Fact Sheet for Healthcare Providers: Interpreting CII-ArboViroPlex rRT-PCR Assay Test Results
August 11, 2017

Dear Healthcare Provider:

The U.S. Food and Drug Administration (FDA) has issued an Emergency Use Authorization (EUA) to authorize the use of the **CII-ArboViroPlex rRT-PCR assay** for the *in vitro* qualitative detection of Zika virus with specified instruments. This assay tests for Zika virus, dengue virus, chikungunya virus, and West Nile virus RNA in human serum. The assay also tests for Zika virus in urine (collected alongside a patient-matched serum specimen). Testing should be conducted on specimens from people who meet Centers for Disease Control and Prevention (CDC) Zika clinical and/or epidemiological criteria for testing and be performed in laboratories in the US 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 (see http://www.cdc.gov/zika/hc-providers/index.html). 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 **CII-ArboViroPlex rRT-PCR assay** (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 (references 1-2). 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 US 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 in clinical specimens in the US.

When should the CII-ArboViroPlex rRT-PCR assay be performed?

If Zika virus infection is suspected based on CDC's published clinical and/or epidemiological criteria, the **CII-ArboViroPlex rRT-PCR assay** may be ordered and should be performed according to the CDC-issued guidance (http://www.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 virus, chikungunya virus, and West Nile virus infections can resemble those of Zika virus infection; this assay may be useful in differentiating dengue, chikungunya, and West Nile virus infections from Zika virus infections or identifying possible co-infections.

Zika, dengue, chikungunya, and West Nile virus RNA is typically detectable in serum during the acute phase of infection (generally up to 7 days post-symptom onset). Zika virus RNA has been detected in serum up to 13 days post-symptom onset in non-pregnant patients, and up to 62 days post-symptom onset in pregnant patients. In addition, Zika virus RNA has been detected up to 53 days after the last known possible exposure in an asymptomatic pregnant woman (references 3-4).

As of August 11, 2017, serum is the primary diagnostic specimen for Zika, dengue, chikungunya, and West Nile virus RNA and serologic testing, and should be the priority specimen for collection and **CII- ArboViroPlex rRT-PCR assay** testing. The **CII- ArboViroPlex rRT-PCR assay** can also be used to test urine specimens (collected alongside a patient-matched serum specimen).

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 collected in serum separator tubes or conventional serum tubes should be 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.

If your patient has been symptomatic but is beyond the recommended window for **CII-ArboViroPlex rRT-PCR assay** testing, serologic testing for antibodies to Zika virus may be helpful.

What does it mean if the specimen tests positive for Zika virus RNA?

A positive test for Zika virus RNA indicates that RNA from Zika virus was detected in the patient's specimen. A positive test result in any authorized specimen collected from a patient is indicative of Zika virus infection. Laboratory test results should always be considered in the context of clinical observations, epidemiologic data, and travel history in making a final diagnosis and patient management decisions. For guidance on Zika virus, please refer to www.cdc.gov/zika/hc-providers/index.html.

The **CII-ArboViroPlex rRT-PCR assay** test has been designed to minimize the likelihood of false positive test results. Cross-reactivity of any of the components of this test resulting in false positive results is not expected. However, in the event of a false positive result, risks to patients could include any or all of the following: 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, other unintended adverse effects.

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 your local and state public health department. For guidelines 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 Zika virus RNA 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 Zika virus RNA, 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 positive for dengue virus and/or chikungunya virus and/or West Nile virus RNA?

A positive test result for dengue virus and/or chikungunya virus and/or West Nile virus from the **CII-ArboViroPlex rRT-PCR assay** indicates that RNA from one or more of the above three viruses was detected in the patient's specimen. Laboratory test results should always be considered in the context of clinical observations, epidemiologic data, and travel history in making a final diagnosis and patient management decisions.

The **CII- ArboViroPlex rRT-PCR assay** has been designed to minimize the likelihood of false positive test results. Cross reactivity of any of the components of this test that may lead to false positive results is not expected. However, in the event of a false-positive result, risks to patients could include impaired ability to detect and receive appropriate medical care for the true source of symptoms, or other unintended adverse effects. Any positive test result for dengue virus, chikungunya virus, or West Nile virus should be reported to your local and state health department.

While co-infections are rare, using the **CII- ArboViroPlex rRT-PCR assay**, it is possible to detect more than one of these four viruses in a patient.

In the United States and its territories, dengue virus, chikungunya virus, and West Nile virus infections are nationally notifiable diseases. Information for clinicians caring for patients with dengue, chikungunya, or West Nile virus infection is available on CDC's websites:

Dengue virus guidance: www.cdc.gov/dengue/clinicallab/index.html

Chikungunya virus guidance: https://www.cdc.gov/chikungunya/hc/index.html

West Nile virus guidance: https://www.cdc.gov/westnile/healthcareproviders/index.html

What does it mean if the specimen tests negative for Zika virus RNA (and/or dengue virus and/or chikungunya virus and/or West Nile virus RNA)?

A negative test result for Zika and/or dengue and/or chikungunya and/or West Nile viruses in the specimen means that RNA from Zika and/or dengue and/or chikungunya and/or West Nile viruses was not present in the specimen above the test's limit of detection. However, a negative result for one or any of these arboviruses does not rule out infection with the virus(es), and should not be used as the sole basis for treatment or other patient management decisions.

It is especially important to note that a negative result in urine, which is not the recommended primary diagnostic specimen type, does not necessarily mean that a person is not infected. When results are negative for a urine specimen, the patient-matched serum specimen should be tested as outlined in the current CDC-issued algorithm (http://www.cdc.gov/zika/laboratories/lab-guidance.html).

A negative **CII- ArboViroPlex rRT-PCR assay** Zika virus test result does not exclude the possibility of Zika virus infection. In serum, negative rRT-PCR test results are known to occur in Zika virus infection, particularly if testing is conducted outside the acute phase of infection (generally up to 7 days post symptom-onset) or in asymptomatic people. When other diagnostic testing is negative, the possibility of a false negative result should be considered in the context of a patient's recent exposures and the presence of clinical signs and symptoms consistent with Zika virus infection. Such patients should have antibody testing performed on their serum sample, as per the CDC testing algorithm (found at http://www.cdc.gov/zika/laboratories/lab-guidance.html).

Absence of laboratory evidence of Zika virus infection cannot definitively rule out Zika virus infection in persons with epidemiologic 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.

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: 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 CII-ArboViroPlex rRT-PCR assay

Contact Information for the Manufacturer:
Center for Infection and Immunity, Columbia University, New York
Address:
722 West 168th Street, 17th floor
New York, NY 10032
Voice: 212-342-9031
Fax: 212-342-9044

Information about any significant new findings observed during the course of the emergency use of the **CII-ArboViroPlex rRT-PCR assay** will be made available at:
https://www.mailman.columbia.edu/research/center-infection-and-immunity.

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; 374:1981–87. DOI: 10.1056/NEJMsr1604338
2. CDC Website – http://www.cdc.gov/zika/
3. Driggers, R.W., et al. Zika virus infection with Prolonged Maternal Viremia and Fetal Brain Abnormalities. New England Journal of Medicine, June 2, 2016; 374:2142-2151. DOI: 10.1056/NEJMoa1601824
4. Meaney-Delman et al. Prolonged Detection of Zika Virus RNA in Pregnant Women. Obstetrics and Gynecology, 128:724–730. DOI: 10.1097/AOG.0000000000001625