South African Family Practice 2016; 58(5):68-72

S Afr Fam Pract
ISSN 2078-6190 EISSN 2078-6204

REVIEW

The Malaria Season Is Upon Us

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Abstract

The arrival of our summer rains brings with it *Anopheles* mosquitos buzzing around our ankles with the prospect of a nutritious meal. Unbeknownst to the female *Anopheles* mosquito, she has increased the risk of our becoming an annual statistic by being infected with malaria. Malaria is endemic in the Limpopo, Mpumalanga and Northern KwaZulu-Natal provinces, but the unpredictable occurrence of Odyssean or airport/suitcase malaria anywhere in South Africa highlights the fact that we should remain vigilant for the possibility of a rogue infection. Unfortunately for those living in sub-Saharan Africa, the likelihood of being infected with potentially lethal *Plasmodium falciparum* is high; necessitating the need to be informed of the initial symptoms of malaria and to ask the right questions about effective measures to prevent mosquito bites and being infected with malaria. The recommendation of taking chemoprophylaxis (mefloquine, atovaquone-proguanil, doxycycline) along with the correct clothing, DEET repellents and insecticidal treated bed nets should be considered when entering these areas during September to May. The definitive diagnosis of malaria warrants the immediate administration of artemether-lumefantrine to clear the parasite; whilst the addition of primaquine is required to eradicate the extra-erythrocytic stages of *P. ovale, P. malariae* or *P. vivax* in a mixed infection.

Keywords: malaria, prophylaxis, treatment, *Anopheles*, South Africa

Introduction

With the onset of the summer rains nearly upon us, the increased risk of malaria infections will necessitate the need for patient awareness of preventative measures and chemoprophylaxis.[1] Although the number of reported malaria cases has dramatically decreased since the last epidemic ten years ago, malaria still remains endemic in South Africa.[2] As such, patients and health care professionals should not be complacent with regards to possible malaria infections, especially during the period of September to May when there is a moderate to high risk of contracting malaria. Malaria is not evenly distributed within South Africa with malaria transmission limited to the north-eastern part of South Africa, mainly in the low altitude (below 1000 m) areas of Limpopo, Mpumalanga and northern KwaZulu-Natal.[3] South Africans however remain at risk from imported or Odyssean malaria from countries such as Swaziland, Mozambique, Angola, Zambia and Malawi where malaria is a risk throughout the year, whilst the risk is seasonal in Zimbabwe, Botswana and Namibia.[2]

Malaria - the parasite and its detection

Malaria is transmitted by the female *Anopheles* mosquito following a blood meal from its second nutritious host, namely humans. *Plasmodium* is the protozoan that specifically infects man, with *P. falciparum* being the most lethal species, infecting more than 90% of patients in sub-Saharan Africa, whilst *P. ovale*, *P. malariae* and *P. vivax* cause milder illness.[1]

The incubation period between infection with malaria and presentation of the initial symptoms ranges from 7–30 days for *P. falciparum*, although this could be longer in patients taking chemoprophylaxis and some antibiotics, whilst it can take up to a year before presenting with symptoms if infected with *P. ovale* or *P. malariae*.[1] The intra-erythrocytic parasitic stage ends with the rupture of the erythrocyte to release the daughter merozoites, resulting in haemolysis which triggers the initial clinical symptoms. There are several symptoms with which patients could present (Table I), with flu-like symptoms and acute fever important indicators, especially if the patient has recently travelled to a malaria area. For those patients living in malaria areas, a possible malaria infection should be urgently investigated regardless of the time of year or if prophylaxis has been taken in order to differentiate with the symptoms of influenza over the months of May to September.

Treatment should ideally be based on microscopically observed parasites, but in areas where the symptoms are well recognised due to high infection rates, treatment is initiated as soon as a patient presents with symptoms to prevent the development of severe malaria.[1,4] Rapid antigen detection diagnostic tests (RDTs) are now more widely available to assist with diagnosis,

Table I: Clinical and laboratory indicators of uncomplicated and severe malaria[4,7-9]

Common presenting symptoms	Physical findings	Laboratory findings: uncomplicated malaria	Symptoms of severe malaria	Laboratory findings: severe malaria
• Headaches • Fatigue • Abdominal discomfort • Myalgia • Fever • Chills • Perspiration • Anorexia • Nausea/vomiting • General malaise	• Elevated temperatures (≥ 37.5°C) • Rigors • Weakness • Splenomegaly • Mild jaundice • Hepatomegaly • Increased respiratory rate	• Microscopic confirmation of malaria/species differentiation • Mild anaemia • Mild thrombocytopenia • Elevated bilirubin • Elevated aminotransferases	• Fever • Impaired consciousness • Multiple seizures • Prostrations • Respiratory distress or pulmonary oedema • Jaundice • Spontaneous bleeding/ DIC	• Parasite density > 4% • Haemoglobin < 5 g/dL • Metabolic acidosis (pH < 7.3; plasma bicarbonate < 15 mmol/L, serum lactate > 5 mmol/L) • Hypoglycaemia (< 2.2 mmol/L) • Renal impairment (oliguria < 0.4 ml/kg bodyweight/hr; serum creatinine > 265 µmol/L) • Thrombocytopenia (< 50,000/µL) • Liver transaminase > 3 times normal

if a laboratory is not readily at hand, and by detecting malarial antigens from *P. falciparum* or *P. vivax*, the appropriate medication can be administered.[5] The only drawback of the RDTs is that they do not quantitate the percentage parasitaemia, thus not differentiating between uncomplicated or severe malaria – as such, the presenting symptoms and additional laboratory tests need to complement the positive RDT result (Table I).[5] If initial RDT and microscopic tests do not confirm a malaria infection, the test should be repeated regularly and urgently until a malaria infection is confirmed, patient recovers or is excluded with another definitive diagnosis.[6] Other infections such as influenza, typhoid, tick bite fever, trypanosomiasis, hepatitis, dengue or other arboviruses, avian influenza, MERS-CoV, HIV, meningitis/encephalitis and viral haemorrhagic fevers should be excluded.[7]

The malaria vector

Not all mosquitoes carry the malaria parasite and of the approximately 430 *Anopheles* species, only 30–40 species transmit malaria.[10] The most common species in southern Africa are *An. arabiensis, An. funestus* and *An. gambiae complex*.[11] In order to differentiate between malaria transmitting *Anopheles* and other mosquito genera, such as *Aedes* and *Culex* species, firstly note how she settles on the skin - her abdomen sticking up in the air rather than parallel to the surface on which she is resting as for non-malaria vectors (Figure 1). *Anopheles* mosquitoes are dark brown to black in colour and can also be distinguished from other mosquitoes by the presence of discrete blocks of black and white spots on the wings.[10]

The *Anopheles* mosquito larvae are at home in a wide range of habitats, including fresh or salt water, at the edges of streams or in temporary rain pools.[11] But any undisturbed water in rain water puddles, empty plant-pots and ponds can be used to nurture the larvae's development. A female mosquito can lay between 50–200 eggs at a time and the eggs normally take 5–14 days to mature under optimal conditions. The adult female can live up to 2–4 weeks, with both male and female feeding on nectar for energy. However, the female requires a blood meal for the development of her eggs.[10] Ideally, if the breeding sites for mosquitoes could be diminished, infection rates could be decreased.

Prevention and treatment of malaria

The progression of a malaria infection can be rapid depending on the patient's health status and severity of infection, requiring mandatory monitoring of a patient to ensure optimal therapy is administered. As such, there are five simple rules that patients should be aware of in order to be excluded as a national statistic (Figure 2).

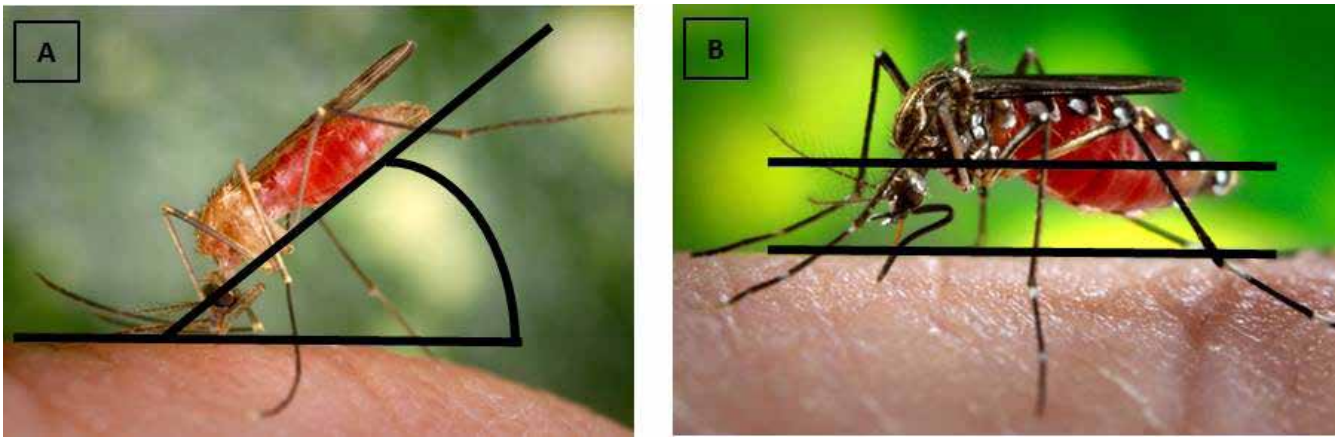

Figure 1: The resting/feeding stance of the female *Anopheles* species (A), which differentiates them from other non-malaria transmitting vectors, such as *Aedes aegypti* (B).[12]

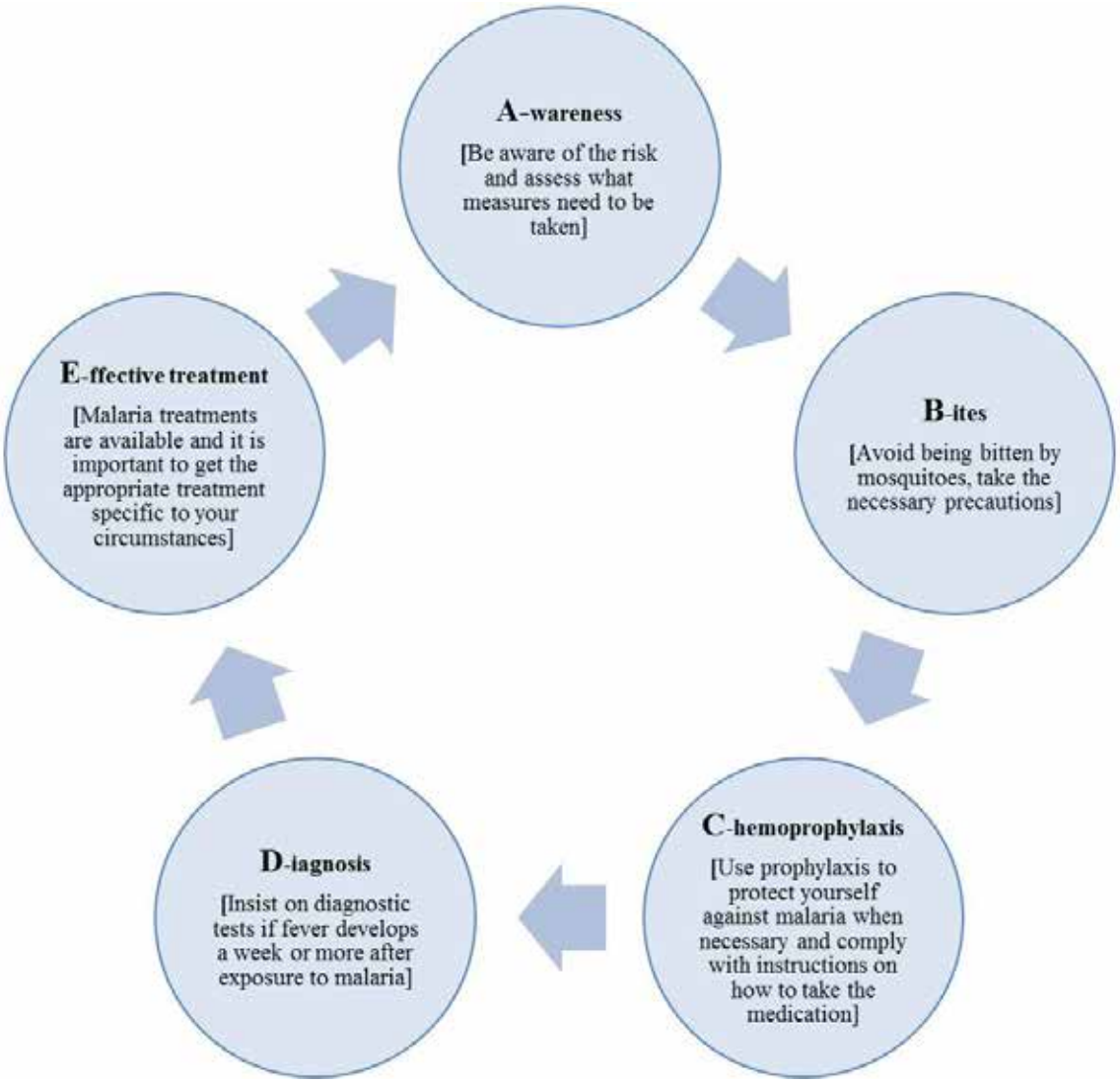

Figure 2: The 'ABC' of malaria prevention.[1]

Avoiding mosquito bites

Prevention of a mosquito bite still remains one of the most important mainstays of malaria prophylaxis. The strict adherence to non-pharmacological measures is essential to reduce the number of bites. All three of the main vectors in southern Africa prefer to feed close to the ground, making unprotected lower legs, ankles and feet the preferred target regardless of whether the host is indoors or outdoors.[13] With this in mind, long sleeves and trousers are effective in deterring mosquito bites. The application of a 20–50% diethyltoluamide (DEET) insect repellent to the exposed skin along with wearing permethrin-impregnated clothing reduces the risk of bites. In addition the burning of insect coils, sleeping under insecticide-treated bed nets and ceiling fans, along with mosquito screens on the doors and windows, provide additional protection.[2,9] However, one needs to remain cautious of novel and non-certified methods of preventing mosquito bites which are flooding the market, as these may create a misleading sense of protection.

Chemoprophylaxis

The chemoprophylatic drugs recommended in South Africa are still mefloquine, doxycycline or atovaquone/proguanil, depending on the patient profile. The latter combination is the prophylaxis of choice as it is well tolerated, efficacious and, importantly, has improved compliance due to its shorter prophylactic course (Table II).[8,9] Ideally pregnant women and young children should be discouraged from entering a malaria area due to their increased risk of being infected and the dire consequences an infection could have on the developing fetus and newborn.[4,9] Although chemoprophylaxis is highly advisable, patients should be cautioned that despite taking the prophylaxis, they should seek immediate medical attention if they develop 'flu-like' symptoms or a fever as no prophylactic antimalarial is 100% effective.[1]

Treatment

With the introduction of an effective vaccine for Southern Africa not expected in the near future,[14,15] efficient management of the currently effective antimalarial agents is essential. The

Table II: Pharmacological profile of prophylactic drugs[1,4,8,9]

Prophylactic antimalarial agents	Dosing schedule			Adverse effects	Contra-indications	Special prescribers notes
	Before entering area	In malaria area	After leaving area			
Mefloquine	once weekly			Dizziness, vertigo, GIT disorders, headache, sleep disturbances, mood changes, visual disturbances	Children < 5kg, depression, epilepsy, anxiety, severe hepatic or renal impairment, thrombocytopenia, cardiac conduction abnormalities, those needing fine motor coordination	• Prophylaxis of choice during pregnancy • Safe in lactation • Take after a meal with plenty of fluid
	1–2 weeks	weekly	4 weeks			
Doxycycline	once daily			GIT intolerance (nausea, vomiting, diarrhoea, oesophagitis), photosensitivity, candidiasis	Pregnancy, children < 8yrs, lactation	• Take with adequate fluid in an upright position, at the same time each day
	1–2 days	daily	4 weeks			
Atovaquone/ Proguanil	once daily			Gastric intolerance (usually subsides), mouth ulcers, stomatitis	Children < 11 kg, severe renal impairment, pregnancy/lactation not established	• Take with a fatty diet/ milk, at the same time each day
	1–2 days	daily	1 week			

development and spread of drug resistance is a factor that needs to be constantly addressed in light of the recent reports of artemisinin resistance in Southeast Asia and the prospect of the resistance emerging in Sub-Saharan Africa.[2] At this time, the South African National Centre of Infectious Diseases has not detected any artemisinin-resistant phenotypes, but the status is being constantly monitored [J. Raman, pers. comm.].

Upon the presentation of malaria symptoms, it is essential to initiate therapy as soon as possible ensuring differentiation between uncomplicated and severe malaria (Table I). In South Africa, uncomplicated malaria is treated with artemether/ lumefantrine, where this combination targets both the intra-erythrocytic stages and interferes with transmission by inhibiting gametocytes.[9,16] Artemisinin-based antimalarial agents should be reserved solely for the treatment of malaria and not used prophylactically to delay the development of resistance in South Africa.[4,6] This combination rapidly decreases the parasite density within 24–48 hours, as long as the appropriate weight-dose has been administered and an adequate concentration of the drug has been absorbed (which is optimised by taking it with a fatty meal or milk). Patients able to ingest tablets should be monitored to ensure adequate absorption and if vomiting occurs within half an hour of taking the tablet, the full dose should be repeated or half the dose if between 30 to 60 minutes.[9] In patients with continued vomiting, medication should be administered intravenously until the patient can take the medication orally. Those who are at a higher risk of developing severe malaria such as pregnant women, children, elderly and immunocompromised patients should be admitted for treatment to ensure close monitoring for any complications. The artemether/lumefantrine combination has a significant effect on mortality outcomes when compared to administration of quinine.[7] In pregnant women in their first trimester and children (< 5kg), oral quinine combined with clindamycin should be administered for a week.[6] Doxycycline can replace clindamycin in combination with quinine when artemether/lumefantrine is unavailable.[4] While, in the treatment of severe malaria, intravenous artesunate is the more efficacious drug compared to intravenous quinine, which potentiates hypoglycaemia and is cardiotoxic.[4] Artesunate is available on a named-patient basis after approval from the South African Medical Control Council (MCC).[9]

In South Africa and countries such as Zimbabwe, Botswana, Ghana and Kenya, there is a low occurrence of *P. ovale* and *P. vivax* (10%). However, when traveling to Brazil, China and India where the occurrence of *P. vivax* is more prevalent (50–100%), the chemoprophylatic drugs used in South Africa are also recommended (Table I).[17] In most countries, resistance to chloroquine and/or mefloquine exists, as such uncomplicated mixed infections that include *P. falciparum* should be treated with artemether/lumefantrine followed by a 14-day course of oral primaquine to eradicate the hepatic stages of *P. malariae* or *P. ovale*. Primaquine is only available on a named-patient basis after approval from the South African Medicines Control Council (MCC).[9] It has been proposed that, due to the gametocidal activity of primaquine, it should be co-administered along with artemether/lumefantrine to reduce transmission.[9,18,19] However, with the higher prevalence of glucose-6-phosphate dehydrogenase (G6PD) deficiency in Africa, adequate laboratory investigations are required before this adjunct therapy is used, as severe haemolysis and fatalities have been reported.[6,7,20] South African-based studies are still to confirm the efficacy and safety of this adjunct. If no immediate medical assistance is available, it is always sage advice for travelers to take standby treatment of a full six dose course of artemether/ lumefantrine to initiate therapy when malaria symptoms are first experienced.[9]

Conclusion

Asking the right questions, knowledge of your travel destination and sound medical advice are all critical to the prevention of malaria infections. Being prepared for a malaria infection by packing appropriate standby medicine and knowing the location of travel or medical clinics that can ensure the immediate initiation of treatment is essential to eradicate the infection and ensure recovery. As such, patients and health care professionals should be ever vigilant against this infectious menace.

Acknowledgements

I wish to acknowledge the support from the School of Therapeutic Sciences to attend the Therapeutic Sciences NUpS Writing Retreat to complete this publication, the South African NRF for financial support for malaria studies and Prof L Koekemoer, Prof A Stewart and Mr M Vally for reviewing the manuscript.

References

1. South African Department of Health. Guidelines for the Prevention of malaria in South Africa. 2009. Accessed June 2016, available at http://www.fidssa.co.za/Content/Documents/Malaria%20Prevention_NDOH%202009.pdf
2. WHO. World Malaria Report 2015. Accessed June 2016, available at http://apps.who.int/iris/bitstream/10665/200018/1/9789241565158_eng.pdf
3. Malaria risk map for SA. 2016. Accessed June 2016, available at http://www.health.gov.za/index.php/component/phocadownload/category/287
4. WHO. Guidelines for the treatment of malaria. Third Edition. 2015. Accessed June 2016, at http://apps.who.int/iris/bitstream/10665/162441/1/9789241549127_eng.pdf
5. Maltha J, Gillet P, Jacobs J. Malaria rapid diagnostic tests in endemic settings. Clin Microbiol Infec. 2013;19:399-407.
6. South African Department of Health. Guidelines for the treatment of malaria in South Africa. 2009. Accessed June 2016, available at http://www.kznhealth.gov.za/medicine/2009malariaguideline.pdf
7. Lalloo DG, Shingadia D, Bell DJ, Beeching NJ, Whitty CJM, Chiodini PL. UK malaria treatment guidelines 2016. J Infection. 2016;72:635-649.
8. Blumberg LH. Recommendations for the treatment and prevention of malaria: Update for the 2015 season in South Africa. S Afr Med J. 2015;105:175-178.
9. SAMF. Antiparasitic products. In: Rossiter D, ed. South African Medicines Formulary. Cape Town: Health and Medical Publishing Group; 2016:514-524.
10. CDC. *Anopheles* Mosquitoes. CDC, 2015. Accessed June 2016, 2016, available at https://www.cdc.gov/malaria/about/biology/parasites.html
11. Brooke B, Koekemoer L, Kruger P, Urbach J, Misiani E, Coetzee M. Malaria vector control in South Africa. S Afr Med J. 2013;103:784-788.
12. CDC Public Health Image Library. Photo ID: 18753 and 9257. Accessed June 2016, available at http://phil.cdc.gov/phil/details.asp
13. Braack L, Hunt R, Koekemoer LL, et al. Biting behaviour of African malaria vectors: 1. where do the main vector species bite on the human body? Parasite Vector. 2015;8:1-10.
14. Gupta A, Chaphalkar SR. Current approaches and problems in malaria vaccine development. Eur J Biol Res. 2016;6:14-10.
15. Delrieu I, Leboulleux D, Ivinson K, et al. Design of a Phase III cluster randomized trial to assess the efficacy and safety of a malaria transmission blocking vaccine. Vaccine. 2015;33:1518-1526.
16. World Wide Antimalarial Resistance Network (WWARN) Lumefantrine PK/PD Study Group. Artemether-lumefantrine treatment of uncomplicated *Plasmodium falciparum* malaria: a systematic review and meta-analysis of day 7 lumefantrine concentrations and therapeutic response using individual patient data. BMC Med. 2015;13:1-19.
17. Gershman MD, Jentes ES, Stoney RJ, Tan KR, Arguin PM, Steele SF. Yellow Fever & Malaria Information, by Country. CDC Health Information for International Travel United States of America: Oxford University Press; 2016.
18. Atroosh WM, Al-Mekhlafi HM, Snounou G, et al. Sustained efficacy of artesunate-sulfadoxine-pyrimethamine against *Plasmodium falciparum* in Yemen and a renewed call for an adjunct single dose primaquine to clear gametocytes. Malaria J. 2016;15:1-11.
19. Cabrera M, Cui L. In vitro activities of primaquine-schizonticide combinations on asexual blood stages and gametocytes of *Plasmodium falciparum*. Antimicrob Agents and Ch. 2015;59:7650-7656.
20. Monteiro WM, Moura-Neto JP, Recht J, Bassat Q, Lacerda MVG. Fatal primaquine-induced hemolysis in a patient with *Plasmodium vivax* malaria and G6PD A(–) variant in the Brazilian Amazon. Clin Infect Dis. 2016;62:1188.