



Merlin disease code: 06010 Zika Virus Disease and Infection, Non-Congenital

[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

Zika virus (ZIKV) is an emerging mosquito-borne virus that has spread rapidly across the Americas in 2015 and 2016. Only about 1 in 5 people infected with Zika virus are symptomatic and some patients may not have fever. ZIKV disease, dengue fever, and chikungunya fever are difficult to differentiate clinically. It is also important to note that co-infections with these viruses can occur. Subsequent investigations have demonstrated vertical transmission of ZIKV to the fetus in pregnant women. These in utero infections have been associated with the potential for devastating outcomes including microcephaly, other central nervous system abnormalities, and spontaneous abortions. There is also an association with ZIKV infection and post-infection Guillain-Barré syndrome (GBS).

## 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** 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** GBS meeting Brighton Collaboration level 1, 2, or 3 or other neurologic manifestations.

## Laboratory criteria for case classification

Confirmatory:

***For all locally acquired cases (including index, sporadic, and locally acquired via mosquito exposure after epidemiologic linkage or transmission in an area has been established), either of the following:***

- Detection of ZIKV by culture, viral antigen, or viral RNA in serum, CSF, tissue, or other specimen (e.g., urine, whole blood, amniotic fluid, semen) by a state public health laboratory (PHL) or the CDC
- **Or** 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 PHL or CDC,
  - **And** positive neutralizing antibody titers by plaque reduction neutralization test (PRNT) against ZIKV by a PHL or CDC,
  - **And** negative neutralizing antibody titers by PRNT against dengue virus (DENV) (or other flaviviruses endemic to the region where exposure occurred) by a PHL or CDC.

***For imported cases, either of the following:***

- Detection of ZIKV by culture, viral antigen, or viral RNA in serum, CSF, tissue, or other specimen (e.g., urine, whole blood, amniotic fluid, semen)
- **Or** all of the following:
  - Positive EIA, MIA, or IF for ZIKV IgM antibodies in serum or CSF;
  - **And** positive neutralizing antibody titers by PRNT against ZIKV;
  - **And** negative neutralizing antibody titers by PRNT against DENV (or other flaviviruses endemic to the region where exposure occurred).

Presumptive:

***For index or sporadic cases acquired locally via mosquito exposure, all of the following:***

- Positive EIA, MIA, or IF for ZIKV IgM antibodies in serum or CSF by a PHL or CDC;
- **And** positive neutralizing antibody titers by PRNT against ZIKV by a PHL or CDC;
- **And** absence of positive EIA, MIA, or IF for DENV IgM antibodies (or other flaviviruses endemic to the region where the exposure occurred).

***For cases acquired locally via mosquito exposure after epidemiologic linkage or transmission in an area has been established, one or more of the following:***

- All of the following:
  - Positive or equivocal EIA, MIA, or IF for ZIKV IgM antibodies in serum or CSF by a PHL or CDC;
  - **And** positive neutralizing antibody titers by PRNT against ZIKV by a PHL or CDC;
  - **And** absence of positive EIA, MIA, or IF for DENV IgM antibodies (or other flaviviruses endemic to the region where the exposure occurred).
- **Or** all of the following:
  - Positive EIA, MIA, or IF for ZIKV IgM antibodies in serum or CSF by a PHL or CDC;
  - **And** negative or equivocal EIA, MIA, or IF for DENV IgM antibodies (or other flaviviruses endemic to the region where the exposure occurred) by a PHL or CDC;
  - **And** absence of a negative neutralizing antibody titers by PRNT against ZIKV;
- **Or** both of the following:
  - Seroconversion from negative for ZIKV IgM antibodies in an acute-phase specimen to positive for ZIKV IgM antibodies in a convalescent-phase specimen by EIA, MIA, or IF in serum or CSF by a PHL or CDC
  - **And** negative or equivocal EIA, MIA, or IF for DENV IgM antibodies (or other flaviviruses endemic to the region where the exposure occurred) by a PHL or CDC;
- **Or** all of the following:
  - Positive EIA, MIA, or IF for ZIKV IgM antibodies in serum or CSF by a PHL or CDC;
  - **And** negative DENV polymerase chain reaction (PCR) by a PHL or CDC;
  - **And** negative or equivocal EIA, MIA, or IF for DENV IgM antibodies by a PHL or CDC;
  - **And** seroconversion from negative for DENV IgG antibodies in an acute-phase specimen to positive for DENV IgG antibodies in a convalescent-phase specimen by EIA, MIA, or IF by a PHL or CDC;

- **Or** all of the following:
  - Positive EIA, MIA, or IF for ZIKV IgM antibodies in serum;
  - **And** positive EIA, MIA, or IF for DENV IgM antibodies (or other flaviviruses endemic to the region where the exposure occurred);
  - **And** epidemiological linkage to a confirmed or probable ZIKV case.

***For imported cases in pregnant women, all of the following:***

- Positive or equivocal EIA, MIA, or IF for ZIKV IgM antibodies in serum or CSF;
- **And** positive neutralizing antibody titers by PRNT against ZIKV;
- **And** absence of positive EIA, MIA, or IF for DENV IgM antibodies (or other flaviviruses endemic to the region where the exposure occurred).

***For non-pregnant, imported cases, one or more of the following:***

- All of the following:
  - Positive or equivocal EIA, MIA, or IF for ZIKV IgM antibodies in serum or CSF;
  - **And** positive neutralizing antibody titers by PRNT against ZIKV;
  - **And** absence of positive EIA, MIA, or IF for DENV IgM antibodies (or other flaviviruses endemic to the region where the exposure occurred);
- **Or** both of the following:
  - Seroconversion from negative for ZIKV IgM antibodies in an acute-phase specimen to positive for ZIKV IgM antibodies in a convalescent-phase specimen by EIA, MIA, or IF in serum or CSF
  - **And** negative or equivocal EIA, MIA, or IF for DENV IgM antibodies (or other flaviviruses endemic to the region where the exposure occurred);
- **Or** all of the following:
  - Positive EIA, MIA, or IF for ZIKV IgM antibodies in serum or CSF;
  - **And** negative DENV PCR;
  - **And** negative or equivocal EIA, MIA, or IF for DENV IgM antibodies;
  - **And** seroconversion from negative for DENV IgG antibodies in an acute-phase specimen to positive for DENV IgG antibodies in a convalescent-phase specimen by EIA, MIA, or IF;
- **Or** all of the following:
  - Positive EIA, MIA, or IF for ZIKV IgM antibodies in serum or CSF;
  - **And** negative DENV PCR;
  - **And** negative or equivocal EIA, MIA, or IF for DENV IgM antibodies;
  - **And** positive for DENV IgG antibodies;
- **Or** all of the following:
  - Positive EIA, MIA, or IF for ZIKV IgM antibodies in serum;
  - **And** positive EIA, MIA, or IF for DENV IgM antibodies (or other flaviviruses endemic to the region where the exposure occurred);
  - **And** epidemiological linkage to a confirmed or probable ZIKV case.

Supportive:

***For locally acquired cases and imported cases in pregnant women, one or more of the following:***

- Both of the following:
  - Positive ZIKV PCR by a commercial laboratory
  - **And** no testing performed by a PHL or CDC on the same specimen
- **Or** both of the following:
  - Positive EIA, MIA, or IF for ZIKV IgM antibodies by a commercial laboratory
  - **And** no testing performed by a PHL or CDC on the same specimen.

***For all cases, one or more of the following:***

- All of the following:
  - Positive, equivocal, or indeterminate EIA, MIA, or IF for ZIKV IgM antibodies in serum or CSF;
  - **And** absence of positive DENV IgM antibodies (or other flaviviruses endemic to the region where the exposure occurred);
  - **And** absence of positive or negative neutralizing antibody titers by PRNT against ZIKV;
- **Or** both of the following:
  - Positive neutralizing antibody titers by PRNT against ZIKV
  - **And** absence of positive DENV IgM antibodies (or other flaviviruses endemic to the region where the exposure occurred);
- **Or** all of the following:
  - Positive ZIKV PCR by a commercial laboratory;
  - **And** negative or equivocal ZIKV PCR by a PHL or CDC for the same specimen;
  - **And** absence of a positive or equivocal EIA, MIA, or IF for ZIKV IgM antibodies by a PHL or CDC for the same specimen;
  - **And** no additional specimens collected;
- **Or** all of the following:
  - Positive or equivocal EIA, MIA, or IF for ZIKV IgM antibodies by a commercial laboratory;
  - **And** negative EIA, MIA, or IF for ZIKV IgM antibodies by a PHL or CDC for the same specimen;
  - **And** positive neutralizing antibody titers by PRNT against ZIKV.

Not a case:

One or more of the following:

- Both of the following:
  - Positive or equivocal EIA, MIA, or IF for ZIKV IgM antibodies by a commercial laboratory
  - **And** negative EIA, MIA, or IF for ZIKV IgM antibodies by a PHL or CDC for the same specimen;
- **Or** all of the following:
  - Positive ZIKV PCR by a commercial laboratory;
  - **And** negative or equivocal ZIKV PCR by a PHL or CDC;
  - **And** negative or indeterminate EIA, MIA, or IF for ZIKV IgM antibodies by a PHL or CDC for the same specimen;
  - **And** negative or indeterminate EIA, MIA, or IF for ZIKV IgM antibodies in a convalescent specimen collected 7 days to 12 weeks after the first specimen;

- **Or** negative ZIKV PCR;
- **Or** negative EIA, MIA, or IF for ZIKV IgM antibodies;
- **Or** testing is otherwise determined to be falsely positive by case reviewer.

## Epidemiological criteria for case classification

### General epidemiological criteria:

#### ***For symptomatic cases, one or more of the following:***

- Resides in or recent travel to an area with **outbreak** ZIKV transmission,
- **Or** received blood or blood products within 30 days of symptom onset,
- **Or** received organ or tissue transplant within 30 days of symptom onset,
- **Or** epidemiologically linked to a confirmed or probable case,
- **Or** sexual contact with a confirmed or probable case of ZIKV infection or person with recent travel to an area with **outbreak** ZIKV transmission,
- **Or** likely vector exposure in an area with suitable seasonal and ecological conditions for potential local vectorborne transmission.

#### ***For asymptomatic cases in pregnant women, one or more of the following:***

- Resides in or recent travel to an area with **outbreak** ZIKV transmission,
- **Or** epidemiologically linked to a confirmed or probable case,
- **Or** sexual contact with a confirmed or probable case of ZIKV infection or person with recent travel to an area with **outbreak** ZIKV transmission,

#### ***For possibly locally acquired asymptomatic cases***

Epidemiologically linked to a confirmed or probable case.

### Confirmatory perinatal linkage:

A mother whose baby is a confirmed congenital Zika case.

### Presumptive perinatal linkage:

A mother whose baby is a probable congenital Zika case.

### Supportive perinatal linkage:

A mother whose baby is a suspect congenital Zika case.

## Case classification

### ***Zika virus disease***

#### Confirmed:

Either of the following:

- A clinically compatible illness in a person with confirmatory laboratory criteria and general epidemiological criteria
- **Or** a clinically compatible illness in a mother with confirmatory perinatal linkage.

## Probable:

Either of the following:

- A clinically compatible illness in a person with presumptive laboratory criteria and general epidemiological criteria
- **Or** a clinically compatible illness in a mother with presumptive perinatal linkage.

## Suspect:

One or more of the following:

- A clinically compatible illness in a person with supportive laboratory criteria and general epidemiological criteria,
- **Or** a clinically compatible illness in a mother with supportive perinatal linkage,
- **Or** a case transferred from another jurisdiction that does not otherwise meet Florida's case definition.

## ***Zika virus infection***

### Confirmed:

Either of the following:

- A person with confirmatory laboratory criteria with general epidemiological criteria
- **Or** a mother with confirmatory perinatal linkage.

### Probable:

Either of the following:

- A person with presumptive laboratory criteria with general epidemiological criteria
- **Or** a mother with presumptive perinatal linkage.

### Suspect:

One or more of the following:

- A person with supportive laboratory criteria and general epidemiological criteria,
- **Or** a mother with supportive perinatal linkage,
- **Or** a case transferred from another jurisdiction that does not otherwise meet Florida's case definition.

## Criteria to distinguish a new case from previous reports

Not applicable.

## Comments

Cross-reaction with related flaviviruses (e.g., dengue, West Nile, yellow fever, Japanese encephalitis viruses) on serological tests is common and results may be difficult to interpret. Due to this cross-reactivity, 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. In addition, people with dengue infection often test positive for ZIKV IgM.

Due to the cross-reactivity seen among flaviviruses, individuals testing positive for both ZIKV and DENV IgM should be reported as flavivirus disease and infection (Merlin disease code: 07000). PRNT is not required to meet these criteria; however, if a PRNT is performed, there should be positive neutralizing antibody titers to both ZIKV and DENV. If an individual with flavivirus results is epidemiologically linked to a confirmed or probable ZIKV or DENV case, the case should not be reported as a flavivirus case.

Clinicians should also consider testing for dengue and chikungunya fever for suspect cases of ZIKV disease if fever was reported. As testing capacity allows, all specimens meeting the requirements for ZIKV disease PCR testing at the Bureau of Public Health Laboratories (BPHL) will also be tested for dengue and chikungunya viruses if the patient reported fever. All specimens collected in the first four days of illness and meeting standard requirements for dengue and chikungunya testing will also be tested for Zika virus by PCR if travel to a ZIKV disease endemic area is reported.

### **Differentiating between ZIKV and DENV infections in PCR-negative patients with positive flavivirus labs**

- Conjunctivitis and pruritic rash are more common with ZIKV disease than dengue fever.
- Thrombocytopenia and leukopenia are more common and severe in cases of dengue fever compared to ZIKV disease.
- ZIKV is not known to cause severe syndromes that can be seen with DENV (dengue hemorrhagic fever or dengue shock syndrome).
  
- ZIKV IgM titers are usually positive in dengue fever patients. DENV IgM titers may or may not be positive in ZIKV disease patients. EIA IgM results from BPHL are not quantitative and the values derived from this assay cannot be compared between illnesses.
- For non-PCR positive cases, dengue fever cases should be created instead of ZIKV disease cases if one or more of the following is true:
  - The clinician ordered dengue testing, did not request Zika testing, and dengue IgM was positive;
  - **Or** the clinician ordered Zika testing and Zika IgM was negative, while dengue IgM was positive;
  - **Or** PRNT testing is positive for dengue and negative for Zika.