Dengue Infections
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Dengue Virus Infections

Overview[1, 2, 3, 7]

Dengue, a *Flavivirus*, is a potentially fatal, acute febrile illness transmitted by mosquitoes. Dengue is a major public health problem in the tropics and subtropics; with as many as 400 million cases occurring annually, inflicting a significant health, economic and social burden on the populations of endemic areas (approx. 40% of the world's population lives in areas with dengue virus [DENV] transmission). Dengue illnesses can result from infection with any of the four serotypes DENV-1, -2, -3, and -4. The illness appears 3-14 days after the infective bite. Infection with one DENV serotype produces lifelong immunity against that type, thus a person has a lifetime risk of up to 4 DENV infections.

About 75% of all DENV infections will be asymptomatic, however as many as 5% of individuals that develop dengue will progress to a severe, life threatening disease. With symptomatic dengue infection, the principal symptoms are high fever, severe headache, severe pain behind the eyes, joint pain, muscle and bone pain, rash, mild bleeding (e.g., nose or gums bleed, easy bruising) and low white cell count. Anorexia, nausea, and vomiting are common. In some patients, this acute phase is followed by an increase in capillary permeability that can lead to serious complications such as severe blood and fluid loss, hemorrhage, and potentially death. The case-fatality rate for individuals with severe dengue can be as high as 10%, but can be reduced to less than 1% with appropriate clinical management. Generally, younger children and those with their first dengue infection have a milder illness than older children and adults. In persons suspected of dengue infection, avoid the use of aspirin, aspirin containing drugs, and other nonsteroidal anti-inflammatory medications, that may aggravate the bleeding tendency associated with some DENV infections and, in children, can be associated with the development of Reyes syndrome.

Because of the approximate 7-day viremia in humans, bloodborne transmission is possible through exposure to infected blood, organs, or other tissues (such as bone marrow). In addition, perinatal DENV transmission occurs (the highest risk appears to be among infants whose mothers are acutely ill around the time of delivery). It is not known if DENV is transmitted through breast milk. In the majority of DENV infections, a mosquito bite is responsible.

Currently, no vaccine, chemoprophylaxis, or antiviral medications are available to treat DENV infection. This makes prevention the most important measure to prevent dengue, which means avoiding mosquito bites when you live in or travel to a dengue-endemic area. Travelers to dengue-endemic areas may find that mosquito bite prevention must occur indoors as well as outdoors, including the use of bed nets and insecticide-treated clothing. Repellents and other general protective measures against biting mosquitoes can provide protection in many settings. DENVs are transmitted primarily through the bite of *Aedes aegypti* and *Ae. albopictus* mosquitoes. While *Ae. aegypti* is adapted to tropical and subtropical climates, *Ae. albopictus* is widely present throughout most of the southern United States and likely including all of Missouri's counties.

For a complete description of dengue virus infections, refer to the following texts:

- *Control of Communicable Diseases Manual* (CCDM), American Public Health Association, 19th ed. 2008.
- American Academy of Pediatrics. *Red Book: 2012 Report of the Committee on Infectious Diseases.* 29th ed. 2012.
- *Centers for Disease Control and Prevention (CDC) Health Information for International Travel 2014 – The Yellow Book.* Travelers' Health Branch, CDC.

2015 Case Definition – Dengue virus infections[4] - (1/15)

Subtype(s): Dengue Dengue-like illness Severe Dengue

Dengue

Clinical Criteria

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/mm^3), **or**
- Any warning sign for severe dengue:
  - Abdominal pain or tenderness
  - Persistent vomiting
  - Extravascular fluid accumulation (e.g., pleural or pericardial effusion, ascites)
  - Mucosal bleeding at any site
  - Liver enlargement >2 centimeters
  - Increasing hematocrit concurrent with rapid decrease in platelet count

Laboratory Criteria for Diagnosis

- **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**

(*Continued on next page*)

- 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 ≥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.

Dengue-like illness

Clinical Description

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

Severe Dengue

Clinical Description

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) ≥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.

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***Case Classification* – all subtypes**

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.

Comment(s)
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).

Information Needed for Investigation

Verify the diagnosis: Obtain demographic, clinical and laboratory information on the case from the health care provider, hospital, and/or laboratory. Does the laboratory test result provide evidence of a recent DENV infection? Obtain the other epidemiological information necessary to complete the Disease Case Report (CD-1) and the Dengue Case Investigation Report (CDC 56.31 A) from the patient or a knowledgeable family member. ***NOTE****: On the* ***"****Dengue Case Investigation Report****" - Please answer ALL questions,*** *especially those in the* ***"Signs and symptoms"*** *section so the dengue "subtype" can be determined.*

Establish the extent of the illness. Determine if household, traveling companions or other close contacts are, or have been ill, by contacting the health care provider, patient or family members. Strongly urge persons with a dengue-like illness to contact their physician for a medical evaluation. These persons should also be watched for warning signs as temperature declines 3 to 7 days after symptoms began. Persons with a dengue-like illness should go **IMMEDIATELY** to an emergency room or the closest health care provider if any of the following warning signs appear: severe abdominal pain or persistent vomiting, red spots or patches on the skin, bleeding from nose or gums, vomiting blood, black tarry stools (feces, excrement), drowsiness or irritability, pale, cold, or clammy skin, difficulty breathing. ***NOTE:*** Some patients with dengue go on to develop severe dengue, a serious and sometimes fatal form of the disease. ***COMMENT:*** There is no evidence of person-to-person transmission.

Identifying the source of infection. Determine if the case-patient has a history of foreign travel, 14 days prior to illness onset. If yes, obtain:

- Travel history (from the patient or the patient's family, neighbors, co-workers, social worker, or health care provider). Determine the specific dates and location of travel for the 14 days prior to illness onset.
- Is the case-patient:
  - Working in a laboratory or clinical setting?
  - Pregnant or breast feeding?
  - Known to have contacts with a similar illness, or are healthcare providers aware of others with a similar illness in the area? Ill persons should be advised to seek medical attention and alert their medical provider that they may have been exposed to dengue.
  - A recent organ, tissue (e.g., corneas, skin), bone marrow or blood donor, or recipient.
  - If yes, notify:
    - ✓ Notify blood or tissue bank.
    - ✓ Quarantine remaining co-component blood or tissues.
    - ✓ Identify other possibly exposed patients.

If there is no history of foreign travel consistent with acquisition of dengue, it is important to determine the case-patient's recent medical history, including blood transfusions, or medical treatments received in or outside the United States. Also, determine if the case-patient lives, works or has visited international airports, shipyards or other areas in which shipments from international sources may have been located. ***COMMENT:*** Sporadic outbreaks with local transmission have occurred in Florida, Hawaii, and along the Texas-Mexico border. Although the geographic distribution of dengue is similar to that of malaria, dengue is more of a risk in urban and residential areas than is malaria.[7] ***NOTE:*** *Contact the District Communicable Disease Coordinator immediately if an in-state dengue exposure is suspected.*

Provide information on DENV infections to persons at risk for infection and the general public as needed. Efforts should be made to promote dengue awareness among international travelers and persons visiting family and friends in other countries. To the extent possible, travelers should avoid known foci of epidemic disease transmission. Although mosquitoes may bite at any time, peak biting activity for vectors of dengue and chikungunya is during daylight hours. Residents of and travelers to areas with endemic dengue can reduce their risk for DENV infection by using mosquito repellent, wearing long-sleeved shirts and pants, and sleeping in locations with air conditioning or screens on doors and windows. Up-to-date, destination-specific dengue activity reports can be found on CDC's DengueMap webpage. Additional information on "Protection against Mosquitoes" for travelers can be found at: http://wwwnc.cdc.gov/travel/yellowbook/2014/chapter-2-the-pre-travel-consultation/protection-against-mosquitoes-ticks-and-other-insects-and-arthropods.

The "Travelers Can Prevent Dengue" brochure is located on CDC's website at: http://www.cdc.gov/dengue/resources/educationMaterials_pdfs/TravelersCanPrevent_dengue.pdf, along with the "Prevent Dengue on a Mission Trip" brochure at: http://wwwnc.cdc.gov/travel/pdf/dengue-mission-trip.pdf. Additional education and resources are available at: http://www.cdc.gov/dengue/educationTraining/index.html.

Dengue Surveillance. Medical providers should report dengue cases promptly. Local public health agencies (LPHAs) should review WebSurv to determine whether there have been other cases reported. When cases are related by person, place, or time, efforts should be made to identify a common source**.**

Data collected from dengue surveillance is used to monitor trends; identify areas of risk and risk factors in United States travelers; and inform vaccination recommendations when vaccines become available. Further public health surveillance can enhance healthcare provider awareness of dengue so that cases can be rapidly identified, thereby reducing the possibility of local transmission or establishment of endemicity in this country.

Notification

- Contact the Bureau of Communicable Disease Control and Prevention (BCDCP) District Communicable Disease Coordinator, the Senior Epidemiology Specialist for the District, or MDHSS/Office of Veterinary Public Health (OVPH), phone (573) 526-4780, Fax (573) 751-6185; or for afterhours notification contact the MDHSS/ERC at (800) 392-0272 (24/7) immediately if an outbreak* or if in-state transmission of dengue is suspected.
- If a case(s) is associated with a childcare center, BCDCP or the LPHA will contact the Bureau of Environmental Health Services (BEHS), phone (573) 751-6095, Fax (573) 526-7377 and the Section for Child Care Regulation, phone (573) 751-2450, Fax (573) 526-5345.
- If a case(s) is associated with a long-term care facility, BCDCP or the LPHA will contact the Section for Long Term Care Regulation, phone (573) 526-8524, Fax (573) 751-8493.
- If a case is associated with a hospital, hospital-based long-term care facility, or ambulatory surgical center, BCDCP or the LPHA will contact the Bureau of Health Services Regulation phone (573) 751-6303, Fax (573) 526-3621.

*Outbreak is defined as the occurrence in a community or region, illness(es) similar in nature, clearly in excess of normal expectancy and derived from a common or a propagated source.

Control Measures[1, 2, 5, 7, 8, 11]

Clinical guidelines for the management of dengue infection can be found on CDC's website at:

- Dengue Guidelines for Diagnosis, Treatment, Prevention and Control.
- Dengue Case Management.
- Dengue and Dengue Hemorrhagic Fever, Information for Health Care Practitioners.

There is no vaccine available against dengue, and there are no specific medications to treat a dengue infection. This makes prevention the most important measure, and prevention means avoiding mosquito bites. This can be done by:

- Avoidance of mosquito-prone areas, or
- Be aware of peak mosquito exposure times and places, and take appropriate actions.
- Personal protection measures such as long sleeves, mosquito repellents, and bed nets - when accommodations are not adequately screened or air conditioned.
- Mosquito control measures.

***NOTE**: If someone in your home is ill with dengue, take extra precautions to prevent mosquitoes from biting the patient and going on to bite others.*

Upon a determination of DENV transmission in local mosquitoes (i.e., no travel to a dengue endemic area), emergency vector control efforts to reduce the abundance of infected, biting adult mosquitoes should be implemented. Although social media messaging, to promote the use of mosquito repellents, and community mobilization projects, to address sources of breeding mosquitoes, can help protect individuals and at-risk groups, these measures may not be adequate to maintain vector populations at levels sufficiently low to prevent additional human cases.

Insecticides to control larval and adult mosquitoes are registered specifically for that use by the Environmental Protection Agency (EPA). Instructions provided on the product labels prescribe the required application and use parameters, and must be carefully followed. Properly applied, these products do not negatively affect human health or the environment. More detailed information about pesticides used for adult mosquito control is available from the EPA (http://www2.epa.gov/mosquitocontrol/controlling-adult-mosquitoes). Pesticides for adult mosquito control can be applied from hand-held application devices or from trucks or aircraft.

For more detailed information about controlling mosquito-borne infectious diseases consult:

- *Control of Communicable Diseases Manual* (CCDM), *Dengue Hemorrhagic Fever/Dengue Shock Syndrome,* "Methods of control."American Public Health Association, 19th ed. 2008.
- American Academy of Pediatrics, "Section 2 Recommendations for Care of Children in Special Circumstance". *Prevention of Mosquitoborne Infection.* In: Pickering LK, Baker CJ, Kimberlin DW, Long SS, eds. *Red Book: 2012 Report of the Committee on Infectious Disease,* 29th ed. 2012.
- Before The Swarm: Guidelines for the Emergency Management of Mosquito-Borne Disease Outbreaks, Association of State and Territorial Health Officials, Mosquito Control Collaborative, 2008.

Laboratory Procedures

Unequivocal diagnosis of dengue infection requires laboratory confirmation. ***NOTE:*** Laboratory confirmation of a clinical diagnosis depends on when a serum sample is obtained during the course of the illness.[2] Dengue testing is available through commercial clinical laboratories. The "Laboratory Guidance and Diagnostic Testing" document for DENV is available on CDC's website at: http://www.cdc.gov/Dengue/clinicalLab/laboratory.html.

Additional information on the diagnosis of DENV may be found online at: Dengue – Guidelines for Diagnosis, Treatment, Prevention and Control. Assistance will be provided by the Missouri State Public Health Laboratory (MSPHL) for DENV testing to be performed by the Dengue Branch of the CDC. See the Instructions for collecting, preparing and mailing

specimens for dengue testing at CDC Dengue Laboratory. ***Important:*** Contact the Virology Unit at the MSPHL, phone (573) 751-3334 before submitting specimens.

NOTE: FDA approved testing for all four dengue serotypes in laboratories with Influenza equipment; see the following URL for more information: http://www.cdc.gov/dengue/resources/rt_pcr/CDCPackageInsert.pdf.

Reporting Requirements

Dengue is a Category 2 (A) disease and shall be reported to the LPHA or to the Missouri Department of Health and Senior Services (MDHSS) within one (1) calendar day of first knowledge or suspicion by telephone, facsimile, or other rapid communication.

As a Nationally Notifiable Condition, **confirmed, probable** and **suspect** DENV infections are a **STANDARD** report to the CDC. **STANDARD** reporting requires MDHSS to report to CDC by electronic transmission via WebSurv within the next normal reporting cycle.

1. For confirmed and probable cases complete a Disease Case Report (CD-1), and a Dengue Case Investigation Report (CDC 56.31 A).
2. Entry of the completed CD-1 into the WebSurv database negates the need for the paper CD-1 to be forwarded to the District Health Office.
3. MDHSS will report to CDC following the above reporting criteria (see box).
4. Send the completed Dengue Case Investigation Form to the District Health Office.
5. All outbreaks or "suspected" outbreaks must be reported as soon as possible (by phone, fax or e-mail) to the District Communicable Disease Coordinator. This can be accomplished by completing the Missouri Outbreak Surveillance Report (CD-51).
6. Within 90 days from the conclusion of an outbreak, submit the final outbreak report to the District Communicable Disease Coordinator.

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