Malaria

This is a notifiable disease in the UK. See the **Notifiable Diseases** article for more detail.

What is malaria?

Malaria has been recognised as a human disease for thousands of years and remains one of the most common diseases affecting humans worldwide. Malaria impact falls almost entirely on developing countries, with the heaviest toll in Africa. Over half the world's population is thought to be exposed to the risk of contracting malaria. As well as its direct health cost, it carries a significant economic burden in countries where there is endemic disease:

- Malaria slows economic growth in Africa, fuelling the vicious cycle which perpetuates poverty .
- In Africa, it accounts for 40% of public health expenditure and 7% of the household income [1] .
- Malaria deters investment, tourism and labour-intensive cash-crops.

During the 1960s and 1970s, there was optimism that malaria could be eradicated. The 1980s and 1990s saw serious setbacks, such as the development of resistance to commonly used drugs and insecticides as well as the breakdown of control programmes and local primary health services, often in the context of regional political and economic collapse. Child deaths due to malaria doubled in sub-Saharan Africa in the 1990s and malaria re-emerged in Central Asia, Eastern Europe and previously clear areas of Southeast Asia.

The Roll Back Malaria Partnership (RBMP) is a global partnership of countries committed to the eradication of malaria. To this end, the RBMP recently published *Action and Investment to defeat Malaria 2016-2030 (AIM) - for a malaria-free world*[2] and this compliments the *WHO Global Technical Strategy for Malaria 2016-2030*[3] .

Consider malaria in every febrile patient returning from a malaria-endemic area within the last year, especially in the previous three months, regardless of whether they have taken chemoprophylaxis, as prompt recognition and appropriate treatment will improve prognosis and prevent deaths.

Aetiology[4]

Malaria is a parasitic disease caused by infection by species of the genus *Plasmodium*.

	Clinical features	UK cases 2014
Plasmodium falciparum	Responsible for severe disease and malaria-related deaths. Incubation 7-14 days (up to one year if semi-immune); most travellers present within eight weeks. Classical tertian and subtertian periodicity (paroxysms at 48- and 36-hour intervals) are rare; daily (quotidian) or irregular are more common.	1169
Plasmodium vivax	Causes benign tertian malaria - fever every third day. Incubation period of 12-17 days. Relapse due to dormant parasites in the liver.	225
Plasmodium ovale	Relapsing course as with *P. vivax*. Incubation period of 15-18 days.	130
Plasmodium malariae	Causes benign quartan malaria - fever every fourth day - but this is frequently not observed, particularly in early infection. Long incubation period (18-40 days). Parasites can remain dormant in the blood. 5-10% present over a year after infection. With chronic infection, can cause nephrotic syndrome.	41

A fifth species causing malaria in humans, *Plasmodium knowlesi*, has recently emerged. It is distributed across Southeast Asia and is often misdiagnosed by microscopy as *P. malariae.* However, it is potentially more serious, causing severe malaria with a rate of 6-9% and with a case fatality rate of 3%.

Humans acquire malaria after being bitten by an infected mosquito. The sporozoites in the saliva of the mosquito then travel via the bloodstream to the liver where they mature or, in certain species, may lie dormant (when they are known as hypnozoites). The mature organisms then rupture to release further organisms (merozoites) into the blood, where they invade red blood cells and undergo asexual reproduction. Feeding mosquitoes ingest these in a blood meal and in the mosquito gut they undergo sexual reproduction to produce thousands of infective sporozoites, and the cycle continues.

Malaria epidemiology

Malaria occurs almost exclusively in the tropics and subtropics. About 3.2 billion people - nearly half of the world's population - are at risk of malaria. In 2015, there were approximately 214 million cases and roughly 438,000 malaria deaths. Whilst this figure is high, mortality rate has decreased by 60% since 2000 due to increased global prevention and control measures. Sub-Saharan Africa still carries the brunt of the global malaria burden. In 2015, 89% of malaria cases and 91% of malaria deaths occurred in the region [5] .

Malaria is the tropical disease most commonly imported into the UK, with 1,300-1,800 cases reported each year, and 2-11 deaths [6] .

In 2019, 1,719 cases of imported malaria were reported in the UK (1,626 in England, 58 in Scotland, 25 in Wales and 10 in Northern Ireland), 2.1% higher than reported in 2018 . 85.8% of those cases were caused by

P. falciparum, which is consistent with previous years.

Fifteen deaths from malaria were reported in the UK in 2019, which is an increase compared to the previous 10 years with an annual average of 6 deaths . Fourteen deaths in 2019 were from falciparum malaria and were acquired in Africa.

Malaria risk factors

The groups most at risk of developing severe disease are [7] .

- The poor (60% of deaths from malaria worldwide occur in the poorest 20% of the population, due to lack of access to effective treatment).

- Young children and infants.
- Pregnant women (especially primigravidae).
- Elderly people.
- Non-immune people (eg, travellers, foreign workers).

Outside endemic areas, returning travellers from these regions can develop malaria.

The risk of contracting malaria in travellers is proportional to the number of potentially infectious mosquito bites they receive. Therefore, risk factors for malaria in travellers include[4] :

- Travel to areas of high humidity and ambient temperature between 20-30°C (there is no malarial transmission <16°C or at altitudes >2000 m above sea level).
- Travel at times of high seasonal rainfall.
- Visits to rural locations (the risk of contracting malaria in African villages is eight times that in its urban areas).
- Staying in cheap backpacker accommodation.
- Being outdoors between dusk and dawn.
- Longer durations of travel.

There are occasional cases of malaria (<2 per annum) reported in individuals who have never been in a malarious area or come into contact with infected blood (eg, blood transfusion or intravenous (IV) drug abuse). Such cases usually occur around airports and seaports - such 'airport malaria' is presumably caused by infected mosquitoes hitching a ride from endemic regions, in aircraft, ships, containers, luggage or buses. Always consider malaria a possibility in individuals working at or living close to such airports and ports[8] [9] .

Malaria presentation[10]

In view of the life cycle of the malaria parasite, symptoms may occur from six days of naturally acquired infection to many months later. Most patients with *P. falciparum* infection present in the first month or within the first six months of infection. *P. vivax* or *P. ovale* infections commonly present later than six months after exposure and sometimes after years.

There are no specific symptoms of malaria - so it is critical to consider the possibility of the diagnosis. Most missed malarial infections are wrongly diagnosed as nonspecific viral infections, influenza, gastroenteritis or hepatitis. Children, in particular, are more likely to present with nonspecific symptoms (fever, lethargy, malaise, somnolence) and to have gastrointestinal symptoms.

Where malaria is a possibility:

- Take a careful exposure history (countries and areas of travel including stopovers and date of return, etc).
- Determine what prophylaxis has been taken - drug(s), dose and adherence, date of cessation.
- Pursue diagnostic tests urgently.

Malaria symptoms

- Fever, often recurring
- Chills
- Rigors
- Headache
- Cough
- Myalgia
- Gastrointestinal upset

Malaria signs

- Fever

- Splenomegaly
- Hepatomegaly
- Jaundice
- +/- abdominal tenderness

Signs of severe disease (usually *P. falciparum*)

- Impaired consciousness.
- Shortness of breath.
- Bleeding.
- Fits.
- Hypovolaemia.
- Hypoglycaemia.
- Acute kidney injury.
- Nephrotic syndrome.
- Acute respiratory distress syndrome (during treatment).

Malaria differential diagnosis[10] [11]

As the initial presenting malaria symptoms are nonspecific, there are many alternative diagnoses that could be considered; however, in any returning traveller, these should only be investigated once the possibility of malaria has been excluded, due to the serious consequences of a delay in diagnosis. Other travel-related infections that may present with similar symptoms include:

- Typhoid
- Hepatitis
- Dengue
- Influenza
- HIV
- Meningitis/encephalitis

- Viral haemorrhagic fevers

Investigations

Prompt and accurate diagnosis of malaria is vital for effective case management:

- To ensure appropriate drug treatment.
- To prevent presumptive treatment of malaria (widespread in endemic areas).
- To help reduce the mortality rate associated with the disease.

Diagnostic investigations include[12] :

- Thick and thin blood smears stained with Giemsa stain remain the 'gold standard'. Advantages include low cost and high sensitivity and specificity when used by well-trained staff. Where there is suspicion of malaria, a venous blood specimen in an EDTA tube should be sent to the laboratory in under an hour. If there is potential for delay, refer the patient to hospital for testing. Where the blood film is negative, at least two further films should be obtained over the subsequent 48 hours, before excluding the diagnosis. **Be aware that an individual can have malaria despite a negative film**. This is particularly the case in pregnancy where parasite biomass can be sequestered in the placenta - seek expert help early if concerned.
- Rapid diagnostic tests (RDTs) which detect parasite antigens are available and, being dipstick-based investigations, are easier to use for staff without microscopy training. They have less waiting time and indirect costs but have been relatively more expensive. RDTs for P falciparum and *P. vivax* are almost as reliable as blood films for diagnosis, but RDTs for other malarial species are less accurate[6] .
- Nucleic acid-based tests including polymerase chain reaction (PCR) have been developed but require more sophisticated training and equipment than RDTs and are more suited to epidemiological investigations[13] .

All cases of malaria should be notified to public health authorities and a blood specimen sent to the Malaria Reference Laboratory for confirmation. Other investigations frequently performed include:

- FBC - typically reveals thrombocytopenia and anaemia. Leukocytosis is rarely seen but is an indicator of a poor prognosis when present.
- G6PD activity - prior to giving primaquine.
- LFTs - often abnormal.
- U&Es - may show lowered Na^+ and increased creatinine.
- Low blood glucose may be present in severe disease.

Ill patients may also require:

- Blood gases.
- Blood cultures.
- Clotting studies.
- Urine and stool culture.
- CXR.
- Lumbar puncture.

Malaria treatment and management

The management of malaria depends not only on the severity of the disease but also the strain of *Plasmodium* involved and the degree of resistance that it exhibits. All cases should be discussed with infectious disease specialists - the local infectious diseases unit will be able to give advice and initiate appropriate treatment in line with the current UK guidelines [6] . Admission is usual for:

- Severely unwell patients.
- Patients with *P. falciparum* malaria.
- Patients with mixed infections.
- Patients in whom the strain cannot be identified.

Falciparum malaria in pregnancy is more likely to be complicated: the placenta contains high levels of parasites, stillbirth or early delivery may occur and diagnosis can be difficult if parasites are concentrated in the placenta and scanty in the blood.

Non-falciparum malaria

This is usually managed on an outpatient basis, unless the patient has other comorbidities. G6PD activity should be measured in *P. vivax* or *P. ovale* infections, as the primaquine (which is necessary to eliminate the dormant hypnozoites and prevent recurrence) can cause haemolysis in those with G6PD deficiency.

Treatment

Current UK guidelines recommend[6] :

- Either an oral artemisinin combination therapy (ACT), or chloroquine can be used for the treatment of non-falciparum malaria.
- An oral ACT is preferred for a mixed infection, if there is uncertainty about the infecting species, or for *P. vivax* infection from areas where chloroquine resistance is common.

Falciparum malaria

Current guidelines suggest all patients with falciparum malaria should be admitted to hospital for the first 24 hours - even semi-immune patients may worsen quickly . High-quality supportive management is important in patients with severe or complicated malaria: HDU management should be available with facilities for transfer to ICU if further deterioration occurs despite appropriate treatment.

Treatment for uncomplicated falciparum malaria

Current UK guidelines suggest the following regimens for adults[14] :

- Adults should be treated with an artemisinin combination therapy (ACT).
- Artemetherelumefantrine is the drug of choice and dihydroartemisinin-piperaquine is an alternative. Quinine or atovaquone eproguanil can be used if an ACT is not available.
- Quinine is highly effective but poorly tolerated in prolonged treatment and should be used in combination with an additional drug, usually oral doxycycline[15] .

Treatment of severe or complicated falciparum malaria
Severe falciparum malaria, or infections complicated by a relatively high parasite count (more than 2% of red blood cells parasitized) should be treated with intravenous therapy until the patient is well enough to continue with oral medication.

Current UK guidelines suggest[6] :

- The treatment of choice for severe or complicated malaria in adults and children is intravenous artesunate. However, intravenous artesunate is unlicensed in the EU but is available in many centres.
- The alternative is intravenous quinine, which should be started immediately if artesunate is not available. Patients treated with intravenous quinine require careful monitoring for hypoglycemia.
- Patients with severe or complicated malaria should be managed in a high-dependency or intensive care environment.

Dormant parasites
Dormant parasites (hypnozoites) persist in the liver after treatment of *P. vivax* or *P. ovale* infections and the only currently effective drug for eradication of hypnozoites is primaquine. Primaquine is more effective at preventing relapse if taken at the same time as chloroquine.

Spread of drug resistance
Resistance to antimalarial drugs has spread rapidly over the past few decades - monitoring and surveillance have had to become more intensive to enable early detection of changing patterns of resistance so that national malaria treatment policies can be revised as necessary.

There are currently no effective alternatives to artemisinins for the treatment of resistant P. falciparum malaria. Artemisinin, derived from wormwood leaves, has been used in traditional Chinese medicine for centuries to treat malaria and other conditions but its use beyond China has only really happened in the last decade. Synthetic derivatives such as artemether and artesunate have greater bioavailability than artemisinin. Artemisinin-based combination therapies (ACTs) are life-saving in areas of high resistance. In order to preserve the efficacy of artemisinins, the World Health Organization (WHO) has called for a ban on the use of oral artemisinin monotherapies. Despite this, artemisinin-resistant cases have been reported. They are currently confined to Southeast Asia but should resistant parasites spread to Africa, this would represent a public health catastrophe. Genome-based research is currently being conducted to determine why artemisinins have been effective and what can be done to develop alternative therapies [16]

Malaria complications [10] [17]

Complications are almost always associated with *P. falciparum* infection and include:

- Impaired consciousness or seizures (cerebral malaria).
- Renal impairment.
- Acidosis.
- Hypoglycaemia.
- Pulmonary oedema or acute respiratory distress syndrome.
- Anaemia [18] .
- Splenic rupture.
- Disseminated intravascular coagulopathy.
- Shock secondary to complicating bacteraemia/sepsis (algid malaria).
- Haemoglobinuria ('black water fever').
- Multiple organ failure.
- Death.

Malaria prognosis

If no chemoprophylaxis has been taken, or if left untreated, or where treatment is delayed, malaria may be fatal. In the UK there were 15 deaths deaths in 2019, and in the uk cases overall, 87% had not taken prophylaxis . Of those cases, eight cases where time from onset of symptoms to initiation of treatment was known, median time was four days (IQR 2-6 days). Four patients did not receive any treatment for their malaria infection; 3 were found dead at home.

Globally, there were 438,000 deaths in the year 2015 but it has been calculated that since 2000, control and prevention measures have resulted in a 60% reduction in mortality rates. Cerebral malaria has a mortality rate of about 20%.

Malaria prevention

- The World Health Organization (WHO) has recommended the malaria vaccine RTS,S for widespread use among children living in malaria endemic areas[19] .
- Use of effective chemoprophylaxis and insecticide-treated nets (ITNs) prevents about 90% of malaria[4] . Travellers should be encouraged to use a prophylactic regime appropriate to their travel itinerary but **they should be aware that this is not a guarantee against infection**.
- Other behavioural modifications, such as avoiding outdoor activity after sunset, wearing long-sleeved shirts and trousers, using ITNs and insect repellant, must also be recognised as important.
- Encouraging migrant travellers visiting family and friends to take prophylactic medication should be a priority - any immunity to malaria accrued by growing up in a malarious country is rapidly lost on emigration and second-generation family members will have no immunity, rendering them (and particularly children) vulnerable.

Historical[20]

The story of the human struggle to control malaria is not recent:

- Malaria has its origins in the dramatic climate change in Africa 7,000-12,000 years ago (increase in temperature and humidity creating new water sources and the start of agriculture in the Middle East and North East Africa (forest-clearing and pools of water).
- The occurrence and spread of malaria can be traced by the evolution of the G6PD, thalassaemia and sickle cell mutations, which in the carrier state give humans resistance to malaria. The appearance of one variant suggests the spread of malaria by the army of Alexander the Great.
- Described first by the Chinese in the Nei Ching (the Canon of Medicine) in 2700 BC (or BCE - 'before common era', for non-Christians) and then, also described, the use of the qing hoa plant (annual or sweet wormwood) for fever in 340 AD (or CE - 'common era'). The active ingredient, artemisinin, was identified in 1971 and is in modern use as an antimalarial drug.
- Malaria is Italian for 'bad air', as it was noted that shuttering up the houses and not going out in the evening reduced the risk from the gases of the swamp.
- The bark of the Cinchona tree (containing quinine) in South America was found to be effective in treatment; legend describes taking its name from the countess of Chinchon, wife of a Peruvian viceroy who was cured of fever in 1658. It appeared in the British Pharmacopoeia in 1677 and later became known as 'Jesuit's powder' or 'Jesuit's bark' from those who first used it. The Dutch smuggled seeds from Bolivia and successfully grew this in their Indonesian colonies, obtaining a world monopoly on the supply, beating earlier attempts by themselves and the British using a different species which had poor yields.
- Quinine was successfully synthesised in 1944.
- Alphonse Laveran, a French military physician, discovered the protozoan parasite in 1880, whilst working in Algeria (he was later awarded the Nobel Prize for this in 1907).
- The Italians, Grassi and Filetti, named *P. vivax* and *P. malariae* in 1890 and an American, Welch, named *P. falciparum* in 1897. Stephens named the last of the four, *P. ovale*, in 1922.

- Ronald Ross, an officer in the Indian Medical Service, demonstrated the transmission of malaria by mosquito from bird to bird in 1897, earning the Nobel Prize in 1902.
- Chloroquine was discovered in 1934 by the German Hans Andersag, although it was not recognised as an effective and safe antimalarial until 1946.
- A German chemistry student synthesised DDT for his thesis in 1874, although its insecticidal properties were not recognised until 1939 by Müller, who won the Nobel Prize for Medicine in 1948.
- It should not be forgotten that malaria was endemic in the marshes of Southern and Eastern England from the 16th to 19th centuries (species *P. vivax* and *P. malariae*) and briefly reappeared after both the First and Second World Wars.

The number of Nobel Prizes awarded to work on malaria is testimony to its global importance and human impact.

Further reading

- Travax
- Malaria; Centers for Disease Control and Prevention, Yellow Book
- Amelo W, Makonnen E; Efforts Made to Eliminate Drug-Resistant Malaria and Its Challenges. Biomed Res Int. 2021 Aug 30;2021:5539544. doi: 10.1155/2021/5539544. eCollection 2021.
- Walker MD; The last British malaria outbreak. Br J Gen Pract. 2020 Mar 26;70(693):182-183. doi: 10.3399/bjgp20X709073. Print 2020 Apr.

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