

## EDUCATIONAL OBJECTIVES

After completing the continuing education activity, pharmacists will be able to

- RECALL symptoms associated with dengue fever and malaria
- DESCRIBE emerging information about dengue and malaria vaccines
- ASSOCIATE dengue fever and malaria vaccines for specific patients

After completing the continuing education activity, pharmacy technicians will be able to

- RECALL symptoms associated with dengue fever and malaria
- DESCRIBE emerging information about dengue and malaria vaccines
- MATCH dengue fever and malaria vaccines by storage requirements



The University of Connecticut School of Pharmacy is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Pharmacists and pharmacy technicians are eligible to participate in this knowledge-based activity and will receive up to 0.05 CEU (0.5 contact hours) for completing the activity, passing the post-test with a grade of 70% or better, and completing an online evaluation. Statements of credit are available via the CPE Monitor online system and your participation will be recorded with CPE Monitor within 72 hours of submission

ACPE UAN: 0009-0000-26-007-H06-P  
0009-0000-26-007-H06-T

Grant funding: NONE

Cost: Pharmacists \$4  
Technicians \$2

INITIAL RELEASE DATE: February 28, 2026

EXPIRATION DATE: February 28, 2029

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## You Asked for It! CE



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### Stop the Bite: Uncover the Answers to Malaria and Dengue Fever

**TARGET AUDIENCE: Pharmacists and Pharmacy technicians interested in travel medicine, immunization, and global health**

**ABSTRACT:** Malaria and dengue (pronounced deng-ee) fever are not new diseases, but given the emergence of new vaccines, it is critical that pharmacists and pharmacy technicians increase their familiarity with them. These illnesses are both transmitted by mosquitos, but malaria is caused by *Plasmodium* parasites while dengue fever is a viral disease caused by dengue virus. The United States is not a malaria- or dengue-endemic country, but travel to other countries puts people at risk of these conditions. Pharmacy teams should be prepared to identify potential cases and refer patients for appropriate vaccination or treatment when appropriate.

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**FACULTY DISCLOSURE:** The authors have no financial relationships with an ineligible company.

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## INTRODUCTION

Malaria cases in 2020 totaled an estimated 241 million, leading to more than 600,000 deaths, mostly in Africa.<sup>1</sup> Direct costs of malaria prevention and treatment in the United States (U.S.) total about \$12 billion annually, excluding the toll it takes on affected individuals and their families.<sup>1</sup> The World Health Organization (WHO) reports that between 100 to 400 million people are infected with dengue fever each year.<sup>2</sup> About 80% of cases are mild and asymptomatic, but dengue fever can progress to "severe dengue," which is classified as a medical emergency requiring immediate medical care.<sup>2,3</sup>

## Mosquitos, Malaria, and Dengue – Oh My!

*Plasmodium* parasites—common to tropical areas (e.g., Africa, South America, the Caribbean Islands, South Asia)—cause malaria.<sup>1</sup> Most commonly, malaria is transmitted through the bite of infected mosquitoes, specifically the *Anopheles* species, during local outbreaks. There is also a term coined “airport malaria,” describing disease that is transported from an infected country to a non-infected country.<sup>4</sup> Congenital malaria occurs when mothers infected with the disease transmit parasites to the child during pregnancy or birth.<sup>4</sup> Although rare, prompt diagnosis is crucial to ensure infected neonates and infants survive. Transfusion-transmitted malaria is also possible where blood recipients can be infected with malaria accidentally. There are no approved tests to screen blood donations for malaria, only questioning of prospective donors.<sup>4</sup> Although rare in the U.S., complications are severe and organizations should take action to prevent potentially-infected individuals from donating.

Patients with malaria generally present with fever, chills/sweating, headache, and weakness within 10 to 15 days of infection.<sup>5</sup> Diarrhea, abdominal pain, and cough are also possible. As malaria progresses, patients develop a classic paroxysm (i.e., symptoms that come and go) comprising three stages<sup>6</sup>:

1. 15-to-60-minute cold stage (shivering and feeling cold)
2. 2-to-6-hour hot stage (fevers up to nearly 106°F; flushed, dry skin; and often headache, nausea, and vomiting)
3. 2-to-4-hour sweating stage (rapid drop in fever and sweating)

Missed or delayed malaria diagnosis can lead to potentially fatal complicated disease manifesting as severe anemia, renal failure, altered consciousness, and multisystem organ failure.<sup>6</sup> Clinicians diagnose malaria via a blood smear test. Although rapid and polymerase chain reaction (PCR) tests are available, medical professionals confirm diagnosis through microscopic blood smear examination.<sup>7</sup>

Dengue fever is a viral disease caused by mosquitos—mainly females from the *Aedes aegypti* and *Ae. albopictus* species—carrying dengue virus (also known as DENV).<sup>2</sup> Four DENV serotypes exist, so it is possible to contract the disease four times. The virus can be transmitted through mosquito bite, from pregnant mother to child, and via infected blood products/organ donations and infusions. Transovarial transmission within mosquitoes (from parent to offspring) has also been noted.<sup>2</sup>

**PAUSE and PONDER:** How many of your patients are resuming travel as the pandemic winds down, and will they need prophylaxis or these vaccines?

Most dengue cases are asymptomatic or mild and fatalities are rare, but increasing severity can be life-threatening.<sup>2,3</sup> Providers should suspect dengue when a high fever (104°F or greater) is accompanied by any two of the following symptoms<sup>2,3</sup>:

- severe headache
- pain behind the eyes
- muscle/joint/bone pain
- nausea/vomiting
- swollen glands
- rash

This febrile phase lasts about 2 to 7 days, and most people recover after about a week.<sup>2,3</sup> Severe dengue is a potentially fatal complication due to plasma leakage, fluid accumulation, respiratory distress, severe bleeding, or organ impairment.<sup>2</sup> Patients are at risk of severe dengue symptoms about 3 to 7 days after initial symptoms appear.<sup>2</sup> As fever drops to below 100°F, patients enter a “critical phase” for 24 to 48 hours. Warning signs to watch for during the critical phase include<sup>2</sup>

- severe abdominal pain
- rapid breathing
- blood in vomit, stool, gums, or nose
- persistent vomiting
- restlessness/fatigue

Clinicians use commercially available PCR or rapid diagnostic tests to confirm dengue diagnosis.<sup>2</sup> Enzyme-linked immunosorbent assays are also available to confirm active or previous infections.

## Global Implications

Beyond clinical symptoms, malaria and dengue fever inflict social and financial loss for diagnosed individuals and the countries tasked with treating affected populations. Some examples of the indirect burden of these mosquito-borne diseases include<sup>1</sup>

- expenses for traveling and receiving treatment
- absences from work/school
- burial expenses in cases of death
- purchases of medication and supplies
- public health interventions (e.g., insecticide spraying, bed nets)
- opportunity loss for tourism

Populations at increased risk of contracting malaria include infants, children younger than 5 years, pregnant women, immunosuppressed patients, and migrant workers or traveling populations.<sup>5</sup> There is also concern that certain mosquitoes are resistant to insecticide, and by migrating throughout the world they can spread malaria to urban populations.<sup>8</sup> Researchers have identified *Anopheles gambiae* mosquitoes, originally found in India and Iran, as insecticide-resistant. These are projected to put nearly 126 million people in African cities at risk for contracting malaria.<sup>8</sup>

Populations most vulnerable to contracting dengue fever include pregnant women and children.<sup>3</sup> Many asymptomatic or mild dengue cases go unreported. WHO reports most of the dengue burden occurs in Asia, and the number of cases has steadily increased to just over 5 million in 2019.<sup>2</sup>

## PREVENTION AND TREATMENT

Following prevention and treatment guidelines are crucial to lower transmission rates of dengue fever and malaria.

### Dengue Fever

WHO states that countries should be aware of community mosquito presence and develop active mosquito and virus surveillance to prevent further disease spread.<sup>2</sup> They should also remain knowledgeable about the number of infected individuals.

The dengue vaccine (Dengvaxia) has been licensed in other countries since 2015, but the U.S. Food and Drug Administration (FDA) approved the vaccine in 2019.<sup>2</sup> WHO recommends people aged 9 to 45 years be vaccinated, but Dengvaxia is only FDA approved for patients 9 to 16 years old with a history of previous infection who live in high-risk areas. As a live-attenuated vaccine, it is contraindicated in individuals with severe immunodeficiency.<sup>2</sup> Children receiving Dengvaxia need a 3-dose series administered subcutaneously with doses separated by 6 months.<sup>9</sup> Providers should store the vaccine in the refrigerator.<sup>10</sup> After reconstitution, it should be administered immediately or stored in the refrigerator and used within thirty minutes.

WHO and the FDA only recommend Dengvaxia for patients with a history of dengue virus infection.<sup>10,11</sup> This is based on clinical trial evidence that the vaccine is efficacious and safe in patients with a history of previous DENV infection because a subsequent infection is more serious and life-threatening than the first.<sup>11</sup> They also advise countries using the vaccine to control viral spread to implement pre-vaccination screening to confirm previous infection.

As no dengue-specific treatment is available, providers should treat infected patients symptomatically with acetaminophen, rest, and fluids.<sup>2</sup> Patients with dengue fever should avoid non-steroidal anti-inflammatory drugs (e.g., ibuprofen, aspirin) because they thin the blood. Given the risk of hemorrhage in this disease, blood thinners may exacerbate the problem.<sup>2</sup>

### Malaria

WHO recommends that countries engage in vector control and surveillance for the spread of malarial disease.<sup>5</sup> Malaria vaccines have been in development for decades, but no malaria vaccine is available in the U.S.<sup>12</sup> In 2021, however, WHO recommended a new malaria vaccine (Mosquirix) for children aged older than 5 months who live in areas with moderate to high transmission of *P. falciparum*.<sup>13</sup> The vaccine is only recommended for children as malaria is one of the main killers of children younger than 5 years in countries with moderate or high rates of malaria.<sup>14</sup> WHO also

recommends giving the vaccine seasonally in countries where malaria transmission is high during certain seasons.<sup>13</sup>

Initial Mosquirix pilot studies are ongoing, and more widespread vaccine rollout is expected in 2023. For now, people in the U.S. traveling to malaria-endemic countries continue to use oral medications as chemoprophylaxis (i.e., to prevent the disease), including atovaquone/proguanil, chloroquine, doxycycline, mefloquine, primaquine, and tafenoquine.<sup>15</sup>

Clinicians administer Mosquirix as a 4-dose schedule.<sup>16</sup> The vaccine's adverse effects are pain and swelling at the injection site and fever.<sup>17</sup> Providers should store the vaccine in the refrigerator. After reconstitution it should be administered immediately or stored in the refrigerator and used within 6 hours.<sup>16</sup>

Malaria treatment involves the use of antimalarial drugs based on four main factors<sup>15</sup>:

- 1) Infection severity:** Malaria infection is either considered uncomplicated (effectively treated with oral antimalarials) or severe (requiring aggressive intravenous antimalarial therapy).
- 2) Infecting *Plasmodium* species:** *P. falciparum* and *P. knowlesi* infections can cause rapidly progressive severe illness or death, necessitating urgent therapy initiation, while other species are less likely to cause severe disease. *P. vivax* and *P. ovale* infections also require treatment for hypnozoites (parasites that lay dormant in the liver and then re-awaken to become active infectants).
- 3) Drug susceptibility:** In addition to disease severity differences, *Plasmodium* species also have different drug susceptibilities, so providers select an antimalarial therapy based on the species of the infecting parasite. If the species cannot be determined, patients must initiate antimalarial treatment against chloroquine-resistant *P. falciparum* as soon as possible.
- 4) Previous antimalarial use:** Patients using antimalarial medication as chemoprophylaxis, should not receive that same drug or drug combination to treat malaria infection unless no other options are available.

## CONCLUSION

Pharmacists and pharmacy technicians should be familiar with the signs and symptoms of malaria and dengue fever to inform patients when these conditions are suspected and about their appropriate treatment. Pharmacy teams who suspect a case of malaria or dengue fever should refer patients for medical attention and contact their local or state health department.

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