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Overview of Malaria

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ABSTRACT

Malaria is an acute febrile illness with an incubation period of 7 days or longer. Thus, a febrile illness developing less than 1 week after the first possible exposure is not malaria. The most severe form is caused by P. falciparum; variable clinical features include fever, chills, headache, muscular aching and weakness, vomiting, cough, diarrhoea and abdominal pain. Other symptoms related to organ failure may supervene, such as acute renal failure, pulmonary oedema, generalized convulsions, circulatory collapse, followed by coma and death. The initial symptoms, which may be mild, may not be easy to recognize as being due to malaria

Keywords: Overview, Malaria

INTRODUCTION

Malaria is caused by the protozoan parasite Plasmodium. Human malaria is caused by four different species of Plasmodium: P. falciparum, P. malariae, P. ovale and P. Vivax [1]. Humans occasionally become infected with Plasmodium species that normally infect animals, such as *P. knowlesi*. As yet, there are no reports of human-mosquito human transmission of such "zoonotic" forms of malaria [2]. Malaria is an acute febrile illness with an incubation period of 7 days or longer. Thus, a febrile illness developing less than 1 week after the first possible exposure is not malaria [3].

The most severe form is caused by P. falciparum; variable clinical features include fever, chills, headache, muscular aching and weakness, vomiting, cough, diarrhoea and abdominal pain. Other symptoms related to organ failure may supervene, such as acute renal failure, pulmonary oedema, generalized convulsions, circulatory collapse, followed by coma and death [4]. The initial symptoms, which may be mild, may not be easy to recognize as being due to malaria [5].

It is important that the possibility of falciparum malaria is considered in all cases of unexplained fever starting at any time between 7 days after the first possible exposure to malaria and 3 months (or, rarely, later) after the last possible exposure [6]. Any individual who experiences a fever in this interval should immediately seek diagnosis and effective treatment, and inform medical personnel of the possible exposure to malaria infection. Falciparum malaria may be fatal if treatment is delayed beyond 24 h after the onset of clinical symptoms [8].

Young children, pregnant women, people who are immunosuppressed and elderly travellers are particularly at risk of severe disease. Malaria, particularly P. falciparum, in non-immune pregnant travellers increases the risk of maternal death, miscarriage, stillbirth and neonatal death [9].

The forms of human malaria caused by other Plasmodium species cause significant morbidity but are rarely life-threatening. Cases of severe P. vivax malaria have recently been reported among populations living in (sub)tropical countries or areas at risk. P. vivax and P. ovale can remain dormant in the liver. Relapses caused by these persistent liver forms ("hypnozoites") may appear months, and rarely several years, after exposure. Relapses are not prevented by current chemoprophylactic regimens, with the exception of primaquine. Latent blood infection with P. malariae may be present for many years, but it is very rarely life-threatening [10].

In recent years, sporadic cases of travellers' malaria due to P. knowlesi have been reported. Humans can be infected with this "monkey malaria" parasite while staying in rainforests and/or their fringe areas in south-east

Asia, within the range of the natural monkey hosts and mosquito vector of this infection [8]. These areas include parts of Cambodia, China, Indonesia, Laos, Malaysia, Myanmar, the Philippines, Singapore, Thailand and Viet Nam. The parasite has a life-cycle of 24 h and can give rise to daily fever spikes occurring 9–12 days after infection. Symptoms may be atypical. Severe P. knowlesi malaria with organ failure may occur, and sporadic fatal outcomes have been described. P. knowlesi has no persistent liver forms and relapses do not occur [1]. Travellers to forested areas of south-east Asia where human P. knowlesi infections have been reported should protect themselves against mosquito bites between dusk and dawn to prevent infection and take the usual chemoprophylaxis where indicated [2].

Transmission

The malaria parasite is transmitted by female Anopheles mosquitoes, which bite mainly between dusk and dawn [10]. The main mode of transmission of the disease is by bites from infected Anopheles mosquitoes that have previously had a blood meal from an individual with parasitemia. Less common routes of transmission are via infected blood transfusion, transplantation, infected needles, and from a mother to her fetus during pregnancy.

Nature of the disease and Geographical distribution

The current distribution of malaria in the world is shown on the map in this chapter; affected countries and territories are listed both at the end of this chapter and in the Country list. The risk for travellers of contracting malaria is highly variable from country to country and even between areas in a country, and this must be considered in any discussion of appropriate preventive measures.

In many countries or area at risk, the main urban areas – but not necessarily the outskirts of towns – are free of malaria transmission. However, malaria can occur in the main urban areas of Africa and, to a lesser extent, India. There is usually less risk at altitudes above 1500 m, although in favourable climatic conditions the disease can occur at altitudes up to almost 3000 m. The risk of infection may also vary according to the season, being highest at the end of the rainy season or soon after.

There is no risk of malaria in many tourist destinations in south-east Asia, the Caribbean and Latin America.

Risk for travellers

During the transmission season in countries or areas at risk, all non-immune travellers exposed to mosquito bites, especially between dusk and dawn, are at risk of malaria. This includes previously semi-immune travellers who have lost or partially lost their immunity during stays of 6 months or more in countries or areas of no risk. Children who have migrated to countries and areas of no risk are particularly at risk when they travel to malarious areas to visit friends and relatives.

Most cases of falciparum malaria in travellers occur because of poor adherence to, or complete failure to use medicines, or use of inappropriate prophylactic malaria drug regimens, combined with failure to take adequate precautions against mosquito bites. Studies on travellers' behaviour have shown that adherence to treatment can be improved if travellers are informed of the risk of infection and believe in the benefit of prevention strategies. Late-onset vivax and ovale malaria may occur despite effective prophylaxis, as they cannot be prevented with currently recommended prophylactic regimens which act only against blood-stage parasites.

Malaria risk is not evenly distributed where the disease is prevalent. Travellers to countries where the degree of malaria transmission varies in different areas should seek advice on the risk in the particular zones that they will be visiting. If specific information is not available before travelling, it is recommended that precautions appropriate for the highest reported risk for the area or country should be taken; these precautions can be adjusted when more information becomes available on arrival. This applies particularly to individuals backpacking to remote places and visiting areas where diagnostic facilities

and medical care are not readily available. Travellers staying overnight in rural areas may be at highest risk.

Precautions

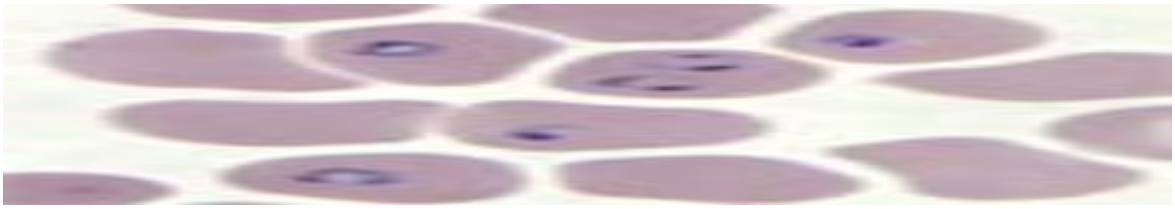
Travellers and their advisers should note the four principles – the ABCD – of malaria protection:

Be Aware of the risk, the incubation period, the possibility of delayed onset, and the main symptoms. Avoid being Bitten by mosquitoes, especially between dusk and dawn. Take antimalarial drugs (Chemoprophylaxis) when appropriate, to prevent infection from developing into clinical disease.

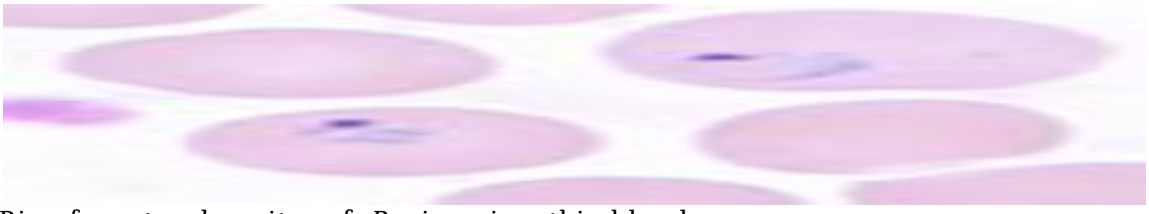
Immediately seek Diagnosis and treatment if a fever develops 1 week or more after entering an area where there is a malaria risk and up to 3 months (or, rarely, later) after departure from a risk area.

Malaria Parasites

Malaria parasites are micro-organisms that belong to the genus *Plasmodium*. There are more than 100 species of *Plasmodium*, which can infect many animal species such as reptiles, birds, and various mammals. Four species of *Plasmodium* have long been recognized to infect humans in nature. In addition there is one species that naturally infects macaques which has recently been recognized to be a cause of zoonotic malaria in humans. (There are some additional species which can, exceptionally or under experimental conditions, infect humans)



Ring-form trophozoites of *P. falciparum* in a thin blood smear.



Ring-form trophozoites of *P. vivax* in a thin blood smear.

Trophozoites of *P. ovale* in a thin blood smear.

Band-form trophozoites of *P. malariae* in a thin blood smear.

Schizont and ring-form trophozoite of *P. knowlesi* in a thin blood smear.

The species infecting humans are the following:

- ***P. falciparum***, which is found worldwide in tropical and subtropical areas, and especially in Africa where this species predominates. *P. falciparum* can cause severe malaria because it multiples rapidly in the blood, and can thus cause severe blood loss (anemia). In addition, the infected parasites can clog small blood vessels. When this occurs in the brain, cerebral malaria results, a complication that can be fatal.
- ***P. vivax***, which is found mostly in Asia, Latin America, and in some parts of Africa. Because of the population densities especially in Asia it is probably the most prevalent human malaria parasite. *P. vivax* (as well as *P. ovale*) has dormant liver stages ("hypnozoites") that can activate and invade the blood ("relapse") several months or years after the infecting mosquito bite.
- ***P. ovale*** is found mostly in Africa (especially West Africa) and the islands of the western Pacific. It is biologically and morphologically very similar to *P. vivax*. However, differently from *P. vivax*, it can infect individuals who are negative for the Duffy blood group, which is the case for many residents of sub-Saharan Africa. This explains the greater prevalence of *P. ovale* (rather than *P. vivax*) in most of Africa.
- ***P. malariae***, found worldwide, is the only human malaria parasite species that has a quartan cycle (three-day cycle). (The three other species have a tertian, two-day cycle.) If untreated, *P. malariae* causes a long-lasting, chronic infection that in some cases can last a lifetime. In some chronically infected patients *P. malariae* can cause serious complications such as the nephrotic syndrome.
- ***P. knowlesi*** is found throughout Southeast Asia as a natural pathogen of long-tailed and pig-tailed macaques. It has recently been shown to be a significant cause of zoonotic malaria in that region, particularly in Malaysia. *P. knowlesi* has a 24-hour replication cycle and so can rapidly progress from an uncomplicated to a severe infection; fatal cases have been reported.

Diagnosis

To diagnose malaria, your doctor will likely review your medical history, conduct a physical exam and order blood tests. Blood tests are the only way to confirm a malaria diagnosis. Certain blood tests can help your doctor by showing:

The presence of the parasite in the blood, to confirm that you have malaria

Which type of malaria parasite is causing your symptoms.

If your infection is caused by a parasite resistant to certain drugs

Other blood tests help determine whether the disease is causing any serious complications.

Some blood tests can take several days to complete, while others can produce results in less than 15 minutes.

Treatment

Malaria is treated with prescription drugs to kill the parasite. The types of drugs and the length of treatment will vary, depending on:

- Which type of malaria parasite you have
- The severity of your symptoms

- Your age
- Whether you're pregnant

Medication

The most common antimalarial drugs include:

- **Artemisinin-based combination therapies (ACTs).** ACTs are, in many cases, the first line treatment for malaria. There are several different types of ACTs. Examples include artemether-lumefantrine (Coartem) and artesunate-amodiaquine. Each ACT is a combination of two or more drugs that work against the malaria parasite in different ways.
- **Chloroquine phosphate.** Chloroquine is the preferred treatment for any parasite that is sensitive to the drug. But in many parts of the world, the parasites that cause malaria are resistant to chloroquine, and the drug is no longer an effective treatment.

Other common antimalarial drugs include:

- Combination of atovaquone and proguanil (Malarone)
- Quinine sulfate (Qualaquin) with doxycycline (Vibramycin, Monodox, others)
- Mefloquine
- Primaquine phosphate

Plasmodium life cycle

The life cycle (Figure 1) is almost the same for all the five species that infect humans and follows three stages:

(I) infection of a human with sporozoites

(II) asexual reproduction

(III) sexual reproduction

The two first stages take place exclusively into the human body, while the third one starts in the human body and is completed into the mosquito organism

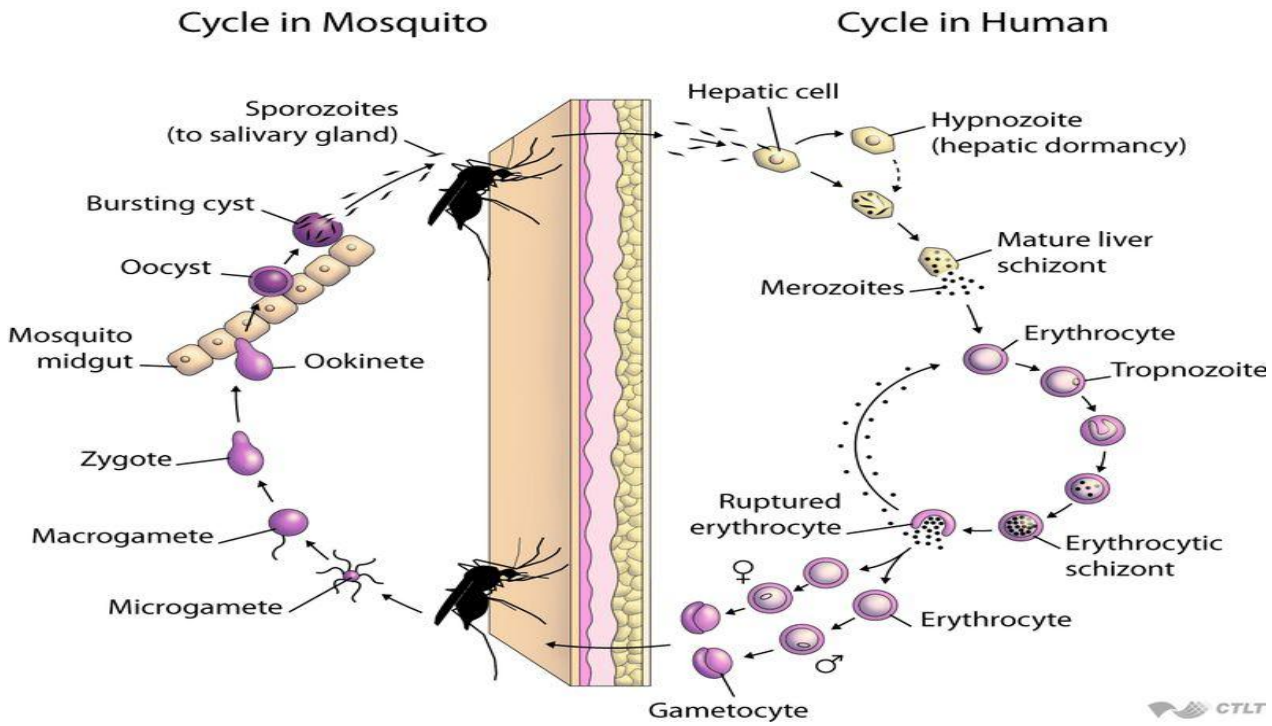


Figure 1. Plasmodium life cycle
(Source: Open Course Ware)

The human infection begins when an infected female anopheles mosquito bites a person and injects infected with sporozoites saliva into the blood

circulation. That is the first life stage of plasmodium (stage of infection).

The next stage in malaria life cycle is the one of asexual reproduction that is divided into different phases: the pre-erythrocytic (or better, exoerythrocytic) and the erythrocytic phase. Within only 30- 60 minutes after the parasites inoculation, sporozoites find their way through blood circulation to their first target, the liver. The sporozoites enter the liver cells and start dividing leading to schizonts creation in 6- 7 days. Each schizont gives birth to thousands of merozoites (exoerythrocytic schizogony) that are then released into the blood stream marking the end of the exoerythrocytic phase of the asexual reproductive stage.

It is worth mentioning that, concerning P. vivax and P. ovale, sporozoites may not follow the reproduction step and stay dormant (hypnozoites) in the liver; they may be activated after a long time leading to relapses entering the blood stream (as merozoites) after weeks, months or even years. The exoerythrocytic phase is not pathogenic and does not produce symptoms or signs of the disease. Its duration is not the same for all parasite species.

Merozoites released into the blood stream, are directed towards their second target, the red blood cells (RBCs). As they invade into the cells, they mark the beginning of the erythrocytic phase. The first stage after invasion is a ring stage that evolves into a trophozoite. The trophozoites are not able to digest the haem so they convert it in haemozoine and digest the globin that is used as a source of aminoacids for their reproduction. The next cellular stage is the erythrocytic schizont (initially immature and then mature schizont). Each mature schizont gives birth to new generation merozoites (erythrocytic schizogony) that, after RBCs rupture, are released in the blood stream in order to invade other RBCs. This is when parasitaemia occurs and cinical manifestations appear. The liver phase occurs only once while the erythrocytic phase undergoes multiple cycles; the merozoites release after each cycle creates the febrile waves.

A second scenario into the RBCs is the parasite differentiation into male and female gametocytes that is a non pathogenic form of parasite. When a female anopheles mosquito bites an infected person, it takes up these gametocytes with the blood meal (mosquitoes can be infected only if they have a meal during the period that gametocytes circulate in the human's blood). The gametocytes, then, mature and become microgametes (male) and macrogametes (female) during a process known as gametogenesis. The time needed for the gametocytes to mature differs for each plasmodium species: 3-4 days for P. vivax and P. ovale, 6- 8 days for P. malariae and 8- 10 days for P. falciparum.

In the mosquito gut, the microgamete nucleus divides three times producing eight nuclei; each nucleus fertilizes a macrogamete forming a zygote. The zygote, after the fusion of nuclei and the fertilization, becomes the so- called ookinete. The ookinete, then, penetrates the midgut wall of the mosquito, where it encysts into a formation called oocyst. Inside the oocyst, the ookinete nucleus divides to produce thousands of sporozoites (sporogony). That is the end of the third stage (stage of sexual reproduction/ sporogony). Sporogony lasts 8- 15 days.

The oocyst ruptures and the sporozoites are released inside the mosquito cavity and find their way to its salivary glands but only few hundreds of sporozoites manage to enter. Thus, when the above mentioned infected mosquito takes a blood meal, it injects its infected saliva into the next victim marking the beginning of a new cycle.

The duration of each above desribed phase is different for each of the plasmodia as shown in Table 1 that follows.

	Plasmodium species			
	P. vivax	P. ovale	P. malariae	P. falciparum
Pro-erythrocytic phase (days)	6-8	9	14-16	5-7
Erythrocytic cycle (hours)	48	50	72	48
Incubation period (days)	12-17 or even 6-12 months	16-18 or more	18-40 or more	9-14
Sporogony (days)	8-10	12-14	14-16	9-10

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