Don't overlook malaria: What the pharmacist needs to know

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Abstract

The COVID-19 pandemic has shifted the focus away from a life-threatening disease, malaria. As the world opens to travel, the focus on malaria needs to be renewed as more travellers seek advice on malaria prophylaxis. Pharmacists need to be properly informed about malaria to effectively counsel travellers going to high-risk areas. An individual approach needs to be adopted when recommending chemoprophylaxis, taking into account the traveller's risk factors, itinerary and likelihood of adherence to a particular dosage regime.

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Introduction

Malaria is a life-threatening disease that affects thousands of travellers to, as well as those living in, endemic areas.[1] Globally, 2019 saw 229 million cases of malaria and 409 000 deaths from the disease. However, under-reporting may not paint a true picture of the real figure.[1,2] Between the years 2015 and 2019, South Africa reported approximately 10 000 to 30 000 cases annually.[3]

Pharmacists, being medicine experts and easily accessible, are ideally positioned to advise those travelling to an endemic malaria area of their individual risk of contracting malaria, as well as the measures that can be taken to prevent malaria.[2]

Understanding malaria

Malaria is caused by a blood parasite of the genus *Plasmodium* and is transmitted to humans via the bite of an infective female *Anopheles* mosquito (the vector).[3,4]

Five species of the *Plasmodium* parasite cause human malaria.[5] The following four species, however, are the most predominant:[5]

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

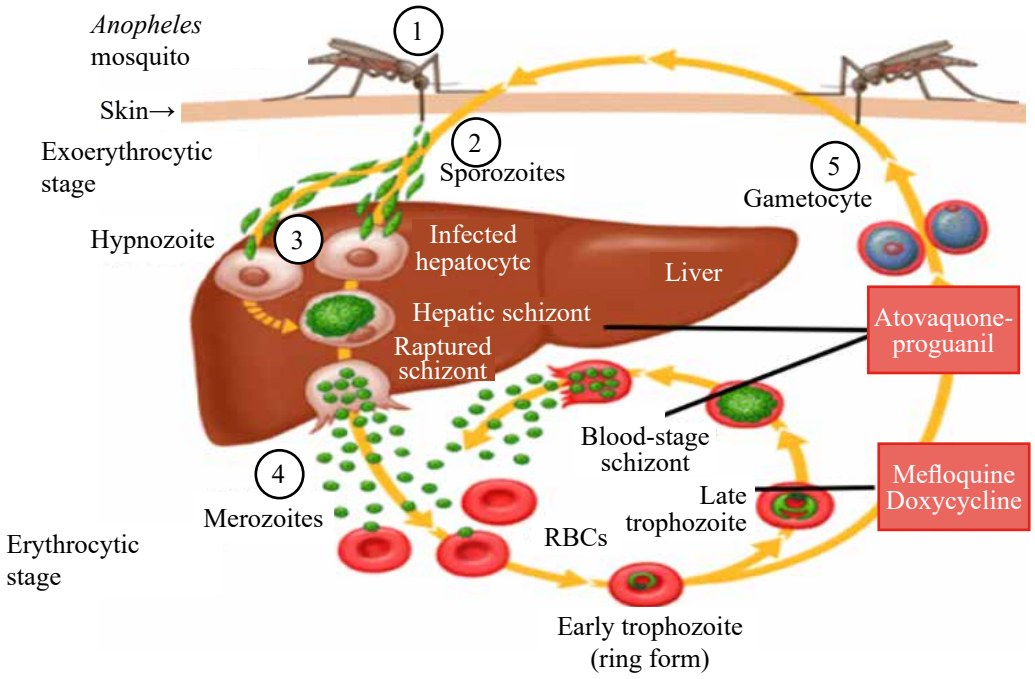

Diagram 1: Lifecycle of the malaria parasite[5,6]

P. falciparum is responsible for the highest malaria mortality of all the species and is the most common species found in sub-Saharan Africa.[2]

The fifth species, *Plasmodium knowlesi,* originally caused malaria only in monkeys. It is, however, now classified as a human malaria parasite after reports of the disease in humans in Southeast Asia.[5]

The lifecycle of the malaria parasite is described in Diagram 1.[6] Destruction of the red blood cells by the malaria parasites induces the symptoms of malaria. The symptoms usually occur around 10 to 14 days (incubation period) after the mosquito bite. The incubation period may be longer, especially if the traveller took malaria chemoprophylaxis.[5]

1. The infective *Anopheles* mosquito bites a human and injects sporozoites into the blood.
2. The sporozoites migrate to the liver and infect the liver cells (hepatocytes) where they multiply and mature into schizonts (exo-erythrocytic stage).
3. Infections with *P. vivax* and *P. ovale* result in a dormant stage in the liver when their schizonts become hypnozoites. These hypnozoites can remain dormant for months or years.
4. Mature schizonts rupture and release merozoites into the bloodstream (erythrocytic stage).
   - In *P. falciparum* and *P. malariae* infections, all schizonts rupture and all merozoites are released into the bloodstream.
   - In *P. vivax* and *P. ovale* infections, some schizonts rupture, releasing merozoites into the bloodstream, but those that have formed hypnozoites remain dormant. A traveller may relapse when these hypnozoites become active and release merozoites, which restarts the erythrocytic stage.

   Merozoites in the bloodstream invade red blood cells, where they multiply, mature and rupture the red blood cell. Released merozoites invade uninfected red blood cells and the cycle continues until the infected traveller receives treatment or the traveller dies.
5. A few of the merozoites differentiate into gametocytes (sexual blood-stage).
   Gametocytes (male and female) are taken up by an *Anopheles* mosquito during a feed.
   Male and female gametocytes fuse in the mosquito's gut and the resulting sporozoites migrate to the mosquito's salivary glands, where they are ready to be inoculated into a new human host.

Malaria chemoprophylaxis

Widespread chloroquine-resistant *P. falciparum* malaria has negated the use of chloroquine as an effective prophylactic.[5]

Three chemoprophylactic options are currently recommended in South Africa, namely:[7]

- Mefloquine
- Atovaquone-proguanil
- Doxycycline

Mefloquine requires a prescription (schedule 4), but at the present time is only available for use via section 21.[8,9] Both atovaquone-proguanil and doxycycline are available as schedule 2 products in South Africa, which means that the pharmacist can recommend and dispense either of these to the public for the prevention of malaria without requiring a doctor's prescription.[10]

Malaria chemoprophylaxis can be referred to as either:[5]

- an absolute prevention of infection (causal prophylaxis), or
- a suppression of parasitaemia and its symptoms (suppressive or clinical prophylaxis).

Blood-stage (suppressive) and liver-stage (causal) prophylaxis

Causal prophylaxis, provided by *tissue schizonticides*, occurs when the drug destroys the exo-erythrocytic forms of the parasite, whereas suppressive prophylactics, known as *blood schizonticides*, act on the erythrocytic stages of the parasite, (where the parasite has already left the liver and entered the red blood cell).[5]

Drugs that act on the liver stage (causal prophylactics) may be discontinued seven days after last exposure.[6]

Drugs that act only on the erythrocytic stages of the parasite (suppressive prophylactics) need to be continued until no more parasites are being released into the blood from the liver (this can occur with *P. falciparum* up to one month after last exposure).[5]

Atovaquone and proguanil work synergistically, and are active against the asexual erythrocytic forms of *Plasmodium* (blood schizonticides) as well as the liver stages of the parasite (tissue schizonticides).[5,6] Proguanil works on the pre-erythrocytic intra-hepatic form of the parasite.[5] On its own, proguanil is not able to completely prevent malaria, but when combined with atovaquone, is a causal prophylactic (Diagram 1).[5] The combination is effective against the actively replicating parasites in the liver, and may therefore be discontinued seven days after the end of exposure.[6]

Mefloquine and doxycycline are blood schizonticides and therefore work only on the asexual blood stages of the parasite (Diagram 1).[6] Both of these products need to be continued for four weeks after leaving the malaria area as they do not have any effect on the liver-stage parasites, and parasites may still emerge from the liver over this 4-week period.[6,11]

The A, B, C and D of malaria prevention

While all three available malaria chemoprophylactic agents have equal efficacy in preventing malaria, it is important to note that no one drug is 100% effective in preventing malaria.[2,5] The prevention of malaria involves taking non-drug measures to prevent the mosquito bites as well as, if necessary, tailoring the most appropriate choice of chemoprophylaxis to the individual.[2]

Assessing the risk of malaria and the choice of malaria prophylaxis involves asking the correct questions:[2,5]

A: Awareness and assessment of the risk

Where are they travelling to? [5,12]

The latest country-specific malaria maps or guidelines should always be consulted to determine the traveller's risk for contracting malaria.[2]

The following websites provide current maps which may be consulted to determine the risk of malaria in a particular country:

- National Guidelines for the Prevention of Malaria, South Africa
  https://www.nicd.ac.za/wp-content/uploads/2019/03/National-Guidelines-for-prevention-of-Malaria_updated-08012019-1.pdf
- Fit for travel
  https://www.fitfortravel.nhs.uk/home

Where, when and for how long will they be staying in the malaria area? [5,13]

Malaria risk may also be dependent on the traveller's itinerary.[2]

Table I is a summary of the risk considerations to be taken into account.

Table I: Risk considerations[13]

Location	• Cities – less risk • Camping near a river – high risk • High altitude – less risk
Accommodation	• Air-conditioned hotels – low risk • Huts or tents – higher risk
Time of year	• Transmission is lower during dry, cold months; however, in some countries, the risk is year-round
Time of day	• *Anopheles* mosquito bites between dusk and dawn
Length of stay	• The risk of malaria is proportional to the length of stay, in other words, the longer one stays in a malaria area, the higher the risk of contracting malaria

Who is travelling?

Anyone living outside a malaria area is considered to be non-immune to malaria and is at risk of developing malaria if they get infected.[5] People who once lived or grew up in a malaria endemic area lose their immunity rapidly after moving away from the endemic area and are at risk of contracting malaria when returning to the endemic area.[4]

Certain population groups are at a substantially higher risk for developing severe and complicated malaria.[5] Travel to malaria endemic areas for these groups should be strongly discouraged.[14] If travel cannot be avoided, strict non-drug measures should be adopted and malaria chemoprophylaxis taken.[2]

High risk groups include:[2,5,6,14]

- Pregnant women
  There is an increased risk of serious pregnancy complications if a pregnant woman contracts malaria, such as maternal and foetal anaemia, stillbirth, spontaneous abortion, low birth weight and neonatal and maternal death.
- Infants and children under 5 years of age
  The under 5-year age group is the most vulnerable, and the majority of deaths due to malaria occur in this age group.[5] Complicated malaria characteristics such as severe anaemia, hypoglycaemia and cerebral malaria are more often seen in children than adults.
- Immunocompromised patients
  Immunosuppressed individuals (e.g., patients with HIV/AIDS, those on long-term steroids, or receiving chemotherapy, splenectomised patients) are more vulnerable to severe malaria and death.

B: Bite prevention (the importance of personal protection methods)

Malaria prevention measures involve a combination of mosquito bite prevention measures as well as appropriate chemoprophylaxis.[4]

Effective mosquito bite prevention measures include:[2,4,13]

- The use of topical repellents, the most effective of which are those containing N,N-diethyl-m-toluamide (DEET), 30–50% (even for pregnant women and children > 2 months of age). DEET should be applied as per manufacturer instructions to all exposed parts of the skin, especially during dusk and dawn when the *Anopheles* mosquito feeds.
- Sleeping under mosquito nets (preferably insecticide impregnated) or in a well-screened air-conditioned room.
- Staying indoors during dusk and dawn, if possible.
- Wearing light-coloured clothing that covers most parts of the body in the evenings.
- Using insecticide sprays or plug-in mosquito repellents indoors.

C: Chemoprophylaxis

Various factors influence the choice of malaria chemoprophylaxis regime.[13] The prophylaxis should be individualised, taking into account the traveller's itinerary, risk factors for malaria, the age of the traveller, comorbidities and the potential for drug interactions.[5,6]

Table II is a summary of the available chemoprophylaxis regimes.[4-7]

D: Diagnose promptly and treat effectively

As no antimalarial agent is 100% effective, all travellers presenting with fever or "flu-like" symptoms during or after returning from a malaria area, must seek immediate medical attention to rule out the possibility of malaria.[7] The traveller should be tested for malaria "regardless of suspected COVID-19 condition, (pending COVID-19 tests or even a positive COVID-19 test)." As the symptoms of COVID-19 overlap with the symptoms of malaria, there is a danger

Table II: Guidelines for the prevention of malaria[5]

	Mefloquine	Doxycycline	Atovaquone-proguanil
Age/weight indications	Contraindicated in children weighing less than 5 kg	Contraindicated in children under eight years of age	Not for use in children under 11 kg
Dosing and directions	Weekly dosing 1 tablet = 250 mg **Adults:** 1 tablet weekly (on the same day of each week), starting one week before entering area, once weekly while in area, and continuing for four weeks after leaving area **Children:** Directions as above, with dose according to weight Weight (kg) – Weekly dosage 5–20 – ¼ tablet 21–30 – ½ tablet 31–45 – ¾ tablet > 45 – Adult dose	Daily dosing 1 capsule = 100 mg **Adults:** 100 mg once daily starting one day before entering the area, continuing daily while in the area, and daily for four weeks after leaving the area **Children:** 2 mg/kg of body weight at the same intervals as for adults Age years – Weight kg – Dosage 8–15 – 31–45 – 2 mg/kg > 15 – > 45 – Adult dose	Daily dosing 1 adult tablet = 250 mg atovaquone plus 100 mg proguanil 1 paediatric tablet = 62.5 mg atovaquone plus 25 mg proguanil **Adults:** 1 adult tablet daily taken one day before exposure, continued daily during exposure and for seven days after the last possible exposure to malaria **Children:** Weight kg – Paediatric tablets 11–20 – 1 daily 21–30 – 2 daily 31–40 – 3 daily > 40 – 1 adult tablet daily
Most common side effects	Dizziness, nausea and diarrhoea, insomnia, unusual dreams, headache, mood changes	Skin photosensitivity, gastrointestinal upset, oesophageal ulceration, vaginal candida superinfection	Headache and abdominal pain
Pregnancy and breastfeeding**	**Pregnancy:** Drug of choice **Breastfeeding:** Insufficient data, WHO states safe to use	**Pregnancy:** Contraindicated **Breastfeeding:** Avoid use unless no other option AAP* states safe to use	**Pregnancy:** Not recommended due to lack of information **Breastfeeding:** Avoid use due to lack of data
Contraindications	Current or history of psychiatric illness (including depression) or epilepsy Underlying cardiac conduction disturbance or arrhythmia Concurrent use of halofantrine (and other cardiotoxic drugs) Infants weighing less than 5 kg Previous severe reaction to mefloquine	Pregnancy Children under 8 years of age Caution in travellers with myasthenia gravis	Pregnancy (due to lack of data) Severe renal impairment (creatinine clearance of < 30 ml/min)
Drug-interactions (List of examples not exhaustive – please consult guidelines or prescribing information for individual products)	Amiodarone Beta-blockers (when used for arrhythmia) Digoxin Phenothiazines Pimozide Ciclosporin Halofantrine Dabigatran Rivaroxaban Quinine or quinidine Rifampicin Tricyclic antidepressants Valproic acid	Alcohol Antacids (separate administration) Carbamazepine, barbiturates, phenytoin Ciclosporin Iron (separate administration) Methotrexate (high doses) Isotretinoin Milk and dairy (separate administration) Oral contraceptives (if diarrhoea or vomiting occurs) Rifampicin Warfarin	Protease inhibitors, Zidovudine Magnesium trisilicate (separate administration) Metoclopramide Rifampicin, rifabutin Tetracyclines Warfarin
Special precautions	Travellers requiring fine coordination	Avoid prolonged, direct exposure to sun 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

*American Academy of Paediatrics
**Babies must receive their own prophylaxis

of missing or delaying a malaria diagnosis, which may be severely detrimental to the traveller.[15] Without prompt, effective treatment, malaria can progress rapidly and be fatal.[2]

Advice in special situations

Which malaria prophylaxis is recommended if someone is going to be in a high-risk area for a year or longer?

The risk of contracting malaria is proportional to the length of stay in the malaria area.[5] The choice of malaria prophylaxis should always be tailored to the individual.[2] There is evidence to support the safety of mefloquine, doxycycline and atovaquone-proguanil for at least two years.[6] In many cases, the justification for long term use is based upon a lack of evidence of harm, as well as the benefit-risk ratio.[5]

People living in endemic areas for long periods of time should be counselled about the importance of not becoming complacent about adhering to malaria chemoprophylaxis and mosquito bite prevention measures.[4]

Recognising the signs and symptoms of malaria is also of utmost importance, as early detection and treatment can save lives. Stand-by antimalarial therapy (SBMT) may be considered for travellers where access to a reliable healthcare facility is not available within 24 hours of onset of symptoms.[5] SBMT does not preclude the need for travellers to seek prompt medical advice.[1]

What happens if a traveller starts malaria prophylaxis and has side-effects from the medications?[4,5]

- Antimalarial prophylaxis is generally well-tolerated. Minor side-effects do not warrant a change of medication.
- If side-effects cannot be tolerated before a full course is completed, a switch to another malaria prophylactic agent may be considered depending on certain factors.
- Factors to consider before recommending a switch of medications:
  - Whether or not the traveller is still in the malaria area
  - Which antimalarial the traveller is currently taking (i.e., a causal or suppressive prophylactic)

Table III is a guide for switching prophylactics.

What should be done if a dose of malaria prophylaxis is missed?

Drugs with a longer half-life, such as mefloquine, are more "forgiving" in that a day or two late is unlikely to affect blood levels noticeably.[4] The traveller can take the missed dose and resume weekly doses on the original scheduled day of the week. If more than two days late, blood levels may not be adequate. The traveller should take the missed dose and then reschedule the following weekly doses on the same day of the week that the missed dose was taken.[4]

Drugs with a shorter half-life (doxycycline, proguanil) are less "forgiving" and blood levels are not expected to be adequate if the traveller is 1–2 days late in taking the dose. The missed dose should be taken as soon as possible, and the subsequent daily doses adjusted to the new time of day.[4]

Table IV: Half-life of various prophylactics[6]

Drug	Half-life
Mefloquine	2–4 weeks
Doxycycline	15–24 hours
Atovaquone	2–3 days
Proguanil	12–25 hours

Does taking malaria prophylaxis "mask" the symptoms of malaria?

Malaria prophylaxis may delay the symptoms of malaria, as most work as suppressive prophylactics. Milder symptoms due to a delay of onset is due to the disease being milder, not masked. As the disease progresses, the symptoms will present with the same intensity. If a traveller who has travelled to, or is travelling in, a malaria area presents with febrile symptoms, malaria should always be ruled out first, even if it seems longer than the typical time for malaria symptoms to appear.[5]

Appropriate malaria prophylaxis greatly reduces the chances of a high-risk person developing fatal disease. However, it is important to note that no malaria chemoprophylaxis is 100% effective and mosquito bite prevention measures are essential.[1,5] Not recommending malaria prophylaxis to a traveller based on the myth that malaria prophylaxis may mask malaria symptoms, can have detrimental consequences.[5]

Table III: Guide for switching prophylactics[5]

Currently taking	Switching to	Comments
Mefloquine	Doxycycline	Can be done without a washout period
	Atovaquone-proguanil	If already in the area, take for 4 weeks (not 7 days) after leaving area (drugs have different action sites)
Doxycycline	Mefloquine	Not advised – mefloquine needs to be taken a week before entering the malaria area
	Atovaquone-proguanil	If already in the area, take for 4 weeks (not 7 days) after leaving area (drugs have different action sites)
Atovaquone-proguanil	Mefloquine	Not advised – mefloquine needs to be taken a week before entering the malaria area
	Doxycycline	Can be done

Conclusion

An awareness and understanding of what is required to effectively counsel a traveller going to a high-risk malaria area is essential. Certain population groups, such as pregnant women, infants and children under 5 years of age, splenectomised patients and the immunocompromised are at highest risk of contracting severe malaria, and travel to high-risk areas for these groups should be discouraged. Where travel cannot be avoided, referral to a medical practitioner is advised. Pharmacists should be aware of the symptoms and signs of malaria and any patient presenting in the pharmacy with a fever or flu-like symptoms and a history of travel to a malaria area in the preceding year must be immediately and urgently referred to a medical facility for a malaria test. Early diagnosis of malaria is essential.

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