

	Merlin disease codes: 06103 Dengue Fever	Paper case report form
	Acute and convalescent sera for infections believed to be Florida-acquired and acute sera for infections believed to be acquired outside Florida must be sent to the Bureau of Public Health Laboratories	Merlin extended data required

Clinical criteria for case classification

Dengue fever:

- Fever as reported by the patient or health care provider.
- One or more of the following signs and symptoms may be present (not required):
 - Nausea/vomiting,
 - **Or** rash,
 - **Or** headache,
 - **Or** retro-orbital pain or ocular pain,
 - **Or** myalgia (muscle pain),
 - **Or** arthralgia (joint pain),
 - **Or** leukopenia (a total white blood cell count of <math><5,000/\text{mm}^3</math>)
 - **Or** one or more of the following warning signs for severe dengue:
 - Abdominal pain or tenderness,
 - **Or** persistent vomiting,
 - **Or** mucosal bleeding at any site (e.g., gums, urinary tract),
 - **Or** liver enlargement >2 centimeters,
 - **Or** thrombocytopenia (platelet numbers of <math><200,000/\text{mm}^3</math>),

Severe dengue (including dengue hemorrhagic fever [DHF] and dengue shock syndrome [DSS]):

- Fever as reported by the patient or health care provider
- **And** one or more of the following:
 - Respiratory distress with one or more of the following:
 - Hypovolemic shock,
 - **Or** pleural effusion (fluid around the lungs),
 - **Or** pericardial effusion (fluid around the heart),
 - **Or** ascites (abdominal fluid),
 - **Or** plasma leakage;
 - **Or** severe bleeding from the gastrointestinal tract (e.g., hematemesis, melena) or vagina (menorrhagia) as defined by requirement for medical intervention including intravenous fluid resuscitation or blood transfusion;
 - **Or** elevated aspartate aminotransferase (AST) or alanine aminotransferase (ALT) $\geq 1,000$ U/L;
 - **Or** impaired level of consciousness or diagnosis of encephalitis, encephalopathy, or meningitis;
 - **Or** heart or other organ involvement including myocarditis, cholecystitis, and pancreatitis.

Laboratory criteria for case classification

Confirmatory:

One or more of the following:

- Isolation of dengue virus (DENV) from a clinical specimen;
- **Or** detection of DENV antigens in tissue by a validated immunofluorescence or immunohistochemistry (IHC) assay;
- **Or** detection of DENV NS1 antigen in serum or plasma by a validated immunoassay;
- **Or** detection of DENV nucleic acid in a clinical specimen by polymerase chain reaction (PCR) or other advanced molecular detection method;
- **Or** fourfold rise in plaque reduction neutralization test (PRNT) end point titer (as expressed by the reciprocal of the last serum dilution showing a 90% reduction in plaque counts compared to the virus infected control) between DENV and other flaviviruses tested in a convalescent serum specimen;
- **Or** both of the following:
 - Seroconversion from dengue IgM-negative in an acute phase specimen collected ≤5 days after symptom onset to dengue IgM-positive in a convalescent-phase specimen collected ≥5 days after symptom onset (e.g., enzyme immunoassay [EIA], microsphere immunoassay [MIA], immunofluorescence assay [IF])
 - **And** negative or indeterminate for Zika IgM antibodies (e.g., EIA, MIA, or IF);
- **Or** both of the following:
 - Seroconversion from dengue IgG-negative in an acute phase specimen collected ≤5 days after symptom onset to dengue IgG-positive in a convalescent-phase specimen collected ≥5 days after symptom onset (e.g., EIA, MIA, IF)
 - **And** negative or indeterminate for Zika IgM antibodies (e.g., EIA, MIA, or IF);
- **Or** both of the following:
 - Virus-specific IgM antibodies (e.g., EIA, MIA, or IF) in CSF
 - **And** negative result for other IgM antibodies in CSF for arboviruses endemic to the region where exposure occurred.

Presumptive:

All of the following:

- Virus-specific IgM antibodies (e.g., EIA, MIA, or IF) in serum or CSF,
- And no other testing for arboviruses endemic to the region where exposure occurred,
- And more than 90 days from most recent previous dengue infection.

Epidemiological criteria for case classification

A person who is epidemiologically linked to a confirmed or probable dengue fever case.

Case classification

Confirmed:

A clinically compatible illness in a person with confirmatory laboratory criteria.

Probable:

A clinically compatible illness in a person with presumptive laboratory criteria.

Suspect:

Either of the following:

- A clinically compatible illness in a person with epidemiological criteria
- **Or** a person with confirmatory or presumptive laboratory criteria.

Criteria to distinguish a new case from previous reports

Not applicable.

Comments

Cases meeting the criteria for severe dengue fever (including DHF and DSS) should be reported as severe dengue fever (Merlin disease code: 06101), not as dengue fever (Merlin disease code: 06100). Zika EIA or PCR is recommended to rule out Zika virus infection. If a case also tests positive for Zika IgM antibodies, please see the flavivirus disease and infection case definition.

Dengue re-infection

There are four DENV serotypes. DENV infection results in long-lasting immunity to symptomatic infection with that particular DENV serotype. However, it is possible to be re-infected with any of the remaining DENV serotype. CDC estimates approximately 20% of dengue cases that have been previously exposed to another DENV serotype may have transient or no significant elevation in dengue IgM titers, making identification of such cases extremely difficult without PCR testing on the acute specimen. An individual with a dengue re-infection may show elevated IgG titers but no IgM titers. During an epidemiological investigation, it is important to ask if there has been any lifetime travel to a dengue endemic country; first dengue infection may have occurred years prior and with few or no symptoms.

Differentiating between DENV and West Nile virus (WNV) infections in patients with positive flavivirus labs

- WNV IgM titers are negative or low positive in dengue fever patients (or vice versa); however the WNV IgG can be quite elevated in dengue patients since IgG strongly cross-reacts between flaviviruses.
- Neuroinvasive disease is relatively uncommon with dengue infections and more likely to be WNV infection than dengue. Confusion differentiating WNV and dengue infections is most likely in patients without symptoms of neuroinvasive disease (fever patients).
- Travel to a dengue endemic country in the two weeks prior to febrile illness onset or travel of a household member to a dengue endemic country in the four weeks prior to patient illness should increase suspicion of dengue.
- Joint pain is often much more severe in cases of dengue fever compared to WNV fever.
- Thrombocytopenia and leukopenia are more common and severe in cases of dengue fever compared to WNV fever.

Guide to Interpretation and Classification of Common Dengue Laboratory Tests

Laboratory test	Days post-onset of specimen collection	Interpretation of positive result	Explanation
Real-time PCR	≤ 5 days	Confirmatory*	Patient viremic while febrile; days 0-7
IgM (paired acute and convalescent specimens)	≤ 5 days for acute, > 5 days for convalescent (ideally 2 weeks apart)	Confirmatory	Negative IgM in an acute specimen followed by a positive IgM in a convalescent specimen
IgG (paired acute and convalescent specimens)	≤ 5 days for acute, > 5 days for convalescent (ideally 2 weeks apart)	Confirmatory	Negative IgG in acute specimen followed by a positive IgG in a convalescent specimen or fourfold increase in titer between acute and convalescent specimen and confirmed by PRNT
IgM (single specimens)	> 5 days	Probable	IgM can remain positive for ≥ 3 months in cases of acute dengue infection

* Only PCR or EIA-based IgM antibody test can be used to diagnosis dengue in single serum specimens.

Previous flavivirus infections and the high prevalence of dengue IgG antibody in some populations (e.g., people who live in or are long-term visitors of dengue endemic countries) complicate interpretation of dengue serological test results. Therefore, a single serum specimen tested using a dengue-specific IgG or combined IgM/IgG (“all antibody”) test is generally not helpful for diagnosis of confirmed or probable cases of dengue. For this reason, suspect cases are defined clinically and epidemiologically, without IgG or combined IgG/IgM serological testing.