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Malaria prevention

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ABSTRACT

Malaria is a parasitic disease transmitted by the bites of Anopheles *mosquitoes. It is a common and life-threatening disease in tropical and subtropical countries. There is no vaccination available, and prevention is based on a combination of chemoprophylaxis and avoidance of mosquito bites.*

Key words: malaria, malaria prevention, mosquito bite prevention, chemoprophylaxis

INTRODUCTION

The development of tourist markets and inexpensive flights, and the stable political situation in the majority of tourist regions in the world encourage travel. The World Tourism Organisation estimates that the total number of international travellers in 2010 will exceed one billion. With increasing international travel, prevention of malaria is an important health issue for travellers and seafarers. Approximately 110 countries endemic for malaria are visited by 125 million international travellers every year, and more than 30 000 of them contract malaria [1]. Imported malaria has been a growing health problem in European countries in the last 2 decades [2].

AETIOLOGY

There are five identified species of the parasite causing human malaria: *Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, Plasmodium falciparum, and Plasmodium knowlesi*. All species are transmitted by the bite of an infected female *Anopheles* mosquito [3–5].

EPIDEMIOLOGY

Malaria threatens nearly 40% of the world's population. The World Health Organisation (WHO) estimates that each year 300–500 million cases occur worldwide and more than two million people die of malaria. Almost 90% of deaths occur in sub-Saharan Africa where young children are the most affected. The infection kills one child every 30 seconds; in absolute numbers, 3000 children under five years of age die each day. Malaria is particularly dangerous for travellers from non-endemic areas, and for pregnant women.

More than 15 000 cases of malaria are imported to European countries every year. Between 1990 and 2003, about 900 people died of malaria in Europe. From the beginning of 1984 to 1st September 2008, there were 22 cases of fatal malaria registered in Poland. The data do not include the deaths of Polish citizens in other countries. All these people were not protected by proper chemoprophylaxis [6–10].

MALARIOUS AREAS

The malarious areas of the world have been divided into four endemic zones, in each which the resistance of parasites to drugs is different.

Zone A. Strains of *P. vivax* and chloroquine-sensitive *P. falciparum* dominate.

Zone B. Ratio *P. vivax/P. falciparum* approximately 1. Strains of *P. vivax* and *P. falciparum* partially or completely resistant to chloroquine occur.

Zone C. Strains of *P. falciparum* fully resistant to chloroquine and partially resistant to sulfadoxine-pyrimethamine and mefloquine dominate.

Zone D. Multidrug resistant strains of *P. falciparum* dominate (resistance to chloroquine, sulfadoxine-pyrimethamine, and mefloquine).

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Zone A comprises Central America and some Caribbean Islands (Haiti, certain parts of the Dominican Republic). Zone B covers the Indian subcontinent. Zone C covers South America (Orinoco delta, the Amazon River basin), sub-Saharan Africa to north-eastern regions of South Africa (including Mpumalanga Province with Kruger National Park, other northern Game Parks, and KwaZulu Natal Province), South Asia, and Oceania (Papua-New Guinea, Vanuatu, Solomon Islands). Zone D covers the Indochinese Peninsula (Vietnam, Lao PDR, Cambodia, Myanmar/Burma, and Thailand).

The big cities and tourist resorts in Southeast Asia are malaria-free. There is no malaria in Bangkok, Chiang Mai, Phuket, Pattaya, Hua Hin, Ko Samui, Kuala Lumpur, Penang, Singapore, Manila, Jakarta, Bali, Hong Kong, or Rangoon [8, 11–13].

RISK FOR TRAVELLERS/SEAFARERS

The risk of acquiring malaria for travellers depends on their destination, length of stay, type of accommodation, and purpose of travel. Other factors determining this risk and the course of disease include: the intensity and duration of exposure to mosquito bites; occurrence of drug or multidrug resistance of the parasite; age, medical history, and health status of the traveller; pregnancy; use of other medications that may be incompatible with antimalarials; itinerary and activities during travel; chances to obtain rapid, qualified medical care if symptoms occur; and personal knowledge about malaria. The risk of being infected is highest at the end of the rainy season. The risk for travellers of symptomatic malaria in non-immune subjects with no chemoprophylaxis during a month-long stay in Central America, South America, West Africa, East Africa, the Indian Subcontinent, the Far East, or the Pacific Islands is 1:10 000; 1:5 000; 1:13; 1:80, 1:250; 1:2 500, and1:16, respectively [6, 8].

PREVENTION OF MOSQUITO BITES

No effective vaccine is currently available. Prevention of malaria encompasses measures that protect against infestation and against the development of plasmodia in infected subjects. Measures that protect against infestation are directed against the mosquito vector. These can be personal protective measures, e.g. protective clothing, repellents to the exposed skin, insecticide-impregnated bed nets, or environmental protection measures, e.g. use of insecticides.

DEET-based and picaridin-based repellents have been shown to be most effective. DEET (diethyl-3-methylbenzamide) remains the gold standard of chemical insect repellents; it is effective against various species of mosquitoes (*Anopheles*, *Aedes*, *Culex*), ticks, and other biting insects [6, 8, 11, 14].

CHEMOPROPHYLAXIS

Measures that protect against disease but not against infection include chemoprophylaxis. Recommendations for antimalarial prophylaxis in specific geographical locations are constantly changing. Authoritative up-to-date sources such as the WHO, CDC, or native guidelines are recommended [15]. Travellers to malarious areas should seek expert advice on the prevention of this disease.

Malaria chemoprophylaxis for North Africa and the Near East

First-line drugs: *chloroquine, chloroquine/proguanil*

Alternative drugs: *atovaquone/proguanil, mefloquine, doxycycline*

Malaria chemoprophylaxis for sub-Saharan Africa:

First-line drugs: *atovaquone/proguanil*

Alternative drugs: *doxycycline*, *mefloquine*

Malaria chemoprophylaxis for Central Asia and Indian Subcontinent

First-line drugs: *chloroquine/proguanil, atovaquone/ /proguanil*

Alternative drugs: *mefloquine, doxycycline*

Malaria chemoprophylaxis for Indochinese Peninsula

First-line drugs: *atovaquone/proguanil*

Alternative drugs: *doxycycline*

Malaria chemoprophylaxis for Southeast Asia (Indonesia, Malaysia, Philippines)

First-line drugs: *atovaquone/proguanil*

Alternative drugs: *doxycycline*

Malaria chemoprophylaxis for Oceania (Papua New Guinea, Vanuatu, Solomon Islands)

First-line drugs: *atovaquone/proguanil*

Alternative drugs: *doxycycline, mefloquine*

Malaria chemoprophylaxis for Central America, and Caribbean

First-line drugs: *chloroquine, atovaquone/proguanil*

Alternative drugs: *mefloquine*

Malaria chemoprophylaxis for South America

First-line drugs: *atovaquone/proguanil, mefloquine*

Alternative drugs: *doxycycline*

ANTIMALARIALS AND THEIR USE

Chloroquine (common trade names: Aralen, Arechin, Aviocior, Nivaquine, and Resochin)

The dosage of chloroquine should be calculated in terms of the base. The normal adult dosage is 300 mg base per week. Chloroquine should be given 1–2 weeks before entering the malarious area, during the stay, and for 4 weeks after leaving the risk zone. The drug should be taken weekly on the same day of the week. In infants and children, the weekly dosage is 5 mg base/kg of body weight but regardless of weight should not exceed the adult dose. Chloroquine should not be taken by persons with a history of retinopathy, psoriasis, porphyria, epilepsy, or psychosis. Chloroquine prophylaxis may cause pruritus, especially among people of African descent. Itching of the palms, soles, and scalp is common in dark-skinned users. Concomitant use with proguanil can cause mouth ulcers. Chloroquine can be taken by pregnant women and children, including infants. Due to widespread chloroquine-resistant *P. falciparum* (CRPF), chloroquine alone as malaria prophylaxis is limited to Central America, Haiti, the Dominican Republic, and North Africa — including Egypt, Turkey, and the Near East. Chloroquine in combination with proguanil is recommended for travellers visiting a few countries in Central Asia, and the Indian Subcontinent [6, 8, 15].

Proguanil (common trade name: Paludrine)

Proguanil is considered a very safe antimalarial drug. The tablets contain 100 mg of proguanil hydrochloride. Prophylaxis with proguanil (in combination with chloroquine) should begin 1 day before entering the malarious area and must be continued during the stay and for 4 weeks after leaving the risk area. The drug may be taken during pregnancy. Use of proguanil alone is not recommended. The adult dosage is 200 mg daily when combined with chloroquine, or 100 mg if in combination with atovaquone. The side effects such as mouth ulcers and inflammation of the mouth occur rarely. The recommended prophylactic regimen for children is 3 mg/kg daily in combination with chloroquine [6, 8].

Mefloquine (common trade names: Lariam, Mephaquin)

Mefloquine is a potent, long-acting blood schizonticide and is effective against all species of *Plasmodium*. The tablets contain 250 mg of mefloquine base. The standard dose for adults and children weighing more than 45 kg is one tablet weekly. Mefloquine prophylaxis should begin 1 week before entering the malarious area. It should be continued throughout the later weeks, on the same day of the week, during the stay in the malarious area, and for 4 weeks after leaving the area. The prophylactic dose for children must be based on their weight. The recommended prophylactic regimen for children weighing more than 5 kg is 5 mg/kg weekly as a single dose. The main side effects include: gastrointestinal disturbances, headache, sleep disturbances, strange dreams, depression, and visual disturbances. Other more severe but rare neuropsychiatric disorders include: mood changes, confusion, hallucination, agitation, aggression, paranoia, psychoses, and seizures. Older travellers and children have fewer adverse reactions than younger adults. Women have more adverse reactions than men [6]. Mefloquine can be started 4 weeks before departure, so that adverse reactions can be detected before travel and possible alternatives considered. The drug is cleared slowly from the body. It has a half-life ranging from 8 to 33 days [12]. This is a disadvantage when side effects occur. Mefloquine can cause symptoms mimicking decompression sickness; consequently, it is contraindicated in scuba divers. Mefloquine should not be taken by people with a history of epilepsy or psychiatric disorders. This drug is contraindicated for use by travellers with a known hypersensitivity to it or to related compounds (e.g. quinine and quinidine), and in cardiac conduction disorders. The drug is contraindicated during the first trimester of pregnancy due to the potential risk of embriotoxic or teratogenic effects. Women of childbearing age should avoid conception during mefloquine prophylaxis and for 3 months thereafter. Mefloquine is considered safe for prophylaxis during the second and third trimester of pregnancy. Inadvertent use of mefloquine during the first trimester is not an indication for therapeutic abortion [6, 8, 16].

Doxycycline (common trade names: Doxycyclinum, Dotur, Supracyclin, Unidox Solutab, and Vibramycin)

Doxycycline should be taken daily, starting 1 day before entering the malarious area and continuing until 28 days after leaving such an area. The normal adult dosage is 100 mg per day. Doxycycline is contraindicated in pregnant or lactating women and children under 8 years of age. The main side effects include: esophagitis, gastrointestinal disturbances, oral candidiasis, vulvovaginitis, and pruritus, especially in the anogenital region. Doxycycline may cause photosensitivity of the skin (an exaggerated sunburn reaction to strong sunlight). Risk is reduced by avoiding prolonged, direct exposure to the sun, using highly protective and broad-spectrum sunscreen (these contain both a UVA and UVB blocker), and taking the drug in the evening [6, 8, 11].

Atovaquone/proguanil (common trade name: Malarone)

The combination shows synergistic activity. The drug acts against both the blood and liver phases of the parasite. Malarone prophylaxis should be started one day before entering a malaria zone. It should be continued daily in the malarious area and for 7 days after departure from it. The standard dose for adults and children weighing more than 40 kg is one tablet for adults (containing 250 mg of atovaquone and 100 mg of proguanil) daily. Malarone should be taken with food or milky drinks at the same time each day. Paediatric tablets contain 62.5 mg of atovaquone and 25 mg of proguanil. Dosages for children are as follows: 5–8 kg — 1/2 paediatric tablet daily; 8–10 kg — 3/4 paediatric tablet daily; 10–20 kg — 1 paediatric tablet daily; 20–30 kg — 2 paediatric tablets daily; and 30–40 kg — 3 paediatric tablets daily [14]. Atovaquone/proguanil (Malarone) is recommended by the Centre for Disease Control (CDC) for the prevention of *P. falciparum* malaria in chloroquine-resistant and multidrug-resistant areas. However, the drug will not kill the hypnozoites of *P.vivax* and *P.ovale* so travellers at high risk of these infections should receive terminal prophylaxis with primaquine.

In Europe, atovaquone/proguanil (Malarone) is only licensed for malaria prophylaxis for 28 days of travel. France holds a national license that allows prophylaxis to be used for up to 3 months. In the United Kingdom, atovaquone/proguanil can be used for period of up to one year. The USA, Canada, and Australia allow unrestricted prophylaxis use [11, 13, 16–18]. Malarone has a low incidence of side effects, compared to other antimalarials. The most common adverse reactions are loss of appetite, abdominal pain, nausea, diarrhoea, dizziness, and headache. Malarone is not recommended for pregnant women or breast-feeding women because insufficient data are available for this drug. Malarone is contraindicated in persons with a known hypersensitivity to atovaquone, proguanil, or any component of the formulation [11, 14–16].

CONCLUSIONS

Antimalarial drugs should be taken with unfailing regularity. Increasing drug resistance of *Plasmodium species*, especially *P. falciparum* and *P.vivax* to basic antimalarial remedies gives rise to concern. Drugs which previously worked well are now becoming ineffective. Numerous *P. falciparum* strains have developed resistance to chloroquine, sulfadoxine-pyrimethamine, and mefloquine. Resistance to mefloquine is rapidly increasing in the Indochinese Peninsula [11, 14].

The superficial knowledge of malaria (especially on chemoprophylaxis) of family doctors, general practitioners, and physicians of other specialities leads to numerous mistakes with prophylaxis. Data concerning drug resistance are currently being brought up to date. Unfortunately, many doctors who rarely deal with malaria prophylaxis in everyday practice often miss information on regions where *Plasmodium falciparum* and *Plasmodium vivax* resistant strains occur. Hence, constant education and training of physicians (especially general practitioners) on malaria is necessary. Unfortunately, there is no antimalarial drug which is perfectly effective and perfectly safe. However, adequate chemoprophylaxis protects against severe, complicated, and fatal infestation.

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