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Malaria in Children



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KEYWORDS

- Malaria • Travel medicine • Fever • Diagnostics • Antiparasitic therapy
- Chemoprophylaxis

KEY POINTS

- Malaria is common worldwide and travel to malaria-endemic destinations is increasing.
- Travel history should be obtained for all children presenting with fever.
- Antigen-based malaria tests can provide rapid malaria diagnosis, although blood smears are still necessary.
- Treatment of malaria depends on severity of illness, species of malaria parasite, and epidemiologic likelihood of drug resistance.

INTRODUCTION

A century ago, malaria was a major public health threat in the United States, with ongoing transmission in 13 Southeastern states as late as the 1930s.¹ Although extensive efforts ultimately eliminated local malaria in North America, this mosquito-borne infection remains endemic throughout much of the world. Indeed, more than half of the children on our planet live in malaria-endemic countries. Despite continued success in malaria control, there are more than 200 million new infections each year and nearly half a million deaths, mostly in infants and children younger than 5 years old.² Importantly, in our increasingly global society, malaria and other imported infectious diseases remain of particular concern to the North American traveler, with nearly all American malaria cases acquired abroad.^{3–6}

This article offers a brief overview of the *Plasmodium* parasite responsible for malaria, the epidemiology of infection, clinical features associated with uncomplicated

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and severe malaria presentations, preventative measures for travelers, and current treatment strategies for childhood malaria infections.

DESCRIPTION OF THE PATHOGEN

Malaria is caused by infection with intracellular protozoan parasites of the genus *Plasmodium*, transmitted by the bite of a female *Anopheles* spp mosquito.^{7,8} While feeding, the infected mosquito leaves behind sporozoites, the infectious motile form of the parasite. Sporozoites then migrate to the liver, asymptotically invade hepatocytes, and amplify infection through the release of tens of thousands of daughter parasites. This release initiates the asexual erythrocytic replication stage of the parasite life cycle, the stage of parasite responsible for the malaria pathogenesis. Two species of *Plasmodium*, *P vivax* and *P ovale*, uniquely develop dormant parasite forms called hypnozoites, which may remain in the liver for months or years after primary infection before causing relapse and recurrent symptomatic disease.^{9,10}

The clinical symptoms of malaria are due to cycles of asexual replication within red blood cells (Fig. 1). Fever is a hallmark symptom, triggered by erythrocyte rupture and parasite release every 2 to 3 days, depending on *Plasmodium* species.⁷ Severe, life-threatening malaria may result from high parasite burdens, causing hemolysis and severe anemia, or from end-organ damage due to vascular adherence of infected erythrocytes and microocclusion.^{11,12} Person-to-person transmission is mediated by mosquitoes, in which the sexual form of the parasite (gametocytes) infects a feeding mosquito to thus complete the parasite's complex life cycle.^{7,8}

EPIDEMIOLOGY

More than half the world's population lives in areas where malaria transmission occurs, and the disease continues to cause a major public health burden to populations in areas of Africa, Asia, and Central and South America (Fig. 2).² In 2015, more than 200 million

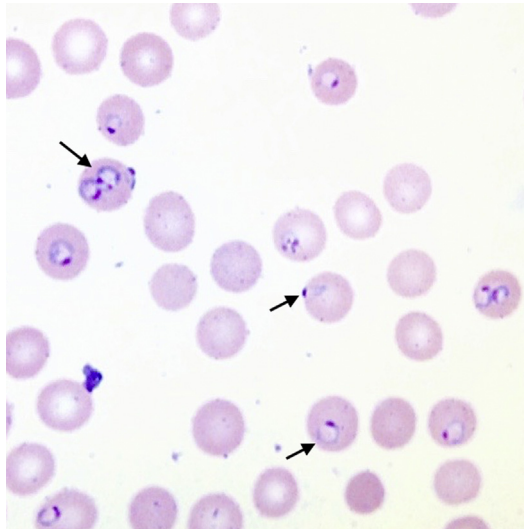


Fig. 1. Blood smear from patient with *P falciparum* malaria. Intraerythrocytic parasite forms are visible in nearly 20% of red blood cells, some of which are doubly-infected. Arrows: typical signet ring, headphones, and appliqué forms of the parasite. (Courtesy of Amruta Padhye MD, Columbia, MO.)

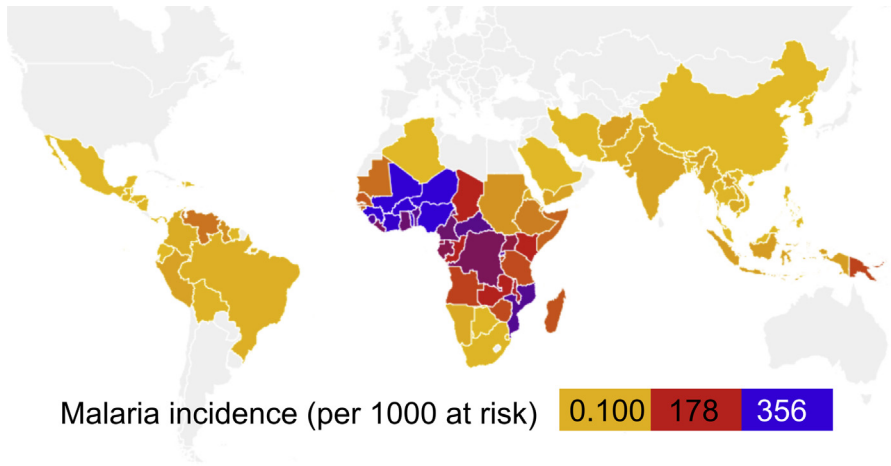


Fig. 2. Malaria incidence in 2015. Incidence of malaria per 1000 population at risk. Map created using OpenHeatMap (www.openheatmap.com). (Data from World Health Organization. World malaria report 2015. Geneva (Switzerland): World Health Organization; 2016. Available at: <http://www.who.int/malaria/publications/world-malaria-report-2015/report/en/>.)

cases of malaria were reported, resulting in nearly half a million deaths, an estimate 3 times higher than the number of people lost to armed conflicts that same year.^{2,13} Most of malaria-associated deaths are caused by *P falciparum* species in sub-Saharan Africa, which kills about 1200 African children younger than the age of 5 years daily.¹⁴

Global malaria control efforts have focused on both mosquito vector control strategies and improved access to effective antimalarial therapies. There have been tremendous gains in the last decade; from 2000 to 2015, the incidence of malaria has dropped by 37%, and deaths have decreased by 60% globally.^{2,15} However, drug resistance continues to hamper control efforts worldwide, with widespread resistance to the former first-line agents chloroquine and sulfadoxine-pyrimethamine.¹⁶ The remarkable discovery of artemisinin by Nobel Laureate Youyou Tu ultimately led to development of rapidly parasitocidal artemisinin-based combination therapies (ACTs), powerful weapons in the face of rising resistance to older antimalarials.^{17,18} Unfortunately, the emergence of artemisinin-resistant *P falciparum* in Southeast Asia, only a few years after ACT implementation, emphasizes the importance of sustaining control measures and the ongoing need for antimalarial development.^{19,20}

Though malarial transmission remains possible in areas of the United States where anopheline mosquitoes are found, nearly all of the 1500 or so annual reported cases of malaria in the United States are infections acquired abroad.^{3,5,21} Rare and unusual modes of transmission have also been reported, which include inadvertent airplane transport of mosquitos from endemic areas, congenital transmission, transfusion-associated malaria, and contaminated needles and syringes.^{22–26}

CLINICAL FEATURES OF MALARIA

Uncomplicated malaria infection typically manifests as a nonspecific febrile illness, similar in presentation to influenza and other common viral infections.^{27,28} Travelers with acute malaria most often present within 7 days to 3 months following an infected mosquito bite, and malaria should be suspected in any febrile traveler.³ Malaria symptoms are highly variable, and may include chills, rigors, sweating, headaches, lethargy, myalgias, and cough. Gastrointestinal symptoms may be prominent, including

nausea, emesis, diarrhea, and abdominal pain.²⁹ In addition to fever, physical findings may reflect end-organ involvement, including pallor, tachycardia, hepatosplenomegaly, jaundice, and increased respiratory rate, as well as, in the case of cerebral malaria, altered mental status.³⁰ The course of disease may be indolent or fulminant, and delays in or lack of treatment beyond 24 hours following onset of clinical symptoms may result in rapid progression to life-threatening, severe malarial disease.³¹

Children younger than 18 years of age tend to present sooner and are more likely to develop severe malaria. Of note, the classic cyclical fever patterns described for malaria may not be present in travelers and young children because parasite life cycles may not have synchronized by the time treatment is sought.^{27,28} Unsurprisingly, travelers are more likely to present with severe malaria, compared with the semi-immune residents of endemic areas.^{3,5} Additional risk factors for development of severe malaria include recent travel to *P falciparum*-endemic regions (especially sub-Saharan Africa), age older than 65 years or younger than 18 years, pregnancy, existing medical conditions, lack of malaria prophylaxis, and treatment delay.^{5,30}

Severe malaria may manifest as 1 or more of the following syndromes^{30,32}:

1. Cerebral malaria: Caused by parasite adherence to cerebral vasculature, symptoms may include altered mental status, coma, seizures, and evidence of increased intracranial pressure
2. Blackwater fever: Acute renal failure and hemoglobinuria caused by intravascular hemolysis
3. Severe anemia: Defined as hemoglobin less than 7 g/dL and caused by high parasite burden and hemolysis of infected erythrocytes
4. Acute respiratory distress syndrome
5. Hyperparasitemia: Typically defined as malaria parasite infection of greater than 5% of circulating red blood cells
6. Metabolic complications: Common abnormalities include severe metabolic acidosis and life-threatening hypoglycemia.

Although fever is an almost universal symptom of malaria, infections with different *Plasmodium* species may have somewhat variable clinical presentations (**Table 1**).

<i>Plasmodium</i> Species	Endemic Regions	Typical Drug Resistance
<i>P falciparum</i>	<ul style="list-style-type: none"> • Sub-Saharan Africa • Haiti • Dominican Republic • Southeast Asia 	<ul style="list-style-type: none"> • Chloroquine • Sulfadoxine-pyrimethamine • ACT therapies (in Southeast Asia)
<i>P vivax</i>	<ul style="list-style-type: none"> • Indian subcontinent • Central and South America • Southeast Asia 	<ul style="list-style-type: none"> • Chloroquine (some areas)
<i>P ovale</i>	<ul style="list-style-type: none"> • Most cases reported in West Africa • May also be present in Asia 	—
<i>P malariae</i>	Less common Wide global distribution	—
<i>P knowlesi</i>	Rare Cases in forested regions of Southeast Asia, associated with long-tailed macaques	—

Severe malaria is most often due to infection with *P falciparum*, which can reach higher parasite levels than other species.⁸ *P falciparum* accounts for 80% of United States malaria cases seen in child travelers.² In contrast, *P vivax* and *P ovale* infections are rarely fatal but carry the risk of reactivation of dormant liver-stage parasites.^{9,10} Chronic asymptomatic bloodstream infection may result from *P malariae* infection, which can also cause a nephrotic syndrome from immune complex deposition in the kidney.³³ Less often seen in travelers, *P knowlesi* is a zoonotic malaria parasite of long-tailed macaques, increasingly recognized as a cause of severe human infections that may be misdiagnosed as the less harmful *P malariae* species.³⁴

MALARIA PREVENTION FOR TRAVELERS: AWARENESS AND BITES

Protective strategies against malaria infection are strongly recommended for all travelers to malaria-endemic regions. Because there is no approved vaccine for malaria, malaria prevention requires awareness of the risks of malaria infection, preventing mosquito bites and encouraging adherence to antimalarial chemoprophylactic regimens.³⁵

A health care provider must first help to assess a traveler's risk of contracting malaria by determining the endemicity of a particular locale and the season of travel. Urban areas, air-conditioned locations, and geographic regions above 3300 m are typically free of malaria.³⁵ Clinicians who provide pretravel counseling should consult the most current and detailed information on health risks, including malaria, which may be found on the Centers for Disease Control and Prevention (CDC) Web site (www.CDC.gov/malaria), as well the World Health Organization Web site (<http://www.who.int/malaria/travellers/en/>). Parents and guardians are strongly cautioned against taking very young children to high endemicity areas, in part because it is challenging to provide a suitable preventative chemotherapeutic regimen that is approved for use in small infants (**Table 2**). Furthermore, malaria may be rapidly fatal in young pediatric patients, in whom early symptoms of *P falciparum* infection may go unrecognized.³⁶

All species of malaria are mosquito-transmitted and, therefore, the first line of protection against infection is to prevent bites from *Anopheles* spp. Insect repellents containing DEET, picaridin, or IR3535 are recommended to protect exposed skin and should be reapplied every few hours in warmer climates. Protective clothing should be worn, with long sleeves and pants tucked into socks with appropriate footwear. A helpful tip is to treat clothing with repellent or long-lasting insecticides such as permethrin (readily available from online retailers), which lasts through several clothing washes. Finally, travelers are strongly recommended to use insecticide-treated mosquito bed nets with mesh sizes smaller than 1.5 mm, which are particularly effective against the night-feeding *A gambiae* vector.³⁶

MALARIA PREVENTION FOR TRAVELERS: CHEMOPROPHYLAXIS

In addition to barrier protection, chemoprophylaxis should be offered to adults and children traveling to endemic malaria regions. Specific regimens are dictated by a traveler's risk of acquiring malaria and local antimalarial-resistance patterns, and providers are encouraged to follow country-specific recommendations from the CDC (https://www.cdc.gov/malaria/travelers/country_table/a.html). In the United States, approved malaria chemoprophylaxis options include atovaquone-proguanil, chloroquine, doxycycline, mefloquine, and primaquine (see **Table 2**).³⁷

Most cases of *P falciparum* malaria infection result from inadequate adherence to prophylactic regimens or failure to take precautions against mosquitoes, with self-reported adherence rates in American military personnel of less than 50%.^{38,39}

	Treatment Recommendations	Contraindications	Target Population
Atovaquone-proguanil	Prevention and treatment of chloroquine-resistant <i>P falciparum</i>	Not recommended for pregnant or breastfeeding women, children <11 kg, or patients with impaired renal function	Last-minute travelers or travelers with short-term exposure to endemic regions Well-tolerated but may be more expensive than other options
Doxycycline	Can be used for prophylaxis but not treatment	Contraindicated in children <8 y old and pregnant women Gastrointestinal discomfort and sun sensitivity are common	Daily dosing, inexpensive option, suitable for last-minute travelers
Mefloquine	Effective against chloroquine-resistant parasites	Safe during pregnancy but not approved by the US Food and Drug Administration for children weighing <5 kg or younger than 6 mo Neuropsychiatric effects can be pronounced, contraindicated in patients with seizure disorders or cardiac conduction abnormalities	Weekly dosing regimen, preferred for long-term travelers
Primaquine	Recommended for prophylaxis in areas with <i>P vivax</i> malaria	Cannot be taken by pregnant or breast-feeding women Testing is necessary to exclude patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency	Daily dosing
Chloroquine	Limited use due to widespread resistance	Safe for infants, young children, and pregnant women	Weekly dosing, must be started 1–2 wk before travel

Proper education about the risks of malaria and the efficacy of prevention methods has been shown to improve adherence to preventative measures, and this is particularly important with rising rates of international travel.^{6,36} In summary, the ABCs of malaria prevention are as follows³⁶:

- A: Awareness of the risks of malaria. This can include understanding incubation periods, the possibility of delayed onset symptoms, and symptoms, especially fever.
- B: Bites. Efforts to reduce the likelihood of mosquito bites.
- C: Chemoprophylaxis. Using antimalarial drugs that target blood and liver-stage parasites to prevent progression of infection to disease.

D: Diagnosis. Prompt diagnosis and treatment is key to prevent complications of disease caused by malaria infection.

DIAGNOSIS OF MALARIA INFECTION

Because the symptoms of malaria can be highly variable, clinicians should maintain a high index of suspicion for all returning travelers presenting with fever. Clinicians should continue to consider routine pediatric infections, such as viral and bacterial respiratory tract infections, infectious diarrhea, and urinary tract infections. In patients with fever and altered mental status or seizure, cerebral malaria may mimic bacterial meningitis, which is of particular concern in young children who may not have completed routine vaccinations and in travelers returning from the Hajj or other parts of the meningitis belt of sub-Saharan Africa. Important additional considerations in travelers include typhoid fever (especially in children younger than 5 years) and dengue, both of which are common in malaria-endemic regions.³⁵ Clinicians should maintain awareness of any ongoing global infectious disease outbreaks, such as Ebola and severe acute respiratory syndrome (SARS), which may have immediate infection control implications.

When malaria is suspected, thick and thin blood films of peripheral blood should be examined.³¹ Thick blood films provide for more sensitive detection of malaria parasites, whereas thin blood films permit speciation and quantification of parasitemia. Blood films should be repeated every 12 to 24 hours during the initial 72 hours of suspected malaria infection, regardless of whether parasites are observed.³⁷

Lateral flow-based rapid diagnostic tests (RDTs) have recently become available to provide initial screening for malaria infection, especially for smaller facilities that may not have trained microscopists on staff at all times. Beginning in 2007, the US Food and Drug Administration (FDA) approved the BinaxNOW malaria RDT for use in commercial laboratories and hospitals. This antigen detection kit has high sensitivity and specificity for *P falciparum* and *P vivax* infection, with reduced sensitivity for *P ovale* and *P malariae*.^{40,41} Because both false-positive and false-negative results have been reported with RDTs worldwide, suspected malaria should continue to be evaluated by blood smears, regardless of the results of rapid testing.⁴²⁻⁴⁴

Nucleic acid testing for malaria remains the gold standard, with the highest sensitivity and specificity^{42,45}; however, such testing is unavailable at most North American facilities. Polymerase chain reaction testing for diagnostic confirmation and species identification is provided free-of-charge for referring facilities in the United States.³

TREATMENT OF MALARIA INFECTION

Single-agent (monotherapy) approaches to malaria treatment are a major contributor to drug resistance and are not recommended.³² In general, antimalarial decision-making is based on severity of symptoms, parasite species, and likelihood of drug resistance (Fig. 3). Uncomplicated *P falciparum* (or unknown malaria species) infection is effectively treated with a 3-day regimen of ACT, which combines the fast-acting artemisinin derivative with a longer-acting antimalarial partner drug. In the United States, artemether-lumefantrine (Coartem), a single orally available ACT for treatment of uncomplicated malaria, is commercially available.⁴⁶

P vivax, *P ovale*, *P malariae*, and *P knowlesi* infections acquired in chloroquine-susceptible endemic areas may be treated with chloroquine, otherwise treatment with an ACT is recommended.³¹ Importantly, for radical cure and elimination of latent liver stages, *P vivax* and *P ovale* infections must additionally be treated with a 14-day

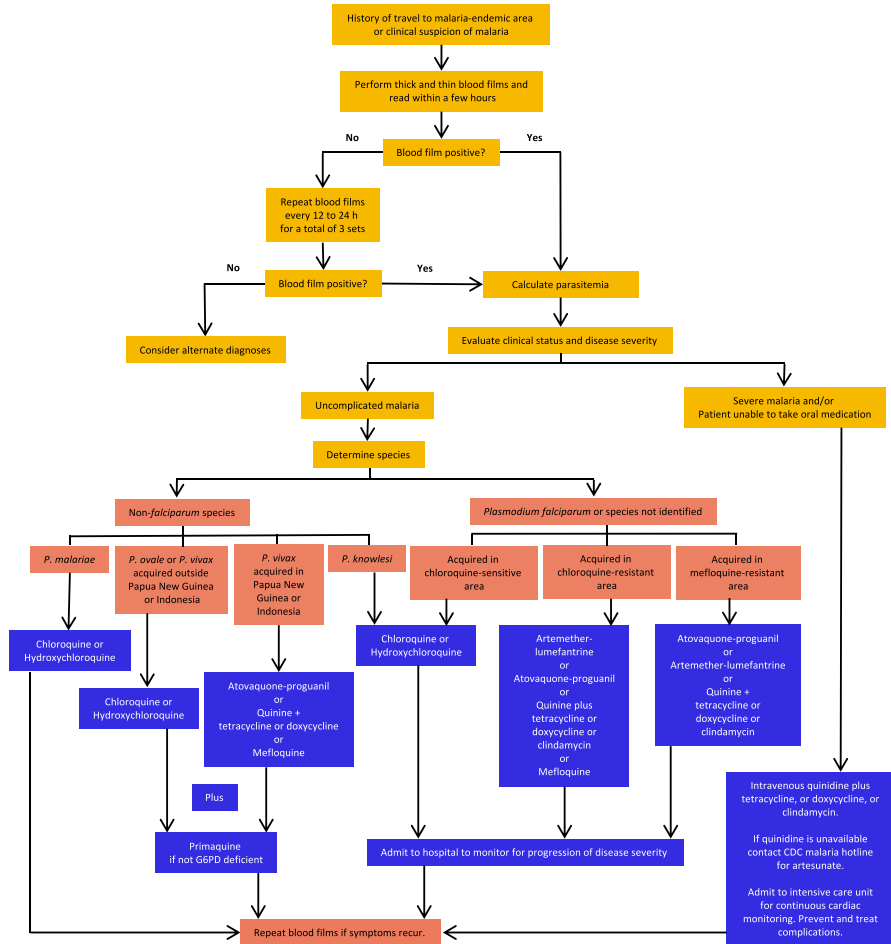


Fig. 3. Decision-tree for malaria treatment. G6PD, glucose 6-phosphatase. (Courtesy of CDC, Atlanta, GA. Available at: <https://www.cdc.gov/malaria/resources/pdf/algorithm.pdf>.)

course of primaquine to prevent future relapse. Note that patients must be evaluated for the presence of glucose 6-phosphatase (G6PD) deficiency before initiation of primaquine, which can precipitate hemolytic crisis.³⁷

Patients with severe malaria will require intensive supportive care and parenteral treatment with intravenous antimalarial treatment. Worldwide, intravenous artesunate is strongly recommended because evidence suggests improved survival compared with quinine.⁴⁷ However, artesunate is not commercially available in the United States and, therefore, intravenous quinidine gluconate is the most commonly available treatment for severe malaria. Due to its arrhythmogenic cardiotoxicity, quinidine treatment requires cardiac telemetry and QTc monitoring.³¹ As of 2007, intravenous artesunate, produced following Good Manufacturing Practices, has been made available on an emergency basis, through an investigational new drug protocol (FDA IND protocol # 76,725) for the treatment of severe malaria in the United States. Clinicians treating pediatric patients with severe malaria are encouraged to consult the CDC Malaria Hotline, which provides expert clinical advice and release of intravenous artesunate

with severe malaria patients in whom quinidine is not appropriate.⁴⁸ Additional malaria treatment guidelines and dosing specifications can be found on the CDC Web site (https://www.cdc.gov/malaria/diagnosis_treatment/treatment.html). Monotherapy for malaria is not recommended and, therefore, all cases of severe malaria require a second agent, such as tetracycline, doxycycline, or clindamycin (intravenous or oral).^{32,37} There is no consensus about the efficacy of exchange blood transfusion for severe disease.^{32,49,50}

A few pediatric-specific treatment modifications may be necessary for treatment of malaria in children. Pyrimethamine should be avoided in the first few weeks of life because it competes with bilirubin and may aggravate neonatal hyperbilirubinemia. Data are limited on the safety and tolerability of primaquine in young infants, which is, therefore, contraindicated in children younger than 6 months of age, and tetracyclines are contraindicated for children younger than 8 years of age. Parenteral anti-malarial treatment may be required for treatment of uncomplicated malaria in children with prominent gastrointestinal symptoms, until oral administration is possible.^{32,37}

Best Practices

What is the current practice?

Pediatric malaria infection

Best practice, guideline, and care path objectives

- Counsel travelers to malaria-endemic regions on the ABCs of protective measures against infection, including limiting mosquito contact and chemoprophylaxis.
- Consider malaria in the differential for any infant or child presenting with nonspecific febrile illness, particularly in returning travelers.
- Rapid recognition and diagnosis of malaria infection is necessary to prevent disease progression.
- Treatment of malaria depends on disease severity, *Plasmodium* species, and likelihood of antimalarial resistance.

What changes in current practice are likely to improve outcomes?

- Improve adherence to antimalarial regimens and other prevention techniques through proper traveler education.
- A travel history should be obtained for all pediatric patients presenting with fever or flu-like symptoms.
- Monotherapeutic regimens that promote development of drug resistance should be avoided.

Treatment recommendations

- Diagnosis depends on microscopic analysis of rapid antigen testing and thick and thin blood smears.
- Combination malaria treatment is based on disease severity, parasite species, and likelihood of drug resistance.
- For *P vivax* and *P ovale*, primaquine treatment (following G6PD testing) is necessary to prevent relapse from latent liver stages.

Summary

Properly informing travelers to malaria-endemic regions about preventative measures for infection is the most effective means of promoting adherence and preventing transmission. In the event of malaria infection, a high index of suspicion, rapid diagnosis, and immediate treatment is critical to prevent the morbidity and mortality associated with disease progression, particularly in pediatric patients.

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