Fact Sheet for Healthcare Providers: Interpreting ZIKV *Detect*™ 2.0 IgM Capture ELISA Results

Updated: May 18, 2018

Dear Healthcare 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*™ 2.0 IgM Capture ELISA. This assay provides *in vitro* qualitative detection of human IgM antibodies to Zika virus. This ZIKV *Detect*™ 2.0 IgM Capture ELISA is intended for use in serum of individuals meeting CDC Zika clinical and/or epidemiological criteria for testing (see 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. This test should be performed according to CDC 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 ZIKV *Detect*™ 2.0 IgM Capture 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).

At this time, there are no FDA approved/cleared tests available that can detect Zika virus infection in clinical specimens in the US. Therefore, Inbios has developed the ZIKV *Detect*™ 2.0 IgM Capture ELISA to detect evidence of Zika virus infection.

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.

When should the ZIKV *Detect*™ 2.0 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. If Zika virus infection is suspected based on CDC's published clinical and/or epidemiological criteria, the ZIKV *Detect*™ 2.0 IgM

Capture 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 May 18, 2018 serum is the primary diagnostic specimen for Zika virus RNA and serologic testing, and should be the specimen for collection and ZIKV *Detect*™ 2.0 IgM Capture ELISA testing.

Specimens tested with ZIKV *Detect*™ 2.0 IgM Capture ELISA 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.

How should results from the ZIKV *Detect*™ 2.0 IgM Capture ELISA be interpreted?

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

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

  A positive test (i.e., presumptive Zika positive) for Zika virus infection from the ZIKV *Detect*™ 2.0 IgM Capture ELISA indicates that anti-Zika IgM antibodies were detected in the sera of the patient. Confirmation of ZIKV *Detect*™ 2.0 IgM Capture ELISA presumptive Zika positive 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://www.cdc.gov/zika/hc-providers/index.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.

  Presumptive Zika positive 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 and West Nile 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*™ 2.0 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 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 ZIKV *Detect*™ 2.0 IgM Capture 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.

- **Specimen tests positive for "other flavivirus" IgM**

A presumptive positive test result for "other flavivirus" from the ZIKV *Detect*™ 2.0 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*™ 2.0 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.

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

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 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 ZIKV *Detect*™ 2.0 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*™ 2.0 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., 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