2016 APHL™ ANNUAL MEETING

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# The EUA Process at CDC


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Office of Infectious Diseases

# DECLARATION OF EMERGENCY OR THREAT JUSTIFYING EMERGENCY USE

Before FDA may issue an EUA, the HHS Secretary must declare that circumstances exist justifying the authorization (section 564(b)(1)). This declaration (referred to in this guidance as a "declaration of emergency or threat of emergency"), must be based on one of the following actions:

- A determination by the Secretary of Homeland Security that there is a domestic emergency, or a significant potential for a domestic emergency, involving a heightened risk of attack with a CBRN agent or agents[10]
- A determination by the Secretary of Defense that there is a military emergency, or a significant potential for a military emergency, involving a heightened risk to United States military forces of attack with a CBRN agent or agents[11]
- A determination by the Secretary of HHS that there is a public health emergency, or a significant potential for a public health emergency, that affects, or has a significant potential to affect, national security or the health and security of United States citizens living abroad, and that involves a CBRN agent or agents, or a disease or condition that may be attributable to such agent or agents[12] or
- The identification of a material threat, by the Secretary of Homeland Security pursuant to section 319F-2 of the PHS Act, that is sufficient to affect national security or the health and security of United States citizens living abroad.[13]

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# Historical CDC Assays Distributed Under EUA

| Date of Authorization | Assay |
|---|---|
| April 29, 2009 | CDC Swine Influenza Virus Real-time RT-PCR Detection Panel |
| May 2, 2009 | CDC Human Influenza Virus Real-time RT-PCR Detection and Characterization Panel with additional specimens and reagents |
| August 24, 2009 | CDC rRT-PCR Swine Flu Panel on the Joint Biological Agent Identification and Diagnostic System (JBAIDS) Instrument |
| October 10, 2014 | CDC Ebola Virus VP40 Real-time RT-PCR Assay |
| October 10, 2014 | CDC Ebola Virus NP Real-time RT-PCR Assay |

# Assays Currently Available Under EUA

| Date of Authorization | Assay |
|---|---|
| April 22, 2013 | CDC Human Influenza Virus Real-Time RT-PCR Diagnostic Panel-Influenza A/H7 (Eurasian Lineage) Assay |
| June 5, 2013 | CDC Novel Coronavirus 2012 Real-time RT-PCR Assay |
| March 2, 2015 | CDC Ebola Virus VP40 Real-time RT-PCR Assay |
| March 2, 2015 | CDC Ebola Virus NP Real-time RT-PCR Assay |
| May 12, 2015 | CDC Enterovirus D68 2014 Real-time RT-PCR Assay * |
| February 26, 2016 | CDC Zika Immunoglobulin M (IgM) Antibody Capture Enzyme-Linked Immunosorbent Assay |
| March 17, 2016 | CDC Trioplex Real-time RT-PCR Assay |

** Authorized for Emergency Use but not currently distributed by CDC*

# New CDC Laboratory Test for Zika Virus Authorized for Emergency Use by FDA

*Emergency action expected to bolster US laboratory capacity for Zika testing*

In response to a request from the Centers for Disease Control and Prevention, the U.S. Food and Drug Administration (FDA) today issued an Emergency Use Authorization (EUA) for a diagnostic tool for Zika virus that will be distributed to qualified laboratories and, in the United States, those that are certified to perform high-complexity tests.

The test, called the CDC Zika IgM Antibody Capture Enzyme-Linked Immunosorbent Assay (Zika MAC-ELISA), is intended for use in detecting antibodies that the body makes to fight a Zika virus infection. These antibodies (in this case, immunoglobulin M, or IgM) appear in the blood of a person infected with Zika virus beginning 4 to 5 days after the start of illness and last for about 12 weeks. The test is intended to be used on blood samples from people with a history of symptoms associated with Zika and/or people who have recently traveled to an area during a time of active Zika transmission.

The FDA can use the EUA to permit use, based on scientific data, of certain medical products in certain circumstances, including when there is a determination, by the Secretary of Health and Human Services, that there is a significant potential for a public health emergency that has a significant potential to affect national security or the health and security of United States citizens. As there are no commercially available diagnostic tests cleared or approved by the FDA for the detection of Zika virus infection, it was determined that an EUA is crucial to ensure timely access to a diagnostic tool. CDC's Zika MAC-ELISA is the first diagnostic test authorized for use in the U.S. for the detection of Zika virus during this situation in which there has been a determination that there is a significant potential for a public health emergency that has a significant potential to affect national security or the health and security of United States citizens living abroad and that involves Zika virus.

Results of Zika MAC-ELISA tests require careful interpretation. A positive test result indicates that a person was likely infected recently with the Zika virus. However, the test can give an incorrect positive. These false-positive results can occur when someone has been infected with another closely related virus (such as dengue virus). When positive or inconclusive results occur, additional testing (plaque reduction neutralization test) to confirm the presence of antibodies to Zika virus will be performed by CDC or a CDC-authorized laboratory.

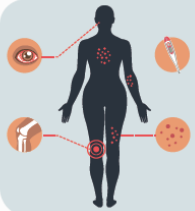
Moreover, a negative test result does not necessarily mean that a person has not been infected with Zika virus. If a sample is collected just after a person becomes ill, there may not be enough antibodies for the test to measure, resulting in a false negative. Similarly, if the sample was collected more than 12 weeks after illness, it is possible that the body has successfully fought the virus and antibody levels have dropped below the detectable limit.

As with any test, it is important that health care providers consult with their patients about test results and the best approach to monitoring their health.

CDC will begin distributing the test during the next two weeks to qualified laboratories in the Laboratory Response Network, an integrated network of domestic and international laboratories that can respond to public health emergencies. The test will not be available in U.S. hospitals or other primary care settings. Public health officials anticipate that distribution of the tests will improve laboratory testing capacity for Zika virus in the United States.

**Media Statement**
**For Immediate Release:** Friday, February 26, 2016
**Contact:** Media Relations,
(404) 639-3286

# **ZIKA** DIAGNOSTIC TESTING



Symptomatic patients within 1 to 2 weeks from symptom onset

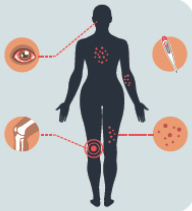
Real-Time, Reverse-Transcription Polymerase Chain Reaction (RT-PCR) RNA Test

Positive

Report results

Negative

Symptomatic patients at least 4 days to 8-12 weeks from symptom onset or asymptomatic pregnant women



Antibody test (IgM)

Negative

Report results

Presumptive positive and inconclusive

Confirmatory Plaque-Reduction Neutralization Test (PRNT)

U.S. Department of Health and Human Services
Centers for Disease Control and Prevention

CS266331A May 31, 2016

| | RT-PCR* RNA Test | IgM Antibody Test | PRNT |
|---|---|---|---|
| **Description of Test** | Testing symptomatic patients within 7 days of symptom onset for blood or 14 days for urine | Testing symptomatic patients or asymptomatic pregnant women 4 days to 8-12 weeks after symptom onset or exposure | Confirmatory step for presumptive positive and inconclusive IgM test results to distinguish between Zika and related viral infections |
| **Processing Time** | Lab processing time 1 day<br>Total testing turn around time approximately 4-8 days (depending on arrival, testing, and analysis time). | Lab processing time 3 days<br>Total testing turnaround time approximately 6-10 days (depending on arrival, testing, and analysis time) | Lab processing time 4-5 days<br>Total testing turnaround time approximately 8 days (requires previous IgM test) |
| **Current Locations** | As of May 27, 40 states and territories and CDC Fort Collins and CDC San Juan<br>States: AL, AK, AR, AZ, CA, CO, CT, DC, DE, GA, HI, IA, ID, IL, KY, LA, MA, MI, MN, MO, MS, MT, NH, NJ, NM, NY, NC, ND, OH, OK, OR, PA, RI, TN, TX, UT, VA, VT, WI, and WY | As of May 27, 31 states and territories and CDC Fort Collins and CDC San Juan<br>States: AZ, CA, CT, DC, FL, GA, HI, IA, IL, KY, LA, MA, MD, MI, MN, MO, MS, NC, NE, NJ, NM, NY, OK, OR, RI, SC, TX, UT, VA, WI, and WY | CDC and New York State laboratories |
| **Number of Tests** | CDC Trioplex rRT-PCR: Anticipated more than 20,000 tests per week† | Anticipated 8,000 tests per week† | Anticipated 500 tests per week |

*CDC Trioplex Real-time RT-PCR Assay, which simultaneously tests blood or urine for RNA indicating current infection with Zika, chikungunya, or dengue; Focus Diagnostics, Inc.'s Zika Virus RNA Qualitative Real-Time RT-PCR test, which tests blood for current infection with Zika; altona Diagnostics RealStar Zika Virus RT-PCR, which tests blood or urine for current infection with Zika.

†Capacity can double with surge

# Creation of Assays

- **Initial development of assays by SMEs in many different CDC labs**
- **Adaptation to clinical use includes extensive validation and standardization**
  - ***Often still learning about the disease itself, operating with limited knowledge about the pathogen, clinical utility of specimen types at various times post infection, etc.***
  - ***Initial decisions can be based on experience with closely related pathogens (e.g. SARS/MERS).***

# Creation of Assays

- **Rare and emerging diseases present special challenges**
  - ***Limited specimen availability***
  - ***Specimen type and collection methods often not standardized (especially at first)***
  - ***Approach is stepwise: Assays can be deployed before they have been validated with every instrument system with the intent to add and improve with subsequent amendments.***

# Criteria for consideration

- **Clear need**
  - ***Agent has been shown to, or is considered likely to, spread to multiple jurisdictions***
  - ***Proven (or likely) significant public health impact***
  - ***No readily available alternative assay***
- **Assay Utility**
  - ***Could be used in Public Health Labs***
    - ***Readily available equipment and techniques***
    - ***Validation methods and materials available***
  - ***Manufacture and distribution systems in place for special reagents and supplies***

# Centers for Disease Control and Prevention's formal request for Emergency Use Authorization (EUA) regarding the distribution and use of the Zika MAC-ELISA

*"At this time, there are no adequate, approved (cleared), and available alternative diagnostic tools that can detect evidence of Zika virus infection in the United States. Therefore, this EUA is designed to utilize the CDC Zika MAC-ELISA to expand testing capabilities within the U.S. public health system by providing a diagnostic tool to qualified laboratories for the detection of Zika virus-specific IgM antibodies in clinical specimens during the public health emergency.*

*The CDC Zika MAC-ELISA is a presumptive assay intended for use in conjunction with clinical and epidemiological information in specimens from persons meeting the CDC Zika clinical and epidemiological criteria for testing. The assay will be used for the qualitative detection of Zika virus-specific IgM antibodies only by qualified laboratories."*

# CDC Zika MAC-ELISA Clincal Data

| R number | Age | Sex | Date Collected | Onset Date | Days post onset | Specimen Type | Pregnant | Yellow Fever Vaccination | Zika MAC-ELISA | Zika MAC-ELISA Interpretation | PRNT Zika | PRNT Dengue 2 | Dual PRNT and Zika PRNT Interpretation |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 102027 | 23 | M | 1/20/2015 | 1/12/2015 | 8 | Serum | | | 7.4 | pos | 10 | 320 | Dengue |
| 102118 | 53 | M | 3/11/2015 | 3/8/2015 | 3 | Serum | | | 1.3 | neg | <10 | 80 | Dengue |
| 102156 | 50 | M | 4/1/2015 | 3/31/2015 | 1 | Serum | | | 4.6 | pos | 10 | <10 | neg |
| 102227 | 41 | F | 5/6/2015 | 4/27/2015 | 9 | Serum | | yes | 7.7 | pos | 80 | 1280 | Dengue |
| 102350 | 23 | F | 5/11/2015 | 5/6/2015 | 5 | Serum | | | 9.6 | pos | <10 | 80 | Dengue |
| 102372 | 22 | M | 6/11/2015 | 6/6/2015 | 5 | Serum | | | 2.3 | eq | <10 | 80 | Dengue |
| 102408 | 42 | M | 6/17/2015 | 5/31/2015 | 17 | Serum | | | 4.3 | pos | <10 | | neg |
| 102494 | 33 | M | 7/9/2015 | 6/30/2015 | 9 | Serum | | | 13.9 | pos | 640 | 80 | Zika |
| 102611 | 62 | M | 7/27/2015 | 7/5/2015 | 22 | Serum | | | 2 | eq | <10 | | neg |
| 102698 | 35 | F | 8/4/2015 | 7/21/2015 | 14 | Serum | | | 17.1 | pos | 20,480 | | Zika |
| 103178 | 36 | F | 10/22/2015 | 10/1/2015 | 21 | Serum | | | 8.6 | pos | 10 | 10240 | Dengue |
| 103179 | 11 | F | 10/22/2015 | 10/1/2015 | 21 | Serum | | | 8.8 | pos | 10 | 5120 | Dengue |
| 103228 | 41 | M | 11/12/2015 | 10/25/2015 | 18 | Serum | | | 12.7 | pos | 640 | 320 | Flavivirus |
| 103229 | 47 | F | 11/12/2015 | 10/25/2015 | 18 | Serum | | | 28.5 | pos | 40 | 2560 | Dengue |
| 103281 | 30 | F | 11/29/2015 | 11/23/2015 | 6 | Serum | | | 21.5 | pos | 320 | <10 | Zika |
| 103304 | 45 | M | 11/24/2015 | 10/19/2015 | 36 | Serum | | | 8.9 | pos | <10 | 1280 | Dengue |
| 103318 | 66 | M | 12/8/2015 | 11/11/2015 | 27 | Serum | | | 6.1 | pos | <10 | 320 | Dengue |
| 103320 | 75 | F | 11/5/2015 | 10/31/2015 | 5 | Serum | | | 2.1 | eq | 320 | 1280 | Dengue |
| 103325 | 43 | F | 12/1/2015 | 11/25/2015 | 6 | Serum | | | 21.7 | pos | 640 | <10 | Zika |
| 103326 | 45 | M | 12/1/2015 | 11/29/2015 | 2 | Serum | | | 29.9 | pos | 5120 | 20480 | Dengue |
| 103327 | 21 | M | 12/1/2015 | 11/29/2015 | 2 | Serum | | | 8.4 | pos | 160 | <10 | Zika |
| 103328 | 41 | F | 11/19/2015 | 11/14/2015 | 5 | Serum | | | 48.8 | pos | >20480 | >20480 | Flavivirus |
| 103390 | 55 | M | 12/17/2015 | 12/3/2015 | 14 | Serum | | | 18 | pos | >20480 | >20480 | Flavivirus |
| 103396 | 16 | F | 12/7/2015 | 11/24/2015 | 13 | Serum | | | 23.5 | pos | 20480 | <10 | Zika |
| 103405 | 79 | M | 12/16/2015 | 12/16/2015 | 0 | Serum | | | 2.5 | eq | <10 | <10 | neg |
| 103414 | 36 | M | 12/28/2015 | 12/22/2015 | 6 | Serum | | | 26.2 | pos | >2560 | 1280 | Flavivirus |
| 103427 | | | 12/22/2016 | | | Serum | | | 5 | pos | <10 | 160 | Dengue |
| 103436 | | F | 1/8/2016 | 1/1/2016 | 7 | Serum | | | 44.9 | pos | 1280 | <10 | Zika |
| 103447 | 37 | F | 1/11/2016 | 10/16/2015 | 87 | Serum | yes | | 0.94 | neg | <10 | <10 | neg |
| 103449 | 29 | M | 1/6/2016 | 1/3/2016 | 3 | Serum | | | 15.9 | pos | 1280 | 10240 | Dengue |
| 103450 | 30 | F | 1/6/2016 | 1/7/2016 | -1 | Serum | yes | | 1.3 | neg | 80 | 640 | Dengue |
| 103452 | 36 | F | 1/6/2016 | 12/31/2015 | 6 | Serum | yes | | 0.78 | neg | <10 | <10 | neg |
| 103453 | 48 | M | 1/6/2016 | 12/30/2015 | 7 | Serum | | | 1.8 | neg | <10 | 160 | Dengue |
| 103454 | 17 | M | 1/6/2016 | 12/22/2015 | 15 | Serum | | | 35.8 | pos | 20480 | <10 | Zika |
| 103457 | 44 | F | 12/30/2015 | 11/12/2015 | 48 | Serum | | | 57.6 | pos | 20480 | >=2560 | Zika |
| 103458 | 29 | F | 1/4/2016 | 1/3/2016 | 1 | Serum | | | 11.9 | pos | 1280 | 640 | Flavivirus |
| 103460 | 15 | F | 1/8/2016 | 1/5/2016 | 3 | Serum | | | 2.6 | eq | 80 | <10 | Zika |
| 103469 | 41 | F | 12/30/2015 | 12/2/2015 | 28 | Serum | | | 21.9 | pos | 2560 | <10 | Zika |
| 103474 | 35 | F | 1/13/2016 | 12/21/2015 | 23 | Serum | yes | 2013 | 2.6 | eq | <10 | <10 | neg |

# Assay Support

- **Training and protocol review sessions**
  - ***Teleconference***
  - ***Webinar***
  - ***Helpdesk support***

- **Biosafety Guidance**
  - ***Specimen collection, handling and transport***
  - ***Laboratory manipulations***

- **Testing Algorithm**

# Assay Support

- **Validation and proficiency panels**
  - ***Starting with Zika assays, CDC has begun working with CMS to ensure that the panels are recognized by CLIA inspectors as sufficient to stand up an emergency assay in the participating laboratories.***

- **Performance monitoring**
  - ***Data is reported to CDC on assay performance for situational awareness and response.***
  - ***May result in assay or algorithm modification and/or amendment of EUA***

# Assay Support

- **Results Interpretation**
  - ***Fact Sheet for Health Care Providers***
  - ***Fact Sheet for Patients***
  - ***Other Fact Sheets as needed for special situations***
    - ***Case contacts (MERS, Ebola)***
    - ***Pregnant women (Zika)***

# Key Points

- **These are EMERGENCY assays**
- **EUA Assays and their documentation are likely to change as knowledge increases and situation changes**
  - ***Algorithms may be revised to optimize process and ensure most consistent and accurate results***
  - ***Additional platforms may be added if needed***
  - ***Biosafety guidelines may be revised based on further characterization of pathogen***
  - ***Results interpretation may be modified based on experience as case numbers increase***

# Key Points

- **EUAs are temporary**
  - **The Public Health Emergency may pass**
  - **The pathogen may establish continued circulation in the population (e.g., pandemic influenza)**
- **Assays authorized under normal, non-emergency regulatory authority will become available if the demand is present.**

# Acknowledgements


- CDC:
  - Julie Villanueva
  - Laura Rose
  - Influenza Division
  - Division of Viral Diseases
  - Division of High Consequence Pathogens and Pathology
  - Division of Vector-Borne Diseases
  - Division of Preparedness and Emerging Infections
  - Division of Scientific Resources
- DHHS
- APHL
- FDA: *Their support has been invaluable for our efforts to ensure meaningful and specific guidance is available to those tested and for their physicians*.