



**A Complex Virus,  
A Coordinated Response:**  
**PUBLIC HEALTH LABORATORIES BATTLE ZIKA**



The Association of Public Health Laboratories (APHL) works to strengthen laboratories serving the public's health in the United States and globally. A national nonprofit, the organization represents state and local governmental health laboratories in the United States. These members, known as public health laboratories, monitor and detect health threats to protect health and safety.

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## ACKNOWLEDGMENTS

Public health is a collaborative enterprise, especially as new, complex threats like Zika challenge our understanding of viruses, diagnostics, and prevention. Collaboration is also key when telling the story of a virus to the public we protect and the decision-makers who make this work possible.

In addition to the many participants (listed on page 81) who shared their invaluable insights and experiences for this book, we would like to thank a core team from APHL and CDC for their expert resources and guidance.

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**WARNING!**

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**UGANDA VIRUS RESEARCH**

**INSTITUTE LAND**

**DON'T TRESPASS**

## INTRODUCTION

In 2015–2016, the devastating effects of Zika made headlines throughout the world. Less well known are the behind-the-scenes efforts of U.S. public health laboratories to understand this previously obscure tropical virus and protect the public — especially pregnant women and babies.

APHL's book *A Complex Virus, A Coordinated Response: Public Health Laboratories Battle Zika* tells this story. It relates surprises like Zika's connection to birth defects and sexual transmission, both of which had never been seen with a mosquito-borne virus. It details labs' race against the clock to revive underfunded infrastructure, roll out tests, determine which tests to administer when, and collect and track surges of samples. And it goes inside unprecedented partnerships across the public health community for mosquito control, maternal health outreach, and beyond.

Read on to learn more about how the public health community responded to Zika — and strengthened its capabilities for the next emergency.

## CHAPTER 1:

# FROM OBSCURITY TO EMERGENCY



In **Puerto Rico**, the owner of an auto repair shop feels a headache coming on. He takes an aspirin and resumes work in the shop's backyard, where stacks of tires have collected water from a recent rain.




In **Miami**, a woman joins her friends after visiting family in Brazil. They pay no attention to the mosquitoes buzzing around their ankles. A few bugs are a small price to pay for living in a summer climate year-round.



A professor drives back after a full day of classes in **Juarez, Mexico**, excited to get home to his pregnant wife in **El Paso, Texas**. At the same time, an OB/GYN ends her day telling newlyweds that they're about to become parents. The couple is off to plan a "babymoon" in the **Caribbean** to celebrate.





Little did these people know how quickly their lives would change, and how they would soon share a connection with thousands of others around the world.

That connection:  
a virus called **Zika**

Meanwhile, public health lab staff from **Hawaii** to **New York** spend their days testing specimens for flu, foodborne illnesses, HIV, and more.



# A VIRUS GOES GLOBAL



*Aedes aegypti*

Zika was first discovered in 1947 when yellow fever researchers in Uganda's Zika Forest found the virus in a rhesus monkey. It took more than half a century for Zika to ascend on the global public health radar. As connections emerged in Brazil between the virus and serious birth defects, these birth defects raised questions for public health officials and concerns for pregnant women around the world.

**W**hat caused Zika's transformation from an obscure tropical virus into a global public health emergency?

Part of the answer is buzzing around our feet, sneaking through our screen doors, and laying eggs in pools of water as small as a bottle cap. It's a mosquito.

Zika is an arbovirus: a virus transmitted by mosquitoes, ticks, and other arthropods. The *Aedes* family of mosquitoes transmits Zika, as well as other diseases in the flavivirus family like dengue fever, yellow fever, and West Nile virus.

*Aedes* mosquitoes like to live among and feed upon people. And they need only small amounts of water to thrive. Give them a flower pot or an old tire with standing water, and they'll feel enough at home to lay their eggs.





**“If you go to the border, there are so many places where there are bridges, people continually going back and forth to work every day.”**

**— Grace Kubin**  
Director of Laboratory Services, Texas Department of State Health Services

Although *Aedes aegypti*, the mosquitoes behind most Zika cases, generally need temperatures warmer than 50 degrees Fahrenheit to survive, one “sibling,” *Aedes albopictus*, can have a higher tolerance for cold.

On average, these mosquitoes only venture the length of a few football fields in their lifetimes. Yet some of them traverse much greater distances. They travel through sewers or as stowaways in vehicles. *Aedes albopictus* is believed to have arrived in the United States via shipping containers. Furthermore, eggs can live in dry conditions for up to a year, which means they’re able to survive winters in basements and heated garages.



*Aedes albopictus*



## A Mobile Virus Spreads Across Our Modern World

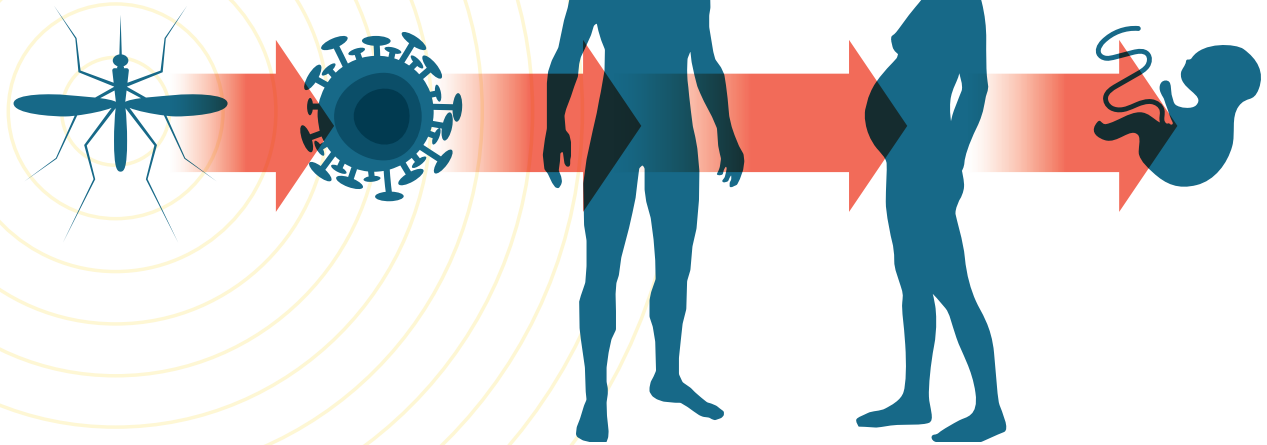
**P**lanes, trains, and automobiles have made the spread of Zika all too easy. As international travel becomes more affordable, it’s entirely possible for residents of Minnesota or Massachusetts to become victims — and carriers — of a tropical disease.

Thanks to the mobility of the virus, public health communicators for the Zika emergency soon found themselves in the travel advisory business, distributing posters, videos, flyers, ads, and tweets with tips about protection from the virus.

In Florida and Texas, travel advisories have been particularly important. These states are not only warm and mosquito-rich, they’re international gateways with highly mobile populations. For many people, travel to another country to visit family or conduct business happens monthly, weekly, or even more frequently. And every trip to a country with Zika brings the risk of transporting the virus back home.

**“This outbreak showed the importance of vector control.”**

**– A. Christian Whelen**  
Laboratory Director,  
Hawaii State Department of Health



### **Human carriers and local transmission**

In the United States, most Zika patients were infected during their travels elsewhere, rather than through local transmission. Local virus transmission happens when a mosquito becomes a carrier of the virus through biting an infected person, then spreads the virus by biting a second person.

Local transmission heightens concerns among public health officials because now the virus is spreading within a region through human and mosquito carriers.

### **Mild (or nonexistent) symptoms mask the threat**

If you're infected with the dengue virus, your fever can reach 104 degrees Fahrenheit, accompanied by pain behind your eyes and in your muscles, bones, and joints. Blood vessels can weaken and leak, and the number of platelets in your blood can drop, causing problems with your lungs, liver, and heart. The infection can be fatal.

Get chikungunya, and even though you'll recover, you might feel like you're dying. With chikungunya, patients' heads ache and joints swell. The pain can be disabling and last for months.

Zika, however, doesn't announce itself through its symptoms. People often confuse its mild fever with a common cold. Its headache and malaise can be misinterpreted as allergies.

### **A lack of symptoms helps the virus travel**

Doctors tell patients with Zika symptoms to take medicine to reduce the fever and pain, drink fluids, and get plenty of rest. But many people with Zika — some estimate up to 80 percent — don't experience any symptoms at all.

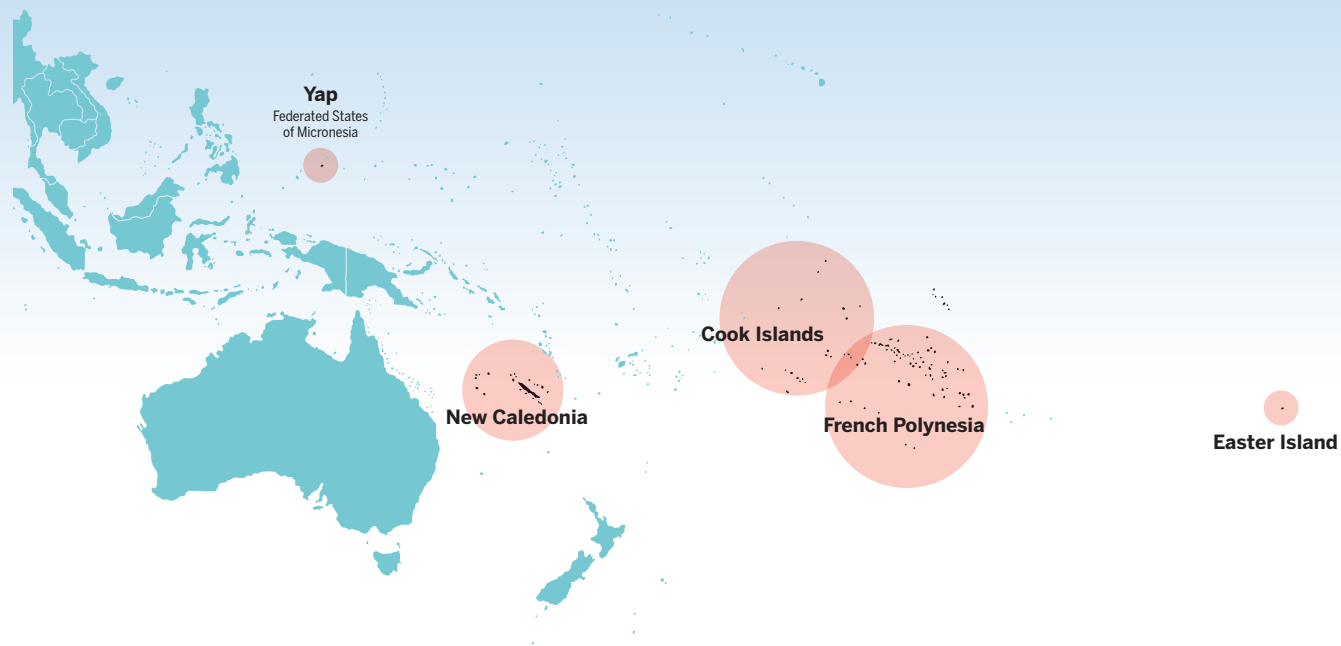
This lack of symptoms helps the virus spread undetected by people who don't realize they're sick.

Experts believe this is what happened with Zika during the mid-20th century. From 1952–1983, researchers detected Zika in Africa and Asia. Yet very few humans were actually diagnosed with the disease. In fact, the World Health Organization reports only 14 documented cases of Zika in humans before 2007 — the year the outbreaks began to emerge.

## An epidemic hits the South Pacific

Just over 100,000 people live in the Federated States of Micronesia, a nation of over 600 islands in the South Pacific. In 2007, residents of Micronesia's Island of Yap started experiencing rashes, pink eye, and joint pain. People on Yap had a history of dengue fever, which often gives one immunity to other flaviviruses, such as Zika. But the particular strain of flavivirus that arrived in 2007 was new to the island. Ultimately, an estimated 73 percent of those living on Yap became infected with Zika.

In 2013 and 2014, outbreaks hit the Cook Islands, Easter Island, New Caledonia, and French Polynesia.



Thousands of people were infected, and those infected included two mothers and their newborns, indicating that Zika might have transferred to the babies through

the placenta or during delivery. Troublingly, associations were beginning to emerge between Zika and severe neurological, autoimmune, and congenital complications.



*Island of Yap, part of the Federated States of Micronesia*

## A swift journey across the Americas

Half a world away in Brazil, public health officials understood the dangers of tropical diseases and the mosquitoes that carry them. Despite nationwide spraying of DDT in the 1950s, which all but eradicated *Aedes aegypti* in the country, these flavivirus vectors came back from neighboring countries. For 2016, Brazil's Ministry of Health reported over 1.4 million cases of dengue and over a quarter million cases of chikungunya.

Zika joined Brazil's roster of public health emergencies in 2015. From February through April, nearly 7,000 people in northeastern Brazil reported skin rash (another Zika symptom), and in July, laboratories confirmed cases in multiple states. In November, Brazil — preparing to host the 2016 Summer Olympics — declared a national public health emergency.

Zika reached the United States in December 2015, when the tropical island territory of Puerto Rico reported its first locally acquired case.

U.S. public health labs sprang into action.



## A Rapid Spread: First Reported Zika Cases by Country

<b>OCTOBER 2015</b>	Cabo Verde, Colombia
<b>NOVEMBER 2015</b>	El Salvador, Guatemala, Mexico, Paraguay, Suriname, Venezuela
<b>DECEMBER 2015</b>	French Guiana, Honduras, Martinique, Panama, United States (Puerto Rico)
<b>JANUARY 2016</b>	Barbados, Bolivia, Curacao, Dominican Republic, Ecuador, Guyana, Haiti, Jamaica, Nicaragua, Saint Martin, St. Croix
<b>FEBRUARY 2016</b>	Argentina, Aruba, Bonaire, Saint Vincent and the Grenadines, Samoa, Sint Maarten, Trinidad and Tobago

## Big concerns for the littlest patients

If mild fever and fatigue were Zika's only repercussions, the virus might have remained in the background of the public health world. But when health officials across the globe began to notice a correlation between increases in Zika cases and a rise in severe fetal brain defects, Zika became an urgent public health emergency.

Babies infected before birth with congenital Zika syndrome may experience decreased and damaged brain tissue, damage to the back of the eye, congenital deformities such as clubfoot, hypertonia (restricted body movement), and microcephaly, which is smaller-than-average head size for age and gender. Microcephaly has been linked with seizures, developmental delays in speech and mobility, and intellectual disabilities. It is a lifelong condition with no known cure.



“That was a pretty horrifying moment, when we realized that a mosquito-borne virus was creating such a devastating effect. No one ever thought a flavivirus would cause severe congenital defects.”

— Kirsten St. George

Chief of the Laboratory of Viral Diseases, Wadsworth Center,  
New York State Department of Health

1 in 10

According to the Centers for Disease Control and Prevention (CDC):



Pregnant women with Zika are **20 times more likely** to give birth to a baby with birth defects.

Morbidity and Mortality Weekly Report, March 2, 2017



**One in 10** Zika-infected pregnant women in 2016 had a fetus or baby with Zika-related birth defects.

Vital Signs, April 4, 2017



The lifetime cost of care for a child born with Zika-related birth defects could be over **\$10 million**.

Zika Summit Press Conference, April 1, 2016

\$10M

20 X



### More complications emerge

Researchers also discovered a link between Zika and Guillain-Barré Syndrome (GBS), a disease in which a patient's immune system attacks the nervous system. With GBS, muscles weaken, particularly in the arms and legs. In the most severe cases, GBS can affect the muscles that control breathing and even lead to paralysis.

Zika affects the eyes as well. In mild cases, usually in adults, Zika can cause conjunctivitis. And one-third of babies born with congenital Zika syndrome have eye disease in the form of inflammation of the optic nerve, retinal damage, or blindness.

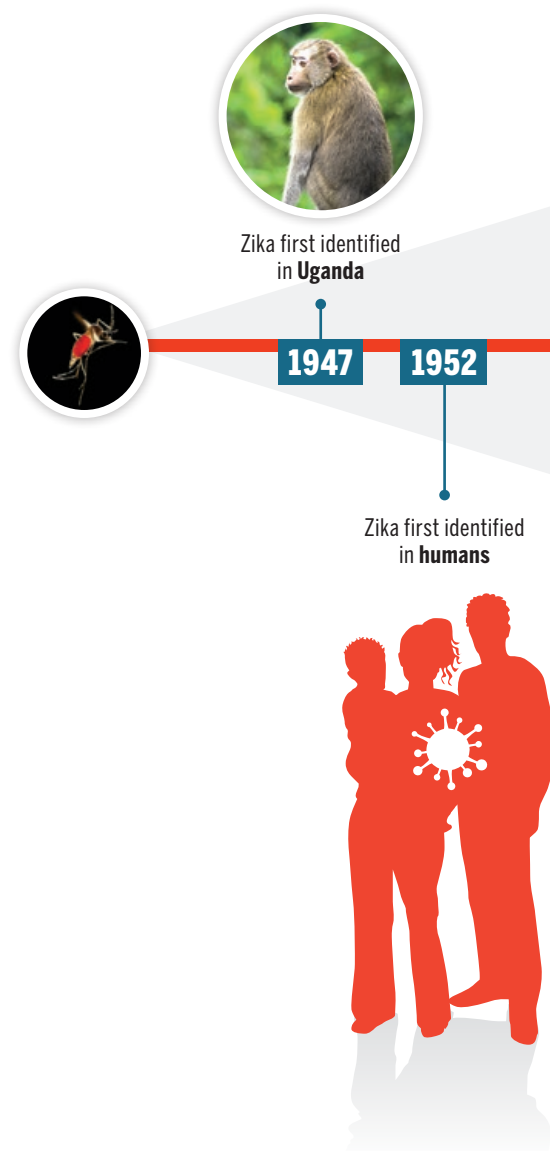
### New modes of transmission complicate the response

In February 2016, Dallas County Health and Human Services received CDC confirmation of Zika in the blood of a person with no recent travel history or risk. But this patient hadn't gotten the virus from a mosquito. Instead, the infection had come from a sexual partner who had recently returned from a country with Zika cases. By August, 15 sexually transmitted cases of Zika had been reported to CDC.

Zika's new identity as the first sexually transmitted arbovirus added new complications to the public health response, from identifying who might have this largely mild disease to educating people on how to protect themselves. Concerns emerged about other possible modes of transmission. Can you get Zika from a blood transfusion, breast milk, tears, or sweat?

Zika has become a virus with many unexpected angles. As scientists seek greater understanding, vaccines, and cures, another arm of the medical community has been operating on another front. Across the country, public health labs have been hard at work helping people find out if they've been infected. They've been working with limited resources, amid potentially devastating consequences, in a situation that keeps changing.

## ZIKA TIMELINE THE



# GLOBAL SPREAD OF ZIKA

**2007**

First Zika outbreak in **Micronesia**

**2013–2014**

Zika outbreaks in **French Polynesia, Cook Islands, Easter Island, New Caledonia**

**2015**

**FEB–APR 2015:** Nearly 7,000 cases of a disease with a mild skin rash are reported in northeastern **Brazil**

**MAY 2015:** **Brazil** confirms the first locally transmitted case of Zika in the Western Hemisphere

**OCT 2015:** **Brazil** reports an unusual increase in infants with microcephaly

**NOV 2015:** **Brazil** declares a public health emergency

**2016**

**DEC 2015:** **Puerto Rico** reports first case of local transmission

**JAN 2016:** Laboratory-confirmed Zika cases are reported in **American Samoa**

**JAN 15, 2016:** **Hawaii** reports first Zika case linked to microcephaly in the U.S.

**FEB 2, 2016:** **Texas** reports first sexually reported Zika case in the U.S.

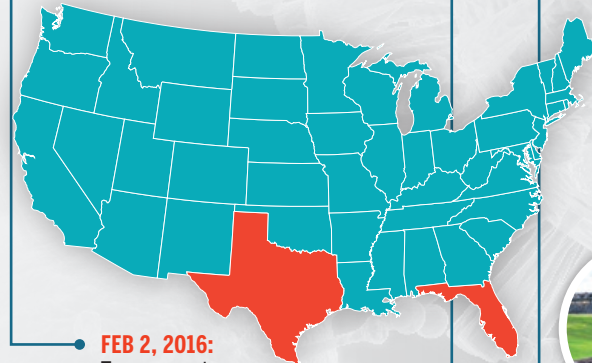
**JUL 29, 2016:** **Florida** reports first local Zika transmission on the U.S. mainland

**AUG 12, 2016:** HHS declares Zika public health emergency in **Puerto Rico**

**FEB 26, 2016:** **116 people** across **33 U.S. states** have shown evidence of Zika infection since January 1, 2015

**MAR 10, 2016:** 2 cases of Guillain-Barré Syndrome are linked to Zika in the **U.S.**

**JUN 16, 2016:** 3 babies are born with Zika-related microcephaly in the **U.S.**





# GLOSSARY

**Algorithm:** The set of steps and processes to follow to determine if someone has a disease like Zika

**Antibodies:** Protein molecules produced in an immune response to something foreign in the bloodstream, like the Zika virus

**Arbovirus:** A virus transmitted by mosquitoes, ticks, or other insects and spiders

**Assay:** An analysis to determine the presence and amount of a substance — e.g., Zika antibodies in blood

**Centers for Disease Control and Prevention (CDC):** Part of the U.S. Department of Health and Human Services, CDC is the nation's health protection agency, conducting research and providing information to protect Americans against health threats

**Epidemic:** A widespread occurrence of a disease in a particular region at a particular time

**Epidemiologist:** Someone who studies the incidence, distribution, and control of disease

**Local transmission:** When a person who has not traveled outside their local area is bitten by an infected mosquito in the community where they live and becomes infected

**Outbreak:** An increase, usually sudden, above the normal number of cases of a disease in a particular geographic area (usually in a smaller area and with fewer cases than in an epidemic)

**Public health laboratory:** A publicly funded laboratory that works with government agencies like CDC to monitor, detect, and respond to health threats such as infectious diseases, natural disasters, foodborne outbreaks, terrorist threats, and more

**Serum:** A clear, yellowish liquid in blood. Laboratorians separate it from clotted blood to detect disease-indicating antibodies

**Specimen:** Blood, tissue, urine, or other material from a human or animal used in the research, diagnosis, treatment, or prevention of a disease

**Surveillance:** The ongoing collection, analysis, and interpretation of data related to a disease or outbreak, along with timely sharing of this data to prevent and control the disease

**Vector:** Anything — a mosquito, parasite, even a particle of dust — that carries a disease from one organism to another

**Virus:** An infectious agent with a DNA or RNA core that replicates within the cells of a living plant or animal host

## CHAPTER 2:

# SCALING UP TESTING TO MEET AN URGENT DEMAND

**S**ome diagnostics have become remarkably straightforward over time. Take a home pregnancy test, for instance. If a woman suspects she's pregnant, she can buy a test at the drugstore or supermarket without a prescription and conduct the test in the comfort of her home. The result appears in minutes, with a high degree of certainty.

If a woman wants to see if she's been exposed to Zika, it's a different story. With little in the way of telltale symptoms to guide her, she may not think to get tested in the first place. And if she does — say she or her partner lives in or has recently traveled to an at-risk region — she'll soon

discover that Zika testing is neither at home nor do it yourself.

The woman must go to a medical facility, like a clinic or doctor's office. There she'll submit a sample of urine or blood that will be specially labeled and packaged for analysis at a testing facility approved by the requirements of the Clinical Laboratory Improvement Amendments (CLIA) of 1988.

Then she'll wait. Depending on her history of symptoms, mosquito exposure, and travel, several tests may be needed, and confirmatory testing for serology alone takes at least 10 days to complete. In some cases during peak testing demand in the United States, women waited several weeks to learn their Zika status.





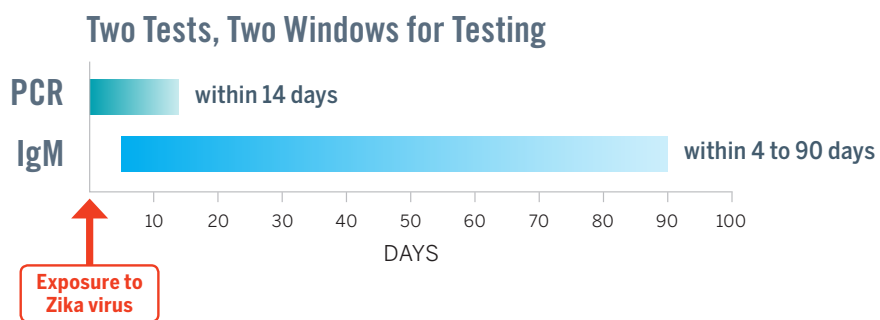
Dr. Jane Basile, a microbiologist at CDC's Division of Vector-Borne Diseases in Ft. Collins, Colorado, prepares reagents for use with the Zika MAC-ELISA test.

## Why is Zika testing so complicated?

Part of the answer lies in what current Zika tests can — and cannot — detect, and when a positive PCR result can be returned quickly to the sender. A negative PCR result or a patient who is asymptomatic requires IgM and possible subsequent PRNT testing, which is lengthy. As of early 2018, laboratorians use three types of tests for identifying Zika.

- The polymerase chain reaction (PCR) test:** Also known as a molecular test or a nucleic acid test (NAT), the PCR detects the DNA or RNA of a virus in a patient's blood or urine. It's faster and less labor-intensive to conduct, and therefore more frequently performed in labs. But Zika RNA can only be detected within a very narrow time window, usually two weeks from when a patient has been exposed to the virus or starts experiencing symptoms.
- The Zika virus immunoglobulin M (IgM):** This test detects IgM antibodies in the blood. Because a patient's immune response to Zika typically lasts about 90 days or longer, an IgM test can be performed during a broader time frame — usually between the fourth day to twelfth week after exposure.

However, the 90-day window only applies to a patient's first infection by a flavivirus. If a patient has previously been infected with dengue or other members of the flavivirus



family (which is the case for many people in tropical regions such as Puerto Rico), the resulting immunity might mean a lower level of Zika antibodies — and a significantly shorter window of detection. And when a previous flavivirus infection turns up in test results and muddies a diagnosis, this phenomenon is known as cross-reactivity.

- **The plaque reduction neutralization test (PRNT):** Laboratorians use the PRNT after an IgM test to help determine if antibodies resulted from a recent Zika infection or from cross-reactivity with dengue or another flavivirus. A PRNT involves the growth of virus cultures and was one of the reasons behind the long waiting periods that frustrated many during the Zika response.

“It’s a five- to seven-day test, very time- and labor-intensive,” said Julie Villanueva, part of the Zika Laboratory Task Force set up by the CDC’s Emergency Operations Center (EOC) during the Zika response. “The turnaround is not quick, and that’s very difficult for a pregnant woman who’s waiting for a test result.”

“You can’t speed up results for a bioassay,” said Michael Shaw with CDC’s Office of Infectious Diseases. “The virus is going to grow at its own rate.”

## The EOC: Swift, Coordinated Response to Catastrophic Threats

Since 2001, CDC’s EOC has been monitoring public health information, preparing for known (and unknown) events, and rallying experts to share information and make quick decisions when emergencies arise.

When public health briefings, field intelligence, or calls to its watch desk notify the center of a potential threat, the EOC activates.

With multiple lab task forces working through the internationally recognized

Incident Management System model for emergency response, the EOC:

- Deploys scientific experts
- Provides state and local public health departments with resources
- Monitors response activities
- Coordinates timely, reliable communications

To date, the EOC has responded to more than 60 public health threats, including cholera in Haiti, the 2009 H1N1 pandemic, hurricanes, foodborne outbreaks, and Zika.



Health officials monitor threats from the CDC Emergency Operations Center in Atlanta, Georgia.



## A Complex and Evolving Algorithm

**T**he testing algorithm for a disease guides health professionals on who should get tested, when, and what diagnostic tool (or tools) to use. Zika's many unusual aspects — its connection to neurological disorders and birth defects, its mild or nonexistent symptoms — make its testing algorithm complicated.

“Testing asymptomatic people was unheard of for a flavivirus,” said Lyle Petersen, who served as interim director of CDC’s Zika response.

To deliver tests and answers for the people most at risk, CDC labs, epidemiologists, policy specialists, communications teams, and other public health professionals collaborated on a Zika testing algorithm. “Everyone had an opinion on when, who, and why, plus difficult questions about timing and how to report the results,” said Edwin Ades, a member of the Zika Laboratory Task Force.

This guidance changed as CDC’s understanding of the virus evolved, especially with surprises such as sexual transmission. The diagram on page 23 shows an example of this guidance for September 17, 2017.



# A Rigorous Series of Tests for Pregnant Women at Risk

**WHOM to Test?**

Pregnant women reporting possible exposure during current pregnancy and symptoms of Zika virus disease

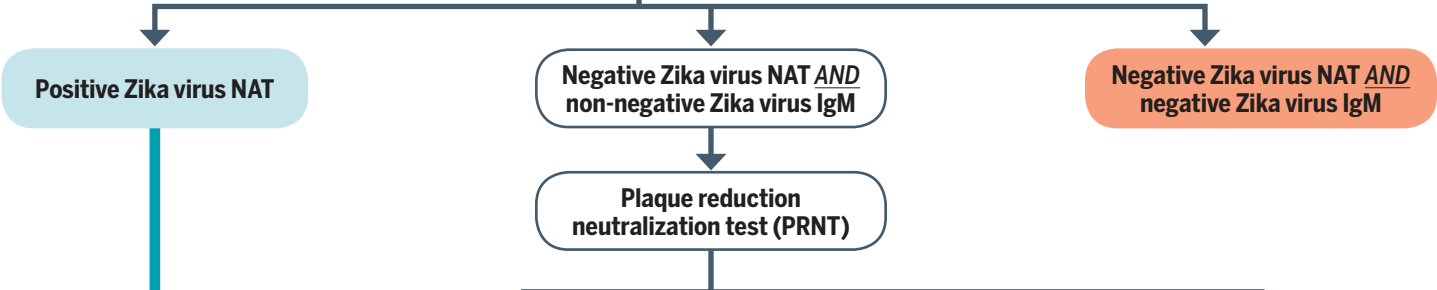
**WHEN to Test?**

Test as soon as possible; through **12 weeks** after symptom onset

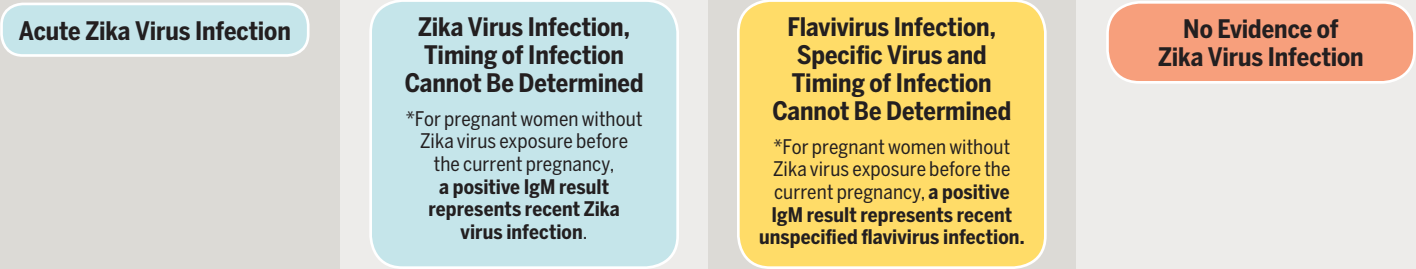
**WHICH Tests?**

Zika virus NAT (serum and urine) **AND** Zika virus IgM serology (serum)

**RESULTS and ADDITIONAL Tests**



**INTERPRETATION**



\*CDC Interim Guidance: Symptomatic Pregnant Women with Possible Zika Exposure, September 17, 2017

## A Multitasking Public Health Team

In Fort Collins, Colorado, staff with CDC's Division of Vector-Borne Diseases and arbovirus disease laboratories have been studying mosquito-borne viruses and flaviviruses for years and concurrently support emergency responses both in the United States and internationally. In fact, during the Zika response, the Fort Collins team was also fighting yellow fever outbreaks in Angola and the Democratic Republic of the Congo.



### Preparing for an outbreak

The Zika crisis that took the media and world by surprise had long been on CDC's radar. CDC had been tracking Zika for nearly a decade from its Atlanta headquarters and from its operations in Fort Collins and Puerto Rico.

"The occurrence of hundreds of cases of Zika on Micronesia's Island of Yap in 2007 was the harbinger when people realized that Zika could be a big outbreak disease," said Christopher Gregory, Arboviral Diseases Branch Chief of CDC's Division of Vector-Borne Diseases.

"Since we anticipated Zika coming to the Americas, we had prepared diagnostic tests for the virus long ago," said Petersen.

CDC had PCR and IgM tests and reagents. Laboratorians use reagents, which cause a chemical reaction, to detect the presence of one substance within another, such as virus antibodies in serum. Yet these diagnostics still needed to be authorized for use outside of CDC and rolled out to state and local public health laboratories to accommodate the incoming surge of samples.

The majority of labs in the United States were not prepared for an emergency like Zika. Labs had built up their testing infrastructure for the first West Nile virus outbreak in 1999. But funding cuts had

chipped away at budgets and resources since then. With competing priorities and limited resources, many labs had elected to cut back on staff and equipment for flavivirus and arbovirus testing, particularly the more complex IgM/serology tests.

This left labs with limited capacity to deliver test results to pregnant women, possible carriers, other infected individuals, and public health officials as evidence grew of Zika's connection to devastating birth defects.

CDC faced an urgent challenge.

Ades recalled the situation his team faced. "We knew we had labs that wanted to run this diagnostic test. We had to get that test up and running and get data to the FDA for Emergency Use Authorization. Then we needed to distribute the test so people could know their exposure."

### Resurrecting and rallying resources

Building testing capacity for Zika wasn't easy. For some viruses, like influenza, numerous tests have already been developed, validated, and approved for widespread use. In Zika's case, however, labs had only the diagnostics they had developed in-house for their internal operations, plus limited capacity to scale these diagnostics up for a surge of testing.

This capacity had once existed. During the West Nile virus emergency, labs had used a test similar to the IgM diagnostic ultimately authorized for Zika. But 15 years of funding cuts had decreased the number of assays, diminished staff expertise for conducting such a challenging diagnostic, and eroded relationships with the manufacturers that supply the vital reagents.

Faced with an urgent emergency, America's resourceful public health labs made the most of the resources they had. CDC's Dengue Branch in Puerto Rico shifted its focus to Zika. The Fort Collins office redirected employees from work on bacterial diseases and other arboviruses. CDC Atlanta pulled in staff from multiple divisions for initiatives such as the EOC's lab task force, which coordinates the rollout of tests, reagents, verification panels, and technical support to participating state laboratories during emergencies.

"It's a full-time job to be a member of a task force," said Wendi Kuhnert-Tallman, who co-led CDC's Zika lab task force.

Meanwhile, CDC's Division of State and Local Readiness convened organizations working at the state and local levels to ensure a consistent Zika response nationwide. These entities included the Association of State and Territorial Health Officials, the National Association of

County and City Health Officials, APHL, and the Council of State and Territorial Epidemiologists, plus groups in related areas such as mosquito control.

Such a rallying of forces was essential for CDC's complex and vital mission: Get authorized PCR and IgM diagnostics operational at labs across the country while handling the nation's early surge of samples.

"At the beginning of 2016, all of Zika testing was being done in Fort Collins," said Gregory. "At the same time we were trying to get other labs up and running so they could start testing for Zika, too."

### **Necessary steps to prove effectiveness**

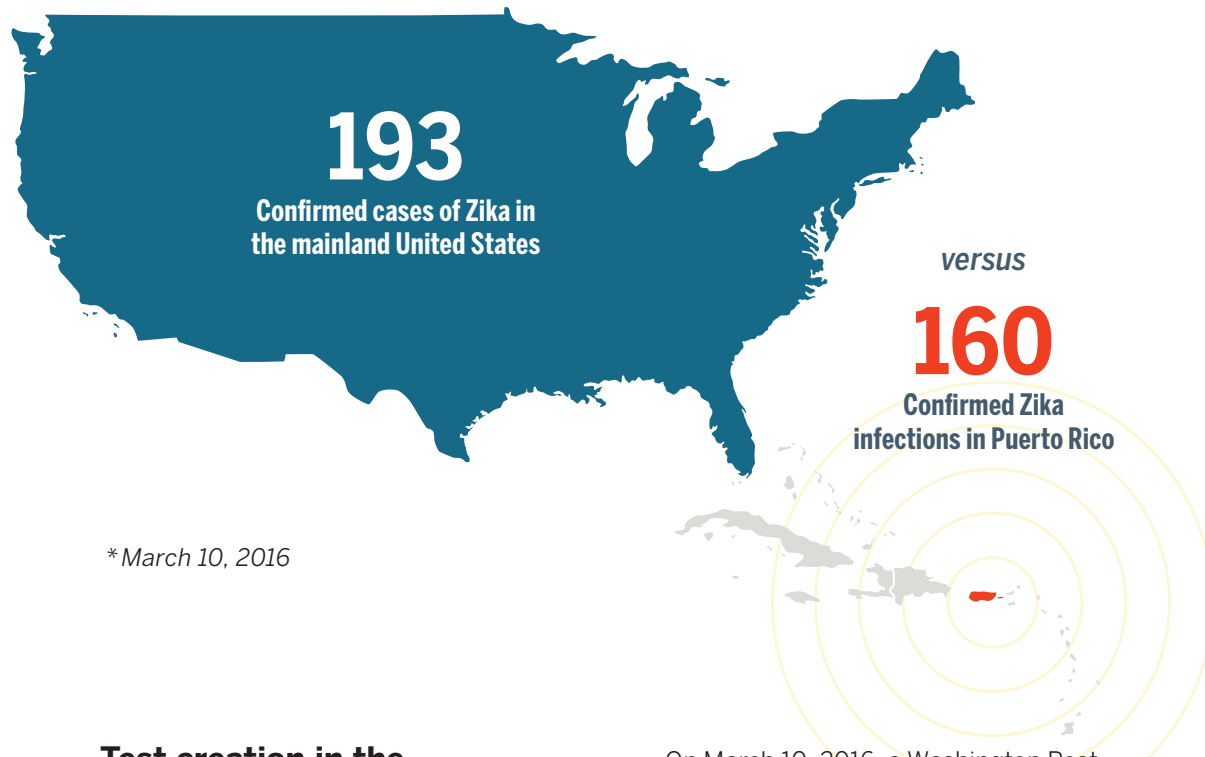
To get a homegrown test ready for widespread use, a lab needs samples — lots of them — to see how well the assay is working. That posed a problem. Zika in early 2016 was still a relatively rare tropical disease with comparatively few cases around the world. The scarcity of samples made test development challenging, as did Zika's cross-reactivity with other flaviviruses.

"You have to know how an assay works on someone with just Zika and nothing else," said Shaw, citing the challenge of testing samples from regions with a longtime history of dengue fever.

Once a test is validated — shown to do what it's designed to do — the test must be authorized for use by the FDA. Fortunately, the FDA had a mechanism, first used for public health during the H1N1 pandemic, for speeding the process along: Emergency Use Authorization (EUA).

EUA lets the FDA approve the emergency use of drugs, devices, and medical products (including diagnostics) that have not yet been approved, cleared, or licensed by the FDA or the off-label use of approved products in certain well-defined emergency situations. EUA balances the mission of protecting public safety against the need for quick response in an emergency. This authorization is not easy to get. Labs must demonstrate and document a test's clinical utility and its safety.

On February 26, 2016, HHS Secretary Sylvia Burwell determined that the Zika virus had significant potential to affect Americans' health and security and that these circumstances justified the emergency use of Zika diagnostics. In late February and mid-March, the FDA granted EUAs to two CDC tests that would prove pivotal in the Zika response: the Triplex Real-time RT-PCR and the Zika MAC-ELISA.



\*March 10, 2016

### Test creation in the heart of the crisis

The Trioplex Real-time RT-PCR assay, already under development before the U.S. public health emergency began, was developed at CDC’s laboratory in Puerto Rico in the mid-2010s due to a confluence of conditions. *Aedes aegypti* lives here in a hot, humid climate with poor mosquito control. Many houses lack screens. Residents often hold on to items in backyards, giving water a place to collect after rains and virus-carrying mosquitoes a place to breed.

On March 10, 2016, a Washington Post article reported roughly 160 confirmed Zika infections in Puerto Rico, compared with 193 confirmed cases in the entire mainland United States. From November 1, 2015, to October 20, 2016, Puerto Rico’s database included the largest number of laboratory-confirmed cases in the world, according to a CDC report.

These growing numbers were a major concern. Cruise ships frequented this popular tourist destination. People traveled back and forth from population centers like

New York City to visit family and friends, vacation, and conduct business. Now all these travelers were potentially putting themselves and their home communities at risk of Zika.

As the emergency unfolded, staff in Puerto Rico, joined by dozens of CDC colleagues from Fort Collins and Atlanta, were studying the situation in real time and making invaluable contributions. These included research into new methods of mosquito control, infection during pregnancy, infection in newborns, and the detection of Zika in semen.

During this time, CDC’s laboratorians in Puerto Rico developed the Trioplex, the first Zika PCR test to gain FDA authorization for use in diagnostic laboratories. The Trioplex accommodates the range of sample types: serum, whole blood, urine, and amniotic and cerebrospinal fluid. Its flexibility proved useful as many labs moved from blood to urine samples. The Trioplex is a versatile tool with the ability to simultaneously test for Zika, dengue fever, and chikungunya.


The Trioplex equipped labs in the United States and around the world with Zika testing capacity. Since the FDA issued its EUA on March 17, 2016, the Trioplex has been used in more than 100 countries.

## Puerto Rico: A Zika Bellwether

The tropical territory was at the epicenter of challenges, complications, and trends during the Zika response.

- **The testing surge:** Puerto Rico provided one of the first indications that demand for Zika testing would outstrip capacity. The small island reports roughly 30,000 births per year. Under the initial recommendations of one test per trimester for every pregnant woman living in an area of local transmission, this would add up to nearly a hundred thousand tests.
- **Doing more with less:** Up until August 2016, only two locations, the island's public health lab and CDC's Dengue Branch, handled all of the territory's IgM testing.
- **Cross-reactivity with other flaviviruses:** Because most of Puerto Rico's population has previously been exposed to dengue fever, serology tests for residents were difficult to interpret.
- **The impact of travel:** When New York, a state with a cooler climate and low risk of local transmission, started reporting high numbers for Zika testing, cases, and pregnancies, the large movement of people between the state and Puerto Rico emerged as a significant factor. This put travel, and travel advisories, on public health professionals' radar.





**“It was a huge effort to validate and get not one but *two* tests out, and manufacture tests for over a year.”**

**– Wendi Kuhnert-Tallman**

Associate Director for Laboratory Sciences, NCEZID, OID, CDC

### **The MAC-ELISA addresses another testing challenge**

The Zika virus doesn't stay for long in the human body, and this posed a big limitation for a PCR test such as the Trioplex. “Our best diagnostic tool had a limited life span in the human host,” said Ades.

“It became clear very quickly that the PCR wouldn't be sufficient,” said Shaw. “One of the biggest surprises with Zika is how long the virus persists, how long someone might be able to transmit it. Looking at antibody response was the next step.”

Enter the Zika MAC-ELISA, a test that approached Zika from the IgM perspective and opened the window of detection to up to 90 days after exposure or the onset of symptoms.

In May 2017, automation became available on the MAC-ELISA. Laboratorians who previously handled all samples manually, even at the peak of testing, were now able to load plates into the system as soon as they were ready, freeing up time for other tasks.

This new test came with several advantages. The MAC-ELISA integrated with lab information management systems (LIMS) and databases, as well as the barcoding systems used for sample tracking — vital when a testing algorithm involves multiple samples and tests for each patient. Such

integration helped reduce human error. For example, laboratorians now had early warning, thanks to data from the LIMS, if the wrong sample was being loaded into the system.

### A nationwide rollout as the emergency unfolds

Getting tests developed and authorized for widespread public health lab use was just part of the battle. “Then you have to scale it up, deliver it, and do it all under CLIA regulations,” said Ades.

CDC’s EOC kept the Zika response moving and coordinated. Through a highly regimented incident command structure and many in-person meetings, the EOC made sure labs, epidemiology, policy, and communications operated as an aligned, cohesive whole, from ramping up testing to communicating the evolving crisis.

“There were a lot of technical questions that needed to be answered quickly and accurately without a lot of data — requests from senators, congressmen, HHS,” said Villanueva.

Behind the scenes, state and local public health labs brought their homegrown PCR and IgM tests up for validation under CLIA guidelines and waited for FDA authorization of the Trioplex PCR and MAC-ELISA.

CDC refocused labs across its Atlanta campus to accommodate Zika testing demand. Subject matter experts trained laboratorians on PCR, serology, and PRNT testing specifically for the virus. “We basically doubled our capacity,” said Kuhnert-Tallman.

When tests became ready, CDC distributed them upon request to qualified laboratories in the Laboratory Response Network (LRN). Created in 1999 by APHL, CDC, and the FBI in response to bioterrorism, the LRN is an integrated network of domestic and international laboratories that responds to public health emergencies such as infectious diseases, natural disasters, environmental contamination, and chemical terrorism.

“We were fortunate to have the LRN there. We could roll tests out to the LRN labs fairly quickly,” said Petersen.

CDC worked through the LRN to support labs with proficiency panels (which show that a lab knows how to conduct a new test properly) and technical assistance, and dedicated an entire group to ensuring state and local readiness. Through its management of the Public Health Preparedness and Response Cooperative Agreement, CDC’s Division of State and Local Readiness made the LRN response possible, administering grants, delivering technical assistance, and more.

### CDC Laboratories Provide Confirmatory Testing and Surge Capacity for the Zika Virus

Laboratory	Number of Specimens Tested by RT-PCR	Number of Specimens Tested by Zika MAC-ELISA
CDC-Atlanta	3,464	2,827
CDC-Fort Collins	3,926	15,571
CDC-San Juan	45,136	48,015
Laboratory Response Network (LRN)	25,439	35,349

Updated January 2017

## DIAGNOSTICS MILESTONES

1986

CDC sets up a lab in **Puerto Rico** to fight **dengue fever**

2016

**FEB 26, 2016:**  
FDA grants EUA for CDC's **MAC-ELISA test**

**MAR 17, 2016:**  
FDA grants EUA for CDC's **"3 in 1" Trioplex test**

**APR 28, 2016:**  
**Quest Diagnostics' RT-PCR test** is the first commercial test to get FDA EUA approval

**“The first months were about EUA assay approval. Then we focused on surge labs. PCR testing was easiest to get up and running, then IgM, then PRNT.”**

— **Edwin Ades**

Member of the Zika Laboratory Task Force

### Commercial diagnostics augment capacity

Since the authorization of the Trioplex and MAC-ELISA for detection and diagnosis of the Zika virus, over a dozen more Zika tests developed by private sector companies and universities have received EUAs. The first commercial assay to receive such approval was the Zika Virus RNA Qualitative Real-Time RT-PCR test, developed by Focus Diagnostics (a business subsidiary of Quest Diagnostics at the time).

The test's protocol was similar to protocols Focus Diagnostics had developed and validated for an RT-PCR assay for chikungunya. Use of testing platforms for RNA isolation and RT-PCR, plus use of published, well-characterized primers and probes, enabled the project's completion in only two months.

“Now doctors can order the \$500 test through Quest, which says it can get results three to five days after it arrives,” NBC News reported on April 28, 2016, the day the FDA granted the test's EUA. “Quest has its own system of vans that pick up samples and get them to an airport for quick, refrigerated shipment.”

### Test refinement continues

The 2016 assays and testing algorithm guided thousands of people to a more informed understanding of their Zika exposure. Yet diagnoses weren't as definitive as such a catastrophic condition demanded, particularly for patients with previous dengue exposure.

To improve testing specificity, more Zika tests are in the pipeline. One example is a microsphere immunofluorescence assay, under development by a partnership between the University of Texas Medical Branch and the Wadsworth Center at the New York State Department of Health. It's designed to detect Zika in the blood for a longer time after infection and reduce false positives due to cross-reactivity with other flaviviruses.

As CDC and manufacturers developed, refined, and rolled out tests in 2016, public health labs worked hard in their role in the field: testing surges of samples for months on end in a high-stakes, constantly changing environment.





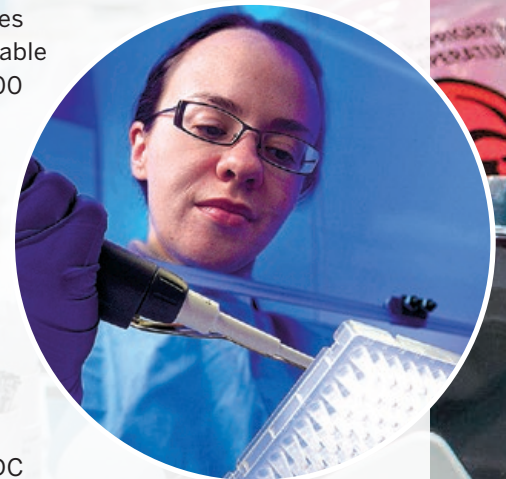
## CHAPTER 3:

# A SURGE OF SAMPLES, A YEAR OF SURPRISES

In 2016, CDC reported over 5,100 cases of Zika in America's 50 states and over 36,000 in U.S. territories. Public health laboratories nationwide contributed to this valuable knowledge by testing more than 60,000 samples of blood, urine, and other serums, guiding patients, health care professionals, and the public health community in vital decisions.

And Zika wasn't the only emergency in the pipeline at the time. A lab in today's multifaceted public health environment might be testing samples for foodborne outbreaks, influenza, rabid animals, opioids, measles, and more. In fact, in 2016, CDC was fighting four emergencies at once: Zika, Ebola, polio, and water contamination in Flint, Michigan.

In the words of Grace Kubin, who directs laboratory services at the Texas Department of State Health Services, "There's always something going on."



For public health labs across the nation, the Zika emergency turned business as usual upside down. Picture morning staff arriving to yet another stack of samples waiting to be examined, triaged, and entered into the system. Now imagine a midday announcement that complicates matters even more: Any pregnant woman, with or without symptoms or history of exposure, can request a free Zika test. The lab director rallies the team to consider staffing and supplies. How can they accommodate such a surge in addition to their existing responsibilities?

Throughout this hypothetical day, lab staff regularly leave vital testing activities on the “bench” (where the actual examination of a sample takes place) to email specimen providers about incomplete paperwork and field calls from health care providers about new and often confusing Zika tests. “My patient wants to know her results.” “What do you mean another test is needed?”

**“When this outbreak came to light with the potential effect on babies – it threw a whole loop to us. Now there’s a whole different side to this thing.”**

**–Andrew C. Cannons**

Tampa Laboratory Director, Florida Department of Health Bureau of Public Health Laboratories

Across America, public health laboratories rose to the occasion, working swiftly and tirelessly to test samples, relay results, and protect public health amid this mysterious and complex new threat.

Highlights follow from their efforts.

### **A “mild” virus becomes an emergency**

In 2015, lab professionals knew about Zika — but mainly as a rare tropical disease, one overshadowed by dengue, West Nile virus, yellow fever, and chikungunya in the roster of priorities.

“At that time, we didn’t see too many specimens we needed to test, mainly travelers from South America and the Caribbean,” said Andrew Cannons, director for the Florida Department of Health’s lab in Tampa.

At Hawaii’s state lab, which also supports American Samoa and the U.S. Pacific Islands, “We were supporting a major dengue outbreak response in Hawaii as we also prepared for the emerging Zika threat,” said Chris Whelen, administrator of Hawaii’s state labs.

And at the Wadsworth Center in New York, “We had been watching Zika move across the globe with interest,” said Kirsten St. George, Chief, Laboratory of Viral Diseases. “We were noticing how it sort of mimics some of the other viruses but is milder — or at least that’s what we thought.”

Then reports grew of babies born with devastating birth defects in Zika-infected areas or by women who’d recently traveled to these areas. This culminated with a February 10, 2016, study in the *New England Journal of Medicine*: “Zika Virus Associated with Microcephaly.”

It was the first time a mosquito-borne virus had been connected to birth defects. Pregnant women across the United States and their doctors grew alarmed.

“With the potential effect on babies, there was suddenly a whole different side to this thing,” said Cannons.

Labs in Zika hot spots rallied to respond.

## “From nothing to bam!”

Florida and New York each reported over 1,000 Zika cases in 2016 — surges in two very different states.

Florida, a popular tourist destination with a year-round subtropical climate, reported its first three travel-related cases in mid-January 2016. In February, laboratorians conducted about 100 to 200 tests a week with the PCR test and a similar number with serology/IgM testing.

By late July, two locally transmitted cases heightened concern. Now it wasn't just returning travelers passing on the virus. You could get Zika from a mosquito or human in your neighborhood.

Determining Zika's potential spread required a urosurvey, a process in which urine is collected and tested from people who live and work within a given radius of documented disease transmission. The Miami lab validated the Trioplex just in time to do the majority of urosurvey testing.

Through the end of the year, the Miami lab processed almost 6,000 tests, or 10 percent of the national total. “It went from nothing to bam!” according to Leah Gillis, director of the Miami lab.

Over a thousand miles north in New York, the climate is cooler, and mosquitoes, sprays, and warnings are not a year-round presence. But this international hub of travel, trade, and immigration sees people coming and

going from all around the world every day — including travelers from Zika hot spots like South America, the Caribbean, and Puerto Rico.

“People move around the country and world constantly,” said St. George. “Global movement is a huge factor in the spread of disease.”

The Wadsworth Center in Albany had Zika testing in place, thanks to its extensive work researching the virus. The center handled Zika testing for the state as New York City's lab ramped up its diagnostics. At one point, the New York City lab alone was receiving Zika-related specimens from over 50 patients per day.

“We went from zero cases per month to about 2,500 specimens at peak. It was a tremendous increase,” said St. George.

## Shifting and sharing expertise

Within labs, Zika testing represented a tremendous increase in workload — different tests for different categories of patients, multiple tests for many people, plus types of tests, like serology, that required special skillsets and licensing.

Bringing any new test into a lab is always a challenging process. Personnel must be trained on both the testing and the paperwork, and workflows need to be readjusted so that other testing activities don't suffer.





When Zika's connection to birth defects became clear, labs knew they needed to get the right people with the right skills and licensing credentials to the Zika bench ASAP.

CDC provided funding for staff and contractors and sent teams out to assist. Meanwhile, labs worked with the resources at their disposal. Florida's lab in Tampa, for instance, already had PCR testing up and validated. It transferred all of its dengue testing to the virology department to make room for Zika.

Cannons recalled that his team got creative in ramping up serology testing. A concurrent project in Florida was testing 1,500 chicken samples a week. The test in use was an arbovirus test with similarities to Zika testing. Unlike Zika testing, however, the diagnostic the lab was using for the poultry samples had no licensing requirements.

To increase lab capacity for Zika testing, Cannons explained, "We put CDC and non-licensed staff on the chicken bench and used licensed staff for Zika."

Texas also turned to colleagues from different specialties to beef up expertise. "We all could do PCR testing, but serology was a little different," said Kubin. For starters, serology testing involves Biosafety Level 2 and 3 practices, which cover everything from handling samples and equipment to maintaining the testing area. So Texas labs brought in a biothreat team to share their critical biosafety knowledge.

The Virginia Division of Consolidated Laboratory Services, which began its prolonged surge with over 200 travel-related samples, took similar measures.

“We did cross-training with bioterrorism staff and staff with experience in serological and PCR testing,” said LaToya Griffin-Thomas, who coordinates bioterrorism and special pathogens response. “We pulled in Biowatch staff, like we did in our Ebola response.”

Hawaii’s Lab Preparedness and Response Program (LPRP) tests for everything from water quality to outbreaks of communicable diseases like dengue fever. Dengue support was keeping it busy during the first three months of 2016.

LPRP accommodated for Zika testing with two microbiologists funded by the Public Health Emergency Preparedness Cooperative Agreement, one cross-cutting microbiologist funded by the Epidemiology and Laboratory Capacity for Infectious Diseases Cooperative Agreement, and its own team of microbiologists.

LPRP started verifying specimens on January 13, 2016, and establishing Zika rti RT-PCR testing on January 26. On March 15, the program received a 100 percent score by CDC’s proficiency testing panel and started testing specimens on March 22.

## Managing the incoming surge

Given Zika’s intricacies and surprises, sample administration presented a heightened set of challenges.

“I don’t think we have ever encountered anything that’s so complex for the lab, with so much to coordinate at every level,” said Sharon Messenger, Chief, Zoonotic and Vector-Borne Diseases Section, California Department of Public Health. California reported over 400 cases of Zika in 2016 and its first sexually transmitted case in March.

“The challenge early on was the complexity of the algorithm and figuring out how to appropriately route samples coming in, especially when you’re getting hundreds of them,” she said.

To identify a sample’s destination at a glance, and streamline its journey through the system, her team created codes for specific testing algorithms. They built up administrative strength by cross-training staff on how to evaluate forms. And they relied on these new tools and processes for months on end.

“H1N1 had been extremely chaotic because we had to manage a sudden and large spike of incoming samples. We were less prepared. But there was one big difference: The H1N1 surge was relatively short compared to Zika,” said Messenger. “Zika was the first time we faced a real surge that just went on and on and on for many, many



months,” she said. “Because of what we learned with H1N1, we were in a better place to respond, but we also had to adapt those lessons to handle a surge that lasted over a year. At peak, testing was over 350 to 400 specimens per week, and we still average over 120 specimens per week.”

In Texas, epidemiologists, or epis (public health professionals who study the incidence, distribution, and control of disease), provided essential support during the critical receiving and routing stage.

“Our epi team would look through specimens that came to the state,” said Kubin. “Was it really appropriate for someone to receive testing? Did the patient meet the testing criteria? They looked at the signs, symptoms, travel history. Our epis did a lot of heavy lifting.”

## Capturing each sample's story

The paperwork that accompanies each Zika sample tells a story — symptoms, travel history, and risk. This story determines whether or not a patient should undergo a time- and resource-intensive series of tests.

Because of paperwork's importance in Zika testing, forms need to be as accurate and complete as possible, asking the right questions and getting the right answers. Only then can lab staff route a sample to where it needs to go.

With Zika, this was easier said than done. Especially in the early days of the response, many of the parties submitting samples, like OB/GYNs and primary care providers, were new to working with public health labs. They were not familiar with the paperwork, like CDC Form 50.34, for Zika submission. To complicate matters even more, the information

they needed to provide with a sample submission — like new fields for “pregnancy status” and “date of exposure” — changed as public health organizations learned more about Zika's diagnosis and transmission.

“There were changes to the guidelines as more information and details came out about the disease,” said Kubin. For instance, forms in Texas originally gave submitters the ability to request PCR or IgM for a sample, and this option resulted in numerous incorrectly labeled samples and calls back to correct matters.

“On the lab side, it was a challenge if a provider selected a PCR test, but the sample really should have had a serology test,” Kubin said.

So her lab took choice out of the equation. They changed their submission forms so that there was one block of text for Zika testing: “*based on signs and symptoms, serology will be recommended if...*” That meant less time needed to contact providers for clarification.

St. George also noted “a lot of stopping lab work to contact submitters to address problems in sample collection, packaging, and shipping. That's a big time sink and a lot of time lost.”



## Sample Transport, Receipt, and Evaluation

**A** Zika sample goes through an extensive journey even before it reaches the bench:

- Providers and testing facilities must collect, package, ship, and transport blood and urine samples according to highly exacting specifications.
- Lab staff must review each sample and accompanying paperwork about the patient's history. Does the sample qualify for testing by a public health lab? If so, where should it fall in the triage process? Has it been properly prepared, shipped, and labeled? If the paperwork contains questions or

errors or is incomplete, someone from the lab must contact the party who submitted the sample for answers.

- If a sample passes this preliminary evaluation, lab staff either prepare it for a PCR or IgM test or store it for later evaluation.



## Tracking samples through the system

How do you get complex sets of samples through a lab more efficiently and effectively? In New York, staff found ways to perform administrative and preparatory tasks concurrently. Virginia used unique ID numbers. “When a specimen came in, we could look the associated patient up and know they were approved for testing,” said Griffin-Thomas.

States also harnessed — and adapted — their IT infrastructure.

California’s labs, like many in the public health lab system, had a LIMS in place for managing test samples. But many LIMS are not designed to accommodate Zika’s more advanced tracking needs, like connecting multiple specimens and tests to a single patient, or more complicated paperwork requirements.

Even though California’s lab had upgraded its LIMS in 2016, the state had to perform several more months of upgrades to get it ready for Zika.

“We spent a good part of the year trying to get the LIMS to become more efficient in managing complex algorithms,” said Messenger. “Most LIMS don’t think of the whole patient, they think only of individual tests.”

During the upgrade, she remembered manual processes for keeping samples on track, “a lot of walking around with pieces of paper trying

## Urine Samples Spur New Thinking

Labs typically use serum, like blood, to test for mosquito-borne viruses and did so for Zika — until lab staff discovered that the Zika virus often remains in urine for a longer period of time, with a higher viral load that is easier to detect.

“We never would have thought that we would detect an arbovirus in urine like this,” said Susanne Crowe, director of the Jacksonville lab.

After New York and Florida labs started testing urine as well as blood for Zika, and picking up results that otherwise would have been missed, urine samples for Zika testing became standard.

This shift necessitated some rethinking of equipment and labeling.

“We went through many iterations of urine collection,” said Lea Heberlein-Larson with the Florida Department of Health. “Cups were always leaking. They weren’t designed to be bounced around in a van.”

After much research, her team finally discovered a container she dubbed “the Cadillac of urine collection.”

Another challenge: Zika testing can involve both urine and blood, and once the substances are properly contained in specimen tubes, “they look very much alike,” according to Heberlein-Larson. Her team addressed this potentially disastrous issue by revising guidance documents. Now the instructions are clear: “Label the specimen types.”

to get all of the results for one patient so you could review them,” she said. “It was a nightmare to deal with all that paperwork.”

Today, California’s LIMS puts a barcode on each sample that links all information about a patient into one record. This eliminates the need to input patient data multiple times. And once the information is in the system, staff can quickly create weekly

and daily reports and conduct queries about specific tests and samples.

“When there are not many samples to deal with, manual tracking feels manageable. But once an outbreak hits, having that computer system is very helpful,” said Messenger.



## Desktop Improvisation

**D**uring a significant part of the Zika emergency, Virginia's LIMS was undergoing upgrades. "So we did all manual reporting during the first six months," said Griffin-Thomas. This involved typing all patient metadata into a Word doc template for over 500 samples — and doing some creative troubleshooting.

"We created an Excel spreadsheet to track the onslaught of specimens and shared it nearly daily with the Zika monitoring team," she said. "It was a quick reference. We got a lot of phone calls about samples, and we were able to search the spreadsheet rather than search in the LIMS."

**"We have a lot of automated equipment. But the manpower for reviewing results and reporting out can be a bottleneck. That's a human work point where we can get staff fatigue."**

**—Kirsten St. George**

Chief of the Laboratory of Viral Diseases, Wadsworth Center,  
New York State Department of Health

## Maintaining momentum and morale

Some public health emergencies are like sprints — intense bursts of effort for short periods. Others, like Zika, are marathons that drag out across months and challenge even the most devoted technician's or director's stamina and dedication.

"With H1N1 you knew that the outbreak was going to finish, and flu season always goes away. But Zika season wasn't going away anytime soon," said Cannons. He recalled staff in Florida's labs working 18 to 20 hours a day at one point. "It was very difficult for morale," he said.

To keep his team's spirits and energy up through the Zika marathon, Cannons queried colleagues and researched

ideas, with varying degrees of success.

"One suggestion was to let staff wear their PJs to work, which doesn't exactly work in a lab," he said.

His team implemented a "Zika-free zone" at the lab, where staff could unwind for a few minutes. And throughout, he said, the team remembered the importance of their mission and why they had been driven to work in public health in the first place.



**"Lab work's always rewarding because you're helping provide information to someone that they might not have known."**

**—Grace Kubin**

Director, Laboratory Services Section,  
Texas Department of State Health Services



## Leveraging partnerships, forging new connections

Some of the most powerful tools in public health response are found beyond the lab bench. They're telephone hotlines, online listservs, webinars, and email inboxes.

Public health response runs on data and relationships: the right information communicated to the right people at the right time, empowering vital decisions about safety, risk, and resource allocation. Labs rely on CDC support and each other for updates on tests and how to administer and report them. Health care providers rely on labs for guidance on whom to test, how, and what results mean. Meanwhile, policymakers and the media are charged to evaluate the implications of a threat, and patients need to know if they or their family members are at risk.

Zika's complexity upped the communications ante. During the 2016 response, information sharing was challenged by:

- Tests that were difficult to interpret, even for experienced lab professionals
- Partners who didn't normally work with public health labs — such as physicians, hospitals, OB/GYN clinics, blood banks, and commercial health labs — and who didn't know how to properly package, label, and submit Zika samples for testing

- Difficulties reaching busy physicians about unusable samples or questionable paperwork, especially those at offices with cumbersome or nonexistent voice messaging systems
- A lack of established communications with commercial labs

Through emergencies like SARS, Ebola, anthrax, and the 2009 H1N1 pandemic, labs gained vital experience in coordinating communications and getting the right messages to the right people, building up valuable relationships and infrastructure for the Zika response as a result.

California is one example. Here over 30 local public health laboratories feed into the state system, with a longstanding history of partnership for bringing on tests and sharing information about findings across several networks geared for specific diseases like measles, norovirus, and arboviruses. “We have a long history of good relationships,” said Diana Singh with the California Department of Public Health.

For Zika, Singh explained, “We did a hotwash of what worked and didn't for measles. Everyone was trained on what the available tests were and CDC guidelines, so we could handle questions and calls.”

One key priority: educating partners old and new on how to submit samples and interpret test results.



**“The requirements are different in every state, and doctors aren't used to getting reports from public health agencies. It comes down to communication. Do it better; do it more often.”**

— Julie Villanueva

Laboratory Preparedness and Response Branch Chief,  
Division of Preparedness and Emerging Infections,  
NCEZID, OID, CDC

“To make sure forms were filled out correctly with the correct information, we held conference calls in the beginning with the labs, then set up different mailboxes to communicate,” Singh said. “People could send us forms securely and ask questions. These questions initially went to my and Maria’s email boxes. Then we set up a general mailbox so anyone on the team could look in.”

In Hawaii, Whelen’s team took similar collaborative steps. “We conducted outreach calls with Guam, Samoa, and local labs to help them understand the PRNT results

to the degree we understood them. We had the benefit of seeing a lot of results together.”

Texas conducted proactive outreach to new submitters such as OB/GYNs. “Because this disease is not very well known and because doctors are busy, they may not have time to look at all of the information out there and educate themselves,” Kubin said. Through information delivered in time-efficient packages, like webinars and 45-minute seminars, “they’ve learned quite a bit about Zika and challenges and threats to their patients.”

Commercial labs were another new partner in California’s Zika response. “Often we don’t have the same relationships with them because they’re usually operating independently,” Maria Salas, a research scientist with the California Department of Public Health, explained. “For commercial labs that needed to submit specimens for PRNT confirmation, we developed a one-page guidance sheet. And we’ve assigned one person to reach out to if anything goes wrong. That’s worked great. Our response rate has been much better.”

## IT Connects a Sprawling State

In Texas, labs and the public health community used technology to keep Zika efforts connected. Through the state’s LIMS, submitters can get test results via web portal, fax, or mail. And at TexasZika.org, an effort with the Department of State Health Services, parties across the public health community can find information on reported cases, advice for pregnant women and travelers, test submittal forms, and guidance on when to report positive tests, to whom, and how.



## The LRN: Established Infrastructure Accelerates Response

**L**aunched in 1999, the LRN connects thousands of private and public laboratories for emergency response.

Messenger cited the LRN as “a tried-and-true communications mechanism” for California’s Zika response. “By using the LRN, labs were able to take advantage of a system that pre-existed,” she said.

For example, “some local labs that weren’t LRN members were well placed for testing but didn’t initially have access to the protocols,” she said. “We worked with the LRN to get tests out to these labs, which was very important for capacity across such a large state.”

The LRN was a communications system ready to go, but Zika’s complexities necessitated some additional ramp-up and training. For instance, features for bulk data uploading and surge reporting existed across the LRN, but they weren’t widely understood or used because labs were accustomed to handling only one or two tests at a time, say for a biological threat, not hundreds. And many laboratorians working in virology and serology were not familiar with the LRN system at all.



## Managing expectations in an evolving situation

Confusion and frustration were common reactions throughout the Zika response.

“The testing and reporting algorithms kept changing, the guidance kept changing, the specimen types kept changing, especially during the early months,” St. George remarked.

New York set up a dedicated phone hotline specifically for OB/GYNs to get convenient, current answers to their questions. This decreased the number of

untestable samples the state’s labs received. Meanwhile, multifaceted, multilingual education materials kept the public informed about the latest ways to protect themselves and prevent infection.

Yet in a world used to instant, conclusive answers, Zika’s testing time frame and lack of certainty frustrated doctors and travelers and worried pregnant women. “Florida’s Zika Test Results Take Weeks,” announced a headline in The New York Times. “Zika Testing: The Delays and The Denials,” a story announced on the website for an NBC affiliate in Indiana.

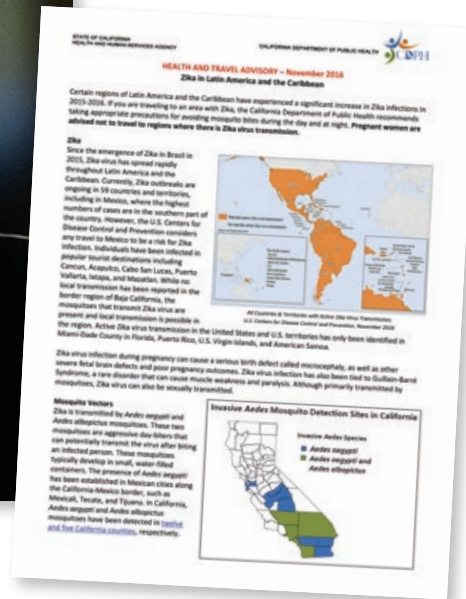
“With the time-intensive test and challenging algorithm, it took conversations to reiterate why results took a certain amount of days,” said Sara Vetter, who manages infectious disease initiatives with the Minnesota Department of Health.

Misunderstandings abounded about the Zika virus, the new tests’ capabilities, how public health labs work, and the process in general.

Some clinicians weren’t accustomed to having specimens referred to a public health laboratory rather than their own lab, or having labs conduct a preliminary test for a public health investigation. Furthermore, with public health lab testing, the party submitting the sample is the one who receives the test results, and this party might not necessarily be the physician in direct contact with the patient.

According to Rebecca Sciulli, who heads biological response for Hawaii’s state labs, “Doctors were often confused on how to access results, especially if they were not the ordering provider. But regulations require us to give our reports to our submitters.”

“We learned that we were more effective if we communicated through existing clinical lab networks who had those relationships,” Virology Supervisor Roland Lee explained. “State labs now work through the lab network to communicate submission



requirements, results, anything on the pre- or post-analytical side of the process.”

In Florida, Heberlein-Larson said, “We had to build files for OB/GYN practitioners. It took time to set these systems up.”

And new systems take time to get established, especially when they involve a complicated diagnostic, Gillis added. “These are the most complex testing algorithms we’ve dealt with. The sample collection date, the symptom onset date, did they travel, are they pregnant?”

“And often so much information we needed to know was just missing from the forms. We spent a lot of time just contacting test submitters to get information, six or seven people just working the phones,” she said. “And there were problems even with the medical community interpreting the test. A lot of patients in Florida happen to have lived or visited a country with flaviviruses at some point in their lives.”

Not only does cross-reactivity complicate test interpretation, it necessitates PRNT confirmation: one of the biggest reasons behind Zika’s longer-than-desirable testing timetable thanks to the several days needed to grow a virus and the fact that few labs were equipped to conduct such a specialized and resource-intensive test.

“These aren’t home pregnancy exams,” said Whelen. “This is hard science.”

## Diminished funding impacts public health infrastructure

While battling Zika, professionals across the public health community concurrently grappled with the funding and budgetary challenges they had faced for more than a decade.

When Zika hit, many labs found themselves needing to rebuild testing capacity, particularly in serology/IgM testing, that had eroded over the past several years. The colleagues they work with in the vital area of surveillance faced a similar challenge.

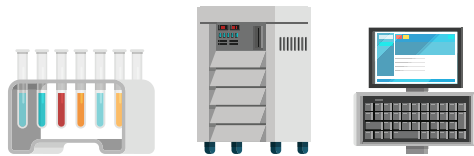
Surveillance is a multifaceted undertaking: entomologists (professionals who study mosquitoes) out in the field trapping *Aedes aegypti*, laboratorians testing samples from humans and mosquitoes, and epidemiologists researching the health effects. Through databases, maps, and more, surveillance provides early warning of impending emergencies, documents the impact of interventions like insecticides, and guides public health priorities and goals.

Arbovirus surveillance at the state and local levels never received federal support until West Nile virus spread to the 48 contiguous states in 1999–2004, causing more than 600 deaths. The federal government allocated roughly \$45 million toward this crisis, and by 2004, this funding had created “a robust and well-integrated national arbovirus surveillance infrastructure,” according to a



survey by the Council of State and Territorial Epidemiologists (CSTE).

When the West Nile threat receded to occasional outbreaks, funding for both surveillance and public health response faded with it. Arbovirus capacity had decreased to such an extent that it might not be sufficient to support a full response to mosquito-borne threats and outbreaks, according to the CSTE report. And by 2012, after a 61 percent decrease in federal funding, many health departments had decreased laboratory testing capacity.



## A Zika Shopping List

**W**hat do labs need to prepare for Zika testing? The assays and reagents from CDC are just the beginning. Other equipment needs include:

- Sterile screw-capped vials
- Thermoplastic, self-sealing lab film
- Reaction cuvettes (which hold samples for experiments)
- Analyzer racks
- Pipettes, gloves, plasticware, and nuclease-free water for RNA testing
- A centrifuge
- A vortex mixer
- A biosafety cabinet
- The capacity for climate-controlled storage and shipping and long-term storage
- Work areas specially set aside for testing
- Equipment and protection that can only be used for Zika tests

## Labs do more with less

When visitors toured Tampa’s public health lab at the height of Zika testing, they encountered a surprise, according to Heberlein-Larson. “They had the impression that there would be more people doing the testing.”

This perception of labs doing more with less was not an illusion.

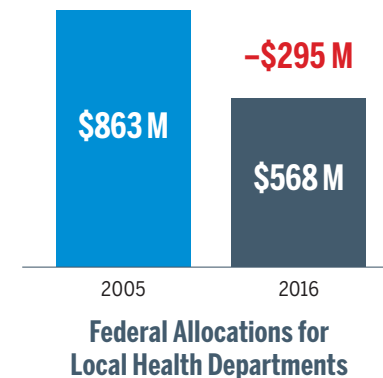
Like many labs, Tampa’s was stretched. For state and public health laboratories, federal funding covers just about everything, including staffing and fellowships, equipment, accreditations, informatics, and the LRN, through which labs get diagnostic assays.

Up to 83 percent of state and local preparedness activities are covered by the Public Health Emergency Preparedness (PHEP) Cooperative Agreement. Since 2001, PHEP has provided more than \$11 billion to support efforts of state and local health departments, responders, CDC, and federal partners in the event of biological threats, natural disasters, chemical and radiological accidents, and terrorism. These funds support labs, training, and staff in the field, like “disease detective” epidemiologists and program management experts.

PHEP initiatives have supported emergency responses to Ebola, foodborne illnesses, meningitis outbreaks, and more. They also

have brought stability, capacity, and an incrementally growing knowledge base to public health operations. But by fiscal year 2015, PHEP funding was only \$74 million — substantially less than its 2004 level of \$180 million.

## Decreased Annual Federal Funding



**Over 60% Decreases**  
in ELC grant funding for vector-borne disease surveillance (FY 2004–FY 2013)  
in funding for the national ArboNET arbovirus monitoring platform (2004–2012)



**“America’s public health professionals have already been stretching every precious tax dollar, doing as much as humanly possible with too little for too long.”**

**— Scott Becker**  
Executive Director, APHL

## **Federal Funding Makes an Impact**

According to APHL and CDC, federal funding for Zika supported:

- Operations of the LRN, which connects more than 150 biological laboratories in all 50 states, Australia, Canada, the United Kingdom, Mexico, and South Korea to respond quickly to high-priority public health emergencies
- Processing of 120,000+ specimens by CDC labs and biological labs in the LRN
- Expansion of testing capacity to all 50 states, Washington, D.C., and Puerto Rico
- Operation of a Zika pregnancy registry that has recorded over 1,300+ Zika-affected pregnancies
- Distribution of 31,000+ Zika Prevention Kits across the United States and its territories

## ELC grants deliver a lifeline

Fortunately, a far-sighted funding mechanism made it possible for labs to hire and train staff, make vital equipment purchases, and more.

In 1995, CDC created the Epidemiology and Laboratory Capacity (ELC) for Infectious Diseases Cooperative Agreement to fund projects that strengthen the nation's infectious disease infrastructure. Some funding focuses on specific diseases, such as influenza and Zika, with money directed to the areas of greatest risk. ELC-funded

Zika programs bolstered laboratory capacity to meet Zika's complex testing demands, strengthened surveillance and investigation infrastructure, and facilitated improved mosquito control and monitoring. ELC funding supports the U.S. Zika Pregnancy and Infant Registry, which helps monitor pregnant women with the disease, and Zika-related activities in U.S. states that border Mexico.

Other ELC funding is "flexible" and not tied to a specific disease, with the aim to increase capacity in overall epidemiology, laboratory work, and health information. It supports collaboration in a wide range of cross-cutting

activities, from integrated surveillance efforts to new ways of communicating test results. It also supports staff training — enabling a lab to swiftly ramp up for new testing priorities, like measles in Minnesota or contaminated water in Michigan or opioids in Indiana.

States put ELC funds to work in many ways. Texas used them for temporary staff and training. Louisiana established a birth defect tracking system in which health officials actively seek out information from birthing centers, according to a PBS Frontline report about the Zika emergency.

## RAPID RESPONSE TO AN EVOLVING SITUATION



**JAN 15, 2016:** CDC issues travel alerts for **14 countries** and territories in **Central and South America** and the **Caribbean**, including **Puerto Rico** and **Brazil**

**JAN 19, 2016:** **Florida** reports Zika infection in three recent travelers to South America

**JAN 22, 2016:** Travel alerts expand to **Barbados, Bolivia, Ecuador, Guadeloupe, Saint Martin, Guyana, Cape Verde, and Samoa**

**FEB 2, 2016:** **Texas** reports first sexually transmitted Zika case

**FEB 4, 2016:** **New York State** offers free Zika testing to pregnant travelers

**FEB 10, 2016:** **"Zika Virus Associated with Microcephaly"** published in the *New England Journal of Medicine*



**MAR 25, 2016:** First sexually transmitted case confirmed in **California**

**APR 12, 2016:** CDC updates clinical guidance for **reproductive-age women and men**

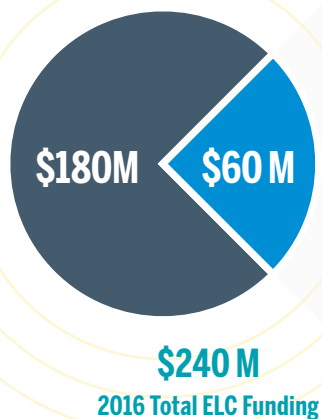


2016



Labs used ELC funding to rapidly expand their testing capacity, add equipment, and improve efficiencies. They invested in new methods for sharing data and transporting specimens. ELC grants, PHEP funds, and other government dollars kept Zika from becoming an even greater emergency in 2016 and 2017.

ELC funding was just one of the ways “strength in numbers” made the Zika response possible in 2016. Efforts to understand the disease and protect the public sparked partnerships among parties old and new — mosquito control, maternal health, test manufacturers, epidemiologists, and beyond.



**These grants to states, cities, and territories support:**

- Epidemiologic surveillance and investigation
- Improved mosquito control and monitoring
- Strengthened laboratory capacity
- Participation in the U.S. Zika Pregnancy and Infant Registry
- Zika-related activities in U.S.-Mexico border states

**Additional funding (awarded July–August 2016)**

- **\$25 million** for preparedness and response efforts to at-risk states, cities, and territories (PHEP funding)
- **\$10 million** to states and territories for efforts to quickly identify Zika-related birth defects and refer affected families to services (ELC funding)



**JUL 29, 2016:** First local transmission in the mainland U.S. reported in **Florida**

**AUG 3, 2016:** **Florida** offers pregnant women free Zika testing

**AUG 23, 2016:** CDC posts travel notice for the **Bahamas**




**SEPT 30, 2016:** CDC updates its response plan based on the latest knowledge about the virus and its **effects on pregnant women and infants**

**OCT 19, 2016:** CDC strengthens travel and protection recommendations for **Miami-Dade County**, an area of active Zika transmission



**DEC 9, 2016:** **Florida** declared free of locally transmitted virus



**“Whenever you go through  
a crisis together, it  
strengthens you in the end.”**

**— Lea Heberlein-Larson**

Virology Administrator, Florida Department of Health,  
Bureau of Public Health Laboratories



## CHAPTER 4:

# ATTACKING ZIKA FROM EVERY ANGLE

**A**s lab staff developed assays and tested samples, a constellation of specialists across science, health, and medicine supported their efforts to understand Zika and keep the public safe. Mosquito control districts surveyed, sprayed, and studied the tiny vector behind it all. Maternal health professionals provided a vital link to pregnant women and their babies. Commercial manufacturers stepped in to safeguard another area of vulnerability: the nation's blood supply. And epidemiologists worked in the field and conference rooms to shape a common understanding of risk.

Throughout, over 80 organizations from across public health banded together in an unprecedented fight for dedicated federal funding.

Public health emergency response is always a collaborative effort, and Zika's mysteries and complexities made joining forces even more essential.





**“Vector control is a preventative service. It’s designed to keep problems from getting worse.”**

**– Joe Conlon**

Technical Advisor, American Mosquito Control Association

### **Reining in an elusive vector**

Where are the mosquitoes responsible for spreading Zika? How can they be stopped? These are the questions addressed by vector control professionals, and Zika posed multiple challenges to their search for answers.

Most mosquito control efforts in the years leading up to the emergency had focused on *Culex* mosquitoes, the carriers of West Nile virus, not the *Aedes* mosquitoes that transmit Zika, according to Christopher Gregory, Arboviral Diseases Branch Chief at CDC’s Division of Vector-Borne Diseases. Even though *Aedes aegypti* had been in the United States for hundreds of years, these mosquitoes hadn’t been seen as much of a threat. In fact, *Aedes albopictus*, the “Asian tiger mosquito” that had arrived in the country in the 1980s, was viewed as a much more invasive pest.

Furthermore, the infrastructure that did exist — like ArboNET, a national arboviral surveillance system managed by CDC and state health departments — had eroded over time due to funding cuts. And vector control at the state and local levels was disconnected and uneven. In California, for instance, vector control is spread out across more than 70 agencies, some staffed with only a few people, others wielding budgets of \$10 million or more.

During the Zika response, CDC laboratorians, medical epidemiologists, entomologists, and more worked on sharpening their understanding of transmission. One example: *Aedes albopictus*. Initial studies indicated that this mosquito was a somewhat ineffective Zika vector. However, researchers knew from their work with chikungunya carriers that the ability to transmit disease can improve over time.

Knowledge circulated as CDC deployed staff to Florida, Texas, and other areas where local transmission had been reported to help set traps, collect specimens, and assist with surveillance and control. CDC teams, public health agencies, and mosquito control organizations collected valuable observations throughout the Zika response. For instance, *Aedes aegypti* was spotted in puddles at the bottom of elevator shafts and feeding on birds as well as humans, which differs from the mosquito’s habits elsewhere in the world. In California, Zika responders noted mosquitoes that preferred to live outdoors, rather than indoors as usually observed.

To complicate matters, the eggs of *Aedes aegypti* are able to survive even after drying out completely. “So even if you dump out that container of standing water, those eggs can still hatch if they are flooded,” warned Vicki Kramer, who heads the California Department of Public Health’s Vector-Borne Disease Section.

## Revisiting conventional spraying wisdom

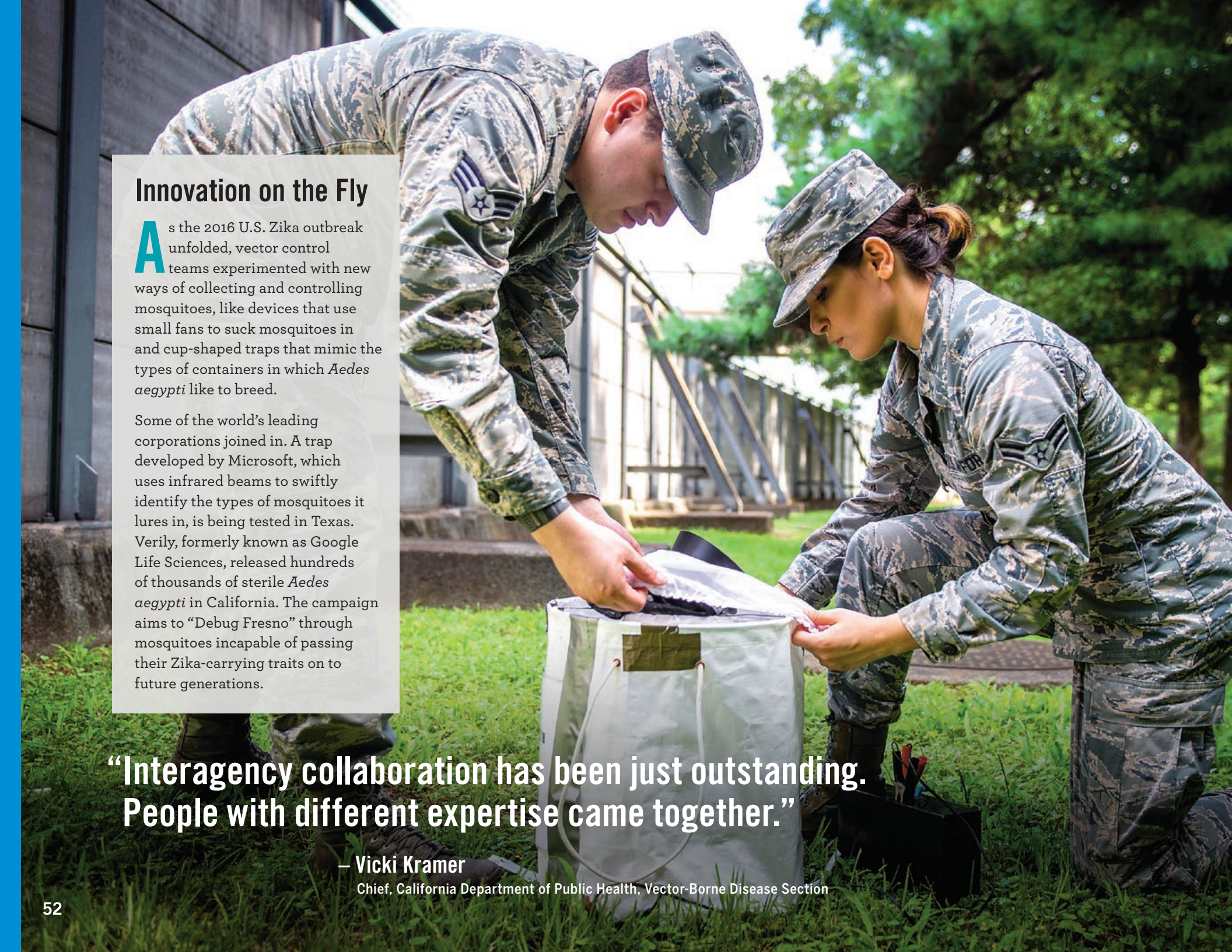
Zika also delivered surprises in terms of pesticide administration. “It had been dogma over the past 50 years that you don’t control *Aedes aegypti* mosquitoes by aerial spray,” said Joe Conlon from the American Mosquito Control Association. “But that was wrong.”

When Zika appeared in downtown Miami, rather than in Key West as expected, vector control teams had to consider new approaches. “The hand-held sprayers used in Key West to fight dengue were not practical for Zika,” said Conlon. “The area we needed to cover was just too large.”

Vector control teams tried ground-based spraying at first — with little success because *Aedes aegypti* had built up resistance to the type of insecticide used in this approach. Teams then looked to the airspace above downtown Miami. It was an initiative challenged by high-rise buildings, updrafts, and ocean breezes — not to mention naysayers convinced that aerial spraying wouldn’t work. “We really didn’t have a lot of options,” said Lyle Petersen, who served as interim director of CDC’s Zika response.

Spraying planes took to the air. Vector control teams monitored the situation with traps. And, to the team’s happy surprise, “mosquito counts went down 95 percent in a matter of days,” Petersen said.



A photograph of two military personnel in camouflage uniforms working outdoors. A man on the left is leaning over a white bag, and a woman on the right is kneeling and looking into the bag. They appear to be conducting a field inspection or experiment. The background shows a building and trees.

## Innovation on the Fly

**A**s the 2016 U.S. Zika outbreak unfolded, vector control teams experimented with new ways of collecting and controlling mosquitoes, like devices that use small fans to suck mosquitoes in and cup-shaped traps that mimic the types of containers in which *Aedes aegypti* like to breed.

Some of the world's leading corporations joined in. A trap developed by Microsoft, which uses infrared beams to swiftly identify the types of mosquitoes it lures in, is being tested in Texas. Verily, formerly known as Google Life Sciences, released hundreds of thousands of sterile *Aedes aegypti* in California. The campaign aims to “Debug Fresno” through mosquitoes incapable of passing their Zika-carrying traits on to future generations.

**“Interagency collaboration has been just outstanding. People with different expertise came together.”**

— Vicki Kramer

Chief, California Department of Public Health, Vector-Borne Disease Section

## Vector control regains public health prominence

CDC has its roots in mosquito-borne disease; the federal government established it as the Communicable Disease Center in the 1940s in response to malaria. Yet after malaria disappeared from the United States, vector control became focused on, in Gregory's words, "the mosquito that can drive you crazy but might not give you a nasty disease."

Then Zika became associated with birth defects, and mosquito control organizations ascended on the public health radar, working on state task forces alongside epidemiologists, diagnostic professionals, vaccine developers, and more.

"There were a lot of conference calls to discuss what was going on and why," Conlon recalled about the Zika response.

In Florida, the governor's office included vector control in its daily Zika task force meetings. On the other side of the country, the Los Angeles County Health Department Emergency Management Group shared mosquito control information via conference calls, a listserv, and regular meetings, and piloted a tabletop preparedness exercise that has since been replicated across the country. Kramer

holds regular Zika-related calls with local health departments. If a local health department suspects a case of Zika, vector control can follow up and attempt to reduce the risk of local transmission.

Before the Zika outbreak, not much communication existed between the worlds of public health and mosquito control. "Zika response built these connections so they can work together," said Gregory.

Connections, once established, can be invaluable. Petersen cited ArboNET, though recently underfunded and originally designed for West Nile virus. The network's existence meant that "we didn't have to build an entirely new system. We were able to bring up surveillance nationwide," he said.

Conlon emphasized the importance of maintaining infrastructure of all types. "We need to keep up with sewage, screens, and trash disposal so these diseases don't gain a foothold. Because Zika might reappear — or something worse next year."

"The world is getting smaller," he said. "With tourism, trade, ease of transport, and rapid transport, we're continually confronted with diseases we're not prepared to deal with. They're coming here every day, and there's no way of keeping them out."

## The "3 Ds" of Mosquito Control

**A** *edes aegypti* mosquitoes will breed in a wide variety of places, from the corrugated black tubes of gutters to the most elegantly landscaped yard. People in Zika-prone areas can protect themselves by:

- **Draining standing water** every five days. Check small containers like water vases. Don't keep dishes under plant pots. And make sure to scrub the sides of containers, because *Aedes aegypti* mosquitoes lay eggs right above the water line.
- **Dressing properly** in light-colored clothing that covers the lower legs.
- **Defending** themselves with EPA-registered repellent that works for at least two hours.





## **Making connections to protect mothers and babies**

Meanwhile, other teams in public health were striving to expand overall understanding of the disease among pregnant women and OB/GYNs and resources for maternal health.

With its bustling ports, large population of international travelers, and culture of outdoor living, California was ripe for a Zika outbreak. Every year, nearly half a million babies are born in the state — babies now possibly at risk. How could the state comprehend this risk, relate guidance to doctors and women's health providers, and keep track of affected babies who would need significant support for the rest of their lives?

It would take a multifaceted team of health professionals, constant communication, and robust tools like the U.S. Zika Pregnancy and Infant Registry.

When reports of microcephaly in Brazil became global news in late 2015, California's Center for Family Health paid close attention. Three divisions — Women, Infants, and Children (WIC); Maternal, Child, and Adolescent Health (MCAH); and the Genetic Disease Screening Program — engaged at once for regular conference calls and knowledge-sharing. Through presentations and personal outreach, they rallied a full spectrum of stakeholders to join them, including the state district office of the American College of Obstetricians and Gynecologists, local MCAH directors,



local WIC directors, the directors of prenatal diagnosis centers and regional perinatal programs, and professionals who work with children with special health care needs.

The team emphasized two-way communication from the very beginning. In its first press release in early February 2016, the team asked travel organizations, mosquito control organizations, and health care providers to report suspected Zika cases to their local health department.

“The reported data would provide information to help identify the supports families might need: resources, referrals, enrolling them in programs,” said Richard Olney, who heads the Genetic Disease Screening Program at the California Department of Public Health (CDPH). “These early data would also provide an impetus for California’s eventual participation in CDC’s U.S. Zika Pregnancy and Infant Registry.”

Concerned health care professionals proactively offered their expertise and support as well. An expert in maternal and fetal medicine and infectious disease from Los Angeles County was among the first clinical physicians to volunteer to help. “We were on the phone with him to talk through the basics of what he was seeing in his practice, what he was hearing from his colleagues,” Olney recalled.

According to Karen Ramstrom with the Center for Family Health, local partners let their team know if their materials were meeting the needs and addressing the questions of the people they served. The questions that arrived in the team’s dedicated Zika email inbox each day also drove communication priorities.

Initial inquiries involved breastfeeding — was that still safe? Then came: “I’m traveling and plan to get pregnant. When is it safe to try to conceive?” And did the highest Zika risk occur in the first trimester or throughout pregnancy?

“It was very challenging and concerning for a lot of our constituents,” said Ramstrom. “People were trying to make decisions, and we really didn’t know what the risk was.”

Then came news of Zika’s sexual transmission. “This was unheard of for a virus that causes birth defects,” said Olney.

Now health care providers and public health professionals had to be concerned about a pregnant woman’s partner as well. Working with colleagues from WIC and other local programs serving pregnant women, who had experience with this type of messaging, the team developed toolkits for communicating



Zika risk and precautions with patients, over social media, and beyond.

Whenever CDC updated its guidance, the CDPH Zika communications team integrated updates into outreach to clinicians, public health partners, and the public at large.

“As CDC tries to give us the most recent information possible, there’s a big flurry of activity,” said Ramstrom. “We have to take it in, digest it, and think of the implications for health care providers, for our website, and our education materials.”

## Reaching Out to All Vulnerable Travelers

**W**ith Zika, you don't have to be on a tropical vacation to be at risk. Any kind of travel to a Zika-infected area — even if it's a quick, routine trip — can make a person vulnerable and risk spreading the virus further upon the return home. Public education materials need to communicate this danger, particularly in border areas.

“We learned that how we talked about travel wasn't necessarily resonating with people who are just going to their jobs or visiting their families,” said Ramstrom.

Their team is working with consulates, partners on both sides of the border, and the California Department of Public Health network to help all cross-border travelers realize their risks.

U - TURN  
TO USA

## A pregnancy registry tracks and connects

Scientific, medical, and public health organizations use registries to collect health information from individuals with a certain condition or who are taking certain medications. Patients or their health care providers submit data by phone, fax, email, or electronic forms. The goal: Get an ongoing snapshot of a specific condition or treatment.

CDC created a nationwide pregnancy registry for Zika. The U.S. Zika Pregnancy and Infant Registry collects data for pregnant women with any laboratory evidence of a Zika infection. Data is collected as available at the initial infection, second and third trimester, and at delivery, plus data for infants at two, six, and 12 months.

Twice a month, CDC reports on its Zika website figures for live infants born with birth defects, pregnancy losses with birth defects, and the total number of women in the registry. These figures supplement weekly Zika reports from ArboNET. Participation in the pregnancy registry is voluntary, and data is encrypted and de-identified (disconnected from the patient's identity) for security purposes.

As America's most populous state, and as a state with the third-highest number of Zika cases in the nation, California had

much to gain from and contribute to the national registry effort. So Ramstrom and Olney leveraged their working group's connections to ensure participation.

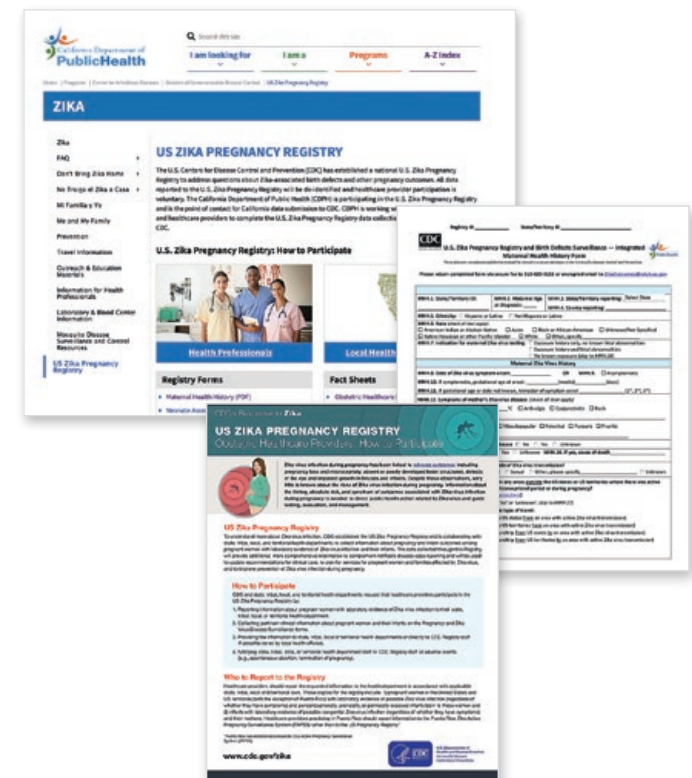
The California Department of Public Health served as the liaison for collecting the data. A CDC ELC grant made their team's registry efforts possible, including funding for two state coordinators to join the initiative.

The team, including the lead epi, the registry coordinators, and state lab, relied heavily on local health departments and health care providers who were working directly with pregnant women. They worked with these partners to understand what conditions would trigger an entry into the Zika pregnancy registry and how to collect and report a patient's information.

They created a dedicated webpage rich with information and established an email address and phone number for questions. The team worked through their registry coordinators to deliver guidance as needed and used the data that came in to look at the big picture.

"We integrated Zika pregnancy registry activities with our birth defects monitoring program," said Olney. "This gives us the capacity to look at the data in a combined way and have coordination between the two initiatives."

Throughout, Ramstrom and Olney let their partners know that the registry team shared their commitment to serving their communities. "It's not just collecting numbers. It's making sure that the children who could be affected are getting services," said Olney.



## Protecting America's blood supply

As public health labs hustled to test the blood of individuals for the Zika virus, concurrent efforts safeguarded another aspect of America's public health: the blood donated to blood banks, hospitals, and health care providers.

Blood donation is a big and essential enterprise in the United States. Every day, up to 36,000 units of red blood cells, 7,000 platelet units, and 10,000 units of plasma are needed for patients across the country for surgeries and often life-saving transfusions.

To prevent the transmission of blood-borne diseases, every unit of blood collected in the United States is screened. Based on previous experience with West Nile virus — the first mosquito-borne virus proven to be transfusion-related — CDC knew that Zika could threaten the nation's blood supply. When evidence grew of Zika's ability to be transmitted through a blood transfusion, the virus joined CDC's list of pathogens for screening.

"We started discussing Zika with the FDA even before the virus was proven to be transfusion-related," said Petersen. "We knew something needed to be done to protect the blood supply."

The private sector had delivered vital support throughout the Zika response. Commercial labs handled serology testing for states that lacked this capacity, and private sector companies developed tests that joined CDC's Trioplex and MAC-ELISA for emergency use. Roche Molecular Systems Inc. played a valuable role in developing and administering diagnostics to protect the nation's blood supply.

On February 16, 2016, the FDA issued its Zika guidance for blood donations, adding questionnaires about recent Zika exposure to the screening process and deferring blood donations from people who had recently traveled to areas of Zika risk. However, no assay had been developed and authorized for screening blood for the Zika virus.

In early March, after more than 700 cases of Zika had been confirmed in Puerto Rico, blood collection stopped in the U.S. territory. This forced the import of all blood from the continental United States. Ultimately, Puerto Rico airlifted in more than 5,000 units of blood every week.

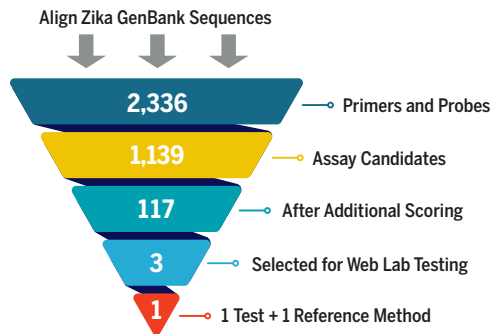
It was "an expensive and unsustainable solution," according to Lisa Pate, who directs clinical research for blood screening initiatives at Roche. She explained that when blood banks can't collect donations, they reduce their operations, run out of money, and lay people off. "Successfully resurrecting an infrastructure once you shut it down may or may not happen."



## Accelerated response for an onslaught of samples

“We knew the time frame had to be weeks, not months,” said Tony Hardiman, who leads blood screening initiatives at Roche. “We moved very aggressively, but we were also very mindful of the appropriate requirements for any blood screening assay.”

### Roche Zika Assay Design Process



Roche worked from a foundation of over 2,000 primers and probes — the single strands of DNA and RNA that jumpstart replication and make testing possible — to develop three assay candidates, then an investigational assay. Teams in Europe and the United States pre-staged reagents and samples. To save time, they worked concurrently to develop assays, prepare clinical studies, and perform test validation. They drew from considerable past experience. The nucleic acid tests had been used to screen blood for West Nile virus, and the testing equipment had proven itself in efforts against HIV, HPV, and many other viruses.

By March 30, 2016 — six weeks after the FDA issued its recommendations and 10 weeks after the assay design was initiated — the FDA granted Investigational New Drug approval for the cobas® Zika test. Collection of blood donations in Puerto Rico resumed three days later.

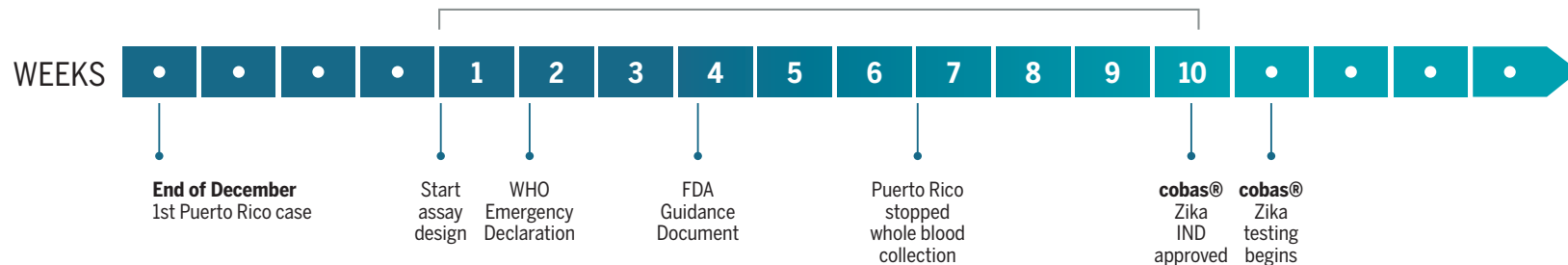


**“We have to do this, we have to do it right, and we have to do it fast.”**

— Tony Hardiman

Lifecycle Leader for Blood Screening, Roche Molecular Systems Inc.

### cobas® Zika in 10 weeks





## Real-Time Intel on Zika's Spread

**N**ot only is the partnership between Roche, the FDA, and CDC safeguarding America's blood supply against Zika contamination, it is generating invaluable surveillance intelligence.

Testing labs notify Roche of reactive results within 24 hours. Roche then shares this data with CDC and FDA. This data, tracked by zip code, helps public officials know where the virus is moving, so they can target mosquito control efforts to specific areas.

"If you look at standard assay development or a clinical trial, you'd be looking at 30 to 36 months," said Hardiman. For Zika testing, the team accomplished it all in just 10 weeks.

In the first week, the Roche team tested 1,500 samples. The first batch of samples on the first day of testing contained a reactive test.

Testing ultimately scaled up to 3,000 to 5,000 samples a week. The team had an agreement to call FDA and CDC immediately whenever a reactive test came in, "usually in the evening and on weekends," Pate joked. She estimated that she was on calls with FDA and CDC every day for five to six weeks.

"No sooner had we started testing in Puerto Rico than did we start getting inquiries from other blood-testing labs," said Pate. "In the southeastern United States, Zika was on everybody's mind."

On August 26, 2016, when FDA recommended blood screening for all U.S. states and territories, the rollout kicked into high gear. Each lab that adopted the test needed to install instruments, train staff, create protocols, and get protocols approved by the institutional review board. Then the labs had samples coming in from hundreds of collection sites. "It was an all-hands-on-deck exercise," Pate said.

Operational activities and training for setting up a test usually take six to nine months "if you're moving pretty fast," according to Pate. "We did that for Puerto Rico in a little over three weeks."

Today, Zika testing is integrated into the blood-testing environment. "It's part of everyday operations," said Pate.

Pate attributed the success of the test development and rollout to "timely, collaborative leadership by FDA and CDC and lots of intelligent, hardworking people inside and outside of Roche. None of us could have done what we did without the others."

Regular calls, reports, and data exchange continued among Roche, blood-testing centers, FDA, and CDC. Hardiman called this collaboration between industry and regulatory agencies "a phenomenal model for the future."

## “Disease detectives” work in — and guide — the field

Amid all of this activity, epidemiologists were out from dawn to dusk trying to figure out how much this elusive virus had spread and where it would turn up next, with the goal of guiding a common understanding of the disease.

Epidemiologists (epis) are often referred to as “disease detectives.” Even before a hospital or clinic detects an outbreak, they’re on alert to illness chatter on social media or reports that don’t look quite right. They jump into discovering the who, what, where, when, and how of disease, using complex equipment, sophisticated analytics, and in-the-field research.

“We knew Zika was a distinct possibility,” said CSTE President Janet Hamilton, who also works in surveillance at the Florida Department of Health. “But where would it emerge?”

Thanks to prior episodes with dengue and chikungunya, Miami was on the epi radar. Here, high-end hotels with constantly running irrigation systems stand just miles from lower-income neighborhoods with broken window screens. Suburban backyards and construction sites alike are home to tarp-covered storage and vehicles, which collect slow-to-evaporate rainfall. And year-round warmth, sunshine, and hospitality mean people spend much of their time outdoors: working, playing, dining, and



relaxing. The disease detectives were on high alert.

Epis identified key groups to watch: travelers, women of childbearing age, and people with friends and relatives in tropical regions with poor mosquito control. Then they took to the field. In the communities of Little River, Wynwood, and Miami Beach, epis went from door to door to collect urine samples for testing and to educate communities about how to protect themselves against this emerging threat.



Communications were challenging. Miamians speak a mélange of languages — English, Spanish, Tongan, Vietnamese, and more. Some languages, such as Haitian Creole, are more often spoken rather than written. And some people in immigrant communities were hesitant to interact with epi teams, especially later in the Zika response when news reporters started following surveillance teams into communities.

“It was definitely labor-intensive, but worth the effort,” said Andrea Bingham, who works in vector-borne disease surveillance with the



Florida Department of Health. “It helped us identify areas of active transmission.”

The team set up a clinic in a well-trafficked area where anyone could get tested, particularly people whose work might bring them in contact with mosquitoes: construction workers, valet attendants, staff of outdoor restaurants, even technicians who fix elevators. Miami’s modern, air-conditioned skyscrapers were far from safe from Zika-bearing mosquitoes, according to Bingham. “People take breaks outdoors, and bugs fly inside when the doors open.”

“We had investigators out all day, alternating times of day to get people on different work shifts,” said Hamilton.

Samples showed up en masse at labs at night, waiting to be efficiently tested by hard-

working laboratorians. Established epi-lab partnerships made it possible. “We’d get emails at midnight or 1 a.m. with initial preliminary results,” said Hamilton. “This allowed us to assess what was needed. The rapid turnaround and communication was really critical.”

### Uniting Zika responders in shared standards

When not out in the field, epis were working to establish standards for the disease. What constitutes a good specimen? How can cases be consistently counted over time? What policies should govern notification and communication?

The questions were copious and complicated, and CSTE served as the hub for crafting answers that reflected a shared, science-based understanding of the disease and its diagnosis, surveillance, and treatment.

At the peak of the Zika emergency, up to 20 organizations were involved in CSTE-hosted calls — nonprofits and associations from across health care, OB/GYN groups, groups representing blood and tissue bank entities, and many more. Their goal: Create a position statement, establish standardized case definitions (criteria epidemiologists use to link patients to a specific disease), and create policies to guide the Zika response.

In April 2016, CSTE began hosting webinars to engage further discussion and in May examined interim case definitions for the disease and congenital infections. Then the team:

- Added case definitions and classifications for asymptomatic blood donors and pregnant women
- Established standards for confirmed cases and different types of specimens
- Expanded clinical criteria for confirmed cases in newborns
- Set standards for establishing and reporting to pregnancy registries

The next step involved adding Zika to CDC’s Nationally Notifiable Diseases List, which makes reporting mandatory by state epidemiologists and public health departments. By September, participants viewed a demo of the National Notifiable Diseases Surveillance System database for Zika, complete with definitions and standardized vocabulary.

CSTE also created a work group that shared perspectives of the constantly changing environment on regular conference calls. “We learn the most from each other,” said CSTE Executive Director Jeff Engel.

“To share information with people struggling with the same issue and see how others were dealing with it — I found these calls unbelievably helpful,” Engel said.



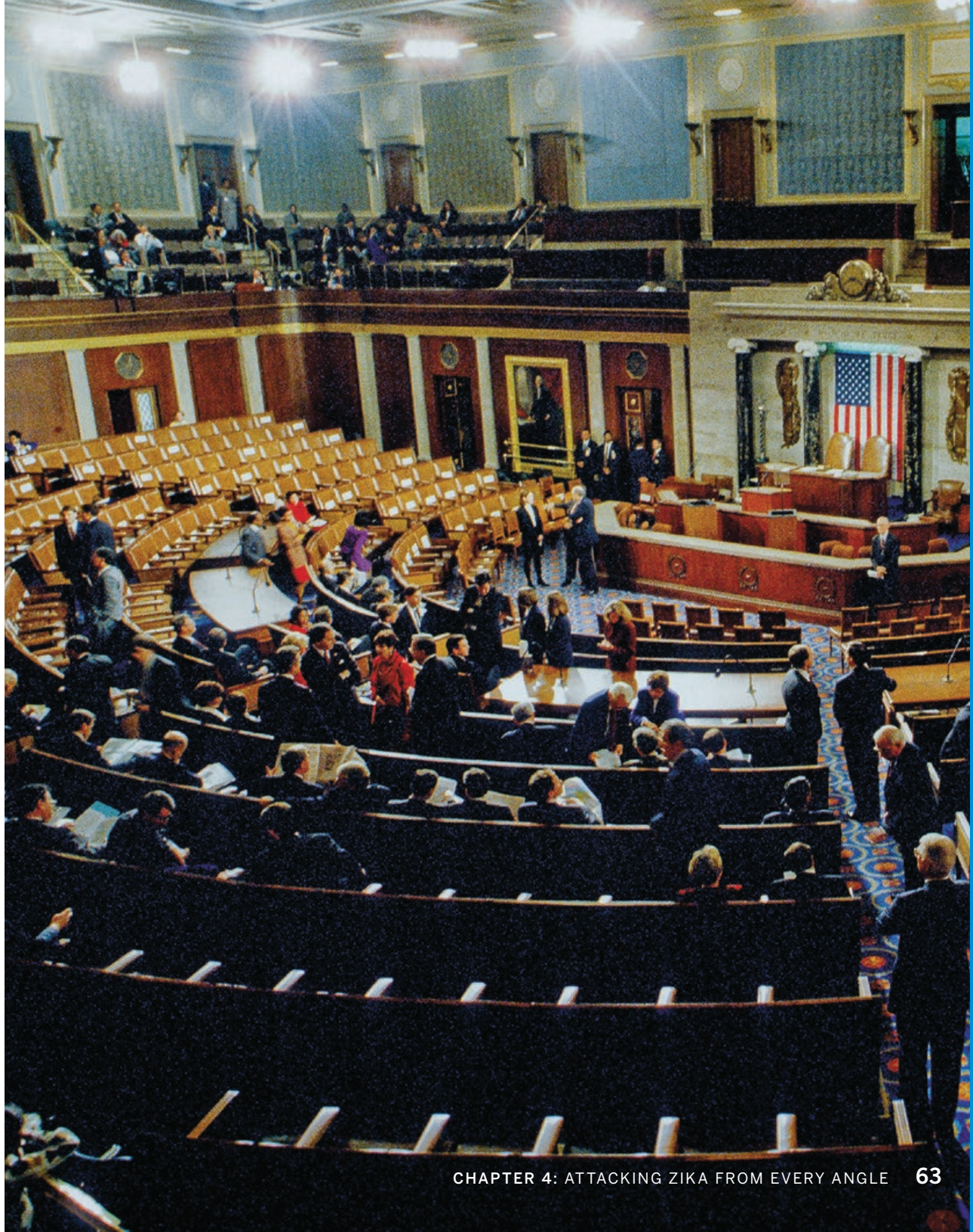
## The Zika Coalition fights for funding

Laboratory testing, mosquito control, public education, disease surveillance, and scientific research — none of the activities to fight a devastating virus happen without funding. Yet despite Zika's threat, obtaining money for the response proved an arduous and protracted challenge.

The battle began in February 2016. Seeing the unfolding crisis, the Obama Administration requested \$1.9 billion for emergency Zika funding. Yet not until the end of September — several months and 75 meetings later — did the money begin to flow, and at that point it was just \$1.1 billion rather than the full \$1.9 billion requested.

Unlike funding requests for West Nile virus and SARS, the journey to obtain Zika funding was neither smooth nor swift. It was yet another way in which the Zika response differed from previous public health emergencies.

“What usually happens with such advocacy efforts is that a funding request moves along and is taken up pretty quickly, with groups encouraging and shaping things along the way,” said Cynthia Pellegrini, who heads public policy and government relations for the March of Dimes. “There’s an established pathway.”



By the end of February, more than 100 cases of Zika had been confirmed across 33 states — and Congress still had not taken action on the request for emergency funding. Labs had CDC guidance. They were ready to start testing. But they had no resources. “You need materials for testing, highly specialized equipment, training, staffing,” said Peter Kyriacopoulos, APHL’s senior director of public policy.

APHL and other leaders recognized the urgency of the situation and the potential power of a shared voice. APHL immediately

responded to the call to action issued by the March of Dimes to form the Zika Coalition, a group representing public health professionals, health care providers, and communities served by public health.

Within a week, more than 80 organizations had signed on, representing a diverse range of constituencies and missions. This coalition quickly got to work, writing letters and meeting with lawmakers and staffers on the Hill.

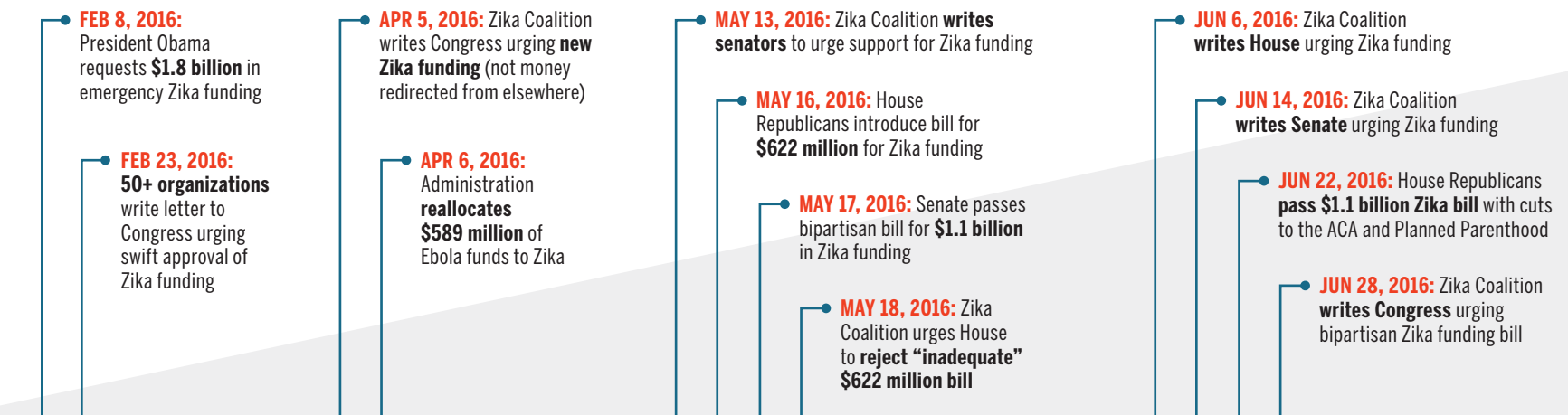
The first letter went out April 5. Its message: Provide emergency

supplemental funding for Zika at once — without taking money away from other critical public health functions:

*Our nation has a brief window of opportunity to slow the spread of the Zika virus and avert a wave of preventable birth defects.*

*With emergency supplemental funding to respond to the Zika virus, state and local public health professionals would have access to increased virus readiness and response ... to reduce the opportunities*

## FUNDING TIMELINE



2016

for Zika transmission and ... limit potential clusters of Zika virus in the United States. ...

*Without action, however, we fear the number of newborns born with debilitating birth defects will only continue to rise.*

On April 6, the administration moved \$598 million out of Ebola funding and into Zika response.

The coalition pointed out in meeting after meeting and letter after letter the dangers of redirected funding. What would be the toll on public health if another crisis flared up — dengue, influenza, a tick-borne disease, or a foodborne outbreak?

“A lot of offices don’t understand that agencies have limited authority to reallocate funding. When money is allocated to a program, it can’t necessarily get moved around,” Pellegrini explained.

## An overshadowed and misunderstood cause

When the Zika Coalition launched its outreach, policymakers were feeling “emergency fatigue” from a confluence of public health crises, including the opioid epidemic and Flint, Michigan’s water crisis. To many people, those crises felt more urgent and pertinent than Zika.

**JUL 13, 2016:** Zika Coalition writes Congress urging lawmakers to pass a Zika funding bill before the summer recess

**AUG 3, 2016:** Zika Coalition writes Congress urging swift Zika funding passage after recess

**SEPT 6, 2016:** Congress returns from recess, receives letter from Zika Coalition urging swift, adequate Zika funding

**SEPT 28, 2016:** Senate and House pass \$1.1 billion in Zika funding as part of massive government funding package

**SEPT 29, 2016:** President Obama signs \$1.1 billion stopgap Zika funding bill



“It’s in Brazil; it’s not our problem,” Kyriacopoulos recalled. “Policymakers weren’t hearing from people in their districts and states.”

Incomplete and evolving knowledge about the virus, its causes, and its potential effects didn’t help matters. “People wondered if maybe it’s not Zika causing the birth defects in Brazil. Maybe it’s the insecticide, maybe it’s dengue and Zika combined,” Kyriacopoulos remembered.

Zika wasn’t as immediate or graphic as recent diseases either. Ebola for instance, announces itself with a sudden onslaught of raging fever, vomiting, diarrhea, severe headache, and hemorrhaging. Infections often end in death.

In contrast, Zika feels like a mild cold or flu — if a person who contracts it gets any symptoms at all. It appears relatively simple to prevent. Put up a screen window or door, wear long sleeves and pants, and use bug spray. And its most catastrophic effects don’t happen until months after the infection.

As more cases of Zika and more incidences of devastating birth defects were reported in the United States — and as definitive scientific information linked the virus to these birth defects — “the tide turned,” Kyriacopoulos said.

## Efforts escalate

In June, the House and the Senate introduced legislation for new funding. But proposed cuts to the Affordable Care Act and Planned Parenthood caused a partisan stalemate. The Zika Coalition responded with letters to House and Senate leadership urging immediate, bipartisan funding.

### June 6, to U.S. House conferees:

*Unless Congress acts immediately, we risk squandering our nation’s opportunity to prevent the Zika virus from gaining a foothold in the United States this summer. ...*

### June 14, to U.S. Senate conferees:

*Research is rapidly uncovering the ways Zika evades the mother’s immune system, invades the placenta, and wreaks havoc upon the fetal brain. Our nation has never before faced a situation where a single mosquito bite could result in dreadful, permanent, life-altering birth defects. ...*

### June 28, to U.S. Senate leadership:

*Let us be clear: Zika is a public health emergency. ... Our nation is perilously close to the point where it will be impossible to distribute funding to states and localities in order to make a meaningful difference this year. Many at-risk jurisdictions have been forced to lay off trained staff due to cuts and the lack of new resources, even as they are being asked to battle this new threat.*

As Congress prepared for summer recess, the Zika Coalition turned up the heat.

### July 13, to U.S. House and Senate leadership:

*We implore Congress to send a bipartisan Zika emergency spending bill to the President by the end of this week to combat the terrible threat this virus poses to pregnant women and their babies. ... Biotechnology researchers will be forced to abandon Zika projects if the U.S. government cannot demonstrate a commitment to funding research and development. ...*

Recess came and went, with the bill still stalled. On August 12, the Department of Health and Human Services declared Zika a public health emergency in Puerto Rico. When lawmakers returned to Washington, they found a letter from the Zika Coalition on their desks:

*Our nation faces billions of dollars in medical costs just from screening pregnant women for Zika infection and its consequences. It is imperative that all parties return to the negotiating table immediately to craft a Zika funding package that can be passed by the House and Senate and signed into law by the President.*

Yet more weeks passed.

**September 6, to House and Senate leadership:**

*As the virus gains a foothold in the mainland U.S., Americans have grown increasingly disillusioned with Congress' failure to act. Six months have elapsed since the Administration's request for emergency funds to combat Zika, time that could have been spent better preparing for and preventing the virus. The opportunity for total prevention has been squandered; Congress must act now to contain Zika and prevent it from spreading to other communities.*

**Incomplete funding, over half a year later**

At the end of September, Congress approved and President Obama signed a funding bill for \$1.1 billion. It was indeed vital funding. It supported staffing in high-incidence areas and it left many labs "in pretty good shape," Kyriacopoulos said. But valuable time had been lost — time that could have been spent "making better tests, getting tests to work better, and getting more definitive results." And the money fell \$800 million short of the full request.

The Zika Coalition's work continues. "We remind people on the Hill of our need to improve diagnostics, to work on vaccine

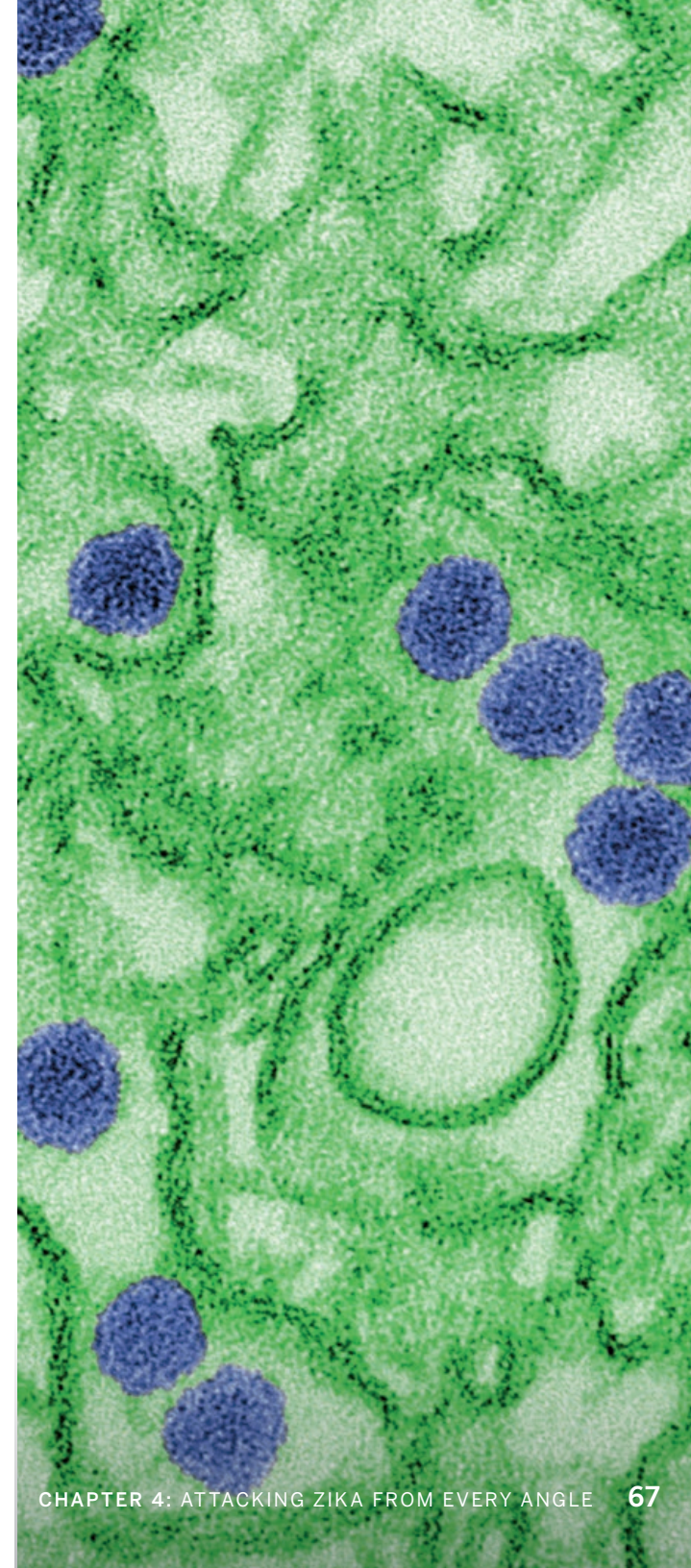
development, and to provide funding for the families of children with severe birth defects," said Pellegrini. "Lifetime health care costs can be as high as \$10 million per child."

**June 1, 2017, Zika Coalition testimony to the Senate Appropriations Committee:**

*We urge you to include ample funding to combat the Zika virus in the Fiscal Year (FY) 2018 appropriations bills. We commend Congress for providing supplemental funding for FY 2017, but it is imperative that Congress sustain that investment in FY 2018 and beyond. Zika virus remains a significant public health threat. ...*

*Among these [infected] are roughly 1,800 pregnant women, whose pregnancies are at risk for the serious birth defects Zika can cause. These numbers are dramatically higher in the U.S. territories, where more than 36,000 people and roughly 3,800 pregnant women, mostly in Puerto Rico, have been infected locally. We are disappointed that the President's Budget Request does not provide adequate resources to combat this ongoing public health threat.*

Current funding for Zika will run out in 2018.



## Members of the Zika Coalition

(as of June 2018)

- AABB
- American Association for Clinical Chemistry
- American Association for Pediatric Ophthalmology and Strabismus
- American Association of Colleges of Pharmacy
- American Association on Health and Disability
- American Clinical Laboratory Association
- American College of Nurse-Midwives
- American College of Preventive Medicine
- American Congress of Obstetricians and Gynecologists\*
- American Medical Association
- American Public Health Association\*
- American Sexual Health Association
- American Society for Reproductive Medicine
- American Society of Tropical Medicine and Hygiene
- Association for Professionals in Infection Control and Epidemiology
- Association of American Veterinary Medical Colleges
- Association of Maternal and Child Health Programs\*
- Association of Public Health Laboratories\*
- Association of Reproductive Health Professionals
- Association of Schools and Programs of Public Health
- Association of State and Territorial Health Officials
- Association of University Centers on Disabilities
- Association of Women's Health, Obstetric and Neonatal Nurses
- Avery's Angels Gastroschisis Foundation
- Big Cities Health Coalition
- Children's Environmental Health Network
- Commissioned Officers Association of the U.S. Public Health Service, Inc. (COA)
- Community Action Partnership
- Cooley's Anemia Foundation
- Council of State and Territorial Epidemiologists
- Easterseals\*
- Endocrine Society
- Epilepsy Foundation of New Jersey
- Every Child By Two
- Family Voices
- GBS|CIDP Foundation International
- Genetic Alliance
- Grifols
- Healthcare Ready
- Infectious Diseases Society of America\*
- Johnson & Johnson
- March of Dimes\*
- National Association of County and City Health Officials\*
- National Association of Pediatric Nurse Practitioners
- National Birth Defects Prevention Network
- National Coalition of STD Directors
- National Environmental Health Association\*
- National Foundation for Infectious Diseases
- National Hispanic Medical Association
- National Indian Health Board
- National Mosquito Control Association
- National Organization for Rare Disorders (NORD)\*
- Newborn Foundation
- Novavax
- OraSure Technologies
- Organization of Teratology Information Specialists
- Pregistry
- Public Health Institute
- Research!America
- RESOLVE: The National Infertility Association
- Society for Maternal-Fetal Medicine
- Society for Women's Health Research
- Spina Bifida Association
- Teratology Society
- The American Society for Clinical Pathology
- The Arc\*
- The National Campaign to Prevent Teen and Unplanned Pregnancy
- The Society for Healthcare Epidemiology of America
- Trisomy 18 Foundation
- Trust for America's Health\*
- University of South Florida Birth Defects Surveillance Program

\*designates Steering Committee Member

## CHAPTER 5:

# THE ZIKA STORY ISN'T OVER

In the world of Zika response, 2017 looked very different from 2016. With trained staff, updated tests and systems, and expanded connections, public health labs began the year prepared.

As of September 2017, more than a dozen diagnostics had received EUA letters from the FDA. And some tests in the pipeline, like more specific serology tests and assays that distinguish Zika from dengue, promise to someday eliminate the time-consuming step of PRNT confirmation altogether.

“The next generation of diagnostic tests is building off our current Zika experience,” said Gregory.

Labs that had streamlined their processes and increased their throughput capacity during the Zika response — with barcoding for tracking samples, online portals for reporting results, and updated LIMS capable of linking multiple samples to individual patients — found themselves better equipped to get vital test results to doctors and their patients in a clear, timely fashion. And the relationships needed to move samples and expedite trusted results had strengthened and expanded.



**“This disparate group of people was virtually writing the literature on Zika as it unfolded.”**

**– Lyle Petersen**

Director of the Division of Vector-Borne Diseases, National Center for Emerging and Zoonotic Infectious Diseases, CDC



Public health materials — often in multiple languages, with informative, easily comprehensible graphics — had become fixtures in airports nationwide. Screens, sprays, and the removal of standing water even from the smallest spaces were common practices in Zika-prone areas. Zika had become a topic discussed between pregnant women and their OB/GYNs, families, and partners nationwide.

And \$1.1 billion in federal funding — finally allocated after six months of tireless advocacy by the Zika Coalition — was supporting Zika efforts nationwide.

As is the case after every outbreak or incident, public health labs immediately harnessed lessons learned and resources gained from their Zika experience to prepare for the next emergency. “We did want to make changes in our serology lab and increase biosafety. Zika pushed us in that direction more quickly,” Kubin said about efforts in Texas.

“We’re trying to use this outbreak to really analyze all our processes and make them more efficient, particularly with our LIMS and pre- and post-analytical processes,” Messenger said about her team’s work in California. “This experience is going to make our lab so much better prepared for the next emergency.”

As for Zika’s mosquito carriers, “We found that we need to work on building up our

control capacity nationwide,” said Petersen. “We need a more sustained system of maintaining capacity. What I think Zika is telling us, coming on the heels of West Nile virus, is that it’s inevitable that we’re going to have more of these outbreaks come to our shores.”

### **The threat remains**

Viruses tend to decline after an outbreak. Dengue, yellow fever, and West Nile virus did — and Zika has been no exception.

In fact, a September 2, 2017, New Yorker headline posed the question: “Is Zika Gone for Good?”

The answer, according to many public health professionals, is no — not as long as humans and mosquitoes continue to be traveling species and viruses continue to be subject to mutation.

In 2017, mosquitoes capable of carrying Zika were reported in New Mexico, Wisconsin, even Canada. The *Aedes albopictus* joined its fellow Zika carriers *Aedes aegypti* in California for the first time. In September 2017, the Journal of Medical Entomology reported suitability for *Aedes aegypti* in 71 percent of U.S. counties, and that about 75 percent of U.S. counties are suitable for *Aedes albopictus*.

Conditions man-made and natural exacerbate the risk. In July 2017, Human



Rights Watch warned of Zika's potential to resurge in Brazil, spurred by poor sanitation and water conditions for more than one-third of the nation's population. According to the report, years of neglect contributed to the water and wastewater conditions that allowed the proliferation of the *Aedes* mosquito and the rapid spread of the virus. In the United States, concerns heightened in high-risk areas as Hurricanes Harvey in Texas, Irma in Florida, and Maria in Puerto Rico left devastated infrastructure in their wake.

Many of the regions most affected by Zika and other mosquito-borne illnesses reported record temperatures, Dr. Jonathan Patz from the University of Wisconsin-Madison pointed out in remarks to the American Association of Pediatrics.

**“The Zika story is not over yet. We’re in the midst of an evolving story.”**

– Sharon Messenger

Chief, Zoonotic and Vector-Borne Diseases Section, California Department of Public Health

“Even though climate is not the full story of Zika, it is a majorly enabling story.”

Developments at a much smaller scale might also lead to new dangers. “RNA viruses like Zika tend to change more than DNA viruses,” St. George said. “Chikungunya is a classic example. It was restricted to a specific vector. With one mutation in one gene it gained the ability to be transmitted by another mosquito to other regions of the world.”

In fact, such a mutation may have caused Zika's evolution from mild tropical virus to a serious threat to mothers and babies. According to a September 2017 study by Chinese researchers, a single mutation in a single amino acid in the Zika virus may be behind its connection to increased incidence of fetal microcephaly.



### A Steep Decline from 2016 to 2017

Location	Reported in 2016	Reported in 2017
California	491	127
Florida	1,107	110
New York	1,002	64
Puerto Rico	35,395	620
Texas	312	54

*Laboratory-confirmed symptomatic Zika virus disease cases and presumptive viremic blood donors reported by the California Department of Public Health (California figures) and to ArboNET by states and territories*



**“Another valuable thing from the experience was better connection between public health and mosquito control. Zika built these connections.”**

**— Christopher Gregory**

Arboviral Diseases Branch Chief,  
Division of Vector-Borne Diseases,  
NCEZID, OI, CDC

## **Knowledge grows for public health recommendations**

Behind every public health poster, PSA, and warning — and guiding every evolution of Zika’s testing algorithm — is extensive research by government, academic institutions, and the private sector. By 2017, the scientific community had a rich foundation of patients, samples, and outbreak experience to draw upon for answers.

Sexual transmission has been one of Zika’s biggest surprises. Studies of the 2013–2014 outbreak in French Polynesia suggested a potential connection, and in early 2016, a French patient was found to have 100,000 times the virus in his semen than in his urine or blood more than two weeks after experiencing symptoms. Researchers studying another Zika case proved sexual transmission by summer 2016.

With this connection established, the next question involved timing. How long can a man harbor the Zika virus after being infected?

A team from CDC and Colorado State University used a mouse model (because collecting specimens from the same human subjects over months is a logistical challenge) and discovered that Zika RNA can be detected in seminal fluids for up to 58 days, long after Zika symptoms usually disappear.

Ongoing research is also shaping guidance for Zika’s troubling complications in older patients. Petersen recalled the initial reports from islands in the Pacific suggesting increased rates of GBS during Zika outbreaks. “It was plausible because dengue and West Nile virus cause GBS, but the data were sparse,” he said.

During the first half of 2016, CDC tested these anecdotal findings in Puerto Rico by examining patients with suspected cases of GBS. Most of the patients were female with a median age of 55. Sixty-one percent had some kind of flavivirus infection, and 18 percent had confirmed cases of Zika.

In 2017, CDC worked with Brazil’s Ministry of Health to further study associations between Zika and GBS. These patients, from the city of Salvador, had a median age of 47.

“It may also be prudent to target public health messaging about GBS to older adult populations during ZIKV outbreaks,” researchers wrote in the discussion of their findings.



## For Zika Babies, a Lifetime of Complications

**A**ccording to an April 4, 2017, CDC report, 24 of the 250 pregnant women who had a confirmed Zika infection in 2016 gave birth to a fetus or baby with birth defects. The life of a baby born with Zika can be permanently impacted by conditions like microcephaly.

Babies with microcephaly can have medical problems like joint deformities, vision and hearing problems, and seizures.

They may experience:

- Poor appetite/feeding, weight gain, and growth
- Difficulties with movement and balance
- Speech delays and mild to severe learning disabilities

“The babies wailed in almost constant pain,” reporters for the Milwaukee Journal Sentinel wrote in their July 2017 special report on the virus.

For children affected by the virus and their families, the Zika story is a daily battle.



## Future progress depends upon sustained support

Currently there is no FDA-approved treatment for Zika. Researchers are exploring a spectrum of options, from malaria drugs to compounds used in traditional Chinese medicine.

No FDA-approved vaccine exists for Zika either — yet. Candidates under development at the National Institute of Allergy and Infectious Diseases include vaccines similar to those being developed for West Nile virus and dengue, a vaccine that uses a genetically engineered version of a virus that affects cattle, and a vaccine designed to protect against multiple mosquito-borne diseases.

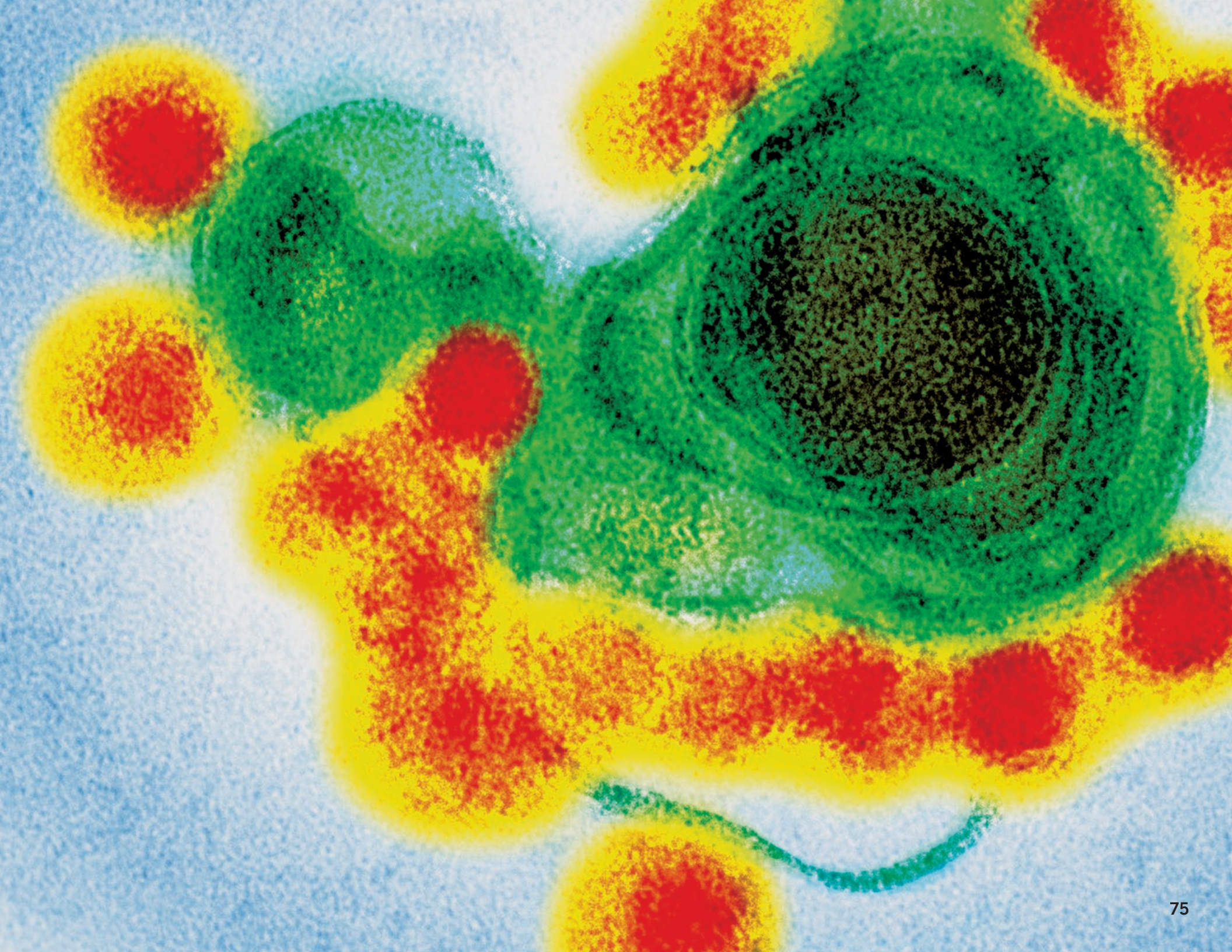
As researchers and innovators focus in on solutions, public health labs will continue their work conducting the tests that help policymakers, health providers, communities, and families nationwide.

Challenges to this work will mount if current Zika funding runs out in 2018. Without sufficient renewal of resources, “It’s going to take us longer to discover that people are becoming ill, longer to realize the connection between them, and longer to figure out how to treat them,” Kyriacopoulos said.

“The next arbovirus or infectious disease is a very real threat. We cannot let this infrastructure and funding erode again,” said Becker.

The scientific community is still learning about Zika’s complications and effects. Meanwhile, people and goods continue to transport diseases across the globe at an unprecedented rate, and vectors like mosquitoes continue to adapt to new surroundings. The question isn’t if another complex, surprising public health emergency like Zika will happen, it’s when.

With dedicated resources and sustained support, public health labs and their partners will be ready.



1947

1952

1986

2007

1947: Zika is first identified in **Uganda**

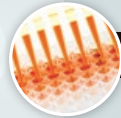
1952: Zika is first identified in **humans**

2007: First Zika outbreak in **Micronesia**

1986: CDC sets up a lab in **Puerto Rico** to fight **dengue fever**



**THE SPREAD OF ZIKA**



**DIAGNOSTICS MILESTONES**

# ZIKA VIRUS TIMELINE

2013–2014

2015

**2013–2014:** Zika outbreaks in **French Polynesia, Cook Islands, Easter Island, New Caledonia**

**FEB–APR 2015:** Nearly 7,000 cases of a disease with a mild skin rash are reported in northeastern **Brazil**

**MAY 2015:** **Brazil** confirms the first locally transmitted case of Zika in the Western Hemisphere

**OCT 2015:** **Brazil** reports an unusual increase in infants with microcephaly  
First reported cases in **Cabo Verde, Colombia**

**NOV 2015:** **Brazil** declares a public health emergency  
First reported cases in **El Salvador, Guatemala, Mexico, Paraguay, Suriname, Venezuela**

**DEC 2015:** Puerto Rico reports first case of local transmission  
First reported cases in **French Guiana, Honduras, Martinique, Panama**

**JAN 2016:** Laboratory-confirmed Zika cases are reported in **American Samoa**. First reported cases in **Barbados, Bolivia, Curacao, Dominican Republic, Ecuador, Guyana, Haiti, Jamaica, Nicaragua, Saint Martin, St. Croix**

**JAN 15, 2016:** Hawaii reports first Zika case linked to microcephaly in the U.S.

**FEB 2016:** First reported cases in **Argentina, Aruba, Bonaire, Saint Vincent and the Grenadines, Samoa, Sint Maarten, Trinidad and Tobago**

**FEB 2, 2016:** Texas reports first sexually reported Zika case in the U.S.

**FEB 26, 2016:** 116 people across 33 U.S. states have shown evidence of Zika infection since January 1, 2015

**MAR 10, 2016:** 2 cases of Guillain-Barré Syndrome are linked to Zika in the U.S.



**THE SPREAD OF ZIKA**



**DIAGNOSTICS MILESTONES**

**FEB 26, 2016:** FDA grants EUA for CDC's **MAC-ELISA test**

**MAR 17, 2016:** FDA grants EUA for CDC's **"3 in 1" Trioplex test**

**APR 28, 2016:** Quest Diagnostics' **RT-PCR test** is the first commercial test to get FDA EUA approval

**JAN 15, 2016:** CDC issues travel alerts for 14 countries and territories in **Central and South America** and the **Caribbean**, including **Puerto Rico** and **Brazil**

**JAN 19, 2016:** Florida reports Zika infection in three recent travelers to South America

**JAN 22, 2016:** Travel alerts expand to **Barbados, Bolivia, Ecuador, Guadeloupe, Saint Martin, Guyana, Cape Verde, and Samoa**

**FEB 2, 2016:** Texas reports first sexually transmitted Zika case

**FEB 4, 2016:** New York State offers free Zika testing to pregnant travelers

**FEB 10, 2016:** "Zika Virus Associated with Microcephaly" published in the New England Journal of Medicine

**MAR 25, 2016:** First sexually transmitted case confirmed in **California**

**APR 12, 2016:** CDC updates clinical guidance for **reproductive-age women and men**



**RAPID RESPONSE**

**FEB 23, 2016:** 50+ organizations write letter to Congress urging swift approval of Zika funding

**FEB 8, 2016:** President Obama requests **\$1.8 billion** in emergency Zika funding

**APR 5, 2016:** Zika Coalition writes Congress urging **new Zika funding** (not money redirected from elsewhere)

**APR 6, 2016:** Administration **reallocates \$589 million** of Ebola funds to Zika



**FUNDING**



# MAY

# JUNE

# JULY

# AUGUST

**JUN 16, 2016:**  
3 babies born with Zika-related microcephaly in the **U.S.**

**JUL 29, 2016:**  
**Florida** reports first local Zika transmission on the U.S. mainland

**AUG 12, 2016:**  
HHS declares Zika public health emergency in **Puerto Rico**

**JUL 29, 2016:** First local transmission in the mainland U.S. reported in **Florida**

**AUG 3, 2016:**  
**Florida** offers pregnant women free Zika testing

**AUG 23, 2016:**  
CDC posts travel notice for the **Bahamas**

**MAY 13, 2016:** Zika Coalition **writes senators** to urge support for Zika funding

**MAY 16, 2016:** House Republicans introduce bill for **\$622 million** for Zika funding

**MAY 17, 2016:** Senate passes bipartisan bill for **\$1.1 billion** in Zika funding

**MAY 18, 2016:** Zika Coalition urges House to **reject "inadequate" \$622 million bill**

**JUN 6, 2016:** Zika Coalition **writes House** urging Zika funding

**JUN 14, 2016:** Zika Coalition **writes Senate** urging Zika funding

**JUN 22, 2016:** House Republicans **pass \$1.1 billion Zika bill** with cuts to ACA and Planned Parenthood

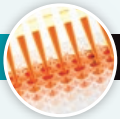
**JUN 28, 2016:** Zika Coalition **writes Congress** urging bipartisan Zika funding bill

**JUL 13, 2016:**  
Zika Coalition **writes Congress** urging lawmakers to pass a Zika funding bill **before the summer recess**

**AUG 3, 2016:** Zika Coalition **writes Congress** urging swift Zika funding passage **after recess**



THE SPREAD OF ZIKA



DIAGNOSTICS MILESTONES

SEPT 30, 2016: CDC updates its response plan based on the latest knowledge about the virus and its **effects on pregnant women and infants**

OCT 19, 2016: CDC strengthens travel and protection recommendations for **Miami-Dade County**, an area of active Zika transmission

DEC 9, 2016: **Florida** declared free of locally transmitted virus



RAPID RESPONSE

SEPT 6, 2016: Congress returns from recess, receives **letter from Zika Coalition** urging swift, adequate Zika funding

SEPT 28, 2016: **Senate and House pass \$1.1 billion** in Zika funding as part of massive government funding package

SEPT 29, 2016: President Obama signs **\$1.1 billion stopgap Zika funding bill**



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