

Malaria in developing countries

Gema Ruíz López del Prado¹, Cristina Hernán García¹, Lourdes Moreno Cea¹, Virginia Fernández Espinilla¹, M^a Fe Muñoz Moreno², Antonio Delgado Márquez¹, M^a José Polo Polo¹, Irene Andrés García¹

¹ Servicio de Medicina Preventiva y Salud Pública, Hospital Clínico Universitario, Valladolid, Spain

² Unidad de Apoyo a la Investigación, Hospital Clínico Universitario, Valladolid, Spain

Abstract

Malaria still poses a real threat to travellers, particularly in areas with high transmission rates such as sub-Saharan Africa, Papua New Guinea, and the South Pacific islands. Malaria causes an estimated 660,000 deaths each year from 219 million cases of illness. It is a preventable and curable disease. Malaria symptoms appear after a period of seven days or longer, and without treatment, the disease can lead to death. Mosquito bite prevention is the main way to reduce malaria transmission. Chemoprophylaxis recommendations depend on travelers' age, destination, type of travelling, or length of stay. Pregnant women, children, and immunosuppressed travelers are the most susceptible. There are currently no licensed vaccines against malaria. Results about a research vaccine candidate known as RTS,S/AS01 are expected in 2015.

Key words: malaria; travelers; transmission; *Plasmodium falciparum*; preventive measures

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Malaria epidemiology

Malaria is a life-threatening disease caused by *Plasmodium* parasites that are transmitted to people through the bites of infected *Anopheles* mosquitoes. There are five different types of parasites that infect humans: *P. falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi*. Of these, *P. falciparum* and *P. vivax* are the most prevalent, and *P. falciparum* is the most dangerous, with the highest rates of complications and mortality. Each year, 219 million cases of malaria are estimated to occur around the world. In 2010, malaria caused an estimated 660,000 deaths (with an uncertainty range of 490,000 to 836,000), mostly among African children. An estimated 5.1 billion dollars is required to control malaria each year. In 2012, the total international and domestic funding for malaria was estimated to be less than US\$2.5 billion [1].

Non-immune travelers from malaria-free areas are very vulnerable to the disease when they get infected. Malaria mortality rates have fallen by more than 25% globally since 2000 due to prevention and control measures. Malaria is preventable and curable. Partial immunity is developed over years of exposure, and while it never provides complete protection, it does reduce the risk that malaria infection will cause severe

disease. For this reason, most malaria deaths in Africa occur in young children [2].

Malaria is an acute febrile illness. In a non-immune individual, symptoms appear seven days or more (usually between 10 and 15 days) after the infective mosquito bite. The first symptoms – fever, headache, chills and vomiting – may be mild and difficult to recognize as malaria. If not treated within 24 hours, *P. falciparum* malaria can progress to severe illness, often leading to death. Children with severe malaria frequently develop one or more of the following symptoms: severe anaemia, respiratory distress in relation to metabolic acidosis, or cerebral malaria [3].

At present, malaria surveillance systems detect only around 10% of the estimated global number of cases. Malaria still poses a real threat to travelers, particularly in areas with high transmission rates such as sub-Saharan Africa, Papua New Guinea, and the South Pacific islands. In recent years, only four countries have been certified by the World Health Organization (WHO) Director-General as having eliminated malaria: United Arab Emirates (2007), Morocco (2010), Turkmenistan (2010), and Armenia (2011).

Risk of transmission in travelers

Each year, some 25-30 million international travelers from non-tropical regions visit malaria-endemic countries. Up to 10,000 cases of malaria are imported into industrialized countries, with an average case fatality rate of around 1%. An increasing proportion of imported cases has been seen in migrants and foreign-born residents visiting friends and relatives (VFR) in endemic countries [4].

Risk assessment requires basic knowledge of true risk among travelers with specific potential exposure related to their travel destinations. Prior to their travel to malaria-endemic countries or regions, individuals should consult their national disease control centers for information about the preventive measures that should be taken. In Spain, the national travel and health website for pre-travel consultation is <http://www.msssi.gob.es/profesionales/saludPublica/sanidadExterior/salud/centrosvacu.htm>.

Specific population risk groups include young children, pregnant women, people with HIV/AIDS, international travelers from non-endemic areas (because they lack immunity), and immigrants from endemic areas and their children living in non-endemic areas and returning to their home countries (because they have waning or absent immunity).

Travel recommendations

Malaria prevention

Vector control is the main way to reduce malaria transmission at the community level. For individuals, personal protection against mosquito bites represents the first line of defense for malaria prevention. Insecticide-treated nets (ITNs), long-lasting insecticidal nets (LLINs) or conventional nets treated with pyrethroids, and indoor residual spraying with insecticides are effective in a wide range of circumstances.

Malaria is a potentially lethal illness for which preventive measures are not optimally used by all travelers. It can be prevented through

chemoprophylaxis, which suppresses the blood stage of malaria infections, thereby preventing malaria disease. It has been reported that almost half of the VFRs travelling to West Africa had not started chemoprophylaxis [5]. Depending on the malaria risk in the area to be visited, international travelers may also need to take preventive medication prior to, during, and upon return from their travel (Table 1). Chemoprophylaxis recommendation depends on several variables largely related to travelers' behavior and characteristics such as age, reason for travelling, length of stay, type of travelling, host risks, or preexisting illness. Indications, contraindications, dosage, and comments about malaria chemoprophylaxis are available on the following website:

<http://www.msssi.gob.es/profesionales/saludPublica/sanidadExterior/salud/viajesInter/cap7.htm>.

Malaria diagnosis

Early diagnosis and treatment of malaria reduces disease and prevents deaths. The WHO recommends that all cases of suspected malaria be confirmed using parasite-based diagnostic testing – either light microscopy or rapid diagnostic test (RDTs) – before treatment is administered.

If a person has fever one week or more after entering a malaria risk area, he/she should immediately consult a doctor or go to a qualified laboratory for proper diagnosis and effective treatment.

Malaria treatment

The best available treatment, particularly for *P. falciparum* malaria, is artemisinin-based combination therapy (ACT). Without a second drug given as part of a combination, these resistant parasites survive and can be passed on to a mosquito and then to another person. In recent years, parasite resistance to artemisinins has been detected in four countries of the Greater Mekong Subregion: Cambodia, Myanmar,

Table 1: Malaria risk and type of prevention

	Malaria risk	Type of prevention
Type I	Low-transmission settings	Only mosquito bite prevention
Type II	<i>P. vivax</i> or <i>P. falciparum</i> with no evidence to resistance to chloroquine	Mosquito bite prevention and chemoprophylaxis with chloroquine
Type III(a)	<i>P. vivax</i> or <i>P. falciparum</i> and chloroquine resistance	Mosquito bite prevention and chemoprophylaxis with chloroquine and proguanil
Type IV	High risk-transmission settings by <i>P. falciparum</i> and antimalarial drug resistance or moderate/low-transmission with high antimalarial drug resistance	Mosquito bite prevention and mefloquine or doxycycline or atovaquone/proguanil

(a): Type III risks are Nepal, Sri-Lanka, Tayikistán, and parts of Colombia or India

Thailand, and Viet Nam. If resistance to artemisinins develops and spreads to other large geographical areas, the public health consequences could be dire, as no alternative antimalarial medicines will be available for at least five years [6].

Uncomplicated *P. falciparum* malaria should be treated with an ACT. The five ACTs currently recommended for use by WHO are artemether plus lumefantrine, artesunate plus amodiaquine, artesunate plus mefloquine, artesunate plus sulfadoxine-pyrimethamine, and dihydroartemisinin plus piperazine. The choice of the ACT should be based on the therapeutic efficacy of the combination in the country or area of intended use. Both chloroquine and ACTs should be combined with a 14-day course of primaquine for the radical cure of *P. vivax* malaria. Severe malaria should be treated with injectable artesunate and followed by a complete course of an effective ACT as soon as the patient can take oral medications. In areas where there is a threat of artemisinin resistance, a primaquine dose should be given to all patients with confirmed *P. falciparum* malaria on the first day of ACT treatment, except to pregnant women and infants under one year of age. Details about antimalarial drugs for treatment are available online http://www.who.int/malaria/publications/world_malaria_report_2012/wmr2012_no_profiles.pdf.

Recommendations for risk groups

Some groups of travelers, especially those with weakened immune systems, are at particular risk of developing serious illness if they become infected with malaria. In pregnant women, malaria increases the risk of maternal death, miscarriage, stillbirth, and low birth weight, as well as the associated risk of neonatal death. Pregnant women should avoid traveling to areas where malaria transmission occurs, and parents are advised not to take infants or young children to areas where there is risk of *P. falciparum* malaria. When travel cannot be avoided, it is very important to take effective preventive measures against malaria.

In addition, the WHO recommends intermittent preventive treatment (IPT) with sulfadoxine-pyrimethamine for pregnant women living in high-transmission areas at each scheduled antenatal visit after the first trimester. Similarly, for infants living in high-transmission areas of Africa, three doses of intermittent preventive treatment with sulfadoxine-pyrimethamine are recommended to be delivered alongside routine vaccinations. Travelers with

complicated medical histories may warrant evaluation by an experienced travel medicine specialist [7].

The expected malaria vaccine

There are currently no licensed vaccines against malaria or any other human parasite. One research vaccine against *P. falciparum*, known as RTS,S/AS01, is the most advanced. This vaccine is currently being evaluated in a large clinical trial in seven countries in Africa. Vaccine efficacy was consistent with the target put forward by the WHO-sponsored Malaria Vaccine Technology Roadmap for a first-generation malaria vaccine. The final results are expected in late 2014, and a WHO recommendation as to whether or not this vaccine should be added to existing malaria control tools is expected in 2015; this recommendation depends on the final results from a phase three trial and on the outcomes of regulatory processes [8].

The updated Malaria Vaccine Roadmap represents the result of a review process facilitated by the WHO. Originally launched at the 2006 WHO Global Vaccine Research Forum and supported by the Funders Group, the Roadmap forms a strategic framework that underpins the activities of the global malaria vaccine research and development [9,10]. The world should aim to have vaccines which reduce malaria cases by 75%, and is capable of eliminating malaria by 2030 [11].

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Corresponding author

Gema Ruíz López del Prado
Servicio de Medicina Preventiva y Salud Pública
Hospital Clínico Universitario de Valladolid
Avda. de Ramón y Cajal 3, CP: 47005 Valladolid. Spain
Phone: 0034 983 42 00 00 (Ext: 86 129)
Email: cordoba_sweet@hotmail.com

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