

Fact Sheet for Health Care Providers: Interpreting ZIKV *Detect*[™] IgM Capture ELISA Results

August 17, 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 InBios International, Inc. (InBios), ZIKV *Detect*[™] IgM Capture ELISA. This assay provides *in vitro* qualitative detection of human IgM antibodies to Zika virus. It is intended for use in sera from individuals meeting Centers for Disease Control and Prevention (CDC) Zika clinical and/or epidemiological criteria for testing (<http://www.cdc.gov/zika/hc-providers/index.html>) by laboratories in the United States that are certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. §263a, to perform high complexity tests, or by similarly qualified non-U.S. laboratories. When there are positive Zika results from the test, confirmatory testing, consistent with the latest CDC guideline for the diagnosis of Zika virus infection is required.

FDA issued this EUA based on data submitted by InBios 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/or diagnosis of 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 ZIKV *Detect*[™] IgM Capture 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?

Public health officials have determined that Zika virus poses a potential public health emergency. 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 individuals to their sexual partners.

At this time, there are no FDA approved/cleared tests available that can detect Zika virus or diagnose Zika virus infection in clinical specimens in the United States. InBios has developed the ZIKV *Detect*[™] IgM Capture ELISA test to detect evidence of Zika virus infections in human sera. 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 CDC clinical and/or epidemiological criteria recommended by public health authorities, the ZIKV *Detect*TM IgM Capture ELISA may be ordered. As chikungunya virus infection and dengue virus infection can have early symptoms resembling those of Zika virus, and co-infection with these viruses is possible, in addition to testing for Zika virus, testing should be considered for chikungunya and dengue. Please contact your state or local health department to facilitate testing.

The results of this test 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.

As of August 17, 2016, serum is the primary diagnostic specimen for collection and serological 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, joint pain, rash, 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 virus clinical manifestations overlap significantly with those seen in other viral infections. Although the exact incubation period is 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 fetuses and infants. In addition, it has been linked to central nervous system injury, placental insufficiency, fetal growth restriction, fetal loss, eye abnormalities, and hearing impairment.^{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-Barré syndrome associated with Zika virus infection.

When should the ZIKV *Detect*[™] IgM Capture 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 ZIKV *Detect*[™] IgM Capture ELISA test should be performed according to the CDC-issued algorithm available at <http://www.cdc.gov/zika/state-labs/index.html>.

How should results from the ZIKV *Detect*[™] IgM Capture ELISA be interpreted?

This test may give one of four possible results: (1) presumptive Zika positive, (2) possible Zika positive, (3) presumptive other flavivirus positive, or (4) negative.

- **Specimen tests positive for Zika virus IgM (i.e., presumptive Zika or possible Zika positive)**

A positive test (i.e., presumptive Zika positive, possible Zika positive) for Zika virus infection from the ZIKV *Detect*[™] IgM Capture ELISA indicates that anti-Zika IgM antibodies were detected in the sera of the patient. Confirmation of ZIKV *Detect*[™] IgM Capture ELISA presumptive and possible Zika positive results requires additional testing and/or consideration alongside test results for other patient-matched specimens, using the latest CDC guideline for the diagnosis of Zika virus infection (as described in the authorized Instructions for Use document). For guidelines on Zika virus, please refer to <http://www.cdc.gov/zika/hc-providers/index.html>.

Presumptive Zika positive and possible Zika positive results are not definitive for diagnosis of Zika virus infection. 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 should be reported to your local and state health authorities. 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>.

False positive results may occur in some patients with recent, closely-related flavivirus infections, such as dengue and West Nile viral 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 ZIKV *Detect*[™] IgM Capture 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; in the case of pregnant women, an unnecessary increase in the monitoring of a woman's pregnancy; or other unintended adverse effects.

It should be emphasized that the identification of (presumptive or 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, and the relevance of symptomatic versus asymptomatic infection. Detection of Zika virus infection in the mother does not mean there is definite harm to the fetus.

- **Specimen tests positive for “other flavivirus” IgM**

A presumptive positive test result for “other flavivirus” from the ZIKV *Detect*[™] IgM Capture ELISA indicates that either anti-dengue or anti-West Nile IgM antibodies were detected in the sera of the patient, which requires follow up testing for other flaviviruses, as described in the authorized Instructions for Use document. Laboratory test results should always be considered in the context of clinical observations and epidemiologic data in making a final diagnosis and patient management decisions. Any positive test result for dengue or West Nile virus should be reported to your local and state health departments.

- **Specimen tests negative**

A negative ZIKV *Detect*[™] IgM Capture 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.

Further information on Zika virus infection for health care providers is available at <http://www.cdc.gov/zika/hc-providers/index.html>. Guidance for Health Care Providers Caring for Pregnant Women and Women of Reproductive Age with Possible Zika Virus Exposure is available on the CDC website at <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/Safety/MedWatch/default.htm>, by submitting a MedWatch Form 3500 (available at <https://www.accessdata.fda.gov/scripts/medwatch/index.cfm?action=reporting.home>), or by calling 1-800-FDA-1088.

Pregnant patients should receive the Fact Sheet for Pregnant Women: Understanding Results from the ZIKV *Detect*TM IgM Capture ELISA.

All other patients should receive the Fact Sheet for Patients: Understanding Results from the ZIKV *Detect*TM IgM Capture ELISA.

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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 ZIKV *Detect*TM IgM Capture ELISA will be made available at the InBios website: www.inbios.com.

References

- 1) Rasmussen, S.A., Jamieson, D.J., Honein, M.A., Petersen, L.R. Zika Virus and Birth Defects – Reviewing the Evidence for Causality. *New England Journal of Medicine*, April 12, 2016. DOI: 10.1056/NEJMSr1604338.
- 2) CDC Website - <http://www.cdc.gov/zika/>.