All you need to know about Malaria

Although we have tried to provide as much information as possible, our list is not exhaustive and it is the responsibility of each attendee to do their own research and enquiries and ensure that they take the necessary precautions required. We as the South African organizing committee do not take responsibility should someone fall ill, even if precautions were followed.

The website links on the main page given to the South African home affairs as well as to the USA travel info website is good. There are a few things I would like to highlight:

- Government hospitals in South Africa are grossly understaffed and under resourced. As such it is imperative that people coming from outside of South Africa have adequate international medical insurance in order to attend private hospital/medical facilities should the need arise.
- Please note that a full time doctor is available at the Skukuza Camp should there be any medical need.
- Please buy and drink only bottled water, not all the tap water in South Africa is safe to drink and could lead to diarrhea and vomiting, which will just spoil your holiday.
- Malaria, the most important things to note are:
    - As mentioned on the Kruger Park website there has been a drastic increase of Malaria diagnoses in South Africa since September 2017 and as such we strongly recommend that the Malaria Prophylaxis for both National and International visitors be taken before travelling to the area. Even though the conference takes place in winter, when Malaria is not as prevalent and even if the medication makes you feel ill for a few days, Malaria is not an illness to mess around with and the prevention there of should be taken seriously.
    - If you should experience flu like symptoms or any of the other symptoms mentioned on the website https://www.sanparks.org/parks/kruger/tourism/malaria.php, 12-35 days after your visit to the area it is recommended that you consult with a medical doctor to begin treatment. Symptoms normally develop within 2 weeks after the parasite has entered the body but symptoms can occur up to 6 months after you have left the Malaria area. The tests to identify Malaria are often unable to detect the parasite in your bloodstream even if it is there so if you experience any of the symptoms, doctors in South Africa recommend treatment regardless of what the test results are. When consulting a doctor, it is imperative to mention that you have been in a Malaria area and the dates when you were there. Should you still be in South Africa and require treatment, after consulting a medical doctor, you will be able to obtain the medication at any independent Pharmacy, Dis-Chem or Clicks Pharmacy's with a prescription from a medical doctor in South Africa.

Dis-Chem PHARMACIES

CLICKS Pharmacy

Link GOOD HEALTH PHARMACY

Additional preventive measures for residents and visitors to malaria areas:

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

Precautions to minimise insect repellent side effects:

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

- note DEET can opacify spectacles, binoculars and other plastics National Department of Health South African Guidelines for the Prevention of Malaria
- keep repellents out of the reach of children

Choosing appropriate chemoprophylaxis

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

Currently in South Africa there are three effective chemoprophylactic options available. Recommended prophylactic regimens:

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

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

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

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

Table 1: Benefits and risks of prophylactic regimens recommended for travelers

	Mefloquine	Doxycycline	Atovaquone-Proguanil
Prophylactic Efficacy	Highly effective against *P. falciparum* in areas where it has been tested. Effective against acute infections caused by *P. vivax.* Limited data on efficacy against other species. Relapses can occur.	Highly effective against *P. falciparum* in areas where it has been tested. Limited protection against acute *P. vivax* infections. Relapses can occur.	Highly effective against *P. falciparum* in areas where it has been tested. Also effective against acute infections caused by *P.vivax, P. ovale* and *P. malariae.* Relapses can occur.

Most common side effects	Nausea, strange dreams, dizziness, mood changes, insomnia, headache and diarrhoea.	Skin photosensitivity (three per cent in one study), oesophageal ulceration, gastrointestinal symptoms, candida superinfection of the gut and vagina.	Well tolerated. Headache and abdominal pain most frequent adverse effects.
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). Infants weighing less than five kilograms.	Pregnancy. Children under eight years of age. Caution in travelers with myasthenia gravis.	Severe renal impairment (creatinine clearance of <30ml/min). Pregnancy due to lack of data.
Special Precautions	Travelers requiring fine coordination.	Avoid excessive UV exposure, use high SPF sunscreen. Take after a meal with a full glass of water. Do not lie down for at least one hour after taking.	Take with milk or food for better absorption.
Dosage interval	Once weekly.	Daily dose.	Daily dose.
Time period needed before entering malaria area	General recommendation: One week. For first time use: Two to three weeks.*	24-48 hours.	24-48 hours.
Resistance	Resistance appears to be rare - mainly SE Asia.	Resistance appears to be rare.	No known resistance.

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

In order to choose a safe and appropriate prophylactic agent for a person travelling to a malaria area, various clinical and drug-related factors need to be taken into account: (See **Table 2**)

- pregnancy or planning a pregnancy shortly after the trip
- breastfeeding
- age
- pre-existing medical conditions such as psoriasis, epilepsy, diabetes, renal impairment, cardiac complications or psychiatric problems

- other medication being taken (including prescription, over-the-counter and complementary or traditional medicines)
- activities requiring fine coordination and spatial discrimination, e.g. piloting, scuba-diving, mountain climbing
- length of visit to the area.
  The cumulative risk of contracting malaria is proportional to the length of stay in a malaria area. A visit of three months carries a risk six times greater than a two-week visit. Long term safety of some chemoprophylactic drugs has not been evaluated
- the level of compliance expected with each of the options

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

Condition/situation	Mefloquine	Doxycycline	Atovaquone-proguanil
Pregnancy - **Avoid travelling to a malaria area**	Drug of choice if pregnant women is at risk of malaria	Contraindicated	Not recommended due to lack of information
Women of child-bearing potential or on oral contraceptives	Use reliable contraception during and for three months after taking last dose. Will not compromise contraceptive efficacy.	Avoid pregnancy during and for one week after taking last dose. Contraceptive failure may occur if traveler presents with vomiting or diarrhea.	Avoid pregnancy during and for two to three weeks after taking last dose. Will not compromise contraceptive efficacy.
Breastfeeding - **Baby must be given their own prophylaxis**	Insufficient data, but WHO states that it is safe to use.	Avoid use unless no other option. AAP* says it is safe to use.	Avoid use, if infant weighs <11kgs
Young children - **Avoid taking children under the age of five years to a high risk area**	Can be used in children over three months of age or weighing more than five kilograms. Generally well tolerated by children.	Use only in children older than eight years of age.	Pediatric tablets can be given to children weighing 11kgs or more.
Epilepsy	Contraindicated. May also interact with valproic acid.	May interact with certain anticonvulsants, reducing the half-life of doxycycline and possibly resulting in prophylaxis failure.	Can be used.
Psychiatric conditions	Contraindicated, even if there is only a history of depression.	Can be used.	Can be used.
Psoriasis	No documented problems - can be used.	Can be used.	No documented problems – can be used.
Porphyria	Appears to be well – tolerated.	Likely to be safe	Likely to be safe.
'Sulfa' allergy	Contains no 'sulfa' moiety - safe to use.	Contains no 'sulfa' moiety - safe to use.	Contains no 'sulfa' moiety - safe to use

Renal impairment	Use with caution - lack of safety data.	Safe to use.	Contraindicated in severe renal failure creatinine clearance <30ml/min).
Hepatic impairment	Contraindicated in severe impairment	Administer with caution to hepatically impaired patients or those receiving hepatotoxic drugs.	Safe to use in mild to moderate hepatic impairment, but no data on use in severe hepatic impairment
Individuals requiring fine motor coordination and spatial discrimination e.g. pilots	Do not use.	Safe to use.	Safe to use.
Travelers with myasthenia gravis	Insufficient data – stop therapy if muscle weakness occurs.	May aggravate symptoms of myasthenia gravis.	No data available.
Travelers requiring long-term therapy	Can be used for up to three years and even longer if justified by risk of exposure.	Can be used for two years and even longer if justified by risk of exposure.	Can used for up to one year and even longer if justified by risk of exposure.
Travelers on Warfarin **Caution: Changes in INR can be very dangerous, resulting in bleeding or clotting. Preferably avoid high risk malaria areas**	Insufficient data - monitor INR. Start therapy in advance to monitor possibility of interaction.	May potentiate anticoagulant effect. Monitor INR.	Proguanil may potentiate the effect of oral anticoagulants. Monitor INR.
Travelers with G-6-PD deficiency	No problems documented - safe to use.	Safe to use.	Safe to use.
Diabetics	Insufficient data - monitor blood glucose levels.	May increase hypoglycemic effect of insulins - monitor blood glucose levels.	No known problems. Monitor blood glucose levels.
Cardiotoxicity and use in combination with cardiac drugs	May cause conduction abnormalities. Use with caution in people taking beta-blockers, calcium antagonists, and quinidine.	Safe to use.	Safe to use.

***American Academy of Paediatrics**

Measures to ensure effective and safe use of chemoprophylaxis

- Chemoprophylaxis needs to be used in addition to, and not instead of, personal protection measures.
- Dosing schedules for children should be based on body weight.
- Antimalarials (particularly doxycycline and atovaquone-proguanil) should be taken with food and adequate fluids.
- Patients need to be well educated and motivated to ensure the highest possible level of compliance.

- All antimalarials should be started before entering a malaria area (one to two days before for doxycycline and atovaquone-proguanil; one to two weeks before for mefloquine).
- Antimalarials should be taken with unfailing regularity for the duration of possible exposure and for the correct duration after leaving the malaria area (four weeks for mefloquine and doxycycline, and seven days for atovaquone-proguanil).
- Antimalarials taken weekly must be taken on the same day each week.
- Antimalarials taken daily must be taken at the same time each day.
- Doxycycline can be obtained from a pharmacy without a prescription - other available effective chemoprophylaxis options require a medical prescription for purchase.
- There is currently no scientific evidence to support use of complementary, alternative and homeopathic preparations for the prevention (or treatment) of malaria.

Efficacy and adverse reactions of recommended chemoprophylactic regimens

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

Mefloquine

Mefloquine is the most thoroughly documented option for long-term prophylaxis and is therefore the best option for those requiring prophylaxis for more than six months, if tolerated. Mefloquine is active against *P. falciparum* parasites including those that are resistant to chloroquine and sulfadoxine-pyrimethamine and against the other three *Plasmodium* species that affect humans. Weekly dosing should encourage compliance. It is recommended for use for up to three years and even longer if use is justified by risk of malaria.

Adverse effects associated with mefloquine include insomnia, strange dreams, mood changes, nausea, diarrhoea and headache. These effects are usually experienced within the first three weeks of medication and do not become worse in subsequent weeks of use. If not experienced during the first use of mefloquine they are unlikely to appear during subsequent use for prophylaxis. Severe neuropsychiatric reactions (psychosis, convulsions) are infrequent with prophylactic doses, and occur in approximately 1/10 000 to 1/13 000 persons. The frequency of mild neuropsychiatric effects is probably much higher in the general population and in women, specifically. More recently, an increased risk of eye disorders, including cataracts, retinal disorders and optic neuropathy, which may even occur after treatment, has been reported. These present with visual impairment and blurred vision. The FDA has strengthened their warning with regards to neuropsychiatric effects. The neurologic side effects can include dizziness, loss of balance, or ringing in the ears. The psychiatric side effects can include an anxious feeling, mistrust, depression, or having hallucinations. These can even last after mefloquine has been stopped. Occasionally mefloquine-associated side-effects are sufficiently severe to force the discontinuation of prophylaxis while still in a malaria area. To prevent such an occurrence it is recommended that when mefloquine is to be taken for the first time, prophylaxis is started three weeks before exposure to a malaria area to enable a timely drug change should side effects occur.

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

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

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

Doxycycline

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

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

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

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

Atovaquone–proguanil

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

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

Reference:

National Department of Health. 2017. South African Guidelines for the Prevention of Malaria.
Accessed on: 29 November 2017.
Available online: http://www.nicd.ac.za/wp-content/uploads/2017/09/Guidelines-South-African-Guidelines-for-the-Prevention-of-Malaria-2017-final.pdf