

Malaria and the traveller

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Key words

Malaria, travel medicine, tourism, review article

Abstract

Malaria remains a significant health risk to millions of people living in endemic areas of the world. An increase in drug-resistant parasites combined with an increase in international travel, has seen a concordant increase in the number of cases of malaria imported by travellers into the industrialised world annually. Malaria in travellers can nearly always be prevented by the application of personal protective measures and by taking appropriate chemoprophylaxis. The vast majority of cases of malaria in travellers are contracted as a result of noncompliance with taking antimalarial agents, or inappropriate prescribing. When assessing an individual need for malaria chemoprophylaxis, a number of factors must be taken into account, including a detailed travel history, past medical history, contraindications to specific medications, and the drug resistance pattern of the parasite in the destination. It is imperative that the traveller actually be at risk of malaria before a prophylactic agent is prescribed; these medications are not innocuous and adverse events should be avoided if possible. The traveller should be involved in the decision-making process regarding antimalarial medication, they need to be aware of the potentially fatal nature of the disease, the importance of complying with their chosen regimen, and the symptoms of malaria so they can act promptly should their prophylaxis fail. There are a number of alternative chemoprophylaxis regimens available to travellers that are discussed here.

Introduction

*"The history of malaria contains a great lesson for humanity – that we should be more scientific in our habit of thought, and more practical in our habits of government."*¹

So wrote Robert Ross in 1911, and, sadly, these words still ring true today.

Malaria continues to pose a significant public health threat in over 100 countries of the developing, tropical world. An estimated 650 million clinical cases of malaria occur worldwide annually, and these result in between two and three million deaths, the majority of which occur in the children of Africa. In developed nations of the 'First World', malaria is a disease of travellers to endemic countries, whether these be tourists, the military, refugees or migrants. It is estimated that around 30,000 travellers from industrialised countries contract malaria each year.² Australia records around 1,000 cases of imported malaria annually, and New Zealand about 100 cases.

During the 1950s and 1960s, significant inroads were made into worldwide malaria control. However, complacency in the 1970s resulted in a dramatic resurgence of the disease, a trend that has continued unabated into the 21st Century. The world seems to be losing the battle for malaria control and a number of factors have been implicated, including:

- Lack of money. The annual budget of the World Health Organisation (WHO) malaria control project is less than the cost of one Stealth bomber.
- The lack of a vaccine in the foreseeable future.
- Resistance to both prophylactic and treatment drugs that continues to develop and spread unabated.

- Development projects that have changed local ecology thus promoting vector breeding sites.
- A lack of interest from the pharmaceutical industry in developing new drugs.

As one prominent malaria researcher has said:

"Medicines that offer an adequate commercial return for major pharmaceutical companies are those that treat diseases that make rich people sick, not those diseases that kill poor people. Except for travellers from the developed world who visit tropical countries, malaria is a poor person's disease. This painful dilemma has had a negative impact on malaria drug development for many decades."³

In the year 2000, WHO launched the 'roll back malaria' strategy in an attempt to reverse this worsening situation. However, it will be quite some time before there is any obvious impact on the current situation.

Human malaria transmission and distribution are directly related to the interaction between the vector, the parasite and the human host. Re-emergence of disease transmission is often linked to environmental or behavioural change combined with low socioeconomic status. It is predicted that future malaria-endemic areas will probably be those socioeconomically underdeveloped areas currently on the fringe of infected areas.⁴

The vector

Malaria is transmitted via the bite of an infected female *Anopheles* mosquito. Between 40 and 60 species are known to be receptive to human malaria. Transmission is limited by

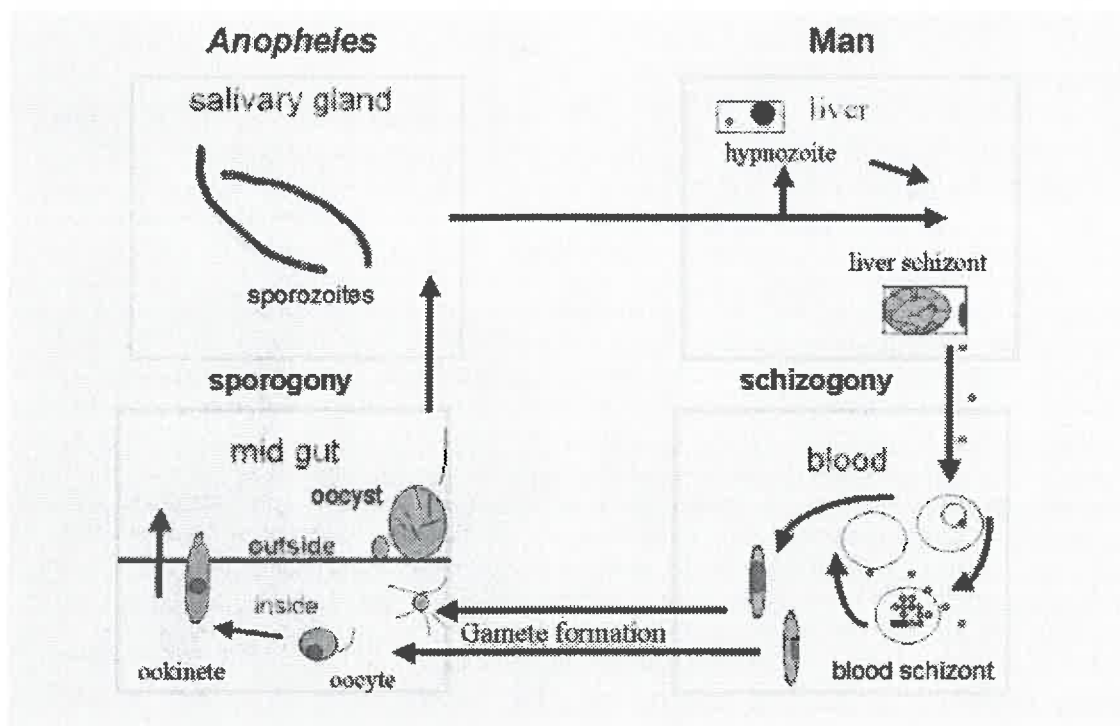


FIGURE 1

LIFE CYCLE OF MALARIA PARASITES INFECTING MAN

Reactivated dormant liver stages (hypnozoites) are responsible for relapses. (Reproduced from reference 5.)

temperature and humidity – little biting takes place below a relative humidity of 52%. It is rare to find *Anopheles* above 2,000 metres of altitude. Different species have different preferred feeding times, but in general the mosquito actively feeds between dusk and dawn.

The parasite

Four species of the *Plasmodium* parasite naturally infect man. These can be divided into two groups of functional clinical relevance: the relapsing species, *P. vivax* and *P. ovale*; and the non-relapsing species, *P. falciparum* and *P. malariae*. The majority of human cases are caused by either *P. vivax* or *P. falciparum*. Eighty three per cent of the world's *P. falciparum* cases occur in Africa, whereas 74% of the world's *P. vivax* cases occur in Australasia. *P. falciparum* provides the greatest threat to human life, as this species may be rapidly fatal in the non-immune individual.

The *Plasmodium* life cycle involves a process known as sporogony in the mosquito and schizogony in man. Whilst feeding, the infected *Anopheles* female injects between 20 and 200 sporozoites into the blood stream. These enter the infected human's hepatocytes within half an hour. Within the hepatocytes, one asexual multiplication stage (tissue schizogony) takes place, resulting in the production of thousands of infective merozoites. In the relapsing forms of malaria, some of these sporozoites become hypnozoites. Hypnozoites are quiescent liver forms that may become active many months after infection. The production of merozoites

occurs typically within 7–14 days for *P. falciparum*, and may take up to 30 days for the other species.

The merozoites are released into the blood stream where they invade red blood cells and undergo a series of asexual multiplication cycles (blood schizogony). These asexual multiplication cycles generally coincide with a fever in the infected individual, as they are associated with the release of tumour necrosis factor by the lymphoid system in response to released antigens.⁵ This process results in a rapid amplification of the parasite in the human host – a single sporozoite may yield up to 1 million copies of itself through just the first cycle of blood schizogony.⁶

In *P. falciparum* infections, this process is limited only by the number of red blood cells available and the death of the host, thus explaining the severity of this species of *Plasmodium*. *P. vivax* and *P. ovale* preferentially invade reticulocytes and hence the parasite load is much lower than in *P. falciparum*. Some of the blood merozoites will develop into gametocytes, the potentially sexual gamete. This stage is a dead end in humans, but if ingested by an *Anopheles* mosquito when it bites an infected human, these forms carry on their life cycle within the mosquito host.

Malaria in travellers

The risk of contracting malaria varies considerably from region to region (Figure 2). Countries such as Papua New Guinea, Bougainville, the Solomons and regions such as

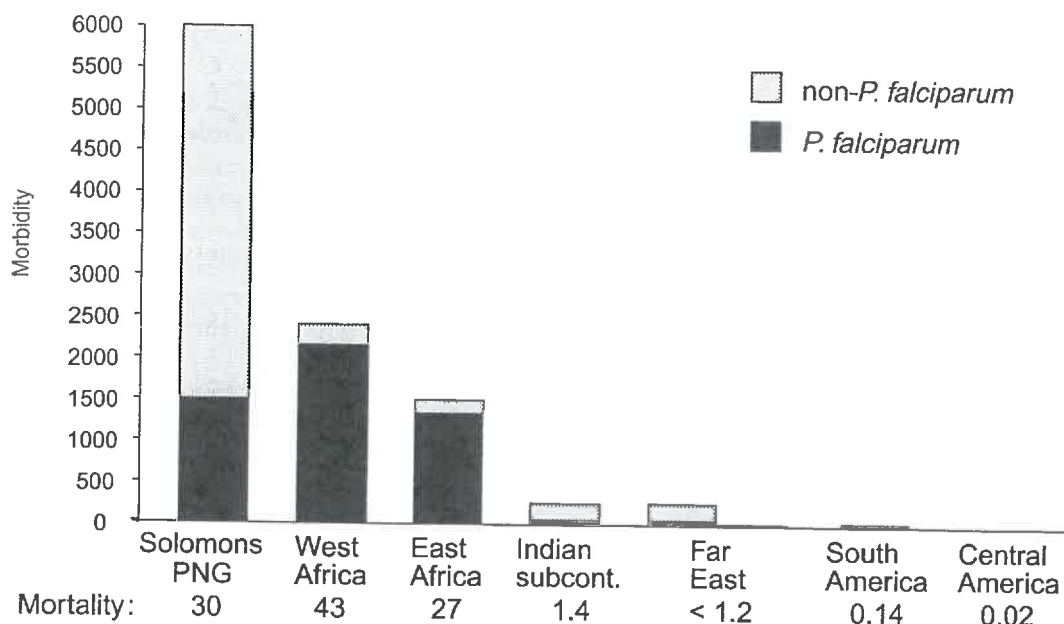


FIGURE 2
MORBIDITY IN 100,000 NON-IMMUNE TRAVELLERS EXPOSED FOR ONE MONTH WITHOUT CHEMOPROPHYLAXIS (Australian, German and Swiss malaria register). (Reproduced from reference 10.)

West Africa have considerably higher risk than other areas of the world.

It is difficult to quantify the risk to travellers. However, two good studies have been published that examine travellers to the high-risk area of East Africa. These studies utilised the detection of *P. falciparum* anti-circumsporozoite antibodies (CSAb). These antibodies are produced if an individual has been infected with *P. falciparum* even if their chemosuppressive medication has prevented clinical disease. This test is 100% specific but only 56% sensitive, so is likely to underdetect infections.

One study of 222 non-febrile returned travellers from Africa found that 21% were CSAb positive.⁷ This study group included both independent and tour group travellers who spent between two and eight weeks in Africa. Significantly, independent travellers were nine times more likely to have a positive CSAb result. The second study looked at 262 German travellers on a two-week package tour to the coast of East Africa.⁸ All took either mefloquine or chloroquine combined with Paludrine chemoprophylaxis. The positive antibody rate was 5% but there were no clinical cases, showing the effectiveness of appropriate chemoprophylaxis.

Repeatedly, studies of malaria in travellers show that inadequate or no chemoprophylaxis is the greatest risk factor for contracting the disease. An analysis of 246 cases treated in Melbourne showed that only 56% of individuals had taken chemoprophylaxis. Of these, only 29% took the medications according to standard recommendations and 76% had been prescribed inadequate prophylaxis by their doctor.⁹ Ignorance of the risk of malaria, inadequate training

in travel medicine at the general practice level, fear of drug side effects, cost issues, and cultural perceptions (particularly in returning migrants) all contribute to this worldwide phenomenon. One travel medicine expert states:

“Travellers’ malaria is a failure, and the major cause of this failure is lack of adherence to prevention methods. The key to the solution is identifying innovative and creative ways of communicating health advice to travellers so that they will be convinced of their vulnerability and will take responsibility for disease prevention. Education must be patient centred. This involves patients taking part in the decision making process and may involve negotiating what is most reasonable, depending on variables such as cost, convenience and adverse effect profile.”⁴

Malaria is a serious disease in the non-immune individual. Recognition and treatment of malaria is often inadequate in non-endemic areas and delayed treatment is linked with increased mortality. In developed countries, the case fatality rate (CFR) ranges from 0.6% to 7% in *P. falciparum*. Severe malaria has a 20% mortality rate even in first-class intensive care facilities.²

Strategies for prevention

Adequate chemoprophylaxis is essential, but other strategies are also of importance:

- adequate assessment of the individual’s risk;
- personal protective measures;
- appropriate chemoprophylaxis;
- prompt recognition, diagnosis and treatment.

When assessing an individual’s risk one needs to take into

TABLE 1
FEATURES OF COMMONLY PRESCRIBED ANTI-MALARIALS¹⁰

Feature	Mefloquine	Doxycycline	Malarone
Efficacy against chloroquine resistant <i>P. falciparum</i>	Very good (>90%)	Very good	Very good
Efficacy against <i>P. vivax</i> and other species	More limited	More limited	More limited
Most notable adverse events	Neuropsychiatric	Gastrointestinal Photosensitivity	Minimal
Half-life	3 weeks	18–22 hours	Proguanil – 17 hours Atovaquone – 2–3 days
Frequency of administration	Weekly	Daily	Daily
Duration after leaving risk area	4 weeks	4 weeks	7 days
Main contraindications	Early pregnancy Epilepsy Psychiatric problems	Pregnancy Children <8	Pregnancy

account a number of features:

- travel characteristics – destination (e.g., urban versus rural versus resort), length of trip, travel style, activities. Will the traveller actually visit a risk area within their destination country?
- host factors – behavioral issues (compliance), pre-existing medical conditions, age, pregnancy;
- entomological inoculation rate – season, infectivity;
- the parasite – drug resistance pattern at the destination;
- medical infrastructure in host country and country of residence – what is the local case fatality rate (CFR)?

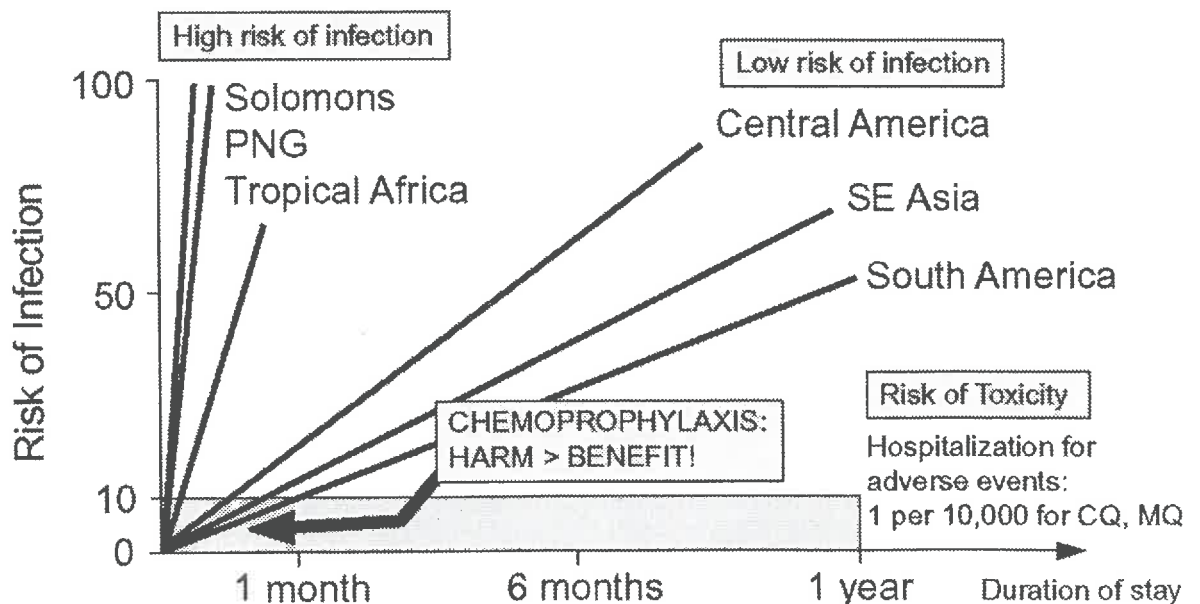
- medications – adverse effects, budget, availability overseas (Table 1).¹⁰

Personal protective measures should always be emphasised as they offer protection against other vector borne diseases:

- Clothing should be light coloured, loose and long.
- Repellants should be used appropriately. Products containing 30% DEET are recommended.¹¹
- Mosquito nets are essential and ideally should be impregnated with the insecticide Permethrin.

Permethrin can also be used to impregnate clothing for those travelling to high risk destinations.

FIGURE 3
RISK OF MALARIA INFECTION WITHOUT CHEMOPROPHYLAXIS VS HOSPITALISATION FOR ADVERSE EVENT (per 100,000). (Reproduced from reference 10.)



Chemoprophylaxis

As prescribers, we must remember "primum non nocere" (first do no harm). Travellers are usually healthy individuals who are being asked to take a medication that may result in unpleasant side effects. Once again it behoves the prescriber to ensure the medication is in fact necessary and appropriate for the individual. In some instances, the risk of an adverse event from the chemoprophylactic agent will outweigh the risk of contracting malaria (Figure 3).¹²

TERMINOLOGY OF CHEMOPROPHYLAXIS

There is often confusion surrounding the terminology of chemoprophylaxis. As previously discussed, the malaria parasite passes through distinct stages of its life cycle within the human. Each stage has unique susceptibilities to antimalarial agents (Figure 4).

Suppressive chemoprophylaxis refers to drugs that kill the asexual blood stage of the parasite before the parasite causes disease (also known as schizonticides). These drugs have no discernible effect on the liver stage of the parasite. Of the commonly prescribed drugs, chloroquine, proguanil, mefloquine and doxycycline are in this category. Although some suggest doxycycline does have some limited effect in the liver, this has not been proven. Suppressive chemoprophylaxis requires maintenance of protective levels of the drug in the blood stream for a period of time from before the release of the first merozoites until four weeks after the final exposure to infected *Anopheles*, as it can take this long for the merozoites to be released from the liver.

Causal prophylaxis refers to drugs that kill the liver stages of the parasite (except the hypnozoites) before they enter the blood stream. Of the currently commercially available medications, only atovaquone (found in Malarone) and primaquine are causal prophylactics. The advantage of these drugs is that they can be commenced just prior to exposure and can be discontinued soon after exposure ceases.

Terminal prophylaxis is directed against the hypnozoite stages of *P. vivax* and *P. ovale*. Primaquine is the only commercially available drug that acts as a terminal prophylactic.

Relatively few double-blind randomised trials comparing chemoprophylactic regimens have been published.¹² Those that have been published are limited by small study populations or special groups (most commonly they have been performed in the military, a study population dominated by healthy young men). Retrospective cohort studies have been the most influential on guideline formulation. However, this is less than satisfactory due to the bias inherent in this type of study.¹³ It is unlikely that this situation will change. For example, if one wanted to show that the new drug Malarone was statistically significantly superior to mefloquine, one would need to enroll 60,000 travellers in a study. Clearly, this is not practical.¹⁴

Chloroquine

Chloroquine remains the drug of choice in those areas of the world in which it is still effective. Essentially, these areas are limited to Central America and some parts of the Middle East, both very low risk destinations. For all other destinations, the degree of drug resistance now present makes chloroquine alone an unacceptable prophylactic regimen. The drug is safe in pregnancy and in children. It should not be taken by anyone with a sulpha allergy, or with a history of epilepsy or psychosis.

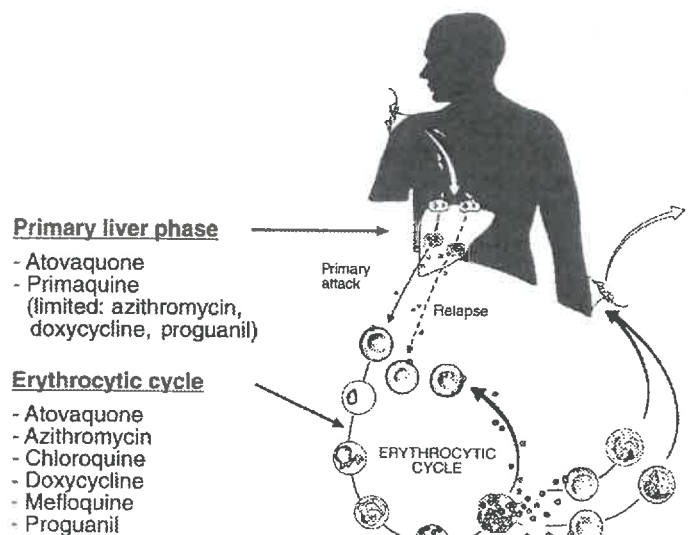
Proguanil

Proguanil is usually only prescribed in combination with chloroquine. The combination of chloroquine and proguanil has been a popular option in the UK and Europe for many years and has a strong safety profile in all groups, including pregnant women and children. It is, however, a complicated regimen. Proguanil is taken daily, whereas chloroquine is taken weekly. The risk of noncompliance is high, and if the tablets are confused there can be serious consequences. Increasing drug resistance is making this combination increasingly inadequate, particularly in Africa and many parts of Asia and Oceania. Travellers should be aware that this combination is less than optimal and it should only be used if no other option is suitable.

Doxycycline

Doxycycline, at a dose of 100 mg daily, offers good protection against *P. falciparum*, however, it is less effective against *P. vivax*. Comparative trials in Irian Jaya and Africa have shown doxycycline to have an efficacy equivalent to mefloquine against *P. falciparum*.^{15,16} Compliance with daily dosing is required for adequate efficacy, and this is one of the limiting

FIGURE 4
SITE OF ACTION OF ANTIMALARIAL DRUGS
(Reproduced from reference 10)



Special groups

Pregnant women have been discussed in a previous paper.²³

CHILDREN

Special care should be taken with children in malaria areas. In fact, WHO recommends against taking young children to areas of drug-resistant *P. falciparum* malaria. Children are more vulnerable to malaria than are adults, and the disease can be rapidly fatal for them. Personal protective measures must be emphasised. In terms of drug chemoprophylaxis, WHO has approved mefloquine down to 5 kg body weight. Children seem to tolerate mefloquine better than do adults, and the once weekly dosage schedule is far more convenient than other options. Doxycycline is contraindicated in children under eight years of age. Malarone has been licensed down to a weight of 15 kg in the United States. Chloroquine and proguanil are safe in children, however the dosing regimen is inconvenient (Table 2).

EPILEPSY

Both mefloquine and chloroquine are contraindicated in those with a history of epilepsy. Malarone or doxycycline are the drugs of choice. Although phenytoin, carbamazepine, and barbiturates reduce the half-life of doxycycline, there is no direct evidence that an increase in doxycycline dosage is required.¹²

RENAL FAILURE

Proguanil is excreted by the kidney. Mefloquine and doxycycline are the drugs of choice in renal failure.

POST SPLENECTOMY

Travellers without a spleen are at particular risk of severe malaria. They need to be scrupulous with their personal protective measures and should take the most effective prophylaxis available to them.

How to get up-to-date, country-by-country information

For most doctors working outside of the specialised travel medicine clinic setting, this is the most difficult aspect of providing good quality advice to the traveller. Many travel medicine specific databases have good information, but they are expensive and often not practical for the doctor seeing one or two travellers weekly. The WHO guide, *International Travel and Health*, provides the most reasonable summary of risk areas.²⁴ This guide can be downloaded from the WHO website <www.who.int/wer/>. Outbreaks are reported via Promed on the Internet. It is useful to have some basic knowledge of the geography of commonly visited countries in order to make reasonable recommendations. Frequently

TABLE 2. DOSAGE FOR PAEDIATRIC PROPHYLAXIS AGAINST MALARIA.⁶

Drug Formulation	Weight	Dosage
Mefloquine 228 mg base tablet	5–15 kg	¼ tab weekly
	16–30 kg	½ tab weekly
	31–45 kg	¾ tab weekly
	>45 kg	1 tab weekly
Doxycycline 100 mg capsule	2 mg/kg	max 100mg/day (> 8 years old)
	(> 8 years old)	
Malarone 250mg Atovaquone 100 mg Proguanil	10–20 kg	¼ tab daily
	21–30 kg	½ tab daily
	31–45 kg	¾ tab daily
	>45 kg	1 tab daily
Chloroquine 300 mg base tablet	5 mg/kg/week	max 300 mg/wk
Proguanil 100 mg tablet	5–8 kg	¼ tab daily
	9–16 kg	½ tab daily
	17–24 kg	¾ tab daily
	25–35 kg	1 tab daily
	36–50 kg	1 ½ tabs daily
	>50 kg	2 tabs daily

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WHO awarded US\$1.5m to test new treatment for malaria

The Tropical Disease Research (TDR) Programme of the World Health Organization (WHO) has received US\$1.5 million from the Gates Malaria Partnership at the London School of Hygiene & Tropical Medicine to support introductory trials on a new treatment for malaria. The Gates Foundation grant will fund a research initiative to assess the public health benefits of Lapdap (chlorproguanil/dapsone). Lapdap, a long term drug evaluation project of the University of Liverpool, has been developed as the result of a collaboration between TDR, the UK Government's Department for International Development and the manufacturer of the drug, GlaxoSmithKline. The objective of the collaboration has been to produce a drug that would be safe, effective and, importantly, affordable for the treatment of malaria in Africa.

Chloroquine and sulphadoxine-pyrimethamine are the two main low-cost drugs used to treat malaria across Africa. They are becoming dangerously ineffective as the malaria parasites become more resistant and new drugs are urgently needed.

Work on Lapdap started 15 years ago, when scientists at the University of Liverpool and Kenya Medical Research Institute first came to believe that chlorproguanil/dapsone might offer an affordable alternative antimalarial drug. Before a newly approved drug can be considered for use in the wider community, further research on usage and rare adverse drug reactions is necessary, as studies conducted prior to regulatory approval are performed on relatively small numbers of patients in a controlled manner.

WHO recommends that in countries where there is widespread resistance to chloroquine and sulphadoxine-pyrimethamine, countries consider introducing artemisinin-based combination drug treatments. In keeping with these recommendations, Lapdap may form an important partner drug with artemisinins for combination therapy for Africa, and this potential is being explored in a parallel drug development project.

This grant will be used to fund TDR-led research which will improve the understanding of the properties of Lapdap. Proposed studies will, in addition to looking for rare adverse drug reactions, assess whether the new drug will be practical to dose and easy to take, and also monitor whether any resistance to the drug is developing within the malaria parasites. Whilst this program will be using Lapdap as an example, it is hoped that lessons learnt will be of benefit to any new treatment for malaria.

For further information, or interest in any of the planned studies, please contact Dr Tom Kanyok, UNDP/World Bank/WHO Special Programme for research and Training in Tropical Diseases. Tel: +41-22-791-3684,
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WHO Press Release, 2002, from: <<http://www.who.int/>>