

CLINICAL ALERT

Recommendations for the treatment and prevention of malaria: Update for the 2015 season in South Africa

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Notified malaria cases in South Africa (SA) decreased significantly over the past 14 years, from over 60 000 in the 1999/2000 malaria season to less than 13 000 in 2013/2014. However, the past two seasons have seen increases in both local and imported cases. Mozambique contributes the highest number of imported cases in SA. This update provides recommendations for malaria treatment and prevention (in travellers and residents) for 2015.

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Management of malaria

Key components of successful management are early and accurate diagnosis (Table 1) and prompt treatment with effective drugs.

Treatment should ideally be based on confirmed parasitological diagnosis.^[1,2] Microscopy of Giemsa-stained thick and thin blood smears remains the diagnostic mainstay.^[3] Rapid antigen detection diagnostic tests (RDTs) are more widely accessible than expert microscopy, provide prompt results and are adequately sensitive for *Plasmodium falciparum* infections. However, RDTs cannot quantify parasite density (so do not detect hyperparasitaemia that indicates severe malaria) and are less sensitive for non-falciparum species than for falciparum infections. RDTs are unsuitable for monitoring treatment response because of antigen persistence.^[4] A negative (rapid or microscopy) test does not exclude malaria; repeat testing within 8 - 24 hours, without attempting to coincide with fever peak timing, is mandatory until a positive result or an alternative definitive diagnosis is achieved. Blood smears should be checked for malaria whenever thrombocytopenia is unexpectedly identified. Test any patient with unexplained fever for malaria, even in the absence of a travel history. Occasionally, infected mosquitoes are transported from endemic areas in suitcases and vehicles (Odyssean malaria).^[5] All malaria cases *must* be notified to local health authorities.

Treatment of malaria

The choice and route of treatment depends primarily on disease severity, which is often underestimated. Uncomplicated malaria is symptomatic infection without signs of severity or evidence of vital organ dysfunction. Persistent vomiting, clinical jaundice, change in mental state or increase in respiratory rate constitutes severe malaria (Table 2).^[6,7]

Treat uncomplicated malaria with artemether-lumefantrine (Coartem) (Table 3).^[2] For optimal absorption it must be taken with milk or fat-containing food. Adequate fluids, temperature control with paracetamol, and careful follow-up are important. Avoid non-steroidal anti-inflammatory agents. Patients should respond clinically and parasitologically within 24 - 48 hours. Consider poor compliance, misdiagnosis and possible drug resistance if no significant improvement occurs within 72 hours. Artemether-lumefantrine remains efficacious in South Africa (SA),^[8,9] with no reports of artemisinin resistance in Africa as yet. In the rare event of artemether-lumefantrine treatment failure despite full compliance, give a full directly observed 7-day course of oral quinine (plus doxycycline or clindamycin) in hospital.

Oral quinine, combined with 7 days of doxycycline, remains an alternative to artemether-lumefantrine (Table 4), but compliance is poor. In pregnancy or children aged <8 years, substitute clindamycin for doxycycline (Table 4). Doxycycline or clindamycin add no early

Table 1. Diagnosis of malaria

Keep a high index of suspicion for malaria in travellers to, or residents of, malaria transmission areas presenting with fever or other 'flu-like illness, irrespective of the time of year, intensity of transmission or use of chemoprophylaxis. Always take an adequate travel history.

Typical presentation: paroxysms of fever and rigors in adults, also headache, myalgia, loss of appetite, nausea and vomiting. In young children, fever, lethargy, poor feeding, vomiting and diarrhoea are most common.

Important differential diagnoses: meningitis, African tick-bite fever, typhoid, viral haemorrhagic fever, trypanosomiasis.

Progression to severe disease may be rapid, particularly in non-immune and immune-compromised persons, young children and pregnant women.

Often missed in patients with comorbid disease.

Frequently misdiagnosed in pregnancy, requiring differentiation from pregnancy complications including intrauterine and urinary tract infections.

treatment benefit, so are started only once symptoms improve, as gastrointestinal side-effects may exacerbate those of quinine.

Drug interactions

Concomitant use of certain other drugs (e.g. efavirenz, rifampicin) may alter blood concentrations of artemether-lumefantrine and quinine. There is no evidence of the clinical significance of these interactions, but full adherence and fat co-administration is advised, and response to treatment should be monitored particularly carefully.

Pregnancy

First trimester. Supervised 7-day course of oral quinine plus clindamycin.

Second and third trimesters. Artemether-lumefantrine is considered safe and efficacious.

Large adults

Artemether-lumefantrine is registered in SA only for use in patients weighing ≤65 kg. Minimal pharmacokinetic data exist for larger patients; one study suggests a trend towards increased risk of treatment failure in patients >80 kg.^[10] Again, adequate adherence and fat co-administration is important, with careful monitoring of response. If adherence is assured, consider administering the same total dose over 5 days (dosing at 0, 8, 24, 48, 72 and 96 hours).

Recommendations for non-falciparum malaria

Malaria species should be confirmed by a reliable laboratory. Non-falciparum infections are usually uncomplicated, but occasionally produce severe illness. Use artemether-lumefantrine for initial therapy of uncomplicated *P. vivax* and *P. ovale* infections. To prevent relapses, this should be followed by a course of primaquine after excluding glucose-6-phosphate dehydrogenase (G6PD) deficiency.

Table 2. Clinical and laboratory criteria for severe malaria (any one or combination of these criteria applies)

Clinical	
Impaired consciousness, multiple convulsions	
Respiratory distress, acidotic breathing, pulmonary oedema	
Circulatory collapse	
Jaundice	
Bleeding	
Prostration	
Laboratory	
Hypoglycaemia (blood glucose <2.2 mmol/L)	
Acidosis (plasma bicarbonate <15 mmol/L or serum lactate >5 mmol/L)	
Hepatic transaminases >3 times normal	
Renal impairment (serum creatinine >265 μmol/L or rapidly rising creatinine or urine output <400 mL/day in an adult)	
Haemoglobin <5 g/L	
Parasitaemia ≥5%	
≥5% neutrophils contain malaria pigment	
Presence of schizonts of <i>P. falciparum</i> in peripheral blood smear	

Table 3. Dosing schedule for artemether-lumefantrine (Coartem)

Body weight (kg)	Time of dosing (hours) and number of tablets					
	0	8 - 12	24	36	48	60
5 - 14	1	1	1	1	1	1
15 - 24	2	2	2	2	2	2
25 - 34	3	3	3	3	3	3
≥35	4	4	4	4	4	4

Table 4. Dosing schedule for oral quinine with doxycycline or clindamycin

Drug	Schedule
Oral quinine	10 mg/kg 8-hourly for 7 days
Doxycycline	200 mg stat, thereafter 100 - 200 mg once daily, or 3.5 mg/kg once daily for 7 days
Clindamycin	10 mg/kg bd for 7 days

Table 5. Dosing schedule and adverse effects for mefloquine, doxycycline and atovaquone-proguanil

Chemoprophylactic	Schedule	Adverse effects
Mefloquine (Lariam, Mefliam)	Weekly, starting 1 - 2 weeks before travel, weekly while there and continue for 4 weeks after Adults: 250 mg weekly Children: 5 mg/kg weekly Not recommended for children <3 months or <5 kg	Gastrointestinal, headache, dizziness, imbalance, mood changes, insomnia, nightmares, and rarely, psychosis. Increased risk of eye disorders Contraindications: epilepsy, neuropsychiatric disorders, those who require fine motor co-ordination, divers and pilots
Doxycycline (daily)	Daily, starting 1 day before travel, daily while there and continue for 4 weeks after Adults: 100 mg daily Not recommended for children <8 years	Skin photosensitivity, oesophagitis, upper gastrointestinal symptoms, vaginal candidiasis or diarrhoea (normal flora disruption)
Atovaquone-proguanil (Malanil, Numal)	Daily, starting 1 day before travel, daily while there and continue for 1 week after Adults: 1 tablet daily Children >11 kg: Malanil Paediatric at prescribed dose per body weight	Adverse reactions uncommon; include headache, nausea, vomiting, abdominal pain, diarrhoea

Table 6. Drug choice according to patient factors

Patient factor	Mefloquine	Doxycycline	Atovaquone-proguanil
Pregnancy – avoid travel to malaria areas.	Now recommended for all trimesters ^[12,13] if travel is necessary.	Contraindicated	Contraindicated owing to lack of data.
Young children – avoid taking children <5 years to high-risk areas.	Can be used in children >3 months or >5 kg. Generally well tolerated by children.	Use only in children >8 years.	Paediatric tablets can be given to children >11 kg. Breaking of tablets is not recommended.
Persons requiring long-term prophylaxis	Can be used for up to 3 years. Longer-term use may be justified by risk of malaria.	Can be safely used for up to 2 years. Longer term use may be justified by risk of malaria.	Can be used confidently for up to 1 year. Longer-term use may be justified by risk of malaria.
HIV-positive (on ARVs) ARVs = antiretrovirals.		Best option	

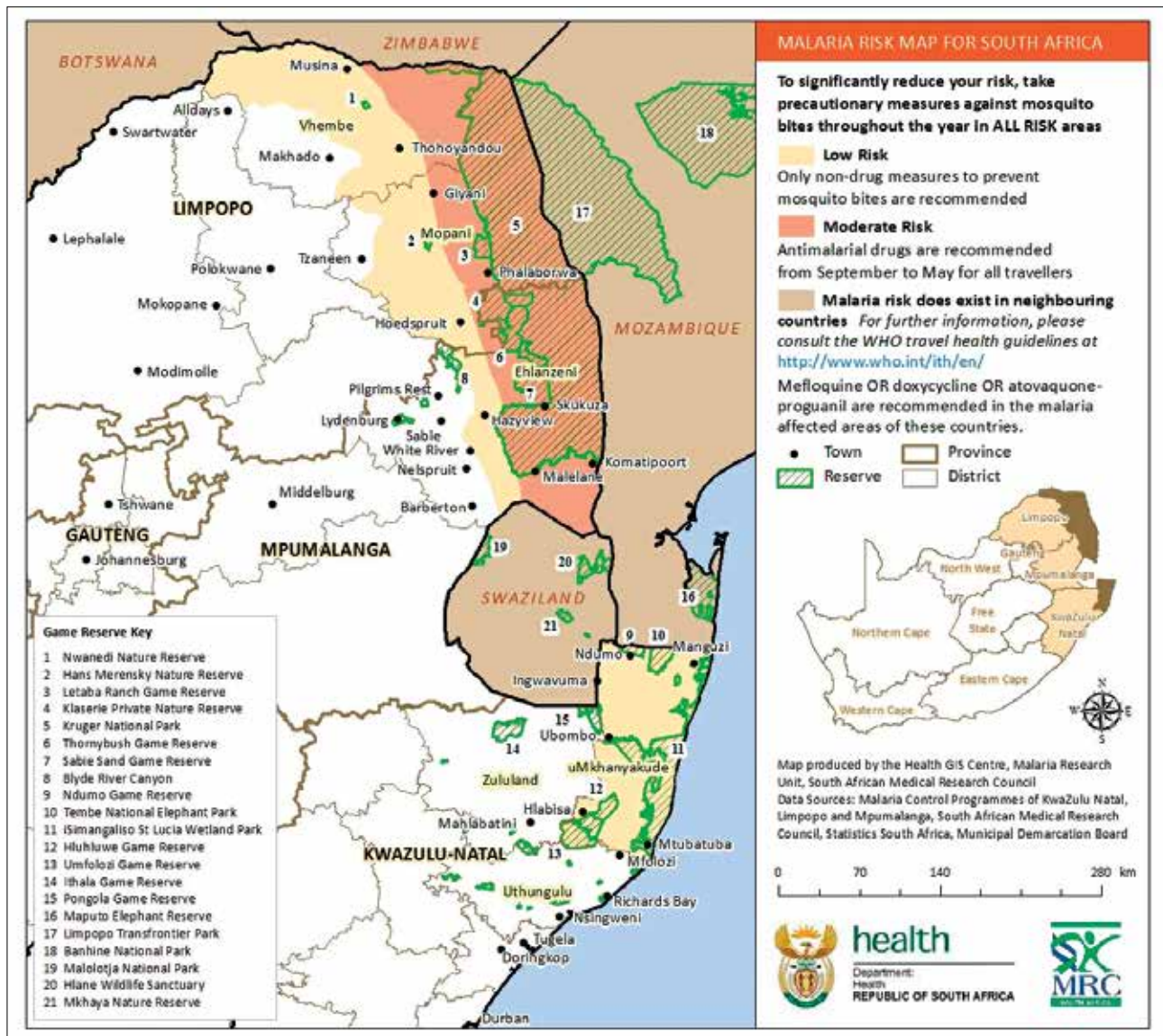


Fig. 1. Malaria risk map for SA (adopted 2014).

The recommended dose in children is 0.25 - 0.3 mg/kg daily for 14 days, and that for adults is 15 mg daily for 14 days. Currently primaquine is only available on a named-patient basis with Section 21 MCC approval.

Severe malaria (Table 5)

Severe malaria is a medical emergency requiring prompt parenteral treatment, intensive nursing care, and careful monitoring and management of complications.^[6,7] Intravenous artesunate (2.4 mg/kg

at 0, 12 and 24 hours, then daily until the patient is able to tolerate oral treatment) is preferred treatment, but is currently unregistered and only available on a named-patient basis with Section 21 MCC approval.^[2,11] When intravenous artesunate is not promptly available, intravenous quinine (with an initial loading dose of 20 mg/kg and then maintenance doses of 10 mg/kg, each dose slowly infused over at least 4 hours) is initiated urgently and given 8-hourly until oral treatment is tolerated. Follow with a complete course of artemether-lumefantrine.^[2] Reassess frequently to ensure that all complications are promptly detected and optimally managed.

Critical issues in management of severe malaria

Hypoglycaemia. Urgently exclude (or administer empiric glucose) if there is a depressed level of consciousness or convulsions. Repeat glucose monitoring 4-hourly.

Renal failure. This is a frequent, early complication in adults. Severe malaria requires careful fluid management, with frequent measurement of renal function (urea, electrolytes and creatinine), ongoing monitoring of urine output and judicious fluid administration. Strictly avoid overhydration, as the acute respiratory distress syndrome is a common and difficult-to-treat complication, particularly in pregnancy.

Prevention of malaria

Prevention of mosquito bites is the mainstay of malaria prevention. Malaria-transmitting mosquitoes generally bite at night, so people in malaria-endemic areas should ideally remain indoors from dusk to dawn, and sleep under insecticide-treated bednets in rooms with screened windows and doors. Fig. 1 shows endemic areas in SA; residents and travellers in these areas should take necessary precautions to avoid mosquito bites.

Effective repellents contain DEET (diethyl toluamide). Use products containing 20 - 50% DEET for long-lasting protection for adults and children aged >2 months. Products containing >50% DEET have no additional benefit. Avoid applying to eyes or mouth.

Additionally, travellers to malaria-endemic areas should use chemoprophylaxis depending on the malaria risk assessment. Three similarly effective chemoprophylactic agents are currently registered in SA (Table 5), all requiring a doctor's prescription. Selection should be based on patient factors (Table 6) and which option is likely to be best tolerated for optimal adherence.

Scope of protection

Chemoprophylactics are most effective against parasite asexual blood stages. While they will prevent initial illness caused by all species, they will not prevent relapses due to *P. vivax* and *P. ovale*.

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