Focus on malaria prophylaxis – Can we conquer the 'mighty' parasite?

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South Africa is one of the countries that has been identified by the World Health Organization (WHO) for elimination of malaria by 2018.[1] Until the end of 2016, the country was doing very well, with most areas in the elimination phase. There was however a significant setback in 2017, with an alarming increase in cases and deaths.[2] This was due to a number of factors, including high rainfall, humidity and ambient temperatures following a year of low rainfall and an unusually mild winter. These environmental factors allowed ongoing mosquito and parasite development. Combined with late indoor residual spraying, due to difficulty in getting insecticides and finances, the stage was set for the malaria mosquito and parasite. This highlights the need to be vigilant and to keep up-to-date. Malaria risk areas are changing all the time due to climatic factors, insecticide resistance and a break down in control methods. Fortunately last year and up until November this year, we have seen far fewer malaria cases in South Africa.

Malaria prevention strategies are of utmost importance in all malaria risk areas. These strategies include measures taken against both mosquito vectors and malaria parasites, such as vector control programmes managed by government health authorities, personal protection measures to avoid mosquito bites and the use of chemoprophylaxis.

With the welcome advent of both doxycycline[3] and atovaquone-proguanil[4] being down-scheduled to S2, travellers can now get antimalarials from pharmacies, facilitating rapid access, often at short notice. Having easier access to antimalarials, hopefully means that more travellers will take prophylaxis and this will assist in getting South Africa back on track for elimination. This article will focus on measures to minimise the risk of malaria in travellers.

Overview of the disease

Malaria is a preventable infection that has a high morbidity and is potentially fatal. It is widespread in many areas of the world and is a risk to both travellers and the local populations. In South Africa, the malaria risk areas are mainly the low-lying northern and eastern areas of Limpopo, Mpumalanga and KwaZulu-Natal. Occasional transmission has occurred in the North West and Northern Cape along the Molopo and Orange rivers. Malaria transmission in South Africa is also seasonal with peaks from September to May.[1]

The infection is caused by a *Plasmodium* parasite which is transmitted to humans by the bite of an infected female *Anopheles* mosquito. She feeds on humans between dusk and dawn to get a blood meal for maturation of her eggs. The parasite has a life cycle which involves both humans and mosquitoes.

The four species that infect humans are:[1]

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

Recently, large numbers of human infection due to the monkey malaria parasite, *Plasmodium knowlesi*, have been reported from forested regions of Southeast Asia.

As many as 92% of the 219 million malaria cases and 93% of the deaths reported in 2017 occurred in Africa. *P. falciparum* is the cause of 99% of these deaths.[5] *P. ovale and P. vivax* are associated with relapses due to dormant liver stages if not treated appropriately. They do not however usually cause severe disease.[1]

The 'ABC' of malaria prevention

The five key components for preventing malaria morbidity and mortality are:

A: Awareness and assessment of malaria risk

B: Avoidance of mosquito bites

C: Compliance with chemoprophylaxis, when indicated

D: Early detection of malaria disease

E: Effective treatment

Awareness – be aware of malaria risk[1]

Consider the following:

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

Bites – avoiding mosquito bites

No chemoprophylaxis is 100% effective and therefore measures to prevent being bitten by mosquitoes are of paramount importance. Travellers should be advised to:[1]

- Remain indoors between dusk and dawn (wherever possible).
- Wear long-sleeved clothing, long trousers (preferably light-coloured) and socks.
- Apply an insect repellent containing DEET (chemical name: N,N-diethyl-meta-toluamide) to exposed skin, and repeating as recommended on the container label. Avoid eyelids, lips, sunburnt or damaged skin; do not spray on the face and do not overdose young children. Products that contain between 20 and 50% DEET are suitable for use in persons over two months of age as well as pregnant women.
- Protect doors and windows with screens, but if not installed, windows and doors should be closed at night.
- Use overhead fans or air conditioners, which are effective in hindering mosquitoes from landing.
- Sleep under a mosquito bed-net (preferably impregnated with an insecticide registered for this purpose, e.g. a pyrethroid), with the edges tucked in. Ensure that the bed-net is not torn and that there are no mosquitoes inside the bed-net.
- Spray inside the house with an aerosol insecticide (for flying insects) at dusk, especially the bedrooms, after closing the windows.
- Use mosquito mats, impregnated with an insecticide (heated electrically or by a non-electric lamp), or burn mosquito coils in living and sleeping areas during the night.
- Treat clothes with an insecticide registered for this purpose, e.g. a pyrethroid.

Compliance with chemoprophylaxis, when indicated

There are two types of chemoprophylaxis – causal prophylaxis (absolute prevention of infection) or suppressive prophylaxis (suppression of parasitaemia and its symptoms). 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. 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.

The following regimens are currently recommended for use in South Africa:[1]

- Atovaquone-proguanil (daily). Start one to two days before entering malaria area, take daily while there and for seven days after leaving the area. This is both a causal and a suppressive prophylactic.
  Or
- Doxycycline (daily). Start one day before entering a malaria area, take daily while there and for four weeks after leaving the malaria area. This is a suppressive prophylactic.
  Or
- 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. This is a suppressive prophylactic.

The protective efficacy of the above three options is considered to be comparable, at around 90% if taken correctly.[1,6] Selection of the most appropriate antimalarial chemoprophylaxis should be based on factors relating to the individual, such as: age and weight; whether they are pregnant or breastfeeding; have any medical conditions such as porphyria, epilepsy or depression; concomitant medication use; how long they will be at risk and whether they will be undertaking activities, such as scuba diving or flying.

Before prescribing chemoprophylaxis:

Determine the need based on factors above.

Ask about any reactions to previous antimalarials, what medication the traveller is taking and what concomitant medical conditions he or she may have. For details regarding drug interactions and precautions please refer to The South African Guidelines for the Prevention of Malaria 2018. Available from: www.santhnet.co.za

Refer to a medical practitioner if they:

- ✓ are pregnant or breastfeeding
- ✓ are taking anticoagulants
- ✓ are taking anti-tuberculosis medicines
- ✓ have renal or liver disease

Focus on atovaquone-proguanil – AP (Malanil®, Malateq®, Mozitec®)

Each adult tablet contains 250 mg atovaquone and 100 mg proguanil. The recommended dose is one tablet daily and is suitable for persons weighing 45 kg or more.

Each paediatric tablet contains 62.5 mg atovaquone and 25 mg proguanil and is suitable for use in children weighing 11 kg or more.

Advantages

- In November 2017, the Medicines Control Council down-scheduled atovaquone-proguanil to S2 *when co-formulated and intended and labelled for the chemoprophylaxis of malaria in those weighing 11 kilograms or more*.[4]
- It is effective against all the malaria strains but not against the hypnozoites of *P. vivax* and *P. ovale*.[1]
- It can be started the day before entering the malaria area and is therefore a good option for the last minute traveller.[1]
- It is a causal prophylactic and therefore it need only be taken for seven days after leaving the area (instead of for four weeks). It is therefore a good option for short-term travel.
- It is well tolerated, with few side-effects.
- There are very few contraindications.
- There is no known resistance.[1]
- It can be used for up to one year and even longer if justified by risk of exposure.[1]
- Some products have a paediatric formulation for children weighing 11 kg or more.

Disadvantages

- It must be taken daily. Atovaquone has a half-life of 32–84 hours and proguanil has a half-life of 12–21 hours.[7] The two ingredients work synergistically.[7]
- Headache, mouth ulcers and abdominal pain are the most frequently reported side-effects.
- It should not be given to pregnant or breastfeeding women as there is a lack of information regarding its safety.
- It is not indicated for children weighing less than 11 kg.
- It may interact with certain antiretrovirals.

Patient counselling

- ✓ Take the first dose at least one day before entering the malaria area and take it daily while in the area and for seven days after leaving the area. It is important to complete the course.
- ✓ Take it in the morning, at the same time, with food or a milky drink. This is important, as it helps with the absorption of the active ingredients.
- ✓ If you miss a dose, take it as soon as possible and carry on as before.
- ✓ Avoid pregnancy during and for two to three weeks after taking the last dose.
- ✓ Take measures to prevent being bitten by mosquitoes.
- ✓ If vomiting occurs within one hour of taking the dose, repeat it.
- ✓ Report any adverse effects that occur.

Focus on doxycycline (Cyclidox®, Doxycyl®)

Each capsule contains either 50 mg or 100 mg doxycycline. The adult dose is 100 mg daily, and the paediatric dose (> 8 years) is 2 mg/kg.

Advantages

- In March 2016, doxycycline was down-scheduled to S2 *when intended and labelled for the chemoprophylaxis of malaria in those 8 years and older, for periods not exceeding 4 months of continuous use*.[3]
- Doxycycline is very effective as prophylactic treatment and works against all Plasmodium species, but not against the hypnozoites of *P. vivax* and *P. ovale*.[1]
- There is no documented resistance.[8]
- It can be used for two or more years.[1]
- It can be started the day before entering a malaria risk area and is therefore an option to consider for the last minute traveller.
- It is the best option for travellers who are HIV+ and on antiretrovirals.
- It is the best option for travellers taking rifampicin.

Disadvantages

- It is a suppressive prophylactic and therefore needs to be taken four weeks after leaving the area. It is important to complete the course.
- Doxycycline has a half-life of 15–24 hours and therefore needs to be taken daily. It is very unforgiving, and if a dose or two is missed, prophylactic failure may occur.[8]
- Contraindicated in pregnant women and in children less than eight years of age.
- Should only be used while breastfeeding if no other option.
- Use with caution in travellers who have myasthenia gravis.
- Take note of normal drug interactions, especially with anticonvulsants such as phenytoin, phenobarbitone and carbamazepine.
- Side-effects experienced include photosensitivity, vaginal candidiasis and gastrointestinal effects, particularly oesophagitis, if not taken correctly.
- Prophylactic failure may occur if the traveller has diarrhoea or vomiting.

Counselling for the traveller

- ✓ Take the first dose at least one day before entering a malaria area and take daily while in the area and for four weeks after leaving the malaria area.
- ✓ Take after a meal, with a full glass of water and do not lie down for an hour after a dose.
- ✓ Do not miss any doses – doxycycline is unforgiving; miss a dose, and prophylactic failure may occur. If a dose is missed, take it as soon as possible.
- ✓ Use an effective sunscreen and wear a hat when going into the sun, as photosensitivity may occur.
- ✓ If vomiting occurs within one hour of taking a dose, repeat it.
- ✓ Take measures to prevent being bitten by mosquitoes.
- ✓ Report any adverse effects that may be experienced.

Profile of mefloquine

Mefloquine has a long half-life (approximately 21 days[9]) and can therefore be given as a once weekly dose.[6] This makes it a good option for long-term travellers. It is effective against all Plasmodium species, but not against the hypnozoites of *P. vivax* and *P. ovale*.

Cases of resistance have been reported in areas of Southeast Asia.

It can be given to children from three months of age (5 kg in weight) and is well tolerated by children.[10]

It is currently the only option recommended for pregnant women, irrespective of their trimester.[6,10]

It has to be started at least a week before entering the malaria area and is therefore not a good choice for the last minute traveller.

It is a suppressive antimalarial and therefore has to be taken for four weeks after leaving the malaria area.

It has numerous contraindications such as epilepsy, psychiatric illness, depression and many common side-effects such as strange dreams, insomnia, anxiety, depressed mood, nausea and dizziness. Visual disturbances and severe neurological side-effects have been reported rarely, but receive much publicity.[1,6] Most side-effects present within the first three doses.

The adult dose is one tablet (250 mg) and the paediatric dose is 5 mg/kg taken once weekly.

Being S4, mefloquine must be prescribed by a doctor.

There is currently no mefloquine product available in South Africa, which means that there is no prophylaxis to offer a pregnant woman or child weighing less than 11 kg. It is therefore advisable that neither should travel to a malaria risk area.

Early detection of malaria disease and effective treatment

As no chemoprophylaxis is 100% effective, there is still a small chance that the traveller may contract malaria in spite of having taken prophylaxis.

Symptoms of malaria infection may present as early as seven days after exposure, but more commonly develop 10 to 14 days after an infective mosquito bite, but this period may be prolonged, especially if prophylactic drugs have been taken. Therefore if any 'flu-like' symptoms such as headache, fever, myalgia and rigors develop up to two months or even longer, after being in a malaria area, one should seek immediate medical attention. Early diagnosis and appropriate treatment are critical to survival.[11]

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