



Merlin disease code: 07000 Flavivirus Disease and Infection

[Paper case report form](#)



Acute and convalescent sera for infections believed to be Florida-acquired must be sent to the Bureau of Public Health Laboratories (sera for infections believed to be acquired outside Florida do not need to be forwarded to BPHL unless the serum is from a pregnant woman, infant, or possible Guillain-Barré syndrome case)

Merlin extended data required

## Background

Viruses in the genus *Flavivirus* can be highly cross-reactive, particularly among exotic arboviruses such as dengue virus (DENV) and Zika virus (ZIKV). In some individuals, IgM antibody testing cannot differentiate between the two infections and IgG antibodies strongly cross-react between flaviviruses. Previous flavivirus infections may further complicate result interpretation and is common in some populations (e.g., those residing in or long-term visitors to dengue endemic countries). Even the completion of plaque reduction neutralization testing (PRNT), often considered the gold standard of flavivirus diagnostics, may not provide a definitive result. Other flaviviruses with potential cross-reactivity include other exotic arboviruses such as yellow fever virus and Japanese encephalitis virus, as well as arboviruses endemic to Florida, such as West Nile virus (WNV) and St. Louis encephalitis virus (SLEV), may also cross-react with DENV or ZIKV.

## Clinical criteria for case classification

A person with one or more of the following not explained by another etiology:

- Clinically compatible illness that includes one or more of the following:
  - Fever (measured or reported),
  - **Or** rash,
  - **Or** arthralgia,
  - **Or** conjunctivitis,
  - **Or** nausea/vomiting,
  - **Or** retro-orbital pain or ocular pain,
  - **Or** headache,
  - **Or** myalgia,
  - **Or** thrombocytopenia (platelet numbers of  $<200,000/\text{mm}^3$ ),
  - **Or** leukopenia (a total white blood cell count of  $<5,000/\text{mm}^3$ ),
  - **Or** abdominal pain or tenderness,
  - **Or** persistent vomiting,
  - **Or** mucosal bleeding at any site (e.g., gums, urinary tract),
  - **Or** liver enlargement  $>2$  centimeters;
- **Or** complication of pregnancy including either of the following:
  - Fetal loss
  - **Or** fetus or neonate with congenital microcephaly, congenital intracranial calcifications, other structural brain or eye abnormalities, or other congenital central nervous system-related abnormalities including defects such as clubfoot or multiple joint contractures;
- **Or** Guillain-Barré syndrome (GBS) meeting Brighton Collaboration level 1, 2, or 3 or other neurologic manifestations.

## Laboratory criteria for case classification

### Supportive:

#### ***For locally acquired cases:***

- All of the following:
  - Positive enzyme immunoassay (EIA), microsphere immunofluorescence assay (MIA), or immunofluorescent assay (IF) for ZIKV IgM antibodies in serum or CSF by a state public health laboratory (PHL) or the CDC,
  - **And** positive EIA, MIA, or IF for IgM antibodies to DENV (or other flaviviruses endemic to the region where the exposure occurred) by a PHL or CDC,
  - **And** no PRNT performed;
- **Or** all of the following:
  - Positive EIA, MIA, or IF for ZIKV IgM antibodies in serum or CSF by a PHL or CDC,
  - **And** positive EIA, MIA, or IF for IgM antibodies to DENV (or other flaviviruses endemic to the region where the exposure occurred) by a PHL or CDC,
  - **And** positive neutralizing antibody titers by PRNT against ZIKV by a PHL or CDC,
  - **And** positive neutralizing antibody titers by PRNT against DENV (or other flaviviruses endemic to the region where the exposure occurred) by a PHL or CDC.

#### ***For imported cases:***

- All of the following:
  - Positive EIA, MIA, or IF for ZIKV IgM antibodies in serum or CSF,
  - **And** positive EIA, MIA, or IF for IgM antibodies to DENV (or other flaviviruses endemic to the region where the exposure occurred),
  - **And** no PRNT performed;
- **Or** all of the following:
  - Positive EIA, MIA, or IF for ZIKV IgM antibodies in serum or CSF,
  - **And** positive EIA, MIA, or IF for IgM antibodies to DENV (or other flaviviruses endemic to the region where the exposure occurred),
  - **And** positive neutralizing antibody titers by PRNT against ZIKV,
  - **And** positive neutralizing antibody titers by PRNT against DENV (or other flaviviruses endemic to the region where the exposure occurred).

## Epidemiological criteria for case classification

### All of the following:

- An illness that is clinically indistinguishable between flaviviruses;
- **And** a person who is not epidemiologically linked to a confirmed or probable case of a known flavivirus (e.g., ZIKV, DENV, WNV, SLEV, yellow fever virus);
- **And** one or more of the following:
  - Resides in or past travel to an area with known transmission of more than one flavivirus,
  - **Or** Likely vector exposure in an area with suitable seasonal and ecological conditions for potential local vectorborne transmission,
  - **Or** Receipt of blood or blood products within 30 days of symptom onset,
  - **Or** Receipt of organ or tissue transplant within 30 days of symptom onset.

## Case classification

### ***Flavivirus disease***

#### Suspect:

A clinically compatible illness in a person with supportive laboratory criteria and epidemiological criteria.

### ***Flavivirus infection***

#### Suspect:

A person with supportive laboratory criteria and epidemiological criteria.

## Criteria to distinguish a new case from previous reports

Not applicable.

## Comments

Due to the cross-reactivity seen among flaviviruses, it is important to ask if there has been any lifetime travel to a flavivirus-endemic country or vaccination for yellow fever or Japanese encephalitis viruses. Testing for other relevant flaviviruses at the Bureau of Public Health Laboratories (BPHL) will occur when applicable. Individuals with neuroinvasive symptoms and no reported travel should be evaluated for WNV and SLEV infection.