Managing Re-emergent Malaria in South Africa

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Abstract

Malaria is a re-emerging disease in South Africa with a sustained upward trend in case incidence and deaths in the past two decades. Burgeoning travel by non-immune travelers into malaria areas, parasite carriers and infected mosquitoes into malaria-free areas, the variable incubation period and life-threatening nature of *Plasmodium falciparum* malaria make malaria one of the most important causes of febrile disease in South Africa. Every case of unexplained or unusual febrile disease presenting to a clinician in South Africa should therefore be investigated to exclude malaria and a careful travel history taken, as delays in diagnosing malaria and initiating effective therapy may prove fatal. Chloroquine resistance throughout sub-Saharan Africa precludes its use as a single prophylactic agent, but it must be emphasized that no chemoprophylactic agent is 100% effective and so careful advice on effective measures to prevent *Anopheline* mosquito bites should be provided to all travelers to malaria-endemic areas. The introduction of rapid card tests has enhanced field diagnosis of malaria. Single dose therapy with sulphadoxine-pyrimethamine (S-P) remains largely effective for treating uncomplicated malaria but careful monitoring is essential. If there are any features of organ dysfunction, treatment with quinine sulphate, preferably in hospital, is indicated. It is envisaged that combination therapy, possibly including an artemisinin derivative to retard the evolution of drug resistance, will characterize the future therapy of uncomplicated malaria.

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Introduction

Malaria accounts for 9% of all disease in Africa and over 1 million people, mainly small children, die due to malaria annually.[1] During the last decade malaria prevalence in Africa has increased, a trend attributed to resistance of plasmodia to chloroquine, resistance of anophelines to insecticides and huge-scale migration, with a concomitant rise in malaria specific mortality.[2,3] South Africa is one of the areas where malaria is re-emerging, with the incidence in humans having markedly increased in the past two decades (Table 1).[4]

Table 1: Malaria cases and deaths notified to the National Department of Health, South Africa

Year	Malaria cases notified	Malaria deaths
1971	364 cases	5 deaths
1981	2343 cases	9 deaths
1991	4693 cases	19 deaths
1998	24313 cases	170 deaths
1999 (July)	36321 cases	248 deaths

The World Health Organization responded to the malaria disaster by launching the Roll Back Malaria initiative in July 1998 with a particular focus on African malaria. The goal of Roll Back Malaria is to reduce the burden of malaria disease and thus poverty in developing countries where there is limited health infrastructure. Key focus areas include early detection of malaria cases, rapid treatment with effective therapy, integrated control strategies and improved collaboration between control programs and researchers.

However while awaiting the benefits of this initiative it is essential for family practitioners working in South Africa to effectively contribute towards preventing unnecessary malaria deaths. Burgeoning travel by non-immune travelers into malaria areas, asymptomatic human parasite carriers and infected mosquitoes into malaria-free areas, the variable incubation period and life-threatening nature of *Plasmodium falciparum* malaria will continue to guarantee the importance of malaria in clinical practice for the foreseeable future.

Diagnosing Malaria

Every case of unexplained or unusual febrile disease presenting to a clinician in South Africa should be investigated to exclude malaria. A careful travel history to ascertain travel into malaria areas during the previous six months is obligatory in every case of fever or flu-like symptoms. A negative history of recent travel does not however preclude malaria as certain forms of malaria may cause recurrent attacks many years after inadequate therapy and "hitch-hiking" infected mosquitoes are also well described.[5]

As the incubation period for *falciparum* malaria is usually 7-10 days, symptoms occurring before 7 days after possible exposure are not due to malaria. A prolonged incubation period may follow inadequate or incorrect prophylaxis or use of medication with anti-malarial effect for other medical conditions e.g. tetracycline, erythromycin, clindamycin, the new macrolides, quinolones or co-trimoxazole.

Uncomplicated malaria is characterized by acute onset of fever, sweating, rigors, severe headache, muscular aches, nausea/vomiting and abdominal pain. However malaria may mimic many other conditions and therefore a history of "fever" should alert the clinician to the possibility of Plasmodia. There are no signs or symptoms exclusively typical to malaria and some patients may have few or no clinical signs of disease, especially between paroxysms. On examination the patient may be febrile, anaemic, jaundiced and have a palpable spleen.

Laboratory tests are very useful to exclude other diseases acquired in high-risk malaria areas that share "malaria-like" symptoms, e.g. typhoid, viral hepatitis, tick bite fever, meningitis. Giemsa stained blood smears are useful for differentiating the various strains of human Plasmodia and for determining parasitaemia levels, but the field utility and accuracy of rapid card tests have made them a popular alternative diagnostic modality.[6] However a single negative laboratory test cannot rule out the diagnosis and tests must be repeated at 6-12 hourly intervals, preferably when the temperature is rising, until the diagnosis is confirmed, the patient is well or another diagnosis has been made. Other useful sophisticated laboratory tests include fluorescent methods and PCR (polymerase chain reaction). Anaemia and especially thrombocytopenia on full blood count make malaria a possible diagnosis.

It should be emphasized that delays in considering malaria or accepting a single negative blood-smear as evidence against malaria, retard initiation of effective therapy with the evolution of severe malaria and a potentially fatal outcome.[7,8]

Preventing Malaria

Increasing resistance of malaria parasites to chloroquine means that prophylaxis with this agent alone is no longer recommended for visitors to any of the malaria areas in southern Africa, including South Africa.[9,10,11] An effective vaccine remains elusive although concerted effort is being expended on developing experimental DNA vaccines with multiple targets in each stage of *Plasmodium* development.[12] It must be emphasized that no chemoprophylactic agent is 100% effective and so the first-line approach to malaria prevention remains reduction of contact between infected mosquitoes and people (Table II - overleaf).

Unfortunately the use of proven strategies is often neglected in South Africa while dubious and unproven means, including garlic or alcohol consumption and ultrasonic buzzers, remain popular.[13] Pregnant women, children under the age of two years and immuno-compromised individuals (e.g. after a splenectomy) are at increased risk of severe malaria disease and should be cautioned to avoid high risk malaria areas.

Chemoprophylaxis should be individualized and take into account patient's age, pregnancy status, accessibility and quality of medical care, medical history (including immune-disorders & drug allergies), length of stay and degree of exposure.[14] For example, a person staying in a screened, air-conditioned hotel and not venturing outside at night is at considerably lower risk than a pregnant camper in an area riddled with mosquito breeding sites. There are special categories of persons for chemoprophylaxis that should be noted by the family practitioner as in Table III (overleaf).

There are two forms of chemoprophylaxis recommended for visitors to any of the high risk malaria areas in southern Africa: "Chloroquine

& Proguanil" (C&P) and "Mefloquine." (Table IV - overleaf). Mefloquine provides superior protection in higher risk areas while provoking an excess of mild, neuropsychiatric adverse events amongst South African travelers compared to an excess of gastrointestinal adverse events in travelers using C&P.[15] Doxycycline is usually considered where there are contraindications to the first choice medications.

Table II: Effective Personal Protection Measures

- Preferably visit malaria areas during the lowest risk period (the winter months in South Africa);
- Avoid outdoor activities between dusk and dawn where possible, as this is the preferred vector mosquito-feeding period. When venturing outside at night cover skin surface with clothing, including closed shoes, long trousers and sleeves preferably of light-coloured material. As mosquitoes may still feed through clothing it is preferable to impregnate clothes with a synthetic pyrethroid as this is more effective in preventing mosquito bites;
- Apply insect repellents containing DEET (di-ethyl toluamide) to exposed skin surfaces from dusk to dawn. Repeated application is necessary as the repellent action usually only lasts for 4-6 hours. Repellents should be used sparingly on young children and rather avoided with babies because of concerns about encephalopathy;
- Choose dwellings with good quality window- and door-screens;
- Sleep under mosquito nets, preferably impregnated with pyrethroid insecticides;
- Use knock-down insecticides in dwellings;
- Burn mosquito coils. Some people prefer the less irritating vaporising mats where electricity is available.

Table III: Special Categories for Chemoprophylaxis

Special Category	First Choice
Pilot / diver / mountaineer	C&P
Pregnant – first trimester	reconsider visit; if essential, use C&P
Infant	reconsider visit; if essential, use C&P
Epilepsy	difficult; consider proguanil alone
Porphyria / psoriasis	insufficient data

General Principles of Chemoprophylaxis [16]

- Begin a week before entering the malaria area. If there are intolerable side-effects then medication may be changed
- Weekly doses should be taken on the same day each week
- Continue for four weeks after leaving the area to ensure a suppressive cure
- Gastro-intestinal side effects may be reduced by taking drugs with meals

Specific Drugs

Chloroquine alone (e.g. *Nivaquine, Daramal*) cannot be recommended in southern Africa at the present time because of documented chloroquine resistance.

Chemoprophylaxis with **Doxycycline** (e.g. *Vibramycin*) is recommended in parts of the world where there are high levels of multiple drug resistance. It should preferably be used continuously for less than 2 months and never used in children less than 8 years of age. Certain side effects are common including gastro-intestinal upset, vaginal candida and photosensitivity.

Pyrimethamine & dapsone (*Maloprim*) should not be used for prophylaxis because of the risk of agranulocytosis.

Pyrimethamine & sulphadoxine (*Fansidar*) may rarely result in Stevens-Johnson syndrome and cannot be recommended for prophylaxis.

Amodiaquine may cause bone-marrow suppression with agranulocytosis and should not be used for prophylaxis.

Myths about Chemoprophylaxis

"It is better not to take chemoprophylaxis because it makes diagnosis difficult".

The correct prophylaxis and personal protection considerably reduce the chances of developing malaria disease and therefore unnecessary complications and death. Even if malaria does develop after the correct prophylaxis the severity of disease may be much reduced. A high index of suspicion with repeated testing where necessary will almost always confirm the diagnosis.

"Chemoprophylaxis is toxic and expensive".

The benefits of chemoprophylaxis should always be weighed against the risk of disease. Although side effects to the drugs are relatively common, these are usually mild. A high risk of contracting malaria usually outweighs the costs of drugs and side effects.

Table IV: *Features of Chloroquine & Proguanil and Mefloquine*

	Chloroquine & Proguanil	Mefloquine
Dose –Adults	Chloroquine – 300mg base (two tablets) weekly & Proguanil – 200mg (two tablets) daily	250mg (one tablet) weekly
Dose –Children	Chloroquine-5mg/kg weekly & Proguanil -3mg/kg daily	Not recommended for children under 15 kg. Above this mass, may be given at 5mg/kg weekly
Pregnant Women	Considered safe in pregnancy	Not recommended in first trimester of pregnancy or in 3 months before conception
Long-period prophylaxis	Considered safe, but retinal examination is mandatory after 5 years of continuous use	Not recommended for more than a year
Side-effects	Gastro-intestinal are common and mouth ulcers and skin eruptions may occur	Mild effects, gastrointestinal and dizziness, are commonly transient. Rarely there are neurological and psychiatric disorders
Contra-indications	Chloroquine should not be used in epileptics. This combination should be used with extreme caution in renal failure patients. Proguanil dose must then be reduced in consultation with a specialist physician. The combination should not be used in patients with heart block	Known hypersensitivity Children under 15 kg mass History of neuropsychiatric or cardiac disease When requiring fine co-ordination (e.g. pilots, divers, mountaineers) extreme caution should be used
Other medication	Use with Warfarin requires extreme caution	Use with caution with Beta blockers and Calcium antagonists

Treating Uncomplicated Malaria

Malaria must be treated as a medical emergency, as the disease is unpredictable and may progress rapidly to severe disease if inadequate therapy is administered.[17] This progression may take less than 48 hours from the first symptoms, particularly in children and pregnant women. Ideally diagnosis should be confirmed before initiating therapy. Chloroquine should no longer be used for the treatment of *falciparum* malaria in South Africa due to unacceptable levels of parasite drug resistance.

Although uncomplicated malaria is currently treated only with a single drug, fears have arisen that affordable

therapy could soon be lost through development of antimalarial drug resistance due to selection of spontaneously occurring parasite mutants with reduced drug sensitivity. The most promising solution appears to be the use of combinations of antimalarials that do not share the same resistance mechanisms and field trials are currently underway to explore combination therapy with artemisinin derivatives.[18]

Recommended therapies for malaria contracted in southern Africa are Fansidar (sulpha-doxinepyrimethamine: S-P): 3 tablets stat or quinine sulphate: 10mg/kg every 8 hours for 7 days. Fansidar should only be used for definite cases of uncomplicated malaria i.e. the ambulant patient with no other features of organ dysfunction, well orientated and appearing well. If in any doubt, treatment with quinine is preferable. Quinine is given orally but if there is severe vomiting, or moderate to severe malaria disease it should be administered intravenously. Non-immune patients are at risk of rapidly developing severe *falciparum* disease, so they should receive the most effective treatment regimen available and ideally this treat-ment should be initiated in hospital. It is easy to underestimate the severity of disease and careful regular monitoring is important.

If laboratory diagnosis confirms malaria due to the other species of *Plasmodium* parasites (*vivax, ovale* or *malariae*), then oral chloroquine therapy is usually sufficient but primaquine (7.5mg every 8 hours for 14 days) will effect a long lasting cure and prevent later recurrences.

General principles

- The first dose of therapy should be given immediately and under supervision. If the patient is to be treated as an outpatient, then he/she should be cautioned to return immediately if there is deterioration, severe medication side effects or if there is no clinical improvement within three days.
- Fever should be controlled using anti-pyretics and tepid sponging.
- Plenty of oral fluids should be given, particularly to young children who may dehydrate rapidly.
- Patients should be counseled to complete the course of therapy.
- Patients must be advised that if vomiting occurs within 30 minutes after swallowing a dose, another full dose of therapy should be taken. If vomiting occurs between 30 minutes and an hour after a dose, another half dose should be taken.
- In children it is helpful to give malaria tablets with chocolate, syrup or crushed bananas.

Standby therapy may be provided to travelers who are visiting high-risk malaria areas for longer than a week and who will be unable to get medical advice within 24 hours of becoming ill. Fansidar (3 tablets immediately on clinical suspicion of disease) is the preferred standby therapy. Although Halofantrine (three 6 hourly doses of 500mg for adults, repeated after a week) has been used for standby therapy, unpredictable absorption and fatal cardiac events have characterized its use. Halofantrine should never be used in a person with an abnormal QT interval on ECG or where Mefloquine was used for prophylaxis because of synergistic cardiac toxicity.

Severe Malaria

A discussion of the intensive hospitalized therapy of severe malaria is beyond the scope of this article and there are outstanding texts on diagnosis and therapy.[19,20] Common features include depressed consciousness and convulsions (cerebral malaria), severe haemolytic anaemia (Hb < 6gm/l), hypoglycaemia (blood glucose < 2.4 mmol/litre), acidosis, non-cardiogenic pulmonary oedema, acute renal failure (mainly in adults), haemoglobinuria and complications such as aspiration pneumonia or gram-negative septicaemia. Jaundice and hyperparasitaemia (>5%) are also common features of severe disease. Any indication of complicated disease deserves immediate referral to a hospital centre competent to effectively monitor and treat severe disease, while initiating quinine therapy and correcting life-threatening complications, e.g. hypoglycaemia, in transit. The mortality of severe malaria, a condition that could largely be prevented through adequate malaria prevention measures and prompt diagnosis and effective therapy, remains in excess of 20%.

Conclusion

Malaria is a priority disease in South African family practice. Adequate advice to travelers and residents of malaria areas can prevent the disease. The fatal nature of neglected disease mandates that malaria should always be considered in cases of acute febrile illness, diagnosis immediately confirmed and effectively treated as a medical emergency. Common errors in diagnosis and management of malaria are listed in Table V.

Table V: Common Errors in Diagnosing & Managing Malaria

Errors in diagnosis	Errors in management
• Failure to do a malarial blood film • Failure to take a travel history • Misjudgment of severity • Faulty parasitological diagnosis • Missed hypoglycemia • Failure to look for absence/presence of retinal haemorrhages	• Errors of fluid and electrolyte replacement • Delay in starting antimalarial drug • Use of inappropriate drug e.g. chloroquine in areas of resistance • Dosage not correctly calculated • Inappropriate route of administration • Failure to elicit a history of recent chemotherapy • Failure to switch patients from parenteral to oral therapy as soon as they can take oral medication • Failure to recognize and treat severe anemia • Delay in starting peritoneal dialysis or haemodialysis

Practical Points

- Delay in considering malaria or accepting a single negative blood-smear as evidence against malaria retards initiation of effective therapy with the evolution of severe malaria and a potentially fatal outcome.
- Chloroquine should no longer be used for the treatment of falciparum malaria in South Africa due to unacceptable levels of parasite drug resistance.
- Single dose therapy with sulphadoxine-pyrimethamine (S-P) remains largely effective for treating uncomplicated malaria but careful monitoring is essential.

References

1. Kondrachine AV, Trigg P. Malaria: hope for the future. *World Health* 1995; 2: 26-27.
2. Nchinda TC. Malaria: A reemerging disease in Africa. *Emerg Infect Dis* 1998; 4: 398-403.
3. Marsh K. Malaria disaster in Africa. *Lancet* 1998; 352: 924.
4. Wilson ME. Emerging infections and disease emergence. *Emerg Infect Dis* 1999; 5: 308-309.
5. Dürrheim DN. Taxi rank malaria. *BMJ* 1995; 311: 1507.
6. Dürrheim D N, la Grange J J P, Govere J, Mngomezulu N M. Accuracy of a rapid immuno-chromatographic diagnosis of *Plasmodium falciparum* malaria in a control programme setting. Trans Roy Soc Trop Med Hyg 1998;92:32-33.
7. Dürrheim DN, Fieremans S, Kruger P, Mabuza A, de Bruyn JC. Confidential inquiry into malaria deaths. *Bull World Health Organ* 1999;77::263-6.
8. Blumberg L, Lee RP, Lipman J, Beards S. Predictors of mortality in severe malaria: a two year experience in a non-endemic area. *Anaesth Intensive Care* 1996; 24: 217- 223.
9. Schapira A. Chloroquine resistant malaria in Africa: the challenge to the health services. *Health Policy and Planning* 1989; 4: 17-28.
10. Freese JA, Sharp BL, Ngxongo SM, Markus MB. *In vitro* confirmation of chloroquine-resistant *Plasmodium falciparum* malaria in KwaZulu. *S Afr Med J* 1988; *74: 576-578.*
11. Kruger P, Dürrheim DN, Hansford CF. Increasing chloroquine resistance-the Mpumalanga Lowveld story, 1990-1995. *S Afr Med J* 1996; 86: 280-281.
12. Kwiatkowski D, March K. Development of a malaria vaccine. *Lancet* 1997; 350: 1696-1701.
13. Dürrheim DN, Leggat P. Prophylaxis against malaria. Preventing mosquito bites is also effective. *BMJ* 1999; 318:1139.
14. Dürrheim DN, Ogunbanjo GA, Blumberg L. Malaria - prevention, recognition and cure. *S A Family Practice* 1996; 17: 367-374.
15. Dürrheim DN, Gammon S, Waner S, Braack LEO. Antimalarial prophylaxis – use and adverse events in visitors to the Kruger National Park. *S Afr Med J* 1999; 89:170-5.
16. Department of Health. *Guidelines for the prophylaxis of malaria.* Pretoria 1996.
17. Cook GC. Prevention and treatment of malaria. *Lancet* 1988; i: 32-37.
18. White N. Antimalarial drug resistance and combination chemotherapy. *Phil Trans Roy Soc London* 1999; 354: 739-749.
19. Severe and complicated malaria. WHO Division of Control of Tropical Diseases. *Trans R Soc Trop Med Hyg* 1990; 84 (suppl): 1-65.
20. White NJ. Malaria In: *Manson's Tropical Diseases, 20th edition*, Cook GC (editor). London: WB Saunders, 1996: 1138-1143.