DENGUE FEVER
(Breakbone Fever, Dandy Fever)

REPORTING INFORMATION
- **Class B:** Report by the end of the next business day after the case or suspected case presents and/or a positive laboratory result to the local public health department where the patient resides. If patient residence is unknown, report to the local public health department in which the reporting health care provider or laboratory is located.
- Reporting Form(s) and/or Mechanism:
  - The Ohio Disease Reporting System (ODRS) should be used to report lab findings to the Ohio Department of Health (ODH). For healthcare providers without access to ODRS, you may use the Ohio Confidential Reportable Disease form (HEA 3334).
  - The ODH Mosquito-borne Illness Case Investigation worksheet is available for use to assist in local disease investigation. Information collected from the form should be entered into ODRS and not sent to the ODH, unless otherwise requested. If requested, the form can be faxed to ODH at (614) 564-2456 or uploaded to the ODRS record.
  - For samples being sent to CDC's Dengue Branch for testing, the CDC Dengue Investigation Report form (CDC 56.31) must accompany the samples.
- Key fields for ODRS reporting include: import status (whether the infection was travel-associated or Ohio-acquired), date of illness onset, symptoms, all fields in the Epidemiology module and travel details in the Travel History module (with accurate departure and return dates along with city, province/county, state and country).

AGENT
Dengue virus is an RNA virus in the genus *Flavivirus* of the family Flaviviridae. There are four serogroups of the dengue virus: 1, 2, 3 and 4. There is substantial serologic cross-reaction with other flaviviruses (e.g., Japanese encephalitis, Powassan, St. Louis encephalitis, West Nile, yellow fever, Zika viruses).
   Infectious Dose: A single bite of an infectious mosquito.

CASE DEFINITION
   Clinical Description
- Dengue-like illness is defined by fever as reported by the patient or healthcare provider.
- Dengue is defined by a 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 cm or
    - Increasing hematocrit concurrent with rapid decrease in platelet count.

- 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 units per liter (U/L),
    - Impaired level of consciousness and/or diagnosis of encephalitis, encephalopathy or meningitis or
    - Heart or other organ involvement including myocarditis, cholecystitis and pancreatitis.

Laboratory Criteria for Diagnosis
Diagnostic testing should be requested for patients in whom there is a high index of suspicion for dengue, based either on signs and symptoms or epidemiologic linkage to a confirmed or probable dengue case.

Confirmatory:
- Detection of dengue virus nucleic acid in serum, plasma, blood, cerebrospinal fluid (CSF) or other body fluid or tissue by validated reverse transcriptase-polymerase chain reaction (PCR) or
- Detection of dengue virus antigens in tissue by a validated immunofluorescence or immunohistochemistry assay or
- Detection in serum or plasma of dengue virus NS1 antigen by a validated immunoassay or
- Cell culture isolation of dengue virus from a serum, plasma or CSF specimen or
- Detection of the dengue virus immunoglobulin M (IgM) antibody by a validated immunoassay in a serum or CSF specimen in a person living in a dengue-endemic or non-endemic area of the United States without evidence of other flavivirus transmission (e.g., West Nile virus, St. Louis encephalitis virus, or recent vaccination against a flavivirus like yellow fever virus or Japanese encephalitis virus) or
- Detection of the dengue IgM antibody in a serum or CSF specimen by a validated immunoassay in a traveler returning from a dengue-endemic area without ongoing transmission of another flavivirus (e.g., West Nile virus, Japanese encephalitis virus, yellow fever virus), clinical evidence of co-infection with one of these flaviviruses or recent vaccination against a flavivirus (e.g., yellow fever virus, Japanese encephalitis virus) or
- Dengue virus IgM antibody 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
- Dengue virus IgG antibody seroconversion or a ≥ 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 dengue virus IgM antibody by a validated immunoassay in a serum or CSF specimen in a person living in a dengue-endemic or non-endemic area of the United States with evidence of other flavivirus transmission (e.g., West Nile virus, St. Louis encephalitis virus) or recent vaccination against a flavivirus (e.g., yellow fever

virus, Japanese encephalitis virus) or
- Detection of dengue virus IgM by a validated immunoassay in a serum or CSF specimen in a traveler returning from a dengue-endemic area with ongoing transmission of another flavivirus (e.g., West Nile virus, Japanese encephalitis virus, yellow fever virus), clinical evidence of co-infection with one of these flaviviruses or recent vaccination against a flavivirus (e.g., yellow fever virus, Japanese encephalitis virus).

Suspected:
- The absence of dengue virus IgM antibody by validated immunoassay in serum or CSF specimen collected <5 days after illness onset and in which molecular diagnostic testing was not performed in a patient with epidemiologic linkage.

Epidemiologic Linkage Criteria
- Travel to a dengue-endemic country or presence at a location with an 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, neighbor) with a confirmed or probable dengue case.

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 U.S. 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.

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 a 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.

Criteria to Distinguish a New Case from an Existing Case
Dengue virus infection results in long-lasting immunity to symptomatic infection (dengue) with that dengue virus 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 dengue virus types confirmed by molecular diagnostic testing would be classified as two different cases. However, for two clinical episodes of dengue in the same person diagnosed only by dengue virus IgM on

the second episode; to be considered separate cases, they would have to occur >90 days apart due to the persistence of detectable dengue virus IgM for approximately 90 days.

SIGNS AND SYMPTOMS
Dengue is characterized by a sudden onset of high fever (103°F-106°F), severe headache, backache, intense pain in joints and muscles, retro-orbital pain, nausea and vomiting and a generalized erythematous rash. Minor bleeding phenomenon such as petechiae, epistaxis or gum bleeding may occur during the febrile phase of illness. Generally, younger children and those with their first dengue infection have a milder illness than older children and adults. Remission usually develops on day three, lasting 2-3 days. Fever and pains recur for about 1-2 days. Eruption recurs. Severe dengue (e.g., dengue hemorrhagic fever, dengue shock syndrome) occurs in approximately 5% of patients. Hemorrhagic symptoms are thought to result upon second encounter with a dengue virus of a different serotype.

DIAGNOSIS
Preliminary diagnosis is often based on a patient's clinical features, places and dates of travel (if patient is from a non-endemic country or area), activities and epidemiologic history of the location where infection likely occurred. In addition to the other more common causes of encephalitis and aseptic meningitis (e.g., herpes simplex virus and enteroviruses) and febrile illnesses, arboviruses such as chikungunya, Eastern equine encephalitis, Jamestown Canyon, LaCrosse, Powassan, St. Louis encephalitis, West Nile, Western equine encephalitis and Zika viruses should also be considered in the differential etiology.

The diagnosis of dengue fever can be confirmed by isolating dengue virus from the acute blood sample, by detecting dengue RNA by polymerase chain reaction (PCR), by detecting dengue-specific protein antigens, by demonstrating specific IgM antibody in appropriately timed serum sample(s) (obtained $\leq$5 and 6-60 days after onset of illness) or by demonstrating a 4-fold or greater change in IgG antibody titer to dengue virus in a serum pair. Individuals who have had one or more flavivirus infections, including yellow fever immunization, may produce heterologous antibodies to a wide range of flavivirus antigens. A specific dengue diagnosis can still be made, however, by virus isolation or inferred from epidemiologic associations.

The CDC in San Juan, Puerto Rico and Fort Collins, Colorado can perform ELISA IgM and virus isolation on the acute serum. A convalescent serum should be obtained two weeks later and also sent to CDC. Proper protocol is to send the sample(s) to the CDC Dengue Laboratory via the ODH Laboratory.

For clinical samples being sent to CDC's Arbovirus Diagnostic Laboratory for testing, the CDC Specimen Submission Form must accompany the samples. Be sure the date of illness onset and travel history fields are completed. Use test order code CDC-10282 for arbovirus serology. Please contact ODH's Bureau of Infectious Diseases at (614) 995-5599 to arrange for testing at CDC.

EPIDEMIOLOGY
   Source
   Humans are the vertebrate reservoir, with monkeys possibly being involved. The principal vector is the *Aedes aegypti* mosquito, and transmission usually occurs in tropical and subtropical areas.

Susceptibility
All individuals not previously infected with dengue (naïve individuals) are at risk for infection and developing disease. Infection with one dengue serotype does not protect against the others, and sequential infections put people at greater risk for severe dengue. Generally, younger children and those with their first dengue infection have a milder illness than older children and adults.

Occurrence
Dengue is endemic in tropical Asia, East and West Africa, Polynesia, Micronesia and Tahiti. Dengue is also endemic in the Caribbean, northern South America and Central America. Dengue is periodically epidemic in the Western hemisphere, with thousands of cases diagnosed. Travelers are always at risk when visiting endemic countries. About 10 imported cases are identified annually in Ohio.

Mode of Transmission
Dengue virus is spread by the bite of an infected mosquito. The yellow fever mosquito, *Aedes aegypti,* is the principal vector and is not known to be established in Ohio. However, the Asian tiger mosquito, *Aedes albopictus*, is established in many Ohio counties and may serve as a potential vector. These mosquitoes become infected when they feed on a person infected with dengue virus. Infected mosquitoes can then spread the virus to other humans when they bite. Because the dengue virus circulates in the blood for about 7 days, it can be transmitted through blood products, organs, tissues, percutaneous blood exposure, in utero or at birth.

Period of Communicability
Humans are infectious to biting *Aedes aegypti* or *Aedes albopictus* from the day prior to onset of symptoms to day five of illness. No human-to-human transmission occurs outside of blood and organ/tissue donation and congenital transmission, which are rare.

Incubation Period
3-14 days, usually 4-7 days.

PUBLIC HEALTH MANAGEMENT
   Case
   Investigation
   With serologic identification of dengue infection, a complete travel history for the two weeks prior to onset should be obtained. Determine the patient's yellow fever, Japanese encephalitis and tick-borne encephalitis vaccine status. The patient should also be questioned about donating or receiving blood, blood products and organs in the 4 weeks prior to onset of symptoms. Female patients should be asked whether they were pregnant at the time of infection, and infants should be checked whether they were breastfed before illness onset. Sites of outdoor exposure and activities can be evaluated for the presence of *Aedes* mosquitoes by standard collection techniques (BG sentinel traps, light traps, larval samples).

   Treatment
   There is no specific medication for treatment of a dengue infection. Persons who think they have dengue should use analgesics (pain relievers) with acetaminophen and avoid those containing aspirin. They should also rest, drink plenty of fluids, avoid mosquito bites while febrile and consult a physician.

Isolation and Follow-up Specimens
No specific isolation procedures are indicated for the acute dengue patient in Ohio. Standard precautions are recommended with attention to the potential for blood-borne transmission. A convalescent serum sample should be obtained 2 weeks after the acute sample. If a convalescent serum sample was not obtained, a late convalescent sample should be obtained. Autopsy blood and/or tissue samples may also be taken. Proper protocol is to send the sample(s) to the CDC Laboratory via the ODHL (See **DIAGNOSIS**, above).

Public Health Significance
High in endemic areas. There is a low probability of endemic transmission occurring in Ohio because of the low prevalence of the vector mosquito. Identification of a locally acquired case of dengue in Ohio warrants a vector investigation and vector control strategies to prevent an outbreak.

Contacts
No treatment or prophylaxis of contacts is indicated.

Prevention and Control
Vaccination
There is no vaccine available.

Travelers
Travelers entering endemic areas should be warned to avoid mosquitoes, use mosquito repellents, occupy screened quarters and use mosquito netting over beds.

Vector Investigation
Acutely infected persons must avoid being bitten by *Aedes* mosquitoes during the week after illness onset to prevent further transmission of the virus. Depending on local resources, environmental assessments around the homes of suspected viremic cases for *Aedes albopictus* mosquitoes may be useful to determine the risk for local transmission of dengue. Those jurisdictions with capacity should consider:
- Adult mosquito control:
  - *Ae. albopictus* (and *Ae. aegypti*) are most active during the day and are not effectively controlled by standard ultra-low volume (ULV) applications. Early morning or late evening applications are recommended.
  - Focus ULV or barrier applications to areas where human cases are present to reduce local transmission.
- Larval mosquito control:
  - Remove larval habitats.
  - Encourage the public to participate in efforts by discarding material or closing containers (e.g., flower pots, buckets, tires, garbage cans).

Mosquito Bite Avoidance
The best way to prevent dengue infection is to avoid mosquito bites. Prevention tips are similar to those for other viral diseases transmitted by mosquitoes, such as chikungunya or West Nile virus:
- Use insect repellent registered with the U.S. Environmental Protection Agency (EPA) on exposed skin. Always follow the directions on the package. When using both sunscreen and insect repellent, apply the sunscreen first then the repellent.
- Wear long sleeves, pants and socks if feasible.
- Wear permethrin-treated clothing to repel and kill mosquitoes.
- Use screens on windows and doors to exclude mosquitoes. And, when available, A/C can make households less hospitable to mosquitoes.

- Participation in community and homeowner based vector-control strategies:
  - Ensure that water does not collect in containers around the home and community by emptying water from containers such as flowerpots, buckets, barrels and tires. Change the water in pet dishes, and replace the water in bird baths weekly. Drill holes in tire swings so water drains out. Empty children's wading pools and store on their sides after use.
  - Use chemical or biological control of larvae and adult mosquitoes when necessary.

Special Information
Accurate travel history and confirmation are desirable to document importation of dengue infections from endemic areas into the United States. Note if travelers had spent any time in the southeastern Atlantic or Gulf Coastal states, where *Aedes aegypti* or *Aedes albopictus* is endemic, before returning to Ohio. The CDC Dengue Branch may be contacted at (787) 766-5181 for special consultation.

What is dengue?
Dengue is a disease caused by any one of four closely related dengue viruses (DENV 1, DENV 2, DENV 3 or DENV 4). The viruses are transmitted to humans through the bite of an infected mosquito.

In the Western hemisphere, the *Aedes aegypti* mosquito is the most import transmitter or vector of dengue viruses, although a 2001 outbreak in Hawaii was transmitted by *Aedes albopictus*. It is estimated there are over 100 million cases of dengue worldwide each year.

Although there are two types of mosquitoes capable of transmitting dengue fever found in some Ohio counties, the virus is not endemic in the state. A few (about ten) human cases are reported in Ohio each year, but all have a history of travel to areas with ongoing transmission of dengue virus.

What is dengue hemorrhagic fever?
Dengue hemorrhagic fever is a more severe form of dengue infection. It can be fatal if unrecognized and not properly treated in a timely manner. Dengue hemorrhagic fever is caused by infection with the same viruses that cause dengue fever. With good medical management, mortality due to dengue hemorrhagic fever can be less than 1%.

How is dengue transmitted?
Dengue is transmitted through the bite of an *Aedes* mosquito that is infected with the dengue virus, most often *Aedes aegypti*. The mosquito becomes infected with the dengue virus when it bites a person who has the virus in their blood. The person can either have symptoms of dengue fever, or they may have no symptoms. After about one week, the mosquito can then transmit the virus while biting a healthy person. Dengue cannot be spread directly from person to person.

What are the symptoms of dengue?
The principal symptoms of dengue fever are a high fever, severe headache, severe pain behind the eyes, joint pain, muscle and bone pain, rash and mild bleeding (e.g., nose or gums bleed, easy bruising). Generally, younger children and those with their first dengue infection have a milder illness than older children and adults.

Dengue hemorrhagic fever is characterized by a fever that lasts from 2 to 7 days with general signs and symptoms consistent with dengue fever. When the fever declines, symptoms including persistent vomiting, severe abdominal pain and difficulty breathing may develop. This marks the beginning of a 24 to 48-hour period when the smallest blood vessels (capillaries) become excessively permeable ("leaky"), allowing the fluid component to escape from the blood vessels into the peritoneum (causing ascites) and pleural cavity (leading to pleural effusions). This may lead to failure of the circulatory system and shock, followed by death, if circulatory failure is not corrected. In addition, a patient with dengue hemorrhagic fever has a low platelet count and hemorrhagic manifestations, a tendency to bruise easily or other types of skin hemorrhages, bleeding nose or gums and possibly internal bleeding.

How long after exposure before symptoms appear?
Symptoms typically develop within 3 to 14 days, usually in 4 to 7 days.

How is dengue fever diagnosed?
The virus can be isolated in a lab or a test for specific antibodies can be performed on blood or other tissues.

What is the treatment for dengue?
There is no specific medication for treatment of a dengue infection. Persons who think they have dengue should use analgesics (pain relievers) with acetaminophen and avoid those containing aspirin. They should also rest, drink plenty of fluids and consult a physician. If they feel worse (e.g., develop vomiting and severe abdominal pain) in the first 24 hours after the fever declines, they should go immediately to the hospital for evaluation.

Is there an effective treatment for dengue hemorrhagic fever?
As with dengue fever, there is no specific medication for dengue hemorrhagic fever. It can, however, be effectively treated by fluid replacement therapy if an early clinical diagnosis is made. Dengue hemorrhagic fever management frequently requires hospitalization. Physicians who suspect that a patient has dengue hemorrhagic fever may want to consult the Dengue Branch at CDC for more information.

Where can outbreaks of dengue occur?
Outbreaks of dengue occur primarily in areas where *Ae. aegypti* (sometimes also *Ae. albopictus*) mosquitoes live. This includes most tropical urban areas of the world.   Dengue viruses may be introduced into areas by travelers who become infected while visiting other areas of the tropics where dengue commonly exists.

What can be done to reduce the risk of acquiring dengue?
There is no vaccine for preventing dengue. The best preventive measure for residents living in areas infested with *Ae. aegypti* is to eliminate the places where mosquitoes lay their eggs, primarily artificial containers that hold water.

Items that collect rainwater or to store water (for example, plastic containers, 55-gallon drums, buckets or used automobile tires) should be covered or properly discarded. Pet and animal watering containers and vases with fresh flowers should be emptied and cleaned (to remove eggs) at least once a week. This will eliminate the mosquito eggs and larvae and reduce the number of mosquitoes present in these areas.

Using air conditioning or window and door screens reduces the risk of mosquitoes coming indoors. Proper application of mosquito repellents containing 20% to 30% DEET as the active ingredient on exposed skin and clothing decreases the risk of being bitten by mosquitoes. The risk of dengue infection for international travelers appears to be small. There is increased risk if an epidemic is in progress or visitors are in housing without air conditioning or screened windows and doors.

How can we prevent epidemics of dengue hemorrhagic fever?
The emphasis for dengue prevention is on sustainable, community-based, integrated mosquito control, with limited reliance on insecticides (chemical larvicides and adulticides). Preventing epidemic disease requires a coordinated community effort to increase awareness about dengue fever/dengue hemorrhagic fever, how to recognize it and how to control the mosquito that transmits it. Residents are responsible for keeping their yards and patios free of standing water where mosquitoes can be produced.

For more information please visit these websites:
- CDC Dengue Fever Information: http://www.cdc.gov/Dengue
- CDC Dengue Fever Information for Healthcare Providers: http://www.cdc.gov/dengue/clinicalLab/clinical.html
- CDC Insect Repellent Use and Safety: http://www.cdc.gov/westnile/faq/repellent.html
- U.S. Environmental Protection Agency (EPA) Registered Insect Repellents: https://www.epa.gov/insect-repellents
- World Health Organization: http://www.who.int/topics/dengue/en/
- Pan-American Health Organization: http://www.paho.org/dengue
- U.S. Geologic Survey Dengue Human Case Maps: http://diseasemaps.usgs.gov/mapviewer