

Fact Sheet for Health Care Providers: Interpreting Zika MAC-ELISA Results

June 29, 2016

Dear Health Care 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's (CDC) Zika IgM antibody capture ELISA (Zika MAC-ELISA). This assay provides *in vitro* qualitative detection of human IgM antibodies to Zika virus. It is intended for use in sera or cerebrospinal fluid (CSF) when submitted with a patient-matched serum sample from individuals meeting CDC Zika clinical and epidemiological criteria for testing (<http://www.cdc.gov/zika/hc-providers/index.html>) in qualified laboratories designated by the CDC. The test is intended for use as part of CDC's algorithm for Zika testing.

FDA issued this EUA based on data submitted by CDC to FDA, and on the U.S. Secretary of Health and Human Services' (HHS) declaration that circumstances exist to justify the emergency use of *in vitro* diagnostic tests for the detection of Zika virus and Zika virus infection. This EUA will terminate when the HHS Secretary's declaration terminates, unless FDA revokes it sooner.

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. For more information on this EUA, please see FDA's website at <http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm>.

Why is this test needed at this time?

As of June 22, 2016, active Zika virus transmission is occurring in 39 countries and territories in the Americas, 8 countries and territories in Oceania/Pacific Islands, and 1 country in Africa (<http://www.cdc.gov/zika/geo/active-countries.html>). Among cases identified in 2015-16, Zika virus transmission has occurred primarily through the bite of infected *Aedes* species mosquitoes. Zika virus can also be transmitted from mother to fetus during pregnancy and through sexual transmission from infected males to their sexual partners.

As of June 22, 2016, over 819 confirmed cases of Zika virus infection have been identified in the continental United States. All cases were in persons with either a recent travel history to areas with ongoing transmission or an epidemiologic link with an individual with such travel history (i.e., through maternal-fetal or sexual transmission). Public health officials have determined that Zika virus poses a potential public health emergency.

At this time, there are no FDA approved/cleared tests available that can detect Zika virus in clinical specimens in the United States. Therefore, CDC has developed this test to detect evidence of Zika virus infections in human sera and CSF. Current information on Zika virus infection for health care providers, including case definitions, is available at

<http://www.cdc.gov/zika/hc-providers/index.html>. All information and guidelines, including those on Zika virus laboratory testing, may change as more data is gathered on this virus. Please check CDC's Zika Virus website regularly for the most current information (<http://www.cdc.gov/zika/index.html>).

If Zika virus infection is suspected based on current clinical and/or epidemiological criteria recommended by public health authorities, the Zika MAC-ELISA may be ordered. As chikungunya virus infection and dengue virus infection can have early symptoms resembling those of Zika virus, testing should be considered for chikungunya and dengue. Please contact your state or local health department to facilitate testing.

The results should be used in conjunction with clinical signs and symptoms, epidemiological information, and travel history to diagnose recent Zika virus infection. This test is authorized for use with serum and with CSF (when submitted with a patient-matched serum sample).

As of February 20, 2016, serum is the primary diagnostic specimen and should be the priority specimen for collection and testing. Specimens should be collected with appropriate infection control precautions and according to the manufacturer's instructions for the specimen collection device. Sera should be collected in serum separator tubes and centrifuged after collection to reduce the likelihood of hemolysis. Please refer to manufacturer's instructions for serum tube processing. Additional guidance for collection of body fluid specimens for Zika diagnostic testing may be found at: <http://www.cdc.gov/zika/hc-providers/body-fluids-collection-submission.html>.

What are the symptoms of Zika virus infection?

Many people with Zika virus infection are asymptomatic. Symptomatic patients typically experience a mild illness characterized by fever, rash, joint pain, or conjunctivitis. Clinical illness is usually self-limited and lasts a week or less. Clinical illness recognition can be complicated in that not all symptomatic patients report all of these symptoms, and Zika manifestations overlap significantly with those seen in other viral infections. Although the exact incubation period is yet to be determined, it is considered to be about 3 days to 2 weeks.

Based on a review of available evidence, CDC has concluded that Zika virus infection in pregnancy is a cause of microcephaly (a birth defect characterized by small head size and impaired cranial and neural development in fetuses and infants) and other serious abnormalities of the brain. In addition, it has been linked to central nervous system injury, placental insufficiency, fetal growth restriction, and fetal loss, eye abnormalities, and hearing impairment (references 1-2).

Limited information is available currently about the spectrum of defects caused by prenatal Zika virus infection, the relative and absolute risks of adverse outcomes among fetuses whose mothers were infected at different times during pregnancy, and factors that might affect a woman's risk of adverse pregnancy or birth outcomes.

It is also important to note that Zika virus infection is not the sole suspected cause of microcephaly in fetuses and infants.

There are also reports of Guillain-Barre syndrome associated with Zika virus infection.

When should the Zika MAC-ELISA be performed?

Anti-Zika IgM is typically detectable starting soon after onset of symptoms and is reliably detectable for approximately 12 weeks following infection. The Zika MAC-ELISA test should be performed according to the CDC-issued algorithm available at <http://www.cdc.gov/zika/state-labs/index.html>.

What does it mean if the specimen tests positive in the Zika MAC-ELISA?

A positive test result for Zika virus from the Zika MAC-ELISA indicates that anti-Zika IgM antibodies were detected in the sera or CSF of the patient. Confirmation of Zika MAC-ELISA positive or equivocal results requires additional testing by CDC or by qualified laboratories designated by CDC and in consultation with CDC, using the CDC-issued algorithm found at: <http://www.cdc.gov/zika/state-labs/index.html>.

False positive serological results are possible (see next paragraph). Laboratory test results should always be considered in the context of clinical observations and epidemiologic information in making a final diagnosis and patient management decisions. Any positive test result for Zika virus infection, including Zika MAC-ELISA positive results, should be reported to your local or state health department. In the United States and its territories, Zika virus disease and congenital Zika virus infection are nationally notifiable diseases. For guidelines 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 infection causing the symptoms, an unnecessary increase in the monitoring of a woman's pregnancy, or other unintended adverse effects.

It should be emphasized that the identification of possible Zika virus infection in a pregnant woman does not provide any definitive information about the state of health of the fetus. Many questions remain about the association between Zika virus infection in a mother and the impact to the fetus, and the impact of factors such as timing, likelihood, and relevance of symptomatic versus asymptomatic infection. Detection of Zika virus infection in the mother does not mean there is definite harm to the 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 IgM levels are expected to become detectable) or more than 12 weeks after the infection is thought to have occurred (as IgM levels are expected to drop). 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. The possibility of a false negative result should especially be considered if the patient's recent exposures or clinical presentation are consistent with Zika virus infection and diagnostic tests for other causes of illness are negative. 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.

Please refer to CDC guidance for Health Care Providers Caring for Pregnant Women and Women of Reproductive Age with Possible Zika Virus Exposure:

<http://www.cdc.gov/zika/hc-providers/clinical-guidance.html>

Reporting Adverse Events

You should report adverse events, including problems with test performance or results, to MedWatch at <http://www.fda.gov/medwatch>, by submitting a MedWatch Form 3500 (available at http://www.fda.gov/medwatch/safety/FDA-3500_fillable.pdf) or by calling 1-800-FDA-1088.

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

Contact Information for the Manufacturer:

CDC Emergency Operations Center (EOC)
1600 Clifton Road
Atlanta, Georgia, USA, 30329
Office phone: **CDC EOC (770-488-7100)**

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>.

References

- 1) Rasmussen S.A., Jamieson D.J., Honein M.A., and Petersen L.R. Zika Virus Birth Defects—Reviewing the Evidence for Causality. *NEJM* (April 12, 2016). DOI: 10.1056/NEJMs1604338.
- 2) CDC Website. <http://www.cdc.gov/zika>.