Malaria prophylaxis — the South African viewpoint

L. BAKER, J. D. VAN SCHOOR, G. A. BARTLETT, J. H. LOMBARD

Abstract **A consensus meeting was held under the auspices of the Department of National Health and Population Development in September 1991 in order to establish local, current consensus on malaria prophylaxis for the South African traveller within South Africa and neighbouring African countries. The meeting was attended by malaria experts and others interested in malaria. The consensus reached took into consideration not only the international literature, but also local clinical experience and viewpoints. As a result, it was decided that prevention of mosquito bites is the mainstay of malaria prophylaxis and that chemoprophylaxis should be individualised. Malaria may still be contracted despite good compliance with the recommended prophylactic regimen.**

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Despite major campaigns to eradicate malaria, the disease remains one of the most significant health problems in many parts of the world. According to the World Health Organisation, 110 million clinical cases of malaria occur each year, and most of these infections are reported from sub-Saharan Africa.[1] The majority of these are infections with *Plasmodium falciparum*. This species gives rise to the most virulent form of the disease which is often life-threatening, particularly if not treated timeously.

Chemoprophylaxis of malaria has become progressively more complex. This is because of increased drug resistance, increased awareness of the side-effects of prophylactic drugs and controversies in drug recommendations. Furthermore, not all of the drugs used in the prophylaxis of malaria are available in every country. While chloroquine is generally considered to be one of the safest, most effective antimalarials, the prevalence of chloroquine-resistant falciparum malaria necessitates the search for alternative drugs.[2] Many of these have a poor safety profile, and/or provide insufficient protection. There may also be insufficient data to substantiate their general recommendation.

It has become increasingly important to avoid blanket recommendations and instead, consider carefully for whom the advice is intended, their immune status, the malaria risk, the length of time they will be in the area and the likelihood of adverse drug effects. An expert committee of the WHO points out that 'it is no longer true that prophylaxis is always better than no prophylaxis, nor is it true that a more effective, but less safe drug is always preferable to a less effective but safer one'.[1] In the light of the above a consensus meeting was held in September 1991 in order to establish uniform South African guidelines for malaria prophylaxis. Local malaria experts and other interested parties were invited to discuss current published literature as well as local clinical experience.

The following information and guidelines are offered.

Prevention of mosquito bites should be considered the mainstay of malaria prophylaxis. Patients should be advised as follows: (*i*) malarious areas should be avoided if the person falls into a high-risk category. High-risk categories include babies and young children, pregnant women, the elderly and immunocompromised individuals; (*ii*) avoid going outside between dusk and dawn as mosquitoes are most active at this time; (*iii*) apply insect repellant to exposed skin; (*iv*) wear long sleeves and long trousers at night; (*v*) use mosquito nets, screens and coils or mats; (*vi*) preferably visit endemic areas during the dry season or in years when rainfall is low.

Drugs used in chemoprophylaxis

Chloroquine

Chloroquine is effective against all forms of malaria except chloroquine-resistant strains of *P. falciparum*.[3] However, it may still be used in areas where chloroquine-resistant falciparum malaria exists, as many strains of *P. falciparum* in these areas are still sensitive to chloroquine.[2]

Chloroquine can safely be used during pregnancy and in young children.[1,2,4] It is usually well-tolerated and most side-effects are mild and reversible (e.g. nausea and vomiting, diarrhoea, headache, skin eruptions, itching of the palms, soles of the feet and scalp, impaired visual accommodation). Serious side-effects are rare but may occur with long-term use. Periodic eye examinations are recommended if chloroquine is used over a long period.

Pyrimethamine with chloroquine

Given reported pyrimethamine resistance, pyrimethamine is no longer recommended on its own.[3] The combination of pyrimethamine and chloroquine is also no longer generally recommended as it is thought to confer only marginal, if any, benefit over the use of chloroquine alone. Furthermore, it may increase the incidence of side-effects such as gastro-intestinal disturbances. If used during pregnancy, a folic acid supplement (5 mg/d) is recommended.

Pyrimethamine with dapsone

Dapsone potentiates the antimalarial effects of pyrimethamine. This combination may cause serious side-effects but these generally occur if the recommended dosages are exceeded.[2,5] Side-effects of this combination include folate deficiency, agranulocytosis, megaloblastic anaemia and methaemoglobinaemia. There is also doubt as to the efficacy of this combination as a malaria prophylactic and it is therefore usually not recommended. This view is not unanimous, however. Zimbabwe health authorities recommend this combination.

The combination should be avoided in the third trimester of pregnancy. If it is used during the other trimesters, a folic acid supplement is recommended (5 mg/d).

TPS Drug Information Centre, Johannesburg
L. BAKER, DIP. PHARM.
J. D. VAN SCHOOR, B. PHARM., B.SC. HONS.
G. A. BARTLETT, M. PHARM.
Department of National Health and Population Development, Johannesburg
J. H. LOMBARD, M.B. CH.B., M.SC.

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Pyrimethamine with sulfadoxine

This combination is no longer recommended for malarial prophylaxis, given the occurrence of serious side-effects.[2,4] It is however recommended as a medicine of choice for stand-by treatment of malaria. It offers an advantage over quinine in the treatment of malaria in that it is administered as a single dose.

Proguanil

Proguanil is no longer recommended on its own, as widespread resistance has developed. It is however used in combination with chloroquine in areas where chloroquine-resistant malaria occurs. The frequency and degree of chloroquine resistance vary and the combination appears to be more effective than monotherapy with either agent on its own.[6]

Proguanil is considered to be one of the best-tolerated antimalarial drugs.[2] It has a good safety profile and can be used during pregnancy and in children.[3] Proguanil rarely causes side-effects at prophylactic doses. However, reported side-effects include mouth ulcers, hair loss, vomiting, and abdominal discomfort.[2,7]

Mefloquine

Mefloquine is used for the prophylaxis and treatment of malaria. It is not recommended as a prophylactic for the general population as its indiscriminate use in South Africa could create drug pressure and bring about mefloquine resistance. It is recommended for short-term travellers only (travellers spending not more than 3 weeks in a malaria area).

Mefloquine has several limitations: (*i*) it is contraindicated in pregnant women and for 3 months before conception, in children weighing under 15 kg, in those with seizure disorders and in depressed patients; (*ii*) it may interfere with fine motor co-ordination and should therefore not be used by people requiring fine co-ordination, e.g. pilots; (*iii*) patients who are on β-blockers, calcium channel blockers, digitalis or cyclic antidepressant therapy should use mefloquine with extreme caution;[1] (*iv*) mefloquine is usually taken for up to 8 weeks and should never be taken for longer than 3 months.

Doxycycline

Doxycycline is a useful and effective prophylactic antimalarial for travellers to chloroquine-resistant areas and can be used as an alternative when mefloquine or proguanil are unavailable or contraindicated. It is recommended for short-term travellers only.

Doxycycline is usually well-tolerated and the most common adverse effects are gastro-intestinal disturbances such as nausea and diarrhoea, photosensitivity, (characterised by an exaggerated sunburn reaction), various dermatological reactions and vaginal candidiasis. It is contraindicated in pregnant women, children under 8 years of age and in breast-feeding mothers.

Recommendations for chemoprophylaxis

These should be individualised wherever possible. Given the variety of factors that influence the efficacy and safety of chemoprophylaxis of malaria, blanket recommendations should be avoided. A number of factors need to be taken into consideration in the selection of the appropriate drug. Such factors include the prevalence of mosquitoes, the incidence of drug resistance of the parasite, duration of stay in the area, availability of drugs. Patient factors that influence the choice of drug include: age, pregnancy, lactation, immune status, medical conditions, drug allergies and concurrent medication.

The prevalence of mosquitoes

When the number of malaria-carrying mosquitoes is low (e.g. during dry seasons, at high altitudes, in air-conditioned buildings and in city centres), drug prophylaxis may not be necessary.

The degree of drug resistance of the malarial parasite

In areas where the incidence of chloroquine-resistant strains of malaria is high, other drugs should be used in addition to chloroquine, or else appropriate alternatives should be used (Table I).

Duration of stay

The potential adverse effects from long-term therapy may influence drug selection. Furthermore, the risk of contracting malaria increases with the length of stay. Doxycycline and mefloquine should not be used for visits of more than 3 weeks. If chloroquine is used for long-term prophylaxis (longer than 5 years), regular biannual eye examinations are recommended.[4]

Availability of drugs

Proguanil is not registered in South Africa. It is however available in some neighbouring countries and travellers may wish to purchase it there on arrival. Mefloquine is not yet registered in South Africa but is currently available on a clinical trial basis from designated doctors.

Patient factors

Age

Both drug selection and dosage are influenced by this. Infants and young children are at special risk since they can rapidly become seriously ill with malaria. They should not be taken into a malarious area unless absolutely necessary. All measures must be taken to prevent them from being bitten by mosquitoes.

Chloroquine and proguanil may safely be given to babies and young children. The combination of pyrimethamine and chloroquine is not recommended for children under the age of 6 weeks. Doxycycline should not be given to children under 8 years of age. Mefloquine should not be given to children weighing less than 15 kg (see Table II for dosage).

Prophylaxis must be given to breast-fed as well as bottle-fed babies since they are not adequately protected by the amount of drug in the breast milk. Given the potential toxicity of chloroquine, it has been suggested that the dose be adjusted as follows: (*i*) fully breast-fed infants (4 or more feeds per day) — half the recommended paediatric dose of chloroquine; (*ii*) partially breast-fed (fewer than 4 feeds per day plus supplementary diet) — the full recommended paediatric dose of chloroquine.

The dose of proguanil need not be adjusted in breast-fed infants.

Pregnant women

Malaria in pregnant women increases the risk of maternal death, neonatal death, miscarriage and stillbirth.[4] Pregnant women should avoid going into a malarious area unless absolutely necessary. If they do enter such an area they must be particularly careful to protect against mosquito bites and should seek medical help immediately if any symptoms of malaria develop.

TABLE I.
Suggested chemoprophylaxis for travellers within RSA and neighbouring African countries

Area	Malaria prevalence	Recommended drugs
Kruger Park Eastern Transvaal Northern Natal KwaZulu (except Ingwavuma and Ubombo districts)	Low — during dry seasons (mainly June to October) and in years when rainfall is very low High — during hot, wet seasons (mainly November to May)	High-risk persons chloroquine Other persons nothing Chloroquine
Ingwavuma and Ubombo districts	Throughout the year	Chloroquine and proguanil Doxycycline Mefloquine Nothing*
Swaziland	Throughout the year in lowveld areas	Chloroquine and proguanil Doxycycline Mefloquine Nothing*
Zimbabwe	Mainly November to June in areas below 1 200 m and throughout the year in Zambezi Valley	Chloroquine and proguanil Doxycycline Mefloquine Nothing*
Angola Comoros Kenya Madagascar Malawi Mozambique Zaire	Throughout the year	Chloroquine and proguanil Doxycycline Mefloquine Nothing*
Botswana	Mainly November to June in the northern parts of the country (e.g. Okavango)	Chloroquine and proguanil Doxycycline Mefloquine Nothing*
Namibia	Mainly November to June in northern rural areas (e.g. Ovambo, Kavango and Etosha)	Chloroquine and proguanil Doxycycline Mefloquine Nothing*
Zambia	Mainly November to June but throughout the year in the Zambezi Valley	Chloroquine and proguanil Doxycycline Mefloquine Nothing*
Seychelles	No malaria	
Mauritius	Only benign form of malaria in rural areas in the North	Prophylaxis is usually not necessary. Chloroquine may be recommended if travelling to rural areas

* In situations where the risk of contracting malaria is low (e.g. in cities, air-conditioned hotels or when rainfall has been low etc.), the traveller may be advised to take no drug prophylaxis but stand-by treatment must be carried unless medical care is readily available.
Note: The drugs are not necessarily in order of priority. Drug selection depends on each individual's situation. Proguanil is not available in South Africa. If travelling to areas where no medical help is available, especially if no chemoprophylaxis is taken, travel with stand-by malaria treatment. If symptoms of malaria develop before leaving the malarious area, take stand-by treatment and seek medical help as soon as possible.

Chloroquine and proguanil can be used safely during pregnancy.[1,3,4] Pyrimethamine and chloroquine have been used during pregnancy but a folic acid supplement of 5 mg/d should be added. Mefloquine and doxycycline should not be used during pregnancy.

Patients with porphyria

Doxycycline and combinations of pyrimethamine with dapsone or sulfadoxine are contraindicated. There is conflicting evidence regarding the use of chloroquine in porphyria, and the safety of mefloquine has not yet been established. Proguanil is considered safe in porphyria.[8]

Epileptic patients

There have been reports of seizures associated with antimalarials.[1,9] Epileptic patients should be warned that drug prophylaxis may interfere with seizure control. Chloroquine should be used with extreme caution. Mefloquine is contraindicated.

Sulphonamide-sensitive patients

Patients who are sensitive to sulphonamides or sulphones should avoid combinations containing dapsone or sulfadoxine as hypersensitivity reactions may occur.

Families moving to malaria areas

It takes a number of years for immunity against malaria to develop. Therefore, it is necessary for these people to adhere to the above recommendations indefinitely. Periodic eye examinations are recommended if chloroquine is used long-term.

It is important to be aware that malaria may be contracted despite good compliance with the recommended prophylactic medicine. There is no chemoprophylactic agent available which can prevent all malaria infections.[1]

TABLE II.
Dosages of antimalarials

Drug	Adults	Children
Chloroquine (sulphate or phosphate) (e.g. Nivaquine®)	300 mg base (2 tablets) once every 7 days starting 1 week before entering area, once weekly while in the area and weekly for 6 weeks after leaving the area.	Prophylactic dose is 5 mg/kg body weight taken at the same intervals as for adults.
Proguanil (e.g. Paludrine®)	Used concurrently with chloroquine. 200 mg (2 tablets) taken once daily starting 1 day before entering area, daily while in the area and daily for 6 weeks after leaving the area.	Prophylactic dose is based on 3 mg/kg body weight at same intervals as for adults: Age — Weight (kg) — Fraction of adult dose < 1 yr — < 10 — 1/8 1-4 yrs — 10-19 — 1/4 5-8 yrs — 20-30 — 1/2 9-15 yrs — 31-45 — 3/4 > 15 yrs — > 45 — adult dose
Mefloquine (e.g. Lariam®) (available from designated doctors)	250 mg (1 tablet) once weekly starting 1 week before entering the area, once weekly while in the area and continuing weekly for 4 weeks on return. Restrict use to 3 months.	Not recommended in children under 2 years (or under 15 kg); prophylactic dose is 5 mg/kg body weight at same intervals as for adults: Age — Weight (kg) — Fraction of adult dose 2-4 yrs — 15-19 — 1/4 5-8 yrs — 20-30 — 1/2 9-15 yrs — 31-45 — 3/4 > 15 yrs — > 45 — adult dose
Doxycycline (e.g. Vibramycin®)	100 mg once daily starting 1-2 days before entering the area and continuing while in the area and for 4 weeks after leaving the area. Not recommended for longer than 8 weeks without medical advice.	Contraindicated in children under 8 years of age; prophylactic dose is 3 mg/kg at same intervals as for adults: Age — Weight (kg) — Fraction of adult dose 8-15 yrs — 31-45 — 3/4 > 15 yrs — > 45 — adult dose
Daraclor® Tablets: chloroquine SO_4 (= 150 mg base) pyrimethamine 15 mg Syrup: chloroquine SO_4 (= 37,5 mg base/5 ml) pyrimethamine 3,75 mg/5 ml	2 tablets once every 7 days starting 1 week before entering area, once weekly while in area and weekly for 6 weeks after leaving the area.	Do not use in infants under 6 weeks. Take at same intervals as for adults: < 1 year old: — 5 ml syrup weekly 1-5 yrs old: — 10 ml syrup weekly or half a tablet weekly 6-12 yrs old: — 1 tablet weekly.
Maloprim® Tablets: dapsone 100 mg pyrimethamine 12,5 mg (Not recommended)	1 tablet every 7 days taken as for Daraclor® above	Do not use in infants under 6 weeks. Take at same intervals as for adults: < 1 year old: — 1/8 of adult dose* 1-4 yrs: — 1/4 of adult dose* 5-10 yrs: — half a tablet weekly Over 10 yrs old: — 1 tablet weekly

* Use dapsone/pyrimethamine syrup (if available) in children under 5 years of age. It is not possible to break tablets into quarters.
Note: The WHO recommends that drug prophylaxis be started 1 week before entering the malarious area. This is partly to confirm that the drug is well-tolerated and partly to establish a prophylactic routine. The exceptions are proguanil and doxycycline which can be started 1 - 2 days beforehand, as they are taken as daily doses. To be effective the drug must be taken at least 24 - 48 hours before entering the area. Where necessary (in cases of obesity or low body mass) the doses of prophylactic agents must take into account the weight of the patient and be adjusted accordingly. It is important to continue prophylaxis for a minimum of 4 weeks after leaving an endemic area to ensure that a suppressive cure is achieved. Many authorities recommend 6 weeks (except with regard to doxycyline and mefloquine for which 4 weeks are adequate). Drugs that are taken weekly must be taken on the same day each week.

Conclusions

In conclusion, it must be reiterated that drug prophylaxis remains controversial and recommendations are constantly changing. Where possible, each case should be assessed individually and blanket recommendations should be discouraged. Measures to prevent mosquito bites remain the mainstay of prophylaxis, and people must be aware of the symptoms of malaria in order to seek medical treatment timeously.

Any individual who returns from a malarious area should undergo a series of blood tests for a malaria infection if he develops any signs of malaria within 6 weeks of his return.

Participants at the meeting: P. E. Folb (Chairman), L. Baker, G. A. Bartlett, N. Coetzee, T. A. Dippenaar, P. J. Fripp, J. Gear, H. Griessel, C. F. Hansford, M. Isaacson, J. H. Lombard, B. Miller, F. Monteagudo, B. Stratton, J. D. van Schoor, C. Young, F. Ziady.

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