should be started 3-4 weeks before travel to monitor INR closely for the possibility of an interaction.

## The immuno-compromised patient

Immuno-compromised patients (e.g. HIV-positive patients, those on long-term steroids, those who have had a splenectomy, and patients receiving chemotherapy) and their doctors should weigh up the risks very carefully before entering a malaria area. Factors such as the degree of immunosuppression, malaria risk in the area being visited and availability of medical resources in the area should be taken into account.

Recent studies have shown that HIV-infected patients have a higher prevalence of parasitaemia and are more likely to get severe malaria. Additionally, acute malaria may increase HIV viraemia. These studies were done in endemic areas among HIV-positive patients who were not taking antiretrovirals (ARV). The relevance of this in HIV-infected travellers taking ARVs is not known.<sup>68</sup>

If immunocompromised patients cannot avoid travel to malaria areas, the most effective chemoprophylaxis should be used and extremely strict non-drug measures should be followed. Drug interactions with concurrent medication should also be carefully considered (especially in patients taking immunosuppressants after organ transplants).

## Travellers on Antiretroviral therapy

Although patients on ARV may no longer be at high risk of contracting other diseases as before, there is a potential for interactions between their ARVs and other medications required, such as vaccines and malaria chemoprophylaxis.

There is a paucity of current data on potential interactions between antimalarials and antiretrovirals, but practical experience has not indicated a high risk of toxicity or serious adverse events when combining these two categories. The major concern regards the protease inhibitors, as they are inhibitors of the cytochrome P450 enzyme system. This may affect mefloquine or atovaquone (although it has not been seen clinically) but, as doxycycline is not metabolised by the liver, it is not affected.<sup>68</sup>

Efavirenz, nevirapine and the protease inhibitors theoretically may reduce the level of mefloquine but this has not been shown to be clinically significant.<sup>68,69,70</sup> The protease inhibitors theoretically may also reduce atovaquone levels, and indinavir levels may be reduced by atovaquone-proguanil.

Zidovudine levels may be increased by atovaquone-proguanil.

There are no known interactions with lamivudine, stavudine or didanosine and the recommended antimalarials.

*In vitro* studies have shown that protease inhibitors (PIs) inhibit the growth of *P. falciparum*.<sup>68</sup>

Currently, doxycycline is the recommended option for malaria prophylaxis in HIV-infected travellers on ARVs, as there are no known drug interactions with any of the ARV regimens<sup>68</sup>. Atovaquone-proguanil is currently not

recommended as first-line because of limited documentation regarding drug interactions and there is a potential for reduced levels of mefloquine in patients on certain ARVs.

Any malaria prophylaxis with a potential for an interaction with the traveller's ARVs, must be started several weeks prior to departure, in order to permit measurement of plasma levels.<sup>68</sup>

### 3.3.7 Partial Immunity (Semi-Immunity)

Individuals who have been repeatedly infected with malaria ("semi-immunes") may develop partial immunity and tolerance to the infection. This state occurs among residents of tropical countries where high levels of malaria transmission are present all year round. These persons may lose this immunity after leaving the malaria endemic area for a period of time and may be at risk for malaria disease on re-exposure. The exact length of time that it takes to lose this partial immunity has not yet been determined. However, due to low intensity seasonal malaria transmission, "partial immunity" will not develop in persons living within malaria areas of South Africa.

### 3.3.8 Stand-by emergency treatment

Where medical attention is not available within 24 hours of the onset of malaria symptoms, provision should be made for emergency treatment. This situation may affect travellers to remote areas. Although travellers often perform these tests inaccurately, the use of rapid diagnostic tests to confirm malaria can be considered in these situations. It is recommended that the traveller, prior to departure should perform a trial test under supervision, as experience has shown that the test is frequently incorrectly performed.

Self-treatment is an interim measure and may be life saving, but medical attention remains urgent and essential. The choice of medication for self-treatment of malaria is a difficult one. The medication needs to be both safe and effective.

In patients with uncomplicated *falciparum* malaria, artemether-lumefantrine would be a reasonable choice for stand-by treatment. This should be taken with a fatty meal (e.g. milk) to ensure adequate absorption.

Prophylaxis should be restarted seven days after treatment has been completed<sup>1</sup>, if the person is still in the malaria risk area.

## 3.4 Ensuring early diagnosis

Malaria should be suspected in any person presenting with any of the symptoms described below, who has a history of travel to, or is resident in a malaria transmission area, irrespective of the time of year or whether or not they have taken chemoprophylaxis.

The majority of deaths and cases of complicated malaria result from delayed diagnosis and/or inappropriate treatment. The most important element in the diagnosis of malaria is to have a high index of suspicion. The diagnosis of malaria should immediately be considered in any patient with fever who has travelled to, or lives in, a malaria area, even if chemoprophylaxis has been taken.

Confirmation of malaria as a cause of illness is made by the examination of blood for parasites, either by blood smear or a rapid malaria test. A negative blood test or rapid malaria test does not exclude the presence of malaria, repeat tests should be made until a diagnosis is confirmed or symptoms resolve. In patients with severe illness in whom the diagnosis cannot be confirmed, treatment for malaria should be given after a malaria smear is made.

In recent years a number of new techniques based on the "dipstick" format, have become available for the diagnosis of malaria. The methods are based on the detection of plasmodial histidine rich protein-2 (HRP-2) or parasite-specific lactate dehydrogenase (pLDH) that is present in *P. falciparum* infections. Some of these "dipstick" methods have been extended to include screening for other species of malaria but are less sensitive.

The advantages of rapid tests are that they:

- are highly sensitive
- give rapid results
- are relatively simple to use in a primary health setting

These tests do however have some limitations:

- They cannot be used to determine severity of infection, as they do not measure parasite load.
- They cannot be used following a recent malaria infection or to monitor progress of treatment or to confirm eradication of parasites, as they may stay positive for some time after successful treatment.
- They must be performed according to instructions and read at the correct time.

### 3.4.1 Signs and Symptoms of Malaria

Symptoms of malaria infections commonly develop 10 – 14 days after an infective mosquito bite, as they only develop once the parasites infect the red blood cells. This period may however be prolonged especially if prophylactic medicines (or certain antibiotics) have been taken.

The symptoms of malaria may initially resemble a non-specific flu-like illness with one or more of the following:

- Fever –(although common, fever may be absent in some cases)
- Rigors
- Headache
- Sweating
- Fatigue
- Myalgia (back and limbs)
- Abdominal pain
- Diarrhoea
- Loss of appetite
- Nausea and vomiting
- Cough

In young children, malaria may present with fever, lethargy, poor feeding and vomiting.

The presentation of *P. falciparum* malaria is very variable and may mimic many other diseases including influenza, hepatitis, meningitis, septicaemia, viral haemorrhagic fever, trypanosomiasis, HIV seroconversion illness and urinary tract infection.

Non-immune patients with uncomplicated malaria are prone to the development of severe *P. falciparum* malaria. Life threatening complications can develop rapidly in these patients. Pregnant women, young children, and persons who have undergone a splenectomy or who are immune compromised and debilitated individuals are high-risk groups for the development of severe and complicated malaria.

## 4. SUMMARY

### Awareness – Be aware of malaria risk

• Location	Cities	– less risk
	Camping near river	– high risk
• Accommodation	Air conditioned hotels	– low risk
	Huts or tents	– higher risk
• Time of the year	Transmission is less during dry cold months	
• Time of the day	Malaria carrying mosquitoes bite at night	
• Length of stay	The longer the stay, the higher the risk	

### Bites – Avoid mosquito bites. Measures taken should include:

- Remain indoors between dusk and dawn
- Wear long - sleeved clothing, long trousers (preferably light - coloured) and socks
- Apply an insect repellent containing DEET to exposed skin, repeat as recommended on the container label. Avoid eyelids, lips, sun burnt or damaged skin, do not spray on the face and do not overdose young children.
- Protect doors and windows with screens, but if not available, windows and doors should be closed at night.
- Use overhead fans or air conditioners, which are effective in hindering mosquitoes from landing.
- Sleep in an insecticide sprayed house.
- Sleep under a mosquito net (preferably impregnated with an insecticide registered for this purpose, e.g. a pyrethroid), with the edges tucked in. Ensure that the net is not torn and that there are no mosquitoes inside.
- Spray inside the house with an aerosol insecticide (for flying insects) at dusk, especially the bedrooms, after closing the windows.
- Use mosquito mats, impregnated with an insecticide (heated electrically or by a non-electric lamp), or burn mosquito coils in living and sleeping areas during the night.
- Treat clothes with an insecticide registered for this purpose, e.g. a pyrethroid.

### Chemoprophylaxis – take appropriate chemoprophylaxis. Compliance is most important.

One of the following regimens is currently recommended for use in South Africa:

- Mefloquine. (Weekly). Start at least one week before entering a malaria area, take weekly while there and for FOUR weeks after leaving the malaria area<sup>1</sup>.
- Doxycycline. (Daily). Start one to two days before entering a malaria area, take daily while there and for FOUR weeks after leaving the malaria area<sup>1</sup>.
- Atovaquone - proguanil. (Daily). Start one to two days before entering malaria area, take daily while there and for SEVEN days after leaving the area.<sup>63</sup>

Choice of regimen depends on patient factors.

- Age and weight
- Pregnant or breastfeeding
- Other medical conditions such as porphyria, epilepsy, depression
- Concomitant medication
- Activities, such as scuba diving or flying

## Diagnosis – early diagnosis is critical to survival

Symptoms of malaria infections commonly develop 10 – 14 days after an infective mosquito bite but this period may be prolonged especially if prophylactic drugs have been taken.

Fever is very common, but may be absent in some cases. In addition some of the following symptoms may present; rigors, headache, sweating, tiredness, myalgia (back and limbs), abdominal pain, diarrhoea, loss of appetite, nausea and vomiting, and cough. “Flu-like” symptoms are particularly common presenting symptoms of malaria.

## Effective treatment

Malaria must be treated as a medical emergency. The sooner effective treatment is started, the better the prognosis.

## 5. MALARIA INFORMATION SHEET

Malaria is one of the most serious tropical diseases and can be fatal if not diagnosed and treated at an early stage.

### Prevention is better than cure!

- Going somewhere? Find out whether there is a risk of getting malaria there. The risk is lower during the cold and dry seasons.
- Take precautionary measures to prevent mosquito bites in all risk areas.
- If recommended, take appropriate medication as directed.
- There is no prophylaxis that is 100% effective, but the correct medicine will reduce your risk of severe illness.
- Seek immediate medical attention if you have any “flu-like” symptoms for up to 6 months after leaving a malaria area.

### Measures to avoid mosquito bites

- Allow your house to be sprayed if living in a malaria risk area.
- If possible, remain indoors between dusk and dawn (mosquitoes carrying malaria bite at night).
- Wear long-sleeved clothing, long trousers and socks when going out at night.
- Apply an insect repellent containing DEET to exposed skin at night.
- Sleep under a mosquito-proof bed-net, preferably one that has been treated with an approved insecticide.
- Spray inside with an insecticide spray, after closing windows and doors.

### Take your medicines correctly

- Take only the medicines that have been proven to be effective for preventing malaria (mefloquine, doxycycline or atovaquone-proguanil) as recommended by a health professional.
- Start before entering the malaria risk area.
- Take the medicine at the same time every day (or week, for weekly medication) with plenty of water, after a meal.
- Continue while in the malaria area and for 4 weeks after leaving the area (unless you are taking atovaquone-proguanil, in which case, take it for 7 days after leaving the area).

### Early symptoms of malaria.

- Fever
- Headache
- Chills
- Muscular pain

Seek medical attention if you have any of the above symptoms.



## 6. TABLES

TABLE 1: DRUG CHOICE ACCORDING TO PATIENT FACTORS

Patient factor	Mefloquine	Doxycycline	Atovaquone-proguanil
Pregnancy - Avoid travelling to a malaria area	Avoid during first trimester. Can be used from 4th month (see page 15)	Contraindicated.	Contraindicated <sup>63,64</sup>
Women of child-bearing potential or on oral contraceptives	Use reliable contraception during and for 3 months after taking last dose. Will not compromise contraceptive efficacy.	Avoid pregnancy during and for one week <sup>1</sup> after taking last dose. May interact with oral contraceptive	Will not compromise contraceptive efficacy
Breastfeeding - Baby must be given its own prophylaxis	Insufficient data, but WHO states that it is safe to use <sup>1</sup>	Avoid use.	Avoid use <sup>63,64</sup>
Young children - Avoid taking children under the age of 5 years to a high risk area	Can be used in children over 3 months old or > 5 Kg. Generally well tolerated by children.	Use only in children > 8 years of age.	Paediatric tablets can be given to children weighing more than 11kgs. <sup>63,64</sup>
Epilepsy	Contraindicated. May also interact with valproic acid	May interact with anticonvulsants, reducing the half-life of doxycycline & possibly resulting in prophylaxis failure	Can be used <sup>64</sup>
Psychiatric conditions	Contraindicated, even if there is only a history of depression.	Can be used	Can be used <sup>64,73</sup>
Psoriasis	No documented problems- can be used.	Can be used	No documented problems- can be used
Porphyria	Appears to be well tolerated <sup>74</sup>	Avoid use	Likely to be safe <sup>74</sup>
'Sulfa' Allergy	Contains no 'sulfa' moiety- safe to use.	Contains no 'sulfa' moiety- safe to use	Contains no 'sulfa' moiety- safe to use
Renal impairment	Use with caution- lack of safety data	Safe to use	Contraindicated in severe renal failure (creatinine clearance < 30ml/min) <sup>63</sup>
Hepatic impairment	Contraindicated in severe impairment	Administer with caution to hepatically impaired patients or those receiving hepatotoxic drugs.	Safe to use in mild to moderate hepatic impairment, but no data on use in severe hepatic impairment <sup>63</sup>
Individuals requiring fine motor co-ordination and spatial discrimination e.g. pilots	Do not use	Safe to use	Safe to use <sup>63,64</sup>
Myasthenia gravis	Insufficient data - stop therapy if muscle weakness occurs.	May aggravate symptoms of myasthenia gravis.	No data available.
Persons requiring long-term therapy	Can be used for up to 3 years <sup>64</sup>	Experience of use for more than 4 - 6 months is limited.	Its use is limited in the UK to 28 days <sup>64</sup> , but no restriction in South Africa <sup>63</sup>
Persons on oral anticoagulants <b>Caution:</b> Changes in INR can be very dangerous, resulting in bleeding or clotting. Preferably avoid high risk malaria areas	Insufficient data - monitor INR. Start therapy in advance to monitor possibility of interaction.	May potentiate anticoagulant effect. Monitor INR.	Proguanil may potentiate the effect of oral anticoagulants. Monitor INR <sup>57</sup>
G6PD deficiency	No problems documented - safe to use.	Safe to use.	Safe to use <sup>72</sup>
Diabetes	Insufficient data - monitor blood glucose levels	May increase hypoglycaemic effect of insulins - monitor blood glucose levels.	No known problems. Monitor blood glucose levels
Cardiotoxicity and use in combination with cardiac drugs.	May cause conduction abnormalities. Use with caution in people taking beta-blockers, calcium antagonists, and quinidine.	Safe to use	Safe to use <sup>67</sup>

**TABLE 2: INTERACTIONS BETWEEN MALARIA CHEMOPROPHYLAXIS AND OTHER DRUG TREATMENT**

Antimalarial	Other drug	Comment
<b>Mefloquine</b>	Amiodarone	Both increase QT interval. Increased risk of torsade des pointes <sup>57</sup> .
	Antipsychotics e.g. phenothiazines, pimozide	Increased risk of ventricular arrhythmias <sup>57</sup> . Mefloquine should not be used in patients with a history of a psychiatric illness.
	Antiretrovirals; Efavirenz, nevirapine	Theoretical risk of reduced levels of mefloquine <sup>68</sup> (Not clinically significant) <sup>69,70</sup>
	Protease inhibitors	Theoretical risk of reduced levels of PIs <sup>68,69</sup> (Not clinically significant) <sup>69,70</sup>
	Beta blockers e.g. atenolol, propranolol etc.	Potential for increased risk of electrocardiographic abnormalities, bradycardia and cardiac arrest <sup>45,57</sup> . Therefore, mefloquine is not recommended for patients with cardiac conduction abnormalities, but mefloquine prophylaxis may be used safely in individuals without arrhythmia who are using beta blockers.
	Calcium channel blockers e.g. nifedipine, verapamil, diltiazem etc.	Possible increased risk of severe bradycardia <sup>57</sup> . However, CDC states that there is no evidence to justify precautions for concomitant mefloquine therapy in patients using calcium channel blocking agents.
	Digoxin	Increased plasma levels of digoxin <sup>57</sup> . Use with caution. Monitor levels.
	Halofantrine	Concurrent use may result in serious cardiac effects. Treatment with halofantrine is contraindicated when mefloquine has been used for prophylaxis <sup>28,57</sup> .
	Oral cholera and typhoid vaccines	Inactivation of the immunization possible. Complete immunization 3 days before taking mefloquine <sup>28,29,57,64</sup>
	Primaquine	May increase the serum levels and side effects of mefloquine <sup>58</sup> .
	Quinine or Quinidine	Quinine may inhibit the metabolism of mefloquine, thereby increasing mefloquine levels <sup>58</sup> . The combination may also produce electrocardiographic abnormalities, cardiac arrest <sup>45</sup> or could result in potentially serious cardiac conduction abnormalities <sup>53</sup> . On the other hand, a small, limited study conducted in 13 adults with single doses of both drugs showed a lack of a clinically significant cardiovascular pharmacodynamic interaction <sup>60</sup> . The combination may also increase the risk of seizures <sup>45,57,58</sup> . A loading dose of quinine should not be given if mefloquine has been used for prophylaxis in the preceding 24 hours <sup>61</sup> .
	Rifampicin	Decreased plasma concentration of mefloquine via induction of mefloquine metabolism.
	Tricyclic antidepressants	Increased risk of ventricular arrhythmias <sup>57</sup> . Mefloquine should not be used in patients with a history of a psychiatric illness.
	Valproic acid	Accelerated sodium valproate metabolism may result in low valproic acid serum concentrations and loss of seizure control. Monitor valproic acid levels. Mefloquine is contraindicated in epileptics <sup>45,50,57,58</sup> .
<b>Doxycycline</b>	Alcohol	In alcoholic patients the serum levels of doxycycline may fall below minimum therapeutic concentrations, but this does not apply to acute intake of alcohol <sup>58</sup> .
	Antacids containing: calcium, bismuth, aluminium and magnesium	Reduces the absorption and serum concentrations of doxycycline significantly, compromising therapeutic efficacy. If possible use alternative therapy, or administer doxycycline at least 2 hours before, or 4 to 6 hours after antacids <sup>45,58</sup> .
	Antiretrovirals	No theoretical or known interaction <sup>68</sup>
	Carbamazepine, barbiturates and phenytoin	Reduce the plasma half-life of doxycycline by approximately 50% and may result in a reduction of efficacy <sup>45,57,58</sup> . (See Epilepsy Section)
<b>Doxycycline</b>	Iron	Decreased absorption of doxycycline and iron salts. Efficacy may be reduced. Separate dosages by as much as possible. Give iron at least 3 hours before or 2 hours after the doxycycline dose <sup>45,58</sup> .

TABLE 2: INTERACTIONS BETWEEN MALARIA CHEMOPROPHYLAXIS AND OTHER DRUG TREATMENT (Continued)

	Methotrexate	One case report exists of a cancer patient who was receiving high-dose methotrexate and developed methotrexate-induced gastrointestinal and haematological toxicities in association with increased methotrexate levels after a course of doxycycline was introduced. Monitor patients closely, especially when methotrexate is administered in high doses <sup>45</sup> .
	Isotretinoin	An increased incidence of pseudotumour cerebri has been reported in patients on other tetracyclines. It is unknown whether doxycycline is also potentially problematic <sup>45</sup> .
	Milk and dairy products	Absorption of doxycycline may be reduced by up to 30% because of the calcium ions found in milk. Avoid for at least 1 hour before or 2 hours after taking doxycycline. The small amounts of milk used in coffee and tea appear not to matter <sup>45,58</sup> .
	Oral contraceptives	May reduce efficacy of contraceptives <sup>58</sup> .
	Rifampicin	Increased doxycycline clearance. Potential loss of doxycycline efficacy. Monitor patient response <sup>45</sup> .
	Warfarin	Potential of anticoagulant effect possible, monitor INR. (see section on anticoagulant therapy)
<b>Atovaquone proguanil</b>	- Antiretrovirals: Protease inhibitors. Zidovudine	Theoretical risk of reduced level of atovaquone. Theoretical risk of reduced level of indinavir Zidovudine levels may be increased. <sup>69</sup>
	Live typhoid vaccine	A decreased immune response to typhoid vaccine. Allow 10 days to elapse between the last dose of live typhoid vaccine and the administration of proguanil <sup>3,71</sup> .
	Magnesium trisilicate	Reduces absorption of proguanil. Separate doses as much as possible. (2-3hours) <sup>58</sup>
	Metoclopramide	Atovaquone plasma levels reduced, resulting in therapeutic failure <sup>1</sup> .
	Rifampicin, rifabutin	Atovaquone plasma levels reduced, resulting in therapeutic failure <sup>1</sup> .
	Tetracyclines	Atovaquone plasma levels reduced, resulting in therapeutic failure <sup>1</sup> .
	Warfarin	May potentiate effect of warfarin, monitor INR <sup>57</sup> .

TABLE 3: BENEFITS AND RISKS OF THE PROPHYLACTIC REGIMENS RECOMMENDED FOR TRAVELLERS

	Mefloquine	Doxycycline	Atovaquone-Proguanil
<b>Prophylactic Efficacy</b>	Highly effective in areas where it has been tested.  Effective against acute infections caused by <i>P. vivax</i> . Limited data on efficacy against other species <sup>64,71</sup> Relapses can occur	Highly effective in areas where it has been tested.  Limited protection against <i>P. vivax</i> <sup>64</sup> Relapses can occur.	Highly effective in areas where it has been tested.  Also effective against acute infections caused by <i>P. vivax</i> , <i>ovale</i> and <i>malariae</i> . Relapses can occur. <sup>66</sup>
<b>Most common Side effects</b>	Nausea, strange dreams, dizziness, mood changes, insomnia, headache and diarrhoea.	Skin photosensitivity (3% in one study), oesophageal ulceration, gastrointestinal symptoms, candida superinfection of the gut and vagina.	Well tolerated. Headache and abdominal pain most frequent adverse effects. <sup>63,64</sup>
<b>Contraindications</b>	Current or history of epilepsy or psychiatric illness, including depression. Past severe reactions to mefloquine. Underlying cardiac conduction disturbance or arrhythmia. Concurrent use of halofantrine (and other cardiotoxic drugs). First trimester of pregnancy. Infants <5kg.	Pregnancy. Lactation. Children under 8 years of age. Concurrent use of oral contraceptive. Must use barrier methods.	Severe renal impairment (creatinine clearance of <30ml/min) <sup>63,64</sup>
<b>Special precautions</b>	Travellers requiring fine coordination.	Avoid excessive UV exposure, use high SPF sunscreen. Take after a meal with a full glass of water. Do not lie down for at least one hour after taking.	Take with milk or food for better absorption. <sup>63,66</sup>
<b>Dosage interval</b>	Once weekly.	Daily dose.	Daily dose
<b>Time period needed before entering malaria area</b>	General recommendation: one week; for first time use: two and a half to three weeks*.	24 – 48 hours.	24-48 hours
<b>Resistance</b>	Resistance appears to be rare - mainly SE Asia.	Resistance appears to be rare.	No known resistance

\* To ensure that protective levels have been reached and to give enough time to change the person to a different drug if adverse reactions have appeared.

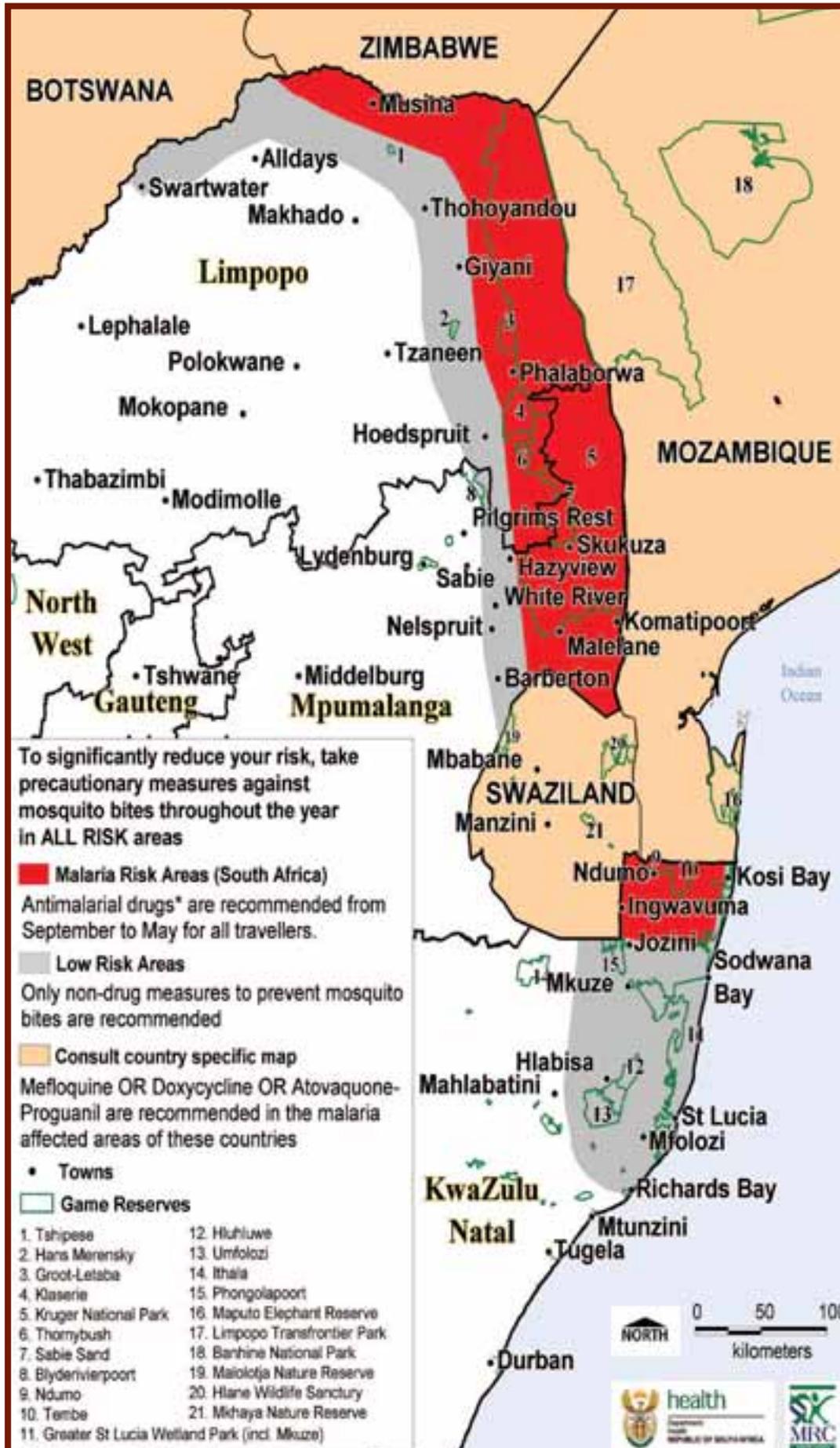
TABLE 4: DOSES OF ANTIMALARIAL DRUGS FOR USE AS PROPHYLAXIS

RECOMMENDED DRUG	ADULTS	CHILDREN
<b>Mefloquine</b>	(1 tablet = 250 mg mefloquine) 250mg (1 tablet) weekly, starting 1 week before entering the area, once weekly while in the area, and once weekly for 4 weeks after leaving the area.	Not recommended for children who are less than 3 months old or who weigh less than 5kg.  Weight (kg)      Weekly Dosage 5 - 20              ¼ tablet 21 - 30             ½ tablet 31 - 45             ¾ tablet >45                 Adult dose
OR		
<b>Doxycycline</b>	(1 tablet = 100mg doxycycline) (1 capsule = 50mg, 100 mg doxycycline)  100mg once daily starting one day before entering the area, continuing daily while in the area, and daily for 4 weeks after leaving the area. Not to be used for longer than 4-6 months.	Contraindicated in children less than 8 years of age.  2mg/kg of body weight at the same intervals as for adults.  Age              Weight              Dosage (years)          (kg) 8 - 15          31- 45              2 mg/kg >15              >45                 Adult dose
<b>Atovaquone – proguanil</b>	1 adult tablet = 250mg atovaquone plus 100mg proguanil. Should be taken 1 day before exposure, continued daily during exposure and for 7 days after the last possible exposure to malaria.	1 paediatric tablet = 62.5 atovaquone plus 25mg proguanil 11 – 20kg          1 paediatric tablet daily 21 – 30kg          2 paediatric tablets daily 31 – 40kg          3 paediatric tablets daily > 40kg              1 adult tablet daily

TABLE 5: DOSES FOR STANDBY THERAPY

<b>Artemether-lumefantrine</b> 1 tablet contains artemether 20mg plus lumefantrine 120mg.	5 - <15kg: One tablet stat, followed by one after 8 hours and then one twice daily on each of the following two days (total course = 6 tablets) 15 - <25kg: Two tablets stat, followed by two after 8 hours and then two twice daily on each of the following two days (total course = 12 tablets) 25 - <35kg: Three tablets stat, followed by three after 8 hours and then three twice daily on each of the following two days (total course = 18 tablets) 35 - <65kg: Four tablets stat, followed by four after 8 hours and then four twice daily on each of the following two days (total course = 24 tablets) □ 65kg: Dose as for > 35kg above, although inadequate experience in this weight group <b>Administer with fat containing food / milk to ensure adequate absorption.</b>
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## 7. MAP OF MALARIA AREAS IN SOUTH AFRICA



## 8. PROPHYLAXIS MASKS THE SYMPTOMS - THE MYTH

It is highly irresponsible not to recommend or prescribe prophylaxis for anyone going to an area where he or she will be at a high risk of contracting malaria, because of the myth that prophylaxis masks malaria symptoms and makes it more difficult to diagnose the disease. Such an approach puts the person at risk of contracting a dangerous and life-threatening disease.

Mefloquine and doxycycline **act on the parasites within the red blood cells, preventing the disease from manifesting and presenting with typical symptoms, which include fever, headache, muscular pains and eventually serious complications.** If however, the prophylaxis is inadequate (due to drug-resistance, or, more often, poor compliance), the parasites will be able to multiply and cause clinical malaria. If the prophylaxis is partially effective, it may take longer for the disease to manifest and therefore for symptoms to present. Although the symptoms may initially be milder, this is because the infection itself is milder and the risk of severe malaria and malaria-related death is lower. **However, once the infection increases in intensity, resulting in clinical disease, the symptoms will present with the same intensity.** The time that it takes for the disease to progress from uncomplicated malaria to severe malaria may be longer if the patient has taken prophylaxis.

As in early disease, when no prophylaxis has been taken, initial difficulties may be experienced in detecting parasites due to low parasitaemia. Diagnosis can however, always be confirmed, either by repeated blood smears or by the use of rapid diagnostic tests.

The fact that a patient may only develop malaria some time after leaving the malaria area may cause a problem, as there may no longer be a high index of suspicion of malaria, especially as many people believe that if they take prophylaxis they cannot get malaria. It is therefore very important to take a travel history of the past couple of months **and to suspect malaria whenever a patient presents with typical febrile symptoms and has been in a malaria area.**

If anyone is at high risk of contracting malaria, **the appropriate prophylaxis will considerably reduce the chances of developing malaria** and therefore of unnecessary illness and death<sup>6,62</sup>. Only those agents registered for malaria prophylaxis are effective. Herbal and similar preparations have not been shown to provide protection against malaria when used in the doses recommended.

## 9. LIST OF ANTIMALARIALS (AND TRADE NAMES) USED FOR PROPHYLAXIS

Generic name	Trade name	Schedule	Indication	Manufacturer
Artemether-lumefantrine	Coartem® tabs	S4	Treatment (used for standby therapy)	Novartis
Atovaquone-proguanil	Malanil® tabs	S4	Prophylaxis	GlaxoSmithKline
Doxycycline hyclate	Doxitab® tabs	S4	Prophylaxis	Cipla Medpro
Doxycycline hydrochloride	Cyclidox® caps Doximal® tabs Doxycyl® caps Dumoxin® caps	S4	Prophylaxis	Merck Gen (Xixia) Cipla Medpro Aspen Pharmacare Aspen Pharmacare
Doxycycline	Doxyhexal® tabs	S4	Prophylaxis	Sandoz Hexal
Mefloquine hydrochloride	Lariam® tabs Mefiam® tabs	S4	Prophylaxis	Roche Products Cipla Medpro

## 10. SOURCES OF MALARIA RISK AND PREVENTION INFORMATION

ORGANIZATION	EMAIL OR WEBSITE	TELEPHONE NUMBER
National Department of Health	www.doh.gov.za www.health.gov.za	012 312 0125
Amayeza Info Centre	amayeza@amayeza-info.co.za	011 678 2332
University of Cape Town Medicines Information Centre	micguest@uctgsh1.uct.ac.za	021 406 6783 or 021 406 6778
Medical Research Council	www.malaria.org.za	031 203 4700
World Health Organization	www.who.int/health-topics/malaria.html	
Center for Disease Control	www.cdc.gov/travel/malinfo.html	
Malaria Info Line		086 166 9943(Mozzie)

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