

Malaria

Investigative Guidelines

February 2021

1. DISEASE REPORTING

1.1 Purpose of Reporting and Surveillance

1. To ensure adequate treatment of cases, particularly those with potentially fatal *Plasmodium falciparum* malaria.
2. To identify case contacts who may benefit from screening or treatment, e.g., fellow travelers or recipients of blood products.
3. To identify loci of malaria acquisition among Oregon travelers.
4. To contribute adequate case reports to the national database, which, in turn, gives us a better sense of the characteristics of and risk factors for malaria in the United States.
5. Conceivably, to identify persons exposed locally and to initiate appropriate follow-up.

1.2 Laboratory and Physician Reporting Requirements

1. Laboratories, physicians, and others providing health care must report confirmed or suspected cases to the Local Health Department (LHD) within one working day of identification or diagnosis.
2. Although not required, diagnostic laboratories are encouraged to send purple-top (i.e., EDTA) whole blood specimens to the Oregon State Public Health Laboratory (OSPHL) for susceptibility testing by the Centers for Disease Control and Prevention (CDC) upon request.

1.3 Local Health Department Reporting and Follow-Up Responsibilities

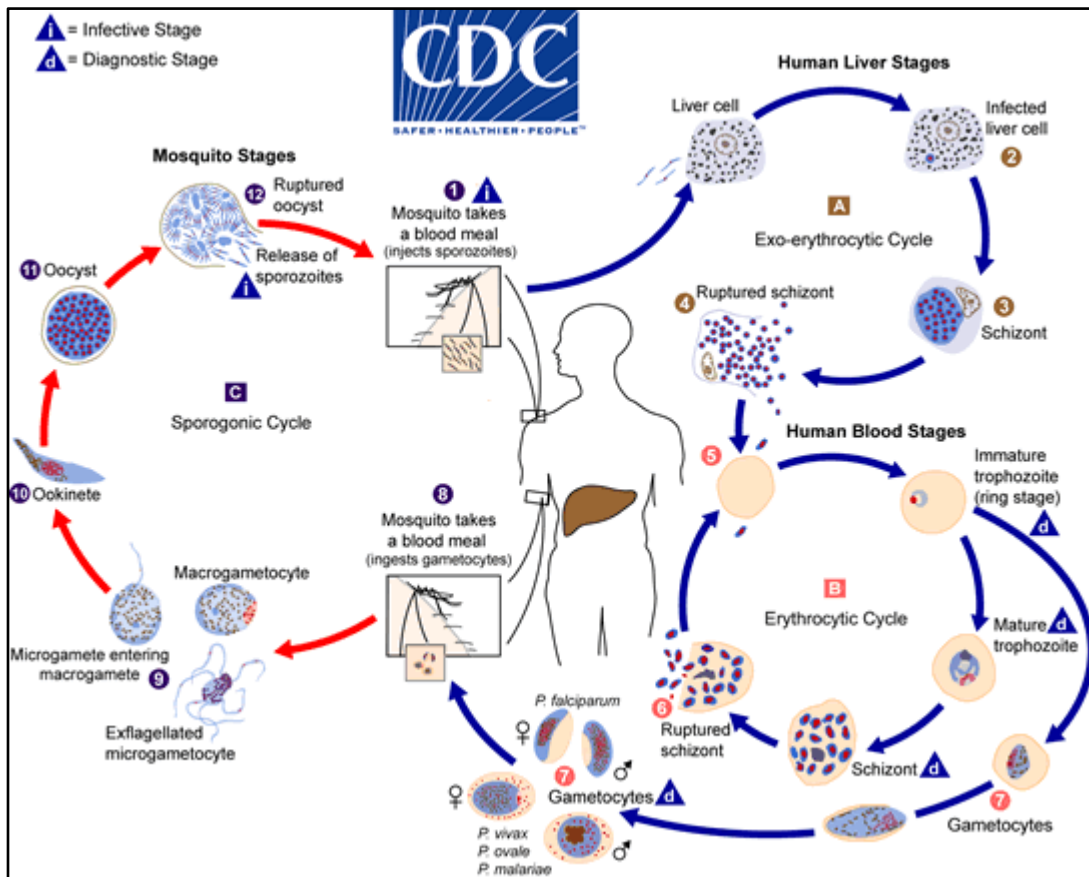
1. Report all confirmed and presumptive (but not suspect) cases (see definitions below) to the Oregon Public Health Division (OPHD) within one working day of initial physician or lab report. See §3 for case definitions.
2. Interview all confirmed and presumptive cases.
3. Identify significant contacts and educate them about the signs and symptoms of illness. Offer testing at OSPHL as appropriate. Enter all data into Orpheus by the end of the week.
4. Encourage diagnostic laboratory to send purple-top (i.e., EDTA) whole blood specimens to OSPHL for susceptibility testing by CDC. These specimens must be accompanied by the "Specimen Information for Lab Testing at the CDC" form, available at <http://bitly.com/OR-CDC-Testing>.

2. THE DISEASE AND ITS EPIDEMIOLOGY

2.1 Etiologic Agent

Malaria is caused by protozoan (one-celled) parasites of the genus *Plasmodium*. Four species commonly cause disease among humans: *P. falciparum*, *P. malariae*, *P. ovale*, and *P. vivax*. These species differ significantly in terms of clinical illness, treatment, and geographical distribution. Mixed infections are possible. Falciparum malaria most often leads to severe illness and, if not treated, death.

Malaria parasites have a complicated life cycle (Figure 1). After injection into the human host from anopheline mosquitoes, the parasites hone in on the person's liver (i.e., human liver stage), where they undergo maturation before being released into the bloodstream where they invade red blood cells. They change form, and multiply inside the red blood cells (RBCs), eventually rupturing the cells, releasing still more parasites into the bloodstream (i.e., human blood stage). This bloodstream cycle can persist for weeks to years, depending on the species involved. In vivax and ovale malaria, some parasites (hypnozoites) can persist indefinitely in the liver. Meanwhile, back in the bloodstream, some of the parasites differentiate into sexual forms (gametocytes) which, if ingested by another mosquito, can lead to the development of another generation of parasites, ready for transmission to another human host (i.e., mosquito stage).



Malaria

Figure 1: Malaria parasite life cycle. Content source: CDC Global Health – Division of Parasitic Diseases and Malaria (<https://www.cdc.gov/malaria/about/biology/>)

Other species affect other mammals, birds, and reptiles; some of these (rarely) cause human illness. Malariology is an extremely complicated field, and these guidelines provide only the briefest of overviews.

2.2 Description of Illness

The classic signs and symptoms of malaria are recurrent bouts of fever, chills, and headache. Illness may include gastrointestinal (vomiting, diarrhea) and respiratory (cough, shortness of breath) symptoms, myalgias, etc.—the gamut of “flu-like” symptoms. Fever crises classically recur at regular intervals (24 or 72 hours, depending on the species) that coincide with a synchronized rupture of RBCs with release of parasites, but this periodicity is often masked. The severity of symptoms varies with the species of parasite involved, the stage of infection, the immunological history of the patient, and other factors. Persons with recurrent exposures in endemic areas may develop “concomitant” immunity—a relative resistance to symptoms that persists only with continued exposure.

P. falciparum infections are potentially life-threatening, because the parasitemia (proportion of red blood cells infected) can increase rapidly, unpredictably, and to very high levels (>15%). Complications of inadequately treated falciparum malaria include anemia, renal failure, shock, acute respiratory distress syndrome, and acidosis. Disease caused by the other species is rarely fatal and can be quite mild.

Malaria is on everyone’s short list of the world’s biggest communicable disease problems. It kills 1–2 million people each year, and sickens and debilitates many times that number. Earlier optimism (particularly in the 1950s and 60s) about our ability to control and sharply reduce the impact of this disease has proven unrealistic, what with the advent of mosquitoes resistant to pesticides and parasites resistant to therapeutic drugs. Malaria in endemic areas is often a recurrent and usually asymptomatic or only a moderate infection among adults. Young children and pregnant women, their immune systems compromised by substandard nutrition or the pregnancy, most commonly suffer severe infections.

Not surprisingly, malaria in Oregon is not typical of malaria in the world at large. Most cases in Oregon occur among tourists, business travelers, mission workers, immigrants, and refugees.

2.3 Reservoirs

Human cases and carriers.

2.4 Modes of Transmission

Transmission occurs by the bite of infected mosquitoes of certain *Anopheles* species. These mosquito species differ enormously in their habits (e.g., breeding in still or fast-moving water, or in fresh or brackish water; feeding in the evening,

Malaria

at night, or in the daytime; living in forests or in peri-urban areas, etc.), with obvious implications for exposure risks and control measures.

Person-to-person transmission can occur through blood contact (e.g., transfusions or needle sharing), although this is rare in the United States.

2.5 Distribution of Disease

Malaria is endemic in much of the world, particularly much of the Western Hemisphere between Mexico and Peru-Bolivia-Brazil, sub-Saharan Africa, South and Southeast Asia, and parts of the Middle East and Turkey. Endemic transmission requires both a pool of infected humans and the presence of competent vector mosquitoes.

Although once common in parts of the country, malaria has become an exotic disease in the United States. Nonetheless, one should remain alert to the potential for local transmission. There are *Anopheles* mosquitoes in Oregon, but they are not very common and, more importantly, not very effective vectors for human malaria. All cases reported in Oregon in recent years have resulted from exposure abroad.

2.6 Incubation Period

Differs by *Plasmodium* species: 9–14 days for *falciparum*; 18–40 days for *malariae*; 12–18 days for *ovale* and *vivax*. The incubation period can be extended, however, by concurrent drug intake and immunological history.

2.7 Period of Communicability

Although malaria parasitemia can sometimes last for years, the disease is not spread directly from person to person, absent significant blood exposure. *Plasmodium* parasites must generally undergo developmental changes in a competent mosquito vector before being passed back to another human; this takes between a week and a month.

2.8 Prophylaxis

Local health department staff are often asked about malaria prevention. Good information is available at many travel clinics and on CDC's web page, including country-specific recommendations (www.cdc.gov/malaria/travelers/country_table/a.html). The risk of malaria is not uniform within most countries because of climate, geography, mosquito control efforts, and other factors, and traveler risk will vary with the style of travel and with the season. CDC's on-line *Yellow Book* (wwwnc.cdc.gov/travel/page/yellowbook-home-2014) is perhaps the best general source of up-to-date information.

Despite decades of effort, no vaccine is available. Prophylaxis consists in taking three measures: avoiding mosquito bites, primary chemoprophylaxis, and preventing recurrence of symptoms down the road.

1. Avoiding Mosquito Bites

Malaria

Staying in well-constructed, air-conditioned buildings, using window or door screens or closing windows and doors at night, and sleeping under an insecticide-treated mosquito net can greatly reduce the risk of being bitten. Travelers should wear long pants and long-sleeved shirts and use insect repellent when mosquito exposure can be anticipated. Repellents that contain DEET, IR3535, or Icaridin are the most effective.

2. Chemoprophylaxis

Chemoprophylaxis (i.e., antibiotics) provides the backstop needed when bite prevention is imperfect — as it always is. Many effective medicines are available in the U.S. and even more elsewhere. Weighing their relative merits and side effects can be complex; consult the *Yellow Book* or a travel expert for individualized advice. Don't wait until the last minute; most drugs should be started before and continued a while after the likely exposure period.

3. Preventing Recurrences

Hypnozoite forms of *P. ovale* and *P. vivax* can be sequestered in the liver and emerge weeks or months after an initial attack to cause a relapse. Drugs used to treat symptomatic disease (i.e., to kill the intraerythrocytic parasites) are not effective against hypnozoites. Therefore, to prevent relapse (which is not a certainty, but a possibility), primaquine is generally indicated for persons who have had an attack of *ovale* or *vivax* malaria. Be aware, however, that there are some contraindications to primaquine use (e.g., G6PD deficiency).

2.9 Treatment

Treatment is complicated by issues of parasite resistance and, to a lesser extent, side effects, and drug availability. Many drugs that are available overseas are not available here; some of them are good.

Treatment of falciparum malaria is more complicated, because of widespread resistance to chloroquine, and, increasingly, mefloquine. Artemisinin-based combination therapy is often the treatment of choice, but an ID consult is generally indicated to get up-to-date treatment recommendations. Because of the potential for rapid clinical deterioration, clinicians should strongly consider admitting patients with falciparum malaria, at least until the success of therapy is assured. Severely ill patients are typically treated with IV artemisinin in an ICU setting. Side effects can be severe and themselves life-threatening.

3. CASE DEFINITIONS, DIAGNOSIS, AND LABORATORY SERVICES

3.1 Confirmed Case Definition

Any person, whether symptomatic or asymptomatic and regardless of whether the person experienced previous episodes of malaria while outside the country, diagnosed with *Plasmodium* infection by a competent U.S. laboratory by one of the following methods:

1. Detection of *Plasmodium* species by microscopy on blood films; or

Malaria

2. Detection of *Plasmodium* species by nucleic acid test. (Note: confirmatory PCR tests must fulfill requirements, including validation studies, of the Clinical Laboratory Improvement Amendments).

Note that parasites are not always readily detectable in every specimen; repeat specimens at 8-hour intervals increases sensitivity. Speciation of parasites can be difficult, although it is often possible to rule out *P. falciparum*.

3.2 Presumptive Case Definition

Any person, whether symptomatic or asymptomatic and regardless of whether the person experienced previous episodes of malaria while outside the country, in whom *Plasmodium* species is detected by rapid diagnostic antigen testing, without confirmation by microscopy or nucleic acid testing at a competent U.S. laboratory.

3.3 Suspect Case (*not reportable to OPHD*)

Persons with fever, chills, and headache and a history of recent travel to an endemic area. Such persons need medical evaluation. If they are epi-linked to someone with a *P. falciparum* infection, this should be done immediately.

Persons who only have results from non-U.S. labs should also be considered suspect cases.

3.4 Services Available at the Oregon State Public Health Laboratories

OSPHL can confirm the identification and speciation of malaria parasites on blood smears. Although not required, if the private lab is unable to identify the species, they should be strongly encouraged to submit specimens to OSPHL for specific diagnosis.

If diagnostic laboratories send purple-top (i.e., EDTA) whole blood specimens to OSPHL for susceptibility testing, OSPHL will forward specimens to CDC. These specimens must be accompanied by the "Specimen Information for Lab Testing at the CDC" form, available at <http://bitly.com/OR-CDC-Testing>.

4 ROUTINE CASE INVESTIGATION

4.1 Basis of Diagnosis

Labs are sometimes unable to speciate the parasites seen on blood smear. Even if no specific identification was made, it is often possible to rule out *P. falciparum*; check laboratory results for speciation results. Encourage submission of the smears to OSPHL.

4.2 Clinical Details

Clinical details are sought so that the severity of individual cases and the overall burden of illness can be characterized. Most of the severe complications listed in Orpheus only occur with *falciparum* infections.

4.3 Potential Exposures

Most of the questions in Orpheus are self-explanatory. They are tailored for U.S. residents who were traveling or living abroad during the likely exposure period, and may be more or less relevant for persons with other exposures. Assess as best you can the consistency with which prophylactic measures were used.

Epilinks are rarely a big deal, but if a case travelled with family, friends, or some kind of group, a diagnosis of malaria in one may suggest a similar risk for the others. Assess the health of family members or fellow travelers who shared the overseas exposures. Persons with possible falciparum exposure should receive particularly close scrutiny.

If the patient has not been out of the United States during the preceding month, or if things don't seem to make sense, contact OPHD immediately.

Here are some possibilities in cases without recent travel:

1. This may be a *relapse* of a previous infection. “Relapse” has a technical meaning for malaria — i.e., a reseeded of the bloodstream from hypnozoites in the liver. This only happens with *ovale* or *vivax* malaria, and implies that the case was infected at some point but inadequately treated or treated only for bloodstream parasites. Primaquine is the only drug that kills the liver-stage parasites; it should be given in addition to whatever is used to treat bloodstream parasites.
2. This may be a recrudescence of a previous infection, meaning that the case had a low-level asymptomatic parasitemia that “blossomed” to cause the current illness. Although there are no long-term liver-stage parasites in these infections (and hence no need for primaquine), such silent infections can persist for 6–18 months or more with *P. falciparum* and decades for *P. malariae*.
3. They may have been infected by direct inoculation of contaminated blood or blood products (e.g., transfusions, needle sharing). Consult with OPHD about this possibility.
4. They may have been infected by mosquito bite, but not in an endemic area. This is another potential hot button. So-called “airport malaria” can occur if infective mosquitoes survive travel on a plane from an endemic area and then fly off and bite people within a few miles of the airport. Oregon doesn't have many flights directly from endemic areas; this is more likely to happen near larger international airports. A most unlikely final possibility is that the infection was acquired via bite from an Oregon *Anopheles* mosquito; this would get OPHD more than a little interested!

5. CONTROLLING FURTHER SPREAD

Regardless of the locus of acquisition, persons with malaria could pass the parasites to another *Anopheles* mosquito if bitten; and following development in the mosquito host, the stage could be set for another round of transmission to humans within Oregon. This kind of transmission has been documented numerous times in California, including an outbreak at a Girl Scout camp in the

Malaria

1960s, and more recently transmission among migrant workers living in squalid encampments near San Diego. Although *Anopheles* mosquitoes can be found in Oregon, local transmission is an unlikely scenario.

As with other mosquito-borne diseases, people infected with malaria should be protected from further mosquito exposure during the first few days of illness to prevent local mosquitoes from becoming infected. Infected persons should also be reminded never to share needles.

5.1 Isolation and Work or Day Care Restrictions

None.

5.2 Case Follow-up

Generally not indicated.

5.3 Protection of Contacts

Not applicable.

5.4 Environmental Measures

None, unless Oregon transmission is suspected.

6. MANAGING SPECIAL SITUATIONS ⁴

6.1 Undertreated Falciparum Case

The high prevalence of chloroquine resistance among *P. falciparum* parasites, as well as the potential severity of the illness, makes chloroquine alone usually a poor choice for therapy. Chloroquine does have some analgesic properties, however, so depending on the level of resistance, it may knock down parasite levels sufficiently or at least make the patient feel better for a while, masking potential treatment failure. If you hear about a *falciparum* case that was treated with chloroquine, verify the treatment information with the patient's physician. Consult with OPHD epidemiologists immediately if the story appears to be true.

6.2 No Recent Travel to Endemic Areas

Consult with OPHD epidemiologists immediately about any case that does not have a history of recent travel to a malarious area. We will discuss the options and develop a plan.

UPDATE LOG

February 2021: Updated reporting timeline from one week to one working day (Ama Owusu-Dommey, Stephen Ladd-Wilson)

November 2016: Case definitions were modified to be in line with CSTE national notifiable disease case definitions, treatment recommendations were reviewed and updated (Meredith Jagger, June Bancroft)

November 2015: Reviewed and in new template (June Bancroft, Leslie Byster)

Malaria

December 2000: Investigative Guidelines written (Bill Keene)