Fact Sheet for Healthcare Providers: Interpreting Zika MAC-ELISA Test Results

Updated: September 27, 2023

Dear Healthcare Provider:

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to authorize the use of the Centers for Disease Control and Prevention (CDC) Zika IgM antibody capture enzyme-linked immunosorbent assay (Zika MAC-ELISA). This assay provides *in vitro* qualitative detection of human IgM antibodies to Zika virus. The Zika MAC-ELISA is intended for use in serum and CSF (cerebrospinal fluid) of individuals meeting CDC Zika clinical and/or epidemiological criteria for testing in qualified laboratories designated by the CDC (see http://www.cdc.gov/zika/hc-providers/index.html). This test should be performed according to CDC's Zika testing guidance (see https://www.cdc.gov/zika/hc-providers/testing-guidance.html).

The information in this Fact Sheet is to inform you of the significant known and potential risks and benefits of the emergency use of the Zika MAC-ELISA (see https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations-medical-devices).

Why is this test needed at this time?
Public health officials have determined that Zika virus poses a potential public health emergency. Current information on Zika virus infection for healthcare providers, including case definitions and information about signs and symptoms, is available at www.cdc.gov/zika/hc-providers/index.html. All information and guidance, including those on Zika virus laboratory testing, may change as more data are gathered on this virus. Please check CDC's Zika virus website regularly for the most current information (www.cdc.gov/zika/index.html).

When should the Zika MAC-ELISA test be performed?
Anti-Zika IgM is typically detectable starting soon after onset of symptoms and is reliably detectable for approximately 12 weeks following infection. However, Zika virus IgM antibodies have been detected for months to years following infection in some individuals. If Zika virus infection is suspected based on CDC's published clinical and/or epidemiological criteria, the Zika MAC-ELISA may be ordered and should be performed according to the CDC-issued guidance (https://www.cdc.gov/zika/hc-providers/testing-guidance.html).

As disease manifestations of dengue and chikungunya virus infections can resemble those of Zika virus infection, additional testing for these viruses should be considered to aid in differentiating dengue and chikungunya virus infections from Zika virus infections. Please contact your state or local health department to facilitate testing.

As of May 3, 2017, serum is the primary diagnostic specimen for Zika virus RNA and serologic testing and should be the priority specimen for collection and Zika MAC-ELISA testing. The Zika MAC-ELISA can also be used to test CSF when collected alongside a patient-matched serum.

Specimens should be collected with appropriate infection control precautions and according to the manufacturer's instructions for the specimen collection device, handling, and storage. Serum should be collected in serum separator tubes and centrifuged after collection to reduce the likelihood of hemolysis. Additional guidance for collection of body fluid specimens for Zika diagnostic testing may be found at: http://www.cdc.gov/zika/laboratories/test-specimens-bodyfluids.html.

What does it mean if the specimen tests positive with the Zika MAC-ELISA?
A positive test result from the Zika MAC-ELISA indicates that anti-Zika IgM antibodies were detected in the patient's specimen. Confirmation of Zika MAC-ELISA positive or equivocal results requires additional testing. The most recent testing guidance can be found at: https://www.cdc.gov/zika/hc-providers/testing-guidance.html.

Laboratory test results should always be considered in the context of clinical observations, epidemiological information, and travel history in making a final diagnosis and patient management decisions. For guidance on Zika virus, please refer to http://www.cdc.gov/zika/hc-providers/index.html.

Positive and equivocal Zika MAC-ELISA results are not definitive for diagnosis of Zika virus infection. False positive results may occur in some patients with recent, closely-related flavivirus infections, such as dengue infections. In patients who have received yellow fever or Japanese encephalitis vaccination, cross-reactive antibodies in both the IgM and neutralizing antibody assays may make it difficult to identify which flavivirus is causing the patient's current illness. It is possible that the Zika MAC-ELISA may generate positive results in patients with a history of non-Zika flavivirus infections. In the event of a false positive result, risks to patients could include any or all of the following: the impaired ability to detect and receive appropriate medical care for the true source of symptoms; in the case of pregnant women, an unnecessary increase in the monitoring of a woman's pregnancy; or other unintended adverse effects.

Due to cross-reactivity of anti-dengue IgM and IgG antibodies in tests to detect recent Zika virus infection, it may be difficult to determine the specific flavivirus causing the recent infection in patients with a history of flavivirus infection or in those who reside in areas where Zika and/or dengue virus have been known to circulate. Due to this limitation, plaque reduction neutralization test (PRNT) is not currently routinely recommended for confirmation of Zika MAC-ELISA results in Puerto Rico. Please refer to CDC guidance, including the CDC laboratory guidance (https://www.cdc.gov/zika/laboratories/index.html) for additional information about diagnostic testing recommendations in the United States and its territories.

In the United States and its territories, Zika virus infection and disease (non-congenital and congenital) are nationally notifiable conditions and should be reported to the local or state health department. For guidance on Zika virus, please refer to http://www.cdc.gov/zika/hc-providers/index.html.

While there is an established association between Zika virus infection during pregnancy and microcephaly, detection of anti-Zika IgM antibodies in specimens collected from a pregnant woman does not provide definitive information about the health of her fetus and does not indicate imminent harm to her fetus. If a pregnant woman is diagnosed with Zika virus infection based on detection of anti-Zika IgM antibodies, issues such as timing of infection during the

course of pregnancy, presence of symptoms and other factors may help determine the risk to her fetus.

What does it mean if the specimen tests negative in the Zika MAC-ELISA?
A negative Zika MAC-ELISA result does not rule out Zika virus infection, particularly if testing is conducted soon after onset of symptoms (before anti-Zika IgM antibodies levels are expected to become detectable) or more than 12 weeks after the infection. As with any test, providers must consider the patient's likelihood of exposure and the possibility of false laboratory results when making treatment or other patient management decisions.

Absence of laboratory evidence of Zika virus infection cannot definitively rule out Zika virus infection in persons with epidemiological risk factors. All results should be considered in the context of clinical signs and symptoms, exposure risk and time since symptom onset, or in the absence of symptoms, time since exposure. Conversely, a negative result in an asymptomatic patient with a lower likelihood of exposure (e.g., a short-term traveler to an affected area) may suggest the patient is not infected.

Guidance for healthcare providers, including those caring for pregnant women and women of reproductive age with possible Zika virus exposure, is available on the CDC website: http://www.cdc.gov/zika/hc-providers/index.html.

What has changed in this update to the Fact Sheet for Healthcare Providers?
The main changes that have been made to the Fact Sheet for Healthcare Providers are the following:

- Language to note that other serologic assays for Zika virus infections have been approved/cleared by the FDA.
- Based on newer data, increased the length of IgM duration seen following Zika virus infection.
- Updated links to relevant testing guidance.
- Noted CSF as a sample type for which the assay is authorized.

What is an EUA?
The United States FDA has made this test available under an emergency access mechanism called an Emergency Use Authorization (EUA). The EUA is supported by the Secretary of Health and Human Service's (HHS's) declaration that circumstances exist to justify the emergency use of *in vitro* diagnostic (IVD) tests for the detection of Zika virus and/or diagnosis of Zika virus infection.

An IVD made available under an EUA has not undergone the same type of review as an FDA-approved or cleared IVD. FDA may issue an EUA when certain criteria are met, which includes that there are no adequate, approved, available alternatives, and based on the totality of scientific evidence available, it is reasonable to believe that this IVD may be effective in diagnosing Zika virus infection.

The EUA for this test is in effect for the duration of the Zika virus declaration justifying emergency use of IVDs, unless terminated or revoked (after which the test may no longer be used).

What are the approved available alternatives?
Any tests that have received full marketing status (e.g., cleared, approved), as opposed to an EUA, by FDA can be found by searching the medical device databases here: https://www.fda.gov/medical-devices/device-advice-comprehensive-regulatory-assistance/medical-device-databases. A cleared or approved test should be used instead of a test made available under an EUA, when appropriate and available. FDA has issued EUAs for other tests that can be found at: https://www.fda.gov/medical-devices/emergency-situations-medical-devices/emergency-use-authorizations-medical-devices#zika**.**

Reporting Adverse Events
Adverse events should be reported, including problems with test performance or results, to MedWatch at https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program, by completing and submitting the online FDA Form 3500 for Health Professionals (available at https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home) or by calling 1-800-FDA-1088.

All patients should receive the Fact Sheet for Patients: Understanding Results from the Zika MAC-ELISA.

Contact Information for the Manufacturer:
reagents2@cdc.gov

Any significant new findings that negatively impact the performance of the test and that are observed during the course of the emergency use of the Zika-MAC ELISA will be made available at http://www.cdc.gov/zika/index.html.