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Problem pathogens: prevention of malaria in travellers

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Human infection with *Plasmodium* spp leading to clinical episodes of malaria probably began very early in the history of humankind and has persistently inflicted disease among human populations. Malaria is currently considered the world's most important parasitic infection. The global impact of malaria is incalculable and appears to be worsening over the past decades. Although most of this burden of disease is carried by developing tropical countries, cases of imported malaria acquired by international travel are increasingly reported. These numbers are growing because of increased travel to malaria-endemic areas and also due to increased risk of transmission in these areas. Indeed, travel has contributed to the global spread of malaria during the history of humankind. Travellers visiting malaria risk areas should use both personal protective measures and chemoprophylaxis. Non-adherence to chemoprophylactic regimens is frequently secondary to drug side-effects. Therefore, a careful risk–benefit analysis on the use of antimalarial prophylaxis should be carried out in every individual travelling to malaria risk areas. Standby malaria self-treatment represents an alternative in some travellers. However, carefully selected and geographically specific antimalarial drug regimens should be recommended to non-immune people travelling to high-risk areas.

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Introduction

Malaria is the most important parasitic infection that produces human disease.[1,2] This condition is caused by infection by one or more of four *Plasmodium* species—*Plasmodium falciparum*, *Plasmodium vivax*, *Plasmodium ovale*, and *Plasmodium malariae*.[1–5] The infection is transmitted to human beings by the bite of the female anopheles mosquito and has afflicted human beings throughout the millennia. Indeed, malaria parasites adapted to infect and replicate within human beings very early in the history of human evolution.[3,6–8] The current social, economic, and medical impact of malaria in tropical underdeveloped settings is immense.[9,10] Furthermore, the impact of malaria morbidity and mortality continues to increase across malaria risk areas, particularly in sub-Saharan Africa.[4,11–13] In addition, as antimalarial drug resistance has risen, there has been a coincident rise in malaria-related death rates and malaria-related hospitalisations in many of these areas.[13] The actual number of clinical cases of malaria and its impact is probably underestimated by current surveillance approaches.[10]

Most of the burden of malaria disease is carried in endemic countries, particularly in the most vulnerable groups.[1,5,9] However, an increasing number of imported cases of malaria have also been reported,[14–21] probably as a result of increasing worldwide travel to regions where there is ongoing risk of malaria transmission.[14,21–25] The origins of *Plasmodium* spp as human parasites have historically involved travel.[3,6–8] To demonstrate the impact of travel in the spread of malaria, it has been recently shown by molecular inference methods that *P vivax* is derived from ancestral macaque parasites acquired when hominoids that emigrated from Africa colonised southeast Asia.[6] Therefore, travel has contributed to the global dissemination of malaria throughout the history of humankind.[3] Nowadays, cases of malaria acquired by international travellers from developed countries probably number 25 000 cases per year, with 10 000 of them reported per year and approximately 150 deaths per year.[20,26,27]

An increasingly large proportion of people are emigrating to developed countries from less developed countries.[28] This particular group are at the highest risk of contracting malaria when they travel to their country of origin due to waning levels of malaria immunity and also to the misperception of their risk of contracting malaria (figure 1).[29–34] In addition, as a group, they are less likely to receive or adhere to malaria chemoprophylaxis recommendations.[30–34] Therefore, the prevention of malaria cases among healthy, non-immune, or semi-immune individuals who travel to malarious areas is critical.[14,19,35] These strategies include personal protective measures such as the use of

AP Photo/Terry Gilliam

Figure 1: **Migrants are at risk of malaria when they return to their country of origin**

Chloroquine resistance*	Options†	Sites of action
Yes	Atovaquone-proguanil or	Blood stage (suppressive) and liver stage (causal)‡
	doxycycline or	Blood stage (suppressive)
	mefloquine§ or	Blood stage (suppressive)
	primaquine‖	Liver stage (causal) and blood stage¶
No	Chloroquine or	Blood stage (suppressive)
	atovaquone-proguanil or	Blood stage (suppressive) and liver stage (causal)
	doxycycline or	Blood stage (suppressive)
	mefloquine or	Blood stage (suppressive)
	primaquine¶	Liver stage (causal) and blood stage**

*Resistance to chloroquine is based on *P falciparum*. However, chloroquine-resistant *P vivax* has been widely identified in Indonesia, Papua New Guinea, and sporadic cases in other Asian countries. Many countries with both urban and rural malaria transmission may not have malaria risk in the most frequently visited major cities. †Equal efficacy; choice depends on traveller, itinerary, side-effects, individual choices, and convenience. ‡Tafenoquine and atovaquone can act also on the liver stage; doxycycline, azithromycin, and proguanil have limited activity in the liver stage. §Not recommended for travelling to Thailand borders with Cambodia and Burma due to mefloquine resistance. ‖Need to check G6PD level before prescribing. Sometimes used as terminal prophylaxis in travellers with prolonged stays in countries with *P vivax* or *P ovale* to eliminate the hypnozoite stage in the liver. ¶Primaquine has an effect on the liver-stage (primary schizont) of all four plasmodium species, and the sexual blood stages of all four species but only the asexual blood stages of *P vivax* but not *P falciparum*.

Table: **Recommended prophylactic regimens according to chloroquine-resistance patterns and sites of action**

impregnated bednets, insect repellents, adequate clothing, and, in case of breakthrough mosquito bites, the use of antimalarial drugs to effectively kill plasmodium parasites acquired from infected mosquitoes.[14,19,36–46]

Epidemiology of imported malaria and malaria risk in travellers

The estimated risk for a traveller acquiring malaria differs markedly from area to area.[2,36,37,45,46] This variability is a function of the intensity of transmission within the various regions, the season of travel, and of the itinerary and type of travel.[36,37] Ongoing malaria transmission occurs in large areas of Central and South America, Hispaniola, Africa, the Indian subcontinent, southeast Asia, the middle east, eastern Europe, and the south Pacific islands.[1,2,5,10,35,36,43,44] There has been a marked increased in tourism, immigration, and refugee, student, and business travel to these malaria-endemic areas.[25,30,47] International migration has risen from 120 million in 1990 to 175 million in 2002.[28] Non-immune individuals are particularly susceptible to develop severe malaria if exposed to an infected mosquito, particularly in areas with high levels of transmission.[2,5,14,19,36,45,46] Some groups are at higher risk. Immigrants to developed countries who are returning to homes and families in endemic countries (visiting friends and relatives) are at much higher risk of acquiring malaria.[24,30–33] Indeed, this particular group of travellers is responsible for a high volume of international travellers and experience excessive rates of travel-related morbidity including malaria and its complications.[31,33] Many of them have not received malaria chemoprophylaxis and are unaware that clinical immunity to malaria, even if intensively exposed previously at some point in their life, wanes over a short period of time.[31] In addition, stigma associated with the acquisition of malaria and the perceived incompetence of physicians in the developed world by some immigrant groups affect their malaria preventive decisions.[34] Furthermore, low insurance coverage, misperception of disease risk, and the health-care provider's level of knowledge of travel medicine may impact pretravel malaria recommendations.[32] Immigrants visiting friends and relatives frequently are prescribed inappropriate prophylaxis or receive not at all. In addition, many of them may be at higher risk of acquiring malaria since they may decide to non-adhere to their chemoprophylactic drug regimen, have prolonged stays in their country of origin, or spend time in high-risk areas without taking any personal protective measures against malaria.[30–34]

International tourist arrivals to sub-Saharan Africa increased from 6·7 million to 17 million between 1990 and 2000.[48] Approximately 30 000 travellers from industrialised countries contract malaria each year, predominantly travellers from Europe and North America. The risk of malaria is higher for travellers to Oceania and sub-Saharan Africa, particularly west Africa.[20,22,24,26,27,30] The proportion of malaria cases caused by particular plasmodia species reflects the traveller's destinations. However, given that most malaria infections in the world are due to *P falciparum* and *P vivax*, imported malaria cases are caused mainly by these two species.[36,49–51] Only a few cases of imported malaria cases due to *P malariae* and *P ovale* are reported annually.[17,52] When malaria cases are caused by *P falciparum* the overall case fatality rate varies from 0·6% to 3·8%.[4,16,21] In most reported fatal cases of imported malaria, travellers failed to use or comply with antimalarial prophylaxis.[4,16,21] It is generally agreed that the clinical features, outcome, and severity of malaria depend upon the level of background immunity.[45] In areas of high stable transmission, the clinical signs and symptoms are confined to childhood. At lower levels of transmission a broader age range becomes susceptible, and at low or unstable levels of transmission, or in non-immune travellers, malaria is symptomatic and therefore *P falciparum* infection is potentially lethal for travellers at all ages.[5,36,45] Approximately 1% of all non-immune travellers who acquire *P falciparum* infection in high-risk areas die.[14,16,21] This risk is proportional to delays in seeking and receiving appropriate medical care.[14,16,21]

Estimating the risk for infection for various types of travellers is difficult and can be substantially different even for people who travel or reside temporarily in the same general areas within a country.[43,44,50] The estimated risk for a traveller contracting malaria differs from area

to area. A review of the global GeoSentinel database of post-travel-related illnesses to identify risk factors associated with malaria in travellers found that most cases of malaria were in travellers visiting sub-Saharan Africa and Oceania, and that cases were more common in travellers visiting friends and relatives, those who have travelled for longer periods, and those who were less likely to have sought pretravel advice.[30] Studies of European travellers have shown similar findings, particularly a high risk of contracting malaria when travelling to sub-Saharan Africa; however, they have also identified male travellers and small children as groups at increased risk.[19,22,24,53,54]

From 1985 to 2002, 11 896 cases of malaria in the USA were reported to the Centers for Disease Control and Prevention (CDC, Atlanta, GA, USA).[43] Of these cases, 59% (6961) were acquired in sub-Saharan Africa, 19% (2237) in Asia, 14% (1672) in the Americas, and the rest in other parts of the world.[43] During this period, 76 fatal malaria infections occurred among them, 93% caused by *P falciparum*. The fact that most cases of *P falciparum* acquired in travellers are reported from sub-Saharan Africa demonstrates: (1) the high risk of malaria transmission in this area, (2) the fact that *P falciparum* is the predominant plasmodium species transmitted within this area, and (3) the occurrence of transmission in both rural and urban settings.[43] In 2003, the CDC reported 1278 cases of malaria. For those on whom information about malaria chemoprophylaxis use was available, 62% (445/709) had not taken any chemoprophylaxis. Of those that reported taking a recommended antimalarial chemoprophylaxis regimen, many reported non-adherence to the regimen.[17] These data underscore the importance of informing patients that clinical episodes of malaria may still occur despite the use of recommended chemoprophylactic regimens.[17,50] Recent reports have demonstrated that malaria-related outcomes in travellers are directly related to failure to take or adhere to recommended chemoprophylactic drug regimens, seek prompt medical care for post-travel fever, and to promptly diagnose and treat suspected cases of malaria.[14,18,21]

Prevention of malaria among travellers

The use of antimalarial chemoprophylaxis should be carefully directed at high-risk travellers where the benefit of using antimalarial drug regimens outweighs the risk of adverse events.[14,19,36] Prophylactic efficacy of antimalarial drugs is assessed by the incidence of infections that break through in individuals taking antimalarial prophylaxis, or in some cases is extrapolated by their usefulness as a therapeutic option.[45] Poor adherence to malaria chemoprophylaxis must be distinguished from drug resistance or pharmacological failure.[45,55–57] Furthermore, the acquisition of delayed-onset malaria in some travellers, despite demonstrated adherence to medical recommendations, may be due to the failure to eliminate the exoerythrocytic stage of *P ovale* and *P vivax* by using only blood-stage schizonticide drugs.[49,50]

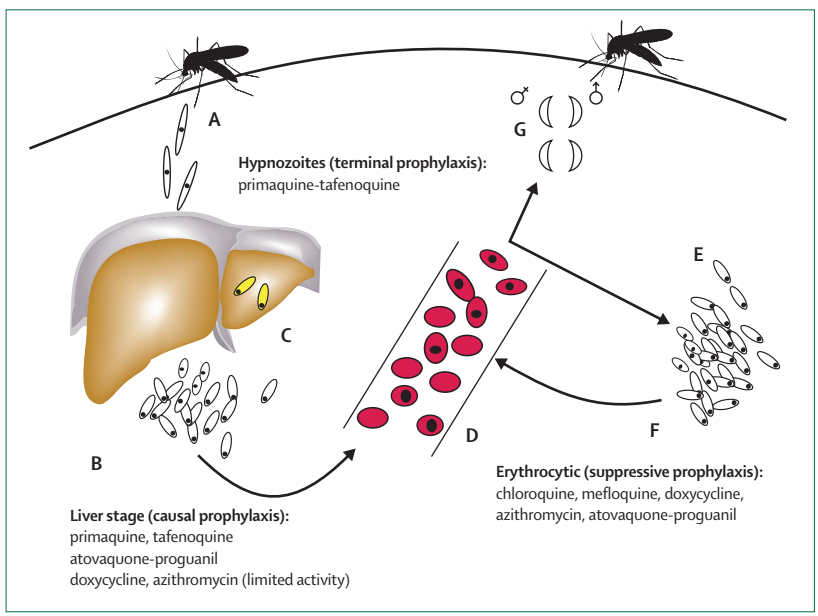

Figure 2: **Life cycle of *Plasmodium* spp in human beings and the site of action of antimalarial chemoprophylactic drugs by type of chemoprophylaxis (causal, suppressive, or terminal)**
(A) Sporozoites injected into human skin by female anopheles mosquito. (B) Release of merozoites by infected hepatic schizont rupture (intrahepatic cycle). (C) Development into hypnozoite forms in case of infection by *P vivax* or *P ovale* intrahepatic cycles. (D) Asexual blood stage causing clinical malaria by maturation of asexual stages of *Plasmodium* spp in erythrocytes. (E) Each cycle of asexual reproduction culminates with the rupture of schizonts and release of merozoites. (F) Released merozoites infect other erythrocytes. (G) Switch to sexual cycle by producing gametocytes. In the case of *P falciparum* this cycle is delayed, whereas with *P vivax, P ovale*, and *P malariae*, this stage occurs concomitantly to the asexual cycle.

When advising travellers, it is generally agreed that antimalarial prophylaxis is indicated if exposure is likely, but it should be emphasised that prophylaxis is never 100% effective, and should be complemented by a strategy of mosquito avoidance (use of impregnated bednets, screens, insecticides, repellents, adequate clothing, and avoidance of exposure during peak biting times).[14,40–44] Although most travellers can avoid becoming ill with malaria by taking these precautions, cases of imported malaria continue to be frequently reported among North American, European, and Australian travellers.[20,24,30] In some reports of travellers to malarious areas, about 50% seek travel health advice, and fewer adhere to insect protection measures and chemoprophylaxis.[38,39,58]

Preventing mosquito bites

Because of the nocturnal feeding habits of haematophagous anopheles mosquitoes, malaria transmission occurs primarily between dusk and dawn.[5,45] Travellers should be advised to take protective measures to reduce contact with mosquitoes as the first line of defence.[43,44] These measures include remaining in well-screened locations, using impregnated mosquito

***Figure 3*: Malaria-endemic countries and choloroquine-resistance patterns in the Americas**

Mexico, Central American countries, and some areas in South America continue to have chloroquine-susceptible strains of *P falciparum*. Chloroquine-resistant strains of *P falciparum* have been identified in many areas in tropical South America. Rare reports of *P vivax* have been reported in the Americas. In some countries, malaria risk varies in different regions. Source of data: CDC, Atlanta, GA, USA.

nets, and wearing, as practical, clothing that covers most of the body surface.[59] In addition, travellers should be advised to use insect repellent on exposed skin.[40,41] The most effective repellent against a wide range of arthropods is N,N-diethyl-3-methyl-benzamide (DEET, also known as N,N-diethyl-*m*-toluamide), an ingredient in many commercially available insect repellents.[40–43] Insect repellents containing as much as 30–50% DEET are recommended for both adults and children over the age of 2 months.[43] DEET-containing formulations with less than 20% DEET provide protection for 1–3 hours, and higher concentrations provide longer lasting protection. DEET-containing repellents should not be applied on wounds or broken skin, and when applying to the face, travellers should avoid contact with the eyes and mouth.[41] Permethrin is available as a spray or liquid to treat clothes and bednets, or bednets that have already been treated with permethrin can be purchased. Picardin, a piperidine derivative, has been shown to be as effective as long-acting DEET formulations.[41] Picardin has been used widely in Europe and Australia and more recently marketed in North America as being as effective as DEET without causing skin discomfort or damage to synthetic fibres.[41] Non-DEET-containing formulations provide only a short duration of protection: 23 minutes with the alanine analog IR 3535, 95 minutes with soy bean oil, and about 20 minutes with citronella-containing products.[40,42] It is also recommended to take a flying-insect insecticides or mosquito coils that contain pyrethroid insecticides to help clear rooms of mosquitoes. The use of impregnated bednets offers about 50% protection for travellers visiting high-risk areas and should be strongly emphasised to travellers by travel health-care providers.[19]

Malaria chemoprophylaxis

No vaccine is currently available to prevent malaria when travelling to high-risk areas.[43,44] However, chemoprophylaxis has been demonstrated to be an effective preventative strategy.[14,19,36] The term malaria chemoprophylaxis encompasses various strategies for the prevention of malaria by the use of drugs with antimalarial activity.[59] These drugs may work either by preventing the pre-erythrocytic development of the parasite (causal prophylaxis) or by suppressing development of the blood stage infection (suppressive prophylaxis; table). Primary prophylaxis uses medications before, during, and after the exposure period to prevent initial infection (figure 2).[59] Terminal prophylaxis uses medications toward the end of the exposure period or slightly thereafter to prevent relapses or delayed-onset clinical presentations of malaria caused by *P vivax* or *P ovale*.[59] This strategy is particularly important in preventing delayed onset of malaria, since it has been shown that more than one-third of travellers infected with species that cause relapsing malaria developed their illness even when taking commonly used and effective blood schizonticides.[50] Liver-stage schizonticides inhibit the development of the primary liver schizonts of all *Plasmodium* spp, preventing primary malaria. In addition, liver-stage schizonticides block the development of the liver hypnozoites forms of *P vivax* and *P ovale* and therefore interrupt secondary relapses (figure 2).[36,37,50] In areas of the world where most cases of malaria are due to *P falciparum*—eg, sub-Saharan Africa—suppressive prophylaxis with blood schizonticides is adequate. However, in many other areas where a large proportion of malaria cases are due to *P vivax* or a combination of *P falciparum* and *P vivax*, prophylaxis against liver-stage prophylaxis may provide the best protection.[14,19,36,46,49,50,60]

Prophylaxis with mefloquine or chloroquine should start 1 week before arriving in the malarial area, and should be continued weekly during exposure and for 4 weeks after leaving the transmission area. Atovaquone-proguanil is begun 1–2 days before exposure, continues daily during exposure, and is continued for 1 week after leaving the malarious area. Doxycycline is begun 1–2 days before exposure, daily during exposure, and must be continued for 4 weeks after exposure.[36,37,43,44,59,60]

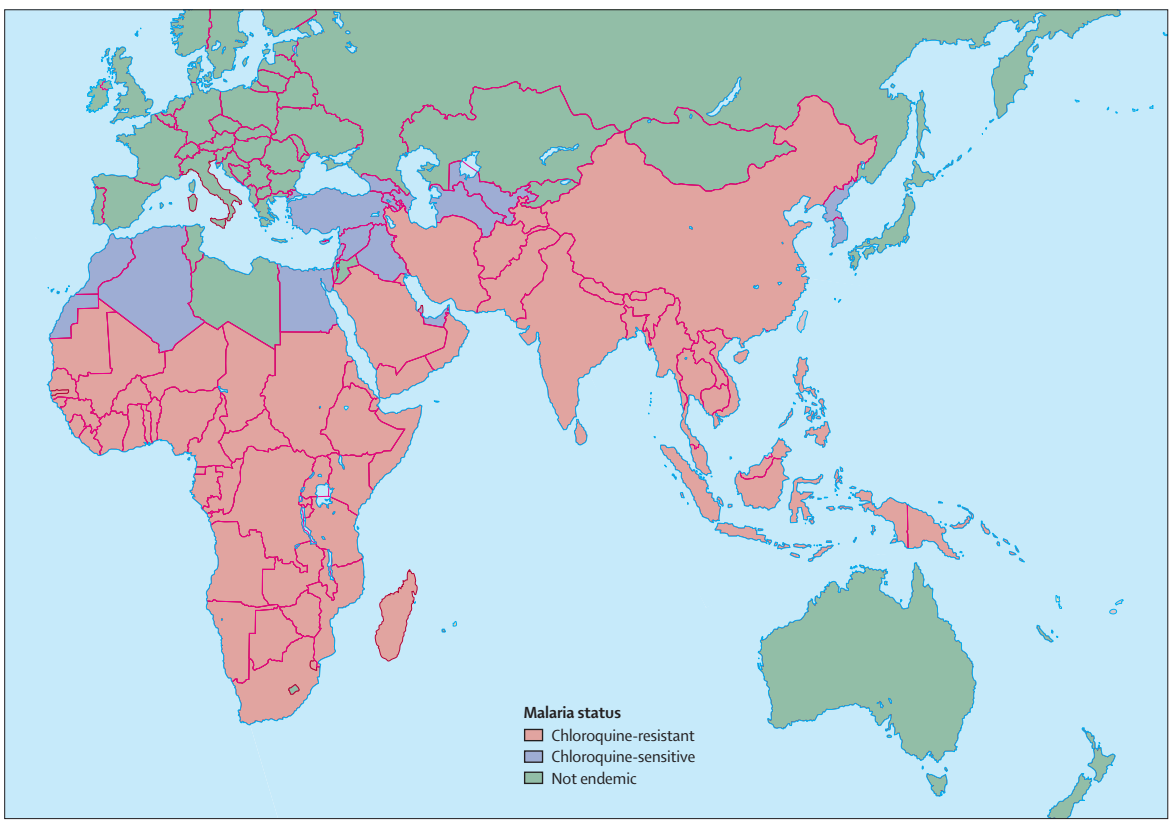

Figure 4: **Malaria-endemic countries and chloroquine-resistance patterns in Africa, the middle east, Asia, and the south Pacific**
P falciparum mefloquine resistance has been identified in the borders of Thailand with Cambodia and Laos. *P vivax* resistance to chloroquine has been described in the Indonesian archipelago and some sporadic cases in other Asian regions. In some countries, malaria risk varies in different regions. Source of data: CDC, Atlanta, GA, USA.

There is no single ideal regimen for all travellers and the health-care practitioner should attempt to match the traveller's risk of malaria to the appropriate drug based on pharmacology, safety profile, efficacy, cost, and convenience.[36] Furthermore, antimalarial drug toxicity is an important aspect to consider when prescribing these drugs for malaria prophylaxis, since adverse events are a major cause of non-compliance.[14,57] When a health-care practitioner is deciding which chemoprophylactic regimen to choose, several factors should be considered. The travel itinerary should be reviewed in detail and compared with the information on malaria risk by country, region within country, and even by season to determine the need for prophylaxis. Compliance with chemoprophylaxis is an important factor when deciding to choose a specific antimalarial drug, because failure to complete the full course of medication places travellers at risk and can cause malaria in travellers returning from abroad.[38,39] Therefore, convenience is an important aspect to consider when choosing a specific antimalarial agent.[61] Most people receiving antimalarial chemoprophylaxis will experience minor adverse reactions, but some may develop moderate side-effects that will prompt them to non-adhere to recommended antimalarial regimens.

Adverse pregnancy outcomes such as stillbirth, preterm delivery, or miscarriage may occur during clinical episodes of malaria in pregnant women. Given the fact that no chemoprophylactic regimen is completely satisfactory, women who are pregnant or likely to become pregnant should be advised to avoid travel to areas with high levels of malaria transmission. If travel cannot be deferred, use of effective antimalarial drugs—eg, chloroquine or mefloquine—is critical. There is evidence that atovaquone-proguanil is safe during pregnancy, however it is not approved by the US Food and Drug Administration for this particular indication yet.[36,43,44,59,62]

Malaria chemoprophylaxis in non-immune travellers should cause less harm than the risk of becoming ill with a clinical episode of malaria.[57,61] Therefore, antimalarial drug toxicity is an important part of the risk–benefit equation on recommending a particular drug regimen to travellers.[14,19] A recent randomised trial[61] compared four commonly recommended antimalarial drug regimens in non-immune travellers and found that atovaquone-proguanil and doxycycline were well tolerated compared with chloroquine and proguanil, and mefloquine. Of note, the group receiving chloroquine and proguanil presented the highest proportion of mild to moderate adverse events followed by mefloquine.[61] Some have

advocated that chemoprophylaxis should be limited to high-risk areas, arbitrarily defined as areas with ten or more cases of falciparum malaria cases per 1000 inhabitants per year.[19]

Most chemoprophylactic regimens are largely inadequate to prevent the occurrence of relapses or recrudescence due to *P vivax* or *P ovale* infection.[49,50] In fact, most frequent malaria chemoprophylactic regimens are intended to prevent the occurrence of severe manifestations—specifically death—of falciparum malaria. Therefore, returned travellers who may have complied with recommended chemoprophylactic regimens may still experience clinical episodes of malaria; most of these episodes are due to infection with *P vivax* or *P ovale*.[17,50] It is of utmost priority to inform travellers of the possibility of developing symptoms compatible with malaria and that travellers should seek prompt medical care after returning from malaria-endemic areas within a year, particularly within the first 3 months.[14]

Global distribution of antimalarial resistance patterns: implications fo chemoprophylaxis

Because of the emergence of multidrug-resistant strains of plasmodia, malaria chemoprophylaxis for international travellers has become a more complex and challenging task. Recognition of the global distribution of antimalarial drug resistance is essential for health-care practitioners to provide adequate advice to travellers. Recommendations vary according to geographic region and should be continually reviewed by providers[43,59] (figure 3 and figure 4).

Resistance of *P falciparum* to chloroquine now occurs throughout most of the tropical world.[1,4,43,44,59] Chloroquine sensitivity is still retained in Central America north of the Panama canal, Haiti, north Africa (Egypt), and parts of the middle east.[1] High-level chloroquine resistance in *P falciparum* is now prevalent in many areas of South America and east Asia; in these areas there is usually no therapeutic response at all to chloroquine.[4] Mefloquine resistance is still relatively unusual. In southeast Asia, high-level mefloquine resistance has developed on the eastern and western borders of Thailand and in the adjacent countries.[63–69] Mefloquine resistance is usually associated with reduced susceptibility to halofantrine and quinine.[66,67] Resistance to chloroquine by *P vivax* is currently a problem in some areas of the world, including the Indonesian archipelago, sporadically in Asian countries, and rarely in South America.[35,60,68,70–72]

Travel to countries without chloroquine-resistant *P falciparum*

For travel to areas of risk where chloroquine-resistant *P falciparum* has not been reported, use of chloroquine alone is usually recommended by some authorities for primary prophylaxis.[36,37,43,44,59] The efficacy of chloroquine as a malaria chemoprophylactic regimen has been validated in only one study.[73] People who experience uncomfortable side-effects after taking chloroquine may tolerate the drug better with meals.[57] Terminal prophylaxis with primaquine may be required in some travellers visiting chloroquine-susceptible areas, depending on their destinations and duration of stay.[50] Chloroquine may be associated with a high rate of side-effects and it can exacerbate psoriasis.[1,10] The occurrence of retinopathy is relatively unusual with prophylactic use of the drug, particularly if a cumulative total of less than 100 g has been consumed. In some countries, chloroquine is sometimes combined with proguanil to provide additional protection against low-level chloroquine resistant *P falciparum* infections.[45,73–76] Both drugs are considered safe in young children and pregnant women.[1,4] Chloroquine-proguanil combinations have been used extensively and continue to be recommended by some travel health-care practitioners.[73–76] Approximately 1–5% of travellers receiving this particular combination may experience mild side-effects including depression, dizziness, headache, mouth ulcers, and sleeping disturbances. More importantly, more than 10% may experience gastrointestinal side-effects and anorexia.[45,74–76] The protective efficacy of chloroquine alone or in combination with proguanil in non-immune travellers has not been shown to be substantially better than proguanil alone or a combination of chloroquine with sulfadoxine-pyrimethamine.[76] The chloroquine-proguanil combination is obsolete in tropical Africa. A French study described a 4·8% incidence of falciparum malaria in soldiers based in central tropical Africa receiving chloroquine-proguanil, compared with 0·6% of those receiving doxycycline.[76] Furthermore, a randomised controlled trial has shown poor tolerability of chloroquine-proguanil compared with doxycycline, mefloquine, or atovaquone-proguanil.[77] Therefore, travellers unable to take chloroquine or hydroxychloroquine should take atovaquone-proguanil, doxycycline, or mefloquine since these antimalarial drugs are also effective against chloroquine-sensitive *P falciparum*.[36,43,44,59]

Travel to countries with chloroquine-resistant *P falciparum*

Malaria chemoprophylaxis recommendations for travellers visiting areas where strains of resistant *P falciparum* have been identified have become a challenging aspect of pre-travel health-care advice. The chemoprophylaxis recommendations are based on geographic patterns of chloroquine or mefloquine resistance.[43,44] In some countries, variation in patterns of resistance may dictate the use of a specific agent or regimen. Additional comprehensive and up-to-date information on malaria risk within a country is available for both health-care practitioners and travellers at the CDC website (http://www.cdc.gov/travel) and the WHO website (http://www.who.int/ith/).

From the clinical standpoint of a travel health-care provider, recommending atovaquone-proguanil chemoprophylaxis as the preferred agent for regions where there is either chloroquine and/or mefloquine resistance may be easiest due to its safety profile, convenience, and shorter course. However, atovaquone-proguanil is far more expensive and thus is impractical for longer term travellers or for those who are on a limited budget.[32–36] Adverse events include headaches and gastrointestinal problems.[32–36,57] Mefloquine continues to be widely prescribed and in special circumstances (eg, long-term travellers, expatriates, children under 11 kg in weight, pregnant women, and the preference of some patients) remains the drug of choice. Doxycycline is another excellent option and is considered an ideal choice when attempting to prevent other infectious diseases such as travellers' diarrhoea, rickettsial illness, and/or leptospirosis in some settings. The most important disadvantage of choosing mefloquine for chemoprophylaxis is its inability to be used in patients who have had neuropsychiatric problems in the past, particularly seizures, depression, and/or anxiety, given its high rate of neuropsychiatric adverse events.[57,78–81] Similarly, doxycycline may be associated with some disadvantages such as gastrointestinal side-effects, photosensitivity, and recurrent vaginitis.[36,57] In some circumstances the combination of chloroquine and proguanil has been used for travellers to areas of chloroquine resistance. However, increasing data are available on the inadequacy of this combination for the prevention of *P falciparum*.[57,75,76,81] This combination is not recommended by the CDC. In some situations, primaquine can be used daily for chemoprophylaxis. Before its use, serum should be obtained to insure a normal level of glucose-6-phosphate dehydrogenase (G6PD) to prevent haemolysis; because of the risk–benefit profile of this agent, a specialist in malaria or tropical medicine should be consulted before prescribing this drug for a traveller.[49,50]

Other antimalarial drugs

Atovaquone-proguanil

Malarone is a fixed combination of two drugs, atovaquone plus proguanil.[36,43,44,82–85] The two components have synergistic mechanisms of action and have the substantial advantage of being effective both as a causal as well as a suppressive prophylactic agent. The prophylactic efficacy of this drug combination against chloroquine-resistant *P falciparum* malaria has been established for semi-immune and non-immune adults and children.[82–86] It is also effective along the Cambodian and Burmese borders of Thailand, where both chloroquine and mefloquine resistance has been documented.[45] Although it is relatively expensive, atovaquone-proguanil is well tolerated and is effective throughout the world, including in areas with multidrug-resistant malaria. Most experience with atovaquone-proguanil has been obtained in adults.[82–84,86,87] Atovaquone-proguanil is now registered for prophylactic use in several countries. The adult dosage is one adult tablet (250 mg atovaquone/100 mg of proguanil) per day, taken with food or milk to promote absorption of the atovaquone moiety. Atovaquone-proguanil is the most effective choice with the least side-effects for short-term travellers. However, its safety and effectiveness in long-term travellers has not been well defined, so far. The most common side-effects reported are abdominal pain, nausea, vomiting, and headache.[57,82–85] In most cases, the side-effects are not serious enough to discontinue its use. In various clinical trials this drug combination was well tolerated and had a safety profile comparable to that of placebo. Atovaquone-proguanil is not recommended for children weighing less than 11 kg, pregnant women, women breast feeding infants weighing less than 11 kg, patients with several renal failure, and patients with previous allergies to either atovaquone or proguanil. Metoclopramide and rifampicin decrease atovaquone levels by 30–50% and tetracycline decreases atovaquone levels by 40%.[36,43,44]

Mefloquine

Mefloquine, taken as 3 mg/kg once weekly, is effective prophylaxis for all malarious areas, except for focal areas in southeast Asia. Most travellers tolerate mefloquine, although reports of reversible but sometimes debilitating nervous system toxicity continue to be problematic. Dysphoria, nightmares, giddiness, and feelings of dissociation are reported commonly by travellers, although in prospective controlled studies their reported incidence is less.[57,78–80,88] Unfortunately in some cases, this adverse event profile has resulted in recommending less effective alternatives.[36] Serious neuropsychiatric reactions occur far less frequently, in the range of one in 10 000 to one in 13 000 people who use the drug for prophylaxis.[57,88] Interestingly, these statistics are similar to the rate calculated years ago for chloroquine users. The more serious adverse events usually occur soon after starting prophylaxis, occurring within the first 3 weeks. Mefloquine should not be used by people with epilepsy, psychiatric conditions (particularly those with a history of depression or anxiety), or those who have recently taken halofantrine for treatment. Despite these shortcomings, mefloquine continues to be a reasonable choice for long-term travellers to high-risk areas, since it has been shown to be the most effective and more tested choice. There is increasing evidence that mefloquine prophylaxis is safe in infants, young children, in pregnancy, and in patients with cardiovascular disease (except those with ventricular arrhythmias), although surveillance continues.[36,46,80]

Doxycycline

Doxycycline is a tetracycline antibiotic and its adult dose for malaria chemoprophylaxis is 100 mg daily. One of the most common side-effects reported by travellers taking doxycycline is sun sensitivity.[43,44,59] To prevent this,

midday sun should be avoided whenever possible, and protective clothing and eye protection should be worn. Sunscreens that protect against ultraviolet A rays should be used as directed. Doxycycline may cause nausea and abdominal pain, as well as oesophagitis. It is recommended that doxycycline be taken with a full glass of water and that one should not lie down for up to 1 hour after taking the drug to prevent oesophageal ulcers. In addition, women may develop vaginal yeast infections while taking the drug. It should not be given to children 8 years old or younger, or to pregnant women[36,43,44]

Primaquine and other antimalarial agents

Recent studies have shown that primaquine in an adult dose of 30 mg/day is well tolerated and effective against both *P vivax* and *P falciparum* as a primary prophylactic agent.[49,50,89,90] However, as mentioned, primaquine can cause fatal haemolysis in G6PD-deficient people and documentation of a normal level should be done before prescribing. Primaquine is the agent of choice—and remains the only available drug—for terminal prophylaxis for the prevention of *P vivax* and *P ovale* infections. It is active against the hepatic hypnozoite forms of the parasites, although increasing resistance has become a problem over the past decade.[35] This phenomenon has been identified in southeast Asia and Oceania. Because of this increasing resistance, the dose of primaquine recommended for terminal prophylaxis has increased over the past few years.[35,49,50,89,90]

Other antimalarial agents used for treatment are not recommended for chemoprophylaxis because of their short half-lives, possible toxicities, and risk–benefit ratios. Quinine is not used as a chemoprophylactic drug due to the frequent occurrence of cinchonism (nausea, vomiting, tinnitus, and headache) and its short half-life.[36,43,44] Halofantrine is used in some countries to treat malaria, but it is not recommended for either treatment or prevention of malaria, again due to its short half-life and its cardiovascular toxicity.[91] Fatal arrhythmias have occurred due to the prolongation of the QT interval, particularly when combined with mefloquine.[57,91] Both amodiaquine and sulfadoxine-pyrimethamine are associated with unacceptable risks of serious toxicity when used continuously for prophylaxis[57,91,92] and should not be prescribed for this indication. Amodiaquine may induce agranulocytosis and hepatitis, while sulfadoxine-pyrimethamine has been associated with severe cutaneous adverse reactions such as Stevens–Johnson syndrome and toxic epidermal necrolysis.[57,92] There is currently no role for artemisin derivatives as a chemoprophylactic agent but their use during therapy of clinical episodes of malaria to prevent both cases of severe malaria and to reduce the rates of malaria transmission and drug resistance have been demonstrated in tropical settings.[11–13] A once weekly administration of pyrimethamine-dapsone has also been used; unfortunately drug resistance as well as bone marrow toxicity limits this combination's usefulness.[36,58,91,92]

Malaria self-treatment or standby malaria treatment

Self-treatment of malaria or standby treatment should be recommended for the following travellers: (1) those who elect not to take prophylaxis; (2) those who will be travelling to areas with low levels of malaria transmission; (3) those who are receiving a less than optimal antimalarial drug regimen due to underlying medical conditions or are receiving other medications with possible drug interactions; and (4) travellers who are taking effective prophylaxis but who will be in remote areas with difficult access to appropriate medical care.[2,51,93,94] These travellers should take along a complete course of effective antimalarial treatment regimen for self-treatment. Travellers should be advised to take this regimen promptly with the occurrence of a clinical picture that could be compatible with malaria (ie, fever, chills, flu-like symptoms) and if professional medical care is not reachable within a 24-hour period.[14,19,43,44,51,93,94]

Despite effective chemoprophylaxis, malaria can still occur.[17,50] Travellers staying in malaria-endemic areas for prolonged periods are often medically treated for misdiagnosed malaria and receive suboptimal medical care while abroad. Standby emergency treatment should not take the place of effective chemoprophylaxis. However, it may be an attractive alternative for some travellers.[2] In addition, travellers need to be educated about the fact that standby treatment is only a temporary measure, since prompt medical attention should be sought immediately.[14,43,44,60,93,94] Standby treatment regimens vary according to national and international guidelines. In general, it is recommended that standby treatment of malaria should be based on a different drug from that used for prophylaxis. Whereas the CDC recommends the use of atovaquone-proguanil for standby treatment, WHO recommends the use of chloroquine, mefloquine, quinine, or quinine plus doxycycline.[2,43,44,59,93,94] The UK guidelines recommend the use of atovaquone-proguanil, artemisin-lumefantrine, or quinine plus doxycycline-quinine[2,93,94] Of note, both sulfadoxine-pyrimethamine and halofantrine are not recommended in any of these guidelines, given widespread resistance and cardiac toxicity, respectively.[2,36,43,44,59,93,94] Travellers should be educated and strongly discouraged from obtaining antimalarial drugs while abroad unless they are obtained from a reliable medical professional, since some products may not be protective or may be fake drugs, or unless the traveller has been diagnosed with severe malaria and no other options are readily available.[95] Given the frequent misdiagnosis of malaria while abroad and the possibility of other life-threatening diseases mimicking the symptoms of malaria, the use of standby treatment may

lead to serious complications if medical care is not sought immediately.[93,94,96,97] Some experts have advocated the use of rapid diagnostic tests to obtain malaria diagnosis confirmation.[2] Some of these rapid diagnostic tests are based on antigen-capture assays to detect *P falciparum* histidine-rich protein II and have demonstrated a sensitivity of 86–95% and specificity of 76–97% for *P falciparum*, but much lower numbers for non-falciparum malaria.[2] The high rate of false-negative rates makes the use of these tests not ideal and their completion by ill travellers may be cumbersome. Given these shortcomings, the use of rapid diagnostic tests is not part of any official recommendation for travellers and may only be recommended in very selected circumstances.

In summary, while standby treatment offers important advantages for some travellers, malaria chemoprophylaxis remains the most important strategy, along with personal protective measures to prevent the risk of life-threatening malaria or dying from malaria in travellers.

Conclusions

Given the lack of previous exposure or non-immunity of most travellers, malaria chemoprophylaxis recommendations have been developed to prevent infection from malaria becoming severe or even leading to death. This important benefit must be weighed against the risk of developing side-effects from the antimalarial chemoprophylaxis regimens. The population at highest risk of acquiring malaria and its complications is by far the group of travellers visiting friends and relatives since they perceive themselves as a low-risk population. The highest risk of acquiring malaria in travellers is among those visiting sub-Saharan Africa. Travel and tropical medicine practitioners need to individually inform and widely disseminate among immigrant communities information regarding travel-related risk.

Travellers to malaria-endemic areas, particularly those with itineraries that place them at highest risk of contracting malaria in areas of high risk of malaria transmission, need to be educated about avoiding mosquito and other insect bites by using adequate preventive measures (mostly bednets and insect repellents). In addition, they should receive a carefully selected malaria chemoprophylactic regimen. However, a major barrier to adherence to these recommendations is poor compliance to drug regimens often secondary to antimalarial drug side-effects. Although standby emergency treatment is not a replacement for chemoprophylaxis, it is an attractive alternative for many travellers, specifically those who choose not to receive chemoprophylaxis or who are receiving a less than appropriate regimen, those visiting areas with a low risk of transmission, or those who will not have access readily to professional medical care within an adequate timeframe. Nonetheless, chemoprophylaxis remains the safest option for malaria prevention, together with personal protective measures, particularly for those visiting tropical regions of Africa with high levels of malaria transmission. Equally important is to inform and educate every traveller on the importance of seeking adequate post-travel medical care urgently in case of malarial symptoms within a 3-month period after returning from an endemic area.

Tafenoquine, a long-acting 8-aminoquinoline,[98,99] is undergoing clinical studies and appears efficacious and may be an addition in the future. Support for ongoing research and development is surely needed as malaria re-emerges, travel to endemic regions increases, and drugs for the chemoprophylaxis of this important disease are few.

Search strategy and selection criteria

Articles for this review were identified through searching Medline, Current Contents, EMBASE, and other electronic databases. Search terms included: "malaria", "chemoprophylaxis", "travellers", "tolerability", "standby treatment", "atovaquone-proguanil", "mefloquine", "chloroquine", "doxycycline", and combinations of these terms. We limited our search to English language papers that were published between 1960 and 2005. We screened all identified articles and cross-referenced studies from retrieved articles. In addition, comprehensive and authoritative websites were also reviewed—eg, Centers for Disease Control and Prevention (http://www.cdc.gov/travel), WHO (http://www.who.int/ith/), and Health Canada (http://www.phac-aspc.gc.ca/tmp-pmv/info/pal_mal_e.html).

Conflicts of interest

We declare that we have no conflicts of interest.

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