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CME: Infectious Diseases

Malaria: Past, present and future<sup>☆</sup>Jo Salkeld<sup>1,\*</sup>, Andrew Duncan<sup>1</sup>, Angela M. Minassian

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## ABSTRACT

Malaria remains a major global health problem. Transmission occurs in 84 countries across five continents, with almost 250 million cases and over 600,000 deaths each year. Primary and secondary care clinicians in the UK need to be alert to the prospect of malaria presenting in returning travellers. They must be aware of the signs of severe malaria, the need for prompt diagnosis and treatment, and the importance of seeking specialist advice. With emerging resistance, climate change and the roll-out of the first malaria vaccines, the landscape of malaria is changing. Here we discuss the past, present and future of malaria.

## Past

Malaria, the mosquito-borne disease caused by the protozoa *Plasmodium*, has been present in the human population for thousands of years; fevers most likely caused by malaria were described in China in 2700 BC and in Greece in 800 BC.<sup>1</sup> The close relationship between humans and malaria has shaped the human genome, driving mutations responsible for conditions such as sickle cell disease, thalassaemia and glucose-6-phosphate dehydrogenase (G6PD) deficiency.<sup>1</sup> Although now considered a traveller's disease in the UK, malaria is believed to have historically been endemic, causing 'marsh fever' or 'ague' in certain low-lying areas of England.<sup>2</sup>

## Present

## Epidemiology

Concerted global health efforts to increase the distribution of vector control methods, diagnostics and treatments have averted 2.1 billion malaria cases and 11.7 million deaths since 2000.<sup>3</sup> However, progress has stalled, and even reversed, since 2015. According to the World Health Organization (WHO) World Malaria Report 2023, an estimated 249 million cases of malaria occurred in 2022, leading to 608,000 deaths. Most deaths (75%) occur in children under 5 years in sub-Saharan Africa.<sup>3</sup>

An average of 1,600 imported malaria cases are recorded in the UK each year.<sup>4</sup> After a dip caused by the COVID-19 pandemic, 2,093 cases

were reported by the UK Health Security Agency in 2023, the highest number in the past 25 years (Fig. 1).<sup>4</sup>

## Aetiology

Malaria is introduced by the bite of an infected female *Anopheles* mosquito. Multiple *Plasmodium* species cause malaria in humans, including *P. falciparum*, *P. vivax*, *P. ovale* (*wallikeri* and *curtisi*), *P. malariae* and *P. knowlesi*.<sup>5</sup>

*P. falciparum* accounts for 97% of global malaria cases, mainly in sub-Saharan Africa. It is the most likely species to cause severe illness due to its propensity to 'sequester' infected erythrocytes in end-organ microvasculature.<sup>5</sup> *P. vivax* is geographically the most widespread species; 3.3 billion people live in endemic areas, primarily in South America and south and south-east Asia.<sup>3,6</sup> *P. vivax* and *P. ovale* spp. cause relapsing disease due to the development of hypozooites, which reside in the liver and can reactivate to produce blood-stage infections (clinically indistinguishable from acute primary infection) weeks, months or even years after the initial inoculation. Relapses account for approximately 60–80% of all *P. vivax* clinical cases in endemic areas.<sup>5</sup>

## Clinical features

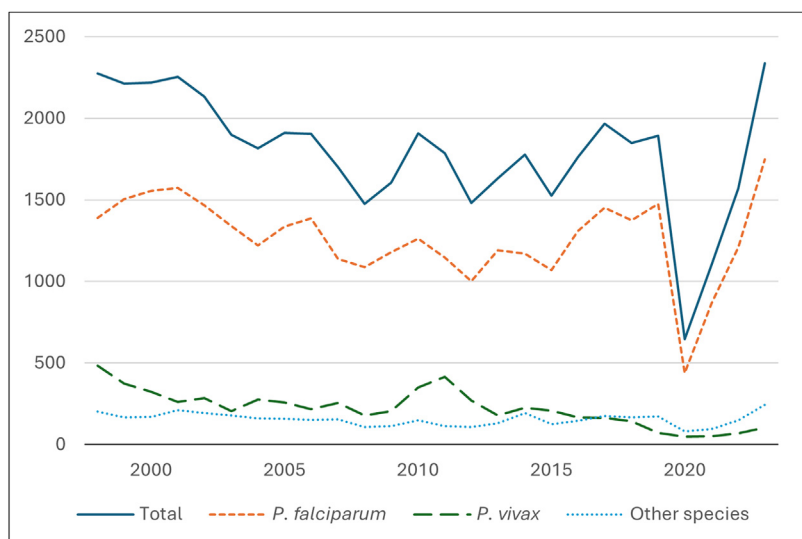
The symptoms and signs of malaria are variable and non-specific. It is impossible to diagnose or exclude malaria on clinical features alone. The most important first step is to consider the possibility of malaria (Table 1).<sup>7</sup>

<sup>☆</sup> This article has an accompanying continuing medical education (CME) activity. Completion of this CME activity enables RCP members to earn two external CPD credits. The CME questions are available at: <https://cme.rcp.ac.uk/>.

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**Fig. 1.** Annual number of UK imported malaria cases (1998–2023). Adapted from UK Health Security Agency data.<sup>4</sup>

**Table 1**  
Common pitfalls in the management of malaria.<sup>7</sup>

- Failure to take a detailed travel history
- Failure to consider the diagnosis of malaria and perform diagnostic tests
- Failure to recognise that malaria may present with non-specific symptoms and lack a classical fever pattern
- Assumption that adherence to malaria prophylaxis excludes possibility of malaria infection
- Failure to consider additional diagnoses, especially in patients with naturally acquired immunity who may have ‘asymptomatic’ parasitaemia
- Assumption that growing up in an endemic area confers protective immunity
- Assumption that a negative RDT rules out malaria infection
- Failure to repeat blood films if the initial blood film is negative but clinical suspicion of malaria is high
- Failure to seek specialist advice
- Assumption that only children get severely unwell
- Assumption that *P. falciparum* is the only species to cause severe malaria
- Failure to prescribe primaquine for *P. vivax* or *P. ovale* spp. malaria to prevent relapse

**Table 2**  
Signs of severe *P. falciparum* malaria in adults.<sup>7,12</sup>

- One or more of the following criteria without an identified alternative cause:
- Impaired consciousness (Glasgow coma score < 11) or seizures
  - Renal impairment (creatinine > 265  $\mu\text{mol/L}$  or urine output < 0.4 mL/kg/h)
  - Acidosis (pH < 7.3)
  - Hypoglycaemia (< 2.2 mmol/L)
  - Pulmonary oedema or acute respiratory distress syndrome
  - Anaemia (haemoglobin  $\leq$  80 g/L)
  - Spontaneous bleeding or disseminated intravascular coagulation
  - Shock (blood pressure < 90/60 mmHg)
  - Haemoglobinuria (without glucose-6-phosphate dehydrogenase deficiency)
  - Parasitaemia > 10%<sup>+</sup>

<sup>+</sup> In a UK setting, consider managing any patient with a parasitaemia of >2% as severe malaria.

Common symptoms include fever, chills, myalgia and headache. Gastrointestinal symptoms (diarrhoea is common in children), jaundice or respiratory symptoms may occur and can contribute to misdiagnosis. Most patients do not have a specific fever pattern.<sup>7</sup>

Individuals who experience repeated malaria infections (eg in high transmission areas) develop a degree of naturally acquired immunity. They may experience fewer symptoms or have asymptomatic parasitaemia. However, immunity is lost quickly and does not guarantee protection from future illness.<sup>8</sup>

Malaria is classified as either uncomplicated or severe. Features of severe disease are outlined in Table 2. A parasitaemia of >10% is an indicator of severe malaria. In the UK, a lower threshold (>2%) is adopted due to a largely non-immune population.

Malaria should be considered in any patient presenting with a febrile illness within 1 year of travel to an endemic area.<sup>7</sup> *P. falciparum* has a minimum incubation period of 6 days, and most cases occur within 3 months of exposure. Antimalarial prophylaxis may delay the onset of symptoms. Relapse infections due to *P. vivax* and *P. ovale* spp. may present later than 6 months.

### Diagnosis

Travellers returning from malaria-endemic areas with a history of fever must undergo urgent investigation. This usually requires referral to secondary care. Examination of thick and thin blood smears by microscopy remains the gold-standard investigation.<sup>9</sup> If the initial blood film is negative, and clinical suspicion is high, it should be repeated after 12–24 h and again after a further 24 h. Rapid diagnostic tests (RDTs), based upon detection of parasite antigens, may be performed, but do not offer an equivalent alternative to blood films due to lower sensitivity, histidine-rich protein 2 mutations preventing detection of *P. falciparum*, and an inability to fully speciate (eg if mixed infections) or quantify parasitaemia.<sup>9</sup> Molecular tests (including quantitative real-time PCR) are becoming increasingly available.<sup>9</sup> Malaria is a notifiable disease.<sup>10</sup>

### Treatment

#### *Falciparum* malaria

The first-line treatment for non-severe falciparum malaria is an oral artemisinin combination therapy (ACT) such as artemether-lumefantrine (Riamet).<sup>7</sup> If an ACT is not immediately available (or

**Table 3**  
Malaria treatment in adults.<sup>7,11,12</sup>

Uncomplicated <i>P. falciparum</i> malaria	
Artemether-lumefantrine (Riamet)	Recommended first-line ACT Four tablets at 0, 8, 24, 34, 48 and 60 h (>35 kg) Take with milk or fatty food
Dihydroartemisinin-piperazine	Second-line ACT Three tablets daily for 3 days (36–60 kg) or four tablets daily for 3 days (>60 kg)
Atovaquone-proguanil (Malarone)	Four tablets daily for 3 days Not to be used if patient took Malarone prophylaxis Take with milk or fatty food
Quinine PLUS doxycycline or clindamycin	Quinine 600 mg 8 hourly for 5–7 days PLUS doxycycline 200 mg daily or clindamycin 450 mg 8 hourly for 7 days
<b>Severe or complicated malaria</b>	
IV Artesunate	First-line treatment 2.4 mg/kg at 0, 12 and 24 h, then once daily If not available, do not delay treatment, give IV quinine as alternative Can cause QTc prolongation – check ECG
IV Quinine	Alternative if IV artesunate not available 20 mg/kg loading dose over 4 h, followed by 10 mg/kg three times a day
Complete full course of oral treatment when patient can tolerate oral therapy	
<b>Non-falciparum malaria</b>	
Artemether-lumefantrine (Riamet)	Recommended first-line ACT Four tablets at 0, 8, 24, 34, 48 and 60 h (>35 kg) Take with milk or fatty food
Chloroquine	620 mg initially, 310 mg at 6, 24 and 48 h (NB Avoid if infection acquired in areas with known chloroquine resistance)
Severe/complicated malaria – treat as per severe/complicated <i>P. falciparum</i> malaria	
<b>Prevention of relapse (<i>P. vivax</i> / <i>P. ovale</i> spp.)</b>	
Primaquine	30 mg daily for 14 days ( <i>P. vivax</i> ) or 15 mg daily for 14 days ( <i>P. ovale</i> spp.) Check for G6PD deficiency prior to treatment Reduced dosing may be used in mild-moderate G6PD deficiency – consult a specialist
<b>Pregnancy</b>	
Artemether-lumefantrine (Riamet)	First-line treatment in second/third trimester Seek specialist advice regarding use in first trimester
Quinine plus clindamycin	Safe in all trimesters
Severe malaria	IV artesunate IV quinine can be given as an alternative until IV artesunate available
Relapse prevention	Do not give primaquine during pregnancy Treat with chloroquine 310 mg weekly until pregnancy complete Do not use primaquine while breast feeding until infant G6PD status is known

contraindicated), an alternative antimalarial should be started instead (Table 3). If a patient has taken malaria prophylaxis, the same drug should not be used for treatment.<sup>11</sup> If a patient is vomiting or cannot tolerate oral therapy, parenteral therapy should be used as for severe malaria.<sup>11</sup>

#### Severe/complicated malaria

This is a medical emergency. Patients should be managed on a high dependency unit and specialist advice should be sought.<sup>7,11</sup> The first-line treatment is IV artesunate (Table 3). If this is not available, IV quinine should be started without delay.<sup>7</sup> Once patients can take oral medication, a full course of ACT or alternative should be completed.<sup>7</sup> Response to treatment should be assessed by serial blood films to ensure clearance of parasitaemia.

Supportive management should include:

- careful management of fluid balance to ensure perfusion but prevent pulmonary oedema
- close monitoring of blood glucose and correction of hypoglycaemia
- monitoring for signs of secondary bacterial infection or shock, taking blood cultures and treating with broad spectrum antibiotics if present
- renal replacement therapy if required for correction of acidosis or fluid/electrolyte imbalance
- control of seizures.

- exchange transfusion is no longer recommended. Blood transfusion may be indicated for symptomatic anaemia.<sup>7</sup>

#### Non-falciparum malaria

Patients with non-falciparum malaria can often be managed as outpatients. However, admission should be considered as severe, even fatal, cases can occur.<sup>11</sup> First-line treatment is artemether-lumefantrine. Chloroquine is an alternative if unavailable (Table 3).<sup>11,12</sup>

In *P. vivax* and *P. ovale* spp. malaria, additional treatment is needed to prevent relapse. Primaquine is the treatment of choice in the UK (Table 3).<sup>7</sup> G6PD screening should be performed before initiating treatment, as life-threatening haemolysis may occur in patients with G6PD deficiency.<sup>7</sup>

#### Pregnancy

Malaria in pregnancy is associated with a higher risk of severe disease in the mother and an increased risk of miscarriage or stillbirth.<sup>7</sup> Patients should be managed promptly by infectious diseases and obstetric specialists. Congenital malaria can occur, and neonatal testing may be indicated. Artemether-lumefantrine is the treatment of choice in the second and third trimester (Table 3).<sup>7</sup> Recent updates to the WHO guidelines also recommend the use of artemether-lumefantrine in the first trimester.<sup>12</sup> Quinine plus clindamycin may be used at any stage of pregnancy. IV artesunate is advised for severe malaria at all stages of pregnancy due to the high risks of undertreated malaria.<sup>7</sup> Primaquine

is contraindicated in pregnancy. Relapse prevention should be managed as outlined in Table 3.

#### Follow-up

A repeat full blood count and blood film are recommended approximately 14 days after treatment due to a risk of post-treatment haemolysis, particularly following severe malaria or artemisinin therapy.<sup>7</sup>

#### Future

The WHO Global Technology Strategy calls for a reduction in malaria cases and deaths of 90% by 2030 from 2015.<sup>3</sup> However, climate change, conflict, and drug and insecticide resistance are impeding progress towards this target.<sup>3</sup>

Malaria vaccines have the potential to close some of this gap. Two vaccines, RTS,S/AS01 and R21/Matrix-M, have been recommended by the WHO for the prevention of *P. falciparum* malaria in children living in endemic areas from 5 months of age.<sup>3</sup> They target the initial pre-erythrocytic stage of infection and have an efficacy of approximately 75% after three doses over one malaria season when given with seasonal malaria chemoprophylaxis.<sup>13–15</sup> A fourth dose is required at 12 months. RTS,S/AS01 reduced all-cause mortality in early childhood by 13% in a pilot malaria vaccine programme in Ghana, Kenya and Malawi, illustrating the remarkable potential of malaria vaccines when combined with current control methods.<sup>3</sup> However, efficacy is partial and wanes over time, highlighting a need for more efficacious and durable vaccines. One strategy to achieve this is to target multiple stages of the parasite's life cycle, including the blood-stage of infection.<sup>16,17</sup> Vaccines are not currently recommended for travellers.

Clinicians treating returning travellers in the UK need to be alert to emerging resistance patterns. Artemisinin resistance is increasing, particularly in south-east Asia,<sup>3</sup> and is of great concern. Treatment options continue to evolve, such as the licensing of tafenoquine in the USA and Australia in 2018 as a single dose anti-hypnozoite drug for *P. vivax*.<sup>18</sup>

Climate change is also impacting mosquito-borne diseases. The geographical distribution of vector populations is increasing, and floods are causing disease outbreaks.<sup>3</sup> The UK currently has six mosquito species capable of transmitting malaria. Modelling suggests favourable conditions for *P. vivax* transmission could occur in south-east England by 2030.<sup>19</sup> Although sustained indigenous transmission of malaria in the UK is unlikely, imported cases may occur more frequently, even from countries in Europe.<sup>20</sup> Primary and secondary care clinicians in the UK must therefore remain vigilant to the prospect of malaria presenting in returning travellers.

#### Declaration of competing interest

Angela M Minassian has an immediate family member who is an inventor on patent applications relating to RH5 malaria vaccines. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

#### CRediT authorship contribution statement

**Jo Salkeld:** Writing – review & editing, Writing – original draft, Conceptualization, Visualization. **Andrew Duncan:** Writing – review & editing, Writing – original draft, Conceptualization, Visualization. **Angela M. Minassian:** Writing – review & editing, Conceptualization, Supervision.

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