



Merlin disease code: 06012 Zika Virus Disease and Infection, Congenital

[Paper case report form](#)



Specimens for all cases must be sent to the Bureau of Public Health Laboratories

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 (CNS) 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 liveborn infant with congenital microcephaly, intracranial calcifications, structural brain or eye abnormalities, or other congenital CNS-related abnormalities not explained by another etiology.

## Laboratory criteria for case classification

### Confirmatory:

Either of the following:

- Detection of ZIKV by culture, viral antigen, or viral RNA in fetal tissue, amniotic fluid, neonatal serum, cerebrospinal fluid (CSF), urine, or umbilical cord blood\* performed by a state public health laboratory (PHL) or the CDC in a specimen collected within 2 days of birth (or later if perinatal infection has been ruled out)
- **Or** all of the following:
  - Positive enzyme immunosorbent assay (EIA) or immunofluorescent assay (IFA) test for ZIKV IgM antibodies in neonatal serum, CSF, or umbilical cord blood\* collected within 2 days of birth (or later if perinatal infection has been ruled out);
  - **And** positive neutralizing antibody titers by plaque reduction neutralization test (PRNT) against ZIKV;
  - **And** negative neutralizing antibody titers by PRNT against dengue virus (DENV) or other flaviviruses endemic to the region where exposure occurred.

### Presumptive:

- Both of the following:
  - Positive or equivocal EIA or IFA test for ZIKV IgM antibodies in neonatal serum, CSF, or umbilical cord blood\* collected within 2 days of birth (or later if perinatal infection has been ruled out)
  - **And** positive neutralizing antibody titers by PRNT against ZIKV;

- **Or** all of the following:
  - Positive or equivocal EIA or IFA test for ZIKV IgM antibodies in neonatal serum, CSF, or umbilical cord blood\* collected within 2 days of birth or later if perinatal infection has been ruled out;
  - **And** negative or equivocal EIA or IFA test for DENV IgM antibodies or IgM antibodies to other flaviviruses endemic to the region where the exposure occurred;
  - **And** no PRNT performed.

## Supportive:

- All of the following:
  - Positive or equivocal EIA or IFA test for ZIKV IgM antibodies in neonatal serum, CSF, or umbilical cord blood\*;
  - **And** no DENV IgM testing performed;
  - **And** no PRNT performed;
  - **And** mother's test results do not rule out recent ZIKV infection;
- **Or** both of the following:
  - Positive neutralizing antibody titers by PRNT against ZIKV in a sample collected  $\geq 18$  months after birth
  - **And** no travel to an area with known ZIKV transmission reported for the infant since birth;
- **Or** both of the following:
  - Positive neutralizing antibody titers by PRNT against ZIKV in a sample collected  $\geq 18$  months after birth
  - **And** case reviewer determined low ZIKV exposure risk postnatally after reviewing postnatal travel history and 18-month test results;
- **Or** both of the following:
  - Positive EIA or IFA for ZIKV IgM antibodies from a commercial laboratory
  - **And** no testing performed by a PHL or CDC on the same specimen;
- **Or** both of the following:
  - Positive ZIKV PCR by a commercial laboratory;
  - **And** no testing performed by a PHL or CDC on the same specimen.

## Not a case:

One or more of the following:

- Both of the following:
  - Positive or equivocal EIA or IFA for ZIKV IgM antibodies by a commercial laboratory
  - **And** negative or indeterminate EIA or IFA 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 PCR by a PHL or CDC,
  - **And** absence of a positive or equivocal EIA or IFA for ZIKV IgM antibodies by a PHL or CDC for the same specimen;

- **Or** positive neutralizing antibody titers by PRNT against ZIKV in a sample collected <18 months after birth;
- **Or** negative neutralizing antibody titers by PRNT against ZIKV;
- **Or** negative ZIKV PCR;
- **Or** negative or indeterminate EIA or IFA for ZIKV IgM antibodies;
- **Or** testing is otherwise determined to be falsely positive by case reviewer.

\*Note: While collection of umbilical cord blood was initially recommended, neonatal serum is the preferred specimen type. Umbilical cord blood should only be submitted for testing when no serum is available.

## Epidemiological criteria for case classification

Infant's mother meets one or more of the following:

- Resides in or recent travel to an area with known ZIKV transmission,
- **Or** sexual contact with a confirmed or probable case of ZIKV infection or person with recent travel to an area with known ZIKV 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,
- **Or** association in time and place with a confirmed or probable case,
- **Or** likely vector exposure in an area with suitable seasonal and ecological conditions for potential local vectorborne transmission.

## Case classification

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

#### Confirmed:

Clinically compatible congenital disease in a neonate with confirmatory laboratory criteria whose mother meets the epidemiologic criteria.

#### Probable:

Clinically compatible congenital disease in a neonate with presumptive laboratory criteria whose mother meets the epidemiologic criteria.

#### Suspect:

Clinically compatible congenital disease in a neonate with supportive laboratory criteria whose mother meets the epidemiologic criteria

### ***Zika virus infection***

#### Confirmed:

A neonate with confirmatory laboratory criteria whose mother meets the epidemiologic criteria.

#### Probable:

A neonate with presumptive laboratory criteria whose mother meets the epidemiologic criteria.

#### Suspect:

A neonate with supportive laboratory criteria whose mother meets the epidemiologic criteria

## Criteria to distinguish a new case from previous reports

Not applicable.

## Comments

As part of the complete evaluation of congenital microcephaly or other CNS birth defects, testing for other congenital infections such as syphilis, toxoplasmosis, rubella, cytomegalovirus infection, lymphocytic choriomeningitis virus infection, and herpes simplex virus infections should be considered. An assessment of potential genetic and other teratogenic causes of the congenital anomalies should also be performed.

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 by the mother 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. It is also important to get the lifetime travel history for the infant, particularly if PRNT testing is going to be performed at 18 months of age to assess congenital exposure.