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PREFACE

The prevention of malaria in South Africa poses a major challenge to health care practitioners. Whilst chemoprophylactic approaches for the prevention of malaria are available, they may not always be the best option. These guidelines, produced by the National Department of Health, provide detailed approaches to a variety of options for preventing malaria transmission in South Africa.

The objective of these guidelines is to provide health care practitioners with information on the most appropriate interventions to take when advising and treating people who enter into malaria affected areas in South Africa.

These guidelines are in keeping with the World Health Organization's guidelines for the prevention of malaria.

These guidelines include information on various prevention options, selecting the most appropriate chemoprophylaxis to use, various interactions between malaria chemoprophylaxis and other drug treatments and the benefits and risks of chemoprophylactic agents. Detailed tables on antimalarial drug dosages have also been included.

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

Or ME Tshabalala-Msimang
Minister of Health

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I would like to express my sincere gratitude to the Sub-Committee for Chemoprophylaxis and Therapy (SCAT) of the Malaria Advisory Group who were responsible for drafting these guidelines. The SCAT members include:

Mrs Lee Baker, medicines information consultant, Pharmnet Amayeza Information Centre; Dr Lucille Blumberg, Department of Microbiology and Infectious Diseases, University of the Witwatersrand and the National Health Laboratory Services; Dr Karen Barnes, Department of Pharmacology, University of Cape Town; Dr Frank Hansford, Department of Health (Chairperson); Dr Cornelia Duvénage, Department of Internal Medicine, 1 Military Hospital; Dr Hervey Vaughan Williams, Mosveld Hospital, Kwazulu-Natal; Professor David Durrheim, James Cook University, Australia (previously of the Mpumalanga Department of Health); Mr Devanand Moonasar, National Department of Health; Ms Caron Johnson, National Department of Health; Mrs Hanlie Nel, National Department Health; Dr Jan van den Ende, Drs Du Buisson, Bruinette and Kramer Inc and Dr Bernice Harris, Mpumalanga Department of Health.

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Ayanda Ntsaluba
Director-General Department of Health

Guidelines for the prevention of Malaria in South Africa

EXECUTIVE SUMMARY

Malaria poses a risk to travellers to and residents in malaria areas. Stringent non-drug measures should be taken to avoid mosquito bites throughout the year, even in areas of low malaria transmission intensity. In addition, effective chemoprophylaxis should be taken whenever and wherever the risks of acquiring malaria exceed the probability of experiencing a serious adverse reaction to the chemoprophylaxis. The risk of acquiring malaria is determined by the intensity of malaria transmission in the area and season of visit as well as the length of stay, type of accommodation, and likely activities between dusk and dawn. The choice of chemoprophylaxis is determined by local antimalarial drug resistance patterns and patient factors including, co-morbid disease, drug interactions and activities. Mefloquine or doxycycline are the preferred prophylactic agents due to their greater efficacy, but chloroquine plus proguanil may be considered in certain circumstances¹. Patients should be made aware that malaria should be urgently excluded with ANY febrile illness occurring within 1 week to 3 months after visiting a malaria area, regardless of whether or not chemoprophylaxis was taken or mosquitoes were seen. Early effective treatment is essential to prevent progression to potentially fatal severe malaria.

SUMMARY BOX 1

The “ABC” of Malaria prevention

- A: Awareness of malaria risk
- B: Avoidance of mosquito Bites
- C: Compliance with Chemoprophylaxis, when indicated
- D: Early Detection of malaria
- E: Effective treatment

Disclaimer

This material is intended for use by healthcare professionals. It has been compiled from information currently available, and although the greatest care has been taken the Department of Health and its Malaria Advisory Group do not accept responsibility for errors or omissions. Readers are referred to the reference articles for further information and should exercise their own professional judgement in confirming and interpreting the findings presented in the publication. These guidelines were issued on the 1 March 2003 by the National Department of Health, and replace all previous guidelines.

INTRODUCTION

Malaria is a common and life-threatening disease in many tropical and subtropical countries. In some tropical districts over half of the residents may be infected with malaria. In Africa alone it is estimated that more than a million children die of malaria each year. Malaria control operations have substantially reduced the prevalence of malaria in some countries. In South Africa, malaria was originally endemic in the low-lying northern and eastern

districts. However, control measures introduced since 1930 have reduced malaria transmission significantly.

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

Parasite resistance to antimalarials used for chemoprophylaxis and treatment has increased significantly over time. Resistance^{3,4} to sulfadoxine-pyrimethamine (in certain areas for treatment²) and chloroquine have reached levels at which these drugs can no longer be used as monotherapy. This has necessitated changes in chemoprophylaxis and treatment policies in South Africa.

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

DISTRIBUTION OF MALARIA

Malaria occurs mainly in tropical developing countries in Central and South America, Africa, Asia and Oceania.

Malaria occurs in limited areas in South Africa, mainly in the low altitude (below 1000m) areas of Limpopo, Mpumalanga and North Eastern KwaZuluNatal¹⁰. (See map of malaria risk areas in South Africa.) Limited focal transmission may occasionally occur in the North West and Northern Cape provinces along the Molopo and Orange rivers.

Malaria is distinctly seasonal in South Africa, with the highest risk being during the wet summer months (October to May)⁵.

MALARIA – THE DISEASE

Human malaria is an infectious disease caused by four species of the *Plasmodium* parasite. (delete in people) –

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

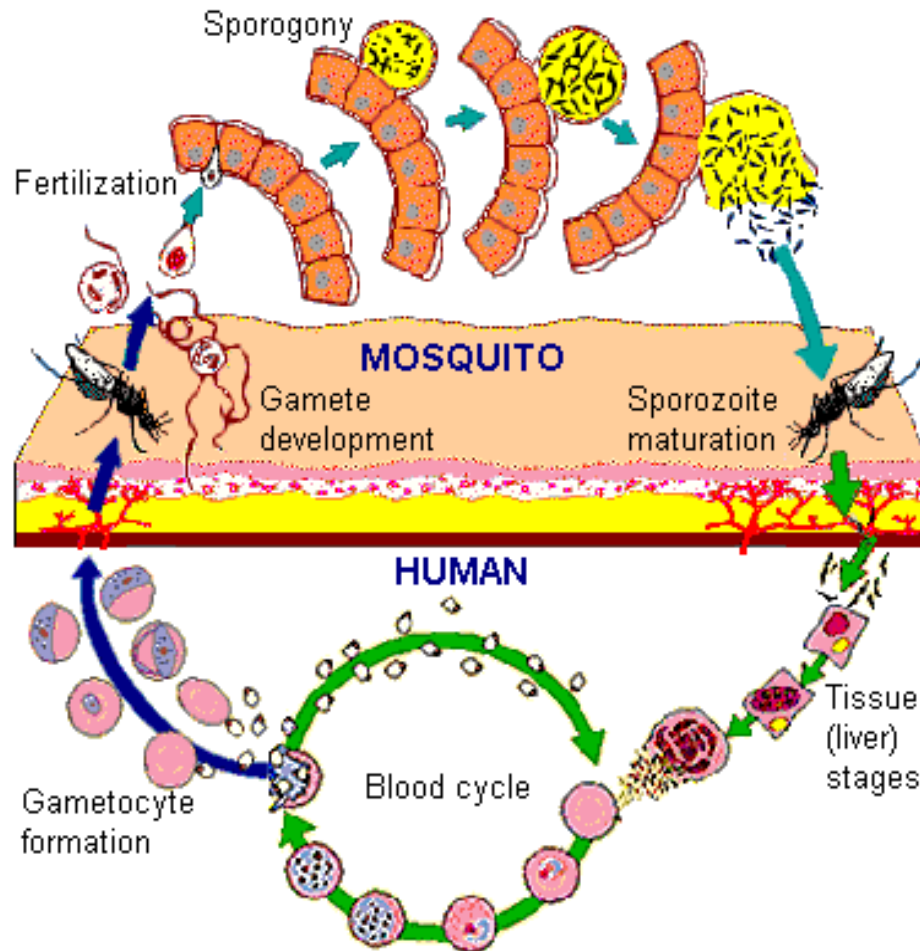
Malaria is transmitted to humans by the bite of an infected female anopheles mosquito. In Sub-Saharan Africa over 90% of human malaria infections are due to *P. falciparum* infection. *P. falciparum* is the only species associated with severe morbidity and mortality^{6,8}. The other three species cause milder illness, however infections with *P. ovale* and *P. vivax* may relapse months

later if appropriate treatment is not provided. Mixed infections involving more than one species may also occur.

Life cycle of malaria parasites in human and mosquito.

Figure: 1

http://www.malaria.org.za/Malaria_Risk/General_Information/general_information



The life cycle of the malaria parasite involves two hosts. During a blood meal, a malaria-infected female anopheles mosquito inoculates sporozoites into the human host. Sporozoites infect liver cells and mature into schizonts, which rupture and release merozoites into the blood stream where they infect red cells. In *P. vivax* and *P. ovale* malaria infections a dormant stage [hypnozoites] can persist in the liver and cause relapses by invading the bloodstream weeks, or even years later. After this initial replication in the liver (exo-erythrocytic schizogony), the parasites undergo asexual multiplication in the erythrocytes (erythrocytic schizogony). The ring stage trophozoites mature into schizonts, which rupture, releasing merozoites. Some parasites differentiate into sexual erythrocytic stages (gametocytes). Blood stage parasites are responsible for the clinical manifestations of the disease.

The male (microgametocytes) and female (macrogametocytes) gametocytes are ingested by an anopheline mosquito during a blood meal. The parasites' multiplication in the mosquito is known as the sporogonic cycle, and sporozoites are released and make their way to the mosquito's salivary glands. Inoculation of the sporozoites into a new human host perpetuates the malaria life cycle.

Following infection during a mosquito blood meal, there is an asymptomatic incubation period of approximately 7 to 30 days while the parasites develop in the liver and during the initial multiplication in the blood. This can be prolonged in patients taking chemoprophylaxis. Reproduction in the blood is extremely rapid and destruction of red blood cells soon induces disease symptoms. Without treatment the illness may deteriorate 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 permanently cured; however, hypnozoites (the dormant stage) in the liver may be responsible for relapses of *P.ovale* and *P.vivax* presenting 2 – 3 months or more after the original infection^{7,8}.

The gametocytes in the blood do not cause symptoms and may persist for several weeks after successful treatment of the acute illness⁸.

The mosquito vector

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

The duration of the larval stage and lifespan of the adult mosquito is strongly influenced by temperature. With ideal hot conditions the larval stage may be as short as 5 – 7 days and adults may survive for 3 – 4 weeks. Water is essential for the larval stage.

Features of anopheline mosquitoes:

- They are relatively small, about 8mm long with dark-spotted or dappled wings.
- Their posture when resting or feeding is distinctive – head down, body at an angle and hind legs raised. This is in contrast with the horizontal position maintained by most other mosquito species.
- They fly more quietly and bite more subtly than other mosquitoes.
- They generally prefer clean water for the development of their larval stages in contrast to the dirty water found in drains, tins and rubbish preferred by the culicine family. Individual anopheline species differ in their preferences – *Anopheles arabiensis* (*An. arabiensis*) larvae are commonly found in small sunlit water collections e.g. hoof prints, small sandy pools, while *Anopheles funestus* (*An. funestus*) larvae are found in deep-shaded clean water.

- Adult *An. arabiensis* rest both indoors and outside under leaves or tree roots, while *An. funestus* and *Anopheles gambiae* (*An. gambiae*) favour resting indoors. This results in residual household spraying being more effective in the eradication of the latter species.
- The adults are carried by wind but few are found further than 1 – 2 km from their larval site. Adults may rest inside motor vehicles, trains, aircraft, and be transported considerable distances. In this way infected mosquitoes have occasionally been responsible for malaria infections in high-lying cities such as Johannesburg, as well as around airports in Europe.
- The adult female anopheles mosquitoes require protein from blood meals for their eggs to mature. They generally only feed between sunset and dawn^{1,6}.
- Anopheles prefer to feed near ground level often selecting feeding on the lower leg rather than arms or upper body, thus it is especially important that insect repellent is applied to the lower leg and foot when in the sitting or standing position.

PREVENTIVE MEASURES

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

A number of factors must be taken into consideration prior to entering an area where malaria is prevalent.⁹ These factors determine the likelihood of a traveller acquiring malaria, or of progression to severe and complicated malaria, and thus should aid a traveller in determining whether chemoprophylaxis is needed in addition to stringent non-drug measures.

These factors are:

- The malaria risk in the area being visited
- The length of stay in the area
- The time of year (in areas of seasonal malaria transmission) or time of day of the visit
- The intensity of transmission and prevalence of drug resistant malaria in the area
- Pregnancy, breast-feeding, age, comorbid disease, immune status (including those who had have a splenectomy) and concurrent medications
- Type of accommodation (e.g. air conditioned rooms, camping)
- Mode of travel (e.g. backpacking, motoring, flying)
- Whether destination is rural or urban
- Activities (safaris/jungle expeditions), especially between dusk and dawn
- Access to medical care

Is the traveller entering a malaria area?

The first step in deciding on appropriate prophylactic measures is to confirm that the area to be visited is indeed a malaria area. Accurately identifying malaria transmission areas is difficult. Within countries and even within regions in those countries, there are often malaria risk areas and other areas that may be free from malaria. Malaria risk areas are not static and may change with time, depending on factors such as rainfall and migration of infected individuals.

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 1000 metres, disease can occur in hot climates at altitudes of up to 3000 metres^{1,9}.

Transmission also depends on the time of year, as many areas have seasonal malaria (including South Africa). Travellers should ideally visit malaria areas when malaria transmission is minimal, usually during winter or the dry season.

Pregnant women, children under the age of five years, and immunocompromised patients should ideally avoid high-risk malaria areas if at all possible¹⁰.

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

Mosquito avoidance

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

Measures that reduce contact with mosquitoes have the advantage that they are less toxic than chemoprophylactic drugs and that their effectiveness does not depend on the drug sensitivity of the parasite.

These measures include:

- Using gauze on windows and doors, particularly for residents of malaria areas.
- Knockdown insecticidal sprays, vaporization mats, mosquito coils etc. should be used to eliminate mosquitoes that have gained entry to a dwelling
- Bed nets are useful in preventing mosquito bites, while those that have been impregnated with insecticide are significantly more effective and can also kill mosquitoes, further reducing malaria risk. One insecticide treatment should last for a whole malaria season, unless the nets are repeatedly washed. Re-treatment kits, usually using a pyrethroid type

of insecticide are widely available but manufacturer's directions should be carefully followed, as the solution is toxic. Nets should not be damaged and must be tucked in under the mattress. In countries with intensive malaria transmission the use of insecticide treated nets (ITN's) have reduced malaria levels by almost 50%¹¹. Baby cots and prams may be covered with mosquito netting for protection against mosquitoes.

- Mosquito repellents containing DEET (N,N-diethyl-3-methylbenzamide), are especially useful for protection during outdoor activities. They should be applied to exposed skin surfaces and repeated after 4 – 6 hours according to the manufacturers' instructions. Repellents should not be sprayed on the face nor applied to lips or eyelids, and the dosage should not be exceeded especially for small children. In infants and young children, insect repellents should be applied to the skin sparingly for a number of reasons, including the relatively large body surface area compared to the body weight in this age group. The American Academy of Paediatrics recommends that insect repellents containing equal to or less than 10% of DEET be used for children¹². Citronella oil is the most effective and most commonly found plant extract. However, even in its pure form it is less active than DEET and it is also shorter acting than most DEET-based products. It must be reapplied every 40-90 minutes for continued efficacy^{13,14,15}.
- Long (preferably light coloured) clothing should be worn to minimize the amount of exposed skin.
- Ceiling fans and air conditioners are also effective in disturbing mosquito feeding.

Precautions that should be taken to minimise insecticide problems:

- Apply repellent sparingly to exposed skin or clothing⁹.
- Repeat applications at intervals according to the duration of action of the particular repellent¹³.
- Re-apply more frequently after bathing, showering, sweating, etc^{13,16}.
- Avoid contact with the eyes, mucous membranes and broken skin^{13,14}. Do not inhale or ingest⁹.
- Avoid applying high concentrations of the products to the skin, particularly in children⁹.
- Avoid applying repellents to the hands of young children, as these are likely to have contact with the eyes and mouth⁹.
- People who are prone to allergy should avoid using plant extracts¹³.
- People with sensitive skin should avoid lotions and gels. These often contain alcohol¹³.
- If a suspected reaction to insect-repellent occurs, wash treated skin and seek immediate medical attention⁹.
- DEET can opacify spectacles, binoculars and other plastics^{13,14}.
- STOP using DEET if a change in the individual's behaviour is noticed and obtain immediate medical advice¹³.
- Read the entire repellent label before use and use only as directed.
- Keep repellents out of the reach of children.

SUMMARY BOX 2; PERSONAL PROTECTION MEASURES

Avoiding mosquito bites is more important than using preventive drugs. Malaria vector mosquitoes feed between dusk and dawn both indoors and outdoors.

The following is advised:

- Remain indoors between dusk and dawn.
- Wear long sleeved clothing (preferably light coloured), long trousers and socks.
- Apply 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.
- Stay in well-constructed and well-maintained buildings in the best-developed part of town.
- Cover doorways and windows with screens, but if not available, windows and doors should be closed at night.
- Ceiling fans and air conditioners are very effective.
- Use a mosquito-proof bed net over the bed, with edges tucked in under the mattress. Ensure that the net is not torn and that there are no mosquitoes inside. Protection will be increased by periodically treating the net with an insecticide registered for this purpose, e.g. a pyrethroid.
- Spray inside the house with an aerosol insecticide (for flying insects) at dusk, especially the bedrooms, after closing the windows.
- 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.

Residents of malaria areas

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

- 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.
- Install gauze screens in front of outside doors and on windows of houses.
- Where standing water exists near habitations and cannot be drained, larvicides should be applied.
- Apply effective non-toxic long-acting insecticides onto the interior walls of houses.
- Personal measures to minimize the risk of mosquito bites should also be used by residents of malaria areas.

Use of antimalarial drugs for chemoprophylaxis

Is chemoprophylaxis necessary?

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

The decision as to whether chemoprophylaxis is necessary is subjective. It depends on the areas to be visited and the risk that the traveller has of being exposed to mosquitoes and of developing malaria. The greater the traveller's risk of contracting malaria and developing complications, the more likely it will be that chemoprophylaxis will be necessary.

Chemoprophylaxis is usually indicated for high-risk persons entering a malaria area. These include the elderly, babies and young children (< 5 years), pregnant women and immunocompromised individuals (e.g. those on long-term steroids, AIDS patients, those who have had a splenectomy, and patients receiving chemotherapy).

Chemoprophylaxis may refer to absolute prevention of infection (i.e. causal prophylaxis) or to suppression of parasitaemia and its symptoms (i.e. suppressive or clinical prophylaxis). Drugs, which act on the erythrocytic stages of the parasite (i.e. once the parasite has invaded the red blood cells) are known as blood schizonticides and are suppressive prophylactics. These medicines suppress the disease by destroying the asexual parasites but have no effect on the intrahepatic forms. Examples of blood schizonticides include chloroquine, mefloquine, quinine, halofantrine, pyrimethamine, sulphonamides and sulfones. 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 about 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 this is not enough to completely prevent malaria. The combination of proguanil and atovaquone (not yet registered in South Africa) may be classed as a causal prophylactic.

When deciding on the need for chemoprophylaxis, it must be remembered that all medicines have adverse effects and that the risk of developing a serious adverse effect must be weighed against the risk of developing malaria. No chemoprophylaxis is 100% effective. However, disease in those taking chemoprophylaxis is likely to be milder or less rapidly progressive even if the parasites exhibit a degree of drug resistance¹⁷. The most reliable way of preventing malaria is to avoid mosquito bites.

Choosing appropriate chemoprophylaxis

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.

- Pregnancy or planning a pregnancy shortly after the trip
- Breast-feeding
- Age
- Pre-existing medical conditions such as psoriasis, epilepsy, diabetes, renal impairment, cardiac complications or psychiatric problems
- Other medication being taken
- Activities requiring fine co-ordination and spatial discrimination, e.g. piloting, scuba-diving
- Length of visit to the area
The cumulative risk of contracting malaria is proportional to the length of stay in a malaria area. A visit of 3 months carries a risk six times greater than a 2-week visit¹⁷. Long-term safety of some chemoprophylactic drugs cannot be guaranteed
- The efficacy and risks of, and patient compliance with, the various regimens will also influence the choice of prophylaxis

See table 3 for a comparison of the benefits and risks of the various prophylactic regimens.

SUMMARY BOX 3 - RECOMMENDED PROPHYLACTIC REGIMENS

One of the following 3 regimes is currently recommended for use in South Africa:

- Mefloquine. (weekly). Start at least one week before entering a malaria area
- Doxycycline. (daily). Start one day before entering a malaria area.
- Chloroquine(weekly) PLUS proguanil (daily) Start at least one day before entering a malaria area, but preferably a week before.^{10,18}

These regimes must be taken for FOUR weeks after leaving the malaria area¹.

The following should be noted:-

- dosing schedules for children should be based on body weight;
- antimalarials (particularly doxycycline) should be taken with food and adequate fluids;
- all antimalarials should be started before entering a malaria area;
- **antimalarials should be taken with unfailing regularity for the duration of exposure and for a further four weeks after leaving the malaria area**, as exposure may be on the last day of travel, the incubation period may be variable and current chemoprophylactics are only effective once the parasites enter the red blood cells. Patients need to be well educated and motivated to ensure the highest possible level of compliance;
- antimalarials taken weekly must be taken on the same day each week;
- both mefloquine and doxycycline require a medical prescription for purchase, chloroquine and proguanil are available from pharmacies; and
- **there is no evidence to support use of homeopathic preparations for the prevention or treatment of malaria.**

Efficacy and adverse reactions of recommended prophylactic regimens

A high percentage of travellers who take malaria chemoprophylaxis will report side-effects, the majority of which are mild and self-limiting. In general, the incidence of mild to moderate and serious adverse events is similar for mefloquine and the combination of proguanil and chloroquine^{17,19,20,21}.

The rate of serious adverse reactions is in the order of 1:10 000 for both regimens. However, the types of adverse events differ. The combination of proguanil and chloroquine commonly causes gastrointestinal adverse events, and mefloquine appears to cause more disabling neuropsychiatric events. Travellers discontinue their drugs because of adverse events at a similar rate for all the recommended regimens¹⁷.

Mefloquine

Mefloquine is active against *P. falciparum* parasites that are resistant to chloroquine and sulfadoxine-pyrimethamine and the other three plasmodial species that affect humans⁸. Weekly dosing should encourage compliance. It is recommended for use for up to 12 months but has been safely used for more than 2 years²⁵.

Adverse effects associated with mefloquine include insomnia, strange dreams, mood changes, nausea, diarrhoea and headache. These would usually be experienced within the first three weeks of medication and do not become worse in subsequent weeks of use^{17,22,23,24,26}. If they are not experienced during the first use of mefloquine they are unlikely to appear during subsequent use for prophylaxis. Severe neuropsychiatric reactions (psychosis, convulsions) are infrequent with prophylactic doses and occur in approximately 1/10 000 to 1/13 000 persons²³. The frequency of mild neuropsychiatric effects is probably much higher²⁴. These effects may be sufficiently severe for the individual to discontinue prophylaxis. To forestall this event it is suggested that when mefloquine is to be taken for the first time that prophylaxis should commence three weeks before exposure to malaria to enable a change to be made timeously to another drug should side effects occur^{1,17}.

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

There is inadequate experience of the safety of mefloquine taken during the first three months of pregnancy. It should not be used during this time but in the event of a pregnancy, available safety data does not support termination^{27,28}. Taking mefloquine while breastfeeding is not recommended because of lack of data^{1,29}.

Mefloquine may cause spatial disorientation and lack of fine coordination and should not be used where fine coordination is required, e.g. for pilots, underwater diving^{1,29}.

Doxycycline

Doxycycline is effective against all four species of human malaria parasites and has comparable efficacy to mefloquine⁸.

This drug affects bone formation during early life and should not be given during pregnancy, breast-feeding and the first eight years of life. Adverse effects including gastrointestinal symptoms and candida infection of the gut and vagina and may be severe enough to discontinue prophylaxis. Severe skin sensitivity to sun burn may develop, excessive exposure should be avoided and the use of sunscreen preparations is advised. Other rare symptoms include dizziness, headache and blurred vision^{1,17,23}.

There is limited experience with long-term use of more than 4-6 months^{1,17,23}.

Chloroquine plus proguanil

This combination provides some protection against chloroquine resistant *P. falciparum* strains of malaria but there is inadequate information on its efficacy against South African strains. Chloroquine resistance is however widespread in Africa. It is currently the only alternative product registered when there are contraindications to the use of mefloquine and doxycycline, e.g. early pregnancy, breastfeeding and intolerance of their use.

Serious side effects are rare, but may occur with long-term use. Periodic eye examinations are recommended after five years of use¹. Mild reversible side effects include headache, gastrointestinal effects, skin rashes and mouth ulcers.

Potential alternative chemoprophylactic agents

Several new agents are being investigated, but at this stage none of them are registered for malaria prophylaxis in South Africa and therefore cannot be recommended for general use.

Atovaquone - proguanil

At present this drug is not registered for use in South Africa. In other countries it is supplied as 250mg atovaquone plus 100mg proguanil per adult tablet and 62.5 plus 25mg respectively per pediatric tablet.

It should be taken one day before exposure, continued daily during exposure and for seven days after the last exposure to malaria¹. Atovaquone-proguanil is a causal prophylactic and acts on the liver stage, hence the reason for the shorter regimen³⁰. This shortened regimen is expected to significantly improve compliance. Lack of safety data preclude its use during pregnancy, breast-feeding or for children under 11 kg and for long term use¹. There is presently a paucity of data regarding the use of atovaquone-proguanil in patients with co-morbid disease, but it should be used with caution in patients with renal failure. Side effects include gastrointestinal symptoms. As it is a relatively new antimalarial, efficacy data in non-immunes is limited. However, available data on efficacy would support its use for chemoprophylaxis.

Azithromycin:

Although azithromycin was well tolerated in a few small studies, its efficacy in preventing malaria is suboptimal. This, together with its high cost, makes it unlikely that azithromycin will be widely used for malaria prophylaxis³¹.

Primaquine:

Limited studies suggest that primaquine may be effective in the prevention of malaria. However, more data are needed before primaquine can be recommended for malaria prophylaxis. The need to test for G6PD deficiency before using primaquine as prophylaxis is also a significant limiting factor³².

Tafenoquine (WR 238605)

WR 238605 is a primaquine analogue that appears to be less toxic, more effective³¹ and has a much longer half-life than primaquine (14 days vs. 6 hours³⁴) which should make less frequent dosing possible. However, a G6PD-deficient subject developed significant haemolysis and thus G6PD testing would be necessary before administration of this drug³³.

Alternative no longer recommended in South Africa

Dapsone-pyrimethamine

This combination is still used in some parts of the world, for example, Zimbabwe, but in general its use is no longer recommended. There is widespread resistance to antifolate agents and it is also associated with a high incidence of agranulocytosis³⁵. Agranulocytosis has been reported in approximately 1 in 2000-5000 courses³⁶.

Patient-specific prescribing problems

- **People taking doxycycline for acne**

One of the many drugs used to manage acne is oral doxycycline. Doxycycline is recommended for prophylaxis in areas of mefloquine-resistant *falciparum* malaria and as an alternative drug for those travellers visiting high risk areas who are unable to take mefloquine¹⁷. 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 area¹.

A person who is already taking doxycycline for acne need only ensure that the daily dose of doxycycline is equivalent to that recommended for malaria chemoprophylaxis.

If a patient is on another tetracycline for acne, such as minocycline, an option is to replace it with doxycycline in the recommended doses for malaria chemoprophylaxis. There are insufficient data to support the use of

minocycline for malaria prophylaxis, and also possibly an increase in adverse reactions in the dose that would be required.

- **People with epilepsy**

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

Chloroquine:

The use of chloroquine for malaria prophylaxis in epileptic patients is controversial. There are some reports of chloroquine causing convulsions even in previously healthy patients. However, these are very rare and most of these cases were in patients given chloroquine in treatment doses^{37,38,39,40,41}.

Some authorities feel that chloroquine should not be taken for prophylaxis in patients with a history of epilepsy^{17,42,43}. Others suggest that patients with epilepsy should be warned that there may be a risk of seizure provocation.

Proguanil:

There have been no documented reports of seizures occurring in patients taking proguanil. In addition, there do not seem to be any interactions between proguanil and phenytoin, carbamazepine or phenobarbitone. Interactions between proguanil and the newer anti-epileptics such as lamotrigine, gabapentin, felbamate and vigabatrin are unknown or have not yet been documented.

Mefloquine:

Mefloquine is contra-indicated for malaria prophylaxis in patients with a history of convulsions²⁹. Several case reports of first-time seizures in patients taking mefloquine in prophylactic doses have been reported^{44,45}.

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

Doxycycline:

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

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

Recommendations:

Doxycycline is currently the best option for epileptics with the above proviso. There is currently insufficient data to support the use of atovaquone/proguanil in epileptic patients.

- **Prophylaxis during pregnancy**

Pregnant women should avoid travelling to malaria endemic areas¹. 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 death¹. Pregnant women are also more likely to suffer from severe malaria than non-pregnant women. This is especially true of the primigravida women. The mechanism is unclear but may be related to cellular immune function suppression, the greatest risk being spontaneous abortion⁴⁷.

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

Chloroquine plus proguanil:

The relative safety of both chloroquine and proguanil for use in malaria prophylaxis during pregnancy is well established^{17,42,45}. Even after more than 30 years of use, proguanil has not been associated with adverse effects on the mother or foetus. Proguanil is however a folate antagonist which may cause or accentuate anaemia in pregnancy. Therefore, folic acid supplementation (5mg/day) is recommended for pregnant persons taking proguanil as prophylaxis⁴⁵.

Although chloroquine is generally considered safe for malaria prophylaxis during pregnancy, some studies have shown a small increase in birth defects⁴⁸. Due to the severity of malaria in pregnancy, the benefits of chloroquine prophylaxis outweigh the risks of possible teratogenicity.

This combination is considerably less efficacious than doxycycline or mefloquine in areas where it has been tested where chloroquine resistance has been reported. Pregnant women who cannot avoid malaria areas should ideally have the most effective chemoprophylaxis available.

Mefloquine:

Although the use of mefloquine in pregnancy is contraindicated by the manufacturers, the international literature suggests that mefloquine may be considered for chemoprophylaxis in women in their second or third trimester of pregnancy when visiting high risk chloroquine-resistant *P. falciparum* areas. Cumulative evidence from clinical trials and reports of inadvertent use of mefloquine during pregnancy do not suggest an association with adverse foetal outcomes^{17,28,45}.

Mefloquine use in the second and third trimester has not been linked with increased congenital malformations^{26,45}. Recent literature also suggests that the use of mefloquine may be considered for chemoprophylaxis in women

during their first trimester of pregnancy when visiting very high risk chloroquine-resistant *P. falciparum* areas²³. Further studies are however needed due to concerns about a possible increase in the occurrence of spontaneous abortion after use in the first trimester²³.

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 discoloration⁴⁵. Inadvertent exposure to doxycycline during pregnancy may not necessarily warrant therapeutic abortion⁴⁷.

Recommendations:

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

- **Breastfeeding mothers**

Infants should not be taken to malarious areas, as they are at a significantly higher risk of developing severe malaria²⁸. If it is absolutely necessary for them to enter a malarious area then breast-fed as well as bottle-fed babies must receive the full recommended paediatric doses of appropriate antimalarials. The amount of antimalarial agent excreted into breast milk is insufficient to provide adequate protection against malaria in the infant⁴⁵.

Mefloquine:

Mefloquine is contraindicated in breastfeeding mothers by the manufacturers^{29,49}. Approximately 4% of a single 250mg mefloquine dose was 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^{48,50}. The levels reached in the infant are insufficient to provide adequate protection against malaria⁴⁸.

Doxycycline:

Doxycycline is excreted into breast milk in low concentrations and may have adverse effects on the breastfeeding infant⁴⁸. However, the American Academy of Paediatrics considers tetracycline to be compatible with breast feeding⁴⁸. The length of exposure to doxycycline in breast milk is a potential hazard to the infant.

Chloroquine-proguanil combination:

Proguanil is excreted into breast milk in insignificant amounts that are not harmful to the infant, but also do not provide adequate protection to the infant against malaria^{45,50}.

Studies analysing the amount of chloroquine excreted into breast milk are contradictory. There is a theoretical risk of chloroquine toxicity developing in infants if they are given the full recommended dose of chloroquine while being exclusively breastfed. However, no reports have been found in the literature substantiating this, and the risk of contracting malaria due to subtherapeutic chloroquine levels does not warrant decreasing the dose in breastfed infants.

Recommendations:

The preferred regimen for breastfeeding mothers travelling to chloroquine-resistant malarial areas is the chloroquine/proguanil combination. In addition, breast-fed babies should receive the full recommended paediatric doses of the appropriate antimalarials.

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

Mefloquine can cause dizziness, disturbed sense of balance and neuropsychiatric reactions during and up to three weeks after its use. Caution must therefore be exercised when driving and operating machines while taking this drug²⁹. The WHO recommends that piloting of aircraft and deep-sea diving should be avoided while taking mefloquine¹.

Although the latest studies do not seem to show significant effects of mefloquine on fine motor co-ordination, it seems prudent to exercise caution when used in persons operating machines, driving, deep-sea diving or flying²⁸. (The drug may cause sleep disturbances which, in the long term, may affect co-ordination).

Chloroquine may cause blurring of vision and dizziness in certain individuals who should then change to another drug²⁸.

Recommendation:

Depending on the risk of malaria in the specific area visited, doxycycline or the combination of chloroquine and proguanil may be considered as prophylactic options. If the combination is chosen, it is recommended to start chloroquine and proguanil two weeks before entering the malaria area to allow sufficient time to change to doxycycline if unacceptable side effects do occur.

- **People with psychiatric problems**

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

Mefloquine:

Mefloquine has been reported to cause serious neuropsychiatric symptoms in approximately 1 in 10 000 users. Symptoms can develop as early as the first

week of use and more than 75% of the adverse reactions are apparent by the third dose. In most cases symptoms resolved 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 cases⁵¹. Reported side effects include depression, anxiety, acute psychotic episodes, subtle mood changes, insomnia, strange dreams, and depersonalisation. Mefloquine is therefore contra-indicated in individuals with a present or prior history of any central nervous system (CNS) disorder²⁹.

Proguanil:

Proguanil has not been associated with adverse CNS effects. However, this agent is not used on its own as prophylaxis⁵¹.

Chloroquine:

Chloroquine has seldom been associated with serious psychiatric effects when used in prophylactic doses. Headache, nausea, dizziness, insomnia and depression have been reported infrequently. The combination of chloroquine with proguanil may be an option for the patient who does not have acutely neuropsychiatric problems provided that there are no drug interactions with his/her other medication.

Doxycycline:

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

Recommendation:

It appears that the use of doxycycline is the safest option for patients with psychiatric symptoms who require oral malaria prophylaxis⁵¹.

- **Malaria chemoprophylaxis in children**

Children are at special risk as they can become seriously ill with malaria very rapidly. Babies and young children under the age of five years should not be taken into malarious areas unless it is absolutely essential. Children must be protected against mosquito bites at all times and mosquito nets must be used to cover bedding. It is advisable to keep babies under mosquito nets as much as possible between dusk and dawn²⁸.

Chloroquine and proguanil can be safely given to babies and young children. The dose of the antimalarial drug is based on the age or weight of the child. To assist in the administration of proguanil the tablet may be crushed and mixed with jam, banana or similar foods²⁸.

Mefloquine can be used in children over 3 months of age or weighing over 5kg and the dose is based on the weight of the child^{29,45}.

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

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

When a child develops a febrile illness either whilst in a malaria area or after having left the area, medical help must be sought immediately. The symptoms of malaria in children may not be typical and therefore malaria should always be suspected. In infants, malaria should even be suspected in non-febrile illness²⁸.

- **Changing from one chemoprophylactic to another**

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

Patients changing from doxycycline to mefloquine or from doxycycline to the combination of chloroquine and proguanil, or vice versa, may do so without a washout period.

Patients changing from mefloquine to chloroquine and proguanil, or vice versa, should change to the new chemoprophylactic agent/s one week after stopping the unsuitable agent. Proguanil must be continued daily until mefloquine is started. At prophylactic doses additive toxicity is unlikely to occur if the new agent is taken when the next dose is due⁹.

- **People already on chloroquine therapy**

Chloroquine has many uses besides preventing and treating malaria. Other indications for which it is frequently used as an adjunct to other therapy include; rheumatoid arthritis, discoid lupus erythematosus and systemic lupus erythematosus⁵⁰.

For these indications patients are usually on daily doses of chloroquine and are therefore taking more than adequate doses of chloroquine should they wish to visit a malaria area. They should simply add the daily dose of proguanil. **Mefloquine should not be taken concurrently with chloroquine because of the danger of toxic cardiac or CNS reactions**⁵².

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

- **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 Centre for Disease Control (CDC), Atlanta, USA has recommended that mefloquine can be used for long-term malaria chemoprophylaxis⁵³. Mefloquine can be used for up to a year. Long-term use of mefloquine does not appear to be related to increased side effects.

The use of doxycycline for malaria chemoprophylaxis is limited to less than 4 months and it can therefore only be taken by individuals who will be exposed to malaria for short periods of time⁵³. Experience with doxycycline use for periods exceeding six months is limited^{1,17,23}.

Proguanil is the only drug that can be used safely for long-term prophylaxis exceeding 6 years. Chloroquine should be discontinued after a cumulative dose of 100g of base, an amount usually reached within 6 years⁵⁴.

Screening for retinal changes is indicated after five years use of chloroquine 300mg weekly.

There is limited data concerning long-term use of atovaquone-proguanil.

People who have grown up in an endemic malaria area and who may have developed immunity, will lose this immunity within a year or so of being out of the malaria area⁵². These individuals must take the necessary precautions when re-entering or visiting a malaria area.

- **The immunocompromised patient**

Immunocompromised patients (e.g. those on long-term steroids, AIDS patients, 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.

Whether splenectomised patients are at higher risk of infection and complications of malaria is not clear. Conflicting opinions are found in the literature^{47,55,56}.

If immunocompromised patients cannot avoid travel to malaria areas, the most effective chemoprophylaxis should be used and extremely strict non-drug measures should be followed. Drug interactions with concurrent medication should also be carefully considered.

TABLE 1: DRUG CHOICE ACCORDING TO PATIENT FACTORS. (SEE SECTION ABOVE FOR MORE DETAIL)

Patient factor	Mefloquine	Doxycycline	Chloroquine + proguanil
Pregnancy - Avoid travelling to a malaria area	Avoid during first trimester. Can be used from 4th month.	Contraindicated.	Regime of choice during the first trimester. Recommend folic acid supplementation (5mg/day).
Women of child-bearing potential or on oral contraceptives	Use reliable contraception during and for 3 months after taking last dose. Will not compromise contraceptive efficacy.	Avoid pregnancy during and for one week ¹ after taking last dose. May interact with oral contraceptive	No known problems or interactions, but contraception will be compromised if diarrhoea occurs.
Breastfeeding - Baby must be given its own prophylaxis	Insufficient data.	Avoid use.	Regime of choice.
Young children - Avoid taking children under the age of 5 years to a high risk area	Can be used in children over 3 months old or > 5 Kg. Generally well tolerated by children.	Use only in children > 8 years of age.	Safe to use, even in infants.
Epilepsy	Contraindicated. May also interact with valproic acid.	May interact with anticonvulsants, reducing the half-life of doxycycline & possibly resulting in prophylaxis failure.	Proguanil safe - chloroquine may cause seizures (rare).
Psychiatric conditions	Contraindicated, even if there is only a history of depression.	Can be used.	Can be used, but rare cases of psychosis have been reported.
Psoriasis	No documented problems - can be used.	Can be used.	May exacerbate psoriasis.
Porphyria	No reported problems, probably safe to use.	Avoid use.	Chloroquine - conflicting data - use with caution.
'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.	Consult expert opinion before using in severe renal impairment.
Hepatic impairment	Contraindicated in severe impairment	Administer with caution to hepatically impaired patients or those receiving hepatotoxic drugs.	Administer with caution to hepatically impaired patients or those receiving hepatotoxic drugs.
Individuals requiring fine motor co-ordination and spatial discrimination e.g. pilots	Do not use.	Regime of choice.	Can be used, although blurred vision and dizziness may rarely occur.
Patients with Myasthenia	Insufficient data - stop therapy if muscle	May aggravate symptoms of	Chloroquine may aggravate symptoms

gravis	weakness occurs.	myasthenia gravis.	
Persons requiring long-term therapy	Can be used for up to one year - data suggest safe for even longer use.	Experience of use for more than 4 - 6 months is limited.	Can be used, but must screen for retinal changes after 5 years of weekly chloroquine.
Persons on oral anticoagulants	Insufficient data - monitor INR. Start therapy in advance to monitor possibility of interaction.	May potentiate anticoagulant effect. Monitor INR.	Use proquanil with caution in people taking warfarin. Anticoagulant effect may be potentiated. Monitor INR.
Persons with G6PD deficiency	No problems documented - safe to use.	Safe to use.	Contraindicated - chloroquine may cause haemolysis.
Diabetics	Insufficient data - monitor blood glucose levels	May increase hypoglycaemic effect of insulins or anticoagulants - monitor blood glucose levels.	No reported 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, quinidine.	Regime of choice	Relatively safe, but cardiotoxicity may rarely occur due to chloroquine.

TABLE 2: INTERACTIONS BETWEEN MALARIA CHEMOPROPHYLAXIS AND OTHER DRUG TREATMENT

Antimalarial	Other drug	Comment
Mefloquine	Amiodarone	Both increase QT interval. Increased risk of torsade des pointes ⁵⁷ .
	Antipsychotics e.g. phenothiazines, pimozide	Increased risk of ventricular arrhythmias ⁵⁷ . Mefloquine should not be used in patients with a history of a psychiatric illness.
	Beta blockers e.g. atenolol, propranolol etc.	Potential for increased risk of electrocardiographic abnormalities, bradycardia and cardiac arrest ^{45,57} . 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 ⁵⁷ . However, CDC states that there is no evidence to justify precautions for concomitant mefloquine therapy in patients using calcium channel blocking agents.
	Chloroquine	Concurrent use may increase risk of seizures ^{45,58} and possibly cause additive cardiac toxicity ²⁸ . Avoid combination.
	Digoxin	Increased plasma levels of digoxin ⁵⁷ . 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 ^{28,57} .
	Oral typhoid vaccine	Inactivation of the immunization possible. Complete immunization 3 days before taking mefloquine ^{28,29,57}
	Primaquine	May increase the serum levels and side effects of mefloquine ⁵⁸ .
	Quinine or Quinidine	Quinine may inhibit the metabolism of mefloquine, thereby increasing mefloquine levels ⁵⁸ . The combination may also produce electrocardiographic abnormalities, cardiac arrest ⁴⁵ or could result in potentially serious cardiac conduction abnormalities ⁵³ . On the other hand, a small, limited study conducted in 13 adults with single doses of both drugs showed a lack of a clinically significant cardiovascular pharmacodynamic interaction ⁶⁰ . The combination may also increase the risk of seizures ^{45,57,58} . A loading dose of quinine should not be given if mefloquine has been used for prophylaxis in the preceding 24 hours ⁶¹ .
	Rabies vaccine, human diploid cell (HDCV)	Use intramuscular route; if intradermal HDCV must be used, mefloquine should not be given concomitantly. Where possible, rabies immunization should be given one to two months before starting malaria prophylaxis ⁴⁵ .
	Tricyclic antidepressants	Increased risk of ventricular arrhythmias ⁵⁷ . 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 ^{45,50,57,58} .
Chloroquine	Amiodarone	Increased risk of ventricular arrhythmias and the risk of torsade des pointes is high ⁵⁷ .
	Antacids and kaolin	Reduced chloroquine bioavailability; separate dosages by at least two to three hours ^{43,45,57,58} .
	Cholestyramine	Reduces chloroquine bioavailability ⁴⁵ and significantly lowers plasma chloroquine levels. Should not be taken together; separation of dosages by a few hours reduces the effect of this interaction ^{43,58} .
	Cimetidine	Reduces the metabolism of chloroquine, which may lead to chloroquine toxicity. Monitor for chloroquine toxicity and adjust dose accordingly or change medication ^{43,45,57,58} .
	Ciclosporin	Raised ciclosporin levels. Monitor the effects of adding chloroquine ^{45,57,58} .
	Dapsone and primaquine	May lead to rise in methaemoglobin in patients predisposed to methaemoglobinaemia (e.g. G6PD Deficiency) ⁴³ .
	Digoxin	Possible increase in digoxin level ⁵⁷ . Monitor levels.
	Halofantrine	Increased risk of cardiac arrhythmias ^{57,58} . Avoid combination.
	Neostigmine / Pyridostigmine	Antagonises the effects of these drugs by increasing the neuromuscular symptoms of myasthenia gravis ⁵⁷ .
	Phenothiazines e.g. chlorpromazine	Potentiates the induction of reversible, acute neurological symptoms such as dyskinesia ^{43,58} .
	Praziquantel	Decrease in bioavailability of praziquantel which may result in a reduction of its anti-schistosomal effects ⁵⁸ . (This is poorly documented)
	Proguanil	Increases incidence of mouth ulcers ^{45,58} .
	Rabies vaccine, human diploid cell (HDCV)	Chloroquine decreases the antibody response to the vaccine when given intradermally. Where possible rabies immunization should be given one to two months before starting malaria prophylaxis ^{45,57} . If HDCV is given intramuscularly, chloroquine may be given concurrently ⁴⁵ .
	Ritonavir	May increase chloroquine serum levels. Monitor patients for signs of toxicity and reduce dose if needed ⁴⁵ .
	Succinylcholine	Chloroquine may enhance the neuromuscular blockade of succinylcholine ⁴⁵ .
Doxycycline	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 ⁵⁸ .

	Antacids containing: calcium, bismuth, aluminium and magnesium	Reduces the absorption and serum concentrations of doxycycline significantly, compromising therapeutic efficacy. If possible use alternative therapy, or administer doxycycline at least 2 hours before, or 4 to 6 hours after antacids ^{45,58} .
	Carbamazepine, barbiturates and phenytoin	Reduce the plasma half-life of doxycycline by approximately 50% and may result in a reduction of efficacy ^{45,57,58} . (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 3 hours before or 2 hours after the doxycycline dose ^{45,58} .
	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 ⁴⁵ .
	Isotretinoin	An increased incidence of pseudotumour cerebri has been reported in patients on other tetracyclines. It is unknown whether doxycycline is also potentially problematic ⁴⁵ .
	Milk and dairy products	Absorption of doxycycline may be reduced by up to 30% because of the calcium ions found in milk. Avoid for at least 1 hour before or 2 hours after taking doxycycline. The small amounts of milk used in coffee and tea appear not to matter ^{45,58} .
	Oral contraceptives	May reduce efficacy of contraceptives ⁵⁶ . (See Contraception Section)
	Rifampicin	Increased doxycycline clearance. Potential loss of doxycycline efficacy. Monitor patient response ⁴⁵ .
	Warfarin	Potential of anticoagulant effect possible, monitor INR.
Proguanil	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 ³ .
	Magnesium trisilicate	Reduces absorption of proguanil. Separate doses as much as possible. (2-3 hours) ⁵⁸
	Warfarin	May potentiate effect of warfarin, monitor INR ⁵⁷ .
Atovaquone - proguanil	All above proguanil interactions	
	Rifampicin, rifabutin	Atovaquone plasma levels reduced, resulting in therapeutic failure ¹ .
	Tetracyclines	Atovaquone plasma levels reduced, resulting in therapeutic failure ¹ .
	Metoclopramide	Atovaquone plasma levels reduced, resulting in therapeutic failure ¹ .

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

SEMI-IMMUNITY

Individuals ("semi-immunes"), who have been repeatedly infected with malaria, may develop a degree of 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. However, intensity of malaria transmission and the duration of the malaria season in South Africa is insufficient for the development of "semi immunity".

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. Ideally, a trial test should be performed by the traveller under supervision prior to departure, as experience has shown that the test is frequently incorrectly performed and reliable results may not be obtained.

Self-treatment is an interim measure and may be life-saving, but medical attention should be sought as soon as possible. The choice of medication for self-treatment of malaria is a difficult one. The drug 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 fat (e.g. milk) to ensure adequate absorption.

Prophylaxis should be restarted seven days after treatment has been completed¹.

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

	Mefloquine	Doxycycline	Chloroquine Plus Proguanil
Prophylactic Efficacy	Highly effective in areas where it has been tested. Considered the drug of choice for travellers to	Highly effective in areas where it has been tested. Useful for prophylaxis in	Considerably less effective than doxycycline or mefloquine in areas where it has been tested where

	high-risk regions such as sub-Saharan Africa and Papua New Guinea Some studies have suggested limited activity against <i>P.vivax</i> and <i>P.ovale</i> .	areas of mefloquine-resistant <i>falciparum</i> malaria and for persons visiting high-risk areas unable to take mefloquine.	chloroquine resistance has been reported.
Most common Side effects	Nausea, strange dreams, dizziness, mood changes, insomnia, headache and diarrhea.	Skin photosensitivity (3% in one study), oesophageal ulceration, gastrointestinal symptoms, candida superinfection of the gut and vagina.	Gastrointestinal intolerance, oral aphthous ulceration.
Contraindications	Current or history of epilepsy or psychiatric illness, including depression. Past severe reactions to mefloquine. Underlying cardiac conduction disturbance or arrhythmia. Concurrent use of halofantrine (and other cardiotoxic drugs). First trimester of pregnancy. Infants <5kg.	Pregnancy. Lactation. Children under 8 years of age. Concurrent use of oral contraceptive. Must use barrier methods.	History of convulsions (relative contraindication). Some populations, especially in Asia, do not metabolise proguanil to its active form.
Special precautions	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.	
Dosage interval	Once weekly.	Daily dose.	Chloroquine weekly and proguanil daily.
Time period needed before entering malaria area	General recommendation: one week; for first time use: two and a half to three weeks*.	24 – 48 hours.	At least 24 hours, but preferably a week.
Resistance	Resistance appears to be rare - mainly SE Asia.	Resistance appears to be rare.	Resistance appears to be widespread.

* 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.

DIAGNOSIS

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 be an early and serious consideration for any patient with fever who has travelled to, or lives in, a malaria area, even if chemoprophylaxis has been taken.

Confirmation of malaria as a cause of illness is made by the examination of blood for parasites, either by blood smear or a rapid malaria test. A negative blood test or rapid malaria test does not exclude the presence of malaria, repeat tests should be made and if doubt remains, particularly in the case of severe illness, treatment for malaria should be given.

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

The advantages of rapid tests are that:

- They are highly sensitive
- Give rapid results
- Are relatively simple to use in a primary health setting

These tests do however have some limitations:

- They cannot be used to determine severity of infection, as they do not measure parasite load.
- They cannot be used to monitor progress of treatment or to confirm eradication of parasites, as they may stay positive for some time after successful treatment.

SIGNS AND SYMPTOMS OF MALARIA

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

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

- Fever – this is very common, but may be absent in some cases.
- Rigors
- Headache
- Sweating
- Fatigue

- Myalgia (back and limbs)
- Abdominal pain
- Diarrhoea
- Loss of appetite
- Nausea and vomiting
- Cough

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

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

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. Malaria should be suspected in any person presenting with any of the above symptoms 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.

Pregnant women, young children, 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.

TABLE 4: DOSES OF ANTIMALARIAL DRUGS FOR USE AS PROPHYLAXIS

RECOMMENDED DRUG	ADULTS	CHILDREN										
Mefloquine	(1 tablet = 250 mg mefloquine) 250mg (1 tablet) every 7 days, starting 1 week before entering the area, once weekly while in the area, and once weekly for 4 weeks after leaving the area. Restrict use to 1 year.	Not recommended for children who are less than 3 months old or who weigh less than 5kg. <table> <tr> <td>Weight (kg)</td> <td>Dosage</td> </tr> <tr> <td>5 - 20</td> <td>¼ tablet</td> </tr> <tr> <td>21 - 30</td> <td>½ tablet</td> </tr> <tr> <td>31 - 45</td> <td>¾ tablet</td> </tr> <tr> <td>>45</td> <td>Adult dose</td> </tr> </table>	Weight (kg)	Dosage	5 - 20	¼ tablet	21 - 30	½ tablet	31 - 45	¾ tablet	>45	Adult dose
Weight (kg)	Dosage											
5 - 20	¼ tablet											
21 - 30	½ tablet											
31 - 45	¾ tablet											
>45	Adult dose											
OR												
Doxycycline	(1 tablet = 100mg doxycycline) (1 capsule = 50mg , 100 mg or 200 mg doxycycline) 100mg once daily starting one day before entering the area, continuing daily while in the area, and daily for 4 weeks after leaving the area. Not to be used for longer than 4-6 months.	Contraindicated in children under 8 years. 2mg/kg of body weight at the same intervals as for adults. <table> <tr> <td>Age (years)</td> <td>Weight (kg)</td> <td>Dosage</td> </tr> <tr> <td>8 - 15</td> <td>31- 45</td> <td>2 mg/kg</td> </tr> <tr> <td>>15</td> <td>>45</td> <td>Adult dose</td> </tr> </table>	Age (years)	Weight (kg)	Dosage	8 - 15	31- 45	2 mg/kg	>15	>45	Adult dose	
Age (years)	Weight (kg)	Dosage										
8 - 15	31- 45	2 mg/kg										
>15	>45	Adult dose										
OR												

<p>Chloroquine</p>	<p>(1 tablet = 150 mg chloroquine base)</p> <p>300mg base (2 tablets) once every 7 days, starting at least one day before entering the area, but preferable one week before, once weekly while in the area, and once weekly for 4 weeks after leaving the area.</p>	<p>5 mg/kg of body weight taken at the same intervals as for adults.</p> <table border="0"> <tr> <td>Age (year)</td> <td>Weight (kg)</td> <td>Dosage</td> </tr> <tr> <td><1</td> <td><10</td> <td>¼-½ tab</td> </tr> <tr> <td>1-4</td> <td>10-19</td> <td>½ tablet</td> </tr> <tr> <td>5-8</td> <td>20-30</td> <td>1 tablet</td> </tr> <tr> <td>9-15</td> <td>31-45</td> <td>1½ tablets</td> </tr> <tr> <td>>15</td> <td>> 45</td> <td>Adult dose</td> </tr> </table> <p>Two strengths of chloroquine syrup are available for children (37,5 mg chloroquine base per 5 ml and 50mg chloroquine base per 5 ml). The dose is 5 mg/kg to be taken at the same intervals as for adults. See package insert for dosages.</p>	Age (year)	Weight (kg)	Dosage	<1	<10	¼-½ tab	1-4	10-19	½ tablet	5-8	20-30	1 tablet	9-15	31-45	1½ tablets	>15	> 45	Adult dose
Age (year)	Weight (kg)	Dosage																		
<1	<10	¼-½ tab																		
1-4	10-19	½ tablet																		
5-8	20-30	1 tablet																		
9-15	31-45	1½ tablets																		
>15	> 45	Adult dose																		
<p>PLUS</p> <p>Proguanil</p>	<p>(1 tablet = 100mg proguanil)</p> <p>200mg (2 tablets) daily starting 1 day before entering the area, continuing daily while in the area and daily for 4 weeks after leaving the area.</p>	<p>3mg/kg of body weight at the same intervals as for adults</p> <table border="0"> <tr> <td>Age (years)</td> <td>Weight (kg)</td> <td>Dosage</td> </tr> <tr> <td><1</td> <td><10</td> <td>¼ tablet</td> </tr> <tr> <td>1-4</td> <td>0-19</td> <td>½ tablet</td> </tr> <tr> <td>5-8</td> <td>20-30</td> <td>1 tablet</td> </tr> <tr> <td>9-15</td> <td>31-45</td> <td>1½ tablets</td> </tr> <tr> <td>>15</td> <td>>45</td> <td>Adult dose</td> </tr> </table>	Age (years)	Weight (kg)	Dosage	<1	<10	¼ tablet	1-4	0-19	½ tablet	5-8	20-30	1 tablet	9-15	31-45	1½ tablets	>15	>45	Adult dose
Age (years)	Weight (kg)	Dosage																		
<1	<10	¼ tablet																		
1-4	0-19	½ tablet																		
5-8	20-30	1 tablet																		
9-15	31-45	1½ tablets																		
>15	>45	Adult dose																		
<p>Atovaquone – proguanil not yet registered in South Africa</p>	<p>1 adult tablet = 250mg atovaquone plus 100mg proguanil.</p> <p>It should be taken 1 day before exposure, continued daily during exposure and for 7 days after the last exposure to malaria.</p>	<p>1 paediatric tablet = 62.5 atovaquone plus 25mg proguanil</p> <table border="0"> <tr> <td>11 – 20kg</td> <td>1 paediatric tablet daily</td> </tr> <tr> <td>21 – 30kg</td> <td>2 paediatric tablet daily</td> </tr> <tr> <td>31 – 40kg</td> <td>3 paediatric tablet daily</td> </tr> <tr> <td>> 40kg</td> <td>1 adult tablet daily</td> </tr> </table>	11 – 20kg	1 paediatric tablet daily	21 – 30kg	2 paediatric tablet daily	31 – 40kg	3 paediatric tablet daily	> 40kg	1 adult tablet daily										
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21 – 30kg	2 paediatric tablet daily																			
31 – 40kg	3 paediatric tablet daily																			
> 40kg	1 adult tablet daily																			
<p>STANDBY THERAPY</p>																				
<p>Artemether-lumefantrine</p> <p>1 tablet contains artemether 20mg plus lumefantrine 120mg.</p>	<p>10 - <15kg: One tablet stat, followed by one after 8 hours and then one twice daily on each of the following two days (total course = 6 tablets)</p> <p>15 - <25kg: Two tablets stat, followed by two after 8 hours and then two twice daily on each of the following two days (total course = 12 tablets)</p> <p>25 - <35kg: Three tablets stat, followed by three after 8 hours and then three twice daily on each of the following two days (total course = 18 tablets)</p> <p>35 - <65kg: Four tablets stat, followed by four after 8 hours and then four twice daily on each of the following two days (total course = 24 tablets)</p> <p>≥ 65kg: Dose as for > 35kg above, although inadequate experience in this weight group</p> <p><i>Administer with fat containing food / milk to ensure adequate absorption.</i></p>																			

SUMMARY

Awareness – Be aware of malaria risk

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

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

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

Chemoprophylaxis – take appropriate chemoprophylaxis. Compliance is most important.

One of 3 regimes currently recommended:

- Mefloquine. (weekly) Start at least one week before entering a malaria area
- Doxycycline. (daily). Start one day before entering a malaria area.
- Chloroquine (weekly) PLUS proguanil (daily). Start at least one day before entering malaria area, but preferably a week before. (Use when mefloquine and doxycycline are not suitable)

These regimes must be taken for FOUR weeks after leaving the malaria area.

Choice of regime depends on patient factors.

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

Diagnosis – early diagnosis is critical to survival.

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

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

Effective treatment.

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

MALARIA INFORMATION SHEET

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

Prevention is better than cure!

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

Measures to avoid mosquito bites.

- 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.

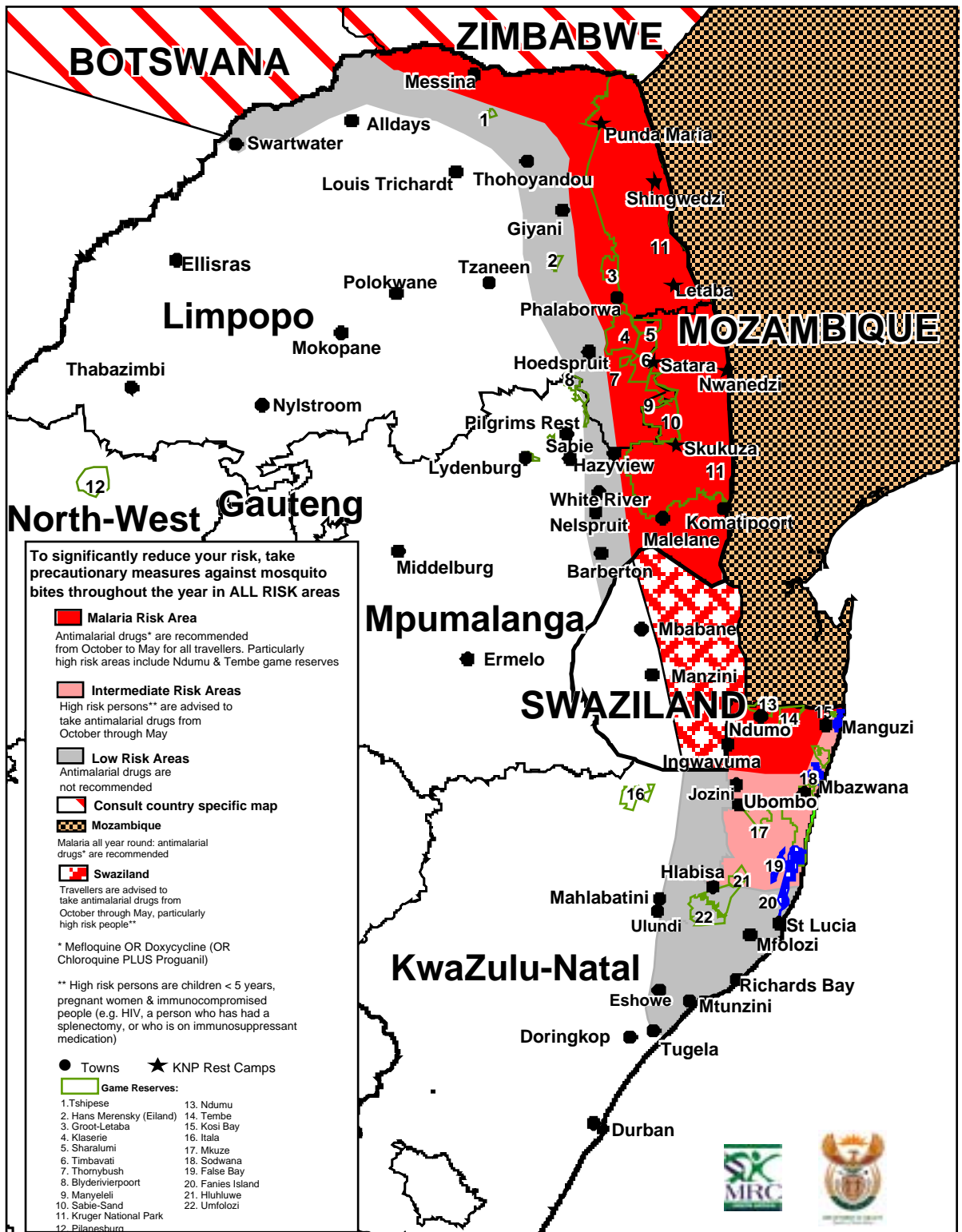
- Take only the medicines recommended by a health professional.
- Start before entering the malaria risk area.
- Take the medicine at the same time every day (or week, for weekly medication) with plenty of water, after a meal.
- Continue while in the malaria area and for 4 weeks after leaving the area.

Early symptoms of malaria.

- Fever
- Headache
- Chills
- Muscular pain

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

MAP OF MALARIA AREAS IN SOUTH AFRICA



PROPHYLAXIS MASKS THE SYMPTOMS - THE MYTH

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

The drugs that are currently available in South Africa for prophylaxis of malaria (called suppressive prophylactics) **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, an incomplete course or drugs taken irregularly), 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. ***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 the new and sensitive antigen-assay 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^{6,62}.

LIST OF ANTIMALARIALS AND TRADE NAMES

Generic name	Trade name	Schedule	Indication	Manufacturer
Artemether-lumefantrine	Coartem® tabs	S4	Treatment	Novartis
Atovaquone-proguanil	Malarone®	Section 21	Prophylaxis	GlaxoSmithKline
Chloroquine sulphate	Daramal® tabs Mirquin® syr Nivaquine® tabs Plasmoquine® caps	S1 & S4 S1 & S4 S1 & S4 S1 & S4	Prophylaxis & treatment	GlaxoSmithKline Aventis Mirren Medchem
Chloroquine phosphate	Rolab chloroquine phosphate® tabs	S1 & S4	Prophylaxis & treatment	Rolab
Dapsone-pyrimethamine	Maloprim® tabs	Not available	Prophylaxis	GlaxoSmithKline
Doxycycline hyclate	Doxitab® tabs Randoclin® tabs Vibramycin® caps	S4 S4 S4	Prophylaxis	Pfizer Medpro Ranbaxy
Doxycycline hydrochloride	Doximal® tabs Doxycyl® caps Dumocin® caps	S4 S4 S4	Prophylaxis	Cipla Medpro Aspen Pharmacare Aspen Pharmacare
Halofantrine hydrochloride	Halfan® tabs & susp	S4	Treatment	GlaxoSmithKline
Mefloquine hydrochloride	Lariam® tabs Mefliam® tabs	S4 S4	Prophylaxis Prophylaxis	Roche Products Cipla Medpro
Primaquine phosphate	Primaquine® tabs	Section 21	Treatment	Sanofi-Synthelabo
Proguanil	Paludrine® tabs	S1	Prophylaxis	AstraZeneca
Quinine dihydrochloride	Adco-quinine dihydrochloride®inj	S4	Treatment	Adcock Ingram Pharmaceuticals
Quinine sulphate	Lennon-quinine sulphate® tabs	S4	Treatment	Aspen Pharmacare
Sulfadoxine-pyrimethamine	Fansidar® tabs	S4	Treatment	Roche Products

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