

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

Updated: December 6, 2016

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 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>). It can also be used in cerebrospinal fluid (CSF) when submitted with a patient-matched serum sample. This test should be performed according to CDC's algorithm for Zika testing (see <http://www.cdc.gov/zika/laboratories/lab-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 <http://www.fda.gov/MedicalDevices/Safety/EmergencySituations/ucm161496.htm>).

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).

The U.S. Secretary of Health and Human Services (HHS) has declared that circumstances exist to justify the emergency use of *in vitro* diagnostic tests for the detection of Zika virus and/or diagnosis of Zika virus infection. This EUA will terminate when the HHS Secretary's declaration terminates, unless FDA revokes it sooner.

At this time, there are no FDA approved/cleared tests available that can detect Zika virus infection in clinical specimens in the US. Therefore, CDC has developed the Zika MAC-ELISA to detect evidence of Zika virus infection.

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. 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 (<http://cdc.gov/zika/laboratories/lab-guidance.html>). The algorithms included within the

guidance illustrate the appropriate Zika testing approach based on the presence of signs and symptoms, pregnancy status, and the time between onset of symptoms or suspected exposure and specimen collection.

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 December 6, 2016, 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 by CDC or by qualified laboratories designated by CDC and in consultation with CDC, using the CDC-issued algorithm published in the CDC laboratory guidance found at: <http://cdc.gov/zika/laboratories/lab-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 (<http://www.cdc.gov/zika/laboratories/lab-guidance.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 is thought to have occurred (as anti-Zika IgM antibodies 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.

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:

- Indications for testing and guidance for interpretation of a negative result have been updated to align with recently posted CDC Guidance for US Laboratories Testing for Zika Virus Infection (<http://www.cdc.gov/zika/laboratories/lab-guidance.html>).

- PRNT is not currently routinely recommended for confirmation of Zika MAC-ELISA results in Puerto Rico.

Reporting Adverse Events

You should report adverse events, including problems with test performance or results, to MedWatch at 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.

All 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/NEJMSr1604338.
- 2) CDC Website. <http://www.cdc.gov/zika>.

Fact Sheet for Patients: Understanding Results from the Zika MAC-ELISA

Updated: December 6, 2016

Dear Patient:

You are being given this Fact Sheet because your blood or cerebrospinal fluid (CSF) was tested for evidence of Zika virus infection. This testing was done because your healthcare provider believes you may have been exposed to Zika virus. The test used on your sample(s) is called the Zika MAC-ELISA, which is a laboratory test designed to help determine if you have recently been infected with Zika virus.

This Fact Sheet contains information to help you understand the risks and benefits of using the Zika MAC-ELISA. You may want to discuss with your healthcare provider the benefits and risks described in this Fact Sheet and any additional questions you may have.

What is Zika virus Infection?

Zika virus infection is caused by the Zika virus and is primarily spread to people through mosquito bites. Zika virus can also be passed by infected individuals to their partner during sex. A woman infected with Zika virus during pregnancy can pass the virus to her developing fetus.

Many people who are infected with Zika virus do not have any symptoms. Those that do, usually have mild illness with symptoms that may include fever, rash, joint pain, or redness of the eyes. These symptoms typically resolve on their own within a week.

Infection with Zika virus during pregnancy can cause microcephaly (a condition where the baby's head is smaller than expected, which is a sign of incomplete brain development) and other severe brain defects in babies. However, detection of Zika virus infection in a pregnant woman does not mean there is definite harm to the developing fetus. Women who are infected with Zika virus while pregnant should be monitored more closely by their healthcare providers throughout their pregnancy. Current information on Zika virus infection is available at <http://www.cdc.gov/zika/symptoms/index.html>. Additional information for pregnant women and those who are considering becoming pregnant is available at <http://www.cdc.gov/zika/pregnancy/index.html>.

What is the Zika MAC-ELISA?

The Zika MAC-ELISA is a laboratory test designed to detect proteins the human body makes to fight a Zika virus infection. These proteins, called antibodies, appear in the blood starting soon after the start of illness and last for up to 12 weeks. In some people, they are present for longer than 12 weeks. If the Zika MAC-ELISA detects these antibodies, the test is positive. If the Zika MAC-ELISA does not detect these antibodies, the test is negative.

Why was my sample tested using the Zika MAC-ELISA?

Your sample(s) were tested because you have signs and symptoms of Zika virus infection, because you live in or have recently traveled to a place where Zika virus infection is known to occur, and/or because you have another possible exposure to Zika virus. The sample(s) collected from you were tested using the Zika MAC-ELISA to help find out whether you may have been infected with Zika virus.

What are the known and potential risks and benefits of the Zika MAC-ELISA?

Besides possible discomfort or other complications that can happen when your sample(s) are collected, there is a risk that the test result is incorrect (see below for more information). The benefit of having this test is that the results of this test, along with other information, can help inform your healthcare providers when making recommendations about your care and, if you are pregnant, the care of your developing fetus. The results of this test may help limit the spread of Zika virus in your community. For more information, see <http://www.cdc.gov/zika/prevention/protect-yourself-and-others.html>

If this test is positive for Zika virus, does it mean that I have Zika virus infection?

If you have a positive result, it is likely that you have had a recent Zika virus infection. It is possible that you may have had a recent Zika virus infection and not have any symptoms. There is a chance that this test can give a positive result that is wrong; this is called a “false positive” result. There are some other very closely related viruses (such as dengue virus) that can cause the human body to produce antibodies that may cause the test to be positive.

If your result from this test is positive or equivocal (unclear), your healthcare provider or health department will determine if your results should be evaluated with additional testing and/or with testing from other samples that may have been collected from you. It is important that you work with your healthcare provider or health department to help you understand the next steps you should take and, if you are pregnant, to monitor the health and development of your fetus.

If you have a pregnant partner and you are positive for Zika virus infection, you should use condoms and/or other barriers (e.g., dental dams) consistently and correctly during sex, or abstain from sex with your partner, for the duration of the pregnancy, to lessen the risk that you may pass Zika virus infection to your partner. If you have a positive test result for Zika virus and you are considering becoming pregnant or have a partner who might become pregnant, then you should discuss risks with your healthcare provider.

Information about steps to take if you are diagnosed with Zika virus infection is available at <http://www.cdc.gov/zika/symptoms/treatment.html>.

If I am pregnant and my test is positive for Zika virus, does it mean that my child will have a birth defect?

No, not necessarily. Although evidence shows that Zika virus infection during pregnancy is a cause of birth defects and other poor pregnancy outcomes, not all Zika virus infections result in these problems. At this time, we do not know how likely it is that a baby will have microcephaly or other problems if his/her mother is infected with Zika virus while she is pregnant.

A positive test result for Zika virus infection during pregnancy signals to your healthcare providers to watch your pregnancy more closely, meaning they might do more ultrasounds or other tests to check the growth and development of your fetus. More information for pregnant women who have tested positive for Zika virus infection is available at: <http://www.cdc.gov/zika/pregnancy/protect-yourself.html>.

If this test is negative, does it mean that I do not have Zika virus infection?

Even if you have a negative test, you may have been infected with Zika virus. If your sample was collected just after you became ill, it is possible that your body had not yet had enough time to make antibodies for the test to measure. If the sample was collected more than 12 weeks after your illness, it is possible that your body has already fought off the virus and the amount of antibodies is so low that they cannot be measured. Your healthcare provider will help you to interpret your test results and work with you to continue to monitor your health and, if you are pregnant, the health of your fetus.

Is this test FDA-approved or cleared?

The U.S. Food and Drug Administration (FDA) has not cleared or approved the Zika MAC-ELISA test or any other test to detect Zika virus infection. However, FDA has authorized the use of this test under an Emergency Use Authorization (EUA).

An EUA is a tool that FDA can use to allow the use of certain medical products for emergencies based on scientific data. The U.S. Secretary of Health and Human Services (HHS) has declared that circumstances exist to allow the emergency use of diagnostic tests for Zika virus infection, such as the Zika MAC-ELISA, under an EUA.

FDA has authorized the emergency use of the Zika MAC-ELISA to test for antibodies to Zika virus in your specimens only for the duration of the emergency, unless it is terminated or revoked by FDA sooner.

How can I learn more?

Information about Zika virus and any significant new findings that are observed during the course of the emergency use of the Zika MAC-ELISA will be made available at the CDC website: <http://www.cdc.gov/zika/index.html>

Please also contact your healthcare provider if you have any questions.