

## Arboviral Infections

**Organism:** Arthropod-borne viruses (arboviruses) are transmitted to humans primarily through the bites of infected mosquitoes, ticks, sand flies, or midges. Other modes of transmission for some arboviruses include blood transfusion, organ transplantation, perinatal transmission, consumption of unpasteurized dairy products, breast feeding, and laboratory exposures. More than 130 arboviruses are known to cause human disease. Most arboviruses of public health importance belong to one of three virus genera: *Flavivirus*, *Alphavirus*, and *Bunyavirus*.

Examples include:

- [Chikungunya Fever](#)
- [Eastern Equine Encephalitis](#)
- [Japanese Encephalitis](#)
- [LaCrosse Encephalitis](#)
- [Powassan](#)
- [Saint Louis Encephalitis](#)
- [Venezuelan Equine Encephalitis](#)
- [West Nile Encephalitis](#)
- [Western Equine Encephalitis](#)
- [Yellow Fever](#)
- [Dengue Fever](#)
- [Zika Virus Disease](#)

**Incubation period:** Variable depending on specific virus; generally 2-3 weeks

**Infectious period:** Usually not person-to-person. However, see Zika virus specific information regarding sexual transmission windows: up to 8 weeks if asymptomatic, up to 6 months if symptomatic.

**Transmission route:** From exposure to an arthropod vector, generally, a mosquito; or infrequently, blood transfusion

**Treatment:** No specific treatment; often symptomatic treatment as needed

### Information Needed for the Investigation

#### Verify the Diagnosis

- Interview the patient for potential exposures and travel history.
- There is an embedded West Nile Virus form in AK STARS, but as a start you can use the WA DOH generic arboviral form available at: <http://www.doh.wa.gov/Portals/1/Documents/5100/210-066-ReportForm-Arbovirus.pdf>
- There is a specific Dengue Fever Form available at: [http://www.cdc.gov/dengue/resources/dengueCaseReports/DCIF\\_English.pdf](http://www.cdc.gov/dengue/resources/dengueCaseReports/DCIF_English.pdf)
- There are several forms and documents required for Zika virus; consult P:drive for most updated lab and epi guidance (P:\Infectious\INFT-TB\Zika).

- Ensure that correct tests have been ordered; consult CDC as appropriate.

### **Case definitions**

- Available on CDC's website: <http://www.cdc.gov/nndss/script/casedefDefault.aspx> (arboviral diseases; dengue; Zika)

### **Clinical Description**

Most arboviral infections are asymptomatic. Clinical disease ranges from mild febrile illness to severe encephalitis. For the purpose of surveillance and reporting, based on their clinical presentation, most arboviral disease cases are often categorized into two primary groups: neuroinvasive disease and nonneuroinvasive disease. Note for Zika Virus Disease, there are additional presentations associated with congenital infection.

#### Neuroinvasive disease

Many arboviruses cause neuroinvasive disease such as aseptic meningitis, encephalitis, or acute flaccid paralysis (AFP). These illnesses are usually characterized by the acute onset of fever with headache, myalgia, stiff neck, altered mental status, seizures, limb weakness, or cerebrospinal fluid (CSF) pleocytosis. AFP may result from anterior ("polio") myelitis, peripheral neuritis, or post-infectious peripheral demyelinating neuropathy (i.e., Guillain-Barré syndrome). Less common neurological manifestations, such as cranial nerve palsies, also occur.

#### Non-neuroinvasive disease

Most arboviruses are capable of causing an acute systemic febrile illness (e.g., West Nile fever) that may include headache, myalgias, rash, or gastrointestinal symptoms. Other physical complaints may include vertigo, stiff neck, or muscle weakness without progression to more clinically apparent neurological involvement.

A clinically compatible case of arboviral disease is as defined as follows:

#### Neuroinvasive disease

- Meningitis, encephalitis, acute flaccid paralysis, or other acute signs of central or peripheral neurologic dysfunction, as documented by a physician, AND
- Absence of a more likely clinical explanation.

#### Non-Neuroinvasive disease

- Fever or chills as reported by the patient or a health-care provider, AND
- Absence of neuroinvasive disease, AND
- Absence of a more likely clinical explanation.

### **Laboratory Criteria for Diagnosis**

- Isolation of virus from, or demonstration of specific viral antigen or nucleic acid in, tissue, blood, CSF, or other body fluid, OR
- Four-fold or greater change in virus-specific quantitative antibody titers in paired sera, OR
- Virus-specific IgM antibodies in serum with confirmatory virus-specific neutralizing antibodies in the same or a later specimen, OR
- Virus-specific IgM antibodies in CSF or serum.

*Note that Dengue Fever is more complicated; consult laboratory and case definition specific for this virus: <http://www.cdc.gov/dengue/clinicalLab/laboratory.html>*

*Note that Zika Virus Disease is also more complicated; consult laboratory and case definition specific for this virus: <http://www.cdc.gov/zika/hc-providers/diagnostic.html>*

## Case Classification

### Probable

#### Neuroinvasive disease

A case that meets the above clinical criteria for neuroinvasive disease and the following laboratory criteria:

- Virus-specific IgM antibodies in CSF or serum but with no other testing.

#### Non-Neuroinvasive disease

A case that meets the above clinical criteria for non-neuroinvasive disease and the laboratory criteria for a probable case:

- Virus-specific IgM antibodies in serum but with no other testing.

### Confirmed

#### Neuroinvasive disease

A case that meets the above clinical criteria for neuroinvasive disease and one or more of the following laboratory criteria for a confirmed case:

- Isolation of virus from, or demonstration of specific viral antigen or nucleic acid in, tissue, blood, CSF, or other body fluid, OR
- Four-fold or greater change in virus-specific quantitative antibody titers in paired sera, OR
- Virus-specific IgM antibodies in serum with confirmatory virus-specific neutralizing antibodies in the same or a later specimen, OR
- Virus-specific IgM antibodies in CSF and a negative result for other IgM antibodies in CSF for arboviruses endemic to the region where exposure occurred.

#### Non-Neuroinvasive disease

A case that meets the above clinical criteria for non-neuroinvasive disease and one or more of the following laboratory criteria for a confirmed case:

- Isolation of virus from, or demonstration of specific viral antigen or nucleic acid in, tissue, blood, or other body fluid, excluding CSF, OR
- Four-fold or greater change in virus-specific quantitative antibody titers in paired sera, OR
- Virus-specific IgM antibodies in serum with confirmatory virus-specific neutralizing antibodies in the same or a later specimen.

*Note that Dengue Fever varies somewhat from this definition; consult the more specific case definition specific for this virus: <https://www.cdc.gov/nndss/conditions/search/dengue/>*

*Note that Zika Virus Disease varies somewhat from this definition; consult the more specific case definition specific for this virus: <https://wwwn.cdc.gov/nndss/conditions/search/ZIKA/>*

### **Determine the Extent of Illness**

- If exposure is suspected to be local (i.e., no travel history), we will need to consult CDC and discuss potential unusual sources of virus and/or changes in vector population.
- Depending on the travel history, information may need to be relayed back to the state/jurisdiction where the exposure occurred.

### **Laboratory Specimens**

Laboratory testing will be generally by a commercial lab; there is no capacity at ASVL to process these specimens. For unique situations, contact CDC to see about specific testing capacity: CDC Fort Collins, [dvbd@cdc.gov](mailto:dvbd@cdc.gov), (970) 221-6400.

- For Dengue, specimens can be routed via ASPHL or ASVL to CDC Fort Collins for testing (no longer sent to Puerto Rico).
- Fillable test request form: <http://www.cdc.gov/laboratory/specimen-submission/pdf/form-50-34.pdf>. Check on the P drive (P:\Infectious\INFT-TB\2016 MMM\Arboviral diseases) for a copy of the form pre-filled with ASPHL/ASVL data.
- Recommend clinician consult with CDC/experts if they are looking for specific details on interpreting diagnostics or patient status.
- Note that for Zika Virus Disease there are specific instructions on the specimens, timing of collection, and testing locations that must be followed. Consult the P:drive for most updated lab and epi guidance (P:\Infectious\INFT-TB\Zika).

### **Hospital Considerations**

#### **Contact and Control Measures**

- None indicated.
- Some of these cases have caused media inquiries and community concern; consider the need for educational materials.

#### **Reporting Requirements**

- FTR: write up cluster investigations
- AK STARS: enter all *confirmed* and *probable* cases. Select “Arboviral diseases” as the disease, then choose the appropriate virus as the Secondary Condition. Ensure that cases with travel history are marked as “imported” in AK STARS. For “Dengue”, select “Dengue virus” as its own category.
- CDC cannot process reports sent through weekly NETSS transmissions and requires reporting via ArboNet: <https://wwwn.cdc.gov/arboNet/login.aspx>
- There may be additional reporting required for Zika Virus Disease, especially for cases that occur in pregnant women or their infants.

#### **Resources**

- USGS Arboviral disease maps: <http://diseasemaps.usgs.gov/index.html>
- CDC/DVBID <http://www.cdc.gov/ncezid/dvbd/about.html>

## **Other CDC Notes:**

### Imported arboviral diseases

Human disease cases due to Dengue or Yellow fever viruses are nationally notifiable to CDC using specific case definitions. However, many other exotic arboviruses (e.g., Chikungunya, Japanese encephalitis, Tick-borne encephalitis, Venezuelan equine encephalitis, and Rift Valley fever viruses) are important public health risks for the United States as competent vectors exist that could allow for sustained transmission upon establishment of imported arboviral pathogens. Health care providers and public health officials should maintain a high index of clinical suspicion for cases of potentially exotic or unusual arboviral etiology, particularly in international travelers. If a suspected case occurs, it should be reported to the appropriate local/state health agencies and CDC.

### Interpreting arboviral laboratory results:

- **Serologic cross-reactivity:** In some instances, arboviruses from the same genus produce cross-reactive antibodies. In geographic areas where two or more closely-related arboviruses occur, serologic testing for more than one virus may be needed and results compared to determine the specific causative virus. For example, such testing might be needed to distinguish antibodies resulting from infections within genera, e.g., flaviviruses such as West Nile, St. Louis encephalitis, Powassan, Dengue, or Japanese encephalitis viruses.
- **Rise and fall of IgM antibodies:** For most arboviral infections, IgM antibodies are generally first detectable at 3 to 8 days after onset of illness and persist for 30 to 90 days, but longer persistence has been documented (e.g., up to 500 days for West Nile virus). Serum collected within 8 days of illness onset may not have detectable IgM and testing should be repeated on a convalescent-phase sample to rule out arboviral infection in those with a compatible clinical syndrome.
- **Persistence of IgM antibodies:** Arboviral IgM antibodies may be detected in some patients months or years after their acute infection. Therefore, the presence of these virus-specific IgM antibodies may signify a past infection and be unrelated to the current acute illness. Finding virus-specific IgM antibodies in CSF or a fourfold or greater change in virus-specific antibody titers between acute- and convalescent-phase serum specimens provides additional laboratory evidence that the arbovirus was the likely cause of the patient's recent illness. Clinical and epidemiologic history also should be carefully considered.
- **Persistence of IgG and neutralizing antibodies:** Arboviral IgG and neutralizing antibodies can persist for many years following a symptomatic or asymptomatic infection. Therefore, the presence of these antibodies alone is only evidence of previous infection and clinically compatible cases with the presence of IgG, but not IgM, should be evaluated for other etiologic agents.
- **Arboviral serologic assays:** Assays for the detection of IgM and IgG antibodies commonly include enzyme-linked immunosorbent assay (ELISA), microsphere immunoassay (MIA), or immunofluorescence assay (IFA). These assays provide a presumptive diagnosis and should have confirmatory testing performed. Confirmatory testing involves the detection of arboviral-specific neutralizing antibodies utilizing assays such as plaque reduction neutralization test (PRNT).
- **Other information to consider.** Vaccination history, detailed travel history, date of onset of symptoms, and knowledge of potentially cross-reactive arboviruses known to circulate in the geographic area should be considered when interpreting results.