

# Dengue Fever

## Surveillance Protocol

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Dengue, also known as dengue fever (DF), dengue hemorrhagic fever (DHF), or breakbone fever, is a mosquito-borne viral infection that manifests with fever and may be accompanied by a combination of nausea/vomiting, rash, aches and pains, leukopenia, and capillary leakage leading to mucosal bleeding and other complications. Although the majority of dengue cases in the United States are travel-associated, recent years have revealed multiple local transmission events in the states of Florida, Hawaii, and Texas. Unlike other arboviral diseases endemic to West Virginia (i.e. West Nile virus, La Crosse encephalitis), **cases of dengue must be reported within 24 hours to the local health department.**

### Provider Responsibilities

1. Report suspect or confirmed cases to your local health department within 24 hours; emerging infectious diseases are considered Category II reportable conditions and require faster responses to facilitate prompt public health prevention and control measures (e.g. home environmental assessments, contact tracing). Supply requested clinical information to the local health department to assist with case ascertainment.
  - a. A serum specimen must be collected. Serum samples are preferred for most molecular and serological dengue tests. The proper diagnostic testing algorithm is detailed by the CDC at the following link: <http://www.cdc.gov/zika/pdfs/denvchikvzika-testing-algorithm.pdf>. Other specimens such as CSF, urine, amniotic fluid, and tissues may be submitted alongside patient-matched serum for evaluation of the utility of these specimen types.
2. Submit a serum sample to the Office of Laboratory Services (OLS) for forwarding to CDC for testing. Assure appropriate testing is completed. The preferred diagnostic test is testing of virus-specific IgM antibodies in serum or cerebrospinal fluid (CSF).
3. Submit paper copies of any positive laboratory results pertaining to DF or DHF to the local health department via fax.

### Laboratory Responsibilities

1. Appropriate testing for patients with suspected arboviral infection includes molecular testing for dengue RNA and usually is performed alongside testing of virus-specific antibodies in serum. Dengue virus RT-PCR kits can be ordered online using the following link: <http://www.cdc.gov/dengue/clinicalLab/realTime.html> There is also an FDA-cleared commercially available anti-DENV IgM antibody kit (InBios, USA): <http://www.inbios.com/elisas/denv-detect-igm-ELISA>
2. Forward copies of any positive dengue test results to the local health department within 24 hours since it is currently considered a Category II reportable condition. Prompt reporting will facilitate timely prevention and control responses at the public health level.
3. Reserve serum from any patient tested for dengue. Submit positive samples to the Office of Laboratory Services for confirmatory testing at the CDC after consulting with WVDHHR's Division of Infectious Disease Epidemiology (DIDE).

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### **Local Health Responsibilities**

1. Conduct an appropriate case investigation.
  - a. Contact the healthcare provider that ordered the laboratory test to obtain the clinical information on the WVEDSS form.
  - b. If needed, contact the patient to obtain information regarding travel history.
  - c. Conduct a home visit and perform an environmental assessment to identify potential risk factors for exposure to mosquitoes.
  - d. Educate the patient and the patient's family on mosquito bite prevention (in order to prevent local transmission of disease) and other appropriate prevention messages.
  - e. Report all case data using WVEDSS.
2. Educate the public about dengue, especially regarding prevention measures when traveling. Spring, summer, and peak vacationing times are optimal opportunities to provide this education.
3. Educate providers, laboratories, and infection control practitioners about diagnosis and reporting of dengue. Emphasize that dengue is different to other arboviruses in that it must be reported to the local health department in the patient's county of residence within 24 hours. Providers should be alert to the clinical symptoms of the viral illness and be educated to inquire about recent travels of the case.
4. If a suspect or confirmed case has no travel history to an enzootic area, contact DIDE immediately. Issue an alert to physicians and infection control practitioners, asking for prompt reporting of additional cases.
5. Consult with DIDE on emerging arboviral diseases for guidance on appropriate case management and public health actions.

### **State Health Responsibilities**

1. Review completed case reports from local health departments as soon as possible within one week.
2. Report all confirmed and probable cases to CDC using ArboNET upon confirmation of case status.
3. Provide training and consultation to local health departments regarding case ascertainment and prevention for arbovirus infection.
4. Conduct yearly mosquito surveillance activities (see mosquito surveillance protocol).
5. Provide regular data feedback to local health departments and public health partners during arboviral disease season (May-October).
6. Ensure that resources and equipment are available for laboratory testing and mosquito surveillance.
7. Coordinate with other agencies, as needed, to monitor arboviral activity and respond to urgent situations.

### **Disease Prevention Objectives**

1. Reduce disease risk through:
  - a. Public education regarding use of personal protective measures.
  - b. Public education regarding travel to areas where dengue and other arboviral diseases are endemic.
  - c. Appropriate mosquito surveillance and control.
2. Educate travelers regarding the importance of reporting onset of illness after travel to endemic countries.
3. Use mosquito surveillance data to provide timely notification to the public and local health departments of arboviral activity in mosquitoes.

### **Disease Control Objectives**

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1. Perform or increase mosquito control activities when human arboviral cases or increased arboviral mosquito activity is detected in an area.
2. Provide or increase public education when human arboviral cases or increased arboviral mosquito activity is detected in an area.
3. With confirmation of a case, emphasize mosquito avoidance (for 7-10 days) and prevention measures until clinical illness resolves.

### **Disease Surveillance Objectives**

1. To identify and monitor the epidemiologic characteristics of locally-acquired and imported dengue infections in West Virginia.
2. To identify and characterize instances of local transmission if they occur. This information would direct vector surveillance (by species and geographic distribution) to evaluate their relative roles in potential transmission within West Virginia.
3. To identify new or invasive mosquito species not previously identified in West Virginia that could be capable of transmitting arboviruses.

### **Public Health Significance**

During the 19th century, dengue was considered a sporadic disease that caused epidemics at long intervals, a reflection of the slow pace of transport and limited travel at that time. Today, dengue ranks as the most important mosquito-borne viral disease in the world. In the last 50 years, incidence has increased 30-fold. An estimated 2.5 billion people live in over 100 endemic countries and areas where dengue viruses can be transmitted. Up to 50 million infections occur annually with 500 000 cases of DHF and 22,000 deaths mainly among children. Prior to 1970, only 9 countries had experienced cases of DHF; since then the number has increased more than 4-fold and continues to rise.

DF and DHF are present in urban and suburban areas in the Americas, South-East Asia, the Eastern Mediterranean and the Western Pacific and DF is present mainly in rural areas in Africa. Several factors have combined to produce epidemiological conditions in developing countries in the tropics and subtropics that favor viral transmission by the main mosquito vector, *Ae. aegypti*: rapid population growth, rural-urban migration, inadequate basic urban infrastructure (e.g. unreliable water supply leading households to store water in containers close to homes) and increase in volume of solid waste, such as discarded plastic containers and other abandoned items which provide larval habitats in urban areas. Geographical expansion of the mosquito has been aided by international commercial trade particularly in used tires which easily accumulate rainwater. Increased air travel and breakdown of vector control measures have also contributed greatly to the global burden of dengue and DHF.

Prospects for reversing the recent trend of increased epidemic activity and geographic expansion of dengue are not promising. New dengue virus strains and serotypes will likely continue to be introduced into many areas where the population densities of *Ae. aegypti* or *Ae. albopictus* are at high levels, as evidenced by the dengue outbreak in Hawaii that began in 2015 and led to a declaration of state of emergency in February 2016. With no new mosquito control technology available, in recent years public health authorities have emphasized disease prevention and mosquito control through community efforts to reduce larval breeding sources. Although this approach will probably be effective in the end, it is unlikely to affect disease transmission in the near future. Therefore, we must develop improved, proactive, laboratory-based

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surveillance systems that can provide early warning of an impending dengue epidemic. At the very least, surveillance results can alert the public to take action and physicians to diagnose and properly treat DF/DHF cases.

### **Clinical Description**

Dengue fever is an acute, viral illness characterized by sudden onset of fever, severe headache, eye pain, muscle and joint pain, and rash. GI upset and loss of appetite often occur. Swollen lymph nodes, petechiae, nosebleeds, and bleeding gums also occur frequently. Recovery is often associated with prolonged fatigue and depression. Dengue hemorrhagic fever is a severe viral illness also characterized by sudden onset of fever as well as hemorrhage from multiple sites. DHF is associated with the abnormal blood clotting, low platelet count (thrombocytopenia), and evidence of plasma leaking through capillaries. Patients with GI bleeding have a greater likelihood of dying. Dengue shock syndrome includes all of the criteria for DHF described above, as well as life-threatening, severely reduced blood pressure (hypotension).

Fatalities associated with DF are rare. With DHF, case fatality rates without treatment have reached 50%, although with intensive treatment, rates are much lower (1-2%).

### **Etiologic Agent**

DF and DHF are caused by the dengue virus (DENV), which belongs to the genus *Flavivirus* in the family Flaviviridae. Dengue virus can be classified into four serotypes (DENV): DEN-1, DEN-2, DEN-3, and DEN-4.

### **Reservoir**

In tropical urban centers, dengue virus is maintained in humans and mosquitoes. In parts of Southeast Asia and West Africa, the virus is maintained in monkeys and mosquitoes.

### **Mode of Transmission**

Dengue is primarily spread through the bite of an infected mosquito.

Additional routes of dengue virus transmission include transplantation, transfusion, in utero transmission, and through breastfeeding. These modes of transmission represent a very small proportion of cases.

Casual person-to-person contact does not result in dengue virus transmission.

### **Incubation Period**

The incubation period for dengue virus ranges from 3-14 days in an infected person.

### **Period of Communicability**

The diseases DF and DHF are not communicable from person-to-person. People are generally infectious to mosquitoes from a few days before onset to the end of the febrile period, usually about 3 to 5 days. The mosquito becomes infectious 8 to 12 days after a blood meal from an infectious person or monkey, and it remains infectious for its lifetime.

### **Outbreak Recognition**

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An outbreak is defined as cases above the expected number. Since dengue virus is not currently circulating in West Virginia, a single locally transmitted case would be considered an outbreak. A case of dengue without recent travel history would require prompt vector abatement intervention and patient education to avoid spreading the virus to local mosquitoes.

### Case Definition

The 2015 case definition is the most current version (CSTE Position Statement Number 14-ID-10).

#### **Subtypes**

- Dengue
- Dengue-like illness
- Severe dengue

### Background

Dengue is a major public health problem worldwide, where an estimated 400 million DENV infections and 100 million clinically apparent dengue cases occurred in 2010. Although ~75% of individuals infected with a DENV will be asymptomatic, ~5% of individuals that develop dengue will progress to severe dengue, an illness characterized by plasma leakage leading to hypovolemic shock, hemorrhage, and potentially death. The case-fatality rate for individuals with severe dengue can be as high as 10% if untreated, or 0.1% with appropriate clinical management.

DENVs are transmitted primarily through the bite of *Aedes aegypti* and *Ae. albopictus* mosquitoes. Because these mosquitoes are endemic throughout the tropics and sub-tropics, an estimated 40% of the world's population is at risk for DENV infection. These mosquitoes are also present in the United States. *Ae. aegypti* is present throughout southern Florida, southern Louisiana, parts of New Mexico and Arizona, southern and central Texas (most prominently around urban centers such as Houston, Dallas, and Austin), and have recently been detected in central California and southern Utah. *Ae. albopictus* is widely present throughout most of the southern United States, and as far north as Illinois and New York, including most counties in West Virginia.

### Laboratory Criteria for Diagnosis

**DENV** = Dengue virus    **WNV** = West Nile virus    **SLEV** = St. Louis encephalitis virus    **YFV** = Yellow fever virus

- **Confirmatory:**
  - Detection of DENV nucleic acid in serum, plasma, blood, cerebrospinal fluid (CSF), other body fluid or tissue by validated reverse transcriptase-polymerase chain reaction (PCR), or
  - Detection of DENV antigens in tissue by a validated immunofluorescence or immunohistochemistry assay, or
  - Detection in serum or plasma of DENV NS1 antigen by a validated immunoassay; or
  - Cell culture isolation of DENV from a serum, plasma, or CSF specimen; or
  - Detection of IgM anti-DENV by validated immunoassay in a serum specimen or CSF in a person living in a dengue endemic or non-endemic area of the United States without evidence of other flavivirus transmission (e.g., WNV, SLEV, or recent vaccination against a flavivirus (e.g., YFV, JEV)); or

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- Detection of IgM anti-DENV in a serum specimen or CSF by validated immunoassay in a traveler returning from a dengue endemic area without ongoing transmission of another flavivirus (e.g., WNV, JEV, YFV), clinical evidence of co-infection with one of these flaviviruses, or recent vaccination against a flavivirus (e.g., YFV, JEV); or
  - IgM anti-DENV seroconversion by validated immunoassay in acute (i.e., collected <5 days of illness onset) and convalescent (i.e., collected >5 days after illness onset) serum specimens; or
  - IgG anti-DENV seroconversion or  $\geq 4$ -fold rise in titer by a validated immunoassay in serum specimens collected >2 weeks apart, and confirmed by a neutralization test (e.g., plaque reduction neutralization test) with a >4-fold higher end point titer as compared to other flaviviruses tested.
- **Probable:**
    - Detection of IgM anti-DENV by validated immunoassay in a serum specimen or CSF in a person living in a dengue endemic or non-endemic area of the United States with evidence of other flavivirus transmission (e.g., WNV, SLEV), or recent vaccination against a flavivirus (e.g., YFV, JEV).
    - Detection of IgM anti-DENV in a serum specimen or CSF by validated immunoassay in a traveler returning from a dengue endemic area with ongoing transmission of another flavivirus (e.g., WNV, JEV, YFV), clinical evidence of co-infection with one of these flaviviruses, or recent vaccination against a flavivirus (e.g., YFV, JEV).
  - **Suspected:**
    - The absence of IgM anti-DENV by validated immunoassay in a serum or CSF specimen collected <5 days after illness onset and in which molecular diagnostic testing was not performed in a patient with an epidemiologic linkage.

### **Epidemiologic Linkage**

- Travel to a dengue endemic country or presence at location with ongoing outbreak within previous two weeks of onset of an acute febrile illness or dengue, or
- Association in time and place (e.g., household member, family member, classmate, or neighbor) with a confirmed or probable dengue case.

### **Criteria to Distinguish a New Case from an Existing Case**

DENV infection results in long-lasting immunity to symptomatic infection (dengue) with that DENV-type. However, cross-protective (heterotypic) immunity against dengue is short-lived with estimated durations of 1-3 years. In dengue endemic areas where infection pressure is high, individuals have been shown to infrequently have sequential episodes of dengue with two different infecting serotypes. Based on these data, a person with two clinical episodes of dengue occurring at least two weeks apart and shown to be due to different infecting DENV-types confirmed by molecular diagnostic testing would be classified as two different cases.

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However, for two clinical episodes of dengue in the same person diagnosed only by IgM anti-DENV on the second episode; to be considered separate cases, they would have to occur >90 days apart due to the persistence of detectable IgM anti-DENV for ~90 days.

### Exposure

- During the two weeks prior to onset of fever, travel to a dengue endemic country or presence in a location experiencing an ongoing dengue outbreak, **OR**
- Association in time and place with a confirmed or probable dengue case.

### Endemicity

The largest burden of dengue in the United States is in the territories of Puerto Rico and the U.S. Virgin Islands where it is endemic. As such, the majority of reported dengue cases in the U.S. come from these two territories, where existing surveillance systems are in place to capture both the incidence and to some degree the spectrum of disease. Other areas of the US where dengue is or has been endemic include American Samoa, the Northern Marianas, and Guam. In addition, hundreds of travel-associated dengue cases occur each year, primarily in the 50 United States and the District of Columbia.

### Clinical Description

#### Dengue:

Dengue is defined by fever as reported by the patient or healthcare provider and the presence of one or more of the following signs and symptoms:

- Nausea/vomiting
- Rash
- Aches and pains (e.g., headache, retro-orbital pain, joint pain, myalgia, arthralgia)
- Tourniquet test positive
- Leukopenia (a total white blood cell count of  $<5,000/\text{mm}^3$ ), **or**
- Any warning sign for severe dengue:
  - o Abdominal pain or tenderness
  - o Persistent vomiting
  - o Extravascular fluid accumulation (e.g., pleural or pericardial effusion, ascites)
  - o Mucosal bleeding at any site
  - o Liver enlargement >2 centimeters
  - o Increasing hematocrit concurrent with rapid decrease in platelet count
- o **Dengue-like illness:**

Dengue-like illness is defined by fever as reported by the patient or healthcare provider.

  - **Comments:** In June 2014, the Council of State and Territorial Epidemiologists (CSTE) recommended Dengue-like illness become nationally notifiable. Dengue-like illness will be added to the list of National Notifiable Infectious Conditions when the CDC receives Office of Management and Budget (OMB) Paperwork Reduction Act (PRA) approval to receive data for this condition.
- o **Severe dengue:**

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Severe dengue is defined as dengue with any one or more of the following scenarios:

- Severe plasma leakage evidenced by hypovolemic shock and/or extravascular fluid accumulation (e.g., pleural or pericardial effusion, ascites) with respiratory distress. A high hematocrit value for patient age and sex offers further evidence of plasma leakage.
- Severe bleeding from the gastrointestinal tract (e.g., hematemesis, melena) or vagina (menorrhagia) as defined by requirement for medical intervention including intravenous fluid resuscitation or blood transfusion.
- Severe organ involvement, including any of the following:
  - Elevated liver transaminases: aspartate aminotransferase (AST) or alanine aminotransferase (ALT)  $\geq 1,000$  per liter (U/L)
  - Impaired level of consciousness and/or diagnosis of encephalitis, encephalopathy, or meningitis
  - Heart or other organ involvement including myocarditis, cholecystitis, and pancreatitis

### Case Classification

#### **Suspected**

A clinically compatible case of dengue-like illness, dengue, or severe dengue with an epidemiologic linkage, as defined above.

#### **Probable**

A clinically compatible case of dengue-like illness, dengue, or severe dengue with laboratory results indicative of probable infection, as defined above.

#### **Confirmed**

A clinically compatible case of dengue-like illness, dengue, or severe dengue with confirmatory laboratory results, as defined above.

#### **Comments**

The 2009 CSTE Dengue Position Statement included the reporting of DENV-positive asymptomatic blood donors identified through pilot screening projects in dengue endemic areas. However, these screening projects have ended, no cases were reported, and the "Asymptomatic Blood or Tissue Donor" reporting category will be deleted, limiting reporting to persons with symptomatic DENV infection (i.e., dengue).

### Preventive Interventions

There are efforts underway to develop a dengue vaccine for humans, but no vaccine is currently approved. The most effective prevention is mosquito avoidance. Repellents such as DEET, oil of lemon eucalyptus, IR3535 and picaridin have demonstrated efficacy against mosquitoes.

Share these prevention messages with the public:

- Empty standing water in old tires, cemetery urns, buckets, plastic covers, toys, or any other container where mosquitoes may breed.



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- Empty and change the water in bird baths, fountains, wading pools, rain barrels, and potted plant trays at least once a week if not more often.
- Drain or fill temporary pools with dirt.
- Keep swimming pools treated and circulating.
- Keep rain gutters unclogged.
- Use mosquito repellents according to the label directions. Apply sparingly to children before they play out of doors, and rinse children off with soap and water when they come back in. Do not apply repellent to the face and hands of young children because they may rub it in their eyes. Follow label directions and precautions closely.
- Wear long sleeves and long pants if you venture into areas with high mosquito populations.
- Make sure window and door screens are bug tight.
- Check travel advisories when traveling out of the United States to determine if mosquito-borne disease transmission is ongoing in the country of upcoming travel.

### **Treatment**

There is no specific medication for treatment of a dengue infection. People who believe they have dengue should use analgesics (pain relievers) with acetaminophen and avoid those containing ibuprofen, Naproxen, or aspirin. They also should rest, drink plenty of fluids, and consult a physician.

As with dengue, there is no specific medication for DHF. It can however be effectively treated by fluid replacement therapy if an early clinical diagnosis is made. Hospitalization is frequently required to manage DHF adequately. Physicians who suspect that a patient has DHF may want to consult DIDE.

### **Surveillance Indicators**

1. Proportion of cases with complete clinical, laboratory, and epidemiologic information including clinical symptoms, testing, and risk factor information (e.g. travel history, outdoor activities).
2. Proportion of cases with a home visit completed for environmental evaluation, including GIS coordinates of location and patient and family education.
3. Percentage of human arboviral infection cases with positive labs with specimens forwarded by OLS to CDC for additional laboratory confirmation (e.g. PRNT).

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