Malaria

Naomi F Walker

Behzad Nadjm

Christopher JM Whitty

Abstract

Malaria remains a leading cause of mortality worldwide and a cause of morbidity in returning travellers in the UK. The management of malaria, recent advances in diagnosis and current areas of controversy are summarized, primarily for clinicians in countries where malaria is non-endemic, who do not routinely encounter it. The most important message is that malaria is very common and its presentation is non-specific, so a malaria test is essential. Early diagnosis and prompt effective treatment prevent unnecessary deaths. Health promotion for travellers to endemic areas is essential to reduce the burden of imported malaria.

Keywords *Anopheles*; antimalarials; falciparum; knowlesi; malaria; malariae; MRCP; ovale; *Plasmodium*; vivax

Key points

- Imported malaria is common in travellers returned from endemic areas, and is associated with considerable morbidity and some deaths every year
- Risk factors for severe disease include falciparum malaria, older age and pregnancy
- Delays in diagnosis lead to worse outcomes — always perform a blood film in a person returned from a malaria-endemic area who presents with a fever or other suggestive symptoms
- For severe malaria, intravenous artesunate is the drug of choice, but if this is not available locally use parenteral quinine
- Seek advice from experienced clinicians for severe and complex cases. The on-call registrars at the Hospital for Tropical Diseases 020 3456 7890 or Liverpool Infectious Diseases Unit (0151 706 2000) are available
- Malaria is preventable. Encourage patients and relatives to seek advice on preventive measures and prophylaxis before travel

Introduction and epidemiology

In the last two decades, investment in malaria control strategies has contributed to a significant reduction in malaria cases and deaths worldwide.[1] Reported deaths from malaria have fallen by a third in the last 5 years. Despite this, malaria remains a leading cause of morbidity and mortality, with an estimated 212 million cases and 429,000 deaths in 2015.

The burden of malaria mortality lies in Africa and is associated with poverty. Most malaria deaths are from falciparum malaria and occur in children <5 years old. In parts of Africa, the average person catches malaria four or more times a year, so the disease is much more common than influenza is in the UK. Globally, access to malaria diagnostics and effective treatments is improving. However, emerging antimalarial drug resistance is a cause for concern.

In non-endemic areas, malaria is an important cause of illness in returned travellers and migrants. Data from EuroTravNet[2] demonstrated that malaria was the leading single cause of significant illness in returned travellers in Europe 2008–2012. In Europe and the USA, tourist travel to and immigration from malaria-endemic areas is increasing, and malaria is likely to remain a significant cause of morbidity.

Although uncomplicated malaria is rarely fatal, European case fatality rates for falciparum malaria are around 1% — higher in patients with severe disease. Risk factors for the development of severe malaria and mortality include falciparum malaria, older age, travel for tourism (versus travel to visit friends and relatives),[3] pregnancy, HIV infection, increased time to presentation and suboptimal antimalarial prophylaxis. Most patients returning to Europe with malaria do not report taking malaria prophylaxis. Delayed diagnosis, incorrect diagnosis and incorrect treatment contribute to mortality.

This article, aimed at clinicians in countries where malaria is non-endemic, addresses clinical aspects of malaria pathophysiology, presentation, diagnosis and management, highlighting recent developments and areas of controversy. Every death from malaria should be preventable if it is diagnosed early and treated promptly with effective drugs. The most important messages from this article are that malaria is common, and that imported malaria can be largely prevented by effective prophylaxis.

Pathophysiology

Malaria is caused by protozoal parasites of the genus *Plasmodium*. Five species of *Plasmodium* cause disease in humans (Table 1). In humans, malaria is transmitted by female *Anopheles* mosquitoes that typically bite after dark. Most infections in Sub-Saharan Africa are caused *by Plasmodium falciparum*, but in South and Central America and South Asia *Plasmodium vivax* is most prevalent.

Naomi F Walker ***PhD MRCP DTM&H*** *is NIHR Academic Clinical Lecturer at the London School of Hygiene and Tropical Medicine and University College London Hospitals NHS Trust, UK. Competing interests: none declared.*

Behzad Nadjm ***MRCP MD DTM&H*** *is Senior Clinical Researcher at the Oxford Clinical Research Unit, Hanoi, Vietnam, and Honorary Consultant Physician at University College London Hospitals NHS Trust, UK. Competing interests: none declared.*

Christopher JM Whitty ***FRCP*** *is Consultant Physician at the Hospital for Tropical Diseases and University College London Hospitals NHS Trust, and Professor of International Health at the London School of Hygiene and Tropical Medicine, UK. Competing interests: none declared.*

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Falciparum malaria causes almost all the deaths and is most commonly responsible for severe disease. However, severe disease can also occur in *P. vivax* and *Plasmodium knowlesi* malaria.

The pathophysiology of disease is incompletely understood. The virulence of *P. falciparum* is related to the blood stage of the parasite and is multifactorial including:

- infection of erythrocytes of all ages, compared with other forms of malaria that are selective for younger cells, enabling higher levels of parasitaemia
- sequestration (sticking down) and rosetting (clumping) of infected and uninfected red blood cells within the microcirculation
- immune activation, leading to cytokine-driven pathology that can result in vasogenic cerebral oedema and a prothrombotic state.

P. knowlesi can cause severe disease, probably owing to rapid replication and consequent high levels of parasitaemia.

P. vivax and *Plasmodium ovale* malaria lay down hypnozoites in the liver. The parasite lies dormant in these cells for months or even years, emerging to cause clinically apparent malaria, often several times. Consequently, infection with these species requires separate treatment directed at eliminating the hypnozoite stage.

Clinical manifestations of disease

Symptoms develop from around 6 days after an infected bite. Most falciparum infections present within 1 month, but they can appear later (usually within 12 months) especially in individuals taking prophylaxis. *P. vivax*, *Plasmodium malariae* and *P. ovale* infections commonly have a longer incubation period, and *P. vivax* and *P. ovale* can relapse or present after an extended period because of activation of hepatic hypnozoites. This is different from recrudescence, in which parasites reappear in the blood following failed treatment that has not completely cleared them. *P. vivax*, *P. ovale* and *P. malariae* are much less likely to cause severe disease than *P. falciparum*, but falciparum and malariae malaria do not relapse. A second episode of falciparum malaria suggests treatment failure or reinfection.

A history of fever is usual, although not invariable; because the temperature fluctuates patients may be afebrile at presentation. Other symptoms are non-specific and can be misleading, commonly resulting in misdiagnoses of, for example, influenza, hepatitis, gastroenteritis or meningitis. If a patient is unwell and has recently returned from a malarial area, the only way to exclude malaria is to do an urgent malaria test.

If malaria is diagnosed (or suspected), it is crucial to assess for features of severe malaria, which differ between children and adults (Table 2). The presence of any of these features constitutes potentially severe malaria. In children with severe falciparum malaria, respiratory distress, anaemia, convulsions and hypoglycaemia are more common than in adults. In cerebral malaria, malarial retinopathy (retinal whitening, white-centred haemorrhages, papilloedema, cotton wool spots) may be seen. Pulmonary oedema, acute respiratory distress syndrome (ARDS) and acute kidney injury rarely occur in children, but occur in over half of all cases of life-threatening malaria in non-immune adults.

Species of *Plasmodium* causing human disease

Species	Distribution	Severe disease	Recurrent disease (relapses)	Features
P. falciparum	Widespread	+++	−	Most fatalities Severe disease
P. vivax	Widespread	+	+	Hypnozoites present: long
P. ovale	West Africa	(+)	+	incubation and relapse possible
P. malariae	Africa	(+)	−	Long incubation possible Cause of nephrotic syndrome
P. knowlesi	South-East Asia	++	−	Zoonosis Microscopically similar to *P. malariae* Severe disease/fatalities

(+), Very rare; +, rare; ++, uncommon; +++, common.

Table 1

Diagnosis

Diagnostic delay, either because the patient presents late, or because a doctor has not suspected the diagnosis, is a key factor in mortality from malaria in non-endemic countries. Suspecting the diagnosis is paramount, and malaria can occur even with perfect prophylaxis. If malaria tests are negative and the patient appears well, they should return for a repeat test the next day as the first test can occasionally be negative. More than three tests are unnecessary to exclude malaria in a single febrile episode unless symptoms change. It is important to consider that travellers returning from malaria-endemic regions who test negative for malaria may have other potentially serious infections, including HIV-related infections (see Assessment of returning travellers with fever on pages xxx of this issue).

Diagnostic tests

Recent decades have seen an expansion in malaria diagnostics, particularly the use of rapid diagnostic tests (RDTs). Despite this, *microscopy* of thick and thin blood films remains the mainstay of diagnosis (Figure 1). All diagnostic tests for malaria are intended to detect blood-stage disease; there are no reliable tests for dormant malaria in an asymptomatic patient.

Rapid diagnostic tests: RDTs for malaria are now widely available. Table 3 summarizes the strengths and limitations of RDTs along with the alternative diagnostic methods. RDTs are particularly useful as an additional test in laboratories with relatively few cases in a year, but do not give information on parasite density (which has prognostic value). They are a useful adjunct to malaria films for diagnosis in a non-endemic setting, but should not be used as a substitute for blood films.

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