The 'where, when and who' of preventing malaria in travellers

The ABC of malaria prevention in travellers.

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Malaria is a common and potentially severe disease that is endemic in more than 100 countries worldwide. It is estimated that more than 125 million international travellers visit these countries every year, many of whom fall ill with malaria while in these countries and more than 10 000 fall ill on returning home.[1] It is said that more than 3 million South African residents travel to malaria areas each year and are at risk of contracting malaria.[2]

Travellers to malaria areas are at higher risk of malaria complications as they have no immunity. In endemic areas, 1% of patients with untreated *Plasmodium falciparum* die from malaria, but the mortality is much higher in non-immune travellers.[1]

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Most cases of falciparum malaria in travellers occur as a result of their failing to take adequate precautions to prevent mosquitoes from biting, or because they take inadequate or no prophylaxis. Inadequate prophylaxis may be as a result of poor adherence or use of inappropriate medicines. A number of studies have substantiated this fact:

- The prophylactic profiles of British travellers to The Gambia over a 3-month period (Nov 2005 - Jan 2006) who contracted malaria were evaluated. A full 50% had taken no prophylaxis while the other 50% had taken inadequate prophylaxis.[3]
- Several malaria-related deaths among US citizens who had travelled abroad were attributed to incorrect prophylaxis.[4]
- In a South African study of 211 patients presenting to a private hospital group with malaria in 2000, 80% had not taken any prophylactic medicines and of the 20% who had taken medicines, 75% had not taken that medicine correctly.[5]

When looking at preventive strategies there are 4 main aspects to be considered – generally known as the ABC of malaria prevention:

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.

A – be **A**ware of the risk

B – prevent mosquito **B**ites

C – take appropriate **C**hemoprophylaxis if required

D – early **D**iagnosis can be life-saving.

Assessing the risk

In order to determine the risk of malaria for a traveller, one first needs to have an understanding of the infection itself.

Malaria is an acute febrile illness with an incubation period of at least 7 days, that is caused, in humans, by four main species of the protozoan parasite *Plasmodium: P. falciparum, P. vivax, P. ovale* and *P. malaria*, of which *P. falciparum* is the most severe and is associated with high morbidity and mortality. *P. falciparum* is responsible for over 90% of cases of malaria in sub-Saharan Africa and this article will therefore focus on this form of malaria.

These parasites are transmitted to humans by the bite of the female *Anopheles* mosquito, which is most active between dusk and dawn.[1] Once the infected mosquito has bitten the human, the sporozoites are taken up by the liver, where they enter the liver cells and develop into schizonts. This takes approximately 7 days. Thereafter these schizonts rupture, releasing merozoites into the blood stream, which then infect red blood cells. Once in the red cell, the parasites grow and multiply, causing the cell to burst. This is when the symptoms of malaria occur. Some of the parasites in the blood cells form sexual stages, gametocytes, which are taken up by a biting female mosquito to complete the cycle.[6]

The optimum climatic conditions for transmission of malaria are high humidity and an ambient temperature of 20 - 30°C. Malaria

transmission does not occur in regions with temperatures below the 16°C isotherm and parasite maturation in the mosquito does not occur at altitudes greater than 2 000 metres above sea level.[6]

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Where?

Taking the above information into consideration, the area being visited should be assessed for the risk of contracting malaria. Fig. 1 illustrates the distribution of malaria risk in South Africa. Several maps are available that indicate the malaria risk areas globally, including:

- http://wwwn.cdc.gov/travel/destinationList.aspx
- http://www.who.int/ith/countries/en/index.html

The prevalence of malaria is generally higher in rural areas than in urban areas, especially in Africa, where it is reported that the intensity of transmission is about 8 times higher in rural villages than in towns.[6] For example, Kenya is considered to be a country with a high risk of malaria transmission, but the risk in Nairobi itself and in the highlands is low.[1]

The type of accommodation also plays an important role. The risk is far less in air-conditioned hotels, and the use of impregnated bed nets further lowers the malaria risk.

When?

Although malaria is endemic in some countries with a high risk all year round, there are other areas that have seasonal

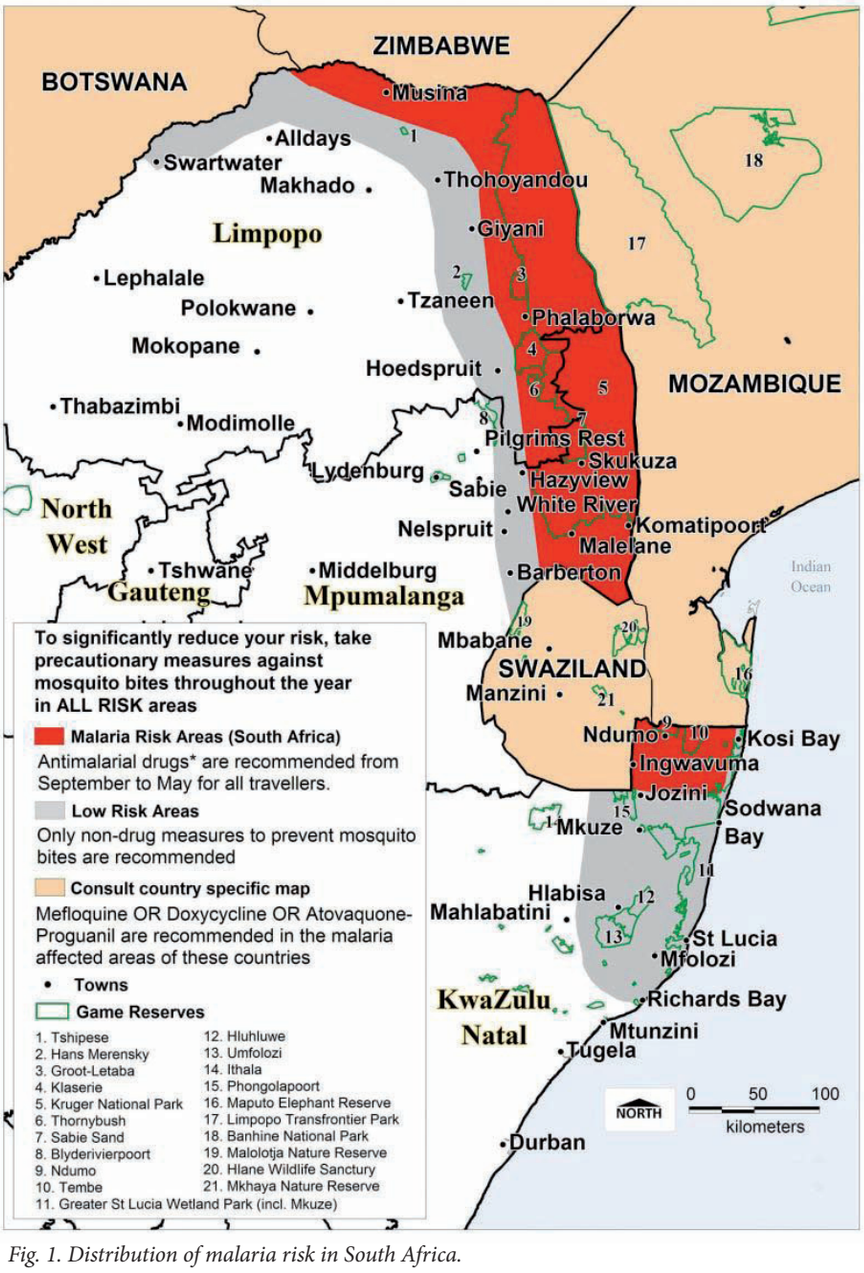

Fig. 1. Distribution of malaria risk in South Africa.

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risk, with the highest risk during the hot wet months. 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, so that the risk of malaria is now low and seasonal. Malaria transmission in South Africa is limited to the north-eastern parts of Limpopo, Mpumalanga and KwaZulu-Natal (Fig. 1), with the malaria risk season being from September to May.

The length of stay in the area is also important – the longer the stay, the higher the risk. This risk is only significant if travel includes an overnight stay in the area (as transmission occurs between dusk and dawn). A day trip to the Kruger National Park, for instance, with an overnight stay in Pilgrim's Rest (which is a very low-risk area), does not warrant taking malaria chemoprophylaxis, although measures to avoid mosquito bites are advised.

Preventing mosquito bites

No chemoprophylaxis is considered to be 100% effective, and measures to prevent being bitten by mosquitoes should be considered the mainstay of malaria prevention. These measures include:

- Applying a DEET (N,N-diethyl-3-methyl-benzamide)-containing insect repellent to exposed skin. Avoid eyelids, lips, sunburnt or damaged skin and do not spray on the face (see note).
- Remaining indoors between dusk and dawn.
- Wearing long-sleeved clothing, long trousers and socks.
- Using insecticide-treated bed nets over the bed, with edges tucked in. Ensure that the net is not torn and that there are no mosquitoes inside. Long-lasting insecticide-treated nets are preferable because they do not require re-impregnation with insecticide every few months, as their insecticide lasts for up to 5 years.

Even the most effective antimalarial will only work if it is taken properly.

- Covering doorways and windows with screens. If these are not available, windows and doors should be closed at night.
- Spraying inside the house (especially the bedrooms) with an aerosol insecticide (for flying insects) at dusk.
- Using mosquito mats, or burning mosquito coils in living and sleeping areas during the night.
- Ceiling fans and air conditioners are also very effective at reducing the risk of mosquito bites.

A note on insect repellents

The American Academy of Paediatrics has recently amended its recommendations and now advocates that DEET-containing insect repellents used for children should contain 30% of the active ingredient, should be applied sparingly and should not be used for children under the age of 2 months.[8] Citronella oil is the most effective and most commonly found plant extract; however, even in its pure form, it is less active than DEET. It is also shorter acting than DEET-based products, so must be reapplied every 40 - 90 minutes for continued efficacy.[7]

Chemoprophylaxis

The choice of chemoprophylaxis is determined in part by local antimalarial drug resistance patterns. Because of this, it is necessary to continually update recommendations for chemoprophylaxis and treatment of malaria. Antimalarial resistance, particularly to chloroquine, has become so widespread that chloroquine is no longer recommended alone or in combination with proguanil for almost all malaria areas.

Who?

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. Patient factors, including co-morbid disease, drug interactions and activities, play a role in determining which prophylaxis is best suited for the individual traveller. Because of these varying factors, it is no longer possible to offer blanket recommendations and each situation must be considered individually.

Certain categories of people are considered to be at a higher risk of developing severe malaria, and should preferably avoid malaria areas. If this is not possible, these people should take meticulous personal protection measures against mosquito bites and take the most effective prophylaxis. Such high-risk groups include:

- pregnant women
- young children (<5 years of age)
- immunocompromised individuals, e.g. patients living with HIV and AIDS, those who have had a splenectomy, and patients receiving long-term steroids or chemotherapy.

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

Chemoprophylaxis can either be causal or suppressive. Causal prophylaxis is directed against the liver stage of the malaria parasite, which takes approximately 7 days to develop. Drugs acting at this site, known as 'tissue schizonticides', prevent the infection and only need to be taken for 7 days after leaving the area (e.g. atovaquone-proguanil). Suppressive prophylaxis by drugs known as blood schizonticides is directed at the red blood cell stage, which only occurs later on in the cycle. These drugs need to be taken for 4 weeks after leaving the area in order to be effective prophylaxis (e.g. mefloquine and doxycycline).[6]

Mefloquine, atovaquone-proguanil or doxycycline are currently the preferred prophylactic agents, and should be prescribed as follows:

- **Mefloquine** (e.g Lariam, Mefliam): Take weekly. Start at least 1 week before entering a malaria area, take weekly while there and for 4 weeks after leaving the malaria area.[1]
- **Doxycycline** (e.g. Cyclidox, Doximal, Doxyhexal). Take daily. Start 1 day before entering a malaria area, take daily while there and for 4 weeks after leaving the malaria area.
- **Atovaquone-proguanil** (Malanil). Take daily. Start 1 - 2 days before entering malaria area, take daily while there and for 7 days after leaving the area.

There is no scientific evidence to support use of complementary, alternative and homeopathic preparations for the prevention of malaria.[6]

In terms of protective efficacy, mefloquine, doxycycline and atovaquone-proguanil are considered similar (around 90%), although the best-quality evidence is available for mefloquine.[9]

- **Mefloquine** is the most thoroughly documented option for long-term prophylaxis and is therefore the best option for those requiring prophylaxis for more than 6 months, if tolerated.[10]
- **Doxycycline** is recommended for prophylaxis in areas of mefloquine-resistant *P. falciparum* malaria and as an alternative drug for those travellers visiting high-risk areas who are unable to take mefloquine.
- **Atovaquone-proguanil** has a favourable safety profile and is considered preferable for the short-term traveller who can afford its substantially higher cost, because the shorter duration of prophylaxis needed after leaving a malaria area is likely to lead to improved adherence.[10]

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All 3 options require a prescription and the prescribing doctor will have to take all the above factors into consideration when choosing the appropriate option. Table I gives some guidance for making this selection.

Even the most effective antimalarial will only work if it is taken properly. To ensure safe and effective use, the following should be adhered to:

- Dosing schedules for children should be based on body weight.
- Antimalarials (particularly doxycycline and atovaquone-proguanil) should be taken with food and adequate fluids.
- All antimalarials should be started before

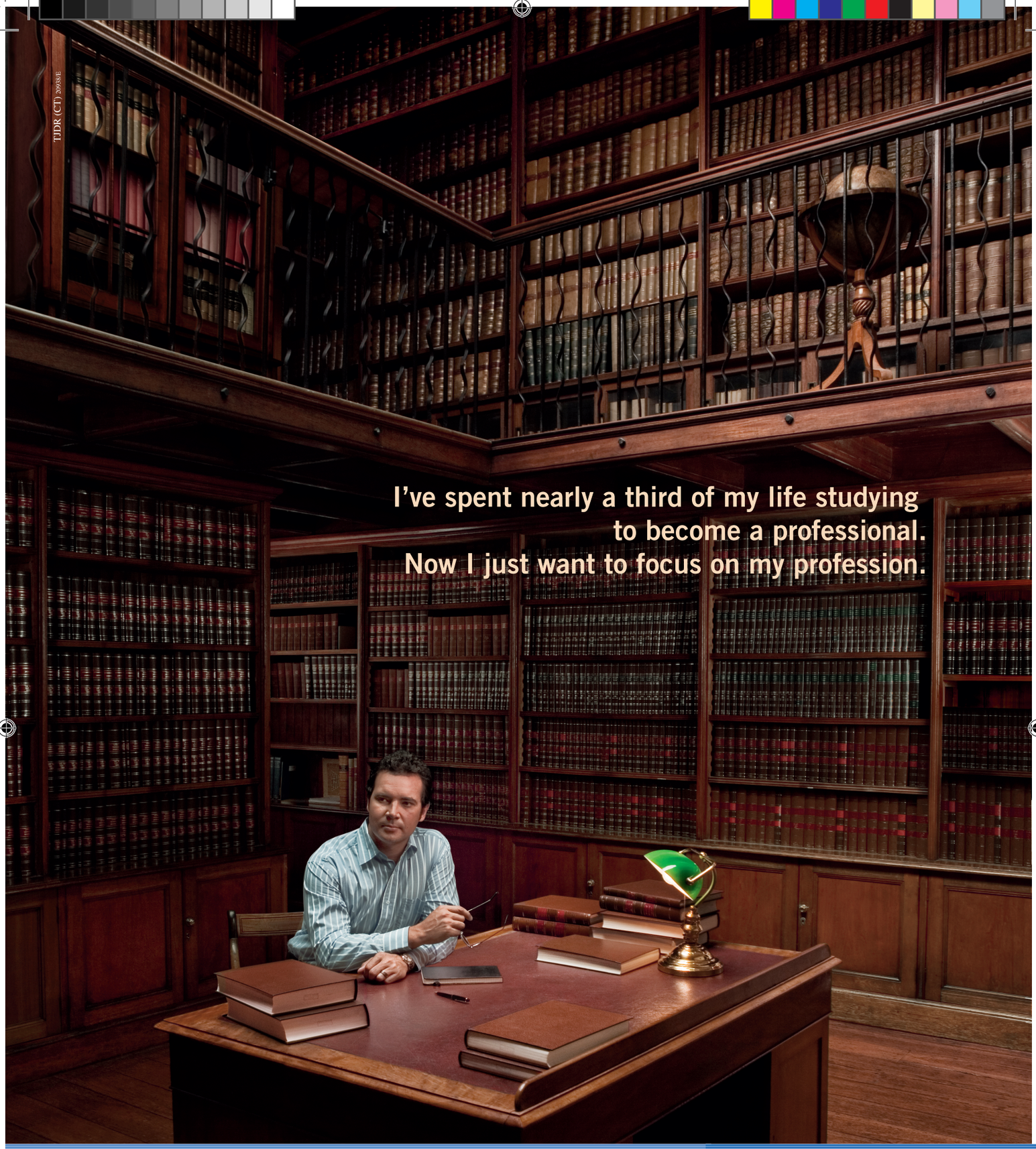

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Table I. Choosing the appropriate chemoprophylaxis

Factor	Mefloquine	Doxycycline	Atovaquone-proguanil
Malaria risk area	Resistance in some areas of SE Asia	Recommended for all areas	Recommended for all areas
Length of time	Best evidence for long-term use. Has been used safely for 3 years[6]	Has been used safely for up to 2 years[6]	Best used for short-term travel, but no evidence of harm from long-term use[6]
Children	Use from 3 months of age (>5 kg)[1]	Contraindicated in children <8 years of age[7]	Not to be used in children weighing <40 kg*
Pregnant women (should preferably avoid travel to malaria areas)	Recommended by the WHO from the second trimester[11]	Contraindicated	Contraindicated because of lack of data[6]
Concurrent medication	See article on drug interactions		
Other contraindications	Depression, epilepsy, neuropsychiatric illness, or any history thereof	Breastfeeding	Breastfeeding, severe renal impairment (creatinine clearance of <30 ml/min)[9,12]
Dosage interval	Once weekly	Daily dose	Daily dose
Time needed before entering malaria area	At least 1 week; for first-time use: 2 - 3 weeks+	24 - 48 hours	24 - 48 hours
Duration of prophylaxis	Continue while in and for 4 weeks after leaving malaria area	Continue while in and for 4 weeks after leaving malaria area	Continue while in and for 7 days after leaving malaria area
Special precautions	Use with caution in travellers requiring fine motor co-ordination[6]	Avoid excessive exposure to the sun. Take after a meal with a full glass of water and do not lie down for 1 hour thereafter	Take with milk or food for better absorption[9]
Most common side-effects	Nausea, strange dreams, dizziness, mood changes, insomnia, headache and diarrhoea	Skin photosensitivity, oesophageal ulceration, gastrointestinal symptoms, candidiasis	Well tolerated. Headache and abdominal pain most frequent adverse effects[9,12]

* Paediatric tablets of atovaquone-proguanil (for children weighing 11 - 39 kg) are not yet registered in South Africa.
+ To ensure that protective levels have been reached and to give enough time to change to a different drug if adverse reactions have developed.

Forward planning and taking the appropriate preventive measures will significantly reduce the risk of contracting malaria.

entering a malaria area (1 - 2 days before exposure for doxycycline and atovaquone-proguanil; 1 - 2 weeks before exposure for mefloquine).

- Antimalarials should be taken regularly for the duration of exposure and for the correct duration after leaving the malaria area.
- Antimalarials taken weekly must be taken on the same day each week.
- Antimalarials taken daily must be taken at the same time each day.

Early diagnosis and effective treatment

Travellers should be warned that malaria must be suspected and diagnosis and treatment sought in anyone presenting with a 'flu-like illness after being in a malaria area, especially for up to 3 months thereafter,[6] even if they have been fully adherent with their prophylaxis. This could be life-saving.

Forward planning and taking the appropriate preventive measures will significantly reduce the risk of contracting malaria. Not recommending appropriate chemoprophylaxis for travellers at risk of malaria is irresponsible and can have dire consequences.

Information sources

Detailed information on malaria risk areas and seasons and the suitability of alternative malaria prophylaxis and treatment options can be obtained through the following information centres:

Amayeza Info Centre
Tel: 011 678 2332 or 0861 MOZZIE (669943)
Fax: 011 476 7697
E-mail: amayeza@amayeza-info.co.za

Medicines Information Centre
UCT Division of Clinical Pharmacology
Tel: 021 206 6289 or 0861 100 531
Fax: 021 448 0503
E-mail: pha-mic@uct.ac.za

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In a nutshell

- Malaria is transmitted by the bite of the female *Anopheles* mosquito, and she feeds at night.
- No chemoprophylaxis is considered to be 100% effective and measures to prevent being bitten by mosquitoes should be considered the mainstay of malaria prevention. Use an insect repellent containing 30% DEET.
- 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.
- Recommendations for chemoprophylaxis must be individualised.
- Currently recommended options for chemoprophylaxis are: mefloquine, doxycycline or atovaquone-proguanil.
- All antimalarials need to be started before entering the area, 1 - 2 days before for doxycycline and atovaquone-proguanil and 1 - 2 weeks for mefloquine.
- All antimalarials must be taken after leaving the malaria area (4 weeks for mefloquine and doxycycline, and 7 days for atovaquone-proguanil).
- Symptoms of malaria only present when the parasites multiply in, and burst the red blood cells; this occurs at least 7 - 10 days after being bitten.
- Homeopathic and herbal products are not recommended, as there are no scientific data to prove their efficacy.