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Malaria prophylaxis in travellers: the current position

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Summary. Malaria prevention is a main challenge for physicians, nurses, health officers and tour operators. The attack rate of malaria in travellers is 1-10/10,000 departures, and the case fatality rate of imported malaria is around 0.5/100. Travellers should be informed about the risk they are going to take, how to protect against mosquito bites, about the antimalarials they will have to take and about what to do when a malaria breakthrough should occur.

The 4-aminoquinolines (chloroquine, amodiaquine) remain the drug of choice for the prevention of *Plasmodium vivax* and of sensitive *P. falciparum* infections. The problem is to find an effective and safe drug combination for travellers to areas where *P. falciparum* is either resistant to chloroquine, to Fansidar (the combination of pyrimethamine plus sulfadoxine) or to both. These travellers will probably best be protected by an individually tailored drug combination, which includes amodiaquine or mefloquine as baseline drugs, and a supplementation with Fansidar, Maloprim (the combination of pyrimethamine with dapsone), paludrine or an antibiotic.

Key words. Malaria; prophylaxis, malaria; Plasmodia; mosquito bite, protection against; antimalarial drugs.

Introduction

Malaria is perhaps the most important parasitic infection worldwide. It covers vast areas in Africa, Asia and Latin America (fig. 1). According to incomplete reportings to WHO there were 13 million malaria cases in 1981[32]. One expert estimates that the disease affects more than 200 million people each year[24]. Of the 179 states where there is a potential for malaria transmis-

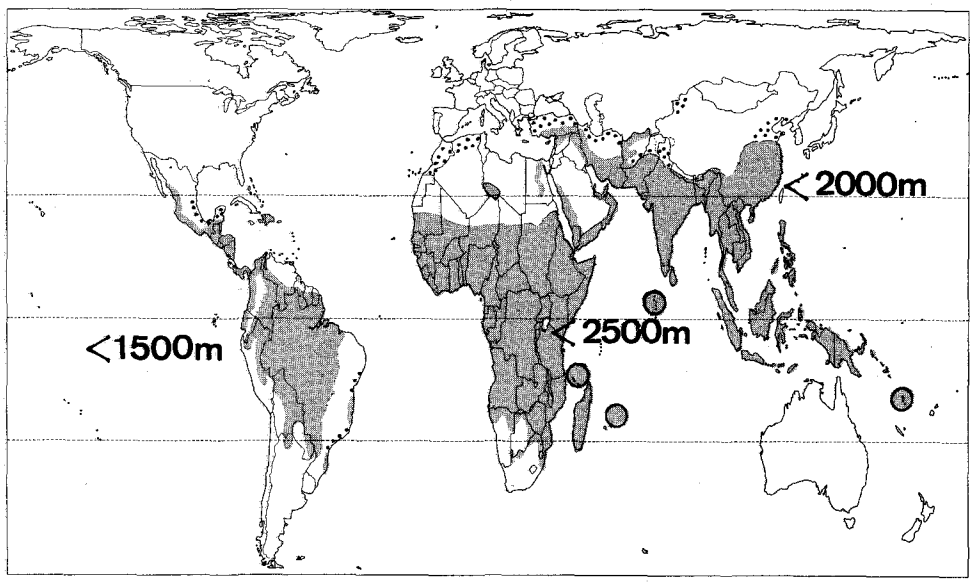

Figure 1. Malaria risk. ▒, High risk, presence of *P.falciparum*. ▓, Limited risk.

sion only 20% were free of indigenous malaria in 1979[6]. Almost 3000 malaria infections have been imported into Europe in 1981[32]. The overall case fatality rate of imported cases is about 0.5/100. It depends to a large extent on the proportion of *Plasmodium falciparum* infections and on the proportion of semi-immune visitors among all imported cases. *P.falciparum* accounts for 10–50% of all infections, while between 20 and 70% of imported malaria cases occur in semi-immunes (table 1). The case fatality rate in non-immunes varies between 0.2 and 3/100 and is nearly exclusively due to malignant *P.falciparum* infections.

The malaria attack rate in non-immune travellers is 0.1–1.0/1000 departures/year (table 1). It is of the same magnitude as the one in semi-immunes, but non-immunes are exposed during a much shorter period than semi-immunes who have lived in endemic areas for months or years. Travellers from Western Europe, North America and the Pacific stay abroad for an average of 6.5, 8.8 and 14.3 days, respectively[27]. This means that if non-immunes were exposed for one full year, their risk to contract malaria would increase 8, 6 or 4 times, respectively.

Truely, there is a real risk for travellers to contract malaria abroad, and to die from it at home. On the other hand, despite the problem of resistant *P.falciparum* infections, malaria prevention is a powerful means of staying healthy while abroad[8,33]. Advice on malaria prevention for travellers usually follows 3 steps: a) to estimate the malaria risk, b) to advise prevention of mosquito bites, and c) to prescribe the specific chemoprophylaxis.

How to estimate the malaria risk

Malaria is at present being transmitted in large parts of Africa, Latin America, Asia and Oceania (fig. 1)[8,31–33]. However, the risk to contract the infection or to develop the disease is not uniform within this global endemic area.

Some countries, regions or cities within malarious areas may be permanently or temporarily free of malaria (table 2). For a traveller who is going to visit a malaria-free area it is not necessary to take antimalarials. However, the following situations should be kept in mind with a visitor to a malaria-free area: a) the information may be inaccurate or the epidemiologic pattern may have changed, b) a stop-over of a few hours' duration in a malarious area on the way to a malaria-free destination may suffice to acquire the infection, c) infectious *Anopheles* mosquitoes can be carried into malaria-free zones by all kinds of transportation including intercontinental flights[14]. Therefore, when in doubt it is safe to assume a risk and to give advice on malaria prevention.

The malaria risk in a given area may be low for several reasons. The malaria transmission may be at low level or focal (because of geographic conditions or effective control measures). Malaria is presently endemic at low

Table 1. Imported malaria in 1981, selected states[a]

	Australia	USA	FRG	Italy	Netherlands	UK
Proportion *P. falciparum*	0.22	0.15	0.35	0.53	0.37	0.24
Semi-immunes						
Number of cases	300	809	185	29	55	893
Proportion of all cases	0.6	0.7	0.5	0.2	0.4	0.6
Attack rate/ 100 arrivals	0.6	0.3	0.06	0.04	0.2	0.6
Non-immunes						
Number of cases	197	281	198	114	73	682
Proportion of all cases	0.4	0.3	0.5	0.8	0.6	0.4
Attack rate/ 1000 departures	0.2	0.6	0.1	?	?	1.0

[a] Data are computed from Senior[27] and WHO[32] and from official health statistics. Cryptic and congenital malaria cases have been removed from the computation. Foreign visitors, immigrants and refugees are counted as 'semi-immunes', civilian and military nationals as 'non-immunes'. 'Arrivals' and 'departures' are estimates and refer to visits from or to tropical areas.

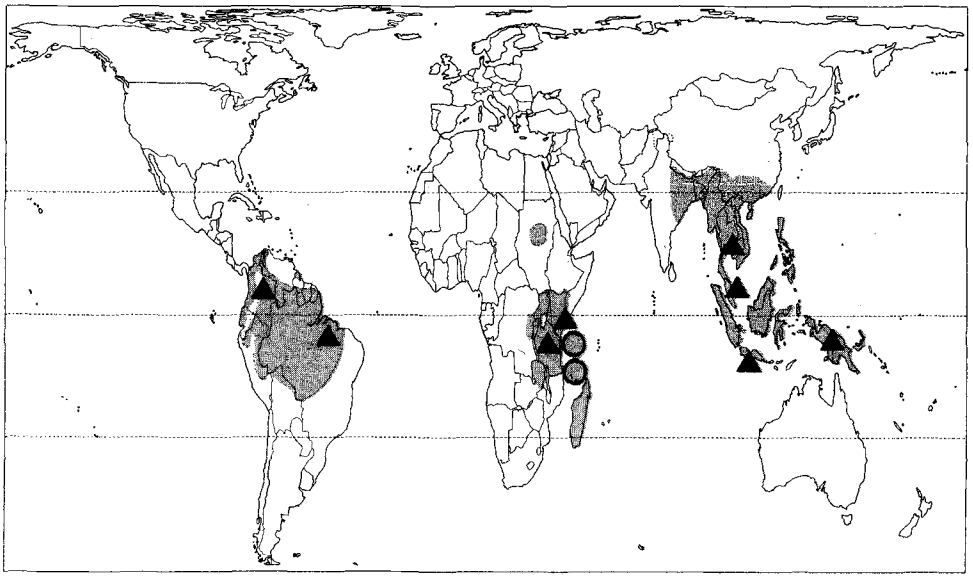

Figure 2. Resistant *P.falciparum* malaria 1984. ▨, Chloroquine; ▲, Fansidar.

level in Algeria, Argentina, Costa Rica, Egypt, Libya, Marocco, Reunion, Syria and Tunisia. The activity of the transmitting vectors may be low (because of high altitude or dry season). Transmission is likely to cease at altitudes above 2500 m (Africa) to 1500 m (Latin America) (fig. 1) or, in the case of *P.falciparum*, when the temperature of the mosquito habitat falls below 20 °C[4]. Exposure to mosquitoes may be low or irregular, for instance in a businessman who will stay abroad indoors, in mosquito-proof rooms, for most of the time. In general, low malaria risk is found in areas where *P. vivax* is the dominant or exclusive *Plasmodium* species. *P. vivax* is prevalent along the Mediterranean basin (North Africa, Turkey) and in the highlands of Africa (Ethiopia), South America (Andes) and Asia (Afghanistan, Xingjiang in China).

Table 2. Malaria-free states and capitals[a]

	Africa	Latin America	Asia and Pacific
States	Lesotho	Caribbean Islands	Australia
	Reunion	*except:* Haiti,	Bahrein
	Seychelles	Dominican Republic	Israel
	St. Helena	Chile	Japan
		Galapagos Islands	Jordan
		Uruguay	Korea:
			North, South
			Kuwait
			Lebanon
			Pacific Islands
			except: Southwest
			Qatar
			Taiwan
Capitals	Algier	Asuncion	Baghdad
	Cairo	Bogota	Hongkong
	Nairobi	Brasilia	Jakarta
	Pretoria	Buenos Aires	Macao
	Rabat	Caracas	Kathmandu
	Tripolis	Guatemala City	Manila
	Tunis	La Paz	Riyadh
		Lima	Singapore
		Panama City	Teheran
		Quito	
		San Jose	
		Tegucigalpa	

[a] Includes states where malaria is not naturally occurring, or where malaria has been eradicated. While the inner cities are malaria-free, a risk of infection may exist further outside, in the outskirts or periurban areas[8, 10, 33].

A high malaria risk should be assumed whenever *P.falciparum* infections are likely to occur. This species is principally intertropical. It accounts for 10–30% of all malaria cases in Latin America, 20–70% in Asia and 80–100% in subsaharan Africa. A high proportion of *P.falciparum* infections is also noted in Haiti, the Dominican Republic and the islands of the Southwest Pacific. In recent years the situation has become dramatic because of the appearance of *P.falciparum* strains which are resistant clinically and/or in vitro to either chloroquine (and other 4-aminoquinolines), to Fansidar (combination of pyrimethamine plus sulfadoxine) or to both (fig. 2)[5, 24, 32].

Chloroquine-resistant *P.falciparum* strains occur a) south of the Panama canal in all of South America, b) in Asia eastwards from the state of Orissa in India, this vast area of resistance includes the south of China, the southeast Asian mainland and all main islands of the Philippines, Indonesia and of the southwest Pacific[22, 23, 29], and c) East Africa, both the mainland countries, as well as the off-shore islands of Madagascar, the Comoros and Zanzibar[7, 26, 30, 34]. The area of resistance seems to expand northwards into the Soudan (Khartoum province), eastwards into Zaire (Lake Kivu area), and southwards into Zambia, Malavi and Moçambique. The proportion of *P.falciparum* strains sensitive to chloroquine is particularly low in SE-Asia and in the SW-Pacific. In Thailand chloroquine has become ineffective for cure of *P.falciparum* infections[22]. Fansidar resistance is now a serious problem at its place of origin, the border area between Thailand and Kampuchea, and in Kenya and Tansania, where it has recently appeared[30a]. It is also occurring in the Amazone basin and in Colombia[12].

Lastly, the traveller himself influences the risk assessment. Infants, pregnant women and travellers with dis-

orders of the immune system are particularly vulnerable. Travelling off the roads and outdoor activities may greatly increase the exposure to mosquitoes.

Protection against mosquitoes

Appropriate measures to prevent mosquito bites can clearly reduce the malaria risk for travellers. Assume that of an anopheline species that is exclusively feeding on man and is the principal malaria vector in the area 0.5% of all females are infected and that an unprotected individual picks up 10 bites in 24 h. The probability to become infected is then 5% each day. If the exposure is reduced to 1/10th by preventing mosquito bites, the likelihood to become infected reduces to 0.5% per day. Prevention of mosquito bites is in fact the only true means of primary prevention of plasmodial infection. The practice of mosquito prevention should be explained in detail to each traveler at risk. Effective measures against mosquitoes include appropriate behavior, clothing, and the use of repellents and mosquito nets in unproofed rooms.

The antimalarials

The number of drugs that can be used for malaria prophylaxis is, unfortunately, very limited. Tables 3 and 4 provide information on the pharmacologic properties and the application of antimalarials.

None of these drugs is effective against sporozoites which represent the infective form of the parasite. Only primaquine and proguanil act on liver schizonts during the incubation period (so-called causal prophylaxis), and primaquine alone acts on dormant liver forms (hypnozoites) during latent infection; it can prevent relapses of vivax or ovale malaria[3]. All other antimalarials are 'suppressive', i.e. they act on blood schizonts, thereby suppressing disease but not latent infection. When taken long enough after a presumptive *P. falciparum* infection (i.e., at least 6 weeks after leaving a malarious area) suppressive antimalarials are able to effect elimination of this parasite because it lacks a dormant liver stage[3] (so-called suppressive cure). In essence, therefore, the goal of malaria chemoprophylaxis cannot be to prevent any infection, rather it should protect the non-immune from contracting a malignant or possibly fatal *P. falciparum* infection (cerebral malaria).

The action of primaquin on asexual blood parasite stages appears at toxic doses only, precluding this drug from use for chemoprophylaxis[4]. The 4-aminoquinolines are excellent drugs for suppressing *P. vivax* and sensitive *P. falciparum* infections. Amodiaquine has preserved some effectiveness against chloroquin-resistant *P. falciparum* strains in Southeast Asia[20] and in

Table 3. Activity and pharmacologic properties of antimalarials[a]

	Generic name	Chemistry	Activity Blood	Liver	Plasma T/2 (h)	Suppressive plasma concentration (mg/l)
Derivatives of quinine	Chloroquine	4-Aminoquinoline	Fast	−	72–120	0.02–0.03
	Amodiaquine	4-Aminoquinoline	Fast	−	72–120	0.02(?)
	Primaquine	8-Aminoquinoline	+	(+)	6	(?)
	Mefloquine	Quinoleine-methanole	+	−	e576	e0.5–1.0
Synthetics	Proguanil	Biguanid	Slow	+	24	0.01–0.1
	Pyrimethamine	Diaminopyrimidine	Slow	(?)	96–120	0.01–0.1
	Sulfadoxine	Sulfonamide	Slow	−	144–216	e60
	Sulfalene	Sulfonamide	Slow	−	72	(?)
	Dapsone	Sulfone	Slow	−	17–33	(?)
	Doxycycline	Tetracycline	Slow	−	17–20	(?)
	Quinghaosu	Dihydrotriazine	Fast	−	4	(?)

[a] Data are compiled from Bruce-Chwatt[5] and Ritschel et al.[25] and from reports on individual drugs. Only main representatives of each chemical group are presented; e, estimated.

Table 4. Prescription of malaria chemoprophylaxis[a]

	Generic name	Brand name	Formulation mg base/tablet	Oral dose mg base/week Adults	Children[b]	Resistance *P.f.*	Resistance *P.v.*
Individual drugs	Chloroquine	Nivaquine Resochin	100 150	300	5/kg	++	−
	Amodiaquine	Camoquin Flavoquine	200	400	6–7/kg	+	−
	Proguanil	Paludrine	90	1260	21/kg	++	+
	Mefloquine	Mefloquine	500	250	4/kg	(+)	?
Pyrimethamine (P) combinations	P plus sulfadoxine (S)	Fansidar	P25 S500	P25 S500	P0.5/kg S10/kg	+	+
	P plus dapsone (D)	Maloprim	P12.5 D100	P12.5 D100	P0.25/kg D1.5/kg	+	+

[a] Only some commonly prescribed drugs are listed. Not all of these are registered for sale worldwide. Drug dosages are those usually prescribed for prolongued use[4,5,7,10]; higher chloroquine doses may be prescribed for short term visitors ('French scheme' with 600 mg of base/week for adults and 10 mg/kg and week for children.

[b] Pediatric dose should never exceed maximum adult dose.

East Africa[7,30,34], at present it should be preferred over chloroquine for malaria prophylaxis in non-immunes. Resistance of *P. falciparum* (and, to a lesser extent, of *P. vivax*) to the dihydrofolatereductase- inhibitors pyrimethamine and proguanil is widespread, both drugs are used or recommended for combination with other antimalarials only[4,10,21]. The antimalarial effect of sulfonamides, sulfones, and the antibiotics doxycycline, erythromycine and co-trimoxazole is slow and unreliable, and they should not be used as single prophylactic drugs either[13,23]. Quinghaosu (artemisin) is a re-discovered, very potent shizonticide[15], which is hampered for prophylaxis by a very short plasma half-life (table 4); it is currently not available in the West. Mefloquine is a new schizontocide that is effective against chloroquine-resistant strains of *P. falciparum* and that is currently under investigation for prophylactic use[17]. However, recent reports on mefloquine-resistant *P. falciparum* infections[2] should preclude its use as single chemoprophylactic agent to prevent further development of resistance. Non-immunes are likely to take antimalarials for a period of less than, say, 6–12 months. The short-term tolerance of preventive antimalarials is excellent apart from drug allergies and slighter gastrointestinal disturbances. For short-term protection higher chloroquine doses than those given in table 4 have been used without untowards effects. There is no doubt, however, that for long-term use the lowest effective dose should be prescribed in order to prevent the rare, but potentially serious side effects. These include the chloroquine-induced retinopathy and hematological disorders by sulfones and sulfonamides[5,9]. The tolerance of antimalarial drug combinations has not well been studied. However, it is good clinical practice not to combine drugs with the same activity (e.g. co-trimoxazole and Fansidar). The 4-aminoquinolines are regarded as safe for the whole period of pregnancy. Fansidar and Maloprim (combination of pyrimethamine plus sulfone) should be avoided in pregnancy; Fansidar is certainly contraindicated in pregnant women who visit areas where Fansidar-resistant *P. falciparum* strains occur. Tetracyclines and sulfonamides cannot be used in preschoolchildren and in neonates, respectively.

Prescribing the chemoprophylaxis

It should have become evident that choosing the appropriate antimalarial for effective prevention may be extremely difficult and has to be done on an individual basis which takes into account the age and health status of the traveller, and the length and type of malaria exposure. The following section provides some guidelines that have to be modified with individual circumstances and the constantly changing epidemiologic situation.

Where there is few malaria risk and most or all malaria is due to *P. vivax* the 4-aminoquinolines (chloroquine, amodiaquine) remain the drug of choice. Similarly, 4-aminoquinolines keep their full value in areas where *P. falciparum* occurs but is sensitive. Currently these areas comprise: a) Central America and the Caribbean Islands, b) the whole western portion of Africa, and c) the Arabian peninsula and Central Asia (excluding India and Sri Lanka).

Problem areas are the Amazone basin, East Africa (mainland and islands), and Southeast Asia and the Southwest Pacific. Here, sensitive, mono- or polyresistant *P. falciparum* strains may coexist with all other *Plasmodium* spp.[32] (fig. 2). Amodiaquine, or mefloquine as an alternative, should be the preferred 'baseline' antimalarial against *P. vivax* and sensitive *P. falciparum* infections. Where the malaria risk is non-trivial, and to prevent further resistance it should be combined with either of the following drugs: Fansidar (in areas with sensitive falciparum infections), Maloprim (in areas with Fansidar resistance), paludrine or doxycycline (outside Thailand). This chemoprophylactic scheme is depicted in table 5.

At the time the traveller gets the prescription or the antimalarials from his physician he should receive further information about the following points. Parasitological and clinical malaria breakthroughs and even cerebral malaria[1] may occur under regular chemoprophylaxis. The only way at present to avoid such fatalities seems to make the traveller aware of the possibility of breakthroughs, so that he can seek immediate medical care. Besides fever disturbances of the gastrointestinal tract or central nervous system may herald a malaria attack. Educated travellers to remote areas could carry along quinine tablets and an instruction sheet as an emergency reserve for stand-by therapy.

The traveller should also be told about possible side effects of antimalarials. Whenever long-term use is necessary, he should see a physician at regular intervals, say every 6–12 months, for early recognition of side effects. The absorption of antimalarials may be decreased because of diarrhea, vomiting or concomitant use of antacids or kaolin[18,19]. In case of diarrhea it is important not to omit a single antimalarial dose. Eventually, the total weekly dose can be split up into small daily doses[19]. It might well be that part of the discrepancies between in vivo and in vitro resistence tests are the result of malabsorption of antimalarials. Drug interactions should be considered, too. The fraction of pyrimethamine, chloroquine, amodiaquine and sulfadoxine that binds to plasma proteins is about 25%, 50%, 90% and 90%, respectively[25].

Table 5. Suggested antimalarial drug combination for areas where mono- or polyresistant strains of *P. falciparum* occur[a]

	South America	East Africa	East Asia and Southwest Pacific
Baseline	Amodiaquine or Mefloquine	Amodiaquine or Mefloquine	Amodiaquine or Mefloquine
Add-ons			
1st choice	Fansidar	Proguanil	Fansidar
2nd choice	Proguanil	Maloprim	Proguanil
3rd choice	Maloprim	Doxycycline	Maloprime

[a] This table expresses the author's personal opinion. Amodiaquine is effective at least against some chloroquine-resistant *P. falciparum* strains and should be preferred to chloroquine as baseline antimalarial. Because of the short plasma half life of dapsone and the low pyrimethamine content of Maloprim, Fansidar is preferable to Maloprim. Fansidar-resistance seems of particular concern for non-immune travellers to East Africa.

Does the traveller get all the information he needs to protect himself appropriately? Is he willing to cooperate and comply with the drug regimen, which may consist of a combination of drugs to be taken at different times of the day or week? Unfortunately the answer to such questions is negative in many instances. Travellers often have not an adequate understanding of the malaria risk. They do not always take satisfactory precautions to protect themselves from mosquito bites. Their compliance with the prescribed chemoprophylaxis is often incomplete. Similarly, the information given by physicians, pharmacists and other health personnel may at times be inadequate. Improving the travellers' knowledge of malaria risk and prevention may be the most effective immediate measure to overcome the dramatic problems of resistant malaria of today.

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