Malaria Surveillance & Case Investigation Best Practices

PURPOSE

This document provides best practices for health departments to consider as part of their usual activities to investigate malaria cases.

If you have questions about malaria investigation or surveillance, please reach out to the state health department (if applicable) or the CDC Malaria Branch (malaria@cdc.gov or 770-488-7788) to discuss.

Additional guidance from CDC is available for jurisdictions with concerns for a possible case of locally acquired malaria. Please request this information from the CDC malaria surveillance epidemiologist or the CDC Malaria Branch (malaria@cdc.gov or 770-488-7788).

BACKGROUND

Plasmodium parasites that cause malaria are transmitted through the bite of an infectious *Anopheles* mosquito. For details about how parasites are transmitted, see Appendix A: Malaria Lifecycle. Five species of *Plasmodium* cause illness in humans: *P. falciparum, P. vivax, P. ovale*, *P. malariae*, and *P. knowlesi*. Because malaria was eliminated from the United States (U.S.) in the early 1950s, it is assumed that U.S. residents do not have protective immunity to malaria and are susceptible to severe illness and death. Around 2,000 people are diagnosed with malaria in the U.S. annually, and most of them acquired malaria while in countries with ongoing mosquito-borne transmission (imported malaria). Potential for malaria transmission from an imported case to a non-traveler within the U.S. is possible (but rare) since *Anopheles* mosquitoes that can transmit malaria are widespread across the majority of states.

Malaria is transmitted from the bite of an infectious *Anopheles* mosquito and not from person to person, although rarely malaria can be transmitted via blood exposures (induced malaria) or to a neonate during pregnancy or birth (congenital malaria).

If someone in the U.S. is infected with malaria and is bitten by an *Anopheles* mosquito, then the mosquito may become infectious and could transmit the parasite to other people in the area. Between 1957 and 2003, CDC documented 63 incidents of locally acquired malaria that resulted in 156 total cases. While no such events were documented between 2003 and 2022, in the summer and fall of 2023 ten locally acquired mosquito-transmitted malaria cases in four states were reported. These cases demonstrate the potential for onward transmission of *Plasmodium* parasites from imported malaria cases to persons who have not traveled outside of the U.S. and the importance of rapid diagnosis, treatment, timely investigation, and control of malaria in the U.S.

CDC U.S. CENTERS FOR DISEASE CONTROL AND PREVENTION

SIMPLIFIED MALARIA CASE DEFINITIONS

More detailed malaria case definitions and classifications are available at https://ndc.services.cdc.gov/case-definitions/malaria-2014/

Suspected

Detection of *Plasmodium* species by rapid diagnostic antigen testing only—BinaxNOW™ Malaria rapid diagnostic test (RDT).

Confirmed

Detection of *Plasmodium* species by blood smear microscopy or polymerase chain reaction (PCR).

CLASSIFYING DISEASE ACQUISITION

Based on the case investigation, CDC classifies each malaria case according to the following definitions. An understanding of these distinctions may be helpful for health departments and investigators to guide follow-up and in conducting any enhanced case investigations.

- **Congenital malaria**: Malaria infection transmitted directly from mother to child during pregnancy or childbirth.
- **Cryptic malaria:** An isolated case of malaria that cannot be epidemiologically linked to additional cases, and for which epidemiologic investigation does not identify the mode of acquisition.
- **Imported malaria:** Malaria acquired outside the U.S. The patient must have a recent (within ~2 years) travel history to a country or territory with ongoing malaria transmission.
- **Locally acquired malaria:** In the U.S., a non-endemic setting without indigenous malaria transmission, locally acquired malaria cases are typically classified into two categories:
    - **Induced malaria:** Malaria transmission through a blood transfusion, tissue or organ transplantation, or another parenteral route, not mosquito-borne or congenital transmission.
    - **Introduced:** Malaria likely acquired by mosquito transmission from an imported case in an area where malaria is not a regular occurrence.
- **Recrudescent malaria:** A repeated attack of malaria due to the survival of malaria parasites in red blood cells can occur for any *Plasmodium* species and typically occurs in the first four weeks after an initial illness due to failure of the antimalarial treatment to clear all parasites. Some explanations for recrudescence include: (i) incomplete adherence to an appropriate antimalarial regimen, (ii) inappropriate use of oral antimalarials for severe illness (especially if there is hyperparasitemia, where ≥5% of red blood cells are infected), and (iii) antimalarial drug resistance.
- **Relapsing malaria**: *P. vivax* and *P. ovale* species can reactivate dormant liver-stage parasites (hypnozoites), resulting in a malaria **relapse**, typically 3 months to 3 years after the initial infection. *P. falciparum* and *P. malariae* species do not have liver hypnozoites that can be reactivated, so illnesses caused by these species do not result in relapses.

LABORATORY CONFIRMATION

Malaria rapid diagnostic test (RDT) results, whether positive or negative, should be confirmed with a blood smear. Although it is possible to determine the *Plasmodium* species on a thin blood smear, this is often difficult to determine by microscopy alone and typically requires expertise. The Council for State and Territorial Epidemiologist (CSTE) recommends a PCR test be performed for all malaria cases to confirm the *Plasmodium* species. Determination of *Plasmodium* species is important to ensure additional treatment for *P. vivax* and *P. ovale* species and thus prevent relapsing illnesses.

The State Public Health laboratory (PHL) (if they have the capacity) should review, as soon as possible, blood smear microscopy and conduct confirmatory PCR for any malaria cases.

- Determine if PHLs can routinely retain whole blood specimens (preferably pre-treatment) from patients with confirmed malaria. This is helpful for investigations where cases in proximity could be assessed for genetic relatedness (via CDC genomic testing).
- CDC can assist with species confirmation (https://www.cdc.gov/dpdx/index.html). Send an email for CDC testing approval and submission instructions:
    - Blood smear images for review via telediagnosis (M – F, 9am – 5pm ET): DPDX@cdc.gov
    - Blood smear slides or whole blood (for PCR): parasiteslab@cdc.gov

Babesiosis is another intraerythrocytic parasitic infection that can have similar signs and symptoms as malaria. *Babesia microti* (and other species) are transmitted in some parts of the U.S. by ticks and can be difficult to differentiate from *P. falciparum* by blood smear. PCR should be ordered for both *Babesia* and *Plasmodium* to distinguish between these illnesses if there is any question, especially for individuals who have not traveled recently in a place where ongoing malaria transmission occurs.

CDC and some PHLs conduct routine molecular surveillance testing.

- Consider routinely sending whole blood specimens for molecular surveillance testing to CDC: malarialab@cdc.gov
- See Appendix B for additional information about malaria molecular testing.

Please copy the malaria hotline malaria@cdc.gov in emails regarding lab testing for cases under investigation.

CASE INVESTIGATION AND PATIENT INTERVIEW

- *Promptly investigate*[1] each confirmed case of malaria. Investigations should establish the presumed route of infection to determine case classification.
- Procedures for conducting a malaria case investigation include reviewing medical records, interviewing the patient, and contacting the ordering healthcare provider.

Reporting

There are multiple ways to submit malaria case investigation reports to CDC. However, the preference is to submit them using the CDC malaria electronic case report form (eCRF) or via HL7 using the malaria message mapping guide (MMG) standards.

- CDC supports HL7 reporting for malaria via two MMGs: GenV2 and the malaria specific MMG. Reach out to the CDC malaria surveillance epidemiologist to discuss onboarding for the malaria MMG. Reporting via GenV2 alone does not cover all aspects of the case investigation and therefore full case reports should still be sent to CDC in another format.
- To complete a malaria electronic case report form (eCRF), follow the instructions provided on pages 4 – 5 of the CDC eCRF. If the CDC eCRF is not used then follow jurisdiction-specific recommendations to complete the investigation using a customized investigation form and online reporting system.
- Instructions specific to the CDC malaria eCRF:
    - Page 3 of the eCRF form collects additional data for multiple hospitalizations, lab tests, travel histories, and other data.
    - Note that Chemoprophylaxis (section 5 a – c of the malaria case report form) refers to medication taken before, during, and after travel to *prevent* malaria illness. Treatments given to cure the acute illness should be documented in section 5 h of the malaria case report form.
    - Submit individual eCRFs (or .csv reports derived from the pdf files) to the CDC domestic malaria surveillance epidemiologist or to the mailbox malariasurveillance@cdc.gov via secure email. Note that some secure email systems require individual credentials, which aren't accessible from the group inbox. Do not include personally identifiable information (PII) in the body or subject of the email.

Relapse

A relapse (only in *P. vivax* or *P. ovale* species) or a subsequent episode of malaria in a person who previously had malaria should be counted as an additional case (requiring a separate case report form) unless the case is indicated as a treatment failure within 4 weeks of initial presentation (recrudescence of original infection).

- The infecting species should be determined, and potentially relapsing cases should be carefully investigated to assess if the person had traveled since their previous illness.
- CDC classifies cases according to where the person acquired the infection. If the initial infection was acquired internationally, then the relapse case is classified as imported. If the initial infection was acquired through a local exposure, for example by locally acquired mosquito transmission, then those relapse cases will also be classified as introduced.

[1] Jurisdiction-specific recommendations should be followed. Typically, the malaria case investigations are initiated between 24 hours and one week from the notification. If there is concern that the case may be locally acquired or doesn't have a travel history to a country with ongoing malaria transmission in approximately the previous two years, or if the patient is severely ill, then urgency is recommended to ensure timely public health responses and appropriate treatment.

- There are rare case reports for persons who have a late recrudescence, occurring many months or years after an earlier illness. A late recrudescence is difficult to prove. These rare cases must be thoroughly investigated to rule out other exposures and are often classified as cryptic.

Case investigation

Provide as much information as possible for the case investigation. CDC uses data to classify risk groups, describe disease severity, and determine if treatment follows CDC's guidelines.

- **Antimalarial treatment:** Note that some antimalarials may not be immediately initiated, so the information available immediately upon diagnosis may not be complete. For example, follow-on treatment for patients with severe malaria is recommended to start subsequent to the intravenous artesunate medication. And primaquine or tafenoquine to prevent *P. vivax* or *P. ovale* relapses are recommended to start after G6PD testing is completed and results received (typically 1 – 2 weeks after diagnosis).
    - More information on malaria diagnosis and treatment can be found in the Malaria Clinical Guidelines Quick Reference (Appendix C).
- **Travel history:** If a person traveled to more than one endemic country, then use the repeating block sections of the eCRF to include all countries traveled in and their dates, if available. If it is not possible to determine the exact country of disease exposure, then indicate the region. For example, if a person traveled for two weeks in Nigeria and two weeks in Benin then indicate the date of departure for each country and the duration they were there. If using a jurisdiction-specific reporting system that does not allow for multiple countries to be reported, then indicate the region. For the above example, indicate West Africa and the total duration there (4 weeks) and the date of departure from the location.
    - If country-specific travel details are missing, then indicate the Region traveled. Partial dates (year and month, or year alone) can be provided. Because travel information is used to classify case acquisition, it is not recommended to indicate 'unknown' for a person who traveled in multiple countries.
- Please follow the CSTE guidelines for completing the "Country of Usual Residence" data element. If the person is establishing residence in the U.S., then "Country of Usual Residence" should be "United States." However, if the malaria exposure occurred when they were previously residents of another country then the "Subject's country of residence prior to most recent travel" should be their former country of residence.

During the patient interview, counsel all patients diagnosed with malaria to avoid mosquito bites during their convalescence.

CDC provides malaria consultations to clinical providers through the CDC Malaria Hotline. If we receive an inquiry from the Malaria Hotline regarding a patient who has delayed parasite clearance or who has recurrent parasitemia within 4 weeks of initial treatment, then we usually request whole blood specimens (pre and/or post-treatment) be sent to CDC for molecular surveillance. In that situation CDC will reach out to the state health department epidemiologists to coordinate specimen shipping from the hospital to the PHL and then to CDC.

For patients who are lost to follow-up, rely on medical records or healthcare provider information to complete the malaria case report. The most important task is to try to determine how malaria was acquired. If it is known that the patient traveled internationally but if all details are not known, then indicate "Yes, traveled outside the U.S.", and leave the specific country and travel dates blank. This will result in classifying the case as "Imported" with travel details "Unknown." If no information is available, then indicate that the case importation status is "Unknown."

If you have any questions or concerns about a case, including the timing of travel and illness onset, reach out to the CDC malaria surveillance epidemiologist or the CDC Malaria Hotline (after hours).

If the initial case investigation does not yield a recent travel history (in the past two years) or prior malaria illness (within 2 – 3 years), then an enhanced investigation is warranted to assess their classification as possibly cryptic or

locally acquired. If you think an enhanced investigation is necessary, please reach out to your state health department (if applicable) and the CDC Malaria Branch immediately (malaria@cdc.gov or 770-488-7788).

Enhanced investigation

For cases under enhanced investigation, a more detailed patient interview should review the risk factors for acquiring malaria, including detailed travel history, sick contacts (e.g., household members), occupation, outdoor activities:

- Ask about lifetime and recent travel to a malaria-endemic country:
    - Identify specific dates the patient was in a malaria-endemic country and the areas visited.
    - If the person previously lived in a malaria-endemic country, when did they immigrate to the U.S. or to another non-endemic country?
- Ask about prior diagnoses of malaria (in lifetime), or previous unexplained febrile illness after international travel:
    - If yes, specific dates and if (and what) treatment received?
    - If diagnosed with a relapsing species (*P. vivax* or *P. ovale*), did they receive antirelapse therapy (primaquine for 14 days, or a single dose of tafenoquine)?
- Ask about blood exposures such as blood transfusions, organ transplants, needlestick injuries, unsafe needle sharing, or home tattoos.
- Prior to illness, were there any visitors, household members, co-workers who were sick with malaria or another febrile illness?
- Has the patient been in an area where Babesia parasites are transmitted? Has the patient had a recent tick bite?
- Has the patient recently slept outdoors? Are they currently or have they recently experienced unstable housing or homelessness?

Obtain additional details from the medical record including past medical history (especially immunocompromising conditions, asplenia, and pregnancy status), recent hospitalizations and medical procedures.

Please contact CDC (CDC malaria surveillance epidemiologist or the CDC Hotline malaria@cdc.gov) for malaria diagnosed in a newborn without travel (congenital malaria). Congenital cases occurring in non-endemic settings have been reported weeks or up to two months after birth.

COMMUNICATION

Maintain consistent outreach to communities to provide education on the importance of precautions for malaria and other diseases before traveling internationally to an area where malaria occurs. Among U.S. civilians, those traveling to visit friends and relatives are the most common group to acquire malaria. Most cases of malaria in the U.S. are diagnosed following seasonal peaks in summer and winter travel. It may be prudent to provide outreach to high-risk travelers on chemoprophylaxis prevention strategies prior to these travel seasons.

There is not a malaria vaccine approved for travelers.

Educate travelers about the importance of seeking care as soon as possible if they develop a fever after travel in a country where malaria is endemic and told to notify care providers of their travel history.

Resources for providers and clinicians can be found at Home - Heading Home Healthy - Helping travelers stay healthy when they are returning home to visit friends and relatives.

Provide education to communities to prevent mosquito-borne illness, including breeding site reduction strategies.

MOSQUITO CONTROL AND SURVEILLANCE

Some U.S. jurisdictions have the capacity to conduct targeted mosquito control around the residence of every imported case of malaria. This is something that jurisdictions with resources could consider.

Although there is no national program for surveillance of *Anopheles* mosquitoes, some local mosquito control associations or local health jurisdictions have access to this information. Where it exists, *Anopheles* data on mosquito presence and abundance over time, seasonally, and geographically may inform risk for local mosquito-borne transmission.

CDC does not recommend mosquito testing for malaria under routine circumstances. However, this may be pursued in response to some local or enhanced case investigations.

RESOURCES

GENERAL

- Malaria Surveillance — United States, 2018 | MMWR (cdc.gov)
- CDC Yellow Book 2024 | Travelers' Health | CDC
- Home - Heading Home Healthy - Helping travelers stay healthy when they are returning home to visit friends and relatives.
- The Carter Center, The Life Cycle of Malaria; CDC Malaria Lifecyle

CLINICAL EDUCATION

- Malaria 101 for Healthcare Providers (CME, CNE, CEU available)
- Webinar Thursday, July 20, 2023 - Review of Malaria Diagnosis and Treatment in the United States (cdc.gov)
- Clinical Guidance: Malaria Diagnosis & Treatment in the U.S.
- Health Alert Network (HAN) - 00494 | Locally Acquired Malaria Cases Identified in the United States (cdc.gov)

INDUCED MALARIA

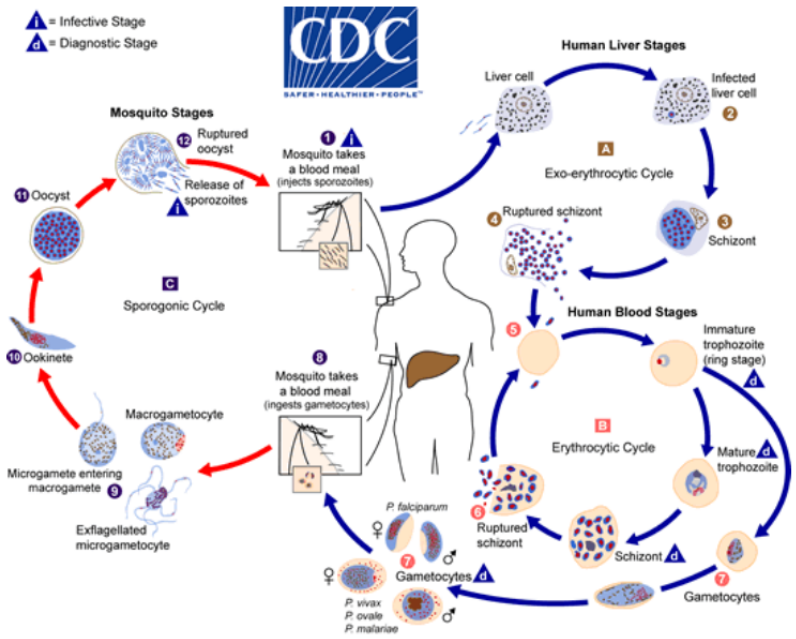
- Investigation of a Case of Suspected Transfusion-Transmitted Malaria. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6334839/
- Transfusion-Transmitted Malaria: Two Pediatric Cases From the United States and Their Relevance in an Increasingly Globalized World. https://pubmed.ncbi.nlm.nih.gov/34559236/
- Healthcare-Associated Transmission of Plasmodium falciparum in New York City https://pubmed.ncbi.nlm.nih.gov/26498730/

FOR THE PUBLIC

- Malaria is a Serious Disease (English PDF)| Spanish PDF
- Prevent Mosquito Bites | Mosquitoes | CDC
- Mosquitoes spread germs that can make you sick (cdc.gov) | Spanish PDF
- How to Protect Against Mosquito Bites (cdc.gov) | Spanish PDF
- Protect Against Mosquito Bites when Traveling (cdc.gov) | Spanish PDF
- Get Rid of Mosquitos at Home (cdc.gov) | Spanish PDF
- Mosquito Control What State and Local Mosquito Control Programs Do (cdc.gov) | Spanish PDF
- Mosquito Control: What You Need to Know About Outdoor Spraying (cdc.gov) | Spanish PDF
- Mosquito Control: What You Need to Know About Indoor Spraying (cdc.gov) | Spanish PDF
- Mosquito Control in Your Community and at Home | Mosquitoes | CDC
- Mosquito Control During an Outbreak: Why it's Important to Kill Mosquitoes NOW (cdc.gov) | Spanish PDF

Appendix A: Malaria Lifecycle

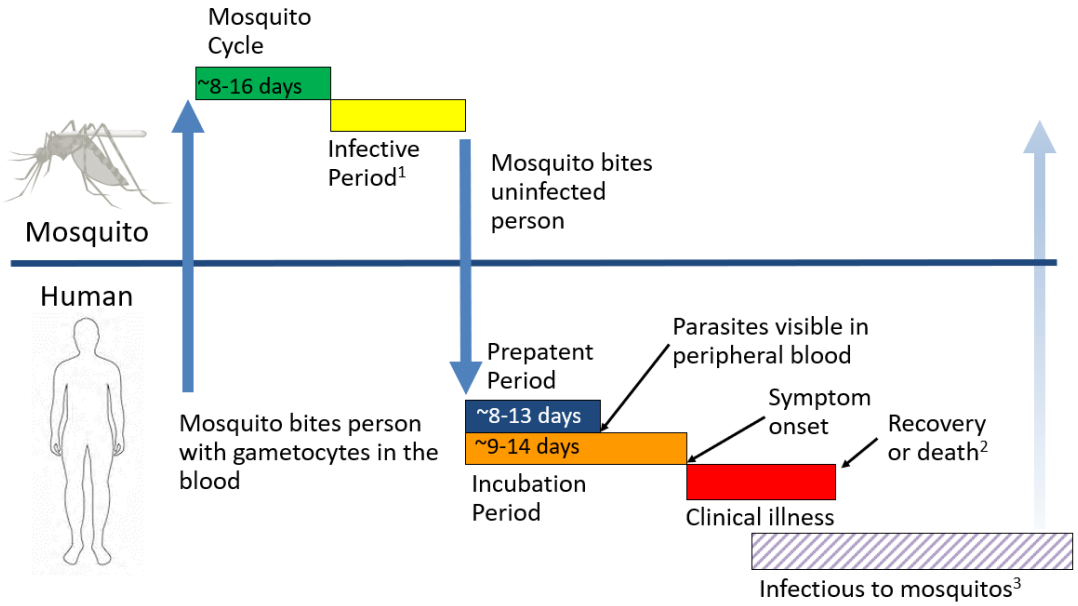
MALARIA LIFECYCLE



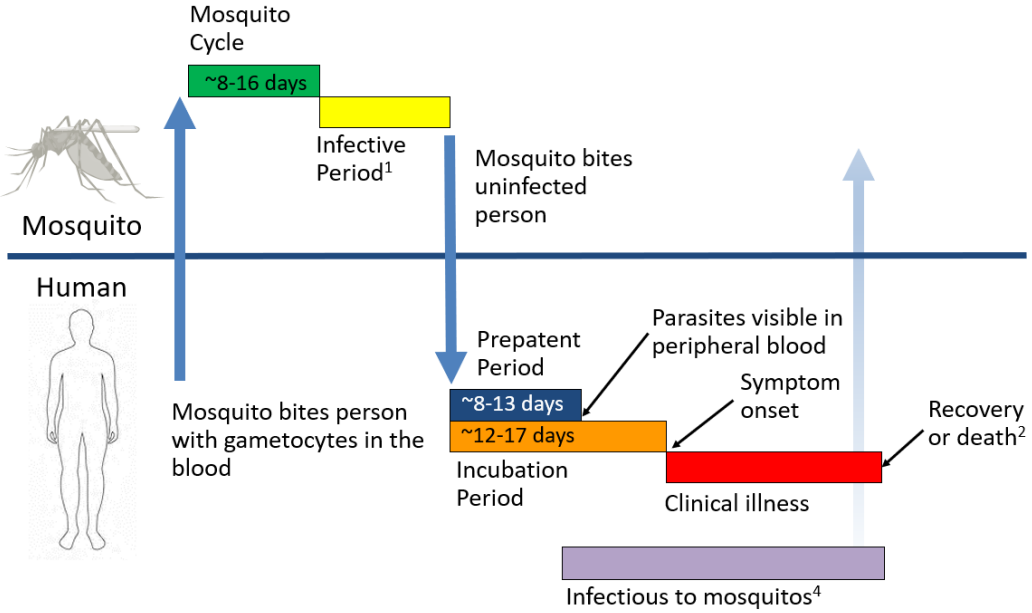
The malaria parasite life cycle involves two hosts. During a blood meal, a malaria-infected female *Anopheles* mosquito inoculates sporozoites into the human host ❶ . Sporozoites infect liver cells ❷ and mature into schizonts ❸, which rupture and release merozoites ❹. (Of note, in *P. vivax* and *P. ovale* a dormant stage [hypnozoites] can persist in the liver (if untreated) and cause relapses by invading the bloodstream weeks, or even years later.) After this initial replication in the liver (exo-erythrocytic schizogony Ⓐ), the parasites undergo asexual multiplication in the erythrocytes (erythrocytic schizogony Ⓑ). Merozoites infect red blood cells ❺. The ring stage trophozoites mature into schizonts, which rupture releasing merozoites ❺. Some parasites differentiate into sexual erythrocytic stages (gametocytes) ❼. Blood stage parasites are responsible for the clinical manifestations of the disease. The gametocytes, male (microgametocytes) and female (macrogametocytes), are ingested by an *Anopheles* mosquito during a blood meal ❽. The parasites' multiplication in the mosquito is known as the sporogonic cycle Ⓒ. While in the mosquito's stomach, the microgametes penetrate the macrogametes generating zygotes ❾. The zygotes in turn become motile and elongated (ookinetes) ❿ which invade the midgut wall of the mosquito where they develop into oocysts ⓫. The oocysts grow, rupture, and release sporozoites⓬, which make their way to the mosquito's salivary glands. Inoculation of the sporozoites ❶ into a new human host perpetuates the malaria life cycle.

TEMPORAL VIEW OF MALARIA LIFECYCLE

P. falciparum



P. vivax



1. *Anopheles* mosquitos can live up to 6 weeks after ingesting gametocytes.
2. Semi-immune individuals (visitors or recent immigrants) may have prolonged infection without overt symptoms and may not recover from malaria or die of malaria.
3. *P. falciparum* gametocytes usually appear ~7 – 10 days after symptom onset, can last up to 10 – 22 days. Blood stage treatment does not kill *P. falciparum* mature gametocytes.
4. *P. vivax* gametocytes can appear before symptom onset, during the prepatent period, and are killed with blood stage treatment.

Appendix B: Malaria Molecular Testing

MALARIA MOLECULAR TESTING

CDC has developed a laboratory method to conduct molecular testing for *P. falciparum* and *P. vivax.* This testing can help identify markers of resistance, strain relatedness, and geographic origin.

State public health laboratories are welcome to submit any malaria specimens to CDC for molecular testing; however, there are some specific circumstances where CDC is particularly interested in conducting this testing.

Cases where malaria molecular testing may be particularly useful

- Any concern of drug resistance or recrudescent illness:
    - If the case-patient was on any type of chemoprophylaxis and developed malaria
    - If the case-patient continued to have positive blood smears after completing treatment
    - If the case-patient continued to have symptoms after completing treatment (if parasite clearance is not documented)
    - Please contact malaria@cdc.gov and malarialab@cdc.gov.
- Any unusual cases under enhanced investigation
    - No history of recent travel or other risk factors
    - Concern for transfusion transmitted malaria or other blood-borne transmission
- Please contact CDC Malaria hotline (770-488-7788 or malaria@cdc.gov) if you would like to submit a specimen for a case with concern of drug resistance or under enhanced investigation.

Preferred sample type is refrigerated whole blood, treated with EDTA:

- If whole blood is not available we may be able to accept other specimens, please reach out to malarialab@cdc.gov to discuss options.
- For detailed instructions on how to send, please reach out to the malaria laboratory (malarialab@cdc.gov).

Appendix C:
Malaria Diagnosis and Treatment Quick Reference

MALARIA DIAGNOSIS AND TREATMENT QUICK REFERENCE[2]

Background

Diagnosing and treating malaria within 24 hours of healthcare presentation (ideally as soon as possible) can prevent severe disease and death and reduce the risk of ongoing local transmission.

Initial clinical evaluation and disposition

- Clinical manifestations of malaria are non-specific and include fever, chills, headache, myalgias, and fatigue. Nausea, vomiting, and diarrhea may also occur.
- **Suspect malaria and perform diagnostic testing** for febrile individuals who:
    - Report recent (weeks to 2 years) travel to a malaria-endemic country.
    - Do not have an alternative diagnosis for fever.
- If malaria is suspected in a patient, but malaria testing is not available at your facility, refer or transfer the patient immediately to a facility with malaria testing capacity.

Key diagnostic tests for malaria

- **STAT thick and thin blood smear is the gold standard.** Collect both for all suspected cases.
    - Blood smears detect parasites and determine parasite density and *Plasmodium* species. Obtain results rapidly (should not be a send-out test).
    - If the initial test is negative and suspicion for malaria is high, repeat the blood smear every 12 – 24 hours until positive, or until three tests are negative.
    - CDC can provide malaria diagnostic assistance. Contact parasiteslab@cdc.gov.
- **STAT BinaxNOW™ Malaria Rapid Diagnostic Test (RDT)[2]** can shorten the time to treatment but must be collected concurrently with a blood smear.
- **Save a pre-treatment whole blood sample (purple top, EDTA tube)** for testing by the public health laboratory if are concerned about antimalarial drug resistance/treatment failure or if malaria is in a patient with no recent international travel.

[2] Package insert for BinaxNOW Malaria test: https://www.globalpointofcare.abbott/us/en/product-details/binaxnow-malaria.html

Treatment considerations

When a blood smear or RDT is positive, start treatment immediately, consider hospitalization, and consult with infectious disease specialists. Find dosing specifics and alternative treatment regimens in CDC's treatment tables, and contact the CDC Malaria Hotline[3] if you have questions.

Treatment of the blood stage of malaria infections

- Malaria can be uncomplicated or severe. A patient has **severe disease** if they meet **ONE OR MORE** of the following criteria:
  - **Parasitemia ≥5%**
  - Impaired consciousness, coma, seizures
  - Circulatory collapse/shock
  - Acidosis
  - Pulmonary edema or acute respiratory distress syndrome
  - Acute kidney injury
  - Disseminated intravascular coagulation (DIC)
  - Severe anemia (hemoglobin <7 g/dL)
  - Jaundice (with other signs of severe malaria)
- **Treat severe malaria** with IV artesunate. Find information on how to acquire IV artesunate in the United States on CDC's malaria website.
- The **parasite's species and country of origin (a proxy for chloroquine sensitivity)** should guide drug selection (see first column in CDC's treatment tables for further guidance).
- **Treat uncomplicated malaria due to *Plasmodium falciparum* (or if species unknown)** with oral antimalarials for chloroquine-resistant malaria.
  - The preferred treatment is artemether-lumefantrine (Coartem®); atovaquone-proguanil (Malarone®) is the next best option[4].
- **Treat uncomplicated malaria due to *Plasmodium vivax* (**from most countries[5]) **or *ovale*,** with chloroquine or hydroxychloroquine. If chloroquine/hydroxychloroquine is not available, use an antimalarial drug for chloroquine-resistant malaria (e.g., artemether-lumefantrin [Coartem®]).
- **Additional treatment is needed to the eliminate the liver hypnozoites of *P. vivax* and *P. ovale*** which cause relapse malaria.

To prevent relapse of confirmed *P. vivax* and *P. ovale* malaria, treat the liver hypnozoite.

Start primaquine or tafenoquine as soon as quantitative G6PD result is available, not before.

If G6PD is normal:

- **Primaquine**: Preferred option (adult dose = 30 mg base per day x 14 days)
  - Give primaquine with food to reduce gastrointestinal side effects.
  - The total dose of primaquine determines effectiveness. When doses are missed, the patient should continue to take the same daily dose for as many days as is needed to complete the course.
  - **For patients > 70 kg, increase the dose** to 6mg/kg base total, divided into 30 mg/day doses for as many days as needed (e.g., 100 kg patient, 30 mg base for 20 days). Max daily dose 30 mg base.

[3] Email malaria@cdc.gov or call Mon – Fri, 9 am – 5 pm EST 770-488-7788 or 855-856-4713. (After hours call 770-488-7100.)

[4] Use of trade names is for identification only and does not imply endorsement by the Centers for Disease Control and Prevention/the Agency for Toxic Substances and Disease Registry, the Public Health Service, or the U.S. Department of Health and Human Services

[5] Chloroquine-resistant *P. vivax* is currently found in Papua New Guinea and Indonesia.

    - **Contraindications:** pregnant or breastfeeding women, or people with G6PD deficiency (intermediate G6PD deficiency requires dose adjustment, see below)
- **Tafenoquine**: Tafenoquine 300 mg single dose is an option for adults (only if chloroquine was given for blood stage therapy)
    - Avoid tafenoquine if the patient's weight is over 70 kg
    - **Contraindications:** <16 years of age, pregnant or breastfeeding women, or people with G6PD deficiency of any severity (G6PD activity <70%)
    - **Not recommended**: in patients with psychiatric illness

If G6PD is intermediate:

- Primaquine adjustment: 45 mg base (adult dose) per week for 8 weeks with close monitoring for hemolysis

If there is G6PD deficiency:

- Chloroquine 300 mg base (adult dose) weekly for 1 year
  Pregnant women can take Chloroquine 300 mg base weekly until delivery.