



# Malaria

*Could You Recognize the World's Number Two Killer?*



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**M**alaria has had a greater impact on world history than any other infectious disease. It has been responsible for the outcome of wars, population movements, and the growth and development of various nations throughout the world. Before the American Civil War, malaria was found as far north as southern Canada; however, by the early 1950s it was no longer an endemic disease within the United States.

With the exception of tuberculosis, malaria kills more people than any other communicable disease in the world. Approximately 300–500 million individuals throughout the world are infected with *Plasmodium* spp., and 1.5 to 2.7 million people a year, most of whom are children, are being killed by the disease. More people are dying from malaria today than 30 years ago. Malaria is endemic in over 90 countries with a population of 2.4 billion people, which is 40% of the world's population (4).

Malaria prevention is difficult, and no drug is universally effective. Vaccine development

studies are ongoing, but malarial vaccines are not yet in general use. There has also been a definite increase in the number of cases of *P. falciparum* malaria reported, which may be related to increased resistance to chloroquine.

Although over 1,000 cases of malaria are reported to the Centers for Disease Control and Prevention each year, the actual number of cases may be much larger. Since 1993, the number of malaria cases among United States and foreign civilians living in the U.S. and U.S. military personnel per year has ranged from about 1,000 to >1,500 (1).

*300 to 500 million people are infected with Plasmodium spp, which is more than it was 30 years ago.*

Clinical symptoms include anemia, splenomegaly, and the classic paroxysm, with its cold stage, fever, and sweats. The typical paroxysm begins with the cold stage and rigors lasting 1 to 2 h. During the next few hours, the patient spikes a high fever

## Malaria species:

- Plasmodium vivax*
- Plasmodium falciparum*
- Plasmodium ovale*
- Plasmodium malariae*
- Plasmodium knowlesi*

and feels very hot, and the skin is warm and dry. The last several hours are characterized by marked sweating and a subsequent drop in body temperature to normal or subnormal.



**Although the febrile paroxysms strongly suggest infection, many patients who are seen in the early stages of the infection, do not exhibit the typical fever pattern. These patients are immunologically naïve, since they have never been exposed to malaria before. However, they tend to become symptomatic with very light parasitemias (0.002% parasitemia). They may have a low grade fever or several small, random peaks each day. Since the symptoms associated with malaria can be very nonspecific, the diagnosis should be considered in any symptomatic [fever of unknown origin (FUO)] patient with a history of travel to an area where malaria is endemic.**

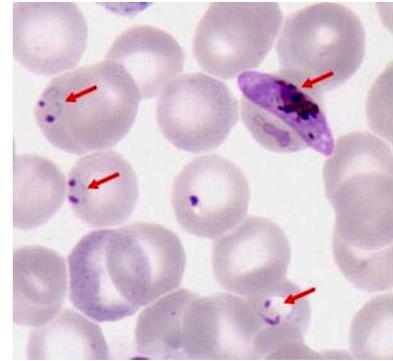
Patients with malaria can present to clinics or emergency rooms for diagnostic blood work when they

are least expected. Laboratory personnel and clinicians should be aware of the "STAT" nature of such requests and the importance of obtaining some specific patient history information.

On microscopic examination of the blood films, the typical textbook presentation of various *Plasmodium* spp. morphologies may not be seen by the technologist. This is particularly true if the blood is collected in EDTA anticoagulant and there has been a time lag between blood collection and preparation/examination of thick and thin blood films. Partial use of antimalarial agents may be responsible for reducing the numbers of organisms in the peripheral blood, thus leading to a blood smear that contains few organisms, which then reflects a low parasitemia when in fact serious disease is present. Patients with a relapse case or an early primary case may also have few organisms in the blood smear. Both thick and thin blood films should be examined at length and under oil immersion (100X oil immersion objective; 300 fields as a minimum). The

***Malaria is one of the few parasitic infections that requires a STAT diagnosis, since the disease can be rapidly fatal.***

most important thing to remember is that even though a low parasitemia may be present on the blood smears, the patient may still be faced with a serious, life-threatening disease (2, 4-6).



***Plasmodium falciparum* infecting red blood cells. *P. falciparum* was responsible for 93% of the malaria deaths of US travelers (source: [www.cdc.gov](http://www.cdc.gov))**

On microscopic examination, identification to the species level is required for good patient management, since the species identification may determine which drug or combination of drugs will be recommended. Some patients with early *P. falciparum* infections may not yet have the crescent-shaped gametocytes in the blood. Low parasitemias with the delicate ring forms may be missed; consequently, oil immersion examination at  $\times 1,000$  is mandatory.

Parasite density usually correlates with disease severity, but peripheral parasitemia does not always reflect the number of

sequestered organisms. Malaria pigment may serve as a peripheral indicator for parasite biomass, since the pigment can be seen within monocytes and polymorphonuclear leukocytes (PMNs) during light microscopy examination. The presence of pigment has been strongly

associated with severe disease rather than with uncomplicated cases of malaria. Pigmented neutrophils (PMNs, monocytes) have been associated with cerebral malaria and with death in children with severe malaria (7).

**Malaria is one of the few parasitic infections considered to be immediately life-threatening, and a patient with the diagnosis of *P. falciparum* malaria should be considered a medical emergency because the disease can be rapidly fatal. Any laboratory providing the expertise to identify malarial parasites should do so on a STAT 24-h basis, 7 days/week. The request for thick and thin blood films is always considered a STAT request.**



*Plasmodium sporozoites are deposited under the skin of the vertebrate host through the bite of an infected female Anopheles mosquito. After injection into the skin, the sporozoites move through the dermis until they contact blood vessels and lymphatic system.*

**It is important for both physicians and laboratorians in areas where malaria is not endemic to be aware of the problems related to malarial diagnosis and the fact that symptoms are often nonspecific and may mimic other medical conditions. Physicians must recognize that travelers are susceptible to malarial infection when they visit an area where malaria is endemic, and they should receive prophylactic medication. Approximately 80% of the *P. falciparum* cases acquired by American civilians are contracted in sub-Saharan Africa. Currently there are 40 cities in Africa with over 1 million inhabitants, and by 2025 over 800 million people will live in urban areas. Malaria has always been a rural disease in Africa; however, it now appears that the urban poor and travelers to urban centers are at a much higher risk of contracting malaria than previously recognized.**

With the documented increase in the number of people traveling from the tropics to malaria-free areas, the number of imported malaria cases is also on the rise. There have been reports of imported infected mosquitoes transmitting the infection among people who live or work near international airports. It is also possible that mosquitoes can reach areas far removed from the airports (8). This situation has been termed "airport malaria," malaria that is acquired through the bite of an infected anopheline mosquito by persons with apparently no risk factors for the

disease (travel, blood transfusions, etc.).



Unfortunately, unless a comprehensive history is obtained, the diagnosis of malaria can be missed. Tests to exclude malaria should be considered in patients who work or live near an international airport and who present with an acute febrile illness.

#### **Important Questions:**

*Where have you been?*

*When were you there?*

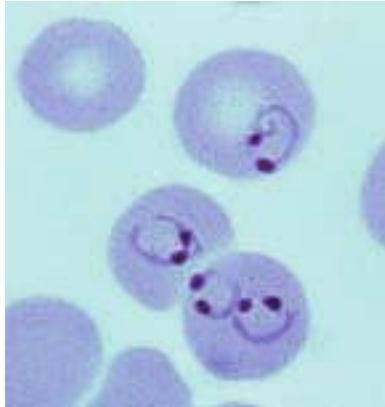
*Have you taken any prophylaxis?*

*Where do you live?*

*Where do you work?*

The possibility of disseminating the mosquito vectors via aircraft is well known; however, current disinfection procedures have not yet eliminated the risk of vector transportation. Not only can insects survive nonpressurized air travel, but also they can be transported further by car or other means after arriving at the airport. Contraction of airport malaria is certainly an unusual event, particularly considering

that the number of air travelers is well over 1 billion annually. However, in addition to asking a patient, "Where have you been, and when were you there, and have you taken any prophylaxis – if so, when?" one should also ask, "Where do you live and where do you work?"



**Plasmodium falciparum rings in RBC's.**

We usually associate malaria with patients having a history of travel within an area where malaria is endemic. However, other situations that may result in infection involve the receipt of blood transfusions, use of hypodermic needles contaminated by prior use (for example, drug addicts), possibly congenital infection, and transmission within the United States by indigenous mosquitoes that acquired the parasites from imported infections (3).

**It is important to remember key issues; such as, patients with FUO, the STAT nature of requests for blood film examination, and the fact that these patients may present for medical care on the second and third shifts.**

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**Table. Parasitemia determined from conventional light microscopy: Clinical correlation<sup>a</sup>**

Parasitemia	Parasites/ $\mu$ l	Clinical Correlation
0.0001-0.0004%	5-20	Number of organisms that are required for a positive thick film (sensitivity) <b>NOTE (TBF):</b> Examination of 100 TBF fields (0.25 $\mu$ l) may miss infections up to 20% (sensitivity of 80-90%); at least 300 TBF fields should be examined before reporting a negative result. <b>NOTE (THBF):</b> Examination of 100 THBF fields (0.005 $\mu$ l); at least 300 THBF should be examined before reporting a negative result; BOTH TBF and THBF should be examined for every specimen submitted for a suspect malaria case. <b>ONE SET (TBF + THBF) OF NEGATIVE BLOOD FILMS DOES NOT RULE OUT A MALARIA INFECTION.</b>
0.002%	100	Patients may be symptomatic below this level
0.01%	500	Patients often come into the ER with parasitemias at or below this level
0.1%	5,000	Rapid BinaxNOW rapid test (Inverness) has sensitivity at this level and above.

Parasitemia	Parasites/ $\mu$ l	Clinical Correlation
0.2%	10,000	Level above which immune patients will exhibit symptoms
2%	100,000	Maximum parasitemia of <i>P. vivax</i> and <i>P. ovale</i> (infect young RBCs only)
2-5%	100,000-250,000	Hyperparasitemia, severe malaria <sup>b</sup> , increased mortality
10%	500,000	Exchange transfusion may be considered, high mortality

<sup>a</sup> Adapted from various references (Bruce-Chwatt '84, Wilkerson '94, and Hanscheid '99). It is apparent that rapid tests are not sensitive enough to replace the microscopic examination of thick and thin blood films for the diagnosis of malaria.

<sup>b</sup> WHO criteria for severe malaria are parasitemia >10,000/ $\mu$ l and severe anemia (hemoglobin <5g/l). Prognosis is poor if >20% of parasites are pigment containing trophozoites and schizonts and/or if >5% of neutrophils contain visible pigment.

ER = emergency room; TBF = thick blood film; THBF = thin blood film

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