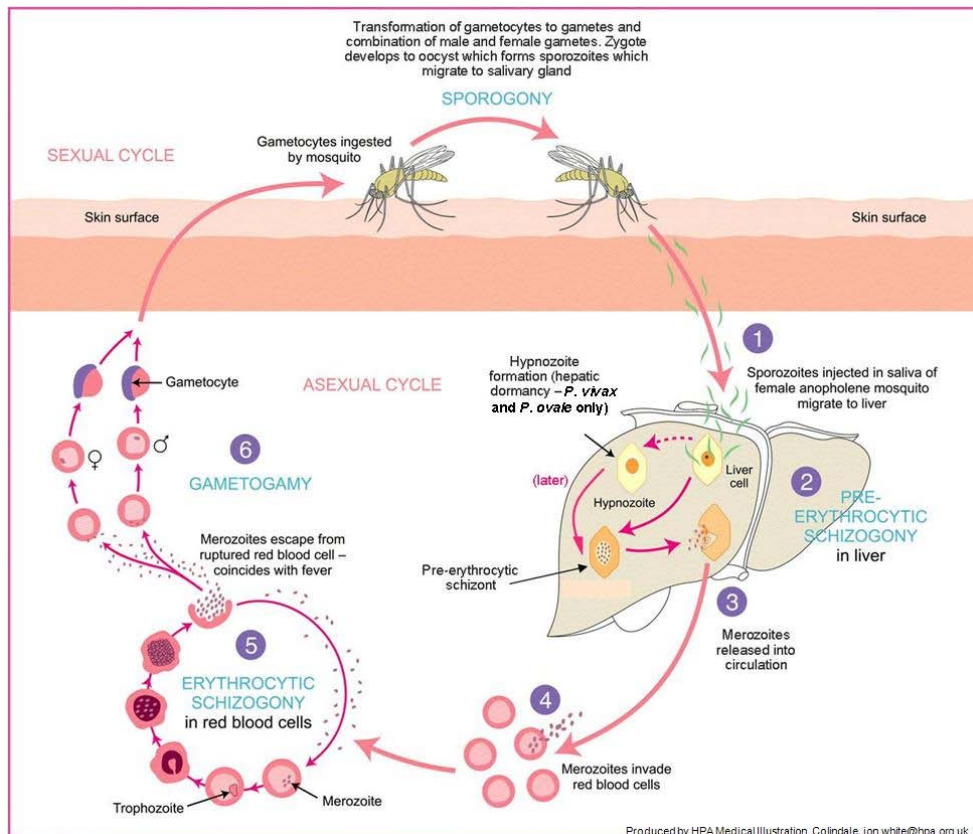


Cryptic malaria

Introduction

The aetiological agents of malaria are *Plasmodium* parasites of which there are five different species that can infect humans (*P. vivax*, *P. falciparum*, *P. ovale*, *P. malariae* and *P. knowlesi*). The lifecycle of *Plasmodium* is complex and involves both mosquito and human hosts [Figure 1].

Figure 1 Life cycle of *Plasmodium*



[Click here for a larger version of this image \[pdf 175KB\].](#)

The standard mode of transmission for malaria is via the bite of an infected female *Anopheles* mosquito. Both the lifecycle of the parasite and the distribution of the mosquito vector are temperature dependent which explains the largely tropical distribution of the disease ([WHO map of geographical distribution of malaria](#)). The different species of parasite vary in their incubation periods and clinical effects [Table 1]. Fever results from infection and destruction of red blood cells. The most serious illness and the vast majority of deaths are caused by *Plasmodium falciparum* as a result of infected cells becoming stuck in the small blood vessels to the brain.

Table 1 Clinical features of the different types of malaria

Type	Geographical distribution	Average incubation period*	Clinical features**	Dormant liver phase?
<i>Plasmodium falciparum</i>	Tropics and subtropics. Predominant form of malaria in Africa.	8-11 days average	<ul style="list-style-type: none"> Fever less regular but approximately every third day. Associated with serious complications including: cerebral malaria, pulmonary oedema, acute renal failure, profound anaemia and black water fever. 	No
<i>Plasmodium vivax</i>	Predominant malaria parasite where malaria is endemic (outside Africa). Range extends to temperate regions.	10-17 days (Sometimes prolonged for months to years)	<ul style="list-style-type: none"> Fever every 48 hours. Relatively benign. Duration of untreated infection 5-8 years. 	Yes
<i>Plasmodium ovale</i>	Tropical Africa, particularly West African coast. Occasionally reported from South America and Asia.	10-17 days (Sometimes prolonged for months to years)	<ul style="list-style-type: none"> Fever every 48 hours. Relatively benign. Duration of untreated infection 12-20 months. 	Yes
<i>Plasmodium malariae</i>	Subtropical, tropical and temperate areas where other species of malaria are found.	18-40 days (Sometimes prolonged for months to years)	<ul style="list-style-type: none"> Fever every third day. Relatively benign; associated with nephrotic syndrome. Duration of untreated infection 20-50 years. 	No
<i>Plasmodium knowlesi</i>	Predominantly a monkey parasite, recently identified in humans in South East Asia	10-12 days	<ul style="list-style-type: none"> Fever spikes daily. Hyperparasitaemia can occur. Rapid clinical course, becoming severe if not treated promptly. Often mistaken for the more benign <i>P. malariae</i> in microscopy. 	No

* Note that there is considerable uncertainty about the upper limits of the incubation period and that the interval between becoming infected and presenting with symptoms may be even more variable. Furthermore, incomplete anti-malarial prophylaxis can extend the incubation period.

** All types of malaria may have an initial flu-like prodrome and a chaotic swinging fever, which only settles into a pattern when synchronous release of parasites is established after 7-14 days. Many patients presenting with malaria in the UK will be seen before a classical pattern has developed. Rigors occur when the temperature rises. ANY FEVER OR FLU-LIKE ILLNESS IN A PATIENT RETURNING FROM A MALARIOUS AREA COULD BE MALARIA.

Classifications

Cases of malaria without an apparent recent travel history should be investigated to establish whether the following reasons may explain the cryptic nature of the infection:

1. Acute infection acquired in an endemic area, but where the initial travel history has been inadequate.
2. Late detection of an infection acquired in endemic area.
3. Importation of an infected mosquito to the UK.
4. Person to person transmission in the UK by direct contact with infected blood/tissues.
5. Unexplained by any of 1 to 4.

1. Acute infection acquired in an endemic area

A detailed travel history may reveal an association with recent travel where none was initially determined. For example, so called 'runway malaria' may occur where a person has not purposely travelled to a malarious area but has been in transit at an airport in a malarious region en route and has been bitten by an infected mosquito there. They may not have even left the plane for this to occur if the doors of the aircraft were opened, e.g. for a refuel or catering stop [1]. In addition to this,

some travellers may inadvertently, or in a few cases deliberately, fail to mention that they have recently been in an endemic area. Travellers may not be aware that malaria is endemic in certain countries and so it is very important to take a detailed travel history.

2. Late detection of an infection acquired in an endemic area

A person may not have travelled recently but may have become infected with malaria some time ago in an endemic area. The infection may even be detected incidentally in the course of a blood examination taken for some other indication. The incubation period of the less severe types of malaria may be very prolonged. In addition, *P. vivax* and *P. ovale* have latent liver phases and so recurrence may occur some time after an initial clinical infection, which may have been missed or unreported. Around 8% of both vivax and ovale malaria cases present more than a year after returning to the UK. Sub-clinical infection or recrudescence may also occur with *Plasmodium* species that do not have a latent liver form, e.g. in people who have spent considerable time in endemic areas and may have developed partial immunity. About 0.8% of falciparum malaria cases present later than six months after the stated date of arrival in the UK, and 0.3% later than one year after arrival [2]. There is ethnic variation in this proportion as those of Caucasian origin present earlier (only 0.3% later than six months after arrival) than those of African or South Asian origin (over 1.3% present after six months and around half of these after more than one year). Haemoglobinopathies are generally believed to be protective against clinical malaria [3]. Not enough, however, is known about the degree of protection afforded and it is possible that chronic, sub-clinical infections may also occur in this group, especially in individuals with haemoglobinopathy trait rather than the actual disorder. Where such infections occur, recrudescence to produce active disease may occur in circumstances of relative immunosuppression, including pregnancy.

3. Importation of infected mosquito to the UK

There is ample evidence that mosquitoes can be transported from one part of the world to another and that malaria can occur where an infected mosquito has been imported and then bites an individual in a non-endemic country [4]. This may occur in an airport [5] or, where climatic conditions allow, in the area around an airport [6]. This is termed 'airport malaria'. In addition, mosquitoes may survive in hand baggage stored in overhead lockers [7], or even in baggage/containers in the hold [8]. This can give rise to 'baggage malaria' where an imported mosquito can infect an individual when released from the baggage, possibly at some distance from the airport and possibly affecting someone other than the person who has travelled with the baggage, e.g. another household member. Aircraft may often be disinfested prior to arrival in the UK from a malarious region but the effectiveness of insecticide sprays when used in isolation is limited. The World Health Organization recommends rigorous methods for disinsection [4] but their recommendations may not always be adhered to.

4. Person-to-person transmission in the UK by direct contact with infected blood or tissues

Although person-to-person transmission is considered rare, malaria can be directly transmitted without the intervention of a mosquito, by transfusion of infected blood [9, 10], implantation of other infected human tissues [11], or by mother to child transmission during pregnancy. It can also be transmitted by injecting drug users sharing needles [12]. By analogy with other blood borne infections, sharing of other personal equipment such as razors/toothbrushes may also pose a theoretical risk though cases of transmission in this way have not been documented [13]. The same applies to invasive procedures such as tattooing, body piercing or acupuncture.

Although transmission has not been documented as a result of infected healthcare workers performing exposure prone procedures on patients, this has been thought to be the most likely, though unproven, explanation in at least one incident [14]. Transmission to a healthcare worker has, however, been documented by a needle stick injury from an infected patient [15]. Nosocomial transmission can also occur via cross contamination of materials/fluids used invasively [16].

5. Unexplained

Cases that cannot otherwise be categorised raise the possibility of 'indigenous transmission', i.e. the transmission of imported malaria by local mosquito vectors. The temperate climate is cited to be the main reason why malaria does not occur naturally in the UK; the parasites requiring significantly warmer temperatures than normally occur in the UK for the insect stage of their life-cycle (particularly for *P. falciparum*). While *P. falciparum* transmission occurred in southern Europe until successful eradication campaigns after World War II, natural transmission of *P. falciparum* hardly ever occurred in northern Europe because of the low temperature. The climate is not, however, the only important factor. Natural transmission of *P. vivax* malaria did occur in south-eastern coastal areas of England until the early part of the twentieth century when a change in agricultural practices largely destroyed the mosquito vector's habitat. Species of *Anopheles* mosquitoes that can carry malaria (including some strains of *P. falciparum*) do occur in the UK [17,18]. The last two recorded cases of natural malaria transmission in the UK were of *P. vivax* in 1953 in Stockwell, central London [19]. There has only been one previous case of presumed natural *P. falciparum* transmission reported in the UK. This occurred in the autumn of 1920 and is postulated to have been the result of acquisition of the parasite by local mosquitoes from infected soldiers returning from the Mediterranean after World War I [20], although this was not proven. Although it is considered unlikely that malaria would become endemic in the UK again, climate change could facilitate a re-emergence of natural transmission of malaria in the UK, and may lead to localised outbreaks [21].

Malaria surveillance

Surveillance of malaria in the UK relies on two main sources of information: notifications and laboratory reports.

Malaria is a statutorily notifiable disease and clinicians diagnosing it have a legal duty to report cases to the Local Authority proper officer (usually the local consultant in communicable disease control (CCDC)). All notifications of malaria are centrally collated at Health Protection Services, Colindale. It is known, however, that notifications of malaria considerably underestimate the true numbers of cases occurring. Malaria is diagnosed in haematology laboratories by examination of blood films. When parasites are seen, samples may be sent to the HPA Malaria Reference Laboratory (MRL) for confirmation. The MRL then requests further information from the reporting laboratory and maintains a database of cases, which also includes other reports received from clinicians and the notifications. This is a more complete source of epidemiological information but still does not capture all cases since some cases are not reported by any route [22]. It is helpful if CCDCs encourage reporting clinicians to complete the [MRL malaria reporting form](#) (pdf 54KB), which includes a travel history, on each malaria case in the UK.

Identifying a case of cryptic malaria

Cryptic cases are primarily identified when the clinician taking the medical history recognises that there is no explanatory travel history. There are two main ways in

which this information may come to the attention of public health authorities: either through notification to the CCDC or through the MRL.

The standard notification form allows the clinician to state whether the disease was acquired abroad and in which country. A CCDC receiving a notification may therefore suspect a cryptic case on the grounds that geographical details of countries visited has been omitted. In order to help identify cases of cryptic malaria CCDCs are encouraged to check that all notification forms for malaria have the travel history section completed.

It is recommended that where the interval between leaving a malarious area and the detection of malaria parasites exceeds six months for Caucasian people with *P. falciparum*, 12 months for people of other ethnic groups with *P. falciparum* (as they may be semi-immune), and 18 months for all people with other types of malaria, the case should be considered as a possible cryptic case.

The MRL may detect a possible cryptic case when a form is returned to them with a history of no recent travel or a history of some other likely transmission route, e.g. a transfusion.

Action to take on identifying a possible case of cryptic malaria

Most possible cases of cryptic malaria can be excluded as such by enquiry of the reporting clinician, who may have omitted a relevant travel history from the report. Addressing this question to the reporting clinician is therefore the first stage in the investigation. This should be done by whoever has identified the potentially cryptic case - either the MRL or the CCDC.

If a case cannot be excluded as being cryptic by this means, then the case should be reported to the Travel and Migrant Health Section (TMHS) at Cfl (Tel: 020 8200 4400 or email: tmhs@hpa.org.uk). If information on a case is not available to the MRL, it is possible that the CCDC may have or be able to access that information, and vice versa. TMHS will liaise between the two to determine whether this is the case.

If, after this process, a case still cannot be excluded as being cryptic, then further investigation will be required. Local CCDCs have statutory responsibility for local communicable disease control [23]. The statutory responsibility for the investigation of cases of cryptic malaria lies with the CCDC who covers the area in which the patient is resident, not the area in which transmission may have occurred. However, close liaison may be required between local teams, e.g. if it is suspected that a patient acquired malaria in a UK hospital outside their area of residence. In such circumstances local agreement would be required as to who would lead the investigation. Any investigation would be supported by both TMHS and MRL.

[A questionnaire has been devised to assist in the initial investigation of cases.](#)

If further information is required directly from the patient it is to be agreed between the CCDC, TMHS and MRL who will undertake to obtain this. In most cases it is likely to be the CCDC but support can be offered where necessary for this task.

Once completed the questionnaire should be returned to the TMHS at Cfl and the MRL.

Close liaison should be maintained between the local team, TMHS and MRL throughout.

In some cases, a satisfactory explanation for the case may be revealed through the use of the questionnaire and the investigation may terminate at this point. For example, if the case can be satisfactorily assigned to class 1, 2, or 3 of the classification scheme, e.g. probable airport malaria. (Note that it is very unlikely that

importation of an infected mosquito will be able to be proven definitively, but there may be circumstantial evidence to support this conclusion).

Further investigations

Where the case is suspected to be in class 4 or 5 further investigation may be necessary. For example, a class 4 case (person-to-person transmission in the UK by direct contact with infected blood/tissues), may require a formal incident control team to be convened to decide upon further action. If all possibilities have been explored and the case can still not be explained then further investigations may be required. These may include entomological investigation at the patient's residence. This would be decided by close liaison between the CCDC, TMHS and MRL.

Media and other communication issues

Possible cases of cryptic malaria may attract media interest. Close liaison should be maintained between the communications officers at HPA, the local Health Protection team and the London School of Hygiene and Tropical Medicine (representing MRL). The most appropriate organisation to lead on media issues will vary depending on the circumstances of the case, and should be decided by agreement between the local Health Protection Team, TMHS and MRL.

Local CCDCs are encouraged to inform their Regional Epidemiologist as well as their Director of Public Health. TMHS will ensure that, where appropriate, the Department of Health is notified.

Records of cryptic malaria cases and feedback

MRL and TMHS hold records of all cryptic malaria cases. Reports on cryptic cases are included with standard reports of malaria epidemiology in the UK and are published on the [malaria pages](#).

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