

### 3 | *PLASMODIUM* SPECIES

#### 3.1 | Disease agent

- *Plasmodium falciparum*, *P. vivax*, *P. malariae*, *P. ovale*, *P. knowlesi*

#### 3.2 | Disease agent characteristics

- Protozoan, 2–4 mm (ring form).
- Order: Haemosporida.
- Family: *Plasmodiidae*.
- All are intraerythrocytic parasites with characteristic microscopic appearance. Some have a dormant stage in hepatic cells and can cause relapse weeks or even years later.
- Life cycle includes asexual and sexual stages.

#### 3.3 | Disease name

- Malaria

#### 3.4 | Priority level

- Scientific/epidemiologic evidence regarding blood safety: low in most nonendemic countries but high in hyperendemic countries. Risk and concern regarding blood safety may be moderate to high in some nonendemic countries based on donor demographics and travel patterns of the donor population.
- Public perception and/or regulatory concern regarding blood safety: Moderate; risk and concern regarding blood safety may be moderate to high in some nonendemic countries based on donor demographics and travel patterns of the donor population.
- Public concern regarding disease agent: Moderate

#### 3.5 | Background

- Generally limited to tropical and subtropical regions where it remains stable despite continued efforts to eradicate the mosquito vector. Local epidemiology can change rapidly in response to local geophysical and sociological conditions.
- Remains major public health concern in endemic regions of the world, particularly for children less than 5 years of age; >90 countries are considered endemic.

- Re-emergent in nonendemic areas because of immigration and travel.
- Sporadic cases attributed to “airport malaria” and autochthonous transmission increasingly reported
- Classically, there have been four *Plasmodium* species associated with human malaria. In 2008, a fifth *Plasmodium* species that causes human malaria was identified in Malaysia, *Plasmodium knowlesi*, whose natural hosts are forest-dwelling macaques (the long-tailed and pig-tailed macaque), has a rapid doubling time (once daily), and rapidly reaches high parasitemia levels in humans with rapid development of anemia, jaundice, renal failure, and fatal outcomes similar to severe *P. falciparum* malaria. Humans acquire monkey malaria when they share the same habitat. In Asia (Malaysia), four fatalities, initially mistaken for *P. malariae* infections, were subsequently attributed to *P. knowlesi*; all were hyperparasitemic and developed marked hepatorenal dysfunction. *P. knowlesi* was detected by PCR in 266 (27.7%) of 960 archived samples from patients with malaria in Malaysia and Malaysian Borneo.
- Autochthonous transmission of *P. vivax* in FL and TX was reported in 2023 (the first such US infections in 20 years). Whether this will be sustained remains to be determined and thus its relevance to US transfusion medicine.

#### 3.6 | Common human exposure routes

- Bite of an infected female anopheline mosquito

#### 3.7 | Likelihood of secondary transmission

- Low
- Transmitted transplacentally by parenteral inoculation including blood transfusion and organ transplantation

#### 3.8 | At-risk populations

- Individuals are at increased risk for exposure to infected mosquitoes because of travel to or residence in areas where *Plasmodium* species are endemic.

#### 3.9 | Vector and reservoir involved

- Female mosquitoes of the genus *Anopheles* are a reservoir and the vector
- Primates including humans are the other reservoir

### 3.10 | Blood phase

- Symptomatic patients: weeks to months before spontaneous clearance unless appropriately treated with anti-malarial drugs
- Asymptomatic patients: persistence with periodic blood phase in semi-immune individuals for years (e.g., from 1 to greater than 50 years, depending on the species of malaria)

### 3.11 | Survival/persistence in blood products

- Generally, 7–10 days, based on historic data, but information on RBCs stored in contemporary anticoagulants/storage solutions is not available, and on-going transfusion transmission cases suggests survival during the lifetime of the product.

### 3.12 | Transmission by blood transfusion

- Multiple cases worldwide.
  - Common in endemic countries.
- Overall, the US case rate has dramatically decreased during the last 50 years. Eleven cases were identified from 2000 to 2020 of which only 4 occurred since 2011 (3 of 4 in patients with sickle cell disease and all 4 in adolescents/children). All cases were from former residents or those having had malaria; none were from travelers. Most transmissions are from RBCs, but platelet components have been implicated, probably because of the presence of contaminating RBCs. None recognized from frozen components.
- Four of five species of *Plasmodium* have been transmitted, but a large majority of recent US cases have been a result of *P. falciparum* and, to a lesser extent, *P. vivax*.

### 3.13 | Cases/frequency in population

- In the United States, approximately 1000–1500 cases of malaria are reported yearly; 75% are attributable to *P. falciparum* and *P. vivax* infections.
- *Plasmodium* species infections are primarily found in tropical and subtropical regions, where current estimates suggest there are more than 200 million clinical cases of malaria and 500,000 or more deaths annually. The frequency varies considerably by location, with highest rates in sub-Saharan Africa

(95% of global cases). Six countries in sub-Saharan Africa account for more than half of all malaria deaths.

### 3.14 | Incubation period

- Varies by infecting species, immune status of patient, and number of parasites transmitted. For *P. falciparum* and *P. vivax*, the incubation period may be 1 week to 1 month but may require several months for *P. malariae*.

### 3.15 | Likelihood of clinical disease

- Low/moderate in semi-immune residents of endemic areas, high in nonimmune visitors.

### 3.16 | Primary disease symptoms

- Periodic fever and rigors, chills, headache, myalgias, arthralgias, splenomegaly, and hemolytic anemia.
- In blood recipients, onset of symptoms may be delayed by weeks to months. The nonspecific nature of the symptoms, plus their delay in onset, makes recognition of clinical disease in blood recipients difficult.

### 3.17 | Severity of clinical disease

- Most severe forms of malaria are associated with *P. falciparum*. High levels of parasitemia observed, leading to microvascular obstruction and severe complications (e.g., cerebral malaria).

### 3.18 | Mortality

- There were 627,000 deaths in 2020, representing an increase that is being ascribed to the disruptions in healthcare caused by the COVID-19 pandemic.

### 3.19 | Chronic carriage

- Occurs classically for infections with *P. malariae*, less commonly with *P. ovale* and *P. vivax*. Chronic infections can also occur with *P. falciparum* but are even less common.

### 3.20 | Treatment available/efficacious

- The variety of drug treatments available worldwide (not all in the United States) come in five classes: (1) endoperoxides (artemisinin derivatives), (2) 4-aminoquinolines (chloroquine), aryl-amino alcohols (mefloquine, quinine), (3) antifolates (pyrimethamine and sulfadoxine), (4) naphthoquinones (atovaquone-proguanil), and (5) 8-aminoquinolines (primaquine, tafenoquine)
- Two drugs (primaquine and tafenoquine) can be employed to eradicate dormant liver-stage parasites (hypnozoites).
  - Widespread drug resistance has developed.
  - In cases with high parasitemia, exchange transfusion is recommended.

### 3.21 | Agent-specific screening question(s)

- Risk questions pertaining to residence in or travel to endemic areas or history of malaria are currently used in the United States.

### 3.22 | Laboratory test(s) available

- No FDA-licensed blood donor screening test exists. Two testing strategies have been discussed—universal screening using NAT to allow consideration of modifying the current donor geographic-risk questions and the “testing-in” strategy for deferred donors. In the United States, the “testing-in” strategy would require test kits to be capable of detecting all *Plasmodium* species infecting humans. NAT platforms for donor screening applications are in development and are *Plasmodium* genus specific.
- Immunofluorescence assay (IFA) and EIA to detect IgG antibodies are used for “testing in” (i.e., shortened deferrals) by several European countries and in Australia (i.e., donors with a travel history that would otherwise lead to deferral are evaluated further by laboratory testing and allowed to donate sooner if their antibody test is negative; in some, plasma, but not RBCs, from seropositive donors can be used during the deferral period).
- Options for diagnostic testing include blood smear microscopy, IFA, EIA, antigen-based rapid diagnostic tests, and NAT.

### 3.23 | Currently recommended donor deferral period

- 3 months for travel to endemic areas by nonendemic resident.
- 3 years for those who have lived for 5 or more years in endemic areas.
- 3 years after recovery for those who previously had malaria and are now asymptomatic.
  - The above applies to the US since the times and conditions for deferral vary by country.

### 3.24 | Impact on blood availability

- Agent-specific screening question(s): Current questions result in the deferral of fewer than 50,000 blood donors each year since 2019 in the United States, with very few likely infected or infectious.
  - The impact of self-deferrals is unknown but likely much greater.
- Laboratory test(s) available: Not applicable.

### 3.25 | Impact on blood safety

- Agent-specific screening questions(s): Transfusion-transmitted cases continue to decline, with only four since 2011.
- Laboratory test(s) available: Not applicable.

### 3.26 | Leukoreduction efficacy

- Unlikely to be effective for this intraerythrocytic parasite

### 3.27 | Pathogen reduction efficacy for plasma derivatives

- No specific data are available, but it is presumed that the agent should be sensitive to many measures used in the fractionation process.

### 3.28 | Other prevention measures

- Mosquito avoidance.
- Antimalarial prophylaxis for visitors to endemic areas.

- Efficacy of pathogen reduction demonstrated using several different compounds and effectiveness studied in a clinical trial in Ghana for a whole blood process.
- Licensed pathogen reduction in the United States is allowed as a substitute for donor deferral due to travel (within the last 3 months) to a malaria-endemic area.

### SUGGESTED READING

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