

Arboviral Diseases, Neuroinvasive and Non-neuroinvasive 2015 Case Definition

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CSTE Position Statement(s)

- 14-ID-04

Subtype(s)

- California serogroup virus diseases
- Chikungunya virus disease
- Eastern equine encephalitis virus disease
- Powassan virus disease
- St. Louis encephalitis virus disease
- West Nile virus disease
- Western equine encephalitis virus disease

Background

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, 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 *Orthobunyavirus*.

California serogroup viruses include:

- California encephalitis
- Jamestown Canyon
- Keystone
- La Crosse
- Snowshoe hare

- Trivittatus viruses

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, arboviral disease cases are often categorized into two primary groups: neuroinvasive disease and nonneuroinvasive disease.

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-Barre' 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, arthralgia, rash, or gastrointestinal symptoms. Some viruses also can cause more characteristic clinical manifestations, such as severe polyarthralgia or arthritis due to Chikungunya virus or other alphaviruses (e.g., Mayaro, Ross River, O'nyong-nyong).

Clinical Criteria

A clinically compatible case of arboviral disease is 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. Other clinically compatible symptoms of arbovirus disease include: headache, myalgia, rash, arthralgia, vertigo, vomiting, paresis and/ or nuchal rigidity.

Non-neuroinvasive disease

- Fever (chills) as reported by the patient or a health-care provider, **AND**

- Absence of neuroinvasive disease, **AND**
- Absence of a more likely clinical explanation. Other clinically compatible symptoms of arbovirus disease include: headache, myalgia, rash, arthralgia, vertigo, vomiting, paresis and/ or nuchal rigidity.

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.

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, with or without a reported pleocytosis, 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.

Comments

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., 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.