MALARIA

1. **Agent**: Protozoan parasites *Plasmodium falciparum*, *P. malariae*, *P. ovale*, *P. Vivax,* and *P. knowlesi*.

2. **Identification:**

a. **Symptoms**:
Uncomplicated Malaria:
The classical (but rarely observed) febrile disease consists of a cold stage (sensation of cold, shivering), a hot stage (fever, headaches, vomiting; seizures in young children) and a sweating stage (sweats, return to normal temperature, tiredness). More commonly, the patient presents with a combination of symptoms including fever, chills, sweats, headaches, nausea and vomiting, body aches, and general malaise. Classically (but infrequently observed) the attacks occur every second day with the "tertian" parasites (*P. falciparum*, *P. vivax*, and *P. ovale*) and every third day with the "quartan" parasite (*P. malariae*).

Severe Malaria:
Severe malaria occurs when infections are complicated by serious organ failures or abnormalities in the patient's blood or metabolism. The manifestations of severe malaria include

- Cerebral malaria, with altered consciousness, seizures, coma
- Severe anemia due to massive intravascular hemolysis
- Acute respiratory distress syndrome (ARDS)
- Coagulopathy, with or without disseminated intravascular coagulation (DIC)
- Renal failure, hemoglobinuria ("blackwater fever")
- Hepatic failure
- Hyperparasitemia, where more than 5% of the red blood cells are infected by malaria parasites
- Metabolic acidosis

Severe malaria is a medical emergency and should be treated urgently and aggressively.

Malaria Relapses:
In *P. vivax* and *P. ovale* infections, patients having recovered from the first episode of illness may suffer several additional attacks ("relapses") after months or even years without symptoms. Relapses occur because *P. vivax* and *P. ovale* have dormant liver stage parasites ("hypnozoites") that may reactivate.

b. **Differential Diagnosis**: Other febrile illnesses associated with international travel, e.g., brucellosis, typhoid fever, and yellow fever, dengue, chikungunya, leptospirosis, viral hemorrhagic fever

c. **Diagnosis**: Demonstration of parasites in thick or thin blood smears is the gold standard. If initial diagnostic evaluation is negative and clinical suspicion for malaria persists, follow-up testing should be done each day for two more days. Detection of antigens using rapid diagnostic tests (RDTs), of parasite DNA by PCR, or of antibodies by indirect flurorescent antibody (IFA) or enzyme-linked immunosorbent assay (ELISA) tests are alternative methods. RDTs can more rapidly determine that the patient has malaria, but they are less sensitive than microscopy and cannot confirm each specific species or parasite density. Only one RDT, BinaxNOW™, is approved for diagnostic use in the United States. Negative RDT results should be confirmed with a blood smear. PCR results are often not available quickly enough to be of value in establishing the diagnosis of malaria infection. PCR is most useful for confirming the species of malarial parasite after the diagnosis has been established by either smear microscopy or RDT. Serology does not detect current infection but rather measures past exposure. CDC also recommends that all cases of malaria diagnosed in the United States should be evaluated for evidence of drug resistance and offers malaria–drug-resistance testing.

3. **Incubation**: Variable, the incubation period in most cases varies from 7 to 30 days; 8-12 days for *P. falciparum*, 18 days or up to years for *P. malariae*; 12-18 days for *P. ovale* and *P. vivax*; 9-12 days for *P.*

knowlesi. Inadequate or inappropriate prophylaxis may extend the incubation period.

Note: *P.* vivax and *P. ovale* strains can occur 8-12 month or years after exposure, due to dormant forms remaining in liver.

4. **Reservoir**: Human.

5. **Source**: Infected female mosquitoes of the genus *Anopheles*. Most of the continental United States has *Anopheles* mosquitoes (particularly *An. freeborni* and *An. quadrimaculatus*), which can spread malaria. Local US mosquito-borne spread has resulted in more than 150 locally acquired cases and more than 60 limited outbreaks in the United States over the past 50 years. In addition, more than 2,000 cases of malaria are reported annually in the United States, with most cases occurring in returned travelers.

6. **Transmission**: Bite of infective anopheles female mosquito, blood transfusion from infected persons, congenital and parenteral transmission.

7. **Communicability:**

   a. **Mosquito infection**: When gametocytes are present in blood of patient.

   b. **Parenteral transmission**: When trophozoites are present in blood.

8. **Specific Treatment:**
   CDC Malaria Treatment can be used as a guide for treatment of malaria in the United States

Additional information is available on the CDC Malaria Webpage.

Malaria can be a severe, potentially fatal disease (especially when caused by *Plasmodium falciparum*), and treatment should be initiated as soon as possible. Treatment should be guided by the following four main factors:

- Infecting *Plasmodium* species;
- Clinical status of the patient;
- Expected drug susceptibility of the infecting parasite as determined by the geographic area where the infection was acquired; and
- Previous use of antimalarials, including those taken for malaria chemoprophylaxis.

a. Acquired in Areas without Chloroquine Resistance:
Patients can be treated with oral chloroquine or hydroxychloroquine.

b. Acquired in Areas with Chloroquine Resistance: artemether-lumefantrine (Coartem) [preferred regimen if available], atovaquone-proguanil (Malarone), or Quinine sulfate plus doxycycline, tetracycline, or clindamycin. Mefloquine when other options cannot be used as associated with rare neuropsychiatric reactions at treatment dose.

c. Infections with *P. vivax* and *P. ovale* can relapse due to hypnozoites that remain dormant in the liver. To eradicate the hypnozoites, patients should also be treated with either tafenoquine (KrintafelTM) or primaquine phosphate

d. Infection by any species transmitted by transfusion, parenteral, or congenital route: chloroquine or consult ACDC physician for suspected resistant strain.

NOTE: Chloroquine (or hydroxychloroquine) remains an effective choice for all *P. malariae* and *P. knowlesi*, *P. ovale,* and *P. vivax* infections except for *P. vivax* infections acquired in Papua New Guinea or Indonesia. Consult CDC yellow book or ACDC physician for details on chloroquine resistant strains.

e. Patients with any manifestations of severe malaria, e.g. impaired consciousness/coma, hemoglobin <7 g/dL, acute kidney injury, acute respiratory distress syndrome, circulatory collapse/shock, acidosis, jaundice (with other signs of severe malaria), disseminated intravascular coagulation, and/or parasite density of ≥5% should be treated promptly and aggressively with parenteral antimalarial therapy with intravenous (IV) artesunate regardless of the species of malaria seen on the blood smear. If clinician cannot obtain commercially within 24

hours, call CDC Malaria Hotline to speak to clinician on call.

9. **Immunity**: Partial immunity for individuals with continuous exposure in endemic areas, e.g., Africa, Central America and Southeast Asia.

REPORTING PROCEDURES

1. **Reportable**. *California Code of Regulations,* Sections 2500, 2586. Malaria smears in local laboratories must be sent to LAC PHL for confirmation of species.

   Report Form: **MALARIA CASE REPORT (CDPH 8657)**.

2. **Epidemiologic Data**:

   a. Residence in or travel to areas endemic for malaria 3 years prior to onset. List countries and cities, dates of stay, and any prophylactic medication.

   b. Transfusion of blood or blood products 12 months prior to onset. Include dates, lot numbers, blood banks and organ procurement organizations. ***Notify CDPH Biologics at once for assistance in follow-up.***

   c. History of blood donation.

   d. Use of parenteral drugs.

   e. Surveillance of travel contacts and persons sharing intravenous drug paraphernalia for symptoms of malaria.

CONTROL OF CASE, CONTACTS & CARRIERS

ACDC will review suspect reports. Case investigation to be completed by ACDC staff.

CASE: Isolation: None.

CONTACTS: No restrictions.

CARRIERS: Not applicable.

PREVENTION-EDUCATION

1. Appropriate chemoprophylaxis for travelers to areas endemic for malaria. Malaria information for travelers is available via the CDC Travelers' Health webpage.

2. Avoid outdoor exposure during hours of peak mosquito activity, i.e., between dusk and dawn.

3. Use mosquito repellent (DEET-based up to 35% protective clothing, and mosquito netting at bedtime when traveling to areas with endemic malaria.

4. Exclude persons with malaria from blood donor programs for 3 years after becoming asymptomatic and after therapy stopped. Asymptomatic U.S. donors not on anti-malarial chemoprophylaxis may donate 1 year after returning from an endemic area.

5. IV drug users may acquire malaria by sharing paraphernalia.

6. Pregnant women should avoid travel to malaria endemic areas unless absolutely necessary.

DIAGNOSTIC PROCEDURES

1. **Microscopy of blood smear**: Remains the gold standard for laboratory confirmation.

   Container: Microscope slides should be shipped in a slide mailer to prevent breakage.

   Laboratory Form: **Test Requisition and Report Form H-3021**

   Examination Requested: Malaria confirmation.

   Material:
   1. Send original slides from which the submitting laboratory made a diagnosis. (thick and thin for confirmation),

   2. Send stained or unstained pretreatment slides (if unstained, fix thin smears in methanol as soon as possible after making the smear).

   3. Whole blood containing EDTA (0.020 g/10 ml of blood) that was collected by venipuncture and is less than 1 hour old for detection of stippling.

Remarks: Obtain smears midway between febrile episodes, if possible.

2. **PCR of blood**: Parasite nucleic acid detection using polymerase chain reaction (PCR).

   Material: EDTA whole blood.

   Also acceptable if EDTA whole blood is not available:
   - Thick **unfixed** blood smears stored at room temperature
   - Thin **unfixed** blood smears stored at room temperature

   Amount: >0.5 mL EDTA whole blood

   Container: Purple top tube.

   Storage: Store EDTA whole blood refrigerated (2-8ºC) until transport. Transport with cold packs to keep at refrigerated temperature. Blood smears can be stored and shipped at room temperature.

   Shipping: Ship diagnostic specimen with cold packs (do not freeze). Ensure that EDTA blood tube (purple top) is additionally sealed with parafilm or tape for additional protection against leaking. If unfixed blood smears are sent, ensure that microscope slides are shipped in a slide mailer to prevent breakage.

   Follow the appropriate DOT/IATA approved shipping procedures. Blood specimens for *Plasmodium* species testing should be shipped as a Biological Substance, Category B (UN3373).

   Laboratory Form: **Test requisition form (H-3021)**.

   Form 416 "Parasitology"

   Exam Requested: *Plasmodium* species (Malaria) Real-Time PCR