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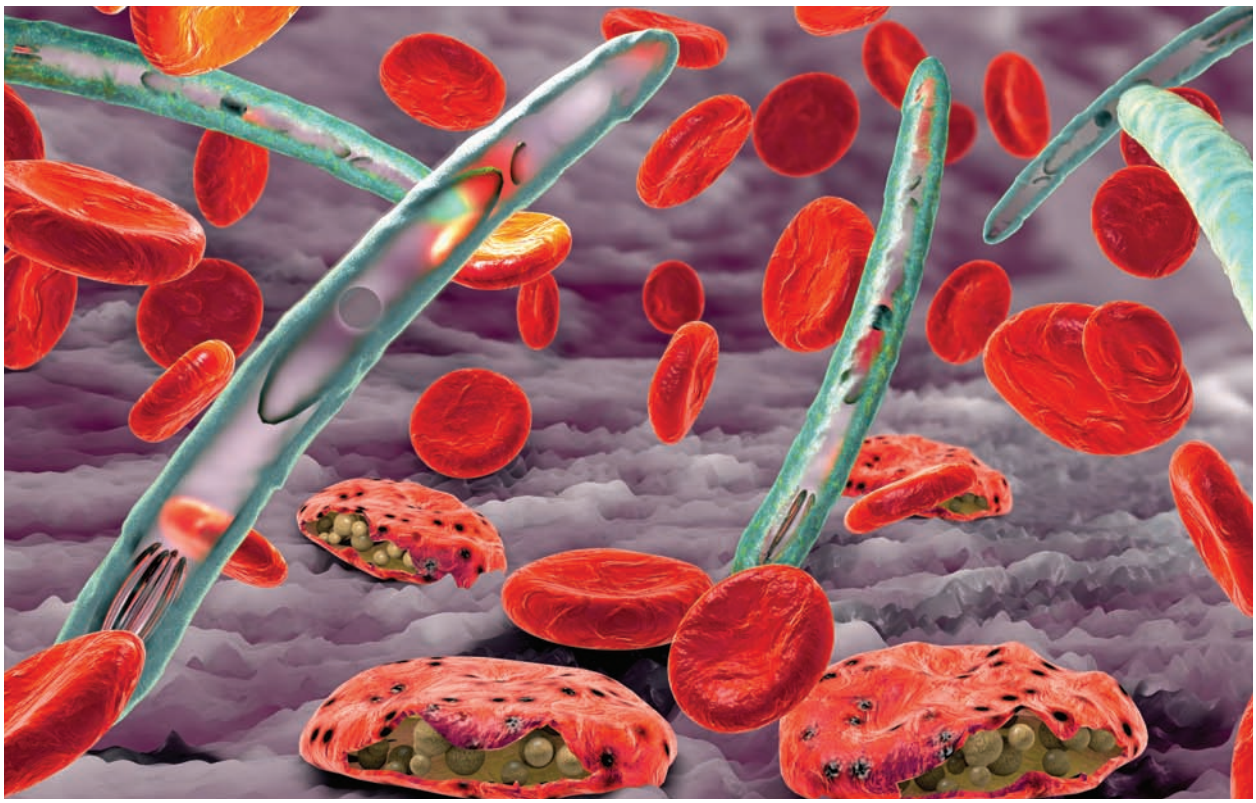

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Preventing malaria spread in the US

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Abstract: Locally acquired malaria is rare in the US; however, in 2023, cases were reported in Florida, Texas, Maryland, and Arkansas. Prompt diagnosis and treatment of malaria are essential to prevent severe malaria disease. This article details malaria and offers treatment guidelines.

Keywords: anopheles mosquito, malaria, *Plasmodium vivax*, prophylaxis, treatment

Between May and October 2023, the CDC and respective state health authorities reported 10 cases of locally acquired malaria in the US.[1-6] The cases were unrelated to travel to malaria-endemic areas and were not related to each other. There were seven cases of *Plasmodium vivax* (*P. vivax*) malaria in Sarasota County, Florida, one case of *P. vivax* malaria in Cameron County, Texas, one case of *Plasmodium falciparum* (*P. falciparum*) malaria in a Maryland resident living in the National Capital Area, and one case of *P. vivax* in Saline County, Arkansas. All patients were treated and recovered.

Investigators conducted surveillance and enacted mosquito control measures in the affected areas. No additional locally acquired malaria cases have been reported in the US as of December 2023.

Notably, the risk of locally acquired malaria remains low in the US.[1,3] Before the 2023 cases, the last locally acquired mosquito-borne malaria in the US occurred in 2003, with eight cases of *P. vivax* reported in Palm Beach County, Florida.[1,3]

Malaria is a preventable and treatable disease; rapid identification and treatment are essential to prevent severe malaria. This article details

malaria and offers identification, prevention, and treatment guidance for nurses.

Epidemiology

Malaria is a serious and potentially deadly disease caused by a protozoan *Plasmodium* parasite. Four species of *Plasmodium* infect humans, the only known reservoirs.[7] *P. falciparum* is the most dominant species, followed by *P. vivax*, *Plasmodium ovale (P. ovale)*, and *Plasmodium malariae (P. malariae)*. *Plasmodium knowlesi* (*P. knowlesi*) is a zoonotic parasite that infects macaques in Southeast Asia but can be transmitted from animals to humans via the *Anopheles* mosquito.[7-9] *P. falciparum* and *P. vivax* are responsible for most malaria cases. *P. falciparum* is dominant primarily in sub-Saharan Africa and the most deadly; *P. vivax* is dominant outside sub-Saharan Africa.[9]

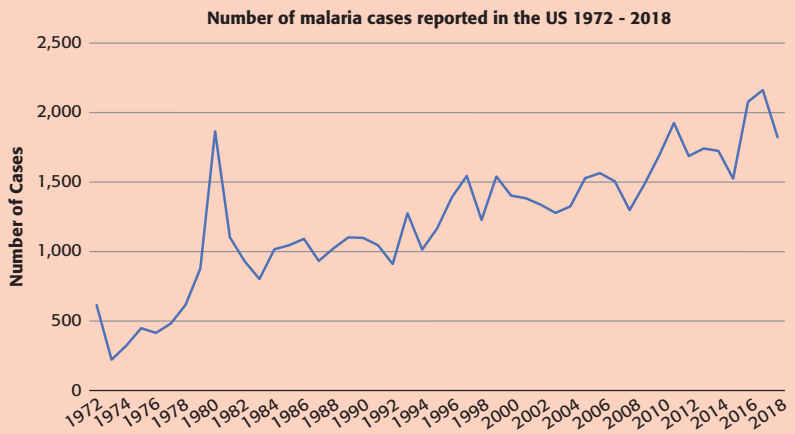
Malaria is primarily noted in tropical and subtropical areas with warm temperatures (≥30 °C or 86 °F), humidity, and sufficient rainfall to support the survival of the *Anopheles* mosquito.[10] In 2022, an estimated 249 million cases of malaria were reported globally in 85 countries and 608,000 people died of malaria, mostly children in sub-Saharan Africa.[9] There was an increase in malaria cases and deaths from 2020 through 2021 due to disruptions in malaria prevention interventions during the COVID-19 pandemic.[11]

Malaria is not endemic in the US. The number of malaria cases reported in the US has increased since the mid-1970s (see *US malaria cases 1972-2018*).[12] More than 99% of the approximately 2,000 malaria cases diagnosed in the US annually are related to travel from a malaria-endemic area.[1,2,12]

In 2018, 92% of severe malaria infections in the US were caused by *P. falciparum*, 6% by *P. vivax* or *P. ovale*, and 2% by other species, or mixed infections.[2,12] About 300 people in the US experience severe malaria disease due to *P. falciparum* annually; likewise, between 5 and 10 people die from the infection each year.[1]

Ninety-five percent of US persons with travel-related malaria failed to complete recommended malaria prophylaxis before, during, and after traveling.[1,2,12,13] Some have stated that they lacked the knowledge or understanding about malaria prevention, were concerned about or had experienced prophylaxis adverse reactions, delayed prophylaxis due to other medications during travel, regarded prior exposure as sufficient immunity, or that they instead chose homeopathic remedies for malaria.[12,13]

US malaria cases 1972-2018[12]



Number of malaria cases among US civilians, US military personnel, and non-US residents—1972-2018.

Transmission

Malaria is primarily vector-borne and transmitted via the female *Anopheles* mosquito (see *Malaria life cycle*).[1-9,14] The female *Anopheles* mosquito bites a person or animal with malaria parasites in the blood. The parasite is ingested by the mosquito, travels to and matures in the mosquito's gut for 10 to 18 days, then moves to her salivary glands, where it is injected into another human or animal as she takes a blood meal.

In the new human host, the parasite migrates to the liver, where it multiplies, then moves into the red blood cells and continues to multiply. Signs and symptoms develop in the new host during this blood phase.[14]

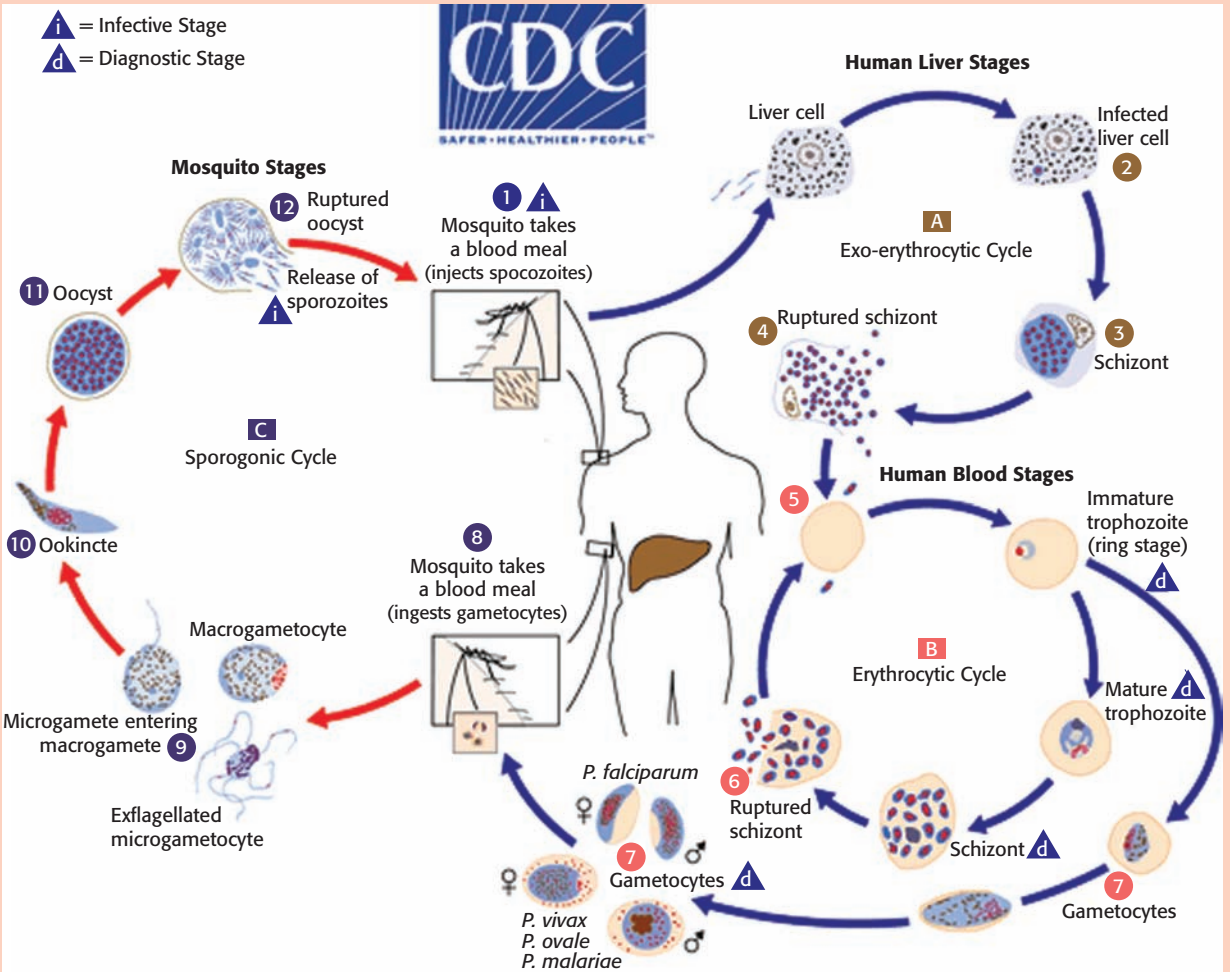
Rarely is malaria transmitted without the mosquito vector.[15-17] However, malaria parasites can be transmitted via organ transplantation, shared needles, blood transfusions, or from infected mother to child during pregnancy or delivery.[15-18] An average of one case of transfusion-transmitted malaria is reported every 2 years in the US.[15]

Individuals who lived in malaria-endemic areas or were diagnosed with malaria within the previous 3 years are generally deferred from donating blood due to the concern for dormant parasites in the liver.[15,16] Individuals who traveled to an area with malaria may be deferred for 3 months to 1 year after their return.[15-18]

Incubation period

The incubation period, or time from the bite of the infectious mosquito until the onset of signs and symptoms, varies by species of *Plasmodium* but averages from 10 days to 4 weeks (see *Plasmodium incubation periods*).[1,7] *P. vivax* and *P. ovale* can remain dormant in the liver and result in relapsing malaria infection unless

Malaria life cycle[14]



A. Exo-erythrocytic Cycle
(1) Malaria-infected female *Anopheles* mosquito inoculates sporozoites into the human host. (2) Sporozoites infect liver cells and mature into schizonts (3), which rupture and release merozoites (4). (In *P. vivax* and *P. ovale*, a dormant stage [hypnozoites] can persist in liver if untreated and cause relapses by invading bloodstream weeks, or even years later.)

B. Erythrocytic schizogony Cycle—asexual multiplication in the erythrocytes
(5) Merozoites infect red blood cells. Ring-stage trophozoites mature into schizonts, which rupture releasing merozoites (6). Some parasites differentiate into sexual erythrocytic states (gametocytes) (7). Blood-stage parasites are responsible for clinical manifestations of the disease. The gametocytes, males (microgametocytes) and female (macrogametocytes), are ingested by an Anopheles mosquito during a blood meal. (8)

C. Sporogonic Cycle—parasite multiplication in the mosquito
(9) While in the mosquito's stomach, the microgametocytes penetrate the macrogametocytes generating zygotes. Zygotes become motile and elongated (ookinetes) (10) which invade the midgut wall of the mosquito where they develop into oocysts (11). The oocysts grow, rupture, and release sporozoites (12), which make their way to the mosquito's salivary glands. Inoculation of the sporozoites (1) into a new human host perpetuates the malaria life cycle.

treated with additional antimalarial drugs specific for those species.[1,2,7]

Cases in the US

Anopheles mosquitoes can be found in most US states and territories, so local transmission is possible; however, local climate conditions may not favor mosquito survival or parasite development.[10,12,14,15] Temperatures lower than 68 °F (20 °C) for *P. falciparum* and 59 °F (15 °C) for *P. vivax* are too low for parasite development in the mosquito.[14] *P. vivax* species can better survive in temperate climates in the southern US states, especially during summer.

Risk factors

Anyone bitten by a mosquito infected with *Plasmodium* can develop malaria; however, the highest risk for acquiring malaria infection exists in malaria-endemic areas.

People with the highest risk for severe malaria include those subject to repeated bites by infected mosquitoes and people with little or no immunity to malaria, such as children younger than 5 years of age, pregnant women, or travelers from areas with no malaria.[1,7,11,17,19]

Malaria is especially troublesome during pregnancy. As with other immune responses, prior immunity to *P. falciparum* is suppressed during

pregnancy.[14] In addition, malaria parasites can hide and replicate in the placenta, leading to difficulty in clearing malaria infection.[20] Possible complications of malarial infection during pregnancy include maternal anemia, premature delivery, a low baby birth weight, congenital malaria infection, miscarriage, stillbirth, or maternal death.[7,11,14,20]

Since malaria is not endemic in the US, the CDC considers all US residents to be nonimmune and, therefore, at risk for severe disease if infected.[2]

In malaria-endemic areas, repeated exposure to bites by malaria-infected mosquitoes over time may provide short-lived partial immunity to malaria and severe disease.[7,12,19] This naturally acquired immunity wanes when individuals are no longer regularly exposed to malaria infection, such as when they leave the malaria-endemic area.[12,19] Individuals who have been away from the malaria-endemic area for at least 6 months are at risk for malaria upon return to the malaria-endemic area.[12,21,22]

Clinical manifestations

Initial signs and symptoms of malaria are nonspecific and may mimic other infections, such as influenza.[1,4,7,9] Frequently reported signs and symptoms associated with malaria include fever, chills, headaches, myalgia, cough, tachypnea, nausea, vomiting, and diarrhea. If treatment is delayed, malaria can progress to severe disease and death. Clinical findings associated with severe malaria include altered mental status, seizures, severe anemia, respiratory distress, severe fatigue, dark urine, jaundice, renal failure, and multiorgan failure.[7,9,12,17,19,23]

Plasmodium incubation periods[7]

Plasmodium species	Incubation period[a]
P. falciparum	6-14 days
P. vivax (can be dormant in the liver and relapse if not treated)	12-18 days; some strains in temperate areas may have longer incubation period of 6-12 months
P. ovale (can be dormant in the liver and relapse if not treated)	12-18 days
P. malariae	18-40 days
P. knowlesi (zoonosis)	9-12 days

[a]All species can have longer incubation periods of weeks to months. The incubation period of infection acquired via blood transfusion depends on the number of parasites infused and is usually short but may be up to 2 months.

Diagnosis

Malaria diagnosis is based on symptoms, physical findings, and lab tests specific to malaria.[1,4,7,12,24,25] Obtaining a travel history should be standard procedure.

In the US, malaria is a medical emergency because US residents are considered at high risk for severe disease if infected.[1,2] Persons suspected of having malaria should be urgently evaluated in a facility that can provide rapid diagnosis and treatment within 24 hours of presentation.[1,4,11,19]

Clinicians should consider the diagnosis of malaria in anyone with an undetermined febrile illness, especially if the person traveled to a malaria-endemic area within the weeks to 12 months before symptom onset.[17]

The gold standard test for malaria is a microscopic examination of thick and thin blood smears stained with a Giemsa stain to distinguish malaria parasites by morphology.[12,20,24,25] Thick blood smears can indicate the presence of malaria parasites; thin blood smears allow investigators to observe parasite morphology—to identify the species—and parasite density (the percentage of infected red blood cells, an indicator of disease severity).

Rapid diagnostic tests (RDTs) for malaria antigen results must be confirmed by microscopic examination of thick and thin blood smears. RDTs may reduce diagnostic time by indicating the presence of malaria parasites in the blood, but RDTs cannot provide specific parasite species or parasite density.[12,23-25]

Malaria parasites can be detected by polymerase chain reaction (PCR), but the results may not be available quickly. PCR testing for malaria is not routinely recommended for initial diagnosis of infection.[23-25]

Serology, such as an indirect immunofluorescence or enzyme-linked immunosorbent assay, can detect antibodies against malaria parasites; however, these antibodies only indicate exposure, not infection. Serology testing for malaria diagnosis is not recommended.[23-25]

Other lab studies, such as complete blood cell counts and chemistry panels, help determine disease severity complications. Lab abnormalities associated with malaria may include anemia, thrombocytopenia, hyperbilirubinemia, and elevated serum transaminases. Lab values may be normal or mildly elevated in uncomplicated (nonsevere) disease to very abnormal in severe disease.[1]

Malaria hotlines[31-33]

CDC Malaria Hotlines for clinician guidance for diagnosis and treatment of malaria[20]	
M-F; 9 a.m.–5 p.m. EST	770-488-7788 or 855-856-4713
Emergency after hours	770-488-7100
Web link	www.cdc.gov/parasites/contact.html

Treatment

Diagnosis of malaria should be confirmed before initiating treatment.[20]

In nonendemic areas such as the US, hospitalization is recommended due to the risk of severe disease in nonimmune persons (see *Malaria hotlines* and *Severe malaria criteria*).[1,2,4,12,20]

Oral antimalarial medications should be started immediately for patients who do not meet the criteria for severe malaria.[20] Medication selection is based on *Plasmodium* species and the species' drug resistance patterns. The first-line drug of choice for uncomplicated (nonsevere) *P. falciparum* or unknown species is artemether-lumefantrine.[20] It is the fastest-acting oral antimalarial combination, is well tolerated, and can be used for all patients including pregnant persons in all stages of pregnancy.[26]

If artemether-lumefantrine is unavailable, atovaquone-proguanil is effective against all *Plasmodium* species, including *P. falciparum*. However, it should not be used during pregnancy (due to limited data) and in those who have developed malaria after taking atovaquone-proguanil as prophylaxis for malaria. Atovaquone-proguanil should not be used in individuals with known hypersensitivity reactions, such as anaphylaxis, erythema multiforma, Steven-Johnson syndrome, angioedema, and vasculitis; allergy to any drug component; or severe kidney disease (creatine clearance less than 30 mL/minute).[22,27,28]

Treatment options in the aforementioned situations include quinine sulfate plus doxycycline, tetracycline, and clindamycin or mefloquine; however, these are usually less well tolerated.[20] Mefloquine has been associated with severe neuropsychiatric adverse events when used at a treatment dose and is generally recommended when no other treatment option is available.[20] Doxycycline is usually not indicated in pregnant women unless other treatment options are not available.[20]

Most non-*falciparum Plasmodium* species are susceptible to chloroquine or hydroxychloroquine.[20] Once species and country of origin are confirmed, these agents may be treatment options for *Plasmodium* species other than *P. falciparum*.

If the malaria species is *P. vivax* or *P. ovale*, additional treatment is necessary to eradicate the parasites from the liver to prevent dormancy and relapsing infection. Antimalarial agents against *P. vivax* and *P. ovale* are primaquine and tafenoquine.[20] A glucose-6-phosphate-dehydrogenase (G6PD) activity assay is mandatory before starting either of these drugs (see *G6PD deficiency*).[20,29] To prevent hemolytic anemia, persons with abnormal G6PD activity should be treated with an alternative drug. Even if G6PD is normal during pregnancy, the patient should be treated as G6PD deficient to protect the fetus whose G6PD enzyme activity cannot be measured.

Patients in the US with severe malaria should receive supportive care in the ICU and receive I.V. artesunate immediately.[1,3,20,30]

I.V. artesunate is the only I.V. antimalarial for severe disease in the US. It is effective against all species of *Plasmodium* and can be used in all trimesters of pregnancy since the benefit of treatment outweighs the risk.[30] The only contraindication is allergy to drug components.[2,20,30] If I.V. artesunate is not immediately available, oral artemether-lumefantine should be administered while acquiring I.V. artesunate or the patient should be transferred to a facility with a supply of I.V. artesunate. I.V. artesunate treatment can continue for up to 7 days.[20,30]

The patient's response to therapy should be monitored by repeating thick and thin blood smears every 12 to 24 hours. Thick and thin blood smears should be drawn 4 hours after the last dose and repeated until 0% parasite density is reached. Once the blood smear indicates that the parasite density is reduced to at least 1% and the patient can tolerate oral treatment, a full treatment course with an oral antimalarial regimen should be completed. This regimen should begin 4 to 24 hours after the last dose of

G6PD deficiency[17,23,29,34,35]

Glucose-6-phosphate-dehydrogenase (G6PD) is an enzyme in the cytoplasm of all cells in the body. Its role is to provide substrates to prevent cell damage caused by reactive oxygen species. G6PD deficiency can result in acute severe hemolytic anemia during increased reactive oxygen species production, such as stress or exposure to foods or medications containing high levels of oxidative substances. Some antimalarial agents are known to cause hemolytic anemia in patients with G6PD deficiency. Primaquine and tafenoquine are two antimalarial drugs that are contraindicated for individuals with G6PD deficiency.

Severe malaria criteria[2,12,30]

- Parasitemia (parasite density) ≥5%
- Impaired consciousness, including seizure and coma
- Shock or circulatory collapse
- Acidosis
- Hypoxia, pulmonary edema, or acute respiratory distress syndrome
- Acute kidney injury
- Disseminated intravascular coagulation
- Severe anemia (hemoglobin less than 7 g/dL). Normal hemoglobin level for males is 14-18 g/dL and for females, range is 12-16 g/dL.

artesunate.[20,30] For all patients with malaria, an urgent infectious-disease consult is recommended.[31-33] The CDC and public health authorities are available for consultation if needed.

Prevention

Malaria is prevented through prophylaxis and vector control for travel to malaria-endemic areas. Individuals should complete the full course of prophylaxis as recommended (see *Malaria prophylaxis*).[12,23,24,34,35]

Avoiding mosquito bites and eliminating mosquito breeding sites, such as standing water, prevent transmissions.[23] Screens may be placed on windows and doors, especially during mosquito feeding hours (dusk to dawn). One may sleep under mosquito netting treated with insecticide.

Clothing and insect repellant containing N,N-diethyl-m-toluamide or N,N-diethyl-3-methyl-benzamide (DEET), picaridin, 3-[N-butyl-N-acetyl]-aminopropionic acid, ethyl ester (IR3535), or lemon eucalyptus oil

Malaria prophylaxis[34,35]

Drug	Reasons to consider this drug	Reasons to avoid this drug
Atovaquone/ Proguanil (Malarone)	• Requires starting drug only 1 to 2 days before travel to a malaria-endemic area. • Daily medicine. • Taken for 7 days after travel. • Well tolerated; adverse reactions uncommon. • Pediatric tablets available.	• Can not be used during pregnancy or breastfeeding a child under 5 kg (11.02 lb). • Can not be taken by people with severe renal impairment. • May be more expensive than other options. • Some people may prefer not to take daily medication.
Chloroquine	• Weekly medication. • Good choice for longer trips since weekly medication (taken on the same day each week). • Some people may already be taking hydroxychloroquine chronically for rheumatologic conditions, so may not have to take an additional medicine. • Can be used in all trimesters of pregnancy.	• Can not be used in areas with chloroquine or mefloquine resistance. • May exacerbate psoriasis. • Some people may prefer not to take weekly medication. • Must continue medication for 4 weeks after travel. • Must be started 1 to 2 weeks before travel.
Doxycycline	• Daily medication. • Requires starting drug only 1-2 days before travel to a malaria-endemic area. • Tends to be the least expensive antimalarial. • Some people take doxycycline chronically for acne, which may suffice for malaria prophylaxis. • Doxycycline can prevent some additional infections, such as Rickettsiae and leptospirosis. It may be preferred by people planning to hike, camp, and wade or swim in freshwater.	• Can not be used by pregnant women and children under 8 years old. • Some people prefer not to take daily medication. • Must take medication for 4 weeks after travel. • May induce vaginal yeast infections. • May increase sun sensitivity. • Potential for dyspepsia.
Mefloquine	• Weekly medication. • Can be used during pregnancy.	• Some regions contain mefloquine-resistant malaria. • Contraindicated in those with psychiatric conditions and seizure disorders. • Contraindicated in persons with a cardiac conduction abnormalities. • Must be started at least 2 weeks before travel. • Must take medication for 4 weeks after travel.
Primaquine	• Highly effective against *P. vivax.* • Only need to take for 7 days after travel. • Only need to start drug 1 to 2 days before travel. • Daily medication.	• Contraindicated in those who have not been tested for G6PD deficiency, with G6PD deficiency and, during pregnancy, and during breastfeeding if the infant has not been tested for G6PD deficiency. • Some may prefer not to take daily medication. • Concern for dyspepsia from primaquine.
Tafenoquine (adults only)	• Highly effective against *P. vivax;* also prevents *P. falciparum.* • Weekly dose. • Only need to start the drug 3 days before travel. • Upon return, only taken for 1 week afterward.	• Contraindicated in children, those who have not been tested for G6PD deficiency, those with G6PD deficiency, and during pregnancy and breastfeeding. • Not recommended in those with psychotic disorders.

Patient education resources

Topic	Resource and reference number
Malaria - general information	• Malaria FAQs. #17 • Malaria is a serious disease. #23
Mosquito avoidance and vector control	• Malaria FAQs. #17 • Malaria is a serious disease. #23 • Insect repellants help prevent malaria and other diseases spread by mosquitoes. #36
Travel to malaria transmission areas	• General travel health information US. #43 • Travel information related to malaria with links to specific information. #42 ◦ Malaria travelers risk assessment (items to discuss with patient prior to travel). #43 ◦ Info about medications for malaria prophylaxis. #34,35 • Information for immigrants from malaria-endemic countries planning to return for visit. #7
Information to address preventing malaria during travel, for example, myths, misunderstandings about prophylaxis	• Stories shared with CDC by people who had malaria. #13

should deter mosquitos.[36] Sunscreen should be applied before repellant. Applying permethrin-containing products to clothing increases protection.

No vaccine against malaria is currently available in the US.[17] The World Health Organization has recommended use of two vaccines, RTS,S/AS01 and R21/Matrix-M, against *P. falciparum* for children younger than age 5 years in areas with moderate to high malaria transmission.[9,19,37,38] Both vaccines are a three-dose primary series beginning around 5 months of age with a fourth dose to be administered 1 year after completion of the primary series. A fifth dose, given 1 year after dose four, may be considered in areas with a remaining significant malaria risk for children.[38] PfSPZ (radiation-attenuated Plasmodium falciparum [Pf] sporozoites [SPZ]) is a potential third vaccine in development.[39]

Nursing considerations

Standard precautions should be used for patients with malaria.[40] They should be diagnosed promptly and treatment initiated urgently.

Suspected and confirmed locally acquired malaria in the US is a public health emergency. Infection prevention and control departments should be notified of cases; they subsequently report cases to state, territorial, local, or tribal health departments.[1,3,12] Travel-associated malaria is reportable in all US states and territories via local public health jurisdictions.

Patients will need to be educated on malaria and the course of illness, how to take antimalarial medications and their possible adverse reactions, prophylaxis before international travel to endemic areas, treatments for malaria disease, and possible blood donation prohibitions after malaria treatment.[15,16,18]

Nurses should ensure that testing for G6PD activity is performed before initiating treatment with primaquine and tafenoquine.

Nurses should educate patients on when to initiate prophylaxis before international travel to malaria-endemic areas, how to take medications during travel, and how to complete the full course of medication upon returning home. They should also discuss measures to avoid mosquito bites during travel (see *Patient education resources*).[41-43] ■

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Unless otherwise specified, the information in the preceding summaries applies to adults, not children. Consult the package insert for information about each drug's safety during pregnancy and breastfeeding. Also consult a pharmacist, the package insert, or a comprehensive drug reference for more details on precautions, drug interactions, and adverse reactions.

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