

# **SOUTH AFRICAN GUIDELINES FOR THE PREVENTION OF MALARIA**

**2017**

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## Preface



South Africa is one among several countries targeting malaria elimination. The national Department of Health's *Malaria Strategic Plan*, emphasises the need for prevention of malaria through drug and non-drug interventions. This approach is required especially for persons travelling to malaria transmission areas in South Africa and to endemic countries. These revised guidelines are therefore an important tool in supporting the South African malaria elimination goal of zero local malaria transmission by 2018.

Malaria is a potentially fatal disease that can be prevented in most instances by taking the appropriate precautions. These guidelines, produced by the national Department of Health, provide detailed options available for preventing malaria transmission.

The primary objective of these guidelines is to provide healthcare practitioners with information on the most appropriate interventions for people entering malaria-affected areas. These guidelines include recommendations from the World Health Organization's (WHO) guidelines for the prevention of malaria.

The guidelines presented here 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. An updated map of malaria risk in South Africa and detailed tables on antimalarial drug dosages have been included.

These revised guidelines are an important tool in supporting the South African malaria elimination goal of zero local malaria transmission by 2018.

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

A handwritten signature in black ink, appearing to be 'AP Motsoaledi'. The signature is stylized and fluid, with a long horizontal stroke extending to the right.

**Dr AP Motsoaledi, MP**  
**Minister of Health**  
**Date: 1 September 2017**

## Acknowledgements



The *Guidelines for the Prevention of Malaria in South Africa* were developed by the national Department of Health in close collaboration with several stakeholders and malaria experts.

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A handwritten signature in black ink, appearing to read 'Matsoso'.

**MP Matsoso**  
**Director-General: Health**  
**Date: 28 August 2017**

## Acronyms

AAP	American Academy of Pediatrics
ACMP	Advisory Committee on Malaria Prevention
AIDS	Acquired Immunodeficiency Syndrome
ARV	Antiretrovirals
AUC	Area under the curve
CDC	The Centers for Disease Control and Prevention
Cmax	Maximum concentration
DEET	N,N-diethyl-3-methylbenzamide or N,N-diethyl-m-toluamide
FDA	Food and Drug Administration
HIV	Human Immunodeficiency Virus
HRP-2	Plasmodial histidine-rich protein 2
INR	International normalised ratio
IRS	Indoor residual spraying
LDH	Parasite-specific lactate dehydrogenase
NOAC	New oral anticoagulants
PI	Protease inhibitors
RDT	Rapid diagnostic tests
WHO	World Health Organization

## 1. Executive summary

Travellers to, and residents in, malaria endemic areas are at risk of acquiring malaria. Stringent non-drug measures should be taken to avoid mosquito bites throughout the year, even in low malaria transmission areas. 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 malaria transmission intensity in the area, season of visit, 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, together with patient factors, including co-morbid disease, drug interactions and activities. Mefloquine or atovaquone-proguanil or doxycycline are currently the recommended prophylactic agents, when chemoprophylaxis is required.

The general population, travellers to, and residents in malaria areas must be made aware that malaria should be considered with **ANY** febrile illness occurring within one week to six months after visiting a malaria area, regardless of whether or not chemoprophylaxis was taken or mosquitoes were seen. Medical assistance at a healthcare facility should be sought within 24 hours of onset of illness as 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 updated based on information currently available, and although the greatest care has been taken, the Department of Health and the South Africa Malaria Elimination Committee do not accept responsibility for errors or omissions. The guidelines for prevention of malaria may change over time as parasite resistance patterns change. Recommendations may therefore need to be revised. Readers are referred to the source 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 2017 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. In some tropical African areas, over 50 per cent of the residents may be infected with malaria (World Health Organization, WHO, 2016). Of the estimated 429,000 deaths from malaria globally, 70% (303,000) occur in children under 5 years of age (WHO 2016). Although malaria case incidence has decreased globally by 21%, there is still a significant risk of infection, particularly in sub-Saharan Africa. Sustained effective malaria control operations have substantially reduced the risk of malaria in many countries. In South Africa, malaria was originally endemic in the low-lying northern and eastern areas of Limpopo, Mpumalanga and KwaZulu-Natal. However, control measures introduced since 1930 have significantly reduced transmission in these areas, so the risk of acquiring malaria is now comparatively low and seasonal.

Malaria prevention comprises measures taken against both mosquito vectors and malaria parasites. These include vector control programmes managed by government health authorities, personal protection measures to avoid mosquito bites and the use of chemoprophylaxis. The emergence of drug-resistant parasites, together with drug side-effects and contraindications, has heightened the importance of controlling vector mosquitoes and avoiding their bites.

Parasite resistance to antimalarials used for chemoprophylaxis and treatment has increased significantly over time. 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 healthcare workers and contain information on malaria transmission, the life cycle of the parasite, advice on both the avoidance of mosquito bites and the use of antimalarial chemoprophylaxis.

### 2.1 Distribution of malaria

Malaria transmission occurs mainly in tropical and sub-tropical countries in Africa, Central and South America, Asia and Oceania (WHO 2016). In the present-day South Africa, malaria transmission occurs in the north-eastern part of the country, mainly in the low altitude (below 1 000m above sea-level) areas of Limpopo, Mpumalanga and northern KwaZulu-Natal. (See map of malaria risk areas in South Africa, Pg. 40). Limited focal transmission may occasionally occur in the North West and Northern Cape 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).

### 2.2 Malaria – the disease

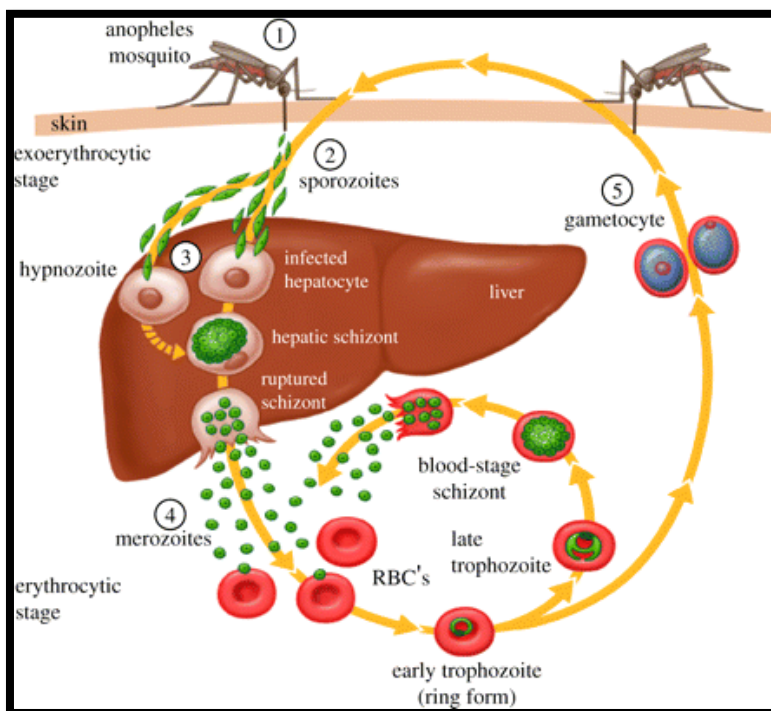
Malaria is transmitted to humans by the bite of an infected female *Anopheles* mosquito. Human malaria is a parasitic infection/disease predominately caused by four species of the *Plasmodium* parasite:

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

Recently, large numbers of human infection due to the monkey malaria parasite, *Plasmodium knowlesi*, have been reported from forested regions of Southeast Asia (WHO 2015a). This has resulted in the re-classification of *P. knowlesi* to the fifth human malaria parasite.

In sub-Saharan Africa over 90 per cent of human malaria infections, and almost all cases of severe disease, are due to *P. falciparum* (WHO 2016). The other three species cause milder illness; however, *P. ovale* and *P. vivax* infections are associated with relapses if appropriate treatment is not provided. Mixed infections involving more than one species may also occur, with *P. falciparum* parasites very frequently found in mixed infections.

The life cycle of the malaria parasite involves two hosts, *Anopheles* mosquitoes and humans (Figure 1). When biting a human host, (1) a malaria-infected female *Anopheles* mosquito inoculates malaria (2) sporozoites into the human host. (3) These sporozoites invade and infect liver cells where they multiply and mature into schizonts (exo-erythrocytic schizogony). (4) Once mature, the schizonts rupture releasing merozoites into the blood stream initiating erythrocytic schizogony. In both *P. falciparum* and *P. malariae* infections, all the schizonts rupture, releasing all the merozoites into the bloodstream. However in *P. vivax* and *P. ovale* infections, some liver stage schizonts become dormant, forming hypnozoites which persist in the liver for months or even years. These hypnozoites cause relapses when they re-awaken and release merozoites into the bloodstream months later, restarting the erythrocytic stage.



**Figure 1:** Life cycle of malaria parasites in *Anopheles* mosquitoes and humans. Adapted from: Image 1. Hill AVS. Vaccines against malaria. Philosophical transactions B. Sept 2011. <http://rstb.royalsocietypublishing.org/content/366/1579/2806.short>

During erythrocytic schizogony, when clinical manifestations of malaria present, merozoites invade red blood cells, multiply and mature. Once mature, the merozoites rupture the infected red blood cell, they re-enter the blood stream and invade uninfected red blood cells. This invasion and release from red blood cells continues until the disease is treated or the human hosts dies.

(5) A small number of merozoites differentiate into sexual blood stage parasites known as gametocytes during erythrocytic schizogony.



These gametocytes do not cause malaria symptoms but are responsible for the onward transmission of malaria and spread of antimalarial drug resistance. While sucking up blood during a blood meal, an *Anopheles* mosquito ingests the male (microgametocytes) and female (macrogametocytes) gametocytes. In the mosquito gut, male and female gametocytes fuse and undergo repeated division to form sporozoites, a process known as sporogony. The resulting sporozoites migrate to the mosquito's salivary glands from where they are inoculated into a new human host perpetuating the malaria life cycle.

Following a bite by an infected mosquito, there is an asymptomatic incubation period of approximately seven to 30 days during which the parasites develop in the liver, and then initially 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 may be responsible for relapses of *P. ovale* and *P. vivax* infections, presenting two to three months or more after treatment of the asexual stages of the original infection.

### 2.3 The malaria vector mosquito

Mosquitoes are scientifically classified into groups based on morphological features. One of these taxonomic groups, the Anopheline subfamily, includes all the species responsible for transmitting malaria. At least three anopheline species have been shown to be significant vectors of malaria in southern Africa.

Mosquitoes have four distinct developmental life cycle stages: egg, larva, pupa and adult. The duration of the larval stage and lifespan of the adult mosquito are strongly influenced by temperature. The average optimum temperature for mosquito development ranges between 25°C and 27°C. Development can be completely arrested at 10°C or over 40°C when the mortality rate is usually high. Under ideal environmental conditions, the larval stage may be as short as four to seven days with adults surviving for three to four weeks. As water is essential for larval development, this may explain why malaria transmission increases in South Africa between September and May, the warm, wet months.

Morphological and behavioural features of anopheline mosquitoes:

- They are relatively small; about eight millimetres long with dark-spotted or dappled wings (Figure 2).
- 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 *An. gambiae* favour resting indoors. This results in residual household spraying being more effective in the control of the latter species.
- Adults can be carried by wind but few are found further than one to two kilometres from their larval site. Occasionally adult mosquitoes will 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 a blood source for egg maturation.
- *Anopheles* mosquitoes generally feed between sunset and dawn. Personal protective measures to prevent mosquito bites need to be ensured at this time.
- *Anopheles* mosquitoes prefer to feed near ground level and feed selectively on the lower legs rather than arms or upper body, thus it is especially important that insect repellent is applied to the lower legs and feet.



**Figure 2:** An *Anopheles gambiae* complex mosquito drawing a blood meal from a human host. Source: Photo Credit: James Gathany Content Providers(s): Centers for Disease Control and Prevention's Public Health Image Library (PHIL), with identification number #7861.

### 3. Prevention of Malaria

Malaria is a potentially life-threatening disease that poses a major health risk for residents and travellers to malaria endemic areas. Appropriate advice and use of antimalarial drugs and, most importantly, non-drug 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 disease

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 transmission occurs. 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 regimen 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 (see for example: <http://www.rollbackmalaria.org/countries/endemic-countries-1>). 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 geographical factors such as rainfall and temperature and human factors such as migration of infected individuals. Detailed and up-to-date information should be sought through information centres or credible websites.

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 1 000 metres, seasonal epidemics can occur in hot, equatorial climates at altitudes of up to 3 000 metres (WHO 2009).

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, generally during winter or the dry season (June to August).

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

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 biting habits of mosquitoes, and precautions during these hours are extremely important.

Factors determining a person's malaria risk:

- the actual 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 include non-immunes, pregnant and breastfeeding women, young children, splenectomised and immunocompromised patients (including those with HIV/AIDS, taking corticosteroids or on chemotherapy)
- certain co-morbid diseases 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

No antimalarial used for prophylaxis is 100 per cent effective, due to a number of factors including drug pharmacokinetics, antimalarial drug resistance and non-compliance. This, together with the inconvenience of continually taking chemoprophylaxis if living in malaria endemic areas, emphasises the importance of preventing contact with mosquitoes.

Avoiding mosquito bites is as important as using chemoprophylactic medicines. Measures that reduce contact with mosquitoes have the advantage of being less toxic than chemoprophylactic drugs and their effectiveness is independent of parasite drug sensitivities.

#### 3.2.1 Preventive measures for residents in malaria areas

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

- Residents are encouraged to allow the interior walls of their houses to be sprayed annually with effective non-toxic long-acting insecticides to control the malaria vector mosquitoes. This intervention, known as indoor residual spraying (IRS), has been and remains 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 bite the occupants and rest on the walls or roofs prior to and/or after biting. If the wall or roof is treated with an effective residual insecticide, the mosquitoes will be exposed to a lethal dose of insecticide while they rest. The provincial malaria control programmes usually conduct IRS activities in malaria areas of South Africa.  
In addition to IRS, which targets adult mosquitoes, other vector control methods are employed by the control programme. They include larviciding or draining of potential breeding sites.
- 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.
- Mosquito proof houses by installing screens in front of outside doors, on windows of houses and open eaves.

### 3.2.2 Additional preventive measures for residents and visitors to malaria areas

Additionally, preventive measures recommended include:

- Remaining indoors between dusk and dawn, when possible.
- Wearing long (preferably light-coloured) clothing to minimise the amount of exposed skin. Using mosquito repellents containing DEET (N,N-diethyl-3-methylbenzamide or N,N-diethyl-m-toluamide), during outdoor activities. Repellents should be applied to exposed skin surfaces and repeated after four to six hours according to the manufacturers' instructions. Repellents should not be sprayed on the face nor applied to lips, eyelids, wounds or broken skin, 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, in particular the relatively large body surface area compared to the body weight in this age group. The American Academy of Paediatrics (AAP) recommends insect repellents containing DEET with a concentration of 30 per cent appear to be as safe as products with a concentration of 10 per cent when used according to the directions on the product labels, and the effect of 30 per cent lasts for a longer period. AAP recommends that repellents with DEET should not be used on infants less than two months old. 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 shorter acting than most DEET-based products. It must be reapplied every 40 to 90 minutes for sustained efficacy. Citronella has been withdrawn in Europe for use as an insect repellent.
- Using knockdown insecticidal sprays, vaporisation mats, mosquito coils and other such measures to eliminate mosquitoes that have gained entry to a dwelling.
- Sleeping under insecticide-treated bed-nets reduces the risk of acquiring malaria by limiting contact with mosquitoes while exposing mosquitoes to lethal doses of insecticide. For maximum protection, the nets should not have holes or be damaged in any way and must be tucked in properly to prevent mosquitoes from entering. Long-lasting insecticide-impregnated mosquito nets are widely available for purchase and remain effective for at least three years. Baby cots and prams may be covered with mosquito netting with an elastic edge for a tight fit to protect against mosquito exposure.
- Ceiling fans and air conditioners are also effective in preventing mosquito bites.

Precautions to minimise insect repellent side effects:

- apply repellent sparingly to exposed skin
- repeat applications at intervals according to the duration of action of the particular repellent
- re-apply more frequently after bathing, showering, sweating, etc.
- avoid contact with the eyes, mucous membranes and broken skin
- do not inhale or ingest
- avoid applying products with concentrations above 50 per cent to the skin, particularly in children
- avoid applying repellents to the hands of young children, as these are likely to have contact with the eyes and mouth
- do not allow young children to apply repellents themselves
- avoid using plant extracts if prone to allergy
- people with sensitive skin should avoid lotions and gels as these often contain alcohol
- if a suspected reaction to insect-repellent occurs, wash treated skin and seek immediate medical help
- stop using DEET and obtain immediate medical advice if a change in behaviour is noticed
- read the entire repellent product label prior to use and use only as directed
- note DEET can opacify spectacles, binoculars and other plastics

- 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 bed-net is not torn and that there are no mosquitoes trapped inside the bed-net. Protection will be increased by periodically treating the bed-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



**Figure 3:** Insecticide residual spraying of eaves in a house in South Africa.



### 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 discussed in 3.2.1 and 3.2.2.

The decision to recommend chemoprophylaxis is complex and depends on the areas to be visited (see map of malaria risk areas in South Africa, Pg. 40) and the risk 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 high risk of developing severe malaria complications include the elderly, babies and young children (younger than five 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 per cent 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. The most reliable way of preventing a malaria infection is to avoid mosquito bites.

#### 3.3.2 Choosing appropriate chemoprophylaxis

Blanket recommendations for malaria chemoprophylaxis are not advised. Instead, the choice of prophylaxis should be tailored to the individual, with additional non-drug measures always recommended.

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

#### Summary box 3

##### Recommended prophylactic regimens

- Mefloquine (weekly). Start at least one week before entering a malaria area, take once weekly while there and for four weeks after leaving the malaria area, OR
- Doxycycline (daily). Start one day before entering a malaria area, take daily while there and for four weeks after leaving the malaria area, OR
- Atovaquone-proguanil (daily). Start one to two days before entering malaria area, take daily while there and for seven days after leaving the area.

See **Table 1** for a comparison of the benefits and risks of these prophylactic regimens.

Chemoprophylaxis can either refer to the absolute prevention of infection (i.e. causal prophylaxis) or to the 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 (as well as atovaquone-proguanil). 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 is a causal prophylactic.

**Table 1: Benefits and risks of prophylactic regimens recommended for travellers**

	<b>Mefloquine</b>	<b>Doxycycline</b>	<b>Atovaquone-Proguanil</b>
<b>Prophylactic Efficacy</b>	Highly effective against <i>P. falciparum</i> in areas where it has been tested.  Effective against acute infections caused by <i>P. vivax</i> . Limited data on efficacy against other species. Relapses can occur.	Highly effective against <i>P. falciparum</i> in areas where it has been tested.  Limited protection against acute <i>P. vivax</i> infections. Relapses can occur.	Highly effective against <i>P. falciparum</i> in areas where it has been tested.  Also effective against acute infections caused by <i>P. vivax</i> , <i>P. ovale</i> and <i>P. malariae</i> . Relapses can occur.
<b>Most common side effects</b>	Nausea, strange dreams, dizziness, mood changes, insomnia, headache and diarrhoea.	Skin photosensitivity (three per cent in one study), oesophageal ulceration, gastrointestinal symptoms, candida superinfection of the gut and vagina.	Well tolerated. Headache and abdominal pain most frequent adverse effects.
<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). Infants weighing less than five kilograms.	Pregnancy. Children under eight years of age. Caution in travellers with myasthenia gravis.	Severe renal impairment (creatinine clearance of <30ml/min). Pregnancy due to lack of data.
<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.
<b>Dosage interval</b>	Once weekly.	Daily dose.	Daily dose.



	Mefloquine	Doxycycline	Atovaquone-Proguanil
<b>Time period needed before entering malaria area</b>	General recommendation: One week. For first time use: Two 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.

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 2**)

- pregnancy or planning a pregnancy shortly after the trip
- breastfeeding
- 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 coordination and spatial discrimination, e.g. piloting, scuba-diving, mountain climbing
- 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 three months carries a risk six times greater than a two-week visit. Long term safety of some chemoprophylactic drugs has not been evaluated
- the level of compliance expected with each of the options

**Table 2:** Drug choice according to traveller's conditions/situations

Condition/situation	Mefloquine	Doxycycline	Atovaquone-proguanil
Pregnancy - <b>Avoid travelling to a malaria area</b>	Drug of choice if pregnant women is at risk of malaria	Contraindicated	Not recommended due to lack of information
Women of child-bearing potential or on oral contraceptives	Use reliable contraception during and for three months after taking last dose. Will not compromise contraceptive efficacy.	Avoid pregnancy during and for one week after taking last dose. Contraceptive failure may occur if traveller presents with vomiting or diarrhoea.	Avoid pregnancy during and for two to three weeks after taking last dose. Will not compromise contraceptive efficacy.
Breastfeeding - <b>Baby must be given their own prophylaxis</b>	Insufficient data, but WHO states that it is safe to use.	Avoid use unless no other option. AAP* says it is safe to use.	Avoid use, if infant weighs <11kgs
Young children - <b>Avoid taking children under the age of five years to a high risk area</b>	Can be used in children over three months of age or weighing more than five kilograms. Generally well tolerated by children.	Use only in children older than eight years of age.	Paediatric tablets can be given to children weighing 11kgs or more.

Condition/situation	Mefloquine	Doxycycline	Atovaquone-proguanil
Epilepsy	Contraindicated. May also interact with valproic acid.	May interact with certain anticonvulsants, reducing the half-life of doxycycline and possibly resulting in prophylaxis failure.	Can be used.
Psychiatric conditions	Contraindicated, even if there is only a history of depression.	Can be used.	Can be used.
Psoriasis	No documented problems - can be used.	Can be used.	No documented problems – can be used.
Porphyria	Appears to be well – tolerated.	Likely to be safe	Likely to be safe.
'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).
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
Individuals requiring fine motor coordination and spatial discrimination e.g. pilots	Do not use.	Safe to use.	Safe to use.
Travellers with myasthenia gravis	Insufficient data - stop therapy if muscle weakness occurs.	May aggravate symptoms of myasthenia gravis.	No data available.
Travellers requiring long-term therapy	Can be used for up to three years and even longer if justified by risk of exposure.	Can be used for two years and even longer if justified by risk of exposure.	Can be used for up to one year and even longer if justified by risk of exposure.
Travellers on Warfarin <b>Caution: Changes in INR can be very dangerous, resulting in bleeding or clotting. Preferably avoid high risk malaria areas</b>	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.
Travellers with G-6-PD deficiency	No problems documented - safe to use.	Safe to use.	Safe to use.
Diabetics	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.

\*American Academy of Paediatrics

### 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.
- Antimalarials (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 (one to two days before for doxycycline and atovaquone-proguanil; one to two weeks before for mefloquine).
- Antimalarials should be taken with unfailing regularity for the duration of possible exposure and for the correct duration after leaving the malaria area (four weeks for mefloquine and doxycycline, and seven 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.
- Doxycycline can be obtained from a pharmacy without a prescription - other available effective chemoprophylaxis options require a medical prescription for purchase.
- There is currently 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 chemoprophylactic regimens

Although the protective efficacy of mefloquine, doxycycline and atovaquone-proguanil are considered comparable at around 90 per cent, the best quality evidence is available for mefloquine. The advantages and disadvantages of the recommended chemoprophylactic options are summarised in **Table 1** above. While a high percentage of travellers who take malaria chemoprophylaxis will report side-effects, most will be mild and self-limiting. Atovaquone-proguanil reportedly has fewer severe reactions than the other two options.

#### **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 six months, if tolerated. 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. Weekly dosing should encourage compliance. It is recommended for use for up to three years and even longer if use is justified by risk of malaria.

Adverse effects associated with mefloquine include insomnia, strange dreams, mood changes, nausea, diarrhoea and headache. These effects are usually experienced within the first three weeks of medication and do not become worse in subsequent weeks of use. If 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. The frequency of mild neuropsychiatric effects is probably much higher in the general population and in women, specifically. More recently, an increased risk of eye disorders, including cataracts, retinal disorders and optic neuropathy, which may even occur after treatment, has been reported. These present with visual impairment and blurred vision. The FDA has strengthened their warning with regards to neuropsychiatric effects. The neurologic side effects can include dizziness, loss of balance, or ringing in the ears. The psychiatric side effects can include an anxious feeling, mistrust, depression, or having hallucinations. These can even last after mefloquine has been stopped (e.g. Van Riemsdijk *et al.* 1997).

Occasionally mefloquine-associated side-effects are sufficiently severe to force the discontinuation of prophylaxis while still in a malaria area. To prevent such an occurrence it is recommended that when mefloquine is to be taken for the first time, prophylaxis is started three weeks before exposure to a malaria area to enable a timely drug change should side effects occur.

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

Mefloquine can be used in all trimesters for pregnant travellers to high risk malaria areas. The WHO guidelines state that mefloquine is safe to use in breastfeeding.

Mefloquine may cause spatial disorientation and lack of fine coordination and should not be used where fine coordination is required, e.g. for pilots, people contemplating underwater diving or operating heavy machinery.

## **Doxycycline**

Protective efficacy of doxycycline has been shown to be between 92% and 96% for *P. falciparum* and 98% for primary *P. vivax* infection (e.g. Anderson *et al.* 1998). It is taken daily starting one day before entering the malaria area and continuing daily while in the area and daily for four weeks after leaving the area.

This drug may affect bone formation during early life and should not be given during pregnancy, breastfeeding and the first eight years of life. Adverse effects include gastrointestinal symptoms and *Candida* infection of the gut and vagina which may be severe enough to warrant discontinuation of prophylaxis with the drug. Severe skin sensitivity to sunlight may develop, so excessive exposure to sun should be avoided and the use of sunscreen preparations is advised. Other rare symptoms include dizziness, headache and blurred vision.

Evidence suggests that doxycycline can be safely used for up to two years and even longer if the risk of malaria justifies it.

Doxycycline is the only antimalarial available from pharmacies without a prescription. Currently, no clinical resistance of *P. falciparum* to doxycycline has been reported. Due to its availability and use across broad spectrum of diseases, it is critical to identify early signs of *P. falciparum* resistance.

## **Atovaquone–proguanil**

Atovaquone-proguanil has the best safety profile and because of compliance requirements is a better option for short-term travellers. The drug combination appears to have a relatively mild adverse event profile, with nausea being the most common symptom. It has no adverse psychomotor effects on aircrew.

Atovaquone-proguanil should be taken one day before entering a malaria area, daily while in the malaria area and for seven days after the last possible exposure to malaria. The drug is a causal prophylactic, acting on liver stage malaria parasites, hence the shorter dosing regimen. This shortened regimen is expected to significantly improve compliance. Lack of safety data preclude its use during pregnancy, breastfeeding or for children under 11 kg. 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 as the elimination half-lives of proguanil and cycloguanil are prolonged resulting in the potential of drug accumulation with repeated dosing. In addition, atovaquone  $C_{max}$  and AUC are reduced in patients with severe renal impairment. Other side effects include gastrointestinal symptoms.

### 3.3.5 Alternatives not recommended for chemoprophylaxis

#### **Artemisinin-derivatives and their combinations**

The artemisinin derivatives are pivotal for the effective treatment of malaria and therefore 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. The World Health Organization (WHO) strongly advocates this as a means of delaying the development of resistance. Furthermore, the extremely short elimination half-lives of artemisinin derivatives render them ineffective for prophylaxis.

#### **Dapsone-pyrimethamine**

Use of this drug combination is generally not recommended due to widespread antifolate resistance and a high incidence of agranulocytosis. Agranulocytosis has been reported in approximately one in 2 000 to 5 000 courses.

#### **Chloroquine plus proguanil**

Chloroquine plus proguanil is no longer effective. The widespread prevalence of extremely chloroquine-resistant parasites has rendered this combination largely ineffective as a malaria chemoprophylactic. Proguanil on its own is no longer available in South Africa.

#### **Alternative/complementary/homeopathic/herbal products**

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

### 3.3.6 Patient-specific prescribing problems

#### **Travellers being treated with rifampicin**

There is no ideal option as all three recommended chemoprophylactic options interact with rifampicin. The safest option is probably doxycycline as the interaction appears to only occur in slow rifampicin metabolisers.

#### **Changing from one chemoprophylactic to another (Table 3)**

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. Currently there is no information available on procedures to follow when changing from atovaquone-proguanil to doxycycline or vice versa. Changing from doxycycline or atovaquone-proguanil to mefloquine less than a week before entering the malaria area is inadvisable, as mefloquine needs to be started at least a week before entering the risk area to ensure adequate blood levels.

Changing from mefloquine to atovaquone-proguanil once in the malaria area is also inadvisable because of the different drug action sites. If a course of atovaquone-proguanil is started after entering the malaria risk area, the drug should be taken for four weeks and not 7 days after leaving the malaria risk area, as one then has to rely on its suppressive prophylactic action. This is to provide maximum protection from acquiring an infection.

**Table 3:** Changing from one chemoprophylactic to another.

From	To	Comment
Doxycycline	atovaquone-proguanil	If already in malaria area, take for four weeks after leaving area.
Doxycycline	Mefloquine	Not advised – mefloquine must be taken a week before entering the area
Atovaquone-proguanil	Doxycycline	Should be fine
Atovaquone-proguanil	Mefloquine	Not advised – mefloquine must be taken a week before entering the area
Mefloquine	Doxycycline	Should be fine – no washout period needed
Mefloquine	atovaquone-proguanil	If already in malaria area, take for 4 weeks after leaving area

### **Travellers 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. 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 traveller is taking another tetracycline, such as minocycline, for acne, one option is to replace minocycline 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 required for effective chemoprophylaxis.

### **Travellers with epilepsy**

Selecting a chemoprophylactic agent for an epileptic patient is rather problematic. Some agents have been reported to cause convulsions while others interact with anti-epileptic medication. To allow travellers with epilepsy to make informed decisions regarding chemoprophylaxis, they must be educated on the possible adverse effects associated with the chemoprophylactic agents and the risk of contracting malaria. It is imperative that these travellers are encouraged to protect themselves against mosquito bites through diligent use of non-drug measures.

## Mefloquine

Mefloquine is contraindicated for malaria prophylaxis in patients with a history of convulsions. Several cases of first-time seizures in patients taking mefloquine in prophylactic doses have been reported.

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 anticonvulsants. Carbamazepine, phenytoin and barbiturates may shorten the half-life of doxycycline by up to 50 per cent, 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 result in increased incidence of side-effects.

In summary, patients with epilepsy who are 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.

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.** 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. Pregnant women are more likely to suffer from severe malaria than non-pregnant women. This is especially true of primigravidae. The mechanism is unclear but may be related to cellular immune function suppression, the greatest risk being spontaneous abortion.

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

## Mefloquine

The manufacturers of mefloquine state that pregnant women should be discouraged from travelling to malaria endemic areas. If they do go, mefloquine may be considered as prophylaxis regardless of

the term of pregnancy but in strict respect of the indication. The WHO and other authorities now recommend that mefloquine may be considered for chemoprophylaxis in pregnant women who visit high risk areas, irrespective of which trimester they are in. Cumulative evidence from clinical trials and reports of inadvertent use of mefloquine during pregnancy do not suggest an association with adverse foetal outcomes.

### **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.

Inadvertent exposure to doxycycline during pregnancy may not necessarily warrant therapeutic abortion.

### **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.

#### **Recommendations:**

If it is absolutely necessary for a pregnant person to enter a malaria risk area, mefloquine, depending on 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 help immediately if any malaria symptoms occur.

#### **3.3.10 Breastfeeding mothers**

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

### **Mefloquine**

Manufacturers recommend that as a precautionary measure, mefloquine should be avoided by breastfeeding mothers, but the WHO guidelines state that it is safe to use. Approximately four per cent 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. The levels reaching the infant from breast milk are insufficient to provide adequate protection against malaria.

### **Doxycycline**

Doxycycline is excreted into breast milk in low concentrations and may have adverse effects on the breastfeeding infant. However, the American Academy of Paediatrics considers tetracycline to be compatible with breastfeeding. The duration 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.

### Recommendations:

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

### Prophylaxis prior to conception

Travellers who wish to become pregnant after being in a malaria risk area, and who would like to do so with minimal drug present should wait the following time intervals after stopping the antimalarial before attempting to conceive.

- Mefloquine: Three months
- Doxycycline: One week
- Atovaquone/proguanil: Two to three weeks

### Travellers involved in activities requiring fine coordination and spatial discrimination

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 the drug. The WHO recommends that piloting of aircraft and deep-sea diving should be avoided if taking mefloquine.

Although the latest studies do not seem to show significant effects of mefloquine on fine motor coordination, it seems prudent to exercise caution when used in persons operating machines, driving, deep-sea diving or flying. (The drug may cause sleep disturbances, which in the long term, may affect coordination).

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

### Recommendation

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

### Travellers 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 given to choosing appropriate prophylaxis for those with mental illness of any kind, as travel may actually increase anxiety.

## Mefloquine

Mefloquine has been reported to cause serious neuropsychiatric symptoms in approximately one in 10 000 users. Symptoms can develop as early as the first week of use and more than 75 per cent 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. 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.

### **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 any problem.

### **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.

### **Malaria chemoprophylaxis in children**

Children are at an extreme malaria risk as they can rapidly become seriously ill with malaria. 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. It is advisable to keep babies under mosquito nets as much as possible, particularly between dusk and dawn.

When a child develops a febrile illness either whilst in a malaria area or after having left the area, medical assistance must be sought immediately. Malaria symptoms in children may not be typical and therefore malaria should always be suspected. In infants, malaria should even be suspected in non-febrile illness.

### **Mefloquine**

Mefloquine can be used in children older than three months of age or weighing over five kilograms; the dose is based on the weight of the child.

### **Doxycycline**

Doxycycline should not be used for prophylaxis in children under eight 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 eleven kilograms of weight due to lack of data.

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

## People already on chloroquine therapy

Mefloquine should not be taken concurrently with chloroquine because of the danger of toxic cardiac or CNS reactions.

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

There is no documented interaction between atovaquone and chloroquine. There were however reports of increased incidence of mouth ulcers when proguanil and chloroquine were used together.

### Long-term chemotherapy for people travelling 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.

The restriction on long-term use of any of the regimes is based on lack of data rather than on any evidence of new toxicity problems from long-term use.

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.

The Centers for Disease Control and Prevention (CDC), Atlanta, USA, has recommended that mefloquine can be used for long-term malaria chemoprophylaxis. 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 three years and even longer if justified by the risk of malaria. Long-term use of mefloquine does not appear to be related to increased side effects.

Evidence suggests that doxycycline may be used safely for periods of up to two years. Longer term use is possible if justified by the risk of exposure. There is no evidence of harm in long-term use. It should however ideally be used by individuals who will be exposed to malaria for short periods of time.

Although both components have been used individually on a long-term basis, there is limited information concerning long-term use of atovaquone-proguanil. It can be used confidently for up to a year and longer term use is possible if justified by the risk of exposure. In South Africa, this combination is registered without a restriction on the length of the course.

### Patients on anticoagulant therapy

#### a. Warfarin

Patients on warfarin therapy should avoid travelling to malaria areas where chemoprophylaxis is indicated. Malaria chemoprophylaxis is very difficult in these patients, especially as monitoring of INR (international normalised ratio) is a challenge in travellers. Both bleeding and clotting, which can occur while trying to regulate the INR, can be very dangerous. The use of non-drug measures should be vigorously encouraged and visits during high season or to high-risk areas strongly discouraged. If travel to these areas is essential, patients should be fully informed of both the potentially life-threatening malaria risks and the potential of chemoprophylaxis to interfere with anticoagulation, which may increase their risk of bleeding or clotting. Mefloquine is the only chemoprophylaxis option that can be considered in these patients, as both doxycycline and atovaquone-proguanil may potentiate the effect of oral anticoagulants. However, there are

insufficient data on the safety of mefloquine in these patients, so prophylaxis should be started three to four weeks before travel so that INR can be closely monitored for the possibility of an interaction.

#### **b. New oral anticoagulants (NOAC)**

Dabigatran and rivaroxaban are the new oral anticoagulants available in South Africa. They have a number of advantages over warfarin as they do not interact with food, do not require laboratory monitoring and have a lower potential for drug interactions compared to warfarin. There is however very little information on the concurrent use of antimalarials with these NOACs.

Rivaroxaban is a substrate of CYP3A4 and p-glycoprotein while dabigatran is a substrate of p-glycoprotein. There is therefore a potential interaction between either of these NOACs and mefloquine, as mefloquine is a weak inhibitor of CYP3A4 and p-glycoprotein. This could result in an increase in plasma levels of the anticoagulants and an increased bleeding tendency. Doxycycline or atovaquone-proguanil would be better antimalarial options for travellers taking NOACs.

#### The immunocompromised traveller

Immunocompromised 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 higher parasitaemias 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.

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 be carefully considered (especially in patients taking immunosuppressants after organ transplants). For a full list of interactions between malaria prophylaxis and other drug treatments, please see Table 4.

#### Travellers on antiretroviral therapy

Although patients on ARVs 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 (PIs), 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.

Efavirenz, nevirapine and the protease inhibitors theoretically may reduce the level of mefloquine but this has not been shown to be clinically significant. Theoretically PIs 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 PIs inhibit the growth of *P. falciparum*.

Currently, doxycycline is the only recommended option for malaria prophylaxis in HIV-infected travellers on ARVs, as there are no known drug interactions with any of the ARV regimens. 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 potential for interaction with the traveller's ARVs must be started several weeks prior to departure, in order to permit measurement of plasma levels.

**Table 4:** 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.
	Antipsychotics e.g. phenothiazines, pimozide	Increased risk of ventricular arrhythmias. Mefloquine should not be used in patients with a history of a psychiatric illness.
	Antiretrovirals; efavirenz, nevirapine protease inhibitors	Theoretical risk of reduced levels of mefloquine, (not clinically significant).  Theoretical risk of reduced levels of protease inhibitors, (not clinically significant).
	Beta blockers e.g. atenolol, propranolol etc.	Potential for increased risk of electrocardiographic abnormalities, bradycardia and cardiac arrest. 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. 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. 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.
	NOACs	May increase plasma levels of dabigatran and rivaroxaban, which may increase risk of bleeding.
	Oral cholera and typhoid vaccines	Inactivation of the immunisation possible. Complete immunisation three days before taking mefloquine.
	Primaquine	May increase the serum levels and side effects of mefloquine.
	Quinine or quinidine	Quinine may inhibit the metabolism of mefloquine, thereby increasing mefloquine levels. The combination may produce electrocardiographic abnormalities, cardiac arrest, or could result in potentially serious cardiac conduction abnormalities. On the other hand, a small, limited study conducted in 13

Antimalarial	Other drug	Comment
		adults with single doses of both drugs showed a lack of a clinically significant cardiovascular pharmacodynamic interaction. The combination may increase the risk of seizures. A loading dose of quinine should not be given if mefloquine has been used for prophylaxis in the preceding 24 hours.
	Rifampicin	Decreased plasma concentration of mefloquine via induction of mefloquine metabolism.
	Tricyclic antidepressants	Increased risk of ventricular arrhythmias. 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.
<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.
	Antacids containing: calcium, bismuth, aluminium, magnesium, calcium supplements	Reduces the absorption and serum concentrations of doxycycline significantly, compromising therapeutic efficacy. If possible use alternative therapy, or administer doxycycline at least two hours before, or four to six hours after antacids.
	Antiretrovirals	No theoretical or known interaction
	Carbamazepine, barbiturates and phenytoin	Reduce the plasma half-life of doxycycline by approximately 50 per cent and may result in a reduction of efficacy. (See Epilepsy Section)
	Iron	Decreased absorption of doxycycline and iron salts. Efficacy may be reduced. Separate dosages by as much as possible. Give iron at least three hours before or two hours after the doxycycline dose.
	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.
	Isotretinoin	An increased incidence of pseudotumour cerebri has been reported in patients on other tetracyclines. It is unknown whether doxycycline is also potentially problematic.
	Milk and dairy products	Absorption of doxycycline may be reduced by up to 30 per cent because of the calcium ions found in milk. Avoid for at least one hour before or two hours after taking doxycycline. The small amounts of milk used in coffee and tea appear not to matter.
	Oral contraceptives	May reduce efficacy of contraceptives, if diarrhoea or vomiting occurs.
	Rifampicin	Increased doxycycline clearance. Potential loss of doxycycline efficacy. Monitor patient response.
	Warfarin	Potential of anticoagulant effect possible, monitor INR.

Antimalarial	Other drug	Comment
<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.
	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.
	Magnesium trisilicate	Reduces absorption of proguanil. Separate doses as much as possible (two to three hours).
	Metoclopramide	Atovaquone plasma levels reduced, resulting in therapeutic failure.
	Rifampicin, rifabutin	Atovaquone plasma levels reduced, resulting in therapeutic failure.
	Tetracyclines	Atovaquone plasma levels reduced, resulting in therapeutic failure.
	Warfarin	May potentiate effect of Warfarin, monitor INR.

### 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.

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

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. The use of rapid diagnostic tests to confirm malaria can be considered in these situations, although travellers often perform and interpret these tests incorrectly. It is recommended that a traveller should perform a trial test under supervision prior to departure.

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 the first treatment dose has been taken.

## 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. Even if there is no travel history, the investigation of a fever of unknown cause, especially if platelets are decreased, should include consideration of malaria.

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. If the test result is negative but there is still a high suspicion of malaria, another blood sample should be collected and sent for additional analysis. If done through microscopy, the retest should be done by another experienced microscopist if malaria is still suspected after a negative first test. In exposed patients with severe illness in whom the diagnosis cannot be confirmed, presumptive treatment for malaria should be given after a malaria smear is made.

In recent years a number of new point-of-care techniques based on the lateral-flow or '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 (LDH) that is present in *P. falciparum* infections.

Some of these rapid diagnostic tests have been extended to include screening for other species of malaria in addition to *P. falciparum* ('combo' tests) but these are less sensitive, and results are often misinterpreted by inexperienced users. Since most malaria infections in South Africa are caused by *P. falciparum*, the routine use of combo tests outside accredited diagnostic laboratories is discouraged.

The advantages of rapid diagnostic tests (RDTs) are that they:

- are reasonably sensitive
- provide rapid results
- are relatively simple to use in a primary healthcare setting

These tests do however have some limitations:

- They are evaluated on ability to detect a minimum parasite load of 200 parasites/ $\mu$ l of blood; while some may detect lower levels of infection of *P. falciparum* and *P. vivax*, very low density infections may be missed (WHO 2015b).
- 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 clearance of parasites, as they may stay positive for some time after successful treatment.
- There are some technical reasons for occasional false negative or false positive results, so RDT results should be confirmed by conventional quality-assured microscopy whenever possible, **particularly when the clinical condition is suggestive of malaria but the RDT is negative.**
- Although the WHO-FIND malaria product testing programme (WHO 2015b) can guide RDT brand selection, it is difficult to monitor RDT quality after delivery, and it is important that users are well trained and understand that most false results are because of user errors.



## Correct use of RDTs

RDTs must be used strictly according to manufacturer's instructions. Storage requirements, especially temperature, must be adhered to.

- Read the instructions carefully.
- Check the sealed package containing the test; if damaged, do not use.
- Check the expiry date of the test; if expired, do not use.
- Put on well-fitting, non-sterile gloves.
- Label the cassette with patient identification details.
- Obtain the amount of blood required for the test, either by fingerprick or venepuncture, using blood transfer device provided by the manufacturer. Brands may vary in their blood volume requirements, and these must be adhered to as accurately as possible.
- Too much, or too little blood may lead to incorrect results.
- Apply the blood to the correct aperture on the cassette; the cassette arrangement varies between brands, so check instructions beforehand.
- Apply the correct number of drops of buffer/reagent to the correct aperture; this varies between brands, so check instructions beforehand.
- Write down the time or start the timer immediately.
- When reading the RDT:
  - Keep the cassette flat on a table & do not tilt.
  - Ensure you have understood the direction of the test & the important landmarks – for blood and buffer.
- Locate the Control and Test windows. Read the result at the manufacturer's stipulated time after starting. **Do not prolong the time until reading**, as false positives can occur in this way. A line that appears after the stipulated reading period must be ignored.
- Check that the control line is present. Any test line, regardless of intensity, is a positive result. Absence of the control line means that any test result cannot be accepted or reported.
- If the control line is absent, check that the correct procedure has been followed, and repeat the test.
- **Common user errors:**
  - Using expired RDTs.
  - Using poorly stored RDTs.
  - Provider opens lancet before cleaning finger, then sets lancet down on table or holds onto it while cleaning finger.
  - Provider opens lancet without paying attention to where it is pointing, exposing himself or patient to accidental prick.
  - Collection of inaccurate volume of blood (too little / too much).
  - Use of incorrect buffer (type and quantity).
  - Placing buffer / blood sample in wrong hole.
  - Not reading the results within the correct time-frame (too early / too late).
  - Failure to label test cassette resulting in mix-up of patient results.
  - Poor lighting for reading of test results.
  - Failure to interpret faint lines as positive results.

Failure to record test results.

Full illustrated instructions for use of RDTs are provided in the national Department of Health's publication, *National Malaria Diagnosis Quality Assurance Guidelines* (2014).

### 3.4.1 Signs and symptoms of malaria

Symptoms of malaria infections are exhibited only once the malaria parasites infect the red blood cells, which is commonly 10 to 14 days after an infective mosquito bite. This window (incubation) 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 and/or sore throat

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, tick bite fever, 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                      Urban 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. Anti-mosquito measures should include:**

- Remain indoors between dusk and dawn (wherever possible).
- 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 installed, 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 bed-net (preferably impregnated with an insecticide registered for this purpose, e.g. a pyrethroid), with the edges tucked in. Ensure that the bed-net is not torn and that there are no mosquitoes inside the bed-net.
- 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.**

The following regimens are currently recommended for use in South Africa:

- Mefloquine (weekly). Start at least one week before entering a malaria area, take once weekly while there and for four weeks after leaving the malaria area, or
- Doxycycline (daily). Start one day before entering a malaria area, take daily while there and for four weeks after leaving the malaria area, or
- Atovaquone-proguanil (daily). Start one to two days before entering malaria area, take daily while there and for seven days after leaving the area.

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 to 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 be 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.

Treatment of uncomplicated malaria

**Treatment of *P. falciparum* infections**

Artemisinin-based combination therapies (ACTs) are the recommended first-line treatment of uncomplicated malaria caused by the *P. falciparum* parasite (WHO 2015a). Five ACTs are currently recommended for use and choice of ACT to administer should be based on therapeutic efficacy studies against local *P. falciparum* malaria strains.

## Treatment of *P. vivax* infections

*Plasmodium vivax* infections are currently uncommon in South Africa. However, treatment with chloroquine is recommended in areas where the drug still remains effective. If the source of infection is from an area with known chloroquine-resistance *P. vivax*, ACTs are the recommended treatment, preferably where the partner drug has a long half-life.

### Treatment of severe malaria

Injectable artesunate (intramuscular or intravenous) is the recommended first-line treatment of severe malaria caused by all *Plasmodium* species. The drug should be administered for at least 24 hours, followed by ACTs when the patient can tolerate oral medicines.

## 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 per cent effective, but the correct medicine will reduce your risk of severe illness.
- Seek immediate medical help if you have any flu-like symptoms at any time up to six 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 four weeks after leaving the area (unless you are taking atovaquone-proguanil, in which case, take it for seven days after leaving the area).

### Early symptoms of malaria.

- Fever

- Headache
- Chills
- Muscular pain

**Seek medical help immediately if you have any of the above symptoms.**

## 6. Dosage Tables

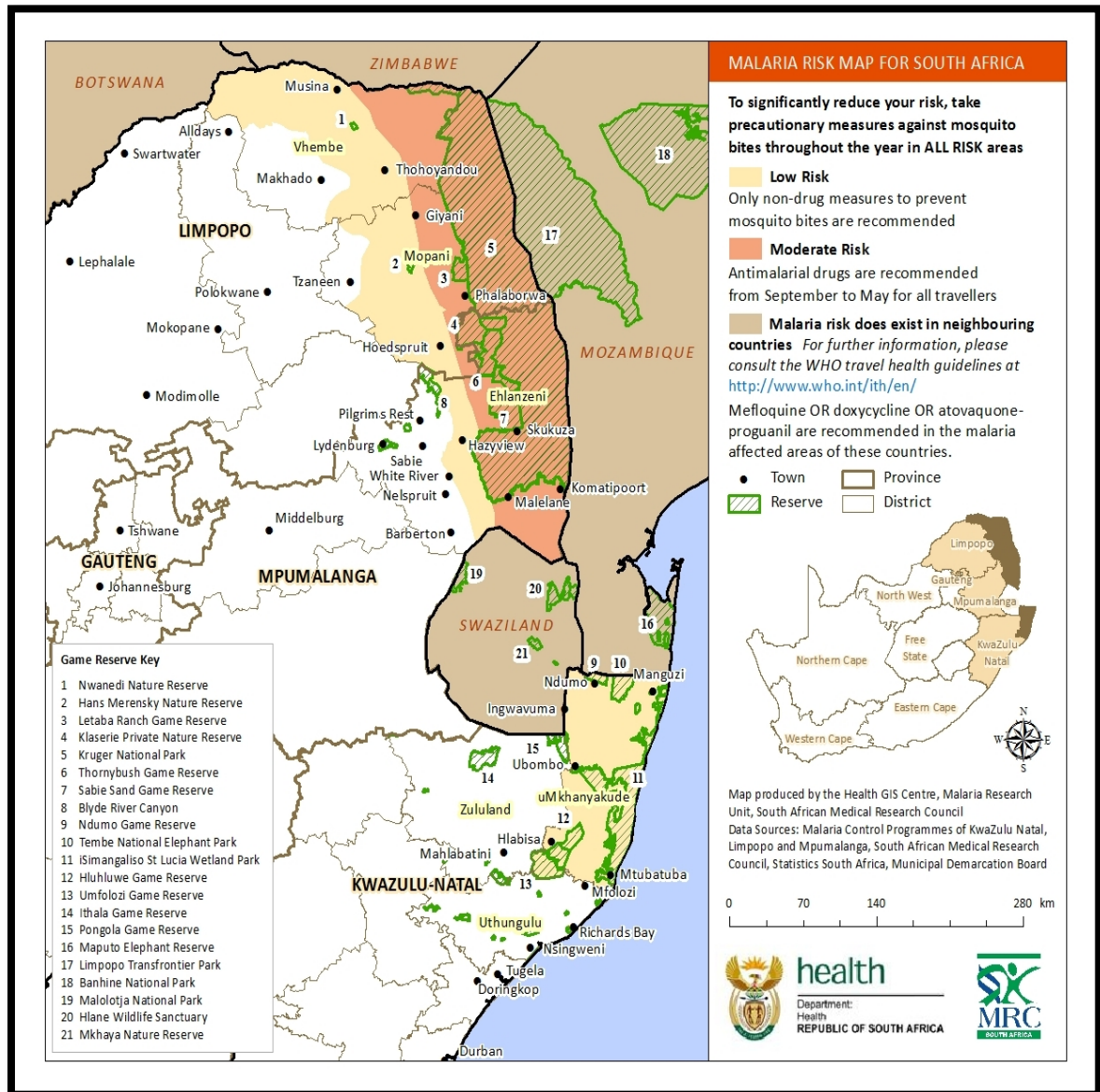
**Table 1:** Doses of antimalarial drugs for use as prophylaxis

Recommended drug	Adults	Children
<b>Mefloquine</b>	(1 tablet = 250 mg mefloquine)  250mg (one tablet) weekly, starting one week before entering the area, once weekly while in the area, and once weekly for four weeks after leaving the area.	Not recommended for children who are less than three months old or who weigh less than five kilogram.  Weight (kg) Weekly Dosage 5 - 20 ¼ tablet 21 - 30 ½ tablet 31 - 45 ¾ tablet >45 Adult dose
	<b>OR</b>	
<b>Doxycycline</b>	(1 tablet = 100mg doxycycline) (1 capsule = 50mg or 100 mg doxycycline)  100mg once daily starting one day before entering the area, continuing daily while in the area, and daily for four weeks after leaving the area.	Contraindicated in children less than eight years of age.  2mg/kg of body weight at the same intervals as for adults.  <b>Age (years) Weight (kg) Dosage</b> 8 - 15 31- 45 2 mg/kg >15 >45 Adult dose
	<b>OR</b>	
<b>Atovaquone – proguanil</b>	1 adult tablet = 250mg atovaquone plus 100mg proguanil.  Should be taken one day before exposure, continued daily during exposure and for seven 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 tablet daily 31 – 40kg 3 paediatric tablet daily > 40kg 1 adult tablet daily

**Table 2:** Doses for standby therapy

<p><b>Artemether-lumefantrine</b> 1 tablet contains artemether 20mg plus lumefantrine 120mg.</p> <p><b>NB.</b> <i>Always administer with fat-containing food/milk to ensure adequate absorption.</i></p>	<p><b>10 - &lt;15kg:</b> 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)</p> <p><b>15 - &lt;25kg:</b> 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)</p> <p><b>25 - &lt;35kg:</b> 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)</p> <p><b>35 - &lt;65kg:</b> 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)</p> <p><b>≥ 65kg:</b> Dose as for &gt; 35kg above, although inadequate experience in this weight group</p>
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## 7. Map of malaria areas in South Africa (2013)





## 8. Prophylaxis masks the symptoms - the myth

It is highly irresponsible not to recommend or prescribe required prophylaxis 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. 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

Generic name	Trade name	Schedule	Indication	Manufacturer
Artemether-lumefantrine	Coartem® tabs	S4	Treatment	Novartis
Atovaquone-proguanil	Malanil® tabs	S4	Prophylaxis	Aspen/GSK
	NuMal® tabs	S4	Prophylaxis	CiplaMedpro
	Malateq®	S4	Prophylaxis	Lamar
	Mozitec® tabs	S4	Prophylaxis	Activo
Doxycycline hydrochloride	A-Lennon doxycycline	S2	Prophylaxis	Merck Gen (Xixia)
	Cyclidox® caps	S2	Prophylaxis	Aspen Pharmacare
	Doxycyl® caps	S2		Aspen Pharmacare
	Dumocin® caps	S2		
Mefloquine hydrochloride	Lariam® tabs	S4	Prophylaxis	Roche Products
	Mefliam® tabs	S4	Prophylaxis	CiplaMedpro

## 10. Sources of malaria risk and prevention information

Organisation	E-mail or website	Telephone number
National Department of Health	<a href="http://www.health.gov.za">www.health.gov.za</a>	012 395 8000
Amayeza Info Centre	<a href="mailto:amayeza@amayeza-info.co.za">amayeza@amayeza-info.co.za</a>	011 475-2994
University of Cape Town Medicines Information Centre	<a href="mailto:micquest@uctgsh1.uct.ac.za">micquest@uctgsh1.uct.ac.za</a>	021 406 6783 or 021 406 6778
The South African National Travel Health Network	<a href="http://www.santhnet.co.za/">www.santhnet.co.za/</a>	011 025 3297
National Institute for Communicable Diseases	<a href="http://www.nicd.ac.za">www.nicd.ac.za</a>	011 386 6400
World Health Organization	<a href="http://www.who.int/health-topics/malaria.html">www.who.int/health-topics/malaria.html</a>	
Centers for Disease Control and Prevention	<a href="http://www.cdc.gov/travel/malinfo.html">www.cdc.gov/travel/malinfo.html</a>	

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