



May 2017

# EMERGING INFECTIOUS DISEASES

## Actions Needed to Address the Challenges of Responding to Zika Virus Disease Outbreaks

# GAO Highlights

Highlights of [GAO-17-445](#), a report to congressional requesters.

## Why GAO Did This Study

Zika virus disease can cause adverse pregnancy and neurological outcomes. Given this ongoing threat, GAO was asked to evaluate progress made and challenges faced by federal agencies in responding to the Zika virus outbreak in the United States.

GAO examined (1) information on what is known and not known about the epidemiology of the Zika virus, and any challenges with conducting surveillance and epidemiological studies, (2) characteristics of different diagnostic tests authorized during the outbreak, challenges test manufacturers and users faced, and the extent to which FDA and CDC followed their own communication guidance, and (3) the strengths and limitations of available mosquito control methods, and challenges federal agencies face supporting these efforts.

GAO reviewed literature and agency documentation, and interviewed federal and state officials about the Zika virus and the U.S. response. GAO also convened an expert meeting with the assistance of the National Academy of Sciences to discuss various issues surrounding the response to the Zika virus.

## What GAO Recommends

GAO is making five recommendations to FDA and CDC, including that CDC establish a transparent process for providing test manufacturers access to diagnostic tests and FDA and CDC provide information to help ensure that users of diagnostic tests can compare performance. Agencies agreed with four recommendations but raised some concerns with the fifth. GAO has addressed these concerns in the report.

View [GAO-17-445](#). For more information, contact Chief Scientist Timothy M. Persons at (202) 512-6412 or [personst@gao.gov](mailto:personst@gao.gov).

May 2017

## EMERGING INFECTIOUS DISEASES

### Actions Needed to Address the Challenges of Responding to Zika Virus Disease Outbreaks

## What GAO Found

Since Zika virus disease was a newly emerging disease threat in the United States, and relatively little was known about the Zika virus prior to the 2016 U.S. outbreak, the Centers for Disease Control and Prevention (CDC), and the states were not fully equipped with needed information and resources at the beginning of the outbreak. This presented several challenges for Zika virus disease surveillance and research efforts, such as challenges related to establishing a national definition for reporting cases. Knowledge about Zika virus epidemiology has increased in the past year, including information about Zika virus disease incidence and distribution of cases, and its associated adverse health outcomes. Most of the 5,197 Zika virus disease cases reported by April 5, 2017 in the United States were associated with travel from affected areas outside the continental United States. Only two states had disease cases of local, mosquito-borne transmission—216 were in Florida and 6 in Texas. While much has been learned about the epidemiology of the Zika virus, many unknowns remain, including the actual number of infections and the full spectrum of outcomes.

The 16 Zika virus diagnostic tests authorized during the outbreak varied in their performance and operational characteristics. For example, they varied in their ability to detect the virus and provide accurate results. In developing the diagnostic tests, manufacturers faced challenges in several areas, including access to clinical samples and other authorized diagnostic tests for comparison purposes. Users of the tests also encountered challenges, including determining the most accurate test to use, and obtaining equipment needed to conduct the tests. Some manufacturers raised concerns about the difficulty in developing diagnostic tests that met the Food and Drug Administration's (FDA) requirements for Emergency Use Authorization and some users expressed concerns about selecting tests amongst those authorized. GAO also determined that CDC and FDA did not follow some of their guidance in communicating with users of diagnostic tests, including providing clear information that would have enabled users to more easily compare performance across different tests.

Mosquito control programs in the United States are implemented at state and local levels and are critical to mitigating the risks associated with the Zika virus. Control methods include applying pesticides, reducing available water sources for breeding, and using personal protection. Each method has its strengths and limitations. For example, some control methods are more effective at reducing mosquito populations while others help prevent individuals from mosquito bites. Similarly, each method has some limitations, for example, there is varied public opposition to the use of certain pesticides. CDC supports state and local mosquito control activities primarily by providing guidance on mosquito control methods and funding to support certain mosquito control efforts. Challenges federal agencies faced in supporting these activities include sustaining staff expertise in mosquito control during periods when there are no outbreaks, funding constraints, and effectively communicating information about the geographical distribution of mosquitoes that transmit the Zika virus.

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## Abbreviations

AMCA	American Mosquito Control Association
APHL	Association of Public Health Laboratories
ASPR	Assistant Secretary for Preparedness and Response
ASTHO	Association of State and Territorial Health Officials
BARDA	Biomedical Advanced Research and Development Authority
BSL	biological safety level
Bti	<i>Bacillus thuringiensis israelensis</i>
CDC	Centers for Disease Control and Prevention
CLIA	Clinical Laboratory Improvement Amendments
CSTE	Council of State and Territorial Epidemiologists
DOD	Department of Defense
EPA	Environmental Protection Agency
EUA	Emergency Use Authorization
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
HHS	Department of Health and Human Services
IgG	immunoglobulin G
IgM	immunoglobulin M
IMM	integrated mosquito management
IVM	integrated vector management
MAC-ELISA	IgM antibody capture enzyme-linked immunosorbent assay
MMWR	Morbidity and Mortality Weekly Report
NACCHO	National Association of County and City Health Officials
NIAID	National Institute of Allergy and Infectious Diseases
NIH	National Institutes of Health
NNDSS	National Notifiable Diseases Surveillance System
NPDES	National Pollution Discharge Elimination System
NSTC	National Science and Technology Council
OSTP	Office of Science and Technology Policy
PAHO	Pan American Health Organization

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PRNT	plaque reduction neutralization test
RNA	ribonucleic acid
RT-PCR	reverse transcriptase-polymerase chain reaction
SARS	severe acute respiratory syndrome
SVAZE	Sistema de Vigilancia Activa de Zika en Embarazos
WHO	World Health Organization
ZAPSS	Zika Active Pregnancy Surveillance System
ZIP	Zika in Infants and Pregnancy

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May 23, 2017

The Honorable Greg Walden  
Chairman  
The Honorable Frank Pallone, Jr.  
Ranking Member  
Committee on Energy and Commerce  
House of Representatives

The Honorable Tim Murphy  
Chairman  
The Honorable Diana DeGette  
Ranking Member  
Subcommittee on Oversight and Investigations  
Committee on Energy and Commerce  
House of Representatives

The Honorable Fred Upton  
House of Representatives

Emerging infectious diseases such as Zika virus disease constitute an ongoing threat to the health of people in the United States and around the world. Many advances in medical research and treatments were made in the past century, but infectious diseases have been nevertheless a leading cause of death worldwide (they account for one of every five deaths). Additionally, infectious diseases impose a heavy societal and economic burden on individuals, families, communities, and countries. Infectious diseases are a continuous threat because of (1) emergence—at times rapid—of new infectious diseases; (2) reemergence of previously known infectious diseases; and (3) persistence of intractable infectious diseases.

Changes in human demographics, behavior, and land use—among other factors—bring people into closer and more frequent contact with pathogens and contribute to infectious disease emergence. This may involve exposure to animal carriers of disease and increased opportunities for pathogens to jump between animal and human reservoirs. In addition to Zika virus, other examples of emerging infectious diseases include Ebola virus disease, severe acute respiratory syndrome (SARS), influenza, dengue, and chikungunya, among others. The Zika virus attracted attention from health officials in the United States and abroad after geographic and time-period similarities between reported

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cases of Zika virus infection and adverse health outcomes, especially in newborns, were reported in Brazil in 2015—a pattern that was also observed during a Zika virus outbreak in French Polynesia in 2014.

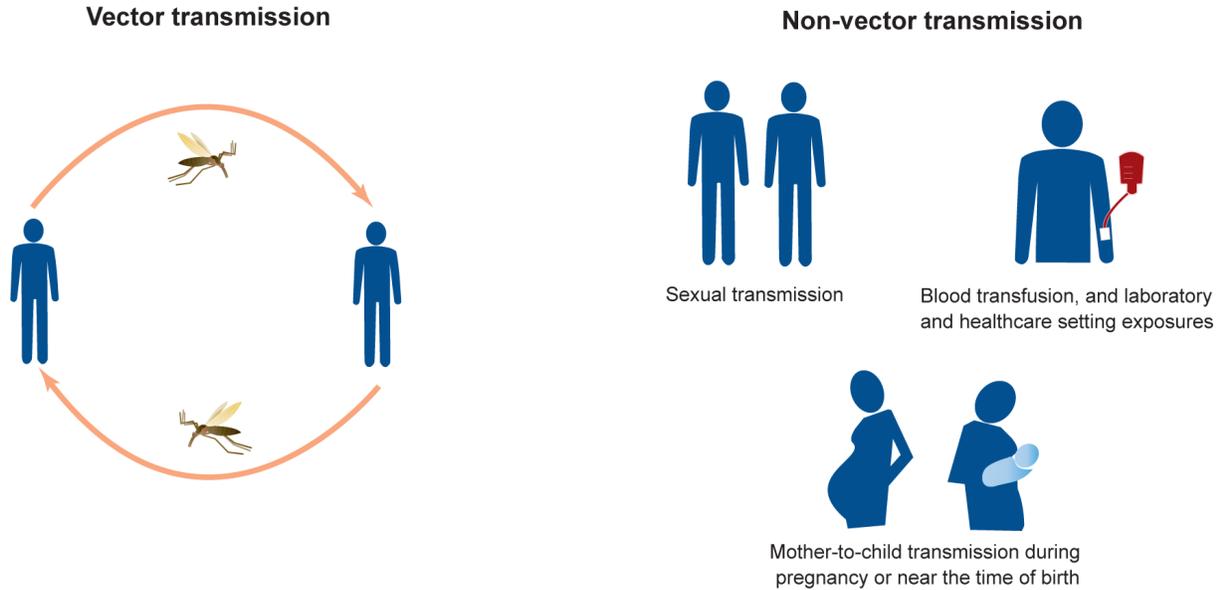
As shown in figure 1, the Zika virus is primarily transmitted to humans by infected mosquitoes but can also be transmitted from mother-to-child during pregnancy or around the time of birth, or from person to person through sexual contact or blood transfusion.<sup>1</sup> The virus can cause signs and symptoms that include fever, rash, conjunctivitis (“pink eye” where the eyes appear red or pink), and joint and muscle pain, although most people with Zika virus infection have only mild or no symptoms. Disease surveillance and epidemiological studies have established that Zika virus infection in a pregnant woman can cause birth defects in newborns and is also associated with increased cases of nervous system illnesses in infected adults.<sup>2</sup>

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<sup>1</sup>Centers for Disease Control and Prevention. “Clinical Guidance for Healthcare Providers for Prevention of Sexual Transmission of Zika Virus,” accessed February 21, 2017. <https://www.cdc.gov/zika/hc-providers/clinical-guidance/sexualtransmission.html>.

<sup>2</sup>Surveillance is the systematic and continuous collection, analysis, and interpretation of data, closely integrated with the timely and coherent dissemination and assessment of the results by those who have the right to know so that action can be taken. See Miquel Porta ed., *A Dictionary of Epidemiology*, 6th ed. (New York: Oxford University Press, 2014), 274. Epidemiologic studies determine the extent and distribution of the disease in a population, its causes and factors, modes of transmission, natural history, and developing preventive strategies or interventions. See Dona Schneider and David E. Lilienfeld, *Lilienfeld’s Foundations of Epidemiology*, 4th ed. (New York: Oxford University Press, 2015).

**Figure 1: Zika Virus Can Be Transmitted by Mosquitoes (Vectors) and in Other Ways**



Source: GAO analysis of Centers for Disease Control and Prevention information. | GAO-17-445

Because of concern about the threat and emergence of Zika virus disease in the United States, you asked us to review a number of issues related to the Zika virus and the U.S. response to the outbreak. This report (1) provides information on what is known and not known about the epidemiology of the Zika virus and determine the challenges, if any, in conducting surveillance and epidemiological studies, (2) determines the characteristics of different Zika virus diagnostic tests and any challenges manufacturers and users faced, and the extent to which the Centers for Disease Control and Prevention (CDC) and Food and Drug Administration (FDA) followed their own communication guidance during the U.S. outbreak, and (3) identifies available mosquito control methods, describes their strengths and weaknesses, and identifies any challenges federal agencies and others face in assisting mosquito control efforts.<sup>3</sup>

To conduct this work, we reviewed relevant documentation, such as FDA's guidance to manufacturers, product labels, and agencies' reports

<sup>3</sup>In this report, users of diagnostic tests include laboratory personnel, health care providers, and others in the medical and scientific communities.

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on epidemiology of the Zika virus. We also interviewed officials from key federal agencies and departments responding to the domestic Zika virus outbreak, including the Department of Defense (DOD), Environmental Protection Agency (EPA), and Department of Health and Human Services (HHS) including CDC, FDA and National Institutes of Health (NIH).

We also convened, with the assistance of the National Academy of Sciences, a 2-day meeting with 16 experts knowledgeable about the Zika virus to discuss issues related to the outbreak. These experts represented academia, the federal government, state government, and industry and combined expertise in epidemiology, diagnostic testing, and mosquito control.

To assess the Zika virus outbreak in terms of epidemiology, diagnostic tests, and mosquito control, we selected two cities for site visits in the continental United States based on their reported Zika virus cases at the time of our site visit selection: New York City, New York, which had the largest number of cases acquired from travel outside the United States, and Miami, Florida. Florida was the only state with local mosquito-borne transmission at the time of our site selection.<sup>4</sup> For both site visits, we interviewed and collected information from officials in the city and state public health departments.

To provide information on what is known about Zika virus epidemiology and the challenges in conducting surveillance and epidemiological studies, we reviewed surveillance case count data from CDC and data reported jointly by the Pan American Health Organization (PAHO) and the World Health Organization (WHO). We reviewed peer-reviewed journal articles, agency documents, and reports about Zika virus infection and associated health outcomes. We interviewed federal and selected state and city officials about challenges in Zika virus surveillance and epidemiology, including initial response efforts. We also interviewed representatives from key public health organizations, including the Association of State and Territorial Health Officials (ASTHO), Council of

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<sup>4</sup>We did not visit Puerto Rico or other U.S. territories with laboratory-confirmed Zika virus disease cases; however, Puerto Rican scientists participated in our expert group meeting.

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State and Territorial Epidemiologists (CSTE), National Association of County and City Health Officials (NACCHO), and PAHO.<sup>5</sup>

To determine the characteristics of different Zika virus diagnostic tests, we reviewed and compared the product labels, letters of authorization, and factsheets for healthcare providers and patients for each test posted on the FDA website in April 2017. To determine the strengths and limitations of different diagnostic tests and the challenges associated with Zika virus diagnostic testing, research, development, and regulatory approval, we interviewed several manufacturers of Zika diagnostic tests. We also interviewed officials at selected public health laboratories and asked officials at selected federal laboratories about the strengths and limitations of different diagnostic tests. We compared the information that we gathered from our interviews and agency documents to *Standards for Internal Control in the Federal Government*.<sup>6</sup>

To determine whether CDC and FDA followed their own communication guidance, we compared information collected from agency interviews, our expert meeting, scientific professional societies, and relevant agencies' documents to internal agency guidance documents, such as FDA's transparency initiative information.<sup>7</sup>

To identify available mosquito control methods and their strengths and limitations, we reviewed agency documents and peer-reviewed literature and interviewed experts and officials from eight mosquito control entities.<sup>8</sup>

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<sup>5</sup>ASTHO is a national nonprofit organization representing public health agencies and their employees in the United States and its territories, including the District of Columbia. CSTE is a professional organization of public health epidemiologists from every U.S. state and territory as well as Canada and Great Britain. NACCHO is an association of nearly 3,000 local health departments across the United States. PAHO provides technical cooperation and facilitates partnerships to improve health and quality of life, is the specialized health agency of the Inter-American System, and serves as the Regional Office for the Americas of WHO.

<sup>6</sup>GAO, *Standards for Internal Control in the Federal Government*, [GAO-14-704G](#) (Washington, D.C.: September 2014).

<sup>7</sup>Department of Health and Human Services, Food and Drug Administration Transparency Task Force, *FDA Transparency Initiative: Improving Transparency to Regulated Industry* (Washington, D.C.: FDA, January 2011), and Department of Health and Human Services, Food and Drug Administration, *FDA Transparency Initiative: Increasing Public Access to FDA's Compliance and Enforcement Data* (Washington, D.C.: HHS, April 2014).

<sup>8</sup>We selected a nongeneralizable sample of mosquito control entities. More information about our selection methods is in appendix II.

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To assess the challenges federal agencies face in assisting mosquito control efforts in the United States, we interviewed federal agency officials from CDC, EPA, and FDA as well as experts in the federal government, academia, state and local governments, and experts from our meeting. (More information on our objectives, scope, and methodology is in appendix II.)

We conducted this performance audit from June 2016 to May 2017 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

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## Background

### Zika Virus: An Overview

The Zika virus is related to dengue, yellow fever, West Nile, and Japanese encephalitis viruses, among others.<sup>9</sup> The virus was first identified in the Zika Forest in Uganda, Africa in 1947, from where it moved east, causing only sporadic human disease until 2007. The first documented outbreak of Zika virus disease was reported in Yap State, Federated States of Micronesia, in 2007 and subsequent outbreaks occurred in Southeast Asia and the Western Pacific.<sup>10</sup> Some researchers have suggested that several combined factors contributed to the current outbreak and that travel was a major factor.<sup>11</sup> Figure 2 illustrates the spread of the Zika virus over time.

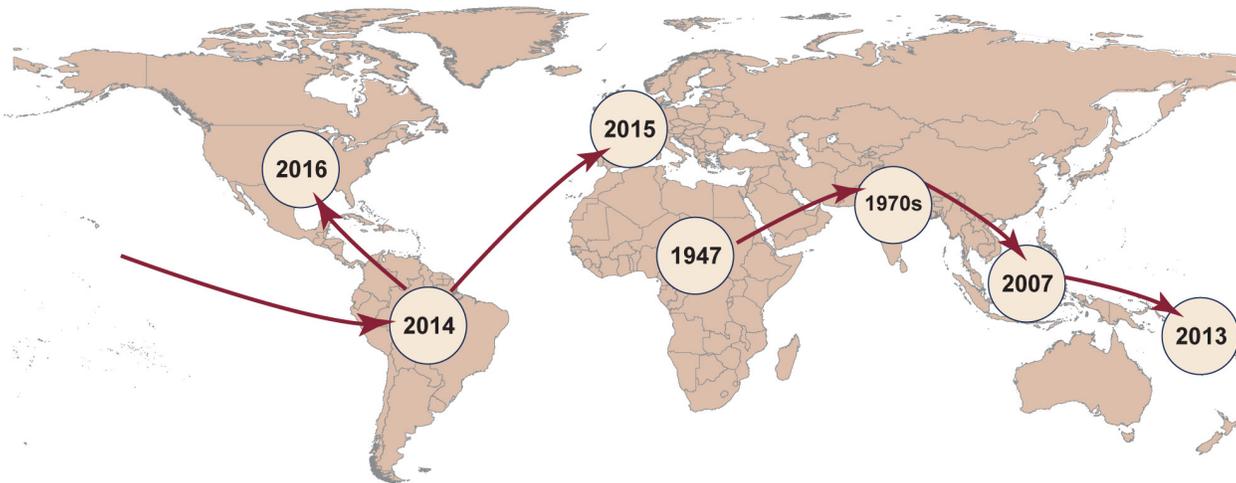
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<sup>9</sup>Zika virus is a member of the genus *Flavivirus* which is made up of positive, single-stranded, enveloped ribonucleic acid (RNA) viruses found in arthropods (primarily ticks and mosquitoes) and can occasionally infect humans and other vertebrates.

<sup>10</sup>Robert S. Lanciotti and others, "Genetic and Serologic Properties of Zika Virus Associated with an Epidemic, Yap State, Micronesia, 2007," *Emerging Infectious Diseases*, vol. 14, no. 8 (2008): 1232–39.

<sup>11</sup>Gretchen Vogel, Jon Cohen, and Martin Enserink. "Zika Virus: Your Questions Answered." *Science*, January 29, 2016.  
<http://www.sciencemag.org/news/2016/01/zika-virus-your-questions-answered>.

Figure 2: Spread of the Zika Virus Around the World, 1947-2016



Source: GAO analysis of World Health Organization information. | GAO-17-445

In February 2016, a WHO emergency committee on the Zika virus noted a strong association in time and place between Zika virus infection and a rise in detected cases of congenital malformations and neurological complications, suspecting a causal relationship. WHO declared that the recent cluster of microcephaly cases and other neurological disorders, including Guillain-Barré syndrome, reported in Brazil and following a similar cluster in French Polynesia in 2013, constituted a Public Health Emergency of International Concern which required urgent and coordinated research.<sup>12</sup> The Secretary of Health and Human Services

<sup>12</sup>In November 2016, WHO declared a Public Health Emergency of International Concern after research demonstrated the link between Zika virus infection and microcephaly; WHO's Emergency Committee on Zika virus determined that a robust technical mechanism is required to manage the global response. However, the Zika virus and associated health outcomes remain a significant public health challenge.

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also designated the Zika virus a public health emergency in Puerto Rico in August 2016.<sup>13</sup>

Microcephaly is a rare nervous system disorder that causes a baby's head to be smaller than expected and not fully developed, which can lead to impaired thought processes, delayed motor function, and other adverse outcomes. Guillain-Barré syndrome is a rare disorder in which the body's immune system attacks the nervous system outside the brain and spinal cord, causing muscle weakness and, in some cases paralysis, although most people recover.

Currently available Zika virus prevention methods include various mosquito control and control methods, guidance on safe sex practices if a person has or is suspected of having Zika virus or has traveled to an area with high rates of local transmission, and guidance for travel to areas affected by Zika virus. Although at present no vaccine has been approved by the FDA to prevent Zika virus disease, several vaccines are in different development phases.

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<sup>13</sup>The public health emergency declaration is a tool the federal government used to provide additional support to Puerto Rico's government to respond to the Zika outbreak and to grant access to certain federal funds. The last time HHS declared a public health emergency was in 2012, after Superstorm Sandy struck the eastern coast of the United States.

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## Zika Virus Surveillance Overview

### Key Terms Related to Epidemiology

**Emerging Infections:** Infectious disease that is newly recognized; one that has been recognized before but is newly appearing in a different population or geographic area than previously affected; one that is newly affecting many more individuals; and/or one that has developed new attributes (e.g., resistance or virulence).

**Epidemiology:** The study of the occurrence and distribution of health-related events, states, and processes in specified populations, including the study of the determinants influencing such processes and the application of this knowledge to control relevant health problems.

**Incidence:** The number of new cases of a disease in a defined population within a specified time.

**Incidence rate:** The rate at which new events occur in a population expressed as the number of new cases divided by the population at risk in a defined time period.

**Outbreak:** An epidemic limited to a localized increase in the incidence of a disease as in a village, town, or closed institution.

**Surveillance:** Systematic and continuous collection, analysis, and interpretation of data, closely integrated with the timely and coherent dissemination of the results and assessment to those who have the right to know so that action can be taken.

Source: Miquel Porta (ed.), *A Dictionary of Epidemiology*, 6th ed. (New York: Oxford University Press, 2014). I GAO-17-445

The Zika virus was added to the list of nationally notifiable diseases in February 2016. CDC collects data on new cases of notifiable diseases through its National Notifiable Diseases Surveillance System (NNDSS), by encouraging states and territories to report laboratory-confirmed cases.<sup>14</sup> Arthropod-borne viruses (also called arboviruses) are also reported in a surveillance system that is specific to arboviral diseases, called ArboNET.<sup>15</sup> Reporting nationally notifiable diseases, including the Zika virus, from states and territories to CDC is voluntary. States and territories rely on healthcare providers or laboratories to report cases to their local, state, or territorial health departments according to the laws or regulations within their jurisdictions. A surveillance case definition is a set of uniform criteria used to define a disease for public health surveillance, with the purpose of enabling public health officials to classify and count cases consistently across reporting jurisdictions.<sup>16</sup>

CSTE—a professional organization of member states and territories representing public health epidemiologists—recommends that state health departments report cases of selected diseases to CDC’s NNDSS, in accordance with CSTE’s position statements that establish case definitions and are reviewed by CDC. The CSTE Zika virus interim case definition position statement was published in February 2016 and revised in June 2016. By April 2017, all states with the exception of Alaska, and three U.S. territories reported Zika virus cases to CDC through the ArboNET system, according to CDC’s reports.

To understand more about Zika virus infection, CDC established the U.S. Zika Pregnancy Registry and is collaborating with state, tribal, local, and territorial health departments to collect information about pregnancy and infant outcomes following laboratory evidence of possible Zika virus

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<sup>14</sup>NNDSS enables public health officials at local, state, territorial, federal, and international levels to voluntarily share notifiable disease-related health information and allows public health officials to use this information to monitor, control, and prevent the occurrence and spread of those diseases. The Zika virus was declared a nationally notifiable condition for surveillance reporting in the United States with the Office of Management and Budget approval of a revision to the system, which authorized CDC to receive case notifications of the Zika virus.

<sup>15</sup>Arboviruses are any of a group of viruses that are transmitted by mosquitoes, ticks, or other arthropods (an animal such as an insect or spider).

<sup>16</sup>Surveillance case definitions are not intended to be used by healthcare providers for making a clinical diagnosis or determining how to meet an individual patient’s health needs.

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infection during pregnancy. According to CDC, the data collected through this registry will be used to update recommendations for clinical care, to plan for services for pregnant women and families affected by Zika virus, and to improve prevention of Zika virus infection during pregnancy.<sup>17</sup> The Puerto Rico Department of Health and CDC developed the Zika Active Pregnancy Surveillance System (ZAPSS)/Sistema de Vigilancia Activa de Zika en Embarazos (SVAZE) to evaluate the association between possible Zika virus infection during pregnancy and adverse outcomes during pregnancy, birth, and early childhood up to 3 years of age.<sup>18</sup> Pregnant women in Puerto Rico with laboratory evidence of possible Zika virus infection (positive or equivocal test results, regardless of whether they have symptoms) and prenatally or perinatally exposed infants born to these women will be actively monitored.<sup>19</sup> According to CDC, this information has been used to inform best practices in care for women infected with Zika virus during pregnancy and their infants. CDC compiles data from the aforementioned systems to regularly update its website information regarding case counts and its Morbidity and Mortality Weekly Report (MMWR) of notifiable diseases.<sup>20</sup>

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## Diagnostic Tests for the Zika Virus

Accurate diagnostic tests have a key role in patient management and the control of most infectious diseases. Good quality diagnostic tests that are fit for purpose and can provide accurate results can help in reducing the burden of infectious diseases. The choice of which diagnostic test to use can depend on several factors, such as: which tests are approved for use by regulatory authorities, which tests are available for use at the patient's health care location, and the physician's decision on which of the available tests he or she judges might be useful in clinical decision making. Zika virus diagnostic testing is now performed in federal, state, and commercial laboratories.

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<sup>17</sup>Centers for Disease Control and Prevention, "U.S. Zika Pregnancy Registry.", accessed April 5, 2017, <https://www.cdc.gov/zika/reporting/registry.html>.

<sup>18</sup>Centers for Disease Control and Prevention, "Zika Active Pregnancy Surveillance System (ZAPSS)/Sistema de Vigilancia Activa de Zika en Embarazos (SVAZE)," accessed April 5, 2017. <https://www.cdc.gov/zika/reporting/zapss.html>.

<sup>19</sup>According to HHS officials, it is important to note that pregnant women have been included in the registries regardless of symptoms from the initiation of these registries because it was recognized at the onset that surveillance of asymptomatic pregnant women was important.

<sup>20</sup>CDC issues annual summaries for notifiable diseases a few months into the following year, once the data have been finalized.

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HHS, through FDA, oversees the safety and effectiveness of diagnostic tests, which are regulated as medical devices sold in the United States.<sup>21</sup> FDA can authorize the use of unapproved medical products, including diagnostic tests or an unapproved use of approved medical products for certain emergencies.<sup>22</sup> Under an Emergency Use Authorization (EUA), these medical products can be used in emergencies under certain conditions, when there are no adequate, approved, and available alternatives. An EUA for a specific diagnostic test is intended to be temporary and only remains in effect for the duration of the declared emergency unless it is revoked, for example because of issues with the diagnostic test.

Before FDA may issue an EUA, the Secretary of Health and Human Services must declare that circumstances exist justifying the authorization (see fig. 3).<sup>23</sup> In appropriate circumstances, an HHS EUA declaration may

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<sup>21</sup>Diagnostic testing devices are called *in vitro* diagnostic products. 21 C.F.R. § 809.3. FDA regulates *in vitro* diagnostic products using a risk-based framework by classifying each device into one of three categories (Classes I-III). The class number determines the level of regulation and the appropriate premarket process required for that diagnostic test to establish a reasonable assurance of safety and effectiveness. See 21 U.S.C. § 360c

<sup>22</sup>The Emergency Use Authorization (EUA) authority allows FDA to help strengthen the nation's public health protections against chemical, biological, radiological, or nuclear (CBRN) threats by facilitating the availability and use of medical countermeasures needed during public health emergencies. Under section 564 of the Federal Food, Drug, and Cosmetic Act, as amended, the FDA Commissioner may allow unapproved medical products or unapproved uses of approved medical products to be used in an emergency to diagnose, treat, or prevent serious or life-threatening diseases or conditions caused by CBRN threat agents when there are no adequate, approved, and available alternatives.

<sup>23</sup>This declaration must be based on one of the following four actions: (1) 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(s), (2) 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(s), (3) a determination by the Secretary of Health and Human Services 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(s), or (4) the identification by the Secretary of Homeland Security of a material threat that is sufficient to affect national security or the health and security of United States citizens living abroad. After the Secretary of Health and Human Services issues an EUA declaration based on one of these four determinations, and after consulting (to the extent feasible and appropriate given the applicable circumstances) with the Assistant Secretary for Preparedness and Response (ASPR), the Director of the NIH, and the Director of CDC, the Commissioner may authorize the emergency use of an unapproved product or an unapproved use of an approved product, provided that other statutory criteria are met. 21 U.S.C. § 360bbb-3(b).

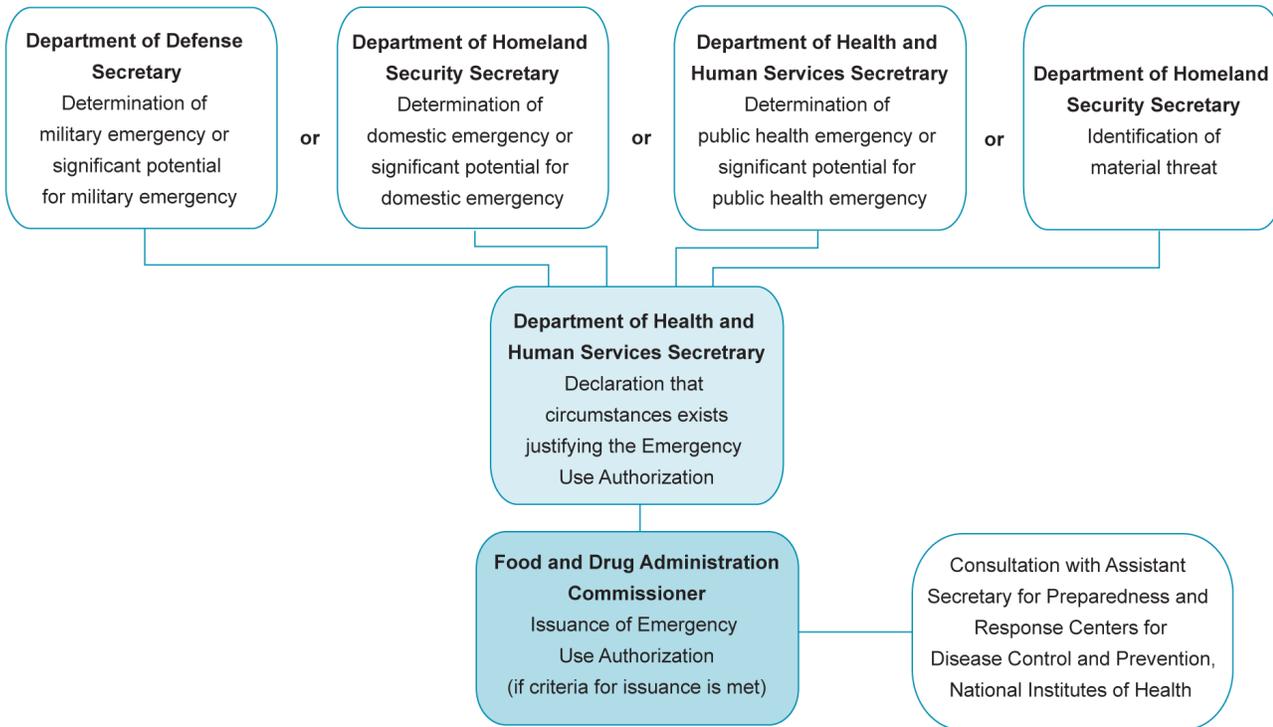
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support issuance of more than one EUA. For example, based on an HHS EUA declaration that circumstances exist to justify the authorization of emergency use of diagnostics for a specified biological agent, FDA may authorize emergency use for multiple diagnostic tests to meet the need, provided that each EUA meets the statutory criteria for issuance.<sup>24</sup> The FDA website includes a current list of available diagnostic tests and associated letters of authorization, fact sheets, and product labels. The letter of authorization includes the criteria for issuance, the scope of the authorization, waiver of certain requirements, and conditions and duration of authorization. Fact sheets are available for public health providers and for patients. Product labels include the intended use, procedures for conducting the test, and performance characteristics, among others.

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<sup>24</sup>Food and Drug Administration, “Emergency Use Authorization of Medical Products and Related Authorities: Guidance for Industry and Other Stakeholders,” accessed April 21, 2017, <https://www.fda.gov/RegulatoryInformation/Guidances/ucm125127.htm>.

**Figure 3: Prerequisites for Issuing an Emergency Use Authorization for Medical Products**



Source: GAO analysis of FDA information. | GAO-17-445

HHS determined that the Zika virus posed a significant potential for a public health emergency affecting national security and declared in February 2016 that circumstances justified EUA of Zika virus diagnostic tests.<sup>25</sup> FDA’s analytical and clinical evaluation of an EUA for a medical product is limited in comparison to the extensive evaluation required for premarket notification (also called a 510(k) review) or premarket approval.<sup>26</sup>

<sup>25</sup>See 21 U.S.C. § 360bbb-3(b)(1)(C).

<sup>26</sup>The premarket notification, or 510(k), process allows developers to demonstrate to FDA that the medical device seeking approval is substantially equivalent to a device already legally on the market. 21 C.F.R. Part 807. Premarket approval is the more stringent approach for new devices, requiring developers to provide scientific evidence, typically clinical data, showing that the device is safe and effective. 21 C.F.R. Part 814.

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Laboratory developed tests, on the other hand, are intended for clinical use, not for commercial sale and distribution, and are designed, manufactured and used within a single laboratory or laboratory network. FDA has generally not enforced premarket review and other applicable FDA requirements for laboratory developed tests because such tests are relatively simple and generally available on a limited basis. However, according to an expert from our meeting, laboratory developed tests have increased in technical and analytical complexity.

FDA has authorized under EUA two different types of diagnostic tests for the Zika virus—molecular and serologic. Molecular tests are used to detect genetic material in samples of bodily fluids, such as serum and urine. Serologic tests are diagnostic tests that detect antibodies against the Zika virus in the blood. CDC manufactured and received authorization for both types of tests, one called Triplex (molecular) and the other, Immunoglobulin M Antibody Capture enzyme linked immunosorbent assay, called MAC-ELISA (serological). Triplex is a real time reverse transcription polymerase chain reaction test (real time RT-PCR) and the MAC-ELISA is used to detect antibodies created against the Zika virus.<sup>27</sup>

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## Mosquito Control Efforts

Because Zika virus disease cannot yet be prevented by drugs or vaccines, mosquito control is critical in mitigating risks associated with this disease. According to a CDC webpage, Zika virus is transmitted to people mainly through the bite of infected *Aedes aegypti* or possibly *Aedes albopictus* mosquitoes, which an article in a CDC journal reports are present in the United States and widely distributed globally.<sup>28</sup> Figure 4 shows the potential range of the *Aedes aegypti* and *Aedes albopictus* mosquitoes in the United States. The *Aedes aegypti* mosquitoes are reportedly the primary mosquito spreading Zika virus in the Americas,

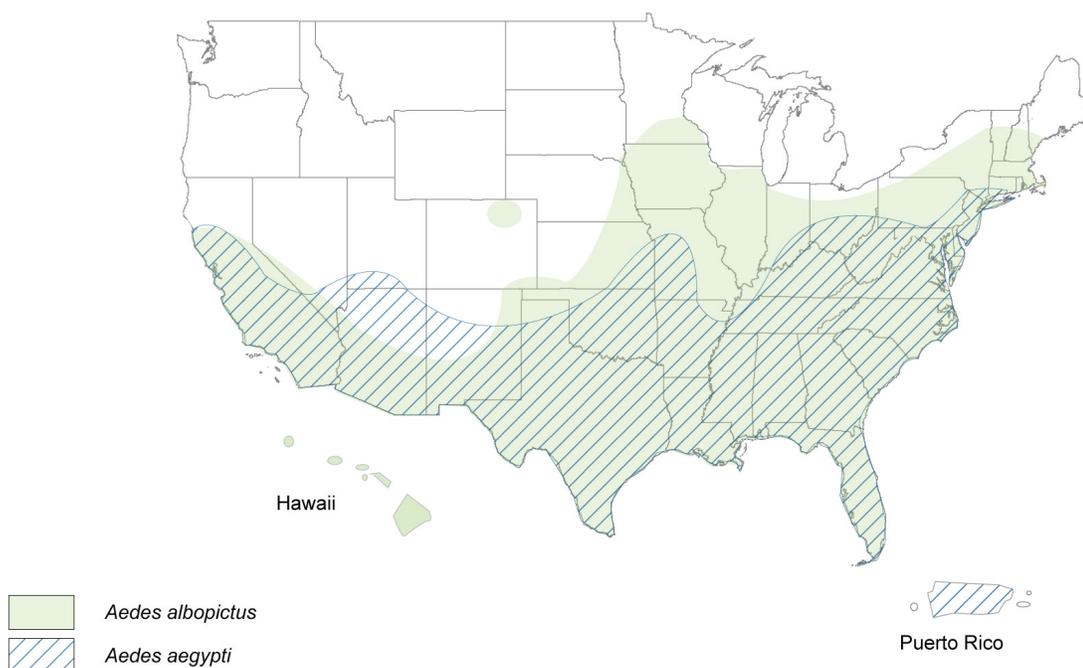
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<sup>27</sup>Reverse transcription polymerase chain reaction (RT-PCR) is a technique to amplify genetic material that uses a reverse transcriptase enzyme to convert ribonucleic acid (RNA) to deoxyonucleic acid (DNA). ELISA is a technique designed for detecting and quantifying substances such as antibodies. Antibodies are made by the body in response to antigens such as viruses.

<sup>28</sup>Anna R. Plourde and Evan M. Bloch, "A Literature Review of Zika Virus," *Emerging Infectious Diseases*, Vol. 22 No. 7 (2016); and Centers for Disease Control and Prevention, Transmission and Risks, accessed May 15, 2017, <https://www.cdc.gov/zika/transmission/index.html>.

while the *Aedes albopictus* mosquitoes share many of the same traits as *Aedes aegypti*.<sup>29</sup>

**Figure 4. Potential U.S. Range of *Aedes aegypti* and *Aedes albopictus* Mosquitoes**



Source: GAO, adapted from CDC. | GAO-17-445

A female mosquito that bites someone with Zika virus of sufficient titer can obtain the virus, allow it to multiply within it, and enter its salivary gland such that subsequent humans bitten by this mosquito can potentially be infected with the Zika virus.<sup>30</sup> According to experts, the

<sup>29</sup>Edward B. Hayes, “Zika Virus outside Africa,” *Emerging Infectious Diseases*, vol.15, no. 9 (2009): 1347–50; and National Science and Technology Council, *A Strategy for Integrating Best Practices with New Science to Prevent Disease Transmission by Aedes Mosquito Vectors*, (Washington, D.C.: December, 2016).

<sup>30</sup>According to the National Science and Technology Council (NSTC), male mosquitoes are needed to fertilize mosquito eggs but do not bite humans or transmit diseases such as the Zika virus. One scientific study reported that an infected *Aedes aegypti*, but not *Aedes albopictus*, mosquito can transmit the Zika virus to some of its progeny. Saravanan Thangamani and others, “Vertical Transmission of Zika Virus in *Aedes aegypti* Mosquitoes,” *American Journal of Tropical Medicine and Hygiene*, vol. 95, no. 5 (November 2016): 1169–73.

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*Aedes aegypti* mosquitoes are primarily daytime biters and can bite multiple human hosts in succession. According to the CDC, mosquito control measures that reduce the number of potentially infectious mosquitoes can help reduce the spread of the Zika virus.

Mosquito control in the United States is implemented and overseen at the state and local levels, by entities such as mosquito control districts and health agencies.<sup>31</sup> CDC, using sources such as the American Mosquito Control Association, identified over 900 entities in the United States that perform mosquito control; however, not all geographic areas within the United States are covered by a mosquito control entity. Federal agencies support such control entities with funding and subject matter experts and may regulate some control methods such as pesticides.

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## Federal Agency Roles in a Zika Virus Outbreak Response

HHS is the lead federal agency for public health and medical response to disease outbreaks and it leverages national public health and medical resources to prepare for and respond to disease outbreaks. For a Zika virus response, HHS coordinates activities across federal agencies to prevent and reduce Zika virus disease transmission and detect Zika virus disease and infection in communities where it may emerge. It would provide clinical guidance for diagnosis and case management. Table 1 shows the role of federal agencies and other agencies with respect to Zika virus disease in the United States.

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<sup>31</sup>Mosquito control districts are established to provide only one or limited number of designated services, in this case mosquito control, and have sufficient administrative and fiscal autonomy to qualify as independent governments.

**Table 1: Federal Agency Roles in Addressing Zika Virus Disease: Diagnostics, Epidemiology, and Mosquito Control**

Agency	Activity
<b>Environmental Protection Agency (EPA)</b>	<ul style="list-style-type: none"> <li>the lead agency for pesticide registrations and pesticide usage information; and</li> <li>focuses on appropriate pesticide use, including technical assistance on wide-area spraying, residential treatments, review of health and safety data in the registration process, including data relating to the efficacy of pesticides used against mosquitoes carrying disease.</li> </ul>
<b>U.S. Department of Health and Human Services</b>	
Assistant Secretary for Preparedness and Response (ASPR)	<ul style="list-style-type: none"> <li>focuses on preparedness planning and response; building federal emergency medical operational capabilities; countermeasures research, advance development, and procurement; and grants to strengthen the capabilities of hospitals and health care systems in public health emergencies and medical disasters;</li> <li>provides federal support, including medical professionals through ASPR's National Disaster Medical System, to augment state and local capabilities during an emergency or disaster;</li> <li>coordinates and aligns key HHS preparedness and response activities within the Department to maximize the use of available resources; and</li> <li>supports collaboration and information sharing between public health and medical partners in the U.S. government.</li> </ul>
Biomedical Advanced Research and Development Authority (BARDA)	<ul style="list-style-type: none"> <li>collaborates with partners from the Public Health Emergency Medical Countermeasures Enterprise to address medical countermeasure needs for the Zika response domestically and globally;<sup>a</sup></li> <li>helps in the transition of medical countermeasure candidates from early development to advanced research and development and then to FDA approval;</li> <li>develops four strategic goals to address medical countermeasure needs for the Zika response through new vaccines, rapid diagnostics, screening tests for donated blood and virus inactivation in blood products; and</li> <li>assists medical countermeasure developers.</li> </ul>

Agency	Activity
Centers for Disease Control and Prevention (CDC)	<ul style="list-style-type: none"> <li>• command center for monitoring and coordinating the emergency response to Zika, bringing together CDC scientists with expertise in arboviruses like Zika, reproductive health, emerging infections during pregnancy, birth defects, developmental disabilities, and travel health;</li> <li>• supports public health investigations and surveillance;</li> <li>• develops diagnostic tests for Zika and conducts studies on the link between Zika and health outcomes;</li> <li>• monitors and reports pregnancy and birth defect cases of Zika;</li> <li>• provides clinical guidance and education to state and local health officials, pregnant women and families and healthcare providers;</li> <li>• supports state and local health departments in improving access to clinical services for maternal child health populations and children with special needs;</li> <li>• conducts surveillance to identify potential mosquito habitats and provides funding for mosquito control;</li> <li>• supports Zika virus readiness and response capacity in states and territories where mosquito populations are known to transmit the Zika virus, with a priority focus on areas with ongoing Zika transmission; and</li> <li>• technical lead for coordinating international public health and medical assistance, including sharing laboratory and clinical samples of biological material and responding to requests for coordinating international deployment of HHS public health and medical personnel and medical countermeasures.</li> </ul>
Food and Drug Administration (FDA)	<ul style="list-style-type: none"> <li>• facilitates development of diagnostic tests by providing manufacturers Emergency Use Authorization review templates that outline FDA’s current recommendations for analytical and clinical validation studies needed to support an EUA submission;</li> <li>• works with manufacturers to support their diagnostic development programs, helping ensure that their tests are properly validated before being used to inform patient care;</li> <li>• with EPA, reviews innovative strategies to help suppress the population of virus-carrying mosquitoes and mitigate the threat of vector-borne epidemics;</li> <li>• engages with commercial and government developers, including the National Institute of Allergy and Infectious Diseases (NIAID) and BARDA, to advance the development of investigational vaccines for Zika virus; and</li> <li>• monitors for fraudulent products and false product claims related to the Zika virus and acts to protect consumers.</li> </ul>
National Institutes of Health (NIH)	<ul style="list-style-type: none"> <li>• works with its partners in government, academia, and the pharmaceutical and biotechnology industries to better understand the Zika virus, the disease it causes, and ways to combat it by supporting investigators through research grants and contracts; and</li> <li>• conducts and supports research in areas such as the natural history of the disease, basic research on the Zika virus, how it causes disease (or pathogenesis), and the consequences of Zika virus infection on pregnant women and infants, diagnostic testing to rapidly determine if someone is or has been infected with Zika and to distinguish from other flaviviruses, and vector biology, as well as treatments and vaccines.</li> </ul>

Source: GAO analysis based on information supplied by agencies listed above. | GAO-17-445

<sup>a</sup>The Public Health Emergency Medical Countermeasures Enterprise coordinates federal efforts to enhance responses to chemical, biological, radiological, and nuclear threats and preparedness for emerging infectious diseases from a medical countermeasures perspective across federal departments and agencies.

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## Challenges to Gathering New Information about Zika Virus Epidemiology

Surveillance and research during the recent Zika virus outbreaks in the United States and abroad have established new information about the epidemiology of Zika virus. Since the Zika virus was a newly emerging infectious disease threat in the United States, and relatively little was known about the virus prior to 2016, CDC and the states were not fully equipped with information and resources needed for a rapid response at the outset of the recent outbreaks. This presented surveillance and research challenges in addressing the Zika virus knowledge gaps.

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## What Is Known about the Epidemiology of Zika Virus

Knowledge about Zika virus epidemiology has increased in the past year, including information about Zika virus disease incidence and distribution of cases and its associated adverse health outcomes.

### Zika Virus Cases Reported in the U.S. States and Territories

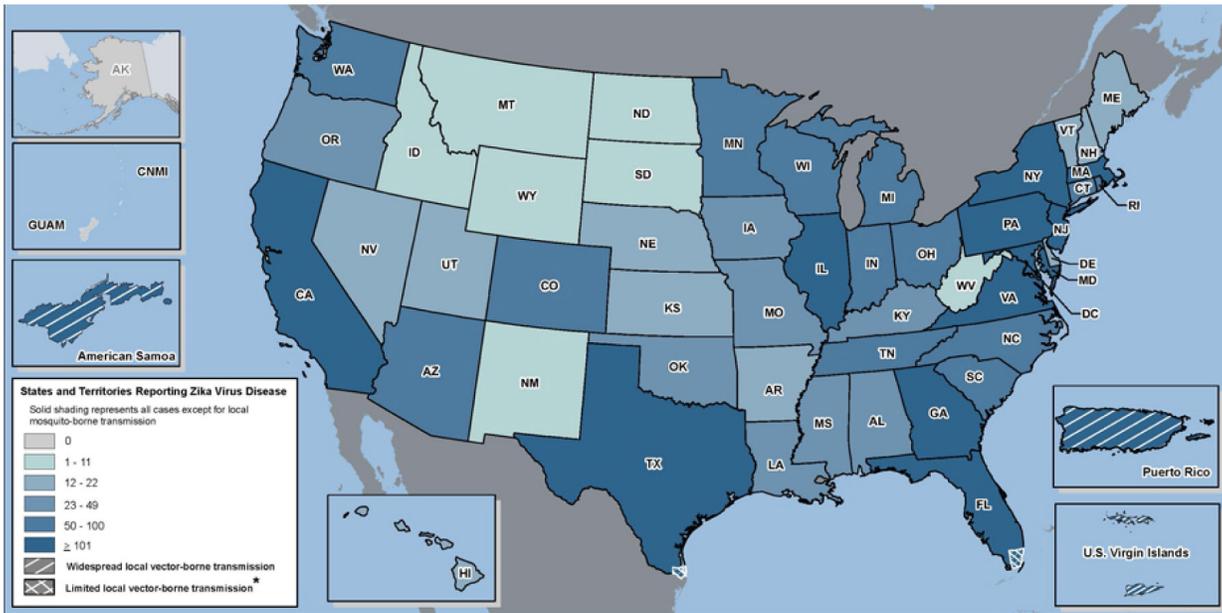
Between January 1, 2015 and April 5, 2017, reported Zika virus disease cases numbered 5,197 in the United States.<sup>32</sup> Florida and New York had the largest number of reported cases, followed by California and Texas.<sup>33</sup>

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<sup>32</sup>“Zika virus disease” case definition includes only cases that meet both laboratory and clinical (symptoms) criteria. (see appendix IV for detailed case definitions for Zika virus surveillance.) CDC provides provisional disease case counts from Zika virus reports from U.S. states and territories. It classifies these data as provisional until a few months into the next year.

<sup>33</sup>Number of reported cases: Florida (N=1,116), New York (N=1,016), California (N=438), Texas (N=320).

**Figure 5: Laboratory-Confirmed Zika Virus Disease Cases That States and Territories Reported to ArboNET, April 5, 2017**



Source: Centers for Disease Control and Prevention (CDC). | GAO-17-445

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With the exception of Alaska, every state and three territories reported at least one Zika virus disease case by April 5, 2017. (See fig. 5.) Ten states reported more than 100 cases each. Ninety-four percent of all cases in U.S. states and the District of Columbia were travel-associated.

According to a CDC analysis of reported cases between January 1, 2016 and July 31, 2016 in U.S. states and the District of Columbia, 66 percent of the 2,354 travel-related cases were associated with travel to countries and territories in the Caribbean, followed by Central America (18 percent), South America (10 percent), North America (5 percent), and Southeast Asia and the Pacific Islands (<1 percent).

According to CDC, the first identified occurrence of local (mosquito-borne) areas of transmission and the first identified outbreak of mosquito-borne Zika virus infection in the continental United States occurred in Florida in Miami-Dade and Broward counties during June–August, 2016.<sup>34</sup> This led to the designation of red zones for those areas and guidance for people living in or traveling to those areas.<sup>35</sup> Texas is the only other state that has since reported locally-acquired cases. As of April 5, 2017, 216 of the total reported cases in Florida and 6 of the total cases in Texas were locally-acquired. Seventy-four reported cases in U.S. states and the District of Columbia were acquired through other routes, including maternal-fetal transmission, person-to-person through sexual transmission, and laboratory transmission.<sup>36</sup>

At 36,504 reported cases, the U.S. territories had about seven times the number of cases as U.S. states, and most of these cases were presumed to have been acquired through local mosquito-borne transmission; only 143 cases reported in the U.S. territories were among travelers returning to territories from other affected areas.<sup>37</sup> CDC reports that with local

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<sup>34</sup>A. Likos. “Local Mosquito-Borne Transmission of Zika Virus—Miami-Dade and Broward Counties, Florida, June–August 2016,” *Morbidity and Mortality Weekly Report*, vol. 65, no. 38 (September 30, 2016):1032–38.

<sup>35</sup>See CDC guidance at <https://www.cdc.gov/zika/intheus/florida-update.html> (accessed May 14, 2017) for more details.

<sup>36</sup>Other routes include sexual transmission (N=45), mother-to-child (congenital) infection (N=27), laboratory transmission (N=1), and person-to-person through an unknown route (N=1).

<sup>37</sup>Number of reported cases: American Samoa (N=132), Puerto Rico (N=35,375), U.S. Virgin Islands (N=997).

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transmission in the territories, it is not possible to determine whether infection was caused by mosquito-borne or sexual transmission.

In addition to routinely updating cumulative Zika virus disease case counts on its Zika webpage, CDC periodically publishes Zika case demographic and other information in its MMWR. For example, 63 percent of the 2,382 Zika virus disease cases reported between January 1, 2016 and July 31, 2016 in U.S. states and the District of Columbia were female, and the same percentage was reported in an analysis of Puerto Rico cases between November 1, 2015 and October 20, 2016.<sup>38</sup> CDC noted that the higher proportion of women with symptomatic disease could be because of care-seeking behavior, differential exposure to mosquitoes or other risks, or testing of pregnant women increased.

The median age of reported Zika virus disease cases was 39 years in U.S. states and the District of Columbia. Preliminary CDC analysis indicated that reported cases in U.S. states typically were among older persons compared to cases in U.S. territories. According to CDC, the age difference observed in this preliminary analysis was most likely due to differences in the traveler population versus the general population. The majority of cases in U.S. states were travel-associated, while most cases in U.S. territories were acquired through presumed local mosquito-borne transmission, according to a CDC Zika case count update report.

### Zika Virus Infection Can Cause Microcephaly and Other Adverse Health Outcomes

In a paper published in May 2016, CDC authors applied criteria for causality in a review of available data and concluded that a causal relationship exists between prenatal Zika virus infection and microcephaly and other serious brain abnormalities.<sup>39</sup> In September 2016, a WHO Zika causality statement concluded that the most likely explanation of available evidence from outbreaks of Zika virus infection and clusters of microcephaly is that Zika virus infection during pregnancy is a cause of congenital brain abnormalities including microcephaly.<sup>40</sup> Other studies

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<sup>38</sup>William L. Walker and others, Zika Virus Disease Cases—50 States and the District of Columbia, January 1–July 31, 2016,” *Morbidity and Mortality Weekly Report*, vol. 65, no. 36 (September 16, 2016): 983–86; Matthew Lozier and others, Incidence of Zika Virus Disease by Age and Sex—Puerto Rico, November 1, 2015–October 20, 2016, *Morbidity and Mortality Weekly Report*, vol. 65, no. 44 (November 11, 2016): 1219–23.

<sup>39</sup>Sonja A. Rasmussen and others, “Zika Virus and Birth Defects—Reviewing the Evidence for Causality,” *New England Journal of Medicine*, 374 (May 19, 2016): 1981–87.

<sup>40</sup>World Health Organization (WHO) *Zika Causality Statement*. accessed May 3, 2017, <http://www.who.int/emergencies/zika-virus/causality/en/>.

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have sought to estimate the risk of adverse health outcomes to pregnant women infected with Zika virus. For example, a CDC study estimated that the risk of microcephaly from Zika virus infection in the first trimester in Brazil was between about 100 to 1300 cases per 10,000 births, compared to an estimated baseline risk of 2 to 12 cases per 10,000 births.<sup>41</sup> According to CDC and WHO, microcephaly is just one of a range of birth defects that could be related to Zika virus infection.<sup>42</sup>

WHO reported that by January 18, 2017, 29 countries or territories had reported microcephaly and other central nervous system malformations that were potentially associated with Zika virus infection.<sup>43</sup> In the United States, the U.S. Zika Pregnancy Registry publicly reports about twice a month the total number of pregnant women with laboratory evidence of possible Zika virus infection who were reported to the registry. The March 28, 2017 update included 1,716 pregnant women in U.S. states and the District of Columbia with laboratory evidence of possible Zika virus infection. Of 1,311 completed pregnancies as of March 28, 2017 with laboratory evidence of Zika virus infection in U.S. states and the District of Columbia, there were 56 live born infants reported to have birth defects and 7 pregnancy losses with birth defects. As of March 28, 2017, 3,461 pregnant women with laboratory evidence of Zika virus infection in U.S. territories were reported to the U.S. Zika Pregnancy Registry or to the Zika Active Pregnancy Surveillance System for Puerto Rico. CDC noted in this update that Puerto Rico was not using the same case inclusion criteria, and CDC was not reporting numbers for adverse pregnancy outcomes in the territories at that time. A CDC report in April 2017 provided data on the impact of Zika virus on pregnant women and babies for 2016, including that 44 states reported cases of pregnant women with

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<sup>41</sup>Michael A. Johansson and others, "Zika and the Risk of Microcephaly," *New England Journal of Medicine*, 375 (2016): 1–4. The estimates of risk due to infection during the first trimester of pregnancy ranged from 0.88 percent with a 95 percent credible interval of 0.80 to 0.97 percent when assuming an 80 percent overall Zika virus infection rate and 100 percent over-reporting of microcephaly cases, to 13.2 percent with a 95 percent credible interval of 12.0 to 14.4 percent when assuming a 10 percent Zika virus infection rate and no over-reporting. A credible interval means that the measure of interest lies with 95 percent probability in the interval.

<sup>42</sup>Centers for Disease Control and Prevention (CDC), "Key Messages—Zika Virus Disease," accessed April 21, 2017, <https://www.cdc.gov/zika/pdfs/zika-key-messages.pdf>; World Health Organization (WHO) Zika Causality Statement, accessed May 3, 2017, <http://www.who.int/emergencies/zika-virus/causality/en/>.

<sup>43</sup>World Health Organization (WHO), *Situation Report: Zika Virus Microcephaly Guillian-Barré Syndrome 20 January 2017 Data as of 18 January 2017*, accessed April 12, 2017, <http://www.who.int/emergencies/zika-virus/situation-report/20-january-2017/en>.

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evidence of Zika virus infection and most were travel-associated, and about 1 in 10 pregnant women with confirmed Zika virus had a fetus or baby with birth defects.<sup>44</sup>

As of January 18, 2017, 21 countries or territories had reported an increase in the incidence of Guillain-Barré syndrome or laboratory confirmation of a Zika virus infection among Guillain-Barré syndrome cases.<sup>45</sup> CDC also reported that its own research suggested a strong association between Guillain-Barré syndrome and Zika virus, but also noted that only a small proportion of persons with a recent Zika virus infection got Guillain-Barré syndrome.<sup>46</sup> CDC reported that of 56 suspected cases of Guillain-Barré syndrome with onset of neurologic signs identified between January 1 and July 31, 2016 in Puerto Rico, 20 patients had no evidence of Zika virus infection, compared to 34 patients who had evidence of Zika virus or flavivirus infection.<sup>47</sup>

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## What Is Not Known about the Epidemiology of Zika Virus

While much has been learned about the epidemiology of Zika virus, many unknowns remain, including

- the total number of infections;
- the biological mechanisms, risks, reasons for geographic differences, and full spectrum of outcomes associated with maternal-fetal transmission;
- the presence and duration of the virus in different bodily fluids;

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<sup>44</sup>Centers for Disease Control and Prevention, “Vital Signs April 2017”, accessed May 17, 2017, <https://www.cdc.gov/vitalsigns/pdf/2017-04-vitalsigns.pdf>.

<sup>45</sup>World Health Organization, *Situation Report: Zika Virus Microcephaly Guillain-Barré Syndrome 20 January 2017 Data as of 18 January 2017*, accessed April 12, 2017, <http://www.who.int/emergencies/zika-virus/situation-report/20-january-2017/en/>.

<sup>46</sup>Centers for Disease Control and Prevention, “Key Messages—Zika Virus Disease,” accessed April 21, 2017, <https://www.cdc.gov/zika/pdfs/zika-key-messages.pdf>.

<sup>47</sup>Two of the 56 patients were pending test results. Of the 34 patients with evidence of Zika virus or flavivirus infection, 26 had confirmed or presumptive Zika virus infection, and 8 had presumptive flavivirus infection. Whether an infection is classified as confirmed or presumptive depends on the laboratory evidence. Emilio Dirlikov and others. “Guillain-Barré Syndrome During Ongoing Zika Virus Transmission — Puerto Rico, January 1–July 31, 2016,” *Morbidity and Mortality Weekly Report*, vol. 65, no. 34 (September 2, 2016): 910-914.

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The Total Number of Infections Is Not Known

- the role of prior Zika virus infections or exposure to other related flaviviruses; and
- the full spectrum of outcomes of Zika virus infection.

Zika virus case counts obtained from the national disease surveillance system underestimate the total number of Zika virus infections over a specified time period, for reasons including that an infected person

- may not seek medical care because they have only mild or no symptoms, or other reasons,
- may not be diagnosed because of limitations in Zika virus diagnostic testing, and
- surveillance reporting can be incomplete for a variety of reasons.

First, the ArboNET surveillance system captures only reported Zika virus disease and infection cases. As such, the case counts does not capture the suspected high proportion of infected people who are asymptomatic and may not seek care and get a diagnosis of Zika virus infection. One study estimated that about 18 percent of Zika-infected persons will have clinical symptoms of the infection.<sup>48</sup> CDC and WHO have reported that about 80 percent of people who have Zika virus infection won't have any symptoms.

Findings from a May 2017 study in Puerto Rico also suggested there is a high rate of asymptomatic people infected with Zika virus who are not diagnosed. The study applied results from a blood donor population that was screened for Zika virus to estimate the number of Zika infections in the population of Puerto Rico and estimated that there were over 450,000 Zika virus infections in Puerto Rico over approximately four months in mid-2016.<sup>49</sup> In comparison, 35,375 disease cases were reported in Puerto Rico from January 1, 2015 through April 5, 2017, according to a CDC Zika virus disease case count update report. The Puerto Rico blood donor

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<sup>48</sup>Mark R. Duffy and others, "Zika Virus Outbreak on Yap Island, Federated States of Micronesia," *New England Journal of Medicine*, vol. 360 (2009): 2536–43. This study estimated that about 18 percent of infected persons have a clinical illness with a 95 percent confidence interval range of 10 to 27 percent.

<sup>49</sup>Michelle S. Chevalier and others, "Use of Blood Donor Screening Data to Estimate Zika Virus Incidence, Puerto Rico, April–August 2016," *Emerging Infectious Diseases*, vol. 23, no. 5 (2017). The estimated number of incident Zika virus infections in Puerto Rico between April 3–August 12, 2016 was 469,321 with a 95 percent confidence interval of 401,477 to 559,126, based on screening of 21,468 blood donors.

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study authors concluded that results from blood donation screening during arboviral outbreaks can supplement routine clinical and surveillance data for improved targeting of prevention efforts.

Second, limitations in Zika virus diagnostic testing can also affect the accuracy of the number of Zika virus cases reported in disease surveillance due to inaccurate laboratory test results. Some Zika diagnostic tests can determine that a recent flavivirus infection has occurred, which may or may not be caused by Zika virus. This is because the antibodies produced in response to flavivirus infection (Zika, dengue, West Nile, yellow fever) are cross-reactive and may produce a positive result in a test for any of these viruses. This is of particular concern in areas where there has been co-circulation of flaviruses, such as dengue virus in Puerto Rico. The ability of the test to detect the virus also depends on the type of test used, when it is used, and the type of specimen collected. CDC recommends additional criteria and testing strategies for pregnant women for definitive diagnoses. The different types of Zika virus diagnostic tests, their challenges, and testing strategies for mitigating these challenges are discussed later in this report.

Third, according to CDC documentation, notifiable disease reporting is likely incomplete, and the completeness varies depending upon the disease and the reporting state or territory. Factors that can influence completeness of reporting include the availability of diagnostic facilities; control measures in effect, public awareness of a specific disease, the state and local health officials responsible for disease control and public health surveillance, changes in methods for public health surveillance, or introduction of new diagnostics tests or other diseases. However, CDC documentation states that it has undertaken efforts to educate providers on Zika virus infection and provided guidance for screening and testing.

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The Biological Mechanisms, Risks, and Reasons for Geographic Differences in Outcomes Associated with Maternal-Fetal Transmission Are Unclear

The mechanisms of causality between Zika virus infection and microcephaly are not well-understood.<sup>50</sup> According to a recent CDC Zika virus key messages document published on its website, questions also remain regarding the timing, risk, and full spectrum of adverse pregnancy outcomes as a result of Zika virus infection.<sup>51</sup> Adding to the complexity, microcephaly is also caused by other environmental and genetic factors, including infections such as rubella during pregnancy, maternal exposure to toxic chemicals such as heavy metals or smoking, injuries to the developing brain, genetic abnormalities such as Down syndrome, and severe malnutrition during fetal life.

The reasons for differences in the reported incidence of microcephaly and other birth defects between geographic areas with Zika virus outbreaks are also not well-understood. For example, in Brazil in 2015, municipalities with high reports (defined as greater than 20 cases per 10,000 municipalities) of confirmed cases (per 10,000 live births) of newborns and children with changes in growth related to Zika virus infection and other infectious etiologies were concentrated in the Northeast region, although there was wider dispersion in other regions in 2016.<sup>52</sup>

There is also wide variation in reported microcephaly cases relative to Zika virus cases in different countries. Using case data from PAHO, we found a wide variation among countries in the ratio of number of reported cases of birth defects associated with Zika virus infection to the total number of confirmed locally-acquired and travel-associated cases of Zika virus as of March 9, 2017 (table 2). For example, there were about 55 Zika virus cases for every birth defect case in Brazil, whereas in Colombia there are about 77 Zika virus cases for every birth defect case.

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<sup>50</sup>Jin-Na Wang and Feng Ling, "Zika Virus Infection and Microcephaly: Evidence for a Causal Link," *International Journal of Environmental Research and Public Health*, vol. 13, no. 1031 (October 2016).

<sup>51</sup>Centers for Disease Control and Prevention, "Key Messages—Zika Virus Disease," accessed April 21, 2017, <https://www.cdc.gov/ZIKA/PDFS/ZIKA-KEY-MESSAGES.PDF>.

<sup>52</sup>Pan American Health Organization / World Health Organization. *Zika - Epidemiological Report Brazil*. (Washington, D.C.: 2017).

**Table 2: Zika Virus Cases and Birth Defects Associated with the Zika Virus Reported in the Americas, 2015–2017, as of March 9, 2017**

Country	Zika virus cases		Confirmed birth defects <sup>a</sup>	Ratio of birth defects to Zika virus cases <sup>b</sup>
	Confirmed locally acquired	Travel-associated		
Brazil	130,840	0	2,386	1:55
Colombia	9,802	0	128	1:77
Dominican Republic	345	0	54	1:6
United States	222	4,813	52	1:97
Guatemala	890	0	37	1:24
Martinique	21	0	22	1:1
French Guiana	483	10	17	1:29
Guadeloupe	382	0	14	1:27
Bolivia	192	4	14	1:14
Puerto Rico	39,339	137	12	1:3290
All other PAHO member countries	22,984	758	31	1:766

Source: GAO analysis of data from the Pan American Health Organization (PAHO). | GAO-17-445

Note: PAHO refers to travel-associated cases as “imported” cases and to locally acquired cases using the epidemiologic term “autochthonous” cases.

<sup>a</sup>Congenital syndrome associated with the Zika virus infection.

<sup>b</sup>Ratio of confirmed congenital syndrome (birth defects) cases associated with Zika virus to the total confirmed and imported Zika virus cases. Ratios in epidemiology can be used when there is not necessarily a relationship between the numerator and denominator, whereas in a proportion, the numerator is always part of the denominator. Proportions are not appropriate for this table because the mothers of the infants with confirmed congenital syndrome may or may not be included in the confirmed Zika virus case counts, as these do not have the same inclusion criteria.

According to literature we reviewed, some possible reasons for these variations include differences in mosquito prevention and family planning practices, environmental factors, population differences, and surveillance system differences (including case definitions).

**The Presence and Duration of the Virus in Different Bodily Fluids Is Not Well-Understood**

It is not well-understood how long the Zika virus can remain in different bodily fluids or how long it can be transmitted to other people. CDC reports that Zika can remain in semen longer than in other bodily fluids, including vaginal fluids, urine, and blood. One case report study found that Zika virus was detectable in semen at 69 days after symptom

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onset,<sup>53</sup> and another study reported a maximum duration of Zika virus genetic material in semen of 125 days after symptom onset.<sup>54</sup>

The Role of Prior Zika Virus Infections or Exposure to Other Related Flaviviruses is Not Clear

The role of previous Zika virus infections or related flaviviruses such as dengue virus is unclear. According to WHO, it is not known whether Zika virus presence in a population over time results in widespread or low-level immune protection or possibly no protection.<sup>55</sup> The cross-reactivity between Zika virus and related flaviviruses has not been established, although some studies are beginning to address this gap. For example, a study published in December 2016 suggests that preexisting dengue virus immunity may enhance Zika virus infection and lead to greater disease severity.<sup>56</sup> Another study published in April 2017 found evidence that antibodies against related flaviviruses such as dengue and West Nile can cross-react with Zika virus and could increase disease severity.<sup>57</sup>

The Full Spectrum of Outcomes of Zika Virus Infection is Not Known

The full spectrum of outcomes from maternal-fetal transmission is not known. A paper published by CDC authors identified research gaps that need rapid and systematic assessment, including a complete understanding of the frequency and full spectrum of clinical outcomes resulting from fetal Zika virus infection and of the environmental factors that influence emergence.<sup>58</sup> Another review paper noted that with causality between Zika virus infection and adverse pregnancy outcomes having been established, the critical research issues can turn to understanding the full spectrum of outcomes and quantifying the relative and absolute risks among infants who are born to women who were infected at different times during pregnancy, and identifying factors that modify the risk of an adverse pregnancy or birth outcome, such as

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<sup>53</sup>Marta Arsuaga and others, "Probable Sexual Transmission of Zika Virus from a Vasectomized Man," *Lancet Infectious Diseases*, vol. 16 (2016):1107.

<sup>54</sup>Gabriela Paz-Bailey and others, "Persistence of Zika virus in Bodily Fluids – Preliminary Report," *The New England Journal of Medicine*, (2017): 1-9.

<sup>55</sup>World Health Organization, "Emergencies: One Year into the Zika Outbreak: How an Obscure Disease Became a Global Health Emergency," accessed April 26, 2017, <http://www.who.int/emergencies/zika-virus/articles/one-year-outbreak/en/>.

<sup>56</sup>Lauren M. Paul and others, "Dengue Virus Antibodies Enhance Zika Virus Infection," *Clinical & Translational Immunology*, vol. 5, no. 12 (2016).

<sup>57</sup>Susana V. Bardina and others, "Enhancement of Zika Virus Pathogenesis by Preexisting Antiflavivirus Immunity," *Science*, vol. 356, no. 6334 (2017): 175-80.

<sup>58</sup>Lyle Petersen and others, "Zika Virus", *The New England Journal of Medicine*, vol. 374 (2016): 1552-63.

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coinfection with another virus, preexisting immune response to another flavivirus, genetic background of the mother or fetus, and severity of infection.<sup>59</sup>

The associations between Zika virus infection and Guillain-Barré syndrome are also unclear. It has been reported that the most likely explanation of an association is that Zika virus infection can trigger Guillain-Barré syndrome.<sup>60</sup> According to CDC documentation, CDC collaborates with state and local health departments to investigate possibly unusually large numbers or clusters of Guillain-Barré syndrome cases, and Puerto Rico has a surveillance system for Guillain-Barré syndrome.

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## Three Key Challenges to Zika Virus Surveillance

CDC, CSTE, and state and local public health agencies faced several challenges in implementing surveillance for Zika virus and its associated health outcomes. These challenges involved establishing early case definitions, timely communication of critical information, and interoperability between surveillance databases.

### Establishing Case Definitions Challenged the Collection of Consistent and Timely Information

We identified several challenges related to establishing case definitions for Zika virus infection and disease surveillance. According to CDC officials, typically, the process for adding a new disease to the national notifiable disease list is that the CSTE votes during its annual meetings whether to add the disease. If approved, the disease is usually made notifiable the following January. According to CDC officials, this allows time to plan and prepare for implementation, including the information technology aspects of reporting the disease. However, because of the emergent nature and emergency response needed for Zika virus, CSTE released an interim case definition in February 2016 so that Zika virus disease would become immediately notifiable.

These interim definitions included only laboratory diagnosed cases in persons who also reported certain clinical criteria. CDC officials and representatives from public health organizations told us that as more was learned about Zika virus, including the need to capture asymptomatic

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<sup>59</sup>Sonja A. Rasmussen and others, "Zika Virus and Birth Defects," 1981–87.

<sup>60</sup>World Health Organization. *Guillain-Barré Syndrome Fact sheet, updated October 2016*, accessed April 26, 2017, <http://www.who.int/mediacentre/factsheets/guillain-barre-syndrome/en/>.

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cases, the interim case definitions were revised. CSTE approved the revised case definitions position statement in June 2016, which included laboratory confirmed, asymptomatic cases (Zika virus infection) and some revisions related to laboratory diagnostic testing.

These changes presented some challenges, according to some public health officials and organizational representatives we interviewed. CDC and CSTE officials told us that because there were two case definitions approved during the year, changes had to be made to the reporting system twice, and all cases classified according to the first definition had to be reclassified based on the new definition, which takes time.<sup>61</sup> CDC officials also told us that another challenge is that jurisdictions use different systems and have different capacities related to surveillance and informatics expertise, which required a lot of resources from CDC and others to assist these jurisdictions.

CDC officials noted that it takes time for states to reclassify their older cases. CDC designates Zika virus cumulative case counts as provisional on its Zika virus case counts website.<sup>62</sup> CDC officials told us that cases can be added or removed as new information becomes available, and that due to lags in investigation, testing, and reporting, newly reported cases often occurred weeks or even months earlier than the reported date.

Experts at our meeting and public health officials at selected sites emphasized the importance of educating health care providers, including on testing and reporting guidelines. For instance, an official from one of the selected sites stated that “a well-informed clinician is the best reporting tool.” HHS officials told us that CDC engaged frequently with key professional organizations such as the American College of Obstetricians and Gynecologists to provide updated information; however gaps remain among providers who do not access up-to-date information provided on the CDC or professional organization websites.

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<sup>61</sup>According to CDC, CSTE recommended that all jurisdictions reclassify all previously reported 2016 Zika virus disease and congenital infection cases according to the new case definitions from June 2016.

<sup>62</sup>See CDC Zika virus case counts website at: <https://www.cdc.gov/zika/geo/united-states.html>, accessed April 10, 2017.

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Information Dissemination and  
Communication Were Not  
Always Timely

Public health officials from a selected site and representatives of public health organizations had some positive things to say regarding the assistance that federal agencies, or more specifically CDC, provided in responding to the Zika virus outbreaks. For example, officials from one selected site told us that a lot of guidance was coming out rapidly from CDC, and in general the guidance was very helpful and made providers more comfortable in patient care. Representatives from a public health organization told us that they viewed the U.S. government's response to Zika as much stronger and more organized, forward leaning, inclusive, and transparent than it was for response to some earlier diseases, especially recognizing the many unknowns about Zika virus. Representatives from another public health organization told us that CDC demonstrated flexibility in its willingness to make modifications to Zika virus reporting based on feedback from states.

Nonetheless, we identified some challenges regarding the communication of guidance from CDC early in Zika virus surveillance implementation. For example, officials from one selected site told us that they were sometimes not able to get guidance consistently because entities within CDC did not talk with each other, and that CDC could not come to a quick conclusion about who to include in the Zika virus case definition. Representatives from a public health organization told us that they were sometimes not informed of changes in Zika-related information before learning about a change from a CDC media release, but that this had improved compared to 5 or 10 years ago.

However, according to HHS officials, CDC frequently uses media outlets to disseminate important information to reach a broad audience. CDC also provided updated guidance for diagnosis and clinical practice, including several clinical guidelines and health alert network messages.<sup>63</sup>

Public health officials in selected sites also told us that earlier in the Zika virus response, challenges resulted from officials from different CDC units needing to establish communication channels that had not existed before the Zika virus outbreak. Officials from one selected site told us about difficulty in communication and the importance of agency-wide communication and partnerships, and relationships that can make things

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<sup>63</sup>Health alert messages are disseminated through CDC's Health Alert Network, which is CDC's primary method of sharing cleared information about urgent public health incidents with public information officers; federal, state, territorial, and local public health practitioners; clinicians; and public health laboratories.

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happen faster. Officials from this site also told us that communication across different units improved over time. CDC officials similarly told us that many people were involved across CDC, including from birth defects and reproductive health, and arboviral diseases units, and that rarely were so many different people involved in a response effort.

### The Interoperability of Surveillance Databases Was Lacking

There are separate systems for Zika virus cases and associated health outcomes surveillance that collect different information but also some of the same information, and these systems are not electronically linked. Officials from selected sites and representatives from a public health organization told us that having several different surveillance systems that were not interoperable was a challenge. Representatives we interviewed from one public health organization noted that states took issue with having to report data to the pregnancy registry that they already reported to other registries. Officials from one site we visited told us that there were questions as to whether different tracking systems are necessary, and that it is a challenge that they have different requirements. In another selected site, officials told us it is challenging when changes need to be made in the system because there's no cross-communication in the data.

However, HHS officials told us that surveillance systems for infectious diseases and surveillance of pregnancies and pregnancy outcomes and birth defects serve very different purposes and are also tailored to each jurisdiction's needs. HHS officials also noted that the different and complementary surveillance systems serve equally important, yet very different critical needs during public health emergencies.

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### Two Key Challenges in Conducting Epidemiological Zika Virus Research

We identified two key challenges for Zika virus epidemiological research: study designs needed for establishing association and causality challenged linking Zika virus and associated health outcomes, and insufficient data and lack of developed models challenged prediction of the spread of the virus.

### Establishing Association and Causality Between Zika Virus Infection and Adverse Health Outcomes Faced Study Design Challenges

We identified challenges in linking the Zika virus with associated health outcomes. CDC was able to report pregnancy outcomes of women who were infected with or are suspected to have been infected with Zika virus and reported to the pregnancy registries. According to HHS officials, combining this prospective monitoring of pregnant women with retrospective birth defect surveillance allows for a comprehensive picture of pregnancy outcomes and has already provided critical information to inform the public health response to Zika virus. However, because the

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Zika pregnancy registry only includes pregnant women who have laboratory evidence of Zika virus infection, there is no control group of pregnant women without Zika virus in the pregnancy registry.

According to HHS officials, studies that prospectively follow an identified group of people over time to monitor for both disease and outcomes are needed. WHO also noted that cohort studies of the populations currently at risk are needed to determine both absolute and relative risks of a Zika-affected pregnancy, the role of co-factors and effect modifiers, and to determine whether there is a specific congenital Zika virus syndrome.

NIH recently launched such a study—Zika in Infants and Pregnancy (ZIP)—that aims to enroll as many as 10,000 pregnant women at up to 15 sites in Puerto Rico and abroad in order to study the outcomes of pregnant women who test positive for the Zika virus as well as those who test negative and their infants.<sup>64</sup> The researchers plan to compare birth outcomes between mothers who were infected with Zika virus and those who were not, documenting the frequency of microcephaly and other adverse health outcomes. The study will also evaluate how the timing of infection affects pregnancy outcomes and the role that environmental influences, social determinants and other infections, such as dengue fever, may have on the health of the study participants and their newborns.

However, there are challenges in conducting prospective cohort studies such as the ZIP study. These studies can take years before complete results are available and published in peer-reviewed journals. For example, the ZIP study start date was June 2016, and the estimated study completion date is June 2018.<sup>65</sup> Prospective cohort studies that follow large numbers of individuals in multiple sites for many months or years are also generally expensive and time-consuming.

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<sup>64</sup>The Zika in Infants and Pregnancy (ZIP) trial will enroll participants in their first trimester of pregnancy and follow them throughout their pregnancies to determine if they become infected with the Zika virus and, if so, the outcomes in mother and infant. The infants will be followed for at least one year after birth.

<sup>65</sup>See <https://clinicaltrials.gov/ct2/show/study/NCT02856984>, accessed May 13, 2017. According to HHS officials, to mitigate delays in using study results, NIH has planned for interim analyses to obtain and disseminate information as the ZIP study proceeds.

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Predicting the Spread of the Zika Virus Was Challenged by Insufficient Data and Lack of Developed Models

Modeling and simulation studies that accurately estimate the number of disease cases in a population or predict cases of a disease can improve planning and allocating scarce public health resources.<sup>66</sup> According to an April 2017 Zika virus key messages report, CDC has not been able to predict how much the Zika virus will spread in the continental United States. CDC officials told us that there was no epidemiologic model that looked at both types of transmission together—sexual and mosquito-borne. In addition, there are several major assumptions that need to be made for descriptive and predictive modeling of the Zika virus, including the number of infections and the overall number of pregnant women. CDC officials told us that as of October 2016, many uncertainties remained for Zika virus modeling. The models are constantly being refined and updated.

A December 2016 report from an intergovernmental committee on infectious disease modeling noted the importance and potential of outbreak prediction and modeling to improve outbreak preparedness. The report outlined three major challenges concerning

- data- and information-sharing, including the need for timely and accurate data and information, especially at the beginning of a novel disease outbreak, when knowledge about the pathogen and data on the epidemiological situation is limited;
- outbreak model development and decision support, including a systematic effort to synthesize results across modeling efforts and support on how to use this information in outbreak response decision-making; and
- science of disease emergence, which involves the need for better understanding of the processes that drive disease emergence and transmission well enough to predict where and when diseases are likely to emerge.

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<sup>66</sup>Descriptive modeling tries to estimate what probably occurred or is occurring now, while predictive modeling predicts cases in the future.

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**Characteristics of Different Diagnostic Tests Varied, Manufacturers and Users Faced Several Challenges, and FDA and CDC Did Not Consistently Communicate Sufficient Information**

Authorized diagnostic tests used for the recent Zika virus outbreak varied in their performance and operational characteristics.<sup>67</sup> Diagnostic test manufacturers faced challenges in several areas, including research and development, testing, and regulatory approval of these tests. Diagnostic test users also encountered challenges, including determining the most accurate test to use, comparing clinical performance characteristics across tests, and obtaining equipment required to conduct authorized tests. Both manufacturers and users we spoke with raised issues about the EUA process. Moreover, CDC and FDA did not consistently communicate sufficient information about Zika virus diagnostic tests that could have enabled users to more easily identify the test that could detect the smallest amount of virus in a sample.

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**Molecular and Serological Zika Virus Diagnostic Tests Varied in Performance and Operational Characteristics**

There are currently no available diagnostic tests cleared by FDA for the detection of Zika virus. By April 12, 2017, FDA had authorized 16 diagnostic tests for the Zika virus (13 molecular tests and 3 serologic tests) under EUAs following the public health emergency declaration. According to FDA officials, they revoked one test, and as a result, 15 diagnostic tests are currently authorized. These authorized diagnostic tests for the Zika virus vary in their performance and operational characteristics. Molecular and serologic tests have different strengths and limitations, but some of the limitations can be mitigated by using an algorithm that CDC published.<sup>68</sup>

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<sup>67</sup>Performance characteristics of a test used to describe the quality of a diagnostic test result including the analysis of accuracy, precision, sensitivity, and specificity, among others. Operational characteristics include among others, the time to perform a test, its technical simplicity or ease of use, users' acceptability, and the stability of the test under user conditions.

<sup>68</sup>The CDC-issued algorithm is a step-by-step protocol intended to assist laboratories in combining results from multiple samples and methods to make appropriate decisions about next testing steps.

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## Molecular Tests Varied in Their Ability to Detect Zika Virus

### Key Terms Related to Diagnostic Tests

- **Comparator assay:** An assay used as the reference method for assessing the performance characteristics of another test method.
- **FDA Reference Materials:** Genetic material from two current Zika virus strains in human plasma and three controls for blind testing to establish performance testing provided by FDA.
- **Limit of detection:** The measure of how much virus needs to be in a sample for the assay to detect the presence of the virus.
- **Operational characteristics:** The time to perform the test, its technical simplicity or ease of use, user acceptability, and the stability of the test under user conditions.
- **Performance characteristics:** A description of quality of a diagnostic test result including the analysis of accuracy, precision, sensitivity, and specificity, among others.
- **Sensitivity:** The proportion of patients with the infection (determined by the result of the reference or “gold standard” test) who have a positive result using the test under evaluation.
- **Specificity:** The proportion of patients without the infection (determined by the result of the reference or gold standard test) who have a negative result using the test under evaluation.
- **Test:** Any method for obtaining additional information regarding a patient’s health status.

Source: Food and Drug Administration, Department of Health and Human Services, and Shabir Banoo and others, “Evaluation of Diagnostic Tests for Infectious Diseases: General Principles, *Nature Reviews: Microbiology* (2010): S17-S29. I GAO-17-445

Authorized molecular diagnostic tests for the Zika virus varied in their performance characteristics, and some may not have been sensitive enough to detect Zika virus infection in samples that were collected when the level of virus was low, namely, towards the end of, or after, the recommended collection time post onset of symptoms. The product labels for these authorized Zika virus diagnostic tests list a variety of different performance characteristics, including: analytical sensitivity, cross-reactivity, interference, and clinical evaluation.<sup>69</sup> The differences between these performance characteristics are important for understanding the accuracy of the diagnostic test. For instance, the limit of detection listed on manufacturers’ product labels using their own samples and protocols range from 5.9 copies/mL (less virus is needed for detection) to 42,000 copies/mL (more virus is needed for detection) (appendix V has more details on these characteristics). If a person had 1,000 copies/mL of Zika virus RNA in his or her blood stream, the test that had the lower limit of detection (5.9 copies/mL) would indicate a positive result, while the test with the higher limit of detection (42,000 copies/mL) would incorrectly indicate a negative result (called a false negative). The limit of detection is an important measure for the Zika virus, which can be present in relatively low levels in the body. It is important to note that a negative result by molecular testing should be followed by serological testing, according to CDC’s guidance, in order to reduce the risk of false negative results.

FDA created Zika virus reference material for molecular tests to compare test results to ensure accuracy. We found that the limit of detection varied between different tests when performed using samples and protocols FDA provided from 100 detectable units/mL to 30,000 detectable units/mL (See appendix V). The diagnostic accuracy of a new test refers to the extent of agreement between the outcome of the new test seeking authorization and the reference standard.<sup>70</sup>

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<sup>69</sup>Analytic sensitivity (limit of detection) is defined as the lowest concentration of virus that can be consistently detected 95 percent of the time in a defined type of specimen. Cross-reactivity is when antibodies to similar viruses react, such as dengue, leading to tests that are not specific for the Zika virus. For example, a person previously infected with another flavivirus such as dengue could be falsely identified as also having been exposed to the Zika virus (and vice versa). Clinical evaluation is a measure of a specific assay evaluated against a comparator assay with clinical samples.

<sup>70</sup>A reference standard is the best available method for establishing the presence or absence of the target condition. The reference standard can be a single test or method or a combination of methods and techniques, including clinical follow-up, according to FDA’s guidance document.

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According to FDA officials, when a new test is evaluated by comparison to a nonreference standard, as with the Zika virus, one cannot directly calculate unbiased estimates of sensitivity and specificity and therefore these terms are not appropriate. Instead, estimates called positive percent agreement and negative percent agreement are calculated and reflect the agreement of the new test with the nonreference standard.<sup>71</sup> According to FDA officials, a major disadvantage with agreement measures is that agreement is not a measure of “correctness.” The two tests could agree; however, agreement does not indicate how good or poor test sensitivities and specificities are (for example, both tests could agree because they are both false negatives). Also, that two tests are not in agreement does not necessarily mean that the new test is inaccurate and the comparator test is correct.

#### Molecular Tests Varied in Ease of Use and Timeliness

The authorized molecular diagnostic tests for the Zika virus after the public health emergency declaration also varied in their operational characteristics. These molecular diagnostic tests vary in their ease of use—some require manual steps, while others have some automation. Automation potentially allows for faster and more consistent processing and fewer staff resources. The time to perform individual authorized molecular diagnostic tests for the Zika virus is around 4 hours. One manufacturer using automation can process multiple samples in 8 hours. However, all the authorized molecular tests for the Zika virus have to be performed at Clinical Laboratory Improvement Amendments (CLIA) high complexity laboratories.<sup>72</sup>

#### Strengths and Limitations of Molecular Diagnostic Tests

Molecular diagnostic tests can be designed to be more specific to a single virus and, as a result, have fewer issues with identifying the specific virus

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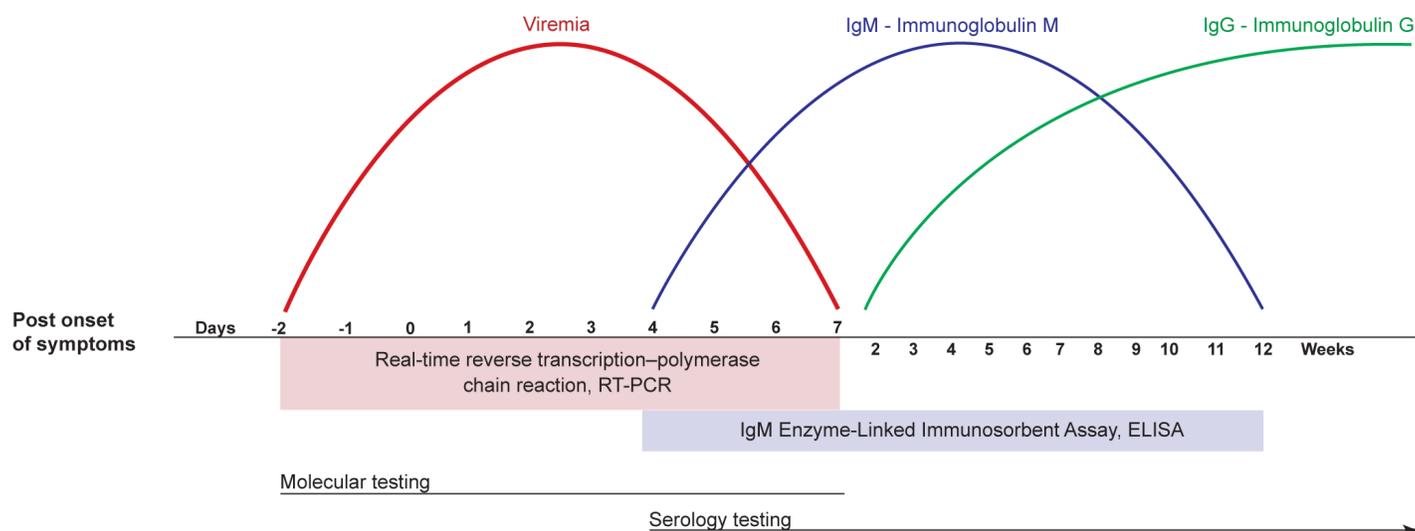
<sup>71</sup>According to FDA’s guidance document, positive percent agreement is the proportion of non-reference standard positive subjects in whom the new test is positive and negative percent agreement is the proportion of non-reference standard negative subjects in whom the new test is negative.

<sup>72</sup>According to its website, the Centers for Medicare & Medicaid Services regulates all laboratory testing (except for research) performed on humans in the United States through the Clinical Laboratory Improvement Amendments (CLIA) and covers approximately 254,000 laboratory entities. The Division of Laboratory Services within the Survey and Certification Group, under the Center for Clinical Standards and Quality, is responsible for implementing the CLIA program. See <https://www.cms.gov/Regulations-and-Guidance/Legislation/CLIA/index.html?redirect=clia/>, accessed April 3, 2017. Laboratories obtain a CLIA certificate that corresponds to the complexity of the testing they conduct. For tests developed by a laboratory or that have been modified from the approved manufacturer’s instructions, the complexity category defaults to high complexity per the CLIA regulations.

compared to serological testing. These tests detect specific virus sequences of genetic material. According to a manufacturer we interviewed, some Zika virus diagnostic molecular tests detect multiple targets, meaning a test detects multiple segments of genetic material from the Zika virus, rendering the test more accurate since it can still detect the virus even if there is an alteration in one of the segments that the test is detecting. Molecular tests can also be used to simultaneously detect other viruses such as dengue, chikungunya, and Zika (see table 3 for strengths and limitations for both types of tests).

.Molecular diagnostic tests give a definitive diagnosis independent of other tests when the result is positive. To reliably detect the Zika virus, molecular diagnostic tests should be performed within two weeks after symptom onset (see fig. 6).

**Figure 6: Zika Virus and Antibodies after Infection**



Source: GAO analysis of Centers for Disease Control and Prevention (CDC) and World Health Organization (WHO) data. | GAO-17-445

Note: This figure is not to scale and for illustrative purposes only. According to a CDC report, viremia (presence of virus in the blood) is expected to occur from several days before onset until a week after illness onset (for the purposes of this figure, we assume that several days is at least two days and a week as seven days).

A negative molecular test does not rule out Zika virus infection because the amount of virus in the sample could be too low to be detected at the time of molecular testing. Some scientists have expressed concern over

the limit of detection of some authorized molecular diagnostic tests, which could have resulted in missed Zika virus infections by molecular testing and increase the need for serological follow-up testing; however, additional testing according to CDC guidance is intended to correct these false negative findings. An expert from our meeting stated that the sensitivity limitation of molecular testing cannot be overcome by additional testing if the molecular test is negative based on low levels of virus but before the body has developed an antibody response. Specifically, CDC guidance specifies that negative samples from molecular tests should be sent for serology testing.

**Table 3: Strengths and Limitations of Molecular and Serologic Diagnostic Tests for Zika Virus Infection Identified by Food and Drug Administration**

Type of test	Strength	Limitation
Molecular	<ul style="list-style-type: none"> <li>For some devices, extraction and detection are automated, increasing the throughput</li> <li>High sensitivity</li> <li>High specificity: no cross-reactivity with dengue, West Nile, and yellow fever viruses</li> <li>Robust and well-understood tests and formats</li> <li>Range of specimen types: serum, plasma, urine, cerebral spinal fluid, amniotic fluid, whole blood</li> </ul>	<ul style="list-style-type: none"> <li>Window of time for detection is limited</li> <li>Asymptomatic pregnant women in area with active Zika transmission: not possible to determine window of time for molecular testing</li> <li>Due to manufacturers design, currently authorized for Clinical Laboratory Improvement Amendments high complexity laboratories</li> </ul>
Serologic (Immunoglobulin M)	<ul style="list-style-type: none"> <li>Covers a wider window of time (up to 12 weeks)</li> <li>Can be used to detect recent exposure to the Zika virus in asymptomatic patients</li> <li>High Sensitivity for primary infection but reports on the sensitivity for secondary infections are mixed</li> </ul>	<ul style="list-style-type: none"> <li>Potential cross-reactivity with other antibodies against other flaviviruses (dengue, West Nile, yellow fever), especially in South America and Puerto Rico</li> <li>Confirmatory testing required by following the CDC-issued algorithm which can include the plaque reduction neutralization test</li> </ul>

Source: GAO analysis based on Food and Drug Administration Information | GAO-17-445

### Serological Tests Varied in Their Ability to Detect Zika Virus Antibodies

Serology tests can be used to detect the Zika virus-specific IgM antibodies that typically develop during the first week of illness and persist for about 12 weeks.<sup>73</sup> As previously mentioned, three serological tests were authorized for the Zika virus, of which CDC manufactured one (the MAC-ELISA) and the two others were commercially manufactured. Officials at a public health laboratory we interviewed said that one of the commercially authorized tests had better specificity than the CDC MAC-

<sup>73</sup>IgM is a basic antibody produced by the immune system created in response to an initial exposure to an antigen; in this case, the antigen is part of the Zika virus. It is the first antibody that the body makes in response to a new infection and can be found in the blood.

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ELISA when compared using 30 different samples. However, the laboratory officials found that the commercially authorized test was easier to perform but more time consuming to interpret and evaluate.

Manufacturers evaluated cross-reactivity by testing specimens from patients with antibodies to other diseases that could potentially cause false positive results. Our analysis of the data provided by manufacturers in their EUA fact sheets and labeling found that one of the commercial tests did not demonstrate any cross-reactivity when compared to other flaviviruses and to nonflaviviruses during the initial qualification testing. An expert from our meeting stated that false positives based on cross-reactivity may depend on complex mixtures of antibodies at different states of infection, so it is complicated to assess this problem in a comprehensive and definitive manner. However, data provided in the EUA fact sheets and labeling for the CDC MAC-ELISA demonstrate that this assay had significant cross reactivity to dengue virus but not to other flaviviruses. CDC did not perform experimental studies for nonflaviviruses for the CDC MAC-ELISA test, stating in the label that the scientific literature indicated that only minimal cross-reactivity is expected with antibodies against other virus families.<sup>74</sup>

The positive percent agreement listed on the label for one of the commercial tests is 100 percent, and for the CDC MAC-ELISA is 93.98 percent.<sup>75</sup> The negative percent agreement is 92.5 percent for one of the commercial tests, but the CDC MAC-ELISA does not list a negative percent agreement in the product label. One of the commercial tests also showed that there is no interference with substances normally found in serum, while the CDC MAC-ELISA test did not include this information in the product label. According to HHS officials, the three diagnostic tests use different antigens for detection of Zika virus antibodies, which may be cross-reactive with antibodies from related flaviviruses. According to HHS officials, a side-by-side comparison of the performance of these

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<sup>74</sup>D. A. Martin and others, "Standardization of immunoglobulin M capture enzyme-linked immunosorbent assays (MAC-ELISA) for routine diagnosis of arboviral infections." *Journal of Clinical Microbiology*, vol. 38 (2000): 1823-26.

<sup>75</sup>The performance of the tests was determined with 55 clinical specimens, and compared to the CDC MAC-ELISA and plaque reduction neutralization test (PRNT) or the CDC Trioplex test. For the CDC MAC-ELISA, the 93.98 positive percent agreement was determined by comparing results with the PRNT using serum submitted to CDC Fort Collins for testing from 2015 to the present with 166 samples.

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## Serological Tests Varied in Their Timeliness and Throughput

diagnostic tests has demonstrated some cross-reactivity to other flaviviruses by each assay.

Of the serologic tests authorized for Zika virus diagnosis, one takes three hours and the CDC MAC-ELISA takes three days to administer. Some diagnostic users we interviewed stated that one of the commercially authorized tests was easier to use and a more efficient assay than the CDC MAC-ELISA because it is automated. According to FDA, automation decreases the time and staff required to run the samples. The CDC MAC-ELISA test takes approximately 2 to 3 days because laboratories are required to perform two overnight incubations in the laboratory to complete the test; in contrast one of the commercial tests only takes about 3 hours, in part because the plates are pre-coated. Similarly, one of the commercially authorized tests can run 28 samples per plate, while the CDC MAC-ELISA test can run 8 samples per plate.

Diagnostic users we spoke with stated that running the CDC MAC-ELISA in this format created issues with test throughput and capacity. One reason for different number of samples per plate between the tests is that the outer wells of the plates are used in one of the commercial tests and not in the CDC MAC-ELISA test. In addition, each CDC test sample was run in triplicate at the same time, decreasing the number of samples that can be run at one time.

## Strengths and Limitations of Serological Diagnostic Tests

Serologic tests for IgM can diagnose a recent infection for a wider range of time (from about 7 days to up to 12 weeks after infection) compared to molecular tests, which generally detect current infections. Another strength of serologic tests is that they can be used to detect recent exposure to the Zika virus in asymptomatic patients.

One limitation of these tests is that antibodies produced against one flavivirus may be cross-reactive to other flaviviruses, so a positive Zika virus IgM result does not necessarily indicate a Zika virus infection. The reason is that related flaviviruses such as dengue, yellow fever, West Nile, and Japanese encephalitis, which can be caused by a previous natural infection or vaccination, can give a positive Zika virus IgM result by a serology test. This has proven to be an issue in South America, Central America, Mexico, and Puerto Rico, where multiple flaviviruses are circulating, according to FDA officials.

Another limitation is that positive results need to be confirmed by using the CDC algorithm, which can include the plaque reduction neutralizing testing (PRNT) that is performed only at CDC or one of CDC's designated

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confirmatory testing laboratories (currently there are five designated state public health laboratories, according to HHS officials).<sup>76</sup> The PRNT requires about six days to complete, and the logistics of specimen shipment can further extend the time, according to HHS officials. According to CDC officials, CDC typically takes three weeks to send PRNT results but reporting time may be longer during the summer. Based on our analysis of a recent FDA document, this prolonged period between getting the IgM results and the PRNT confirmatory results may have led some clinicians and patients to make family planning decisions without confirmation of Zika virus infection.

Because the PRNT measures virus-specific neutralizing antibodies to confirm infection, not only does it take more time, but it is also difficult to perform. The test requires mixing patient serum with live Zika virus to determine how effective the serum is at neutralizing the virus in cell culture.<sup>77</sup> However, neutralizing antibodies may still react to related viruses. According to FDA officials, the PRNT is a well-recognized, established standard laboratory technique and therefore did not have to go through FDA approval or authorization. However, as mentioned above, only a few laboratories are able to perform the PRNT for the Zika virus. According to a CDC document, PRNT is considered the “gold-standard” for confirmatory testing for Zika virus infection. An expert from our meeting stated that there can still be cross-reactivity with PRNT that confounds interpretation of the results. The five state public health laboratories that perform Zika virus PRNT have demonstrated capacity and proficiency to perform PRNT testing on their own, according to HHS officials.

Finally, according to CDC officials, neutralizing antibodies to the Zika virus develop shortly after IgM antibodies and consist primarily of IgG antibodies.<sup>78</sup> Serology testing could be used to detect IgG antibodies; however, the United States has no EUA test for detecting Zika virus

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<sup>76</sup>The plaque reduction neutralization test (PRNT) measures virus-specific neutralizing antibody titers and, according to CDC report, should be performed against various related flaviviruses to rule out false-positive ELISA results.

<sup>77</sup>Cell culture is the growth of microorganisms such as bacteria and yeast, or human, plant, or animal cells in the laboratory. Cell cultures may be used to diagnose infections, to test new drugs, and in research.

<sup>78</sup>Neutralizing antibodies reduce or destroy infectivity of an infectious agent by partial or complete destruction of the agent. Neutralizing antibodies are expected to persist for many years after flavivirus infections.

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Overall Limitations of Diagnostic Testing Can be Addressed Through the Use of Algorithms

specific IgG at this time. The associations between the Zika virus and adverse health outcomes in newborns and the ability to detect infections older than 12 weeks could be relevant to family planning and clinical care of patients, if such tests were available. However, IgG is typically highly cross-reactive to other flaviviruses and can remain elevated for years following an infection or vaccination, so it is difficult to determine when a patient has an elevated IgG if it is elevated for a recent infection, a prior flavivirus infection (possibly years earlier) or both.

As discussed above, different types of diagnostic tests for the Zika virus have different strengths and limitations. As a result, rather than a single diagnostic test being considered in isolation, multiple tests and sample types are often needed to establish a definitive laboratory diagnosis. The window of acute Zika virus infection is small. Viral RNA is the first thing that can be detected in an infected person in multiple specimen types. In blood, as the immune response develops and antibodies rise, levels of viral RNA decline.

Zika virus diagnostic tests that have been authorized since the public health emergency declaration varied in their ability to detect the Zika virus or antibodies to Zika virus. Consequently, a test that is less sensitive may produce a false negative result, while a more sensitive test may detect the virus.

CDC provides guidance for determining the order of testing (known as testing algorithms) with different types of tests based on the strengths and limitations of the different test types, presence of symptoms, pregnancy status, and time between symptom onset or exposure and sample collection. For individuals with symptoms, the time between symptom onset and sample collection dictates test order. For pregnant women who have no symptoms but meet certain epidemiological criteria for testing, time between exposure or return from travel dictates test order. The testing order algorithms are shown in table 4.

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**Table 4: Overview of diagnostic testing algorithms**

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**Samples collected from all individuals with symptoms less than 14 days after the onset:**

Serum or paired urine and serum samples with a Zika virus molecular diagnostic test, a positive result in any specimen is sufficient to diagnose Zika virus infection

If Zika virus molecular results are negative, serum should be tested for the presence of Immunoglobulin M (IgM) antibodies (serology testing). Testing for dengue IgM antibodies should also be performed if the patient is pregnant or potentially exposed to dengue virus. Currently, one Emergency Use Authorization (EUA) serology test recommends that samples with a result of presumptive positive for other flavivirus have follow-up testing with a Food and Drug Administration (FDA) cleared dengue serology test.

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**Serum collected from individuals presenting with symptoms 14 days or more after onset:**

Initial testing should be done with IgM serology test for Zika virus. For non-pregnant symptomatic patients, a reactive IgM serology test result is followed by plaque reduction neutralization test to confirm the diagnosis.

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**Additional criteria and testing strategies apply for pregnant women:**

If a positive IgM serology test is obtained in specimens collected more than 14 days or more after onset of symptoms or potential exposure, testing with a molecular test should be performed. If the Zika molecular test results are negative, testing should proceed to plaque reduction neutralization test to test for the presence of neutralizing antibodies to Zika virus.

IgM serology testing for dengue virus is recommended for symptomatic pregnant women.

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**Asymptomatic pregnant women meeting epidemiological criteria for testing:**

Specimens collected from a pregnant woman presenting less than 14 days from exposure should be tested with molecular testing. If negative, a second serum specimen should be collected 2-12 weeks following exposure and tested by Zika virus IgM serology testing.

Serum specimens collected from asymptomatic pregnant women 2-12 weeks following a potential exposure or from pregnant women without symptoms living in an area of ongoing transmission should be tested by serology testing. If reactive, molecular testing should be performed on all appropriate specimen types available. If the molecular test is negative, plaque reduction neutralization testing\* should be performed for confirmation of the IgM result.

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Source: Centers for Disease Control and Prevention (CDC). | GAO-17-445

Note: For detailed information and the algorithms, information on testing infants, and links to additional guidance on testing pregnant women, see <https://www.cdc.gov/zika/laboratories/lab-guidance.html>.

\*Plaque Reduction Neutralization Test (PRNT) is not currently routinely recommended for testing of any specimens in Puerto Rico.

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## Manufacturers and Users Faced Several Challenges in Developing and Using Zika Diagnostic Tests

We identified five challenges that manufacturers of diagnostic tests faced related to Zika virus diagnostic testing, research, and development, and regulatory approval: (1) biological aspects of the virus and the immune response, including low levels of virus in the bodily fluids of infected patients for short periods of time and the cross-reactivity of antibodies to other flaviviruses, (2) difficulty in accessing well-characterized clinical samples, (3) getting access to EUA tests for use as a comparator assay, (4) gaining cooperation with international entities, and (5) challenges interacting with FDA during review. Challenges users of the diagnostic

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Manufacturers Faced Several Challenges Developing Diagnostic Tests

tests faced included: (1) requirements to purchase new specific equipment to be compliant with the EUA label on a test they wanted to use; and (2) determining the most accurate test because information in the EUA labels for some of the performance characteristics were not easily comparable. Consequently, users could not easily compare diagnostic test performance measures from product labels.

The first challenge to manufacturers developing diagnostic tests was the lack of knowledge of Zika virus biology and infections, especially at the beginning of the U.S. outbreak. The best sample type to use for molecular testing was uncertain at the beginning of the outbreak. For instance, the Zika virus had been found to be present longer in urine than in serum or plasma, but information on just how long the virus could persist in different bodily fluids was still evolving. Compared to related viruses, the Zika virus is present at low levels in bodily fluids of patients during an active infection. Manufacturers also faced challenges in identifying ways to test for antibodies, as well as unique Zika virus antigens to target due to issues with extensive cross-reactivity with other flaviviruses.<sup>79</sup> Information is still evolving about antigens that are unique to the Zika virus and how long the virus persists in various bodily fluids, making it difficult to develop diagnostic tests for the virus.

Second, the lack of well characterized clinical samples for diagnostic test development was identified as a major challenge for developing Zika virus diagnostic tests, according to the federal agency officials and manufacturers we interviewed, and all the experts who participated in our meeting. However, several manufacturers told us that obtaining samples for testing was difficult because of high costs, potential cross-reactivity with other flaviviruses, and an insufficient number of samples. For example, one manufacturer had to pay more than \$200,000 to acquire samples from commercial vendors. According to another manufacturer we interviewed, a single clinical sample for the Zika virus can cost around \$450. Manufacturers told us they requested, but were not able to obtain, samples from CDC in the early stages of the outbreak and one manufacturer stated this was because not enough samples were available. One manufacturer stated that this delayed the development of its test. According to HHS officials, to help address the lack of samples for test development, BARDA, a component of ASPR, provided

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<sup>79</sup>Antigens are epitopes of the virus that are important to the immune response. An epitope is the part of an antigen molecule an antibody attaches itself to.

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characterized samples to test manufacturers, once the samples became available in midsummer 2016. However, HHS officials stated that no test manufacturer received enough samples from BARDA for the EUA testing requirements and had to acquire samples from other sources to support the EUA application.

BARDA officials told us they have worked closely with CDC and manufacturers to collect and characterize clinical samples that can be used to develop and validate diagnostic tests to detect Zika virus infection.<sup>80</sup> Manufacturers also had issues with clinical samples, since samples sourced from Central and South America were not well characterized, because other circulating flaviviruses could cause cross-reactivity, creating uncertainty in the outcome of a given test.

Third, FDA recommends that manufacturers perform clinical evaluation studies that compare their tests to another “comparator” assay that is laboratory developed, an in-house assay, or an EUA test. The selection and quality of the comparator assay directly affects the measurements of the test performance. A CDC document states that CDC rarely has the resources needed to fully respond to public health emergencies but should provide a consistent, fair, and transparent review process for all public-private initiatives. However, according to CDC officials, they did not make their EUA test available to some commercial manufacturers for use as a comparator assay. One manufacturer we interviewed said its request to CDC for reagents to perform the Trioplex test was denied since it was a commercial manufacturer. Another manufacturer told us it attempted to purchase an EUA test from another manufacturer but was unable to because the other manufacturer refused to sell the EUA diagnostic test. According to HHS officials, in order to obviate this challenge, FDA allows manufacturers to use laboratory developed tests as comparator tests. An expert at our meeting, stated a manufacturer had to establish their own assay because commercial manufacturers cannot purchase the Trioplex test or create it since it is unpublished.

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<sup>80</sup>BARDA provides an integrated, systematic approach to the development and purchase of the necessary vaccines, drugs, therapies, and diagnostic tools for public health medical emergencies. BARDA distributes some clinical samples to manufacturers that meet minimal criteria, including manufacturers that have contacted FDA to obtain the EUA template, which indicates interest in developing a test toward FDA clearance that might be considered for use on an EUA. It distributes to manufacturers that either have had a Zika test in development or have the ability to do so (for example, have FDA authorized serologic tests for other viruses). See table 1.

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Two of the 12 authorized molecular diagnostic test labels have CDC's Trioplex listed as their comparator assay. CDC was the first manufacturer to receive an EUA and therefore the Trioplex test was the first authorized molecular test that other tests attempting to get EUA could be compared to. According to CDC officials, diagnostic tests CDC created are distributed only to public health laboratories performing Zika virus clinical diagnoses because in the early stage of the response, CDC did not have the capacity to adequately support public health laboratories and also supply commercial manufacturers with CDC tests for performance testing. CDC officials also stated that issues with intellectual property rights, such as patents, or material transfer agreements, may prevent sharing reagents, individual components and technology. An expert from our meeting stated that this could have been overcome by publishing the test protocol with specific details about the test. However, CDC distributed its tests to four manufacturers through technology transfers, when no shortage of reagents was experienced by September 2016. CDC officials we spoke with were unclear of how the process to transfer authorized CDC tests to manufacturers originally started. *Standards for Internal Control in the Federal Government* state that agencies should document their operational processes to ensure that the organization meets its objectives. Without a clear and transparent process for distributing CDC diagnostic tests, the agency may not be able to develop the capacity of the commercial sector during an outbreak.

Fourth, interacting with international entities to obtain samples and perform testing presented some challenges. Some foreign countries have laws that must be followed when collecting samples. A manufacturer we interviewed faced import challenges trying to perform a diagnostic test in another country. One manufacturer told us it took 6 weeks for diagnostic manufacturers to ship materials to another country for testing, and the import tax was \$30,000. An expert from our meeting also stated that obtaining CDC import permits was challenging.

Fifth, manufacturers had mixed opinions on the effectiveness of communication from FDA. Specifically, representatives of some manufacturers said that FDA did a good job communicating with them throughout the EUA process during the recent outbreaks while some said that communication with FDA could be improved. FDA interacts with manufacturers about potential EUA products to help ensure that manufacturers submit complete EUA applications and thereby enhances

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FDA's ability to review and ultimately authorize the EUA.<sup>81</sup> FDA stated that its review expertise is scarce, making it imperative to prioritize efforts to move the best diagnostic tests forward first (that is, the test that is most effective in addressing an unmet public health need). However, one manufacturer we interviewed stated that the longer time for communication and time to receive authorization from FDA were challenging in developing diagnostic test for Zika virus. According to FDA, the average time between pre-EUA, a time when FDA begins review of fact sheets and other documentation before the submission and EUA submission is 87.6 days, with a range of 14 to 178 days for Zika diagnostic tests. The average time once an application was submitted to the authorization date was 7.4 days, with a range of 1 to 26 days. A manufacturer suggested an improvement would be to shorten the time to respond to inquiries.

FDA developed templates for molecular and serology diagnostic tests and sent them to manufacturers in order to support obtaining an EUA. According to FDA officials, templates provided transparency in terms of the studies required for a successful EUA submission and streamlined submission for the manufacturers. FDA officials stated that updates to studies were communicated to manufacturers as new information became available during the Zika outbreak, including by direct communication with manufacturers and through FDA's webpages. As new information on Zika virus became available, FDA instituted changes to the EUA to ensure that manufacturers were demonstrating adequate performance for their diagnostic tests. However, some manufacturers requested greater clarity. Some manufacturers we interviewed stated that FDA changed its requirements for authorization throughout the process. HHS officials stated that they had to incorporate new information about the Zika virus into their review process as it became available throughout the outbreak, consequently changing the required amount of analytical and clinical data requested from manufacturers before they could make EUA authorizations.

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<sup>81</sup>As of March 2017, FDA had 133 inquiries to request the EUA templates or information on where to source clinical samples. According to FDA officials, 71 of the 133 queries required extensive feedback and interactive communications and resulted in 45 pre-EUA submissions and 16 complete EUA submissions.

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Diagnostic Test Users Faced Challenges Acquiring Equipment and Determining the Most Accurate Test

Zika virus diagnostic test users we interviewed faced challenges because they had to purchase new equipment to be compliant with the EUA label on a test they wanted to use. It was difficult to determine the most accurate test because information on the EUA labels of the performance characteristics of tests were not comparable or not available on the CDC website.

First, although CDC officials stated that all states had at least one public health laboratory that had the equipment to run the CDC MAC-ELISA test, representatives from several laboratories we interviewed stated that they had to acquire new equipment to be able to perform a certain EUA diagnostic test. For instance, implementation of serological testing within another federal laboratory was delayed because additional equipment was needed to perform the authorized test. CDC officials stated that the agency is working to expand diagnostic testing capacity within both public health and commercial laboratories in the United States.

Second, diagnostic test users also faced challenges in determining the most accurate test because information on the labels was not easily comparable. An FDA document states that the agency should share information that is up-to-date, understandable, and easily accessible so diagnostic test users has some basis for choosing medical products to purchase and use.<sup>82</sup> Moreover, according to this document, posting compilation or analysis of data can benefit users since all users may not have the ability or resources to independently analyze raw data.<sup>83</sup> By comparing the diagnostic test labels, we found that the labels had units listed differently for key performance characteristics, data had to be extracted from each product insert, and some of the information could not be readily compared with other data. We also found that performance characteristics are listed on the diagnostic test labels, but it is not available in a consolidated format.

According to FDA officials, the agency began collecting information using FDA Reference Materials because different manufacturers were using different samples and potentially different methods to determine the limit of detection of their tests.<sup>84</sup> Using common samples across

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<sup>82</sup>Food and Drug Administration, Transparency Initiative.

<sup>83</sup>Food and Drug Administration, Transparency Initiative.

<sup>84</sup>FDA Reference Materials were made available to all test manufacturers, free of charge, provided that they demonstrated the feasibility of their assay, according to FDA officials.

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manufacturers allowed FDA to directly compare the limits of detection across different molecular diagnostic tests. However, the FDA Reference Materials were available only after certain diagnostic tests were already authorized under EUA. Therefore, those diagnostic test labels did not initially list the limit of detection using the FDA Reference Materials until their labels were updated.

FDA officials stated that if manufacturers had not previously performed the limit of detection using the FDA Reference Materials, they would need to perform those tests and provide results to FDA. This would allow users to compare limits of detection for tests that were performed using the same samples and procedures. FDA officials stated that they were waiting to receive all the results from all the manufacturers with an authorized diagnostic test before considering consolidating information about performance characteristics, since this information was already publically available in the updated product labels of the individual tests. All authorized molecular test manufacturers had submitted limit of detection data using the FDA Reference Materials to FDA by March 6, 2017.

Until limit of detection data have been extracted and summarized from all the diagnostic test labels, it may be difficult and time-consuming for users to compare the performance characteristics and results of diagnostic tests. By waiting until FDA has all the information before compiling information about performance characteristics, it will be time-consuming for users to compare the limit of detection across the authorized molecular diagnostic tests.<sup>85</sup> This will become especially important with the mosquito season approaching and public health laboratories making decisions about which tests to use.

Another challenge users faced was related to the lack of information on comparator assays. An FDA document recommends that there should be a clear description of all methods used and how and what data were collected when performing comparison testing, including a description of

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<sup>85</sup>For example, three diagnostic tests have the same limit of detection listed for serum (1000 detectable units/mL) using the FDA Reference Materials and have three different limit of detections listed on their product labels when manufacturers use their own samples and protocols (721 copies/mL or 0.05 tissue culture infectious dose /mL, 30 copies/mL and 250 RNA copies/mL).

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the comparator assay “nonreference standard.”<sup>86</sup> Experts at our meeting agreed that identifying the comparator assay would make it easier to compare the risks and benefits of different Zika virus diagnostic tests.<sup>87</sup> The selection and quality of the comparator assay directly affects the legitimacy of the comparison of the test performance.<sup>88</sup> When we compared product labels for different molecular tests, we found that 6 of 12 product labels did not identify the comparator assay and that the comparator assay could fall into one of three types: (1) another EUA test, (2) a laboratory developed test, or (3) an in-house assay (see appendix V).

FDA officials stated that the comparator assay for authorized diagnostic tests can be either another authorized test or a validated reference method and manufacturers are allowed to decide if they will identify the comparator assay. However, the manufacturers are not required to do so. According to FDA officials, comparison studies for EUA diagnostic tests are based on a relatively low number of clinical specimens, and the levels of viral RNA in a number of specimens can be low. In addition, FDA officials stated that these two factors preclude definitive conclusions regarding the comparative performance of devices, and FDA staff are concerned that studies using comparator assays in labeling may be used to make inappropriate claims and could be misinterpreted by end users. The use of FDA Reference Material allows for a more rigorous analysis of the comparative sensitivities of the assays from the various manufacturers, according to FDA officials.

However, without knowing the identity of the comparator assay, it is more difficult for users to compare performance characteristics across different diagnostic tests and determine the most appropriate test to use. According to an expert at our meeting, this information would be helpful for laboratories in determining what test to use in the face of multiple approved tests. Although the criteria for procuring diagnostic tests can vary, for most laboratories the paramount focus is on test performance.

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<sup>86</sup>Food and Drug Administration, *Guidance for Industry and FDA Staff: Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests* (Washington, D.C.: March 13, 2007).

<sup>87</sup>A comparator assay is used as the reference method for assessing the performance characteristics of another test method.

<sup>88</sup>Shabir Banoo and others, “Evaluation of Diagnostic Tests for Infectious Diseases: General Principles”, *Nature Reviews: Microbiology* (2010): S17-S29.

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*Standards for Internal Control in the Federal Government* state that agencies are to communicate quality information externally through reporting lines so that external parties can help an entity achieve its objectives and address related risks.<sup>89</sup> CDC did not make publically available data comparing the performance characteristics of different CDC diagnostic tests that it distributed during the outbreak. CDC’s website has information about the performance of its two authorized diagnostic tests and the PRNT technique, but not the laboratory-developed test it distributed, called the Singleplex laboratory developed test (Singleplex).

According to a HHS report, CDC did not provide information about one of its diagnostic tests because it could potentially create confusion and could have caused public health laboratories to discontinue use of the Trioplex test, and it had not done a comprehensive comparison of the Trioplex and Singleplex assay. Because CDC did not publically provide performance information about its laboratory developed test—which was distributed to some public health laboratories—questions arose regarding the sensitivity of the two CDC tests (Singleplex and Trioplex, see text box).

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<sup>89</sup>GAO, *Standards for Internal Control in the Federal Government*, [GAO-14-704G](#) (Washington, D.C.: September 2014).

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### Issues with Centers for Disease Control and Prevention (CDC) Molecular Diagnostic Test Sensitivity

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A CDC scientist (who later became a whistleblower) alleged that the Emergency Operation Center at CDC endangered public health when it failed to disclose that an emergency use authorized CDC test used to detect Zika virus—called the Trioplex Real-time RT-PCR assay (Trioplex)—was substantially less sensitive than another CDC laboratory developed test (Singleplex). After raising concern about the test’s sensitivity, an Office of Special Counsel (OSC) investigation was conducted.

OSC encouraged CDC to promote scientific debate on this issue and said that whistleblowers should be encouraged to speak out on matters of public concern. OSC also requested the Department of Health and Human Services (HHS) to conduct an independent investigation about the allegations made and CDC’s Associate Director of Laboratory Science and Safety, who conducted the investigation, found that the evidence did not support the allegations. OSC found the CDC investigation reasonable. CDC had three sources of data to compare the different tests’ sensitivities. One was from the whistleblowers’ laboratory, another from the creator of the Trioplex test that was alleged to be less sensitive, and the third was an independent laboratory that compared the Singleplex and Trioplex tests.

The CDC investigation into the whistleblower’s claims did not attempt to gather additional information on comparing the tests from public health laboratories using the Singleplex test. According to CDC officials, they could not do a direct comparison of the two tests because the equipment required for both tests did not exist at either location. The agency acknowledged that the original Trioplex test was authorized only a smaller input volume while the Singleplex is not subject to such limitation because it had never been submitted to the Food and Drug Administration (FDA) for review and was used only as a laboratory-developed test.

CDC submitted a substantial amendment to the Trioplex test for FDA’s authorization to increase the input volume of the test in August 2016, and in January 2017 the authorization was amended again to allow laboratories to use a singleplex reaction on the Trioplex assay. According to CDC, the larger input volume has been demonstrated to increase the sensitivity of the Trioplex assay. According to a CDC website, a “head-to-head comparison of the Trioplex test and the Zika-only assay” has not been conducted. In HHS’ technical comments they stated that a “head-to-head comparison of the Trioplex and the Singleplex laboratory developed test” has been performed and showed equivalent performance.

A journal article later showed that the original Trioplex test was less sensitive than the Singleplex test. Increasing the input volume of the test increased the limit of detection of the Trioplex test approximately 20 to 50 times.

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Source: GAO analysis of HHS and Office of Special Counsel documents; CDC “Updated Laboratory Guidance: Frequently Asked Questions” <https://www.cdc.gov/zika/laboratories/lab-guidance-faq.html> (assessed May 18, 2017); M. Stone and others, “Relative Analytical Sensitivity of Donor Nucleic Acid Amplification Technology Screening and Diagnostic Real-Time Polymerase Chain Reaction Assays for Detection of Zika Virus RNA,” *Transfusion*, (2017) | GAO-17-445.

Representatives of three scientific professional societies told us that information about the development and verification of CDC’s diagnostic test should be made available to the scientific and medical communities. Access to such data would provide transparency and allow for optimal patient care, according to these representatives. According to these societies’ representatives, the lack of access to data on test performance prevented users from making informed decisions about which test to adopt or recommend during the outbreak. Without including information on the performance characteristics of tests it is distributing, CDC cannot ensure that healthcare providers and the public have the information they need to make informed decisions about which test is best for their use.

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## Mosquito Control Methods Have Strengths and Limitations, and Federal Agencies Face Several Challenges Assisting These Efforts

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### Mosquito Control Methods in the United States Are Often Combined Under Integrated Vector Management

Types of mosquito control methods available in the United States include: (1) physical control, or nonchemical mosquito control, (2) larval mosquito control, (3) adult mosquito control, and (4) personal protection. Mosquito control entities and literature identified available methods that may control mosquitoes in general. However, not all methods presented in this report specifically apply to *Aedes aegypti* mosquitoes, in part because not all such entities we spoke with had *Aedes aegypti* in their area. For example, HHS identified ditching as irrelevant for *Aedes aegypti* mosquitoes.<sup>90</sup> These methods can be combined with surveillance of the mosquito population, using integrated vector management (IVM) to optimize the application of multiple methods, depending on knowledge of mosquito biology and distribution.<sup>91</sup>

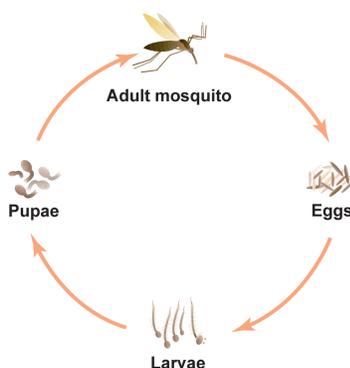
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<sup>90</sup>Discussion targeted more to *Aedes aegypti* mosquitoes is in (1) National Science and Technology Council, *A Strategy for Integrating Best Practices with New Science to Prevent Disease Transmission by Aedes Mosquito Vectors*, (Washington, D.C.: December, 2016); (2) Centers for Disease Control and Prevention, *Surveillance and Control of Aedes aegypti and Aedes albopictus in the United States*, accessed October, 17, 2016, <https://www.cdc.gov/chikungunya/pdfs/surveillance-and-control-of-aedes-aegypti-and-aedes-albopictus-us.pdf>; or (3) Department of Defense, Armed Forces Pest Management Board, *Technical Guide No. 47: Aedes Mosquito Vector Control*. (Silver Spring, MD: March 2, 2016).

<sup>91</sup>IVM is sometimes referred to as integrated pest management or integrated mosquito management (IMM). According to CDC, IMM combines methods to prevent and control mosquitoes that spread viruses, like Zika, dengue, and chikungunya. IMM is based on an understanding of mosquito biology, the mosquito lifecycle, and the way mosquitoes spread viruses. IMM uses methods that have been scientifically proven to reduce mosquito populations and, when followed correctly, are safe.

Different mosquito control methods target different stages of the mosquito lifecycle. The mosquito's lifecycle has two stages—an aquatic stage in which eggs develop into larvae and pupae and a terrestrial stage in which the mosquito leaves the water, can fly, and can transmit pathogens and lay eggs. Figure 7 depicts major lifecycle steps encompassing these stages.

**Figure 7: The Lifecycle of a Mosquito**



Source: GAO, adapted from CDC. | GAO-17-445

### Available Methods for Physical Control of Mosquitoes and their Strengths and Limitations

Physical control, or the use of physical or mechanical means to remove water sources serving as larval development sites or prevent mosquito entry into buildings, includes (1) controlling water sources needed for mosquito breeding and (2) using barriers, such as window screens, to keep mosquitoes away from people.<sup>92</sup> A National Science and Technology Council (NSTC) report stated that physical control includes removing standing sources of water, such as from containers, old tires, or blocked drains, and using well-fitted and intact screens on all house doors and windows.<sup>93</sup>

<sup>92</sup>These categorizations and the methods they include can vary. For example, physical control and water source control are sometimes separated. One textbook categorizes the latter as “environmental management.” See Norbert Becker and others. *Mosquitoes and Their Control*, Second Edition (Berlin: Springer, 2010). HHS officials also told us that bed nets and screening may be considered personal protection methods.

<sup>93</sup>National Science and Technology Council. *A Strategy for Integrating Best Practices with New Science to Prevent Disease Transmission by Aedes Mosquito Vectors*, (Washington, D.C.: December 2016).

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Mosquito control entity officials we interviewed told us that they use a variety of physical control methods. For example, one told us that his mosquito control program still benefits from ditching projects completed in the 1960s and is continuing to use excavators to ditch areas to enhance water run-off.<sup>94</sup> Another official told us that his program includes a “drain and cover” community outreach approach, asking residents to drain standing water, use window screens, and wear long-sleeved clothing. A third official we interviewed included a program for swimming pool management by helping identify and fill in abandoned swimming pools.

Each of these physical control methods has strengths and limitations. Specifically, officials from mosquito control entities told us that water-source control such as by large-scale ditching is very effective and avoids the use of chemicals for certain types of mosquitoes. However, a mosquito control entity official also said that this method is probably challenged in the current regulatory environment. According to a NSTC report, large-scale outdoor water source control may have limited effectiveness against *Aedes aegypti* mosquitoes because breeding requires only small volumes of water (for example, one tablespoon, under certain conditions). Another mosquito control entity stated that inspections of property by mosquito control personnel may be effective but are time-consuming.<sup>95</sup> According to a NSTC report and mosquito control entity officials we interviewed, such property inspections can be challenged by privacy and property rights.

In addition, while physical control of larval development sites can reduce or eliminate mosquito larvae, the local environment may not be suited to such measures if extensive water bodies are present. It may be impractical or impossible to remove or move volumes of water. For example, a mosquito control entity official told us that since nearby swampland cannot be removed, physical control through water management is not an option for them.

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<sup>94</sup>This official said that the goal of ditching projects is to eliminate or reduce the number, size and frequency of mosquito breeding sites.

<sup>95</sup>These inspections are intended to identify mosquito breeding sites such as sources of water.

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Available Methods for  
Controlling Mosquito Larvae  
and their Strengths and  
Limitations

Controlling immature mosquitoes includes using chemical or biological control methods. Chemical larvicides include methoprene and pyriproxyfen, and biologically based larvicides include *Bacillus thuringiensis israelensis* (Bti).<sup>96</sup> CDC guidance includes another method of larvae control—applying certain oils on water surfaces to suffocate mosquito larvae and pupae.<sup>97</sup> Mosquito control entity officials we spoke with all told us they use larviciding, such as with Bti, or with mosquito fish that eat mosquito larvae.

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<sup>96</sup>Literature indicated limited effectiveness of some types of larval control for reducing dengue transmission or morbidity. R. Boyce and others, “Bacillus thuringiensis israelensis (Bti) for the control of dengue vectors: systematic literature review,” *Tropical Medicine & International Health*, vol. 18, no. 5 (2013); and Leyanna George and other, “Community-effectiveness of Temephos for Dengue Vector Control; A Systematic Literature Review,” *PLoS Neglected Tropical Disease*, vol. 9, no. 9 (2015).

<sup>97</sup>Centers for Disease Control and Prevention, Surveillance and Control of *Aedes aegypti* and *Aedes albopictus* in the United States, accessed October 17, 2016, <https://www.cdc.gov/chikungunya/pdfs/surveillance-and-control-of-aedes-aegypti-and-aedes-albopictus-us.pdf>.

### The “Mosquito Fish” Eats Mosquito Larvae



A “mosquito fish” prepares to ingest a mosquito larva. This tiny fish, which can eat its own weight in mosquito larvae each day, has been introduced into waterways throughout the world to aid in controlling mosquitoes, especially where malaria and yellow fever are a threat.

Source: CDC, Office of the Associate Director for Communications, Division of Public Affairs, Public Health Image Library, ID #4958. | GAO-17-445

## Available Methods for Controlling Adult Mosquitoes and their Strengths and Limitations

Using larvicides has strengths and limitations. Specifically, using biologically based larvicides may be more accepted by the public than adult pesticides, but is limited by cost and effectiveness. Officials from mosquito control entities we spoke with told us that residents are more accepting of biologically-based larvicides because they consider them more natural. However, a mosquito control entity official added that larviciding tends to be more expensive than other techniques. A mosquito control official told us that mosquito-borne diseases have not been successfully controlled by using larvicide alone because, while it reduces the population by 70 percent to 80 percent, controlling a disease such as the Zika virus disease requires a population reduction greater than 80 percent to 90 percent.<sup>98</sup> Even very few mosquitoes can lead to an outbreak or epidemic.<sup>99</sup>

A mosquito control entity official told us that larvicide also needs to be applied within a limited window of opportunity and that larvicide application is delayed in its effect. Similarly, control using mosquito fish appears to be “natural” to the public, but is time consuming and has limited applicability for *Aedes* mosquitoes that carry the Zika virus, because *Aedes* mosquito eggs can survive in small containers that dry out.

Adult mosquitoes can be controlled with certain pesticides, or adulticides, applied indoors or outdoors. An EPA official told us it has registered nine active ingredients for use as adulticides, including malathion, naled, and permethrin. CDC and NSTC documents indicate that some adulticides are intended for area-wide space spraying (fogging), while others are intended for residual spraying (in and around buildings), where

<sup>98</sup>EPA officials told us they have issued a joint statement with CDC on mosquito control in the United States that states that mosquito control is based on the fact that the greatest control impact on mosquito populations occurs when they are concentrated, immobile and accessible. This emphasis focuses on habitat management and controlling immature stages before mosquitoes emerge as adults. See <https://www.epa.gov/mosquitocontrol/joint-statement-mosquito-control-united-states>, accessed April 18, 2017. According to EPA, larviciding is an important component, along with other techniques including source reduction, IVM and adulticiding, in mosquito vector population reduction.

<sup>99</sup>The mosquito control official said that the characterization of mosquito threat depends on factors such as the local temperature, mosquito number, and human exposure to mosquitoes.

### The Correct Application of Mosquito Repellent Spray



When someone spends long periods of time outdoors, insect repellent should be reapplied according to product label instructions. The best way to protect yourself and your family from chikungunya, as well as other mosquito-borne illnesses including the Zika virus, is to avoid being bitten by mosquitoes by using insect repellent, wearing long sleeves and pants, using air conditioning or window and door screens to keep mosquitoes outside, and reducing mosquito breeding grounds such as standing water.

Source: CDC, Office of the Associate Director for Communications, Division of Public Affairs, Public Health Image Library, ID #17796. | GAO-17-445

the pesticide remains active on surfaces that mosquitoes land on.<sup>100</sup> Mosquito control entity officials we spoke with said they disperse a variety of adulticides using a variety of methods, including handheld units, helicopters, fixed wing aircraft, and trucks. CDC guidance includes additional methods such as nonpesticide traps—for example, CDC's Autocidal Gravid Ovitrap, which captures egg-laying mosquitoes on a sticky glue.<sup>101</sup>

Using adulticides also has strengths and limitations. Specifically, officials from mosquito control entities told us that adulticide spraying can be effective in controlling mosquito populations. One mosquito control professional noted that mosquito-borne diseases such as West Nile virus disease have historically been controlled by adulticides. However, we identified several limitations with adulticide spraying. One limitation mosquito control entity officials and CDC staff identified is public resistance to pesticides.<sup>102</sup> Another limitation is that adulticiding effectively requires control over droplet size; mosquito control entity officials we spoke with told us they required special equipment to control the dispersal rate and properties of the adulticides. Other limitations include limited effectiveness under certain weather conditions and the potentially deleterious effect of broad-spectrum adulticides on other insects such as bees.

Additionally, *Aedes aegypti* mosquitoes are primarily daytime biters, requiring spraying during certain times for optimal effectiveness.<sup>103</sup> However, one mosquito control entity official was reluctant to spray during commuting hours, including times when schoolchildren go to or return

<sup>100</sup>According to WHO documentation, space spraying is technically a fog (sometimes referred to as an aerosol); it entails dispersing a liquid insecticide into the air in the form of hundreds of millions of tiny droplets.

<sup>101</sup>Centers for Disease Control and Prevention. *Surveillance and Control of Aedes aegypti and Aedes albopictus in the United States*, accessed October 17, 2016, <https://www.cdc.gov/chikungunya/pdfs/surveillance-and-control-of-aedes-aegypti-and-aedes-albopictus-us.pdf>. CDC guidance breaks down control methods differently and refers to these traps as physical control, but HHS officials told us that these traps should be considered adult mosquito control methods.

<sup>102</sup>An expert from our meeting told us that the effectiveness of aerial spraying against *Aedes aegypti* lacks robust, evidence-based support which may affect future response capabilities.

<sup>103</sup>One expert from our meeting added that *Aedes* mosquitoes are found in and in close proximity to dwellings. Another expert from our meeting indicated that certain products, such as Duet and Suspect, may be effective against *Aedes albopictus*.

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from schools. Further, increasing resistance of mosquitoes to existing active ingredients decreases the effectiveness of adulticiding and creates the need for new control methods. Finally, pesticide spraying over waters of the U.S. is subject to permit requirements under the Clean Water Act, which may present a challenge for mosquito control entities in applying pesticides for mosquito control (see appendix VI).

Alternative strategies may enhance the effectiveness of adulticide application. For example, one study demonstrated that data from “contact tracing”—which uses travel histories to help identify potential sites of infection—can be used to target locations for indoor spraying.<sup>104</sup> According to this study, this method may reduce mosquito-borne dengue transmission by about 90 percent. However, the method requires access to indoor environments and permission to spray inside homes.

#### Available Methods for Personal Protection against Mosquitoes and their Strengths and Limitations

Personal protection includes using repellents, wearing long-sleeved clothing, and using bed nets. Repellent ingredients can include dermally applied chemicals such as DEET.<sup>105</sup> Some repellents such as permethrin can be impregnated in clothing.

Personal protection methods also have strengths and limitations. Specifically, NSTC reports that using repellents permits individuals to remain protected as they conduct their daily routines. While personal protection methods are under the individual’s control, they are effective only when properly and regularly applied. For example, one mosquito control expert at our meeting told us that despite having authority over a specific population, compliance related to the usage of bed nets or repellants is still difficult to enforce.

#### Other Issues Related to Available Mosquito Control Efforts

We identified three other related issues that affect available mosquito control efforts:

**Community Awareness of Mosquito Control Efforts.** NSTC reports that the effectiveness of public-health interventions, such as mosquito control, depends on community awareness and perception and the

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<sup>104</sup>Gonzalo Vazquez-Prokopec and others, “Combining Contact Tracing with Targeted Indoor Residual Spraying Significantly Reduces Dengue Transmission,” *Science Advances*, vol. 3 (2017).

<sup>105</sup>According to a CDC factsheet, DEET (or N,N-diethyl-meta-toluamide) is the active ingredient in many insect repellents. Experts from our meeting told us of additional repellent ingredients, including picaridin, IR3535 and para-methane 3-8, diol (PMD).

**Example Mosquito Trap Used to Trap Vectors to Be Tested for Pathogens**



This "light trap" enabled CDC scientists to venture easily into dense, remote areas when conducting arbovirus epidemiological field work that included capturing mosquito vectors. The trap weighs only 1.75 pounds and is easily repaired. Different types of traps are used for different types of mosquitoes. For example, the "light trap" is not used for *Aedes aegypti* mosquitoes.

Source: CDC, Office of the Associate Director for Communications, Division of Public Affairs, Public Health Image Library, ID #6355. | GAO-17-445

implementation of control practices. The risk of the Zika virus is generally under-perceived and misinformation is widespread about vector-control practices. Further, communication and outreach between the mosquito control entities and the community are necessary for effective mosquito control. Mosquito control entity officials we spoke with agreed, noting the importance of public education and outreach. For example, mosquito control entity officials sometimes use a variety of approaches for such efforts, such as going door to door, attending meetings and conferences, holding public events at schools, buying radio time, and communicating online. Mosquito control entity officials told us that two major challenges that mosquito control efforts face are educating the public and ensuring public compliance. One told us that the public generally misunderstands mosquito control methods. Additionally, while reducing sources of water can be effective and people tend to be receptive to such messages, they can forget to implement them.

**Mosquito Control Methods Can Be More Effective with an IVM Approach.** IVM combines control methods with surveillance of the mosquito population.<sup>106</sup> A CDC website describes IVM as combining methods to control mosquitoes and prevent the spread of mosquito-borne viruses based on an understanding of mosquito biology, behavior, and spread of viruses.<sup>107</sup> IVM uses methods that are safe and scientifically proven to reduce mosquito populations when applied correctly, according to this website. An expert from our meeting included education as a critical component of IVM; an NSTC report describes education as a prerequisite for successful IVM. Officials from all the mosquito control entities we spoke with told us they use some form of IVM, and include surveillance of the mosquito population. One mosquito control official also noted that IVM is sometimes tailored to specific mosquito species.<sup>108</sup>

<sup>106</sup>Integrated Vector Management can be defined as "the rational combination of all available control methods in the most effective, economical and safe manner to maintain mosquito vector populations at acceptable levels." Surveillance is considered a prerequisite for successful IVM programs. Norbert Becker and others. *Mosquitoes and Their Control*, Second edition. (Berlin: Springer, 2010)

<sup>107</sup>Centers for Disease Control and Prevention, "Integrated Mosquito Management," accessed January 31, 2017, [https://www.cdc.gov/zika/vector/integrated\\_mosquito\\_management.html](https://www.cdc.gov/zika/vector/integrated_mosquito_management.html). HHS officials told us that IVM includes mosquito species surveillance as well as insecticide resistance monitoring in the surveilled species. They added that vector control methods are specific to each type of mosquito.

<sup>108</sup>According to EPA officials, different mosquito species have different behaviors (e.g., daytime feeding versus morning and evening feeding) and understanding them is key to effective control, and important to successful IVM.

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Additional methods being developed may eventually be incorporated into IVM strategies.

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**Mosquito Control Methods Under Development Show Promise but Their Effectiveness Remains to be Established**

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Mosquito control methods under development include the use of genetically-engineered mosquitoes and mosquitoes infected with the *Wolbachia* bacterium, among others. Some of these approaches can decrease the number of offspring that survive to adulthood. Other approaches under development can decrease the transmission of disease-causing virus. An NSTC report stated that some reported strengths of these approaches include potentially lower impact on other species and minimizing collateral risks to humans by more specific targeting of mosquito species. Some potential limitations include public opposition to some of the methods as well as a lack of studies demonstrating their effect on mosquito-borne disease transmission.

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Source: GAO analysis of literature and agency information | GAO-17-445

**Surveillance Helps Inform Mosquito Control Efforts.** All mosquito control entity officials we spoke with told us that they use surveillance of the mosquito population to assess the presence and abundance of mosquitoes and to direct the use of mosquito control methods. Traps can be used to perform surveillance. Different traps are suited to different species—for example, mosquito control entity officials told us that they use BioGents-Sentinel traps to specifically target Zika virus vectors such as *Aedes aegypti* and *Aedes albopictus*. Mosquito control entity officials also said that sentinel animals, such as regularly monitored chickens, are used for surveillance of mosquitoes that carry West Nile virus. One mosquito control entity uses landing counts, which enumerate the number of mosquitoes landing on a human volunteer over some period such as 1 minute. Finally, mosquito control entities can rely on reported mosquito complaints from the community as part of their surveillance.

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**The Federal Government Faced Challenges Supporting Mosquito Control Efforts**

The federal government has a limited role in implementing mosquito control because mosquito control efforts are implemented at the state and local levels. However, the federal government faced a number of challenges in supporting these mosquito control efforts. According to CDC documentation, the agency developed technical guidance and provides funding and technical assistance to support state and local mosquito control activities.<sup>109</sup> We identified four challenges to the federal

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<sup>109</sup>Centers for Disease Control and Prevention. *Draft Programmatic Environmental Assessment. Mosquito Control Activities Funded by CDC to Combat Zika Virus Transmission in the United States*, (Jan. 9, 2017).

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The Timing of the Availability of Funds and Sustaining Expertise

government's efforts to support mosquito control activities: (1) the timing of the availability of funds and sustaining expertise, (2) communication of data about mosquito distribution, (3) linking the effects of mosquito control to disease outcomes, and (4) limited information about mosquito control entities.

Federal agencies faced challenges related to the cyclic nature of mosquito-borne diseases, including recruiting and maintaining expertise. For example, part of IVM is matching specific methods or tools to specific situations and requires an understanding of mosquito biology.<sup>110</sup>

However, experts at our meeting identified two issues in implementing IVM. First, one expert at our meeting said that vector biology is "kind of a dying field" in which "trained people cannot get jobs," and another expert at our meeting indicated that vector biology program support has not been sustained.<sup>111</sup> CDC officials agreed, stating that it is challenging to study cyclic diseases such as West Nile virus. When the disease fades, the jobs and resources also go away, so that the next time the disease appears, staff must be retrained or new staff trained.

Second, CDC officials told us that mosquito control needs vary with seasonal cycles, resulting in periods of several months that require more resources followed by some periods when little or no resources are needed. For example, CDC officials told us that even though surveillance traps are not perishable, mosquito control entities ran out of certain traps during the 2016 mosquito season and had to wait 6-months to acquire new traps.<sup>112</sup> According to CDC officials, funds for purchasing traps were not available until summer.

Further, grant funds awarded for mosquito control may not make it to some local mosquito control districts. CDC staff stated that CDC awarded funds to combat the Zika virus, including \$56 million between August and December 2016 for mosquito control and surveillance. However, an

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<sup>110</sup>For example, an Armed Forces Pest Management Board official told us that mosquito species number 3,000, with 300 of them transmitting disease.

<sup>111</sup>According to a CDC website, CDC is funding Centers for Excellence in Vector-Borne Disease. The funding period for the Centers of Excellence is 5 years. CDC told us its Strategic Plan for establishing a new "systems approach" to vector control relies on these centers, among other things. See <https://www.cdc.gov/media/releases/2016/p1222-zika-funding.html>, accessed April 6, 2017.

<sup>112</sup>CDC officials told us that mosquito traps have only one domestic manufacturer.

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CDC Faced Challenges  
Communicating the Presence  
of Mosquitoes

expert at our meeting told us that CDC does not directly fund specific mosquito control entities but instead provides funds to grant recipients, typically states.<sup>113</sup> Since the states submit the grant applications and direct the use of certain grant funds after the award, and CDC does not directly monitor mosquito control entities, CDC may face challenges addressing entity needs.<sup>114</sup>

CDC faced challenges in communicating the presence of mosquitoes in a manner that was clear and useful to different groups such as mosquito control entities and the general public. CDC distributed maps of the estimated potential range of the primary Zika virus vector mosquitoes on its webpage and in guidance, but imprecision in the maps can lead to confusion, according to some mosquito control officials. According to CDC officials, the maps allowed states to determine the level of effort needed for more precise mosquito surveillance as well as to show the public where they may encounter certain mosquito species.

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<sup>113</sup>Certain cities, such as New York City, and U.S. territories can apply for funding directly from CDC, independently of the states.

<sup>114</sup>For example, one entity official we interviewed told us of restrictions, including not being able to use funds for public education or having rigid deadlines for expenditures, that decreased the flexibility of their control program.

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One mosquito control official told us that confusion about CDC's maps resulted from people failing to look at the qualifications stated in the map captions and mistakenly concluding that an entire state was infested with Zika virus vector mosquitoes. This official said that CDC's maps of the range of *Aedes* mosquitoes may be unhelpful since they are intended to show the mosquitoes' potential range while some residents who saw the maps were worried that they were in an area with Zika virus.<sup>115</sup> This official also told us the maps created a challenge of reconciling information that their own mosquito control program staff had gathered with that presented on a highly publicized CDC map. For example, one mosquito control entity official we spoke with told us that it has not had *Aedes aegypti* in its county since 2012. However, the state where the mosquito control entity is located is entirely within the potential range identified by the CDC map. An expert from our meeting told us that the CDC map showed regions painted with a broad brush, and such information could spread fear.

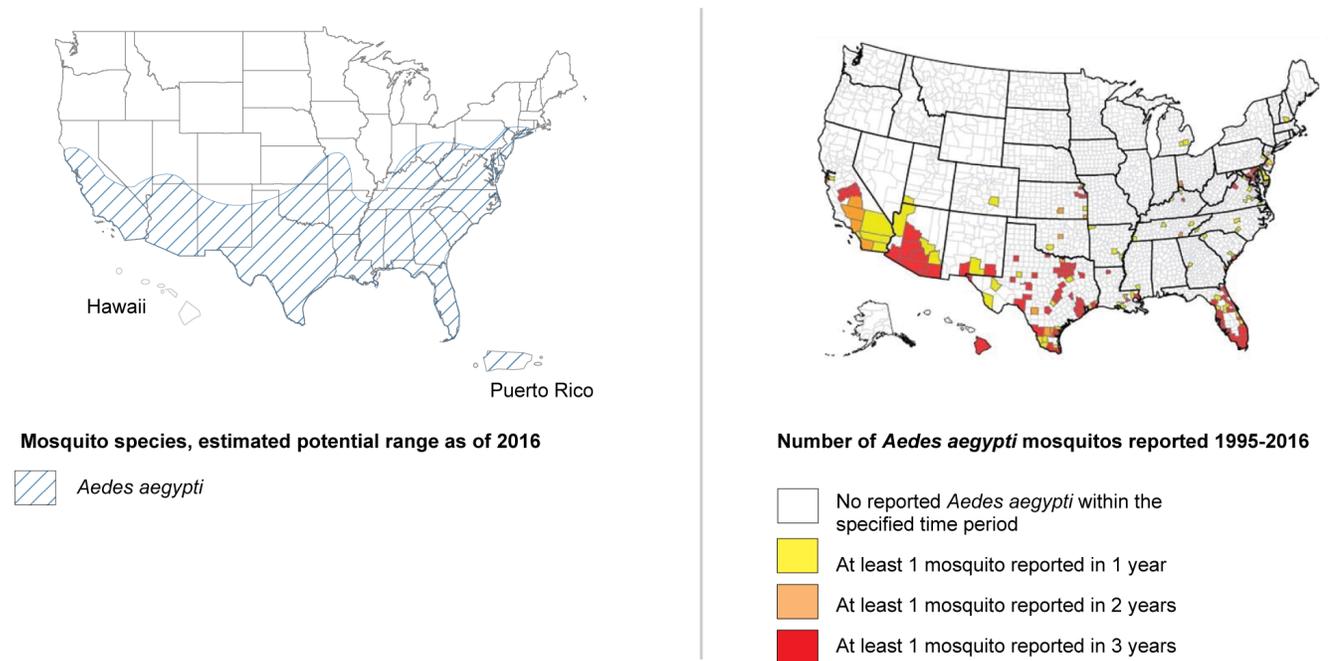
To illustrate some differences between CDC's estimated potential range of *Aedes aegypti* mosquitoes and locations with reported occurrence of the mosquito, we compared the CDC map to a map of historical mosquito data compiled from multiple sources and published in a recent article written by CDC scientists. The map from the article shows a different, much sparser, pattern of recorded presence than CDC's estimated potential range (figure 8).<sup>116</sup>

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<sup>115</sup>One CDC map had an explanation in the footnote and caption that readers ignored, giving the mosquito control official a public relations challenge.

<sup>116</sup>Micah B. Hahn and others, "Reported Distribution of *Aedes (Stegomyia) aegypti* and *Aedes (Stegomyia) albopictus* in the United States, 1995-2016 (Diptera: Culicidae)," *Journal of Medical Entomology*, vol. 53, no. 5 (2016): 1169-75. The mosquito data were compiled from multiple sources, including existing collection records and a survey that the authors designed to capture additional surveillance records from vector control districts, university researchers, and local health departments.

**Figure 8: *Aedes aegypti* in the United States - A Comparison of Estimated Potential Range and Reported Presence**



Source: GAO. Map 1 adapted from CDC, map 2 adapted from Micah B. Hahn. | GAO-17-445

Experts identified limitations with both maps. For example, one expert from our meeting told us that the CDC map may extend the potential mosquito range too far north in some locations. Another expert stated that the CDC map does not account for all the factors that affect mosquito distribution. In addition, one expert told us that the data for the map on the right in figure 8 may be incomplete, and a mosquito control official told us that the map did not convey whether an area reporting no mosquitoes had performed mosquito surveillance.<sup>117</sup>

CDC officials told us that their map was generated with data ranging as far back as 1995, and was sourced from a combination of published records and an understanding of species ecology and U.S. geography.

<sup>117</sup>According to Micah B. Hahn and others, "Reported Distribution of *Aedes (Stegomyia) aegypti* and *Aedes (Stegomyia) albopictus* in the United States, 1995-2016 (Diptera: Culicidae)," *Journal of Medical Entomology*, vol. 53, no. 5 (2016): 1169-75, incomplete information is a known limitation. They stated that "lack of collection records for *Aedes aegypti* . . . should not be interpreted as absence of that mosquito."

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However, the detailed information was not posted on the CDC website or in documentation associated with the map.<sup>118</sup> As a result, the map may not be useful for all of its intended purposes. According to *Standards for Internal Control in the Federal Government*, management should use quality information to achieve the agency's objectives and should select appropriate methods to communicate externally.<sup>119</sup> Additionally, the standards state that agency management should externally communicate necessary quality information to achieve those objectives. This includes selecting appropriate methods to communicate externally, considering factors such as the intended recipients and the nature of the information being communicated. With regards to the information presented on CDC maps, experts suggested including more details, such as (1) collection records, (2) measures of the stability of the mosquito populations (showing how long populations of such mosquitoes would be expected to persist in a given location), and (3) areas of risk for transmission of mosquito-borne diseases. Additionally, understanding the date range and sources of the data can help place map information in context. Without such context, CDC's maps could generate confusion about mosquito presence, resulting in concern among residents and public relations challenges, among other things.

### Challenges in Linking Mosquito Control Efforts to Disease Outcomes

CDC faced challenges in determining whether mosquito control efforts are associated with the reduction of mosquito-borne disease. For example, mosquito control entity officials told us the entity's mosquito control efforts are not directly linked to disease reduction. An official from another mosquito control entity told us that it links mosquito control only to the mosquito population. Another said that it links mosquito control to the presence of West Nile virus in sentinel chickens.<sup>120</sup> Additionally, West Nile virus, CDC officials told us, is a bird disease, so CDC can surveil for West Nile virus and detect this virus 2 weeks before it can affect

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<sup>118</sup>The CDC website at <https://www.cdc.gov/zika/vector/range.html>, (accessed January 27, 2017), for example, states only that the maps have been updated "from a variety of published and unpublished sources."

<sup>119</sup>GAO, *Standards for Internal Control in the Federal Government*, GAO-14-704G (Washington, D.C.: September 2014).

<sup>120</sup>According to a mosquito control district webpage, sentinel chicken serology is performed by placing chickens in an area over an extended period and testing their blood for the presence of antibodies to different viruses. See <http://www.wumcd.org/surveillance/chicken.html>, accessed April 6, 2017.

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people.<sup>121</sup> However, Zika virus lacks this environmental component and enters a country with human travelers. Zika virus is thus picked up by human surveillance before mosquito surveillance and lacks a similar 2-week delay.<sup>122</sup>

Other challenges to analyzing the relationships between mosquito control methods and disease reduction include the dependence of reported disease cases on weather, human susceptibility and immunity. According to CDC officials, data were insufficient to create an analogous link for the Zika virus, in part because the specific data needed to demonstrate the effect were not available, due to privacy considerations for individuals' health records. Therefore, it will be difficult to tease out the effect of mosquito control methods on disease reduction.

#### CDC had Limited Information on Mosquito Control Entities

CDC's capacity to develop a national strategy for mosquito control is limited and depends on its knowledge of mosquito control entities and their capabilities. CDC relied on external sources such as the National Pesticide Information Center, the American Mosquito Control Association, or the National Association of County and City Health Officials to compile a list of mosquito control entities. CDC staff told us that this list is likely to capture the larger, well-funded entities but may miss some smaller ones.

Further, mosquito control capabilities in the United States are variable. According to an assessment by the National Association of County and City Health Officials, 68 percent of the responding mosquito control

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<sup>121</sup>Studies have demonstrated reductions in West Nile Virus disease due to aerial pesticide spraying. Duke Ruktanonchai and others. "Effect of Aerial Insecticide Spraying on West Nile Virus Disease- North-Central Texas, 2012." *The American Journal of Tropical Medicine and Hygiene*, vol. 91, no.2 (2014); and Ryan Carney and others. Efficacy of Aerial Spraying of Mosquito Adulticide in Reducing Incidence of West Nile Virus, California, 2005. *Emerging Infectious Diseases*, vol. 14, no. 5 (2008.).

<sup>122</sup>CDC officials told us they use ArboNET, an online reporting tool for mosquito-borne diseases, to track virus infection in mosquito numbers. They have now launched MosquitoNET, which will include additional information such as mosquito presence, mosquito abundance, and insecticide resistance.

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entities in 10 priority jurisdictions were rated as “needs improvement.”<sup>123</sup> A mosquito control official we interviewed agreed that variability in mosquito control entity capacities is significant. This means that it is challenging for CDC to determine the status of mosquito control efforts in different regions of the United States and to identify regions that may need additional technical guidance or assistance.<sup>124</sup>

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## Conclusions

Emerging infectious diseases such as influenza, Ebola and Zika viruses represent an ongoing threat to the health of people in the United States and worldwide. The recent Zika virus outbreak presented some challenges, some of which are unique to Zika virus disease, in relation to epidemiology, diagnostic tests, and federal agencies’ role in vector control strategies.

With regard to the epidemiology of the Zika virus, CDC and its public health partners established standardized Zika case definitions. However, the estimated high rate of infected persons who had mild or no symptoms and, as a result, did not seek medical treatment made it challenging to obtain an accurate measure of the magnitude and impact of Zika virus in the United States.

With regard to the availability of accurate and reliable diagnostic tests for the Zika virus, FDA authorized several diagnostic tests under EUA, but some performance characteristics were not consistently reported across different diagnostic tests, making it more challenging to compare tests. Information on performance characteristics presented in each diagnostic

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<sup>123</sup>NACCHO Mosquito Surveillance and Control Assessment in Zika Virus Priority Jurisdictions, 2016. NACCHO surveyed 10 jurisdictions that were deemed “high priority for assessing necessary support for Zika response” by CDC and its collaborators. These jurisdictions are Alabama, Arizona, California, Florida, Georgia, Hawaii, Los Angeles County, Louisiana, Mississippi, and Texas. A rating of “needs improvement” signifies a negative answer to at least one of five core questions regarding mosquito control program actions and capabilities. About half the surveyed mosquito control entities responded, with 21 percent of the respondents being rated “fully capable.” The survey was conducted during the latter half of 2016.

<sup>124</sup>CDC’s MosquitoNET can help address this challenge but mostly relies on self-reporting by Epidemiology and Laboratory Capacity for Infectious Diseases Cooperative Agreement (ELC) awardees and may continue to contain gaps in knowledge. ELC funds all 50 state health departments, six of the nation’s largest local health departments (Chicago, the District of Columbia, Houston, Los Angeles County, New York City and Philadelphia), and eight territories or U.S. affiliates, including U.S. Virgin Islands, Puerto Rico and Guam. There are 64 grantees.

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test product label was not consolidated across available tests, and the identity of the comparator assay was not listed on some labels, making it challenging for users to make informed decisions about which test to adopt or recommend to patients.

CDC developed the first two authorized diagnostic tests for the Zika virus and offered these tests to public health laboratories, but not to some manufacturers. Some manufacturers did not have access to the authorized CDC tests and encountered difficulty acquiring authorized tests from other manufacturers. Without a clear and transparent process for distributing CDC diagnostic tests, the agency may not be able to develop the capacity of the commercial sector to be able to meet the needs during an outbreak.

In addition, users were not able to compare clinical performance across authorized diagnostic tests in the absence of a diagnostic test reference standard that all manufacturers use. CDC has not provided detailed information on its website for all the diagnostic tests it distributed during the Zika virus outbreak. Until CDC lists information about all the diagnostic tests it distributes, it may be more challenging for users to determine which test to use.

With regard to vector control methods, federal agencies can provide important information to assist mosquito control efforts implemented at the state and local levels. However, the information that CDC included in its maps did not include sufficient details on its estimates of potential distribution of mosquitoes that carry the Zika virus, which made it challenging for mosquito control experts and the public to correctly interpret and use such data.

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## Recommendations for Executive Action

We recommend that the Secretary of Health and Human Services direct the Commissioner of the Food and Drug Administration to take the following two actions:

- Consolidate information from individual diagnostic test labels and make this information available in a form that enables users to more readily compare information across tests.
- Require manufacturers to list the identity of comparator assays on their diagnostic test labels.

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We also recommend that the Secretary of Health and Human Services direct the Director of Centers for Disease Control and Prevention to take the following three actions:

- Establish a transparent process to provide CDC diagnostic tests, upon request, to manufacturers that are in the final stages of diagnostic test authorization.
- Include information on CDC-developed tests distributed to or shared with public health laboratories on CDC's website, including laboratory developed tests.
- Provide details such as collection records, dates, and data limitations on posted and disseminated mosquito distribution maps to better inform mosquito control experts and the general public.

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## Agency Comments and Our Evaluation

We provided a draft of this report for review and comment to HHS and EPA. HHS's written response is reprinted in appendix III. EPA did not provide a written response. HHS agreed with four of our recommendations, partially agreed with one of our recommendations and provided information on actions it is taking to address these recommendations. HHS and EPA also provided technical comments, which we incorporated as appropriate.

- HHS concurred with our recommendation for FDA to consolidate information from individual product labels and said that this information would be available on FDA's website.
- In response to our recommendation that FDA require manufacturers to list the identity of the comparator assay, HHS stated that it would recommend that manufacturers describe the test used for comparison in order to reduce the risk of confusion by diagnostic test users.
- In response to our recommendation to establish a transparent process to provide CDC diagnostic tests to manufacturers, HHS stated that CDC will work with its existing Technology Transfer Office to implement a transparent process for providing manufacturers with approved CDC diagnostic assays.
- In response to our recommendation that CDC provide details such as collection records, dates, and data limitations on posted and disseminated mosquito distribution maps to better inform mosquito

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control experts and the general public, HHS described several actions taken by CDC to help improve the quality of the data that is used to develop estimated potential ranges of the mosquitoes that spread Zika virus disease, including conducting a rapid review of available data on the mosquitoes that can transmit the Zika virus and conducting surveys to record the location of mosquitoes capable of spreading different diseases.

- In response to our recommendation to include information on CDC-developed tests distributed to public health laboratories, HHS partially concurred and provided clarifying information. HHS agreed that it should share information on CDC-developed tests that have received EUA. However, regarding this recommendation, HHS did not agree that it should share information on CDC's laboratory-developed tests that have not received EUA because CDC is unable to provide detailed information on characteristics of these unstandardized tests. We maintain that sharing information about these laboratory developed tests that are used for comparison testing is important because of the concerns that were raised regarding the sensitivity of one of CDC's EUA tests. We recognize that laboratory-developed tests that have not received EUA are not standardized, but we believe that CDC can provide certain information on the performance characteristics and quality of these tests based on its knowledge about these tests. Sharing this information could help other diagnostic test users make informed decisions about which test to adopt or recommend. HHS also noted that CDC does not distribute laboratory developed tests that have not received EUA but in some circumstances shares them with public health laboratories. In response to this comment, we have modified our recommendation to reflect this information.

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As agreed with your offices, we will send copies of this report to appropriate congressional committees, the Secretary of Health and Human Services, and the Administrator of the Environmental Protection Agency, and other interested parties. In addition, the report will be available at no charge on the GAO website at <http://www.gao.gov>.

If you or your staff members have any questions concerning this report, please contact Timothy M. Persons, Chief Scientist, at (202) 512-6512 or [personst@gao.gov](mailto:personst@gao.gov). Contact points for our Offices of Congressional Relations and Public Affairs may be found on the last page of this report. Key contributors to the report are listed in appendix VIII.



Timothy M. Persons, Ph.D.  
Chief Scientist

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# Appendix I: Participants in GAO's Expert Meeting

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This appendix lists the experts, and their affiliations, who participated in the Zika Virus Expert Meeting held with the assistance of the National Academies of Sciences, Engineering, and Medicine, on November 9–10, 2016, at 500 5th Street, N.W., Washington, D.C.<sup>1</sup>

Amy L. Altman, Ph.D., Vice President, Biodefense and Protein Diagnostics, Luminex Corporation

Jamie A. Blow, Ph.D., Director, Armed Forces Pest Management Board, Defense Pest Management, Department of Defense

Michael Callahan, M.D., M.S.P.H., Director of Translational Therapeutics, Vaccine, and Immunotherapy Center, Massachusetts General Hospital, Harvard Medical School

Joseph M. Conlon, M.Sc., BCE, Technical Adviser, American Mosquito Control Association

Durland Fish, Ph.D., Honorary D.Sc., Emeritus Professor, Yale School of Public Health

Eva Harris, Ph.D., Professor, Division of Infectious Diseases and Vaccinology, School of Public Health and Director, Center for Global Public Health, University of California at Berkeley

Anna M. Likos, M.D., M.P.H., State Epidemiologist and Interim Deputy, Secretary for Health, Florida Department of Health

Jorge L. Munoz-Jordan, Ph.D., Chief, Molecular Diagnostics and Research Laboratory, Division of Vector Borne Infectious Diseases, Dengue Branch, Centers for Disease Control and Prevention

Benjamin Pinsky, M.D., Ph.D., Medical Director, Clinical Virology Laboratory, Stanford University School of Medicine

Brenda Rivera-García, D.V.M., M.P.H., Territorial Epidemiologist, Puerto Rico Department of Public Health

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<sup>1</sup>At the outset of the meeting on November 9, 2016, GAO advised participants that they would not be identified, that no quotes would be attributed to any person, and that they were not expected to speak for their institutions.

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Alfonso J. Rodriguez-Morales, M.D., Ph.D., Chair, Colombian Collaborative Network of Zika (RECOLZIKA)

Daniel A. Strickman, Ph.D., Senior Program Officer of Vector Control, Global Health Program, Bill and Melinda Gates Foundation

Jill Taylor, Ph.D., Director, Wadsworth Center, New York State Department of Health

Gonzalo Vazquez-Prokopec, Ph.D., Assistant Professor, Department of Environmental Sciences, Emory University

Scott C. Weaver, Ph.D., Professor and Chair, Department of Microbiology and Immunology, University of Texas Medical Branch

Kelly Wroblewski, M.P.H., MT, Director, Infectious Disease Programs, Association of Public Health Laboratories

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# Appendix II: Objectives, Scope, and Methodology

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The objectives of this review were to (1) provide information on what is known and not known about the epidemiology of the Zika virus and determine the challenges, if any, in conducting surveillance and epidemiological studies, (2) determine the characteristics of different Zika virus authorized diagnostic tests and any challenges manufacturers and users faced, and the extent to which Food and Drug Administration (FDA) and Centers for Disease Control and Prevention (CDC) followed their own communication guidance during the U.S. outbreak, and (3) identify available mosquito control methods, describe their strengths and weaknesses, and identify any challenges federal agencies and others face in assisting mosquito control efforts.<sup>1</sup>

To conduct this work, we reviewed relevant laws, regulations, and guidance. We reviewed relevant documentation such as, FDA's guidance to the manufacturers, product labels, and agencies reports on the epidemiology of the Zika virus, and interviewed officials from key federal agencies that are involved in the domestic Zika virus response. With the assistance of the National Academy of Sciences, we convened a meeting with 16 experts to discuss issues related to the Zika virus outbreak. These experts represented academia, the federal government, and industry and had combined expertise in epidemiology, diagnostics, and mosquito control.

The Forum on Microbial Threats within the National Academies of Sciences, Engineering, and Medicine solicited nominations for the expert panel from its extensive contacts in academia, government, foundations, and other organizations interested in vector borne diseases, particularly Zika virus disease. These contacts include current and past members of National Academies of Science's Forum on Microbial Threats, selected members of the National Academy of Medicine, and other National Academies of Science stakeholders. The result was approximately 109 nominees. From this initial list, experts were selected for their knowledge and expertise in the science and epidemiology of Zika virus, Zika virus diagnostics, and mosquito control, as well as their experience in the academic, industry, nonprofit, and government sectors.

We chose two U.S. cities to visit to interview about their experiences and challenges in terms of Zika virus epidemiology, diagnostic users, and

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<sup>1</sup>For the purpose of this report, users of diagnostic tests include laboratory personnel, health care providers, and others in the medical and scientific communities.

mosquito control—namely, New York City, which had the largest reported number of travel-associated cases, and Miami, Florida, for the largest reported number of locally transmitted cases.<sup>2</sup> For both site visits, we interviewed and collected information from city and state public health and mosquito officials. We also conducted site visits to three agencies within the Department of Health and Human Services (HHS): CDC, FDA, and National Institutes of Health (NIH).

To provide information on what is known about Zika virus epidemiology and the challenges in conducting surveillance and epidemiologic studies, we reviewed surveillance case data from CDC, the Pan American Health Organization (PAHO), and the World Health Organization (WHO). We reviewed peer-reviewed journal articles and reports about the Zika virus and associated health outcomes. We interviewed federal and selected state and city public health officials about Zika virus surveillance and epidemiology. We also interviewed representatives from public health organizations, including the Association of State and Territorial Health Officials (ASTHO), Council of State and Territorial Epidemiologists (CSTE), and National Association of County and City Health Officials (NACCHO). We asked the representatives about the roles of their organizations in Zika virus surveillance and epidemiologic studies and any challenges they encountered.

To determine the characteristics of different Zika virus diagnostic tests, we focused on those diagnostic tests that were authorized for use under FDA's Emergency Use Authorizations (EUA). This excluded laboratory developed tests. We reviewed and compared the product labels available on FDA's website for 16 diagnostic tests with EUAs as of April 12, 2017. We reviewed product labels and determined the reported limit of detection for each molecular diagnostic test. We reviewed the product labels for information about the FDA reference samples. We also reviewed the letter of authorization and factsheets for healthcare providers and patients available on FDA's website for each authorized diagnostic test.

To determine the strengths and limitations of different diagnostic tests and the challenges associated with Zika virus diagnostic testing, research, development, and regulatory approval, we interviewed several manufacturers that had an EUA diagnostic test for the Zika virus. We

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<sup>2</sup>We did not visit Puerto Rico (or other U.S. territories) but we were able to meet with Puerto Rican scientists for our National Academies of Science expert group meeting.

attempted to interview the manufacturers of the 14 different Zika virus diagnostic tests that had a EUA, including CDC, which manufactured two of the diagnostic tests. We interviewed CDC officials about their tests in site visits to Atlanta, Georgia, and Fort Collins, Colorado. We also contacted the 14 commercial manufacturers of the EUA diagnostic tests through email and were able to interview 10 of them that responded to our inquiry.<sup>3</sup> We used a structured set of interview questions to obtain data from the eight manufacturers that included questions on performance characteristics, operational characteristics, types of samples, strengths and weakness of the diagnostic test as well as limitations, and challenges associated with Zika diagnostic test development, research, testing, and regulatory processes.

We also spoke with various users of the authorized diagnostic tests, including officials from selected state public health laboratories and CDC and Department of Defense (DOD) laboratories about the strengths and limitations of different tests. We selected diagnostic test users by emailing seven different entities that were listed in an HHS report as using a CDC test in their laboratories, and we were able to interview officials at five laboratories that responded to our inquiry.<sup>4</sup> We coordinated with DOD officials and submitted questions to their laboratories that use diagnostic tests for Zika. We asked users of diagnostic tests about the type or types of tests they used, how they decided on which test(s) to use, the origin of specimens tested, the performance of comparison testing performed, and whether they had access to information regarding the potential risks and benefits of EUA tests and knowledge of available alternatives. We also asked for their interpretation of an adverse event for Zika diagnostic tests.

We compared information from our interviews with federal officials and our review of agency documents to internal controls from *Standards for Internal Control in the Federal Government*.<sup>5</sup> To determine current CDC and FDA practices and whether they follow of their own communication guidance, we compared information we collected from agency interviews and from our expert meeting and review of relevant documentation to

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<sup>3</sup>One company declined to be interviewed, and the remaining were unresponsive.

<sup>4</sup>U.S. Department of Health and Human Services, *Report of Investigation*. OSC File Number DI-16-3709 (Washington, D.C.: 2016).

<sup>5</sup>Both the 1999 edition of GAO, *Standards for Internal Control in the Federal Government*, [GAO/AIMD-00-21.3.1](#) (Washington, D.C.: November 1999), and the 2014 revision ([GAO-14-704G](#)).

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internal agency guidance documents, such as the *Emergency Use Authorization of Medical Products and Related Authorities*.<sup>6</sup>

To identify available mosquito control methods and their strengths and weaknesses, we reviewed agency documents and peer-reviewed literature and conducted interviews with a nongeneralizable selection of mosquito control entities. We focused on entities with a high potential abundance of the mosquito species that transmit the Zika virus as reported in a journal article and areas where there was local Zika transmission, among other things. We emailed 13 mosquito control entities and were able to interview eight that responded to our inquiry. We asked these mosquito control entities about challenges with implementing their programs, technologies they use for mosquito control, how they select specific methods, sources of funding, and changes to their programs because of Zika. To assess the challenges that federal agencies face in assisting mosquito control efforts, we spoke with federal agency officials in CDC, EPA, and FDA; experts in federal government and academia; and members of our expert panel. The sample of mosquito control entities we selected for our review is nongeneralizable, meaning that information from our interviews cannot be used to make general statements about mosquito control entities across the United States.

We conducted this performance audit from June 2016 to May 2017 in accordance with generally accepted government auditing standards. Those standards require that we plan and perform the audit to obtain sufficient, appropriate evidence to provide a reasonable basis for our findings and conclusions based on our audit objectives. We believe that the evidence obtained provides a reasonable basis for our findings and conclusions based on our audit objectives.

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<sup>6</sup>Food and Drug Administration, *Emergency Use Authorization of Medical Products and Related Authorities: Guidance for Industry and Other Stakeholders*, OMB Control 0910-0595 (Washington, D.C.: U.S. Department of Health and Human Services, January 2017).

# Appendix III: Comments from the Department of Health and Human Services



DEPARTMENT OF HEALTH & HUMAN SERVICES

OFFICE OF THE SECRETARY

Assistant Secretary for Legislation  
Washington, DC 20201

MAY 17 2017

Tim Persons  
Director, Applied Research and Methods  
U.S. Government Accountability Office  
441 G Street NW  
Washington, DC 20548

Dear Mr. Persons:

Attached are comments on the U.S. Government Accountability Office's (GAO) report entitled, "*Emerging Infectious Diseases: Actions Needed to Address the Challenges of Responding to Zika Virus Disease Outbreaks*" (GAO-17-445).

The Department appreciates the opportunity to review this report prior to publication.

Sincerely,

A handwritten signature in cursive script that reads "Barbara Pisaro Clark".

Barbara Pisaro Clark  
Acting Assistant Secretary for Legislation

Attachment

**GENERAL COMMENTS OF THE DEPARTMENT OF HEALTH AND HUMAN SERVICES (HHS) ON  
THE GOVERNMENT ACCOUNTABILITY OFFICE'S DRAFT REPORT ENTITLED: EMERGING  
INFECTIOUS DISEASES: ACTIONS NEEDED TO ADDRESS THE CHALLENGES OF RESPONDING  
TO ZIKA VIRUS DISEASE OUTBREAKS (GAO-17-445)**

The U.S. Department of Health and Human Services (HHS) appreciates the opportunity from the Government Accountability Office (GAO) to review and comment on this draft report.

HHS notes that the report places significant weight on the ability of users to evaluate Zika tests based solely on performance, when in fact, there is little clinical significance. Although test performance is an important factor for a laboratory to consider when deciding which test to implement, other factors impact the relative utility of different tests for different settings, including whether the test fits the laboratory's needs or requires the laboratory to purchase new instrumentation. In addition, all authorized Zika molecular tests, regardless of the sensitivity, will miss some individuals who were exposed to the virus, given the short window of detection for Zika nucleic acid in symptomatic patients. For that reason, all molecular tests carry the requirement that negative test results be retested with a serological test following the Centers for Disease Control and Prevention (CDC)-issued algorithm. Differences in sensitivity for the authorized molecular tests are less significant than the report suggests, since following the CDC-issued algorithm should account for the relatively few people who were missed by the molecular test and instead were caught by follow up testing. Finally, the Food and Drug Administration (FDA) notes that the systematic use of the FDA Reference Material allows a more rigorous analysis of the comparative sensitivities of the assays from the various manufacturers.

**Recommendation 1**

GAO recommends that the Secretary of HHS direct the Commissioner of FDA to take the following two actions:

- Consolidate information from individual diagnostic test labels and make this information available in a form that enables users to more readily compare information across tests.
- Require manufacturers to list the identity of comparator assays on their diagnostic test labels.

**HHS Response 1**

HHS concurs with the GAO's recommendation. This information will be made available on FDA's website.

HHS also concurs with the GAO's recommendation regarding the inclusion of the identity of comparator assays on diagnostic test labeling, subject to the following clarification. To implement GAO's recommendation, FDA would recommend that sponsors of Zika diagnostic tests provide identification of the comparator assay by describing the assay(s), rather than provide the name of the assay in order to reduce the risk of confusion by end users. An example of a description of a comparator assay might be: "The comparator assay was an rRT-PCR assay authorized by FDA for detection of Zika RNA in serum with analytical sensitivity in the range XX-YY RNA Units/mL." FDA's recommendation is based on the Statistical Guidance on Reporting Results from Studies Evaluating Diagnostic Tests which states: "Comparing a new test to a non-reference standard does not yield true performance. If the new test is better than the non-reference standard, the agreement will be poor." Consequently a "new" device which has "better" sensitivity (lower LoD) than a "comparator" device may appear to have false positive results relative to the "comparator" assay depending on the level of Zika virus in the clinical specimens. End users may incorrectly infer that the "new" device is inferior to the "comparator" device. Alternatively, the agreement could be poor if the comparator is more accurate than the new test thereby compounding the challenges for the end users to decide which test has superior performance.

**Recommendation 2**

We also recommend that the Secretary of HHS direct the Director of CDC to take the following three actions:

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- Establish a transparent process to provide CDC diagnostic tests, upon request, to manufacturers that are in the final stages of diagnostic test authorization.
- Include information on CDC-developed tests distributed to public health laboratories on CDC's website, including any laboratory developed tests.
- Provide details such as collection records, dates, and data limitations on posted and disseminated mosquito distribution maps to better inform mosquito control experts and the general public.

**HHS Response 2**

*Establish a transparent process to provide CDC diagnostic tests, upon request, to manufacturers that are in the final stages of diagnostic test authorization.*

HHS concurs with GAO's recommendation and efforts are underway to implement it. On January 15, 2016, CDC issued a Health Advisory encouraging healthcare providers to report suspected Zika virus disease cases to their state health departments to facilitate diagnosis and mitigate the risk of local transmission. At that time, there were no commercially available tests to diagnose Zika virus and tests were being performed using existing available nonspecific time-consuming PCR methods by state health departments and CDC. In March 2016, CDC secured FDA Emergency Use Authorization (EUA) for the Trioplex rRT-PCR assay, which was the first test that was able to detect and differentiate Zika virus, dengue virus, and chikungunya virus. The EUA permitted CDC to provide the Trioplex assay to qualified laboratories. CDC began manufacturing the Trioplex assay in March, and prioritized distribution of the assay to state/local health departments in geographic areas at greatest risk of Zika transmission.

CDC initially prioritized sharing of assays with state and local health departments for several reasons, including: (1) there was a limited supply of assays available; (2) CDC guidance to healthcare providers recommended that they screen for Zika and seek testing through a state/local health department; and (3) testing conducted by state/local health departments could be easily reported to CDC to help better understand the impact of Zika in the United States. Furthermore, many people infected with Zika do not show symptoms, and those that do have symptoms that are non-specific and similar to a cold or flu. Given the limited availability of the assay during the early part of 2016, CDC did not want to create circumstances where the supply of available assays was exhausted by testing low/no-risk people. This approach during the early part of 2016 ensured that there was a sufficient supply of available assays to screen and diagnose those most at risk. CDC did provide the Trioplex assay to commercial manufacturers for EUA comparison analysis once supplies were available. However, CDC does acknowledge it did not always utilize a transparent process to provide the Trioplex assay to manufacturers for comparison analysis.

Going forward, CDC will work with its existing Technology Transfer Office to implement a transparent process to provide manufacturers engaged in EUA-comparator analyses with approved CDC diagnostic assays. This process will ensure that intellectual property and materials transfer agreements are addressed appropriately, and will also allow CDC to clearly articulate any criteria under which the provision of diagnostic assays may be delayed such as limited availability or some other compelling public health interest.

*Include information on CDC-developed tests distributed to public health laboratories on CDC's website, including any laboratory developed tests.*

HHS partially concurs with GAO's recommendation related to sharing information on CDC-developed tests.

In early 2016, CDC received FDA Emergency Use Authorization (EUA) for two Zika diagnostic assays: Trioplex rRT-PCR assay and the Zika MAC-ELISA assay. In January 2017, FDA approved CDC's request to modify the Trioplex rRT-PCR assay to include a singleplex reaction option. These are the only CDC-developed Zika diagnostic assays that have received EUA. For these assays, CDC provided information consistent with the FDA-

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Instructions for Use requirements for each EUA. This information was posted on CDC's website (<https://www.cdc.gov/zika/hc-providers/types-of-tests.html>) as well as on FDA's EUA website (<https://www.fda.gov/MedicalDevices/%20Safety/EmergencySituations/ucm161496.htm>).

For EUA assays, CDC provides information including but not limited to: specimen handling, materials/equipment requirements provided by CDC to approved external laboratories, quality control instructions, testing algorithms and test validity determination instructions, assay limitations, performance characteristics, clinical performance data and contact information.

For EUA assays, CDC provides the receiving laboratories the specified reagents and approved instructions for conducting the test. The receiving laboratories are required to demonstrate proficiency in order to continue receiving the reagents.

CDC concurs with GAO's recommendation to make this information available for all EUA assays developed by CDC. CDC does not concur with GAO's recommendation that CDC provide similar information for any CDC laboratory developed assays, including those that have not received EUA from the FDA.

CDC does not distribute laboratory-developed assays that have not received EUA. In some circumstances, CDC shares laboratory-developed assay protocols (generally through scientific publications) and laboratory controls with partner public health laboratories to advance technical cooperation.

CDC is unable to provide detailed information for non-EUA laboratory-developed assays on characteristics such as assay performance and quality control instructions because the assay is not standardized. Laboratory-developed assays are designed, manufactured and used within an individual laboratory. Each laboratory can therefore adapt the assays and utilize different products and protocols, which makes it impossible to develop a standardized set of performance and quality characteristics. As a result, each laboratory must determine these characteristics based on use in the individual laboratory.

*Provide details such as collection records, dates, and data limitations on posted and disseminated mosquito distribution maps to better inform mosquito control experts and the general public.*

HHS concurs with GAO's recommendation and efforts are underway to implement it. In the United States, surveillance for *Aedes aegypti* and *Aedes albopictus* mosquitoes was neither systematically nor routinely completed in recent decades. As a result, when the Zika virus outbreak began in the Americas, health departments and vector control districts in the United States did not have a good understanding of where *Ae. aegypti* and *Ae. albopictus* mosquitoes were found at a local or state level.

In early 2016, CDC undertook a rapid review of available data on *Aedes* distribution throughout the United States to provide an informed and timely estimate of the potential range of *Ae. aegypti* and *Ae. albopictus* given the growing concerns related to Zika and link to microcephaly in infants. In addition to publishing the maps that identified the estimated range of the mosquitoes, CDC conducted outreach to state and local partners and other stakeholders to explain the methodology as well as the intended uses of the maps. In these efforts, CDC's primary objectives were to provide clear, accurate and timely information about the potential range of *Aedes* distribution to the public.

In the spring and fall of 2016, CDC conducted surveys to record where these mosquitoes, capable of spreading chikungunya, dengue, and Zika viruses, had been collected from 1995 to 2016. In addition, additional intensified mosquito surveillance across the Southern United States in the summer of 2016 related to the Zika response indicates a substantial increase in the number of counties with records of the mosquitoes. This additional information will help improve the quality of data that is used to develop estimated potential range of these

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mosquitoes. CDC will refine estimated distribution maps when new data warrant changes, and will continue to improve how it communicates data sources and methodology, dates and data limitations on the CDC website and in any outreach to state and local organizations and the general public.

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# Appendix IV: Zika Virus Case Definitions for National Notifiable Disease Reporting

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The following are summarized descriptions of criteria and Zika case classifications that were effective in June 2016, which updated interim definitions published in February 2016.<sup>1</sup>

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## Criteria for a Zika case

Criteria for laboratory evidence of recent Zika virus infection:

- culture of Zika virus from blood, body fluid, or tissue; **OR**
- detection of Zika virus antigen or viral ribonucleic acid (RNA); **OR**
- positive Zika virus immunoglobulin M (IgM) antibody test **with** positive Zika virus neutralizing antibody titers and negative neutralizing antibody titers against dengue or other flaviviruses<sup>2</sup> regularly found to the region where exposure occurred.

Criteria for laboratory evidence of recent flavivirus infection that is possibly Zika virus:

- positive Zika virus IgM antibody test **with** positive neutralizing antibody titers against Zika virus and dengue virus or other flaviviruses regularly found to the region where exposure occurred.
- positive Zika virus IgM antibody test **AND** negative dengue virus IgM antibody test with no neutralizing antibody testing performed.

Criteria for establishing an epidemiologic linkage:

- resides in or recent travel to an area with known Zika virus transmission; **OR**
- sexual contact with a confirmed or probable case within the infection transmission risk window of Zika virus infection or person with recent travel to an area with known Zika virus transmission; **OR**
- receipt of blood or blood products within 30 days of symptom onset; **OR**
- organ or tissue transplant recipient within 30 days of symptom onset; **OR**
- association in time and place with a confirmed or probable case; **OR**

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<sup>1</sup>See <https://www.cdc.gov/nndss/conditions/zika/case-definition/2016/06/> (accessed March 27, 2017) for more details on these criteria and definitions, such as the specific types of specimens used for laboratory criteria.

<sup>2</sup>Flaviviruses are positive, single-stranded, enveloped RNA viruses found in arthropods (primarily ticks and mosquitoes).

**Appendix IV: Zika Virus Case Definitions for National Notifiable Disease Reporting**

- likely vector exposure in an area with suitable seasonal and ecological conditions for potential local vector-borne transmission.

**Table 5: Non-Congenital Zika virus case classifications and definitions for reporting to the national notifiable disease reporting system**

<b>Case classification<sup>a</sup></b>	<b>Definition</b>
Zika virus disease	<p>Clinical criteria:            A person with one or more of the following not explained by another cause:            Clinically compatible illness that includes                acute onset of fever (measured or reported), OR                certain type of rash, OR                joint pain, OR                conjunctivitis            Complication of pregnancy                fetal loss, OR                fetus or neonate with congenital microcephaly or specified other abnormalities            Guillain-Barré syndrome or other neurological symptoms</p>
Confirmed case	<p>Meets clinical criteria for non-congenital disease; AND            Has specified laboratory evidence of recent Zika virus infection</p>
Probable case	<p>Meets specified clinical criteria; AND            Has an epidemiologic linkage; AND            Has specified laboratory evidence of recent Zika virus or flavivirus infection</p>
Zika virus infection	
Confirmed case	<p>A person who does not meet specified clinical criteria; AND            Has specified laboratory evidence of recent Zika virus infection</p>
Probable case	<p>A person who does not meet specified clinical criteria; BUT            Has an epidemiologic linkage; AND            Has specified laboratory evidence of recent Zika virus infection</p>

Source: CSTE and CDC established Zika Virus Disease and Zika Virus Infection 2016 Case Definitions, Approved June 2016. CSTE approved position statement 16-ID-01 in June 2016, which modified the previous February 2016 interim case definitions. I GAO-17-445

<sup>a</sup>There are also specific definitions for these case classifications for newborn infants, referred to as "congenital" cases. See <https://www.cdc.gov/nndss/conditions/zika/case-definition/2016/06/> (accessed March 27, 2017) for these definitions and for more details for the definitions in the table.

# Appendix V: Performance Characteristics Information Presented in EUA Molecular Diagnostic Tests Labels for Zika Virus

**Table 6: Confirmed Limits of Detection (LOD) Results Using the Food and Drug Administration (FDA) Reference Materials As Reported on Product Labels**

Diagnostic Test and Manufacturer	Sample type	S1	S2
Zika Virus Real-time RT-PCR: Viracor-IBT Laboratories, Inc.	Plasma	1000	500
	Urine	1000	500
VERSANT <sup>®</sup> Zika RNA 1.0 Assay (kPCR) Kit: Siemens Healthcare Diagnostics Inc.	Serum	1000	5000
	Urine	3000	5000
xMAP <sup>®</sup> MultiFlex <sup>™</sup> Zika RNA Assay: Luminex <sup>®</sup> Luminex Corporation	Serum	3000	5000
	Urine	3330	5000
Sentosa <sup>®</sup> SA ZIKV RT-PCR Test (4x24): Vela Operations Singapore Pte Ltd	Serum	30000	15000
	Urine	10000	5000
Zika Virus Detection by RT-PCR: ARUP Laboratories	Plasma	3000	1650
	Urine	3300	4500
RealTime ZIKA: Abbott	Serum	1000	500
	Urine	300	500
Molecular Diagnostics Zika ELITE MGB <sup>®</sup> Kit U.S.: ELITechGroup Inc.	Plasma	3300	5560
Zika Virus RNA Qualitative Real-Time RT-PCR: Focus Diagnostics, Inc.	Serum	1000	500
	Urine	1000	1000
Aptima <sup>®</sup> Zika Virus Assay: Hologic, Inc.	Plasma	100	150
	Processed urine	300	150
Trioplex Real-time RT-PCR Assay: Centers for Disease Control and Prevention	Serum	3300	1670
	Urine	1000	1670
RealStar <sup>®</sup> Zika Virus RT-PCR Kit U.S.: altona Diagnostics GmbH	Serum	3162	5000
	Urine	3162	1581, 5000 <sup>a</sup>
Gene-RADAR <sup>®</sup> Zika Virus Test: Nanobiosym Diagnostics, Inc.	Serum	3333	5000

Source: GAO analysis based on product labels. | GAO-17-445

Note: S1 is concentrated stock 1 (FSS13025: Cambodia, 2010 provided by UTMB. GenBank#JN860885)

S2 is concentrated stock 2 (PRAVABC59: Puerto Rico, 2015 provided by CDC. GenBank#KU501215)

The table lists currently authorized molecular test EUA for Zika virus as of April 12, 2017. On March 13, 2017, FDA "revoked the EUA for emergency use" of one Zika virus test because the company requested the test be withdrawn from authorization due to technical performance and business considerations.

<sup>a</sup>1581 and 5000 were reported as point values which differed because two different extraction methods were used.

**Appendix V: Performance Characteristics  
Information Presented in EUA Molecular  
Diagnostic Tests Labels for Zika Virus**

**Table 7: Value Ranges for Limit of Detection of Zika Virus in Plasma, Serum, and Urine in Selected Emergency Use Authorized Diagnostic Tests**

Diagnostic test	Plasma	Serum	Urine
Aptima Zika Virus Assay: Hologic, Inc.	5.9 copies/mL - 13.4 copies/mL <sup>a</sup>	n/a	n/a
RealStar <sup>®</sup> Zika Virus RT-PCR Kit U.S.: altona Diagnostics GmbH	251.62 geq/mL	251.62 geq/mL	79.57 geq/mL
Triplex Real-time RT-PCR Assay <sup>d</sup> : Centers for Disease Control	n/a	1.51 x 10 <sup>4</sup> (GCE/mL) - 3.11 x 10 <sup>4</sup> (GCE/mL) <sup>b</sup>	1.79 x 10 <sup>4</sup> (GCE/mL) - 4.20 x 10 <sup>4</sup> (GCE/mL) <sup>b</sup>
VERSANT <sup>®</sup> Zika RNA 1.0 Assay (kPCR) Kit: Siemens Healthcare Diagnostics Inc.	721 copies/mL or 0.05 TCID <sub>50</sub> /mL	721 copies/mL or 0.05 TCID <sub>50</sub> /mL	721 copies/mL or 0.05 TCID <sub>50</sub> /mL
Zika Virus RNA Qualitative Real-Time RT-PCR: Focus Diagnostics, Inc.	n/a	250 RNA copies/mL	n/a
Zika Virus Real-time RT-PCR: Viracor-IBT Laboratories, Inc.	97 copies/mL	n/a	98 copies/mL
xMAP <sup>®</sup> MultiFLEX <sup>™</sup> Zika RNA Assay: Luminex Corporation	687 copies/mL	687 copies/mL	687 copies/mL
Zika Virus Detection by RT- PCR: ARUP Laboratories	160 copies/mL	160 copies/mL	160 copies/mL
Sentosa <sup>®</sup> SA ZIKV RT-PCR Test (4x24): Vela Operations Singapore Pte Ltd	3x10 <sup>3</sup> copies/mL - 6x10 <sup>3</sup> copies/mL <sup>c</sup>	3x10 <sup>3</sup> copies/mL - 6x10 <sup>3</sup> copies/mL <sup>c</sup>	3x10 <sup>3</sup> copies/mL - 6x10 <sup>3</sup> copies/mL <sup>c</sup>
RealTime ZIKV: Abbott	40 copies/mL	30 copies/mL	40 copies/mL
Molecular Diagnostics Zika ELITe MGB <sup>®</sup> Kit U.S.: ELITechGroup Inc.	270 copies/mL	n/a	n/a
Gene-RADAR <sup>®</sup> Zika Virus Test: Nanobiosym Diagnostics, Inc.	n/a	200 PFU/mL	n/a

Source: GAO analysis based on product labels. | GAO-17-445

Note: n/a means that the test is not authorized for the specimen type listed (serum, plasma, or urine) and therefore the LOD is not listed in the product label. The table lists currently authorized molecular test EUA for Zika virus as of April 12, 2017. On March 13, 2017, FDA "revoked the EUA for emergency use" of one Zika virus test because the company requested the test be withdrawn from authorization due to technical performance and business considerations.

<sup>a</sup>Two different LOD were listed for plasma based on Brazilian donor plasma 2015 and *in vitro* transcript.

<sup>b</sup>Range based on four different LOD listed for different extraction methods.

<sup>c</sup>LOD was determined for two different Zika strains (MR-766 and PRVABC59).

<sup>d</sup>CDC Triplex assay is also approved for cerebrospinal fluid and amniotic fluid, but the LOD is not listed in product label.

**Appendix V: Performance Characteristics  
Information Presented in EUA Molecular  
Diagnostic Tests Labels for Zika Virus**

**Table 8: Six of 12 Authorized Zika Molecular Diagnostic Test Labels That Did Not List the Comparator Assay for Clinical Performance**

<b>Reference assay and Manufacturer</b>	<b>Comparator assay listed<sup>a</sup></b>	<b>Comparator assay type<sup>b</sup></b>	<b>Comparator assay<sup>d</sup></b>
Zika Virus RNA Qualitative Real-Time RT-PCR: Focus Diagnostics , Inc.	Yes	EUA	Triplex Real-time RT-PCR Assay: Centers for Disease Control
	Yes	LDT	Lanciotti Test <sup>c</sup>
Aptima <sup>®</sup> Zika Virus Assay: Hologic, Inc.	Yes	EUA	Triplex Real-time RT-PCR Assay: Centers for Disease Control
Zika Virus Real-time RT-PCR: Viracor-IBT Laboratories, Inc.	No	EUA	n/a
VERSANT <sup>®</sup> Zika RNA 1.0 Assay (kPCR) Kit: Siemens Healthcare Diagnostics Inc.	Yes	LDT	Lanciotti Test <sup>c</sup>
xMAP <sup>®</sup> MultiFlex™ Zika RNA Assay: Luminex Corporation	No	EUA	n/a
Sentosa <sup>®</sup> SA ZIKV RT-PCR Test (4x24): Vela Operations Singapore Pte Ltd	Yes	EUA	RealStar <sup>®</sup> Zika Virus RT-PCR Kit U.S.: altona Diagnostics
Zika Virus Detection by RT-PCR: ARUP Laboratories	No	EUA	n/a
Abbott RealTime ZIKA	No	EUA	n/a
Molecular Diagnostics Zika ELITE MGB <sup>®</sup> Kit U.S.: ELITechGroup Inc.	Yes	EUA	LightMix <sup>®</sup> Zika rRT-PCR Test: Roche <sup>e</sup>
	No	LDT	n/a
Triplex Real-time RT-PCR Assay: Centers for Disease Control	No	In-House Assay	n/a
RealStar <sup>®</sup> Zika Virus RT-PCR Kit U.S.: altona Diagnostics GmbH	Yes	LDT	Lanciotti Test <sup>c</sup>
Gene-RADAR <sup>®</sup> Zika Virus Test: Nanobiosym Diagnostics, Inc.	No	EUA	n/a

Source: GAO analysis based on product labels. | GAO-17-445

Note: The table lists currently authorized molecular test EUA for Zika virus as of April 12, 2017. One Zika virus EUA has been revoked because the company requested the test be withdrawn from authorization due to technical performance and business considerations.

<sup>a</sup>6 of 12 labels did not list the comparator assay for clinical specimens. Note that the Molecular Diagnostics Zika ELITE MGB<sup>®</sup> Kit U.S.: ELITechGroup Inc. has one of the comparator assays listed and one that is not so it is included in the labels that listed comparator assays.

<sup>b</sup>Comparator type is categorized as EUA=emergency use authorized; LDT=laboratory developed test; or an in-house assay.

<sup>c</sup>Performance of the Zika Virus RNA Qualitative Real-Time RT-PCR test was also referenced and reviewed from the publication in Robert S. Lanciotti and others, "Genetic and Serologic Properties of Zika Virus Associated with an Epidemic, Yap State, Micronesia, 2007," *Emerging Infectious Diseases*, vol. 14 (2008): 1232–1239.

<sup>d</sup>EUA Diagnostic Tests that do not have a comparator assay listed would not have a name listed and therefore are listed as "n/a."

<sup>e</sup>The LightMix<sup>®</sup> Zika rRT-PCR Test: Roche is no longer authorized as of March 13, 2017.

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# Appendix VI: Issues with Mosquito Control Pesticide Regulation

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In discussion with mosquito control entities, we heard that certain federal regulations related to pesticide applications may create additional issues for mosquito control. Pesticide use for mosquito control, among other uses, is regulated by the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA),<sup>1</sup> under which vendors register pesticides for sale or distribution and pesticide users are required to follow the labeling for the pesticide application.<sup>2</sup> In addition to using products that have been registered under FIFRA, mosquito control entities must obtain a permit to spray pesticides on or near waters of the United States under the Clean Water Act.<sup>3</sup> Some mosquito control entity officials we spoke with told us the National Pollution Discharge Elimination System (NPDES) permit process has led to an increase in ongoing administrative burdens, such as reporting requirements, with one stating that their burden has increased from 1 hour of daily paperwork to 6 hours.<sup>4</sup>

Mosquito control officials we interviewed told us that some mosquito control entities have discontinued their programs, at least partly because of additional reporting requirements under NPDES permitting. However, an American Mosquito Control Association official told us that while they had a number of second-hand reports, they could not specify actual instances of entities ceasing operations because of NPDES costs. One

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<sup>1</sup>7 U.S.C. § 136 *et. seq.*

<sup>2</sup>The Environmental Protection Agency (EPA) regulates the use of pesticides. EPA officials told us that one of their major challenges is communicating their role to the U.S. public. EPA officials told us the EPA role is to evaluate pesticides and their uses. EPA officials told us that they review and analyze data submitted by pesticide manufacturers for safety approval. EPA does not (1) oversee or perform mosquito control, (2) design or create pesticides, or (3) provide guidance on use of specific pesticides because of factors such as pesticide resistance.

<sup>3</sup>The Clean Water Act prohibits the discharge of pollutants into waters of the United States from point sources unless EPA or a state issues a National Pollutant Discharge Elimination System (NPDES) permit for the discharge. 33 U.S.C. § 1342. EPA issued a final rule in 2006 excluding FIFRA-registered pesticides from the NPDES permitting requirements. 71 Fed. Reg. 68,483 (Nov. 27, 2006). In 2009, the 6<sup>th</sup> Circuit Court of Appeals vacated EPA's final rule and all persons discharging chemical pesticides that leave a residue or biological pesticides into waters of the U.S. must now obtain a NPDES permit. *Nat'l Cotton Council of Am. V. United States EPA*, 553 F.3d 927 (Jan. 7, 2009).

<sup>4</sup>In 2011, EPA issued a final NPDES Pesticide General Permit (PGP) to alleviate some of the administrative burden associated with individual NPDES permitting on pesticide operators. Reissued in 2016, the PGP provides a mechanism for certain dischargers to comply with the Clean Water Act requirements for pesticides for the geographic area where EPA is the NPDES permitting authority. Most states have also developed PGPs for pesticide discharges into waters in their states.

mosquito control official told us that NPDES permitting burdens will largely affect smaller mosquito control entities that may not be as well funded, many of which shut down and have not been replaced with another entity.<sup>5</sup> This official added that the entities shut partially because of the economic downturn and that NPDES paperwork burden was a possible, but not exclusive, cause. A mosquito control professional told us that his program discontinued applying pesticides partly as a result of NPDES permitting, but since the program still supplies pesticides, they know that the use of pesticides has increased.<sup>6</sup> This professional questioned the benefit of NPDES permits if pesticide applicators react by taking actions that result in the use of more pesticides. The American Mosquito Control Association stated that NPDES permits duplicate FIFRA processes, create new avenues for lawsuits, and have no substantive or foreseeable environmental benefit.<sup>7</sup>

A mosquito control official expressed support for NPDES permitting, because following NPDES permitting guidelines allowed his program to minimize adulticide discharges as a first response and to develop a more desirable IVM plan. From 2012 to 2016, this entity was able to reduce adulticiding acres by more than 30 percent, despite an increase in citizen requests for service. However, another official stated that encouraging larvicide use or IVM can be done more effectively than through NPDES permitting, such as through federal funding of programs that implement best practices.

Environmental group representatives we spoke with agreed that documented evidence is scarce on the effects of NPDES permits on pesticide levels in water. However, environmental group representatives

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<sup>5</sup>According to EPA, there is no de minimus exemption in the CWA. All mosquito control districts or similar pest control districts need an NPDES permit to discharge biological pesticides and chemical pesticides that leave a residue to waters of the U.S. However, EPA and most states, in their NPDES permits, provide for automatic coverage under their permits if pesticide applicators do not exceed certain annual treatment area thresholds.

<sup>6</sup>According to EPA, it is difficult to make any definitive conclusions regarding the increase or reduction of pesticide use as a result of NPDES permits. This is because the prevalence of mosquitoes and the need for pesticide use varies due to several factors such as the amount of rainfall, temperature and other weather variables annually. An NPDES permit neither prohibits nor encourages the use of pesticides. An NPDES permit is only required when pesticides are selected as the control method and their application would result in a discharge to waters of the U.S.

<sup>7</sup>EPA officials said they were aware of one ongoing lawsuit related to use of pesticides under a NPDES permit.

told us of benefits to the permit process, including (1) encouraging nonchemical means of control, (2) establishing a limit on the amount of pesticides in specific bodies of water, and (3) enabling the monitoring of pesticide use. Representatives from one group told us that the Clean Water Act fills a regulatory gap that FIFRA does not address. Representatives from another group stated that the permitting application is simple.

Further, an environmental group representative told us NPDES notification and reporting requirements allow the public to be aware of what is being sprayed and how much. One representative told us her office received calls from residents wondering what was being sprayed and saying they are not aware of requirements regarding who notifies the public about spraying.

EPA officials told us that they have not documented evidence that (1) pesticide use has decreased or (2) water quality has changed, in response to NPDES permits for FIFRA-compliant pesticide application. However, an EPA notice states that the cost of compliance with NPDES permits is minimal.<sup>8</sup> Further, EPA documentation states that EPA disagrees that FIFRA and NPDES requirements are duplicative. According to this documentation, NPDES permits minimize discharges of pesticides to waters of the United States beyond FIFRA requirements, among other things.

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<sup>8</sup>Cost analysis EPA presented as part of the 2016 Reissuance for the NPDES Pesticide General Permit was restricted to the areas of EPA permitting authority, including Idaho, Massachusetts, New Hampshire, New Mexico, the District of Columbia, and other federal and Native American territories. Therefore, the results of this analysis do not apply to the remaining states, except for federal and Native American territories within them.

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# Appendix VII: Related GAO Products

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Biodefense: The Nation Faces Multiple Challenges in Building and Maintaining Biodefense and Biosurveillance. [GAO-16-547T](#). Washington, D.C., April 14, 2016.

Emerging Infectious Diseases: Preliminary Observations on the Zika Virus Outbreak. [GAO-16-470T](#). Washington, D.C., March 2, 2016

Biosurveillance: Ongoing Challenges and Future Considerations for DHS Biosurveillance Efforts. [GAO-16-413T](#). Washington, D.C., February 11, 2016.

Air Travel and Communicable Diseases: Comprehensive Federal Plan Needed for U.S. Aviation System's Preparedness. [GAO-16-127](#). Washington, D.C., Dec 16, 2015.

Emerging Animal Diseases: Actions Needed to Better Position USDA to Address Future Risks. [GAO-16-132](#). Washington, D.C., December 15, 2015.

Biosurveillance: Additional Planning, Oversight, and Coordination Needed to Enhance National Capability. [GAO-15-664T](#). Washington, D.C., July 8, 2015.

Biological Defense: DOD Has Strengthened Coordination on Medical Countermeasures but Can Improve Its Process for Threat Prioritization. [GAO-14-442](#). Washington, D.C., May 15, 2014.

Influenza: Progress Made in Responding to Seasonal and Pandemic Outbreaks. [GAO-13-374T](#). Washington, D.C., February 13, 2013.

Biosurveillance: Observations on BioWatch Generation-3 and Other Federal Efforts. [GAO-12-994T](#). Washington, D.C., September 13, 2012.

Biosurveillance: Nonfederal Capabilities Should Be Considered in Creating a National Biosurveillance Strategy. [GAO-12-55](#). Washington, D.C., October 31, 2011.

National Preparedness: Improvements Needed for Acquiring Medical Countermeasures to Threats from Terrorism and Other Sources. [GAO-12-121](#). Washington, D.C., October 26, 2011.

Influenza Pandemic: Lessons from the H1N1 Pandemic Should Be Incorporated into Future Planning. [GAO-11-632](#). Washington, D.C., June 27, 2011.

Influenza Vaccine: Federal Investments in Alternative Technologies and Challenges to Development and Licensure. [GAO-11-435](#). Washington, D.C., June 27, 2011.

Public Health Preparedness: Developing and Acquiring Medical Countermeasures Against Chemical, Biological, Radiological, and Nuclear Agents. [GAO-11-567T](#). Washington, D.C., April 13, 2011.

Biosurveillance: Efforts to Develop a National Biosurveillance Capability Need a National Strategy and a Designated Leader. [GAO-10-645](#). Washington, D.C., June 30, 2010.

Influenza Pandemic: Sustaining Focus on the Nation's Planning and Preparedness Efforts. [GAO-09-334](#). Washington, D.C., February 2009.

Influenza Pandemic: Applying Lessons Learned from the 2004-05 Influenza Vaccine Shortage. [GAO-06-221T](#). Washington, D.C., November 4, 2005.

West Nile Virus Outbreak: Lessons for Public Health Preparedness. [HEHS-00-180](#). Washington, D.C., September 11, 2000.

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# Appendix VIII: GAO Contacts and Staff Acknowledgments

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## GAO Contact

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