



EDUCATIONAL OBJECTIVE: Readers will include dengue in the differential diagnosis of fever in patients who have newly returned from tropical countries and will report suspected, probable, and confirmed cases to public health authorities

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Dengue: A reemerging concern for travelers

ABSTRACT

Dengue, a neglected tropical disease that is reemerging around the world, became a nationally notifiable disease in the United States in 2009. Travel to tropical and subtropical areas in the developing world poses the greatest risk of infection for US residents, and an increase in travel to these areas makes this infection more likely to be seen by primary care physicians in their practices.

KEY POINTS

Dengue results from infection with one of four distinct serotypes: DENV-1, DENV-2, DENV-3, and DENV-4.

The most common outcome after infection by the bite of an *Aedes* mosquito (which bites in the daytime) is asymptomatic infection, a flulike illness, or classic self-limited dengue fever. Severe, life-threatening disease with hemorrhagic manifestations or shock is rare.

Obtaining a history of recent travel to a dengue-endemic area is a key in evaluating a person presenting with undifferentiated fever or a fever-rash-arthralgia syndrome.

Diagnostic testing is based on the natural history of infection; antibody levels begin to rise as levels of viremia begin to decline.

Risk factors help predict who will develop severe dengue after primary or secondary infection.

WHY DO PRIMARY CARE PHYSICIANS in nontropical parts of the world need to be on the lookout for tropical diseases such as dengue?

First, more people are traveling than ever before, and second, more people are traveling to parts of the world where dengue and other tropical diseases are endemic. Thus, dengue should now be included in the differential diagnosis of fever in anyone returning from travel to a part of the world where dengue is endemic (TABLE 1).¹

The number of cases of dengue in returning US travelers has been increasing steadily over the past 25 years.^{2,3} Dengue is a more common cause of febrile illness than malaria in US travelers returning from all tropical and subtropical regions except Africa.⁴

Moreover, dengue may be gaining a permanent foothold in the United States, and in areas of the country where mosquitoes that can transmit the virus are found, primary care physicians are the first line of defense in public health. Specifically, to prevent the virus from becoming established locally, primary care physicians need to quickly identify and report cases to public health authorities, who can promptly follow up and initiate prevention measures.⁵

Underscoring the importance of dengue, this infection was added in 2009 to the list of nationally notifiable infectious diseases in the United States.⁶

A COMMON INFECTION WORLDWIDE

Dengue causes up to 100 million new infections, 500,000 hospitalizations, and 25,000 deaths every year in the 2.5 billion people

TABLE 1
Differential diagnosis in dengue clinical syndromes

| CLINICAL DENGUE PRESENTATION | DIFFERENTIAL DIAGNOSIS | | | |
|--|--|---|-----------|---|
| | VIRAL | BACTERIAL | PARASITIC | OTHER |
| Undifferentiated fever | Influenza-like syndromes Chikungunya virus infection Infectious mononucleosis Lymphochoriomeningitis virus Viral hepatitis | Enteric fever Typhus | Malaria | |
| Dengue fever with non-hemorrhagic rash | HIV seroconversion illness Measles Rubella | Meningococcal disease Leptospirosis Scarlet fever (toxin) | | Acute drug reaction Still disease |
| Dengue hemorrhagic fever | Ebola Yellow fever Marburg Arenaviruses Rift Valley fever virus Icterohemorrhagic phase of leptospirosis | Icterohemorrhagic phase of leptospirosis | | |
| Dengue shock syndrome | | | | Systemic inflammatory response syndrome |

who live in subtropical and tropical areas of the world.⁷ It is transmitted by mosquitoes of the genus *Aedes* (which, unlike most other mosquitoes, often bite in the daytime), and it is the most common arboviral infection (ie, transmitted mainly by arthropods) worldwide.

The dengue virus belongs to the family of flaviviruses, which includes West Nile virus, St. Louis encephalitis, and yellow fever. It has four closely related but antigenically distinct serotypes, designated DENV-1, DENV-2, DENV-3, and DENV-4. Infection with one serotype induces lifetime homotypic immunity but only short-lived heterotypic immunity to the other dengue serotypes.⁸ Hence, a person can be infected over time with each of the four serotypes. The first infection is termed the *primary* infection; subsequent infection with any of the remaining three serotypes is termed a *secondary* infection.

Dengue virus transmission has been expanding since the end of World War II in Asia and since the 1980s in the Americas following the end of many regional vector-control programs.⁹ Although dengue is known to occur

in tropical Africa, its epidemiology is less well defined on that continent (FIGURE 1).¹⁰

Explosive epidemics of dengue occur when there are enough mosquitoes and a susceptible population across a broad age range, ie, both children and adults.^{11,12} Transmission can be halted with vigorous vector-control programs, or it slows and stops when the pool of susceptible people is exhausted.^{13–15}

On the other hand, hyperendemic transmission occurs in areas in which multiple virus serotypes continuously circulate in a large pool of susceptible people. In these areas, dengue seroprevalence increases with age, and most adults are immune.

Anyone of any age who travels from a non-endemic area to an epidemic or hyperendemic area is at risk of infection.¹⁶

DENGUE IN THE UNITED STATES

Reported cases of dengue in South and Central America, the Caribbean, and Mexico, common destinations for US travelers, have increased more than fourfold since the 1980s.

Primary care physicians are the first line of defense against dengue becoming established in the United States



FIGURE 1. Areas of the world where dengue is endemic.

SOURCE: US CENTERS FOR DISEASE CONTROL AND PREVENTION.

There were a total of approximately 1 million cases in the 10-year period ending in 1989, compared with more than 4.5 million in the 8-year period from 2000 to 2007.¹¹

The geographic proximity of these areas to the continental United States and the large numbers of US residents travelling to these areas have raised concern that dengue could emerge in the continental United States in areas where potential vectors exist (see below).¹⁷ Furthermore, several US territories and former territories where tourism is an economic mainstay, including the Commonwealth of Puerto Rico,¹⁸ the US Virgin Islands,¹⁹ American Samoa, and other smaller Pacific island jurisdictions such as Palau,²⁰ have reported dengue virus circulation.

Adding to the concern that dengue could gain a persistent foothold in the United States, competent dengue vectors are found here. Two mosquito vectors, *Aedes aegypti*²¹ and *Aedes albopictus*,^{22,23} live in some areas of the southwestern and southeastern United States (FIGURE 2), with *Aedes aegypti* being the more competent transmitter. Both vectors may be abundant in warmer months. This raises a concern that a returning dengue-infected traveler could initiate an outbreak of autochthonous transmission.²⁴

Notably, endemic dengue transmission has occurred in the past in the United States, and the virus is circulating here again at low levels. From 1946 to 1980, no cases of dengue were acquired in the continental United States. However, since 1980 there have been seven outbreaks of laboratory-confirmed, locally acquired dengue along the Texas-Mexico

border.^{25–27} More recently, local transmission emerged in Key West, Florida,^{28,29} the first outbreak since 1945 of dengue in the continental United States not to occur near the Texas-Mexico border. And in early 2011, nonsustained but locally acquired transmission was confirmed in Hawaii after a transmission-free decade.³⁰

THE CLINICAL SPECTRUM OF DENGUE VIRUS INFECTION

Most primary and secondary dengue infections are asymptomatic.⁸ The common forms of clinically apparent disease include self-limited, undifferentiated fever and classic dengue fever (FIGURE 3). Severe disease, manifesting as either dengue hemorrhagic fever or dengue shock syndrome, is a rare outcome of dengue virus infection, estimated to occur in 1% of cases worldwide.³¹ However, the true proportion of severe infection among all dengue cases seen in travelers is difficult to assess reliably.

Asymptomatic infection

Clinical dengue disease is relatively uncommon, as between 60% and 80% of infections are asymptomatic, particularly in children and adults who never have been infected before.³²

In the recent outbreak in Key West, 28 symptomatic cases of locally acquired dengue were detected. The US Centers for Disease Control and Prevention (CDC) conducted a serologic survey of 240 healthy, randomly selected residents of Key West and found evidence of recent infection in 5.4% of those tested.²⁸ Based on this finding, the CDC es-

Two species of the *Aedes* mosquito that can transmit dengue can be found in the United States

TABLE 2

Dengue: Warning signs of severe disease^a

Abdominal pain or tenderness

Persistent vomiting

Clinical fluid accumulation
(ie, pleural effusion or ascites)

Mucosal bleeding

^aWarning signs may occur at or after defervescence. Dengue hemorrhagic fever or shock syndrome may be evolving.

timated that 1,000 people had been infected, of whom more than 90% had no symptoms. However, no attempt was made to differentiate primary from secondary infection in this serosurvey. (Previous infection with one dengue serotype places some individuals at risk for severe dengue if infected with a different serotype in the future.)

Uncomplicated dengue infection

Undifferentiated fever³³ and classic dengue fever are the most common manifestations of clinical dengue infection. Also known as breakbone fever, classic dengue fever is a fever-arthralgia-rash syndrome.¹

The onset is acute, with a high fever (though rarely greater than 40.5°C [104.9°F]) 3 to 14 days (usually 5 to 9 days) after the patient was bitten by an *Aedes* mosquito. Therefore, a febrile illness beginning more than 2 weeks after returning from travel to an endemic area is unlikely to be dengue, and another diagnosis should be sought.

A prodrome of headache, backache, fatigue, chills, anorexia, and occasionally a rash may precede the onset of fever by about 12 hours.

With fever comes a severe frontal headache, associated retro-orbital pain with eye movement, and conjunctival injection.

Some patients develop a bright, erythematous, maculopapular eruption 2 to 6 days into the illness that appears first on the trunk and then spreads to the face and extremities, with characteristic islands of unaffected skin throughout the involved area.³⁴

Severe back or groin pain occurs in about

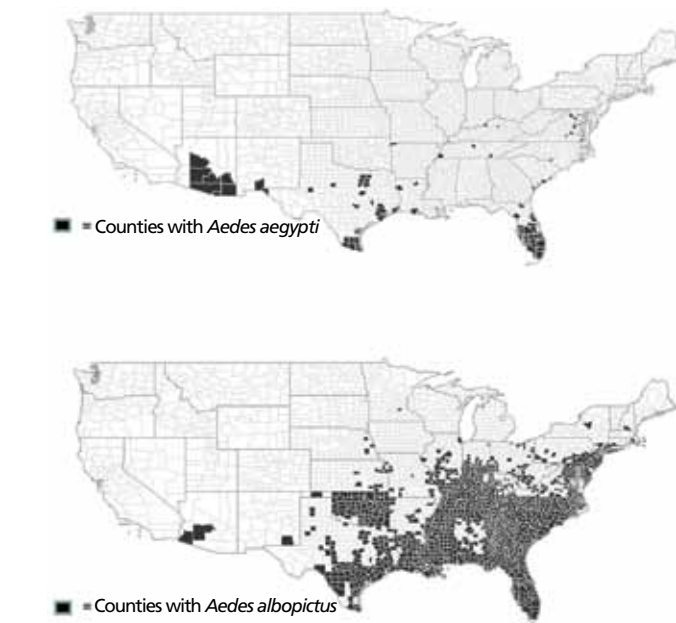


FIGURE 2. US distribution of the *Aedes* mosquito as of 2010.

ARBONET DATABASE, MAINTAINED BY THE US CENTERS FOR DISEASE CONTROL AND PREVENTION.

60% of adult patients.³⁵

Anorexia, nausea, and vomiting are common.

Patients remain febrile for about 5 days, although some experience a biphasic (saddle-back) fever that declines after 2 to 3 days, only to recur in about 24 hours.

In some patients, relative bradycardia is seen 2 to 3 days after fever onset.

Lymphadenopathy, sore throat, diarrhea or constipation, cutaneous hypesthesia, dysuria, dysgeusia, hepatitis, aseptic meningitis, and encephalopathy with delirium have been reported. Splenomegaly is rare.

In classic dengue fever, initial neutropenia and lymphopenia with subsequent lymphocytosis and monocytosis are often noted.

Mild hepatitis can be seen; aspartate aminotransferase and alanine aminotransferase levels can be two to three times the upper limit of normal.

Hemorrhagic manifestations, eg, petechiae, gingival bleeding, and epistaxis, may be seen in patients with mild thrombocytopenia even if they have no evidence of hemoconcentration or evidence of vascular instability.¹⁸

Although clinical dengue infection is usually self-limiting, acute symptoms can be incapacitating and can require hospitalization,³⁶

**In most cases,
dengue
infection is
asymptomatic**

and convalescence may take several months because of ongoing asthenia or depression.³⁷ Furthermore, certain critical findings should alert the clinician to possible impending severe dengue and should lead to hospitalization for further observation until evolution to severe dengue has been ruled out (TABLE 2).

Severe dengue: Hemorrhagic fever and shock syndrome

In a very small subset of patients, dengue infection develops into a severe, potentially life-threatening illness. Fortunately, this has rarely been reported in travelers.³⁸

Dengue hemorrhagic fever and dengue shock syndrome arise just as fever is subsiding. They constitute a spectrum of severe illness (FIGURE 4). Dengue hemorrhagic fever is poorly understood because its hemorrhagic manifestations are not of themselves diagnostic of the condition, as petechiae, epistaxis, and gingival bleeding may be seen in classic dengue fever (FIGURE 3) without progression to more severe illness.

The differentiating characteristic of severe dengue, in addition to hemorrhagic manifestations, is objective evidence of plasma leakage.³⁹ Impending shock is suggested by the new onset of severe abdominal pain, restlessness, hepatomegaly, hypothermia, and diaphoresis.

The mechanisms causing the severe hemorrhagic manifestations characteristic of dengue hemorrhagic fever and the sudden onset of vascular permeability underlying dengue shock syndrome are not understood.⁴⁰ Many hypotheses have been generated and risk factors identified from observational and retrospective analyses. These include T-cell immune-pathologic responses involving receptors, antibodies, and cytokines,⁴¹ as well as specific host-genetic characteristics,^{42,43} age,^{44,45} sex,⁴⁶ comorbid conditions,⁴⁷⁻⁴⁹ dengue virus virulence factors,⁵⁰ sequence of dengue infection, and infection parity.⁵¹ One hypothesis is that antibody-dependent enhancement of virus occurs during infection with a second dengue serotype after infection with a different serotype in the past, and that this may be the root cause of dengue hemorrhagic fever and dengue shock syndrome. However, this has not been proven.⁴⁰

■ DIAGNOSTIC TESTS FOR VIRUS, ANTIGENIC FRAGMENTS, ANTIBODIES

The appropriate test to confirm dengue virus infection is based on the natural history of the infection (FIGURE 4) coupled with the exposure risk in the returned traveler. These tests include isolation of the virus using cell culture, identification of antigenic fragments (test not available in the United States), and serologic tests for specific immunoglobulin M (IgM) and IgG antibodies using enzyme-linked immunosorbent assay (ELISA) or neutralization assays.⁵² During primary infection, viremia and antigenemia usually parallel fever, but when a person is later infected with a different dengue serotype, the period of viremia may be as short as 2 to 3 days, with antigens persisting in the serum for several more days.⁴⁰ Virus isolation is not routinely available but is both sensitive and specific for the diagnosis of dengue virus infection during the viremic period.

If polymerase chain reaction testing, dengue antigen capture ELISA, or virus isolation testing is not available, the ideal confirmatory procedure is to test for dengue IgM (looking for conversion from negative to positive), IgG (looking for a fourfold rise in antibody), or both, in paired serum samples collected 2 weeks apart, with the initial sample collected less than 5 days after the onset of symptoms. A presumptive diagnosis can be made if a single blood sample collected more than 7 days after symptom onset is found to have dengue IgM antibody. A single blood sample for IgM collected earlier than 7 days after the onset of illness may give a false-negative result (FIGURE 4) in infected persons.

■ DIFFERENTIAL DIAGNOSES: INFECTIOUS AND NONINFECTIOUS

The differential diagnosis of uncomplicated dengue in a traveler returning from an endemic area includes viral, bacterial, and protozoal infections as well as noninfectious conditions (TABLE 1).⁵³

Although most dengue virus infections are self-limiting, the clinical presentation may be severe enough to warrant hospitalization so that potentially life-threatening conditions can be systematically dismissed from the differential diagnosis.

Also known
as breakbone
fever, classic
dengue fever
is a fever-
arthralgia-rash
syndrome

Outcomes of dengue infection

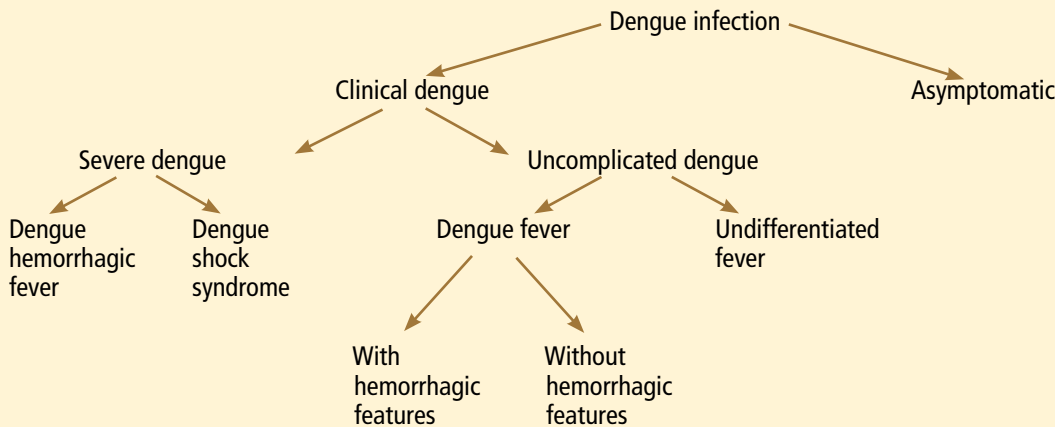
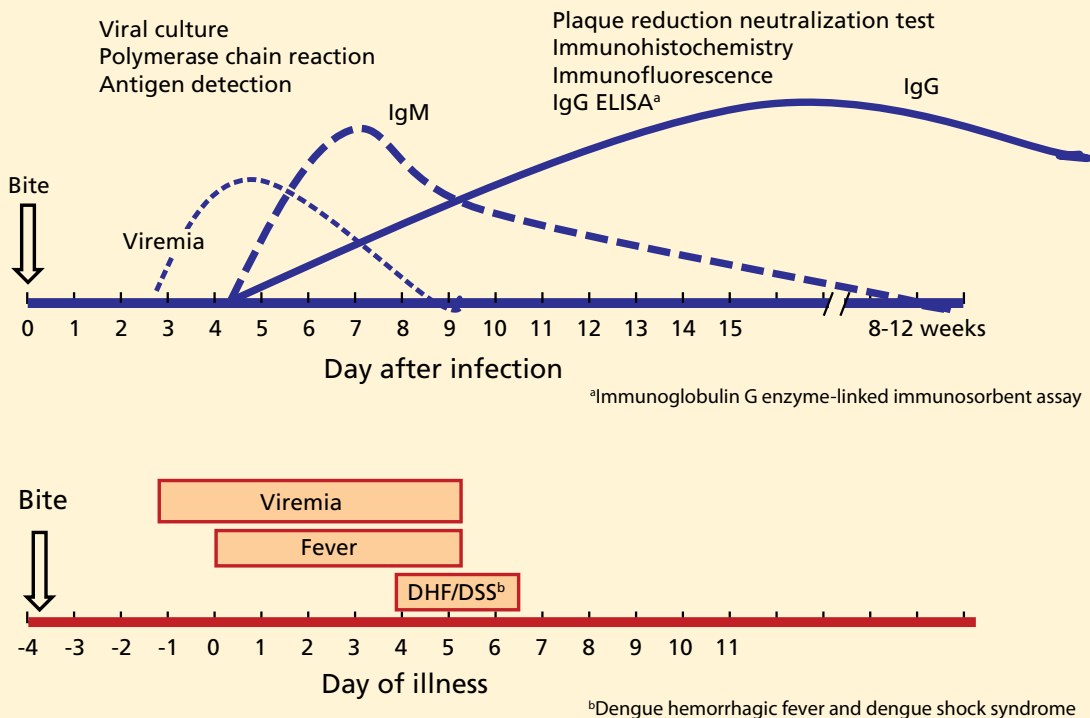


FIGURE 3

Time course of dengue infection



Convalescence may take several months due to ongoing asthenia or depression

FIGURE 4

Infections that can be rapidly fatal, such as malaria and enteric fever, need to be considered in patients who have traveled to endemic areas who present with undifferentiated fever. In cases of fever and maculopapular eruption, the differential diagnosis should include other causes of rash illness, such as measles and rubella. If hem-

orrhagic features are present, potentially fatal conditions need to be considered, including the classic viral hemorrhagic fevers caused by the Ebola and Marburg viruses, meningococcemia, the icterohemorrhagic form of leptospirosis, or other causes of bacterial sepsis. Other nonfatal infections should also be considered.

TABLE 3

Criteria for reporting confirmed, presumptive, and suspected cases of dengue

Dengue fever, confirmed case

Clinical features

Fever lasting 2–7 days AND one or more of the following:

Retro-orbital or ocular pain

Headache

Rash

Myalgia

Arthralgia

Leukopenia

Hemorrhagic manifestations: petechiae, purpura, ecchymosis, epistaxis, gum bleeding, hematemesis, hematuria, melena, vaginal bleeding, positive tourniquet test^a

Laboratory findings (one of the following):

Isolation of virus or demonstration of specific dengue antigen or genomic sequences in tissue, blood, cerebrospinal fluid, or other body fluid by polymerase chain reaction, immunofluorescence, or immunohistochemistry

IgM antibody: seroconversion from negative for dengue-specific serum immunoglobulin (Ig) M antibody in an acute-phase sample (≤ 5 days after symptom onset) to positive for dengue-specific IgM antibodies in a convalescent-phase serum sample collected 14 days after symptom onset

IgG antibody: \geq fourfold rise in reciprocal IgG antibody or hemagglutination inhibition titer to dengue antigen in paired acute- and convalescent-phase serum samples

Neutralization antibody: \geq fourfold rise in plaque reduction neutralization end point expressed as the reciprocal of the last serum dilution showing a 90% reduction in plaque count compared with the infected control between dengue viruses and other flaviviruses in a convalescent-phase serum sample

Virus-specific IgM antibody in the cerebrospinal fluid

Exposure history:

Travel to a dengue-endemic area with ongoing outbreak within the previous 2 weeks of dengue-like illness OR

Association in time and place with a confirmed or probable dengue case

Dengue fever, presumptive case

Clinical features as above

Laboratory findings: Dengue-specific IgM antibodies in serum with a positive sample-to-negative control ratio of ≥ 2

Exposure history as above

Dengue fever, suspected case

Clinical features as above

Exposure history as above

Dengue hemorrhagic fever, confirmed case

All of the following features are required, along with laboratory evidence of infection and history of exposure, as above:

Fever lasting 2–7 days

Evidence of hemorrhagic manifestations or positive tourniquet test

Thrombocytopenia ($< 100,000$ cells/mm³)

Evidence of plasma leakage shown by hemoconcentration

Dengue shock syndrome, confirmed case

Clinical features and exposure history as for dengue hemorrhagic fever, as above, AND:

Rapid and weak pulse and narrow pulse pressure (< 20 mm Hg) OR

Age-specific hypotension and cold, clammy skin with restlessness.

^a Tourniquet test: performed by inflating a blood pressure cuff on the upper arm to a point midway between the systolic and diastolic pressures for 5 minutes. Positive test = 10 or more petechiae per 2.5 cm² observed after the cuff pressure has been released for 2 minutes. The test may be negative or mildly positive during the phase of profound shock. It usually becomes positive, sometimes strongly positive, if the test is conducted after recovery from shock.

SOURCE: US CENTERS FOR DISEASE CONTROL AND PREVENTION AND THE COUNCIL OF STATE AND TERRITORIAL EPIDEMIOLOGISTS.

TREATMENT IS SUPPORTIVE

There is no antiviral treatment for dengue across the spectrum of disease presentations. Treatment is supportive and based on clinical presentation.

Acetaminophen (Tylenol) can be used to control fever, but aspirin and nonsteroidal anti-inflammatory drugs should not be used because they can make bleeding worse. Corticosteroids do not improve the outcome in severe dengue.²

Scrupulous attention to fluid and electrolyte balance is critical in severe dengue cases. Proper support and fluid resuscitation, including blood transfusion if needed, result in rapid recovery from dengue hemorrhagic fever with or without shock.

Suspected, probable, or confirmed cases of dengue should be reported to the local health department on the basis of published criteria (TABLE 3).

ADVICE TO TRAVELERS: DON'T GET BITTEN

There is currently no commercially available dengue vaccine, although several are under development.⁵⁴ Therefore, pretravel counseling on how to avoid mosquito bites when traveling to dengue-endemic areas is the key dengue prevention strategy. Proactive prevention strategies include use of insect repellents such as those containing diethyltoluamide (DEET) or permethrin⁵⁵ and elimination of outdoor locations where mosquitoes lay eggs, such as flower planter dishes, to reduce local mosquito breeding.⁵⁶

Patients who have had a previous dengue infection should be counseled about the possible increased risk of severe disease if infected with a second dengue serotype.

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