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SCIENCE OF ZIKA: THE DNA OF AN EPIDEMIC

HEARING

BEFORE THE

COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY
HOUSE OF REPRESENTATIVES

ONE HUNDRED FOURTEENTH CONGRESS

SECOND SESSION

May 25, 2016

Serial No. 114–79

Printed for the use of the Committee on Science, Space, and Technology

Available via the World Wide Web: http://science.house.gov

U.S. GOVERNMENT PUBLISHING OFFICE
20–876PDF WASHINGTON : 2017

For sale by the Superintendent of Documents, U.S. Government Publishing Office
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SCIENCE OF ZIKA: THE DNA OF AN EPIDEMIC

WEDNESDAY, MAY 25, 2016

HOUSE OF REPRESENTATIVES,
COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY,
Washington, D.C.

The Committee met, pursuant to other business, at 10:25 a.m., in Room 2318 of the Rayburn House Office Building, Hon. Lamar Smith [Chairman of the Committee] presiding.

LAMAR S. SMITH, Texas
CHAIRMAN

EDDIE BERNICE JOHNSON, Texas
RANKING MEMBER

Congress of the United States
House of Representatives
COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY
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Science of Zika: The DNA of an Epidemic

Wednesday, May 25, 2016
10:15 a.m. – 12:15 p.m.
2318 Rayburn House Office Building

Dr. Kacey Ernst, Associate Professor, Department of Epidemiology and Biostatistics, University of Arizona

Dr. Daniel Neafsey, Associate Director, Genomic Center for Infectious Disease, Broad Institute of MIT and Harvard

Dr. Steven Presley, Professor, Department of Environmental Toxicology, Texas Tech University

Mr. Hadyn Parry, Chief Executive Officer, Oxitec

U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY

HEARING CHARTER

Wednesday, May 25, 2016

TO: Members, Committee on Science, Space, and Technology

FROM: Majority Staff, Committee on Science, Space, and Technology

SUBJECT: Full Committee hearing "Science of Zika: The DNA of an Epidemic"

The Committee on Science, Space, and Technology will hold a hearing titled *Science of Zika: The DNA of an Epidemic* on Wednesday, May 25, 2016, at 10:15 a.m. in Room 2318 of the Rayburn House Office Building.

Hearing Purpose:

The purpose of the hearing is to examine the science of the Zika virus and the *Aedes aegypti* mosquito that transmits the disease. The hearing will look at the science of preparing for a potential Zika epidemic in the continental United States, including the forecasting, controlling, preventing and testing for the disease and the basic research of how the mosquito transmits the virus.

Witness List

- **Dr. Kacey Ernst**, Associate Professor, Department of Epidemiology and Biostatistics, University of Arizona
- **Dr. Daniel Neafsey**, Associate Director, Genomic Center for Infectious Disease, Broad Institute of MIT and Harvard
- **Dr. Steven Presley**, Professor, Department of Environmental Toxicology, Texas Tech University
- **Mr. Hadyn Parry**, Chief Executive Officer, Oxitec

Staff Contact

For questions related to the hearing, please contact Raj Bharwani or Jenn Wickre of the Majority Staff at 202-225-6371.

Chairman SMITH. The Committee on Science, Space, and Technology will again come to order.

Without objection, the Chair is authorized to declare recesses of the Committee at any time.

Good morning, and welcome to today's hearing titled "The Science of Zika: the DNA of an Epidemic." Let me recognize myself for five minutes for an opening statement.

For more than a century, humans have been at war with the mosquito. In 1901, a U.S. Army physician named Walter Reed led a team in Cuba studying diseases that proved yellow fever was transmitted by mosquitoes.

Since that discovery, governments, scientists, and individuals have pursued ways to prevent and control deadly mosquito-borne outbreaks. From yellow fever, to dengue fever, to Nile virus, humans are constantly under siege from new mosquito-transmitted diseases.

Today, we will examine the state of science in the most recent battle in the war against mosquito-borne disease: the Zika virus.

While for most people Zika causes only mild illness, the Centers for Disease Control and Prevention have found that there is a link between Zika infection during a woman's pregnancy and severe birth defects. For some adults there could also be serious neurological impacts.

Summer is coming and so are the mosquitoes that spread the Zika virus. The Gulf Coast of Texas, among other places, has been called ground zero for this type of mosquito that carries Zika.

Zika infections have spread to over 80 countries and territories in Latin America and the Caribbean. We have seen local transmission of the virus in U.S. territories. In addition, over 500 people in the United States mainland have acquired the Zika virus while traveling out of the country. Over 300 of these are pregnant women.

These dangers raise serious questions about the Administration's handling of travel alerts. The CDC has issued level two alerts for 49 countries and territories, which advise travelers only to "practice enhanced precautions." They have not issued any level three warnings to "avoid nonessential travel," as they did during the Ebola epidemic in West Africa.

The World Health Organization in February declared Zika a Public Health Emergency of International Concern. Such declaration is reserved for a situation that is "serious, unusual or unexpected, carries implications for public health beyond the affected state's national border, and may require immediate international action."

Why has the Administration not raised the travel alert level for countries with the highest number of Zika infections, such as Brazil and Colombia? Is the Administration so worried about attendance at the Olympics in Brazil this summer that they're willing to endanger American lives by not providing better warnings? At the least, pregnant women should be told to avoid nonessential travel to Brazil and Colombia. Anything less is putting political correctness ahead of the well-being of American women.

Today I hope that we can gather additional scientific information on Zika and the mosquito that spreads it. I also look forward to

hearing about research on the best methods for controlling the spread of the Zika virus.

[The prepared statement of Chairman Smith follows:]

COMMITTEE ON
SCIENCE, SPACE, & TECHNOLOGY
Lamar Smith, Chairman

For Immediate Release
May 25, 2016

Media Contacts: Alicia Criscuolo, Thea McDonald
(202) 225-6371

Statement of Chairman Lamar Smith (R-Texas)
Science of Zika: The DNA of an Epidemic

Chairman Smith: For more than a century, humans have been at war with the mosquito. In 1901, a U.S. Army physician named Walter Reed led a team in Cuba studying diseases that proved yellow fever was transmitted by mosquitos. Since that discovery, governments, scientists and individuals have pursued ways to prevent and control deadly mosquito-borne outbreaks.

From yellow fever, to dengue fever, to Nile Virus – humans are constantly under siege from new mosquito-transmitted diseases.

Today, we will examine the state of science in the most recent battle in the war against mosquito-borne disease: the Zika virus.

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Summer is coming and so are the mosquitos that spread the Zika virus. The Gulf Coast of Texas and other places has been called "ground zero" for the type of mosquito that carries Zika.

Zika infections have spread to over 60 countries and territories in Latin America and the Caribbean. We have seen local transmission of the virus in U.S. territories. In addition, over 500 people in the United States mainland have acquired the Zika virus while traveling out of the country. Over 300 of these are pregnant women.

These dangers raise serious questions about the administration's handling of travel alerts. The CDC has issued only level 2 alerts for 49 countries and territories, which advise travelers to only "practice enhanced precautions." They have not issued any level 3 warnings to "avoid nonessential travel," as they did during the Ebola epidemic in West Africa.

The World Health Organization (WHO) in February declared Zika a "Public Health Emergency of International Concern" (PHEIC).

Such declaration is reserved for a situation that is "serious, unusual or unexpected, carries implications for public health beyond the affected State's national border, and may require immediate international action."

Why has the administration not raised the travel alert level for countries with the highest number of Zika infections, such as Brazil and Colombia?

Is the administration so worried about attendance at the Olympics in Brazil this summer that they're willing to endanger American lives by not providing better warnings? At the least, pregnant women should be told to avoid nonessential travel to Brazil and Colombia. Anything less is putting political correctness ahead of the well-being of American women.

Today I hope that we can gather additional scientific information on Zika and the mosquito that spreads it. I also look forward to hearing about research on the best methods for controlling the spread of the Zika virus.

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Chairman SMITH. That concludes my opening statement, and the gentlewoman from Texas, Ms. Johnson, the Ranking Member, is recognized for her opening statement.

Ms. JOHNSON. Thank you very much, Mr. Chairman, for holding this hearing.

This morning we are talking about the Zika virus, something that has been in the news a lot lately and that we have been debating on the House Floor.

The most common way that someone becomes infected with the Zika virus is by a mosquito bite. The symptoms of the virus may include fever, rash, joint pain, and red eyes. These symptoms are typically mild, and many people who get infected with the Zika virus have no symptoms or do not seek medical treatment.

Although the Zika virus was first identified in the late 1940s, there were no major outbreaks of the Zika virus until 2007. Since then, the Zika virus has been reported in almost 70 countries and territories, including the major Zika outbreak that is happening in Brazil, where more than a million cases have been reported.

In the United States, local transmission of the Zika virus has been reported in several U.S. territories. In particular, Puerto Rico is suffering from a large Zika outbreak in which more than 800 cases have been reported to date. In the continental United States, the only Zika cases that have been reported involve people who have traveled to places that have a Zika outbreak. But the number of those cases is already more than 500, and there is significant concern that the continental United States will start seeing locally transmitted cases of the Zika virus once we get further into the mosquito season.

Even though my home State of Texas only has 35 travel-associated cases of the Zika virus so far, I have been hearing from a lot of concerned constituents about the Zika virus and the potential for a Zika outbreak in Texas this summer.

I would imagine that many of my colleagues on this Committee have been hearing from concerned constituents as well. I am pleased that we will have more information to pass on to them after this hearing.

What is especially troubling about the Zika virus is that it has been associated with several significant health conditions, including birth defects in infants and neurological conditions in adults. Most notably, the Zika virus has been linked to microcephaly, a birth defect where the brain does not develop during pregnancy or after birth. This condition results in significant impairments for the baby and can result in death. Brazil has seen thousands of these cases. In the United States and territories, hundreds of pregnant women who have been infected with the Zika virus are currently being monitored. Unfortunately, last week the first case of microcephaly was reported in Puerto Rico.

Additionally, the Zika virus has been associated with Guillain-Barre syndrome, a disorder where the body's immune system attacks part of the nervous system. People who have this syndrome usually recover, but the syndrome can result in permanent paralysis or death.

Understandably, people are very concerned about this virus and want more information. That is why I am happy we are holding

this hearing to learn more about the science behind this disease and to hear more about the key research questions. For example, how is the virus transmitted from mother to fetus and how is the risk to the fetus related to the timing of the mother's infection? Does Zika cause Guillain-Barre syndrome and if so, is there an intervention that can prevent this terrible condition?

We also need to know where the vector mosquitoes live, the incubation period of the virus in the mosquito, and whether the infected female can transmit the virus to her eggs.

Finally, it is perplexing that the Zika virus was first identified in the late 1940s, but we are only seeing major Zika outbreaks now. What has changed in the last 70 years to make conditions more suitable for the virus to be transmitted? I imagine that the rapid increase in human travel has played a large role, but I do wonder how much other factors like insecticide resistance and climate change may be playing in the spread of this disease.

All of these research questions need to be answered as we plan effective mosquito control programs and prepare to invest our resources. But traditional mosquito control programs will not be enough.

I am looking forward to hearing from our expert witnesses on how emerging technologies that use advanced genetics and biologic technologies could help control the Zika virus.

It is also important to note that to support the necessary research, surveillance, mosquito control, and drug and vaccine development programs that will be needed to control this disease, we must ensure that adequate funding is provided. I am hopeful that Congress can come together to provide that funding. Time is of the essence. And I'm thankful that the experts are here.

And just before I yield back, Mr. Chairman, I want to take a moment to recognize one of my staff, Kim Montgomery, who is sitting beside me now. She's leaving soon to move to Vienna, Austria. She has been an integral part of the staff. Her passion and expertise will be greatly missed. I want to thank you for your service and wish you luck in your new, exciting chapter in Vienna.

Thank you, and I yield back, Mr. Chairman.

[The prepared statement of Ms. Johnson follows:]

OPENING STATEMENT
Ranking Member Eddie Bernice Johnson (D-TX)

House Committee on Science, Space, and Technology
"The Science of Zika: The DNA of an Epidemic"
May 25, 2016

Thank you, Mister Chairman for holding this hearing. This morning we are talking about the Zika virus—something that has been in the news a lot lately and that we have been debating on the House floor.

The most common way that someone becomes infected with the Zika virus is by a mosquito bite. The symptoms of the virus may include fever, rash, joint pain, and red eyes. These symptoms are typically mild and many people who get infected with the Zika virus have no symptoms or do not seek medical treatment.

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In the continental United States, the only Zika cases that have been reported involve people who have traveled to places that have a Zika outbreak. But the number of those cases is already more than 500, and there is significant concern that the continental United States will start seeing locally transmitted cases of the Zika virus once we get further into mosquito season.

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Additionally, the Zika virus has been associated with Guillain-Barré syndrome, a disorder where the body's immune system attacks part of the nervous system. People who have Guillain-Barré syndrome usually recover, but the syndrome can result in permanent paralysis or death.

Understandably, people are very concerned about this virus and want more information. That is why I am happy we are holding this hearing to learn more about the science behind this disease and to hear more about the key research questions. For example, how is the virus transmitted from mother to fetus and how is the risk to the fetus related to the timing of the mother's infection? Does Zika cause Guillain-Barré syndrome and if so, is there an intervention that can prevent this terrible condition?

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It is also important to note that to support the necessary research, surveillance, mosquito control, and drug and vaccine development programs that will be needed to control this disease, we must ensure that adequate funding is provided. I am hopeful that Congress can come together to provide that funding. Time is of the essence.

In closing, I want to thank the expert witnesses for being here today, and I yield back the balance of my time.

Chairman SMITH. Thank you, Mrs. Johnson.

Let me introduce our witnesses, and our first witness today is Dr. Kacey Ernst, Associate Professor, Department of Epidemiology and Biostatistics at the University of Arizona. Dr. Ernst joined the University of Arizona staff in 2008. Her area of specialization is the intersection of environment, humans, and mosquito vectors of disease. As an epidemiologist, her role is to work with a highly interdisciplinary team of scientists to integrate information from climatology, entomology, medical anthropology, and ecology across multiple institutions to develop an understanding of the emergence of infectious diseases. Dr. Ernst received her master's in public health and doctorate in epidemiology from the University of Michigan.

We want to thank particularly Dr. Ernst today for being here because in so doing she is missing her daughter Savannah's graduation from the fifth grade and on to middle school. So tell your daughter that we appreciate your good help in trying to help the Federal Government, and I hope she'll excuse you missing that graduation.

Our second witness today is Dr. Daniel Neafsey, Associate Director, Genomic Center for Infectious Disease at the Broad Institute of MIT and Harvard. In this role, Dr. Neafsey leads a research group studying the DNA of mosquito vectors and the pathogens they transmit. He has developed pioneering resources and computational methodologies for genetic studies of mosquitoes and mosquito-borne pathogens. Dr. Neafsey received his B.A. from Loyola University in Chicago and his Ph.D. from Harvard University.

Our next witness, Dr. Steven Presley, will be introduced by the gentleman from Texas, Mr. Neugebauer.

Mr. NEUGEBAUER. Well, thank you, Mr. Chairman.

Our third witness today is Dr. Steven Presley. He's a Professor in the Department of Environmental Toxicology at Texas Tech University. Dr. Presley's professional career has focused upon vector-borne infectious diseases with an emphasis on biological threat assessment and countermeasures to protect the population from infectious diseases. He's published more than 90 scientific and technical papers, co-edited two textbooks, authored and co-authored 11 book chapters in the fields of biological and chemical countermeasures and diseases of wildlife. He served in the United States Navy in the Medical Services Corps and he was an officer for more than 12 years before joining the faculty at Texas Tech University in 2002. He earned his bachelor of science in animal science from Texas Tech University and master of science and doctorate of philosophy in entomology from Oklahoma State. It's good to have a fellow Red Rider, Dr. Steven Presley, with us today.

Chairman SMITH. Thank you, Mr. Neugebauer.

Our last today is Mr. Hadyn Parry, Chief Executive Officer of Oxitec, a U.K.-based company pioneering the use of genetic engineering to control insects that spread disease and damage crops. During his 15-year career at Zeneca Syngenta, he held various positions including general manager of Zeneca Plant Sciences. Mr. Parry also has served as the European Director and Global Head of R&D for Advanta, one of the world's largest seed companies. More recently, he was CEO of MNL Pharmaceuticals, a company that was focused on pioneering a novel approach to immunology.

Mr. Parry received a bachelor of arts in international history and politics from the University of Leeds.

We welcome you all, and Dr. Ernst, we will begin with you.

TESTIMONY OF DR. KACEY ERNST,
ASSOCIATE PROFESSOR,
DEPARTMENT OF EPIDEMIOLOGY
AND BIOSTATISTICS,
UNIVERSITY OF ARIZONA

Dr. ERNEST. Thank you. Thank you, Chairman Smith and Ranking Member Johnson.

So today I want to give you a little bit of background on the Aedes aegypti mosquito. This is the mosquito depicted here. It is the primary vector of Zika virus. It's highly adaptable and highly invasive. It's originally from sub-Saharan Africa but has been widely dispersed across the globe through the mobilization of people and goods.

Aedes aegypti is tightly linked to humans and their activities. It prefers to feed on human blood, and lays its eggs in manmade containers in and around homes. One of the reasons why it's such a difficult mosquito to control is because it can exploit even as much as one inch of water to go through its entire immature lifecycle.

It's a day biter, which means that it primarily feeds in the morning and in the afternoon, which means things like bed nets are not as effective as protecting against the diseases that it's transmitting.

Not only does this mosquito transmit Zika virus but it is also a primary transmitter of yellow fever, dengue, chikungunya, and one that you probably haven't heard of yet, which is called Mayaro virus. Next slide, please.

[Slide.]

This is the CDC's recently updated maps of the estimated distribution of Aedes aegypti and Aedes albopictus in the United States. Aedes albopictus is a relative of Aedes aegypti, which is also capable of transmitting Zika virus, but it can withstand cooler temperatures and it is a more generalist feeder. That means that it doesn't feed as preferentially on humans as Aedes aegypti. Its role in the current outbreak is not well understood at this time.

The ranges here are only estimates because many of the jurisdictions in these areas do not have active surveillance for Aedes species. Next slide, please.

[Slide.]

The predominant transmission cycle for Zika virus occurs when a female Aedes aegypti mosquito bites an infected human. The virus goes through a development stage in the mosquito of a currently unknown time period, probably about a week is what we estimate at this time, and that is dependent upon the temperature. It would be faster if you have hotter temperatures. This is called the extrinsic incubation period. After that time period, the mosquito is capable of transmitting the virus to the next person that it bites and then remains capable of transmitting for the duration of her life, about two to four weeks.

It's not yet known if the Zika virus can be transmitted through vertical transmission. This means that an infected female mosquito could transmit the virus to her offspring. If it proves to be true, the female Aedes aegypti could emerge infectious from their immature aquatic state and be able to infect people the first time that they bite, shortening the transmission cycle. It would also mean that from season to season, eggs that had over wintered could potentially harbor the virus and it would not need to be reintroduced the next season.

Also depicted in this slide are other transmission modes, which would be sexual transmission from a male partner to a female partner, and then of course, the transmission from the mother to the fetus. Next slide, please.

[Slide.]

In order to create forecasts of when and where transmission of Zika may occur, there are many components of the system that would need to be understood. We can use weather forecasts to drive models of the mosquito because their biology is largely determined by weather and climate. As you can see in this rather complex depiction here, at each stage of the mosquito lifecycle, you have influences of both temperature as well as precipitation and manmade filling of the habitat. Not each of these links is well defined so we use the best knowledge that we have to estimate the relationships that you see here. The mosquito component of this model is much better understood at this point because Aedes aegypti have been studied in the context of dengue and yellow fever for decades. The top row, which depicts the human portion of the transmission cycle—people who are susceptible, exposed, then infectious and then recover from the disease—is the least understood part of this cycle.

It's also important to note that while this is a theoretical model, there are other things that can mitigate this relationship, things like vector control, socioeconomic factors, as well as other human activities that could alter what would be depicted coming out of a model. Next slide, please.

[Slide.]

In the work that we recently published, we initiated the process of exploring some of these complex factors in 50 cities across the United States. What you see on this map is the relative potential abundance of Aedes aegypti as projected from a model using average seasonal climate data. On the top circle, you have the average potential abundance for January, and on the bottom, the potential abundance for July. Some of the areas that have the highest projected abundance coincide with areas where there's been local outbreaks of dengue and chikungunya viruses already.

The size of the circle indicates the average number of monthly arrivals from the countries where Zika virus was circulating in February. The tan shading demonstrates the distribution of where actual observations of Aedes aegypti have been made across this area.

The work we published is only a first step towards actual forecasting. We need better surveillance, improved knowledge of the virus-mosquito-human interactions, and sustained support for the infrastructure and dissemination of forecasts.

Thank you.
[The prepared statement of Ms. Ernst follows:]

Testimony of
Kacey C. Ernst PhD, MPH
Associate Professor, College of Public Health, College of Geography, and College of Animal, and Comparative Biomedical Sciences, the University of Arizona
Before the U.S. House of Representatives Committee on Science, Space, and Technology

Title: Science of Zika: The DNA of an Epidemic

May 25, 2016

Introduction

Chairman Smith and Ranking Member Johnson, my name is Dr. Kacey C. Ernst and it is an honor to be providing this testimony. I am testifying about the current state of knowledge of the mosquito *Aedes aegypti* in the United States as it relates to Zika virus transmission and the current limitations and potential for forecasting Zika transmission in the United States.

I am an Associate Professor in the Department of Epidemiology and College of Public Health at the University of Arizona. I also hold positions in the Colleges of Geography and Animal and Comparative Biomedical Sciences, as well as in three interdisciplinary programs: Entomology and Insect Science; Global Change; and, Arid Lands. My area of specialization is the intersection of environment, humans, and mosquito vectors of disease. As an epidemiologist, my role is to work with a highly interdisciplinary team of scientists to integrate information from climatology, entomology, medical anthropology, and ecology to develop an understanding of the emergence of infectious diseases. I have conducted work on the *Aedes aegypti* mosquito since arriving at the University of Arizona in 2008.

Prior to joining the faculty at the University of Arizona, I held positions in public health as an epidemiologist focused on pandemic threat reduction and bioterrorism preparedness. I graduated from the University of Michigan in 2006 with my doctorate in Epidemiology.

State of knowledge of the *Aedes aegypti* mosquito as it relates to Zika virus transmission

For mosquito-borne transmission of Zika virus, the following conditions must be met: there must be a susceptible human population, presence of the Zika virus, presence of a mosquito that is capable of transmitting the virus, and environmental conditions that allow the interaction of all three. Transmission potential is higher when: 1) there are higher densities of a mosquito that is biologically capable of transmission-- in this case *Ae. aegypti* and to a lesser extent *Ae. albopictus*, 2) these mosquitoes survive long enough to transmit the virus, and 3) the mosquitoes are feeding on humans at higher rates [1]. While seemingly simple, **understanding**

these components in relation to a specific virus can take decades of research, as they are very context specific.

There is a long history of *Aedes aegypti* research that focuses on understanding these components, its biology, and interactions with arboviruses. Arboviruses are diseases carried or vectored by insects or related animals like ticks. Much of the previous work has focused on important viruses transmitted by *Ae. aegypti*, including dengue, yellow fever, and chikungunya, as Zika virus has only recently been perceived as a significant human threat. Much of what we currently assume about Zika virus is based upon the relationship between dengue viruses and *Ae. aegypti,* given they are closely related viruses that have been widely transmitted for hundreds of years [2]. However, the amount of knowledge specific to Zika virus is growing exponentially as the global health crisis has unfolded.

Aedes aegypti is found in many urban areas throughout the Southern United States and its potential range extends into the eastern seaboard (see Figure 1). Yellow fever outbreaks that occurred in the 1640's from southern Florida to New York City indicate that *Ae. aegypti* populations lived in these areas centuries ago. The decline in these diseases is attributed to improved living conditions, including piped water and sewers, and reduction of the introduction of *Ae. aegypti* through shipping due to changes in shipping routes [3]. **We do not really know the complete distribution of *Ae. aegypti* in the United States because surveillance for the mosquito is not consistent across jurisdictions, and many do not have the resources to carry out the mosquito surveillance needed to determine if *Aedes* species are established in their jurisdiction.**

Ae. aegypti is a highly invasive species. It is originally from sub-Saharan Africa but has now spread throughout the warmer regions of the world, often hitchhiking in human-made containers like old tires. **This mosquito exploits the ways we have changed our environment**, including our use of many disposable containers, increasing movement of people and goods, and migration of much of the population to dense urban centers [4]. *Ae. aegypti* strongly prefers to feed on human blood and lives in and around our homes. As will likely be mentioned by others testifying here today, these mosquitoes are extremely difficult to control. The female mosquito lays her eggs above the water line on the side of the container, then the eggs are submersed in water when it rains or the container is filled by people. They can exploit extremely small pools of water and can mature from egg to adult within 7-10 days in only an inch of water [5]. **A single back yard may have dozens of containers such as buckets, birdbaths and old tires, which when filled with water by rain or human activities, like watering plants or storing drinking water, provide habitat for the mosquito.** Adult mosquitoes will also readily enter homes and can lay their eggs in vases, fish tanks and other sources of water. This tight link with humans and the built environment make them very efficient vectors of viruses such as Zika, dengue, chikungunya, and yellow fever. They are also known to carry other viruses, such as Mayaro virus, which are currently considered of minor importance, just as Zika virus was as recently as two years ago.

The transmission cycle of Zika virus between humans and *Aedes aegypti* mosquitoes is similar to the other viruses transmitted by mosquitoes. Most commonly, **transmission of Zika virus occurs when an infected person is bitten by a female mosquito of a particular species.** This includes female *Aedes aegypti* and a related species, *Aedes albopictus* (the Asian tiger mosquito, common in the Eastern United States). Once the mosquito has ingested the infected blood, it takes a specific period of time for the virus to move through the mosquito, replicate itself, and migrate back to the salivary glands. Only then can the transmission cycle be completed during the next blood meal taken by the *Ae. aegypti* female mosquito. As the mosquito feeds on the human blood, she injects virus-infected saliva into the person. The time period between when the mosquito first picks up the virus and when she can pass it to another person is known as the extrinsic incubation period, or **EIP**, and once the EIP is completed, the mosquito can transmit the virus for the rest of her life, which ranges between 2-4 weeks.

The shorter the EIP is, the faster the virus can be transmitted through a population. This is for two reasons: first, it reduces the time between potential infectious bites, and secondly, it increases the chances that a mosquito will be able to survive long enough to transmit the virus. The EIP is regulated by both the amount of virus ingested and temperature conditions. The warmer it is, the more rapid the EIP. **At this time, the EIP is not well-established for Zika viruses.** For dengue viruses, it is 7-10 days. The research group of which I am a member, led by Dr. Michael Riehle, has successfully competed for a grant from the National Science Foundation (NSF) to determine the EIP under different temperature conditions to determine how rapid the EIP is for Zika virus within the mosquito.

In addition to the primary Zika virus transmission cycle between mosquitoes and humans, there is a secondary transmission route in mosquitoes that may be possible, known as **vertical transmission**. Vertical transmission occurs when an infected female mosquito passes the virus directly to her offspring. In this scenario, the female mosquito will emerge from the egg already infected with the virus. When the female mosquito takes the first blood meal after emergence, it could already be capable of transmitting the virus to a human. There is some limited evidence that vertical transmission may occur, including a male mosquito that tested positive for Zika virus (only females feed on blood), and rapid seasonal onset of Zika virus transmission which might suggest the virus was harbored in eggs from the previous season [6, 7].

If vertical transmission of Zika virus proves to be common in *Ae. aegypti* populations, this could have implications for the speed of the spread and would mean that Zika virus might not have to be introduced each mosquito season. Eggs that were laid during one mosquito season could harbor the virus and emerge as adults the following mosquito season ready to transmit the virus. The role that vertical transmission may play in the Zika pandemic is currently unclear. For dengue viruses, vertical transmission is considered relatively uncommon and not a significant contributor to transmission [8]. As part of the experiments proposed for EIP, Dr. Riehle's group will also be conducting laboratory experiments to determine the frequency that it occurs in a laboratory setting. This would need to be coupled with evidence from the field, which

has been proposed by colleague Dr. Kathleen Walker in a National Institutes of Health (NIH) grant application currently under review, to determine whether vertical transmission happens at a significant level during Zika outbreaks.

Key gaps in knowledge about the interactions between the Zika virus and the vector *Ae. aegypti* raise the following questions:

- Is being infected with the Zika virus detrimental to the *Ae. aegypti* mosquito (if the Zika virus shortens the *Ae. aegypti* lifespan, this would reduce transmission potential)?
- Are the sub-species of *Ae. aegypti* found through the United States equally competent vectors of the Zika virus compared to those sub-species attributed to the current pandemic in Latin America?
- What are the minimum infectious doses of virus required for the *Ae. aegypti* mosquito to become infected and subsequently infectious to humans?
- Does co-infection with other pathogens increase or decrease the transmission potential of Zika virus?
- Is the probability of transmission to and from the mosquito influenced by temperature?
- Can people who do not show symptoms of Zika virus transmit the virus to the *Ae. aegypti* and *Ae. albopictus*?

These are fundamental questions that need to be answered before accurate models of disease risk can be constructed. Recent evidence has been generated in laboratory studies from Dr. Thais Chouin-Carneiro of Instituto Oswaldo Cruz, a research center in Brazil, and Dr. Anubis Vega-Rua from Institut Pasteur that indicate *Ae. aegypti* and *Ae. albopictus* mosquitoes from the Americas have low vector competence, or the biological ability of the mosquito to transmit the virus, and attribute the large-scale outbreak to high mosquito numbers and human populations that are completely susceptible [9]. Additional research is needed to confirm these findings and several research groups in the United States have recently received pilot funding from the NSF to address some of these questions, including the research group of which I am a member, Dr. Courtney Murdock's group at the University of Georgia and Dr. Jefferson Vaughan at the University of North Dakota.

Other mosquitoes of potential importance for Zika transmission

It is broadly agreed that *Ae. aegypti* is the most important vector for transmission of Zika virus [10]. However, ***Ae. albopictus* mosquitoes, which have a broader potential range across the United States because they can survive cold weather better than *Ae. aegypti*, are also a capable of transmitting Zika virus**. Recently Zika virus was found in *Ae. albopictus* in Mexico, so they may also be transmitting Zika virus [11]. *Ae. albopictus* has spread over the past decade in the continental United States and its potential range reaches further northward than *Ae. aegypti*. *Ae. albopictus* are more general feeders than *Ae. Aegypti,* which highly prefer human blood meals. Yet, evidence in the Northeastern United States demonstrates that *Ae. albopictus* also take

a substantial proportion of blood meals from humans [12]. When a vector feeds primarily on humans, this increases the likelihood of transmission of viruses infecting human populations. These findings highlight **the importance of enhancing monitoring and surveillance for both *Ae. albopictus* and *Ae. aegypti*.**

The potential and limitations of forecasting Zika virus transmission risk across the United States

Transmission of arboviruses, such as Zika virus, is driven by multiple factors, including environmental suitability to support the vector and the virus, interactions among vectors and the human population, and introduction of the virus into susceptible vector and human populations. Accurate predictions of transmission risk rely on the integration of information from all of these complex processes.

As part of our work to understand the risk of Zika virus infection in the continental United States, our team of scientists, led by Dr. Andrew Monaghan at the National Center for Atmospheric Research (NCAR), modeled seasonal dynamics of the *Ae. aegypti* mosquito vector across 50 cities in the Southern United States [13]. The intention of this map was **to provide information for decision-makers, such as yourselves, on the time periods and geographic areas with higher potential risk for local Zika virus transmission.** These maps depict the areas that are considered *climatically suitable* for the seasonal establishment of *Ae. aegypti* populations, but some of the 50 cities included in this analysis do not have confirmed *Ae. aegypti* populations. Because there is no defined threshold for "number of *Ae. aegypti* needed for transmission," we made a relative comparison between the predicted level of *Ae. aegypti* in 49 cities to the predicted levels in Miami, FL, one of the most climatically suitable areas in the continental United States that has a history of local transmission of other *Ae. aegypti*-borne viruses (dengue and chikungunya). It should further be noted that the standard of Miami, FL, is not the same as a standard from other areas where Zika virus is currently circulating as the southern United States lies at the cool margins of the range of *Ae. aegypti* [3].

The models used to predict the relative periods of climatic suitability for *Ae. aegypti* populations rely on our best, but incomplete, understanding of the processes by which temperature, precipitation, and humidity drive the dynamics of *Ae. aegypti*. Generally, more rainfall means more mosquitoes when man-made containers are present to hold water and provide habitat for the mosquito larvae. Temperature is important because warmer temperatures increase mosquito survival, and the development time between egg and adult mosquitoes becomes shorter, enabling populations to grow quickly. In addition, warmer temperatures shorten the time between blood meals taken by the *Ae. aegypti*. When warm temperature thresholds are exceeded, however, which occurs in some cities in the Southwestern United States during mid-summer, *Ae. aegypti* may not survive as well [14]. These relationships are complex and not all of them are well-defined, making modeling of *Ae. aegypti* populations somewhat uncertain.

To reduce this uncertainty our group used two models that have been validated previously: Skeeterbuster, developed from the original container-inhabiting mosquito simulation model (CiMSiM) by Dr. Dana Focks at University of Florida and refined by Dr. Fred Gould, Dr. Alun Lloyd and others at North Carolina State University [15], and the Dynamic Mosquito Simulation Model (DyMSiM), developed by Dr. Cory Morin, former University of Arizona graduate student and current postdoc at NASA Marshall Space Flight Center [16]. This combined modeling approach is useful when relationships are not well-defined. Our ensemble model appeared to capture the seasonality of the *Ae. aegypti* fairly well in the two locations that had data available, but there are discrepancies between the modeled and field data emphasizing the need to combine both modeling approaches and field collections. **These models will improve when ground-based surveillance for *Aedes* mosquitoes in the United States is more widespread and done at regular intervals.**

Climatic suitability and *Ae. aegypti* populations are critical factors but they alone cannot predict where transmission will occur. To further define high risk areas, we examined the geographic distribution of several important determining human factors: the number of returned travelers from countries with current Zika transmission (as of February 2016); counties in the continental United States that have reported locally-acquired cases of other *Aedes*-transmitted viruses – dengue and chikungunya – since 2010; and, the proportion of individuals who live in poverty by county in the continental United States during the summer months. The travel information is a rough indicator of the potential for viral introduction from countries where Zika virus is currently being transmitted. **An urban area which receives a large number of travelers from areas with transmission are more likely to have travel-related cases.** Given there are currently no locally-acquired cases, the only way that local transmission can occur is if a returned traveler brings the virus into the population. Counties where recent locally-acquired cases of dengue and chikungunya have occurred provide clues to where we might expect to see the emergence of Zika in the contiguous United States; these counties encompass areas of Southern Florida and Southern Texas.

Poverty is related to risk of transmission. Impoverished communities are at higher risk of Zika transmission for several reasons. Low-income neighborhoods with poorer infrastructure and sanitation tend to have more garbage (discarded containers that can serve as habitat for the immature mosquitoes), abandoned lots, and poorly maintained public areas in which water-holding containers that provide mosquitoes with larval habitat accumulate. In addition, homes may lack window or door screens that are intact, allowing the *Ae. aegypti* mosquito to more readily enter the house. And finally, lower income households often lack air conditioning or have lower quality air conditioning options compared to central air conditioning. Without central air conditioning during the summer months, individuals are more likely to keep doors and windows open, also increasing their contact with mosquitoes. Work by Dr. Mary Hayden (NCAR) also demonstrates that, even if individuals reside in homes with central air-conditioning, they may lack the funds to run or maintain the unit. This is **particularly problematic in the U.S.-Mexico border region, where the environment is highly suitable for the mosquito and poverty and crowded conditions are common**, and

there is high mobility between the U.S. and Mexico where Zika transmission is already occurring. The history of dengue outbreaks in this region supports the idea that this is a likely area for transmission of Zika to occur.

Another aspect of risk of particular interest to our research group is the **current infrastructure to support *Ae. aegypti* and *Ae. albopictus* surveillance and control.** We conducted an in depth search of publically available information to glean information on surveillance and control activities in the 50 cities included in our study. What we found, or rather did not find, was disheartening. **Very few jurisdictions actually publically reported any information on *Aedes* species** in the area and it was unclear which jurisdictions actually conducted surveillance for these mosquitoes at all. Given the extremely tight links between humans and the vector, **it is not only critically important to improve surveillance programs for these mosquitoes, but also to ensure that these surveillance data are transparent and available for communities.** To reduce *Aedes* species individuals, households, communities, and government administration must all be involved. People are better able to mobilize and control mosquito populations when they have up-to-date and specific information about the locations of mosquito populations.

It was not our intention to forecast where Zika virus would be present during 2016 in this study and, in fact, our simulations were based on average climatological conditions over the past decade, rather than meteorological forecasts for the upcoming summer season. Our intention was to quickly identify times of year and locations at higher risk with the best data available. **Actual forecasting of transmission is theoretically possible but requires significant improvement in our knowledge across several broad areas.** These include improved field data (including mosquito and disease surveillance) for validation, a better understanding of the interactions among humans and *Ae. aegypti*, more accurate seasonal weather forecasts, and data on the potential distribution and impact of vector control resources and activities on mosquito abundance.

We need better field data for validation of predictions. As noted above, surveillance for *Aedes aegypti* and *Aedes albopictus* is relatively weak across the country with some notable exceptions, such as Phoenix, AZ, Miami, FL, and Key West, FL. A recent review of funding for mosquito (or insect) abatement indicates vast disparities from Tallahassee, FL—a "high risk" area that spends approximately $23.47 per person—to Jacksonville, FL, which spends only $0.06 per capita [17]. However, even in areas where there are high amounts of funding for mosquito control, these numbers do not differentiate between control for mosquitoes that are merely a nuisance and those that transmit disease so it is unclear the actual amount being spent towards disease control and may not represent what is available in a specific geographic location due to the overlap between county and municipal budgets.

Most surveillance programs were formed to survey West Nile Virus following its emergence in 2003. The techniques used to survey for the *Culex* species that transmit West Nile virus do not directly correlate to *Aedes* species of mosquitoes. They inhabit

different ecological niches, and the traps used for *Culex* do not attract *Aedes* species of mosquitoes efficiently. While scaling up of surveillance may not be possible for all jurisdictions, it is critically important for the areas at greatest risk that currently lack good surveillance-- chiefly, the U.S.-Mexico border region. Many jurisdictions in the U.S.-Mexico border region, including Yuma and Nogales, Arizona, where I am from, have personnel that are charged not just with vector-control but also restaurant inspections, pest abatement, and other environmental health hazards. This broad range of commitments limits the time that can be dedicated to conducting surveillance and control for mosquito-borne illnesses.

Forecasting systems would need to be targeted to specific geographic areas to provide greater accuracy. Having better surveillance data on *Ae. aegypti* populations would significantly improve the forecasts of Zika outbreak risks. Integration of this data from multiple sources to validate and improve predictions in real-time is also beneficial. This can come from both traditional surveillance sources and alternative surveillance systems. I am currently involved in an effort to develop a new community-based surveillance "app", Kidenga, along with advisors from the Centers for Disease Control and Prevention (CDC) and Skoll Global Threats Fund. This app will allow smart-phone users to report symptoms that may be consistent with dengue, chikungunya, and Zika viruses and will also allow them to report mosquito activity in their area. The data is aggregated and presented back to the users. Other community-based surveillance activities such as the Great Arizona Mosquito Hunt, led by Dr. Kathleen Walker and partners at the Arizona Department of Health Services, recruit community members to set out simple oviposition traps to collect eggs. The U.S. Department of Agriculture is also encouraging similar participation by community members. Data from these sources can be used to enhance predictions.

We need a better understanding of the relationships between humans and *Aedes* species to quantify transmission potential. Further, while there is a fairly good understanding of the biological processes of *Ae. aegypti* and *Ae. albopictus* that can be included in forecasting efforts, the human-vector interaction components are still relatively under-studied, particularly in the United States. More information is needed on how frequently *Aedes* species feed on humans in different environments. In addition, understanding how to predict the density of containers and available habitat for *Aedes* species across large geographic regions requires further quantification of the relationship between human demographic factors and *Aedes aegypti* and *Aedes albopictus* indicators.

We need sustained support for model-based forecasts of risk for Zika and related viruses. Partners at NASA and NCAR, including Dr. Cory Morin, Dr. Dale Quattrochi, Mr. Bradley Zavodsky, Dr. J. Brent Roberts and Dr. Andrew Monaghan, are currently working towards this goal but more support is needed to generate these forecasts. We believe that, while imperfect, models have reached a level of sophistication that would enable the provision of actionable information to public health and vector control decision makers about when cities will be at highest risk for virus transmission. Ensembles of seasonal climate forecasts could be used to drive mosquito and virus

transmission models to provide forecasts of potential mosquito abundance and virus transmission risk with up to 3 months of lead-time for cities across the United States. Issues to address, if such a forecast capability were to be implemented, would include ensuring sustained support (a necessity for any forecasting capability), determining the entity or entities that would operate it, and engaging the public health and vector control communities to maximize the forecast system's utility and iteratively improve it.

We need more information on the resources available for response and control of *Aedes* species across jurisdictions. To better predict actual risk of transmission, we must also have a better understanding of our capacity to respond. As indicated previously, there is sparse evidence available to develop an understanding of each community's resilience in the face of an outbreak of Zika virus or other mosquito-borne viruses. It is almost certain that many communities, particularly many of those at greatest risk, have little capacity to respond. This information should be obtained in a standardized manner to allow incorporation into the modeling of transmission risk.

Conclusion

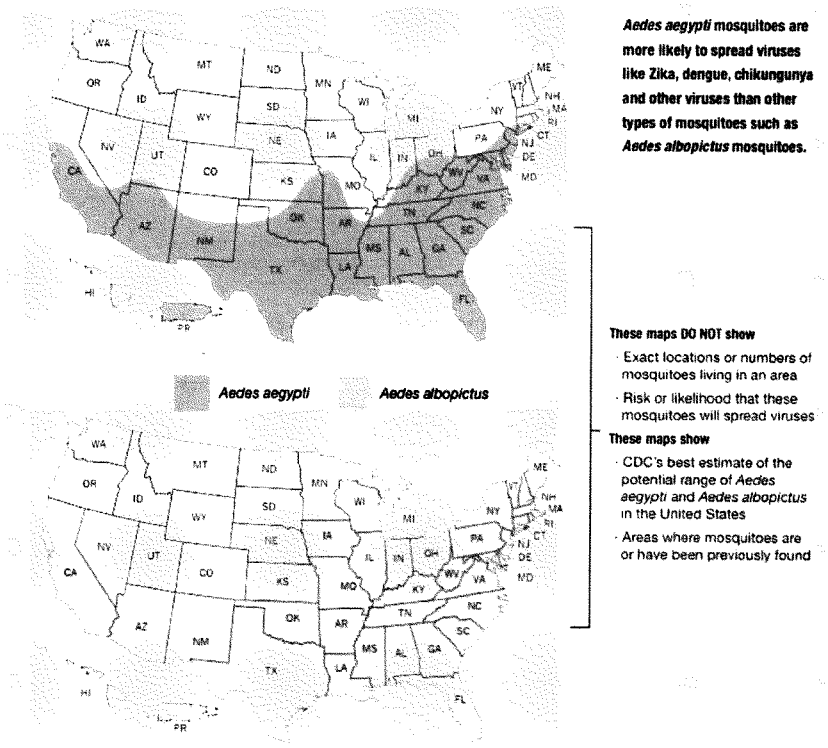
Our knowledge of *Ae. aegypti* (and *Ae. albopictus*) and our ability to assess present conditions or forecast upcoming risk of Zika transmission and related viruses in the continental United States is currently limited by our incomplete understanding of vector-virus-human interactions and our lack of ground-based surveillance of the geographic and seasonal distribution of both *Ae. aegypti* and *Ae. albopictus*. Sustained support is needed to rectify these gaps including enhancing surveillance and reporting of *Ae. aegypti* and *Ae. albopictus* mosquito populations. Investment in developing and testing forecasting systems is needed. Surveillance and forecasting activities, in particular, need long term stable funding mechanisms to ensure scientific progress. The transition of these activities to operational use is a particular challenge. The timely collection and dissemination of epidemiological and entomological information will be critical for both accelerating research and enabling effective operational programs to forecast and prevent pathogen transmission. These types of investments would improve our capacity to respond, not only to the Zika virus pandemic, but to future threats of viruses that can be transmitted by mosquitoes.

Thank you for the opportunity to testify before you today.

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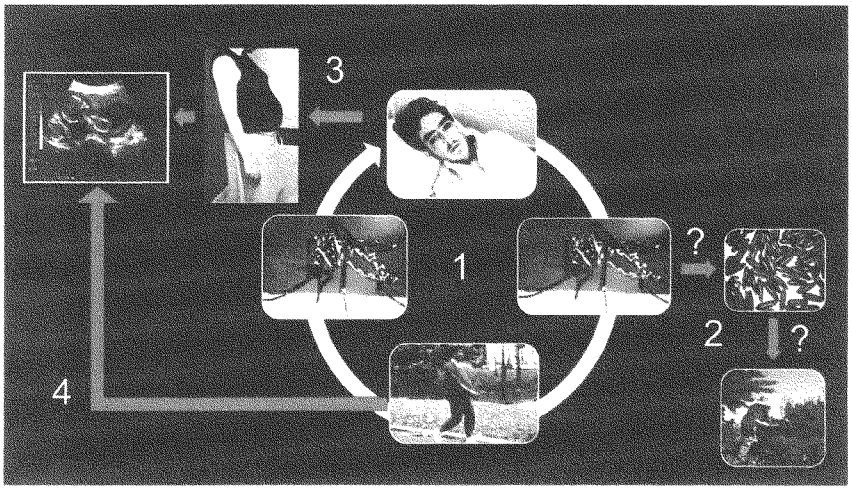
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Figure 1. Estimated range of *Ae. aegypti* and *Ae. albopictus* in the United States in 2016.



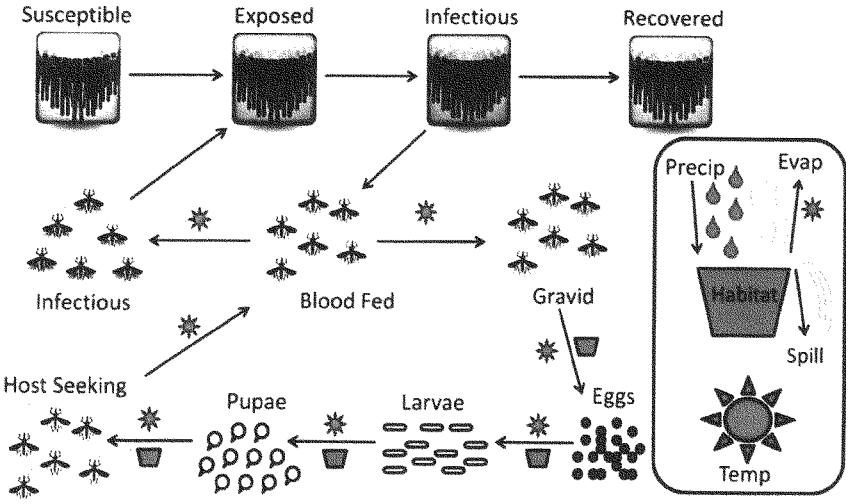
Source: CDC.gov

Figure 2. Transmission cycle of *Ae. aegypti* and Zika virus



(1) Transmission is initiated when an *Aedes* species of mosquito (*Ae. aegypti* is depicted here), feeds on an infected individual. The virus must undergo biological processes in the mosquito before becoming infectious to the next individual. Then that person must go through a period of time before they are infectious to the next mosquito. (2) In addition, it is unknown if infected *Aedes* can pass the virus on to their offspring. If they can then it would be possible for those offspring to transmit the virus to a human when they first feed. Other modes of transmission not discussed here include (3) sexual transmission, and (4) transmission from a pregnant mother to her fetus. Also possible is transmission through the blood supply and transfusions (not depicted here).

Figure 3. Complexities of modeling *Ae. aegypti* – borne viruses



Suns bordering an arrow indicate that the process is temperature dependent and a habitat/container symbol bordering an arrow indicates the process is habitat/precipitation dependent. Water is added to a habitat through precipitation or manual filling and is lost due to spilling and evaporation which is regulated by temperature. After hatching, the mosquitoes develop through their larval and pupal stages before emerging as adults. The adults blood feed, develop eggs, and then lay them in a water habitat. Upon blood feeding, adults can contract the virus from an infectious human. Those mosquitoes can then expose a susceptible human to the virus during a subsequent blood meal.

Source: Morin *et. al.* 2015

Chairman SMITH. Thank you, Dr. Ernst.
And Dr. Neafsey.

TESTIMONY OF DR. DANIEL NEAFSEY,
ASSOCIATE DIRECTOR,
GENOMIC CENTER FOR INFECTIOUS DISEASE,
BROAD INSTITUTE OF MIT AND HARVARD

Dr. NEAFSEY. Thank you. So Mr. Chairman, Ranking Member Johnson, and Members of the Committee, thank you for holding this hearing, and for the opportunity to present today. I also want to acknowledge one of the Committee members, Representative Clark, an important supporter of the strong research community we have in Cambridge, Mass.

My research group at the Broad Institute in Cambridge uses DNA sequencing to understand and control infectious diseases, and I'm here today to speak specifically about how DNA sequencing can help us to understand and inform the control of Zika transmission.

We lack fundamental understanding of how the Zika virus moves from person to person via Aedes mosquitoes, information that is crucial for an effective response to this epidemic.

Mosquitoes are not flying hypodermic needles that passively transmit disease. The successful transmission of mosquito-borne disease depends on complex biological and ecological interactions between mosquitoes, their human hosts, and the pathogens that they transmit.

Insight into the biology of how Aedes mosquitoes are able to spread disease can be gained through sequencing and mapping the Aedes genome, or the entirety of its DNA. We know that because we have demonstrated this with Anopheles mosquitoes, which transmit malaria.

So I led a project at the Broad Institute recently funded by the NIH and involving more than 130 collaborators from 19 countries around the world to build genome assemblies or maps of all the DNA of 16 different kinds of Anopheles mosquitoes, some of them very proficient at transmitting malaria and some of them deficient. We learned a lot of things from this project but—if we can advance the slide—I will show just one small result. This is a figure that we built by comparing the genome maps of these different mosquitoes and identifying those groups of genes that were changing most quickly or most slowly between these different mosquitoes. As you can see, the most rapidly changing genes at the top of this list in red are those genes that we know to influence how mosquitoes taste and smell, and we know that there're important genes in this class that determine whether mosquitoes prefer to bite people or animals, and a strong preference for biting humans is a very important determinant of disease transmission.

So close behind those smell and taste genes are genes that provide mosquitoes with an immune system, and we know that variation in these genes can determine whether or not mosquitoes are able to transmit pathogens or control infections and not transmit them to the next person they bite.

So no comparable set of genomic research yet exists for Aedes mosquitoes despite the fact that they transmit Zika as well as the

three other major viral diseases that Dr. Ernst mentioned. Next slide, please.

[Slide.]

Here's an image showing the current stage of a recent Aedes aegypti mosquito genome map. The map is in approximately 3,700 pieces despite the fact that this mosquito has only three chromosomes, so the target is three. The original map for Aedes mosquitoes published in 2007 was in about 10 times as many pieces, so we're making progress.

So as mosquito season begins in the Gulf states and with Zika on the doorstep of the United States, we lack foundational resources to pursue DNA-based studies of the biology and transmission of Zika. This resource gap is critical. Infectious disease epidemiology has been transformed by DNA during the last ten years into a rich digital information science allowing biologists and public health agencies to track the spread of outbreaks over time and space and learn about what mosquito and human factors contribute to disease spread. We can now tackle emergent infectious diseases like Zika using efficient and innovative genetic tools to build databases and situational awareness of diseases, and the scientific community stands ready to develop and apply these tools to the Zika epidemic to protect vulnerable populations within our borders and around the world.

One example of that readiness is the Aedes Genome Working Group organized just this last January via Twitter by Dr. Leslie Vosshall at Rockefeller University. This upstart group's mission has been to produce an improved genome map for Aedes mosquitoes using new sequencing technology that is 10,000 times cheaper than the technology available ten years ago. With no central funding but a lot of donated time and resources from a range of academic and industry partners just motivated to improve our capacity to respond to Zika, this group has made rapid progress exploring a spectrum of new technologies for building an improved genome map.

So with continued support and follow-up research, this map will yield knowledge that informs disease-control measures. Examples of such measures include insecticide resistance detection and surveillance, mosquito population studies, and genetic modification of the mosquito, new tools for which are creating an increasingly direct connection between basic DNA research and control measures.

The Zika epidemic can become a proving ground for the power of new DNA-based resources and epidemiological tools. Taking advantage of rapidly falling costs, we can demonstrate to the world how new technologies will let us understand, anticipate and control the spread of an epidemic, and we have an obligation to vulnerable populations to seize this opportunity.

So thank you to the Chairman, Ranking Member Johnson, and the Committee for your attention, and I'll be happy to answer any questions you may have later in the hearing.

[The prepared statement of Dr. Neafsey follows:]

Testimony for "Science of Zika: The DNA of an Epidemic"
House of Representatives
Committee on Science, Space, and Technology

Dr. Daniel Neafsey
Associate Director, Genomic Center for Infectious Disease
Broad Institute of MIT and Harvard
Cambridge, MA

SUMMARY
The Zika epidemic has caught the world off guard. We lack fundamental understanding of how the virus moves from person to person via mosquitoes, information that is crucial for an effective response to the epidemic. Though the virus was little studied prior to the recent epidemic that began in Brazil, the *Aedes* mosquito that spreads it is better known, because *Aedes* mosquitoes also spread the viruses that cause Yellow Fever, Chikungunya, and Dengue Fever. Despite the mosquito's importance, we lack foundational resources to pursue DNA-based studies of the biology and transmission of Zika. This resource is gap is critical. Infectious disease epidemiology has been transformed by DNA during the last 10 years into a rich digital information science, allowing biologists and public health agencies track the spread of outbreaks over time and space, and learn about what mosquito and human factors contribute to disease spread. We can now tackle emergent infectious diseases like Zika using efficient and innovative genetic tools, and the scientific community stands ready to develop and apply these tools to Zika to protect vulnerable populations within our borders and around the world.

RATIONALE FOR DNA-BASED EPIDEMIOLOGY
Insight into the biology of how *Aedes* mosquitoes are able to spread disease can be gained through sequencing and mapping the *Aedes* genome (the entirety of its DNA), by studying the DNA of mosquitoes collected across time and space during the outbreak, and by looking for DNA factors that impact interventions and Zika transmission. DNA sequencing will generate foundational resources that benefit a diverse array of scientific studies, leading to the improvement of existing disease interventions, the preservation of their efficacy, and the discovery of new interventions.

It is exceedingly important that we learn more about the nature of Zika transmission, and identify and invest in new approaches to block disease transmission. We do not yet have a drug to treat Zika patients, nor vaccines with which to protect people from infection. **Our primary disease intervention option at the present time is to stop *Aedes* mosquitoes from spreading the disease.** It is unlikely that we will ever eliminate *Aedes* mosquitoes within our own borders using conventional mosquito control measures, and much of the world lacks the socio-political infrastructure to even mount such an effort. Because the mosquitoes are here to stay, we must learn how to disrupt their biology or strategically suppress their populations in a way that impacts Zika transmission.

It is not a coincidence that Zika is spread by the same *Aedes* mosquitoes that transmit Yellow Fever, Chikungunya, and Dengue Fever, but a consequence of the remarkable predilection *Aedes* mosquitoes have for feeding on humans, and their capacity to utilize human-created environments for reproduction. Out of almost 4000 mosquito species on

this planet, very few have assembled the combination of molecular, behavioral, and ecological traits that make *Aedes* such an effective disease vector.

DNA sequencing of mosquito genomes has already given us a glimpse into some of the biological traits that favor human disease transmission by *Aedes*, *Anopheles,* and other mosquitoes[1–3]. We can now appreciate mosquito-born disease transmission as a product of complex biological interactions between a mosquito, the pathogen, and humans. Because Zika is a new and understudied disease, knowledge about the details of these interactions remains thin for this virus.

There are many ways to translate knowledge of mosquito/human/pathogen interactions into disease control measures. Examples include:

1) Insecticide resistance detection and surveillance
Insecticides can be very effective at controlling mosquito populations. The historic elimination of Yellow Fever, Malaria, and other mosquito-borne disease from the US can be attributed to mosquito control. Global Malaria mortality fell by 60% between 2000 and 2015, in large part due to the intensive use of insecticide-treated bednets and indoor insecticidal spraying[4].

The routine consequence of intensive insecticide campaigns is resistance. Scientists are concerned that further gains against Malaria will be limited by the high prevalence of insecticide resistance in many regions of Africa[5]. Resistance to many insecticides is already locally common in *Aedes* mosquitoes[6,7]. The genetic factors behind this resistance are not well understood. DNA-based studies comparing resistant mosquitoes versus susceptible mosquitoes can provide indicators of resistance to use in surveillance programs. Similar to strategies being used to limit antimicrobial resistance in bacterial pathogens, we can maintain insecticide efficacy for longer through rational, judicious use of insecticides, informed by DNA-based markers to track the origin and regional spread of resistance.

2) Mosquito population studies
Using DNA to understand which mosquito populations are connected vs. isolated can tell us much about the Zika epidemic. By comparing the DNA of mosquitoes sampled from different locations, we can address a wide range of fundamental questions. For example: Is the geographic spread of Zika due solely to human movement, or do mosquitoes also play a role? Which mosquito populations harbor high levels of insecticide resistance? Will resistance spread from one region to another? Our DNA-based understanding of *Aedes* mosquito populations is very limited compared to *Anopheles* Malaria mosquitoes, where such information has illuminated many aspects of disease transmission and spread. For example, this information has influenced our understanding of how mosquito populations rebound from control programs and restore themselves after dry seasons, and which mosquito populations are smaller (and therefore ripe targets for control)[8]. A recent small-scale DNA study has determined that *Aedes* mosquitoes have established a year-round population of mosquitoes in the Capital Hill neighborhood[9]. Where else are new *Aedes* mosquito populations establishing themselves, and what is their source?

3) Genetic modification of the mosquito
The prospect of using genetically modified mosquitoes to control disease spread is no longer science fiction. For example, Hadyn Parry's testimony will likely describe the

Oxitec method of inserting 'self-limiting' genes into mosquitoes that are released in large numbers, to achieve sharp reductions in local mosquito populations.

Recently, a powerful new DNA tool has arrived with the potential to translate biological insights into control measures very quickly. The CRISPR-*Cas9* DNA editing system gives us unprecedented power to insert, turn off, or modify genes in virtually any organism, including mosquitoes. When coupled with a 'gene drive', another DNA-based tool that can rapidly spread a CRISPR mutation through a mosquito population, we have the power to modify wild mosquito populations to restore sensitivity to insecticides, or to bite other animals instead of humans, or to kill pathogens they ingest during a blood meal and not transmit them to the next person they bite. CRISPR gene drives have been demonstrated to be viable in the laboratory with fruit flies[10] and *Anopheles* Malaria mosquitoes[11,12]. CRISPR gene drives are an example of the increasingly direct connection between DNA and vector-borne disease control.

IMPROVING THE *AEDES* MOSQUITO GENOME MAP

One example of a specific DNA-based resource that will assist the Zika response is an improved genome map for *Aedes aegypti*, containing virtually all of the DNA sequence in long pieces for all of the chromosomes. The current genome map for the *Aedes aegypti* mosquito was a significant advancement when it was first released in 2007[1], but it was far from perfect. DNA sequences are long strings of nucleotides, or 'letters': A, T, G, and C. At 1.5 billion nucleotides long, the *A. aegypti* genome is far larger than that of many other mosquitoes, and much of that extra length is composed of repetitive DNA sequences, (eg ATC-ATC-ATC-ATC . . .). Most modern DNA sequence is read in small pieces of 100 nucleotides in length. Assembling a non-repetitive genome map from short nucleotide sequences can be a computationally difficult task, akin to putting together a large jigsaw puzzle without a picture to look at as a guide. Assembling a large, *repetitive* genome from short sequencing reads is more like putting together a jigsaw puzzle with no picture, *where most of the pieces have the same color and similar shape.* As a result, the existing reference genome assembly for *A. aegypti* is in over 36 thousand pieces (despite having only 3 chromosomes), and is estimated to be missing as many as 20% of the genes. Furthermore, there is evidence that some of the assembled regions have been put together incorrectly.

While this genome map has led to some important breakthroughs in understanding the vectorial capacity of *A. aegypti*, we can do better. **DNA sequencing technology has improved in quality and price dramatically since 2007, making it more than 10,000 times cheaper to sequence a nucleotide of DNA now compared to then.** In recognition of this opportunity, Dr. Leslie Vosshall at Rockefeller University organized the *Aedes* Genome Working Group (AGWG) in January 2016, to coordinate efforts in the vector genomics research community aimed at improving the genome assembly map[13]. With no central funding, and organized via Twitter, this upstart group has made rapid progress exploring a wide range of approaches to employ new sequencing technology in pursuit of an improved *Aedes* reference genome. For a price tag of a few hundred thousand dollars, this group aims to produce a much improved version of the genome map released in 2007 at a cost of $18 million. Examples of the new technologies that will enable this feat include:

1) DNA sequencing machines that produce very long strings of nucleotides. Pacific Biosciences, a member of the AGWG, manufactures sequencers that can read DNA in strings of more than 10,000 nucleotides, far longer than the 700 nucleotide

strings produced for the 2007 genome map. To return to the puzzle analogy, this is equivalent to increasing the size of the puzzle pieces and reducing their number.

2) Machines and techniques that tell us which pieces of sequenced DNA belong to the same territory in the map. Three biotechnology companies (10X Genomics, BioNano Genomics, and Dovetail Genomics) have been recruited to the AGWG because their technology can inform which DNA sequences are proximal to each other on chromosomes. Application of these tools will mean that genome map puzzle pieces are no longer randomly shuffled in one big pile, but organized into small piles of pieces that correspond to different regions of the puzzle.

3) More sophisticated software to assemble the map. Compared to 2007, there are now many more tools available to put together genome maps. The previously mentioned AGWG corporate partners have their own software to apply their respective data types to the task of genome assembly. This software is often optimized for the attributes of the human genome, however, and may be inexpert at combining different, complementary data types in order to produce the best possible map. Work at academic research institutes in the US to explore the optimal computational use of the new data is therefore a vital component of the AGWG, and is being carried out by investigators with key expertise in several locations, including Rockefeller University, Yale University, the National Human Genome Research Institutes, the University of California San Francisco, Virginia Tech, and the Broad Institute. To use the puzzle metaphor a final time, this advance is equivalent to producing a robot that can scan a field of pieces and quickly find the missing piece to fill a gap.

The AGWG is still in the process of evaluating and optimizing these technologies. The group aims to produce a new genome map for *Aedes aegypti* by late summer of 2016. Finding and labeling all of the genes in the new map will take additional effort, and relating the function of those genes to insecticide resistance and other mosquito traits influencing disease spread will take years of work from dedicated members of the vector research community. This technologically opportune project to produce an improved DNA map will not only be a foundational investment in the control of Zika, however, but also Yellow Fever, Dengue, Chikungunya, and future emerging viral diseases likely to hitch a ride between hosts via *Aedes* mosquitoes.

CONCLUSION

The work of the AGWG represents both a triumph and a tragedy. It is a triumph because of the open and collaborative spirit of the endeavor, and the rapidity with which the community has responded to address the Zika epidemic. It is a tragedy because it took a public health emergency like the Zika epidemic for the research community to remedy the poor quality of a foundational resource for understanding disease transmission. Though the AGWG was founded without a solid base of funding, the maturation of its efforts will require focused investment of resources to ensure the quality and integrity of the new genome map it hopes to deliver. Innovative and effective disease control efforts that make use of the improved *Aedes* genome map are an exciting prospect, but will also require committed investment. **The Zika epidemic can become a proving ground for the power of new DNA-based epidemiological and intervention tools. We have the opportunity to demonstrate to the world how new technologies will let us understand, anticipate, and control the spread of an epidemic, and we have an obligation to vulnerable populations to seize this opportunity.**

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DR. DANIEL NEAFSEY BIOGRAPHY

Dr. Daniel Neafsey is Associate Director of the Broad Institute's Genomic Center for Infectious Disease in Cambridge, MA, where he leads a research group studying the DNA of mosquito vectors and the pathogens they transmit. He has developed pioneering resources and computational methodologies for genetic studies of mosquitoes and mosquito-borne pathogens. Through his leadership of large international collaborations, he has applied those tools to better understand topics such as drug and insecticide resistance, vaccine efficacy, and the population history of vectors and pathogens.

He obtained his BA from Loyola University Chicago and his PhD from Harvard University.

Chairman SMITH. Thank you, Dr. Neafsey.
And Dr. Presley.

TESTIMONY OF DR. STEVEN PRESLEY, PROFESSOR, DEPARTMENT OF ENVIRONMENTAL TOXICOLOGY, TEXAS TECH UNIVERSITY

Dr. PRESLEY. Good morning, Mr. Chairman and Committee Members. Thank you for the opportunity to address this important public health threat. My name is Steve Presley. I'm a medical entomologist and Professor of Environmental Toxicology and the Director of the Biological Threat Research Laboratory at Texas Tech University.

Zika virus, like chikungunya, dengue and yellow fever virus, is transmitted to humans through the bite of Aedes aegypti and Aedes albopictus. The biology and behavior of these mosquitoes differs significantly from vectors of West Nile virus and other arboviruses in the United States, and these differences, those unique challenges for controlling them in urban and suburban areas.

Zika virus infection typically causes less than severe illness with only about 20 percent of infected individuals reporting symptoms. Theoretically, a mosquito taking a blood meal from an asymptomatic but infectious individual could become infected with the virus and transmit it to other people being the initial link in establishing local transmission in an area where no Zika virus cases have previously been reported.

Vectors of Zika virus are mainly daytime biters and they prefer to be in our houses and offices. They are container breeders, and they rest in shaded areas during the heat of the day in the house or outdoors under the eaves of the house or in vegetation in the yard.

My lab at Texas Tech is a component of the CDC's Laboratory Response Network, and a certified human diagnostic testing facility. We're at Texas Department of State Health Services testing lab for the Zika virus and other high-consequence infectious diseases. Testing for Zika virus is limited to designated laboratories using a protocol allowed under the Food and Drug Administration's Emergency Use Authorization. The real-time RT–PCR assay that we use detects and differentiates RNA extracted from dengue, chikungunya, and Zika viruses in various bodily fluid samples.

The Texas Department of State Health Services is coordinating an entomology consultation group to develop strategies and identify resources relative to controlling the Zika virus vectors. The consultation group is composed of entomologists and public health professionals engaged in mosquito and infectious disease research or public health education. Sixty-six percent of Texas counties have no records of Aedes aegypti or Aedes albopictus occurrence, and more than 200 Texas counties have not conducted mosquito surveillance during the last two years. Scientists of the consultation group are fielding teams to update distribution maps for these vectors in Texas, and there are numerous reports of insecticide resistance in Aedes aegypti and Aedes albopictus populations globally where they occur. The consultation group is identifying resources to determine insecticide resistance in these vectors throughout Texas. The

consultation group is drafting Zika prevention information to make available to the public through various online and social networking technologies, providing do-it-yourself information to homeowners on how to eliminate mosquitoes on their property using off-the-shelf commercial pesticide products and application equipment.

The American Mosquito Control Association is developing guidelines for mosquito control by public health agencies and commercial entities, emphasizing approaches applicable to the biology and behavior of Aedes aegypti and Aedes albopictus.

All of the Zika virus cases in the continental United States have been attributed to travel-associated exposure with no local transmission confirmed. Conversely, there're been about 800 locally acquired infections reported in America Samoa, Puerto Rico, and the U.S. Virgin Islands, and only three travel-associated cases in those areas. This significant difference between locally acquired and travel-associated infectious is due to seasonal and climatic differences in most regions. Currently in most regions of the United States, these vectors seasonal activity is just now beginning. All efforts must be made to stay ahead of peak mosquito activity by immediately implementing comprehensive public health education programs and enhancing vector surveillance and control capacity.

I am collaborating with two private companies on projects relative to Zika virus. One company provides a comprehensive digital outcome support system for healthcare professionals, and the other has developed a smartphone-based DNA detection platform that is field deployable and does not require laboratory facilities. The device is a real-time PCR thermocycler that attaches to a smartphone. Results are provided within 40 to 45 minutes and can be tagged with various metadata, synced to a web portal for remote access, and we are planning to conduct field experiments in Florida, Puerto Rico and Central and South America to validate the accuracy of the system.

There is a common realization each time an emerging arthropod-borne disease threatens public health, that being regardless of how modern medical and scientific technologies advance, protecting the public health from vector-borne diseases requires both basic and applied understanding of the vector's biology, behavior, and vulnerabilities.

Thank you for your time.

[The prepared statement of Dr. Presley follows:]

"Science of Zika: The DNA of an Epidemic"

HEARING BEFORE THE

U.S. HOUSE OF REPRESENTATIVES
COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY

TESTIMONY
OF
STEVEN M. PRESLEY, PH.D.

TEXAS TECH UNIVERSITY

25 May 2016

Good morning Mr. Chairman and distinguished committee members. Thank you for convening this hearing and inviting me to address this very important emerging public health threat. My name is Steve Presley, I am a medical entomologist and a Professor of environmental toxicology at The Institute of Environmental and Human Health, and I serve as the Director of the Biological Threat Research Laboratory at Texas Tech University. I have almost 30 years of experience working with zoonotic and vector-borne infectious diseases. A significant portion of that time was as an active duty entomologist in the United States Navy conducting related vector-borne disease operations and research work in Africa, Asia and South America. My current research and teaching activities are focused on gaining a better understanding of the occurrence, transmission and maintenance dynamics, and developing strategies to control or otherwise protect humans and livestock from biological threats in the environment, including arthropod-borne diseases of animals and those that are transmissible to humans (i.e., zoonoses).

As you may be aware from previous testimony, Zika fever is a rapidly emerging mosquito-vectored and sexually-transmitted disease caused by a *Flavivirus*; the same genus as the viruses that cause other mosquito-vectored diseases such as dengue fever, St. Louis encephalitis, West Nile fever and yellow fever. Zika virus, like Chikungunya virus, dengue virus and yellow fever virus, is transmitted to humans through the bite of *Aedes aegypti*, the yellow fever mosquito, and *Aedes albopictus*, the Asian tiger mosquito - which is considered to be the most invasive mosquito species in the world. The biology and behavior of these mosquito species differs significantly from the principle vector species that transmit West Nile virus and other arboviruses in the United States, and these differences pose unique challenges to public health agencies necessary for surveying and controlling them in urban and suburban areas.

In the next few minutes I will address the three specific points requested by this committee, to include: ***(1) A description of the process to screen and test for the Zika virus in the U.S., and in particular Texas; (2) An explanation of my participation in the preparation efforts to prevent and control the spread of Zika virus in Texas and the challenges unique to the Aedes aegypti mosquito and Zika virus; and (3) A description of the public health education efforts currently underway regarding Zika virus including how to prevent its spread, and challenges facing such efforts.***

Effective protection of people from mosquito-transmitted Zika virus presents numerous public health and vector control challenges from many different perspectives. Beyond the very tragic and devastating Zika virus-related cases of microcephaly in infants and Guillain-Barre syndrome, Zika virus infection in otherwise healthy adults typically results in less than severe illness, with only about 20% of infected individuals presenting with symptoms. The other 80% of infected individuals may have very mild or no symptoms at all. So, theoretically, a mosquito taking a blood meal from an unaware, asymptomatic but viremic and infectious individual could become infected with the virus, incubate it, and transmit it to other people – thus being the initial steps in establishing local transmission in an area in which no Zika virus cases were previously reported.

The extrinsic factors associated with *Ae. aegypti* and *Ae. albopictus* and the establishment, maintenance and transmission of Zika virus in an area differ significantly from mosquitoes that transmit West Nile virus and St. Louis encephalitis virus. The mosquito vectors of Zika virus are predominantly daytime biters that prefer to be in our houses and office buildings. They are container breeders, laying their eggs in water reservoirs of flower pots, vases, bird baths, toys, and any discarded debris that may collect water, be it artificial or natural like tree-holes or leaf axils. They prefer to rest in shaded cool areas during the heat of the day, in the house under or behind furniture, or outdoors under the eaves of houses and buildings or in vegetation. These aspects of the vector's biology and behavior offer very difficult challenges to the development of effective vector surveillance and control strategies, and implementation of such operations.

Screening and Testing for Zika Virus

The Biological Threat Research Laboratory at Texas Tech University is a component of the U.S. Centers for Disease Control and Prevention (CDC) Laboratory Response Network for biological threat diagnostics, and is a Clinical Laboratory Improvements Amendment Program (CLIA)-certified human diagnostics testing facility. Within that capacity we are a Texas Department of State Health Services reference laboratory for testing human clinical samples from our region of Texas for the presence of Zika virus and other high-consequence infectious disease pathogens. Human sample diagnostic testing for Zika virus is limited to qualified laboratories designated by the CDC, and is accomplished using a specific CDC protocol allowed under the Food and Drug Administration's emergency use authorization. The *Trioplex Real-time (TaqMan) RT-PCR Assay* detects and differentiates RNA extracted from dengue, Chikungunya and Zika viruses in both serum and cerebrospinal fluid, and detects Zika virus RNA in urine and amniotic fluid. A reverse transcription step produces complementary DNA (cDNA) from RNA present in the sample. The protocol allows multiplex testing and is designed to facilitate simultaneous testing for the presence of these viruses from a single sample. The assay is intended for use with specimens collected from individuals meeting specific Zika virus clinical criteria (e.g., clinical signs and symptoms associated with Zika virus infection) and/or Zika virus epidemiological criteria (e.g., history of residence in or travel to a geographic region with active Zika virus transmission at the time of travel, or other epidemiologic criteria for which Zika virus testing may be indicated as part of a public health investigation).

Additionally the Biological Threat Research Laboratory includes an academic research capability for the collection, processing and testing of environmental samples, including samples or specimens from wildlife and arthropods. Of particular relevance to my testimony today, our research team was the first to detect West Nile virus in mosquito populations in western Texas during 2003, and we have since that time worked directly with local and regional public health agencies to collect and screen mosquitoes from the area for West Nile virus, St. Louis encephalitis virus, and other pathogens. We are prepared to collect and screen *Ae. aegypti* and *Ae. albopictus* mosquito populations for Zika virus, should an active case occur in our region.

Participation in Preparation Efforts to Prevent and Control Zika Virus in Texas, and Challenges Unique to the Vector Mosquitoes

In late February of this year, through coordination by the Texas Department of State Health Services, an Entomology Consultation Group was formed to focus on developing strategies and identifying resources needed for the surveillance and effective control of the mosquito vectors of Zika virus across Texas. The consultation group is composed of medical entomologists and public health professionals that are actively engaged in mosquito and infectious disease research or public health education, and represent both academia and local, regional and state public health agencies. We convene by teleconference as necessary to discuss the most up-to-date information being published about the mosquito vectors and geographic spread of the Zika virus, various appropriate personal protection and individual homeowner resources available for effective mosquito control, as well as educational materials and resources being made accessible to the general public relative to the Zika virus threat.

Specific actions that are underway by the Texas Entomology Consultation Group include a county-specific field surveillance project to determine the presence of *Ae. aegypti* and *Ae. albopictus* throughout the state, development of jurisdiction-specific projects to identify the occurrence and degree of resistance to commonly used insecticides in populations of potential Zika virus vectors, and the development and promulgation of public education resources to heighten awareness and provide guidance for personal protection from exposure to Zika virus.

Presence of Ae. aegypti and Ae. albopictus Across Texas

Currently 66% (168 of 254) of Texas counties have no records documenting the occurrence of *Ae. aegypti* and *Ae. albopictus* over the past decade, and more than 200 counties have not conducted mosquito surveillance during the last two years. Many of these counties are sparsely populated and only have rural small towns and communities with very limited, or lack any type of vector control resources. In coordination with local county leadership, we are organizing and fielding teams of entomologists and public health technicians to survey and update distribution maps for *Ae. aegypti* and *Ae. albopictus* in as many of the 168 counties as possible in order to determine areas potentially at risk for local transmission of Zika, chikungunya, and dengue viruses. Currently teams of entomologists from across Texas are collaborating to conduct the various county surveys, with specimen rearing and identification being performed at Texas Department of State Health Services, Baylor University, Texas A&M University, Texas Tech University, University of Texas-El Paso, and University of Texas-Rio Grande Valley.

Pesticide Resistance in Ae. aegypti and Ae. albopictus Adult Populations

There is much discussion based on both anecdotal and empirical reports regarding the resistance of *Ae. aegypti* and *Ae. albopictus* populations to many of the most commonly used classes and formulations of public health insecticides throughout the regions where the mosquitoes occur. In discussions with research entomologists and vector control professionals from various states, *Ae. aegypti* and *Ae. albopictus* populations from Florida, Louisiana and Texas exhibit some degree of insecticide resistance. Insecticide resistance in a vector population is initially detected and characterized by using some sort of bioassay to determine whether a particular insecticide is efficacious at a given time. Ideally, this fundamental question should be answered before a particular insecticide is acquired for vector control operations.

As a component of the Texas Entomology Consultation Group, we are actively engaged in logistical planning and identifying sources of funding to determine the occurrence and degree of insecticide resistance in *Ae. aegypti* and *Ae. albopictus* populations from throughout Texas. Initial plans are to collect eggs of these mosquitoes from various jurisdictions, rear the eggs to adults, and then utilize the CDC bottle bioassay protocol to screen female mosquitoes to determine populations that may be resistant to insecticides that are most commonly used in that specific jurisdiction. The CDC bottle bioassay is designed to help determine if a particular formulation of an insecticide is able to control a vector at a specific location at a given time.

The CDC bottle bioassay relies on time mortality data, which are measures of the time it takes an insecticide to penetrate an insect mosquito, traverse its intervening tissues, get to the target site, and act on that site. Anything that prevents or delays the compound from killing insects contributes to resistance. Information derived from the bottle bioassay may provide initial evidence that an insecticide is losing its effectiveness. The diagnostic dose is the amount of insecticide that kills 100% of susceptible insects within a given period of time. The expected time for the insecticide to achieve this objective is called the diagnostic time. Insecticide resistance is assumed to be present if a significant portion of the test population survives the diagnostic dose at the diagnostic time. The diagnostic dose and the diagnostic time should be defined for each insecticide, each region, and each vector species that is monitored. Major advantages of the CDC bottle bioassay protocol are that different concentrations of a specific insecticide may be evaluated, and the technique is simple, rapid, and relatively economical.

Public Health Education Efforts Regarding Zika Virus to Prevent Its Spread, and Challenges to the Efforts

Currently the scientists working with the Texas Entomology Consultation Group are very aggressively drafting content and developing approaches to make Zika virus prevention information available to the public through various on-line and social network technologies. These educational resources are primarily focused on providing "do-it-yourself" information to homeowners and other property owners regarding how best to eliminate, or at least reduce, mosquitoes on their property. This guidance emphasizes the fact that the first and most important action for mosquito control, particularly for *Ae. aegypti* and *Ae. albopictus*, is to find and eliminate mosquito breeding sites from in and around homes. In one Texas-based study, approximately one-quarter of residents who called their local health department about mosquito problems were unknowingly allowing mosquitoes to breed in their own backyards. Information detailing how best to search for and drain or treat breeding sites is provided, including a listing of several mosquito control options and a review of commercially available larvacides, adulticides and repellents that can be used by property owners.

The homeowner guidance provides a relatively detailed assessment of the safety (both human health and environmental impact) and effectiveness of various off-the-shelf pesticide products and application equipment. Pesticide application equipment options now available off-the-shelf to homeowners include thermal foggers, residual sprayers such as aerosol sprays, pump-type garden-sprayers, hose end-sprayers, and mister systems. Information is also provided regarding other non-insecticide control approaches such as "bug-zapper" electrocution devices and

vacuum traps baited with carbon dioxide and other lures. These traps are designed to attract mosquitoes that are seeking a blood meal by looking for traces of carbon dioxide, which is normally exhaled by people and other animals and is a natural attractant.

From a national perspective, information regarding Zika virus is most certainly abundant and readily available. For example, on the 18th of May I executed a *Google* search for the words "Zika virus" and had more than 91 million results. Fortunately at the top of the listing of results appeared the *Centers for Disease Control Zika Virus* page (www.cdc.gov/zika), which provides extensive information targeted to a wide audience, including: pregnant women and those planning to become pregnant, health care providers, travelers, parents, mosquito control professionals, state public health laboratories and departments, law and policymakers, and people at risk due to their occupation.

The *Citizen Science Invasive Mosquito Project* (www.citizenscience.us/imp/resources.php) is a "grass roots" effort coordinated through the U.S. Department of Agriculture aimed at monitoring invasive container-inhabiting mosquito species to determine where the invasive and native mosquito species occur throughout the country as a means of identifying at-risk human and animal populations. The project provides students, teachers, and anyone interested the opportunity to collect real data and contribute to a national mosquito species distribution study, and raises awareness of diseases that can be transmitted by mosquitoes.

The American Mosquito Control Association is currently in the process of developing guidelines specifically geared towards the control of *Ae. aegypti* and *Ae. albopictus* by government public health agencies and commercial entities. The guidelines will emphasize urban mosquito control and the paradigm shift in control practices that must be considered due to differences in the biology and behavior of floodwater/salt marsh mosquitoes and container-breeding mosquitoes.

As I detailed above, there are various and numerous public health educational efforts currently being undertaken in response to the significant threat of local transmission of the Zika virus within the continental United States. It is reported as of 11 May 2016 by the CDC that there have been 503 patients tested positive for Zika virus infection throughout the United States, with only six (6) states having not reported positive cases (i.e., Alaska, Idaho, North Dakota, South Dakota, Wisconsin, and Wyoming). All of these Zika virus infections have been attributed to travel-associated exposures, whether directly or through sexual contact with an infective partner, with no local transmission confirmed. Conversely, there have only been three (3) travel-associated cases and 798 locally acquired Zika virus infections reported in the United States Territories of American Samoa, Puerto Rico and the U.S. Virgin Islands, as of 11 May 2016. I believe that this very significant difference between locally acquired and travel-associated infections is due to seasonal and climatic differences between tropical and subtropical areas. In other words, in most regions of the United States *Ae. aegypti* and *Ae. albopictus* seasonal activity is just now on the rise. Therefore I believe it is essential that all efforts be made to stay ahead of peak mosquito activity in areas of the country where the potential mosquito vectors occur by enhancing and implementing very robust and

comprehensive public health education programs at the local, regional and state levels immediately, as well as enhance public health-directed vector surveillance and control capacity.

Other Zika virus Related Projects

In addition to the Public Health Emergency Preparedness and Laboratory Response Network efforts, and various wildlife and zoonotic disease research projects that we are engaged in, my research lab group at Texas Tech University is collaborating directly with two private entities conducting work specific to the development of information resources that are directly applicable to preventing the spread of Zika virus. Those collaborations are with *COR Medical Technologies, Inc.* (26305 Countryside Drive, Spicewood, Texas 78669; www.cormedicaltechnologies.com/landing.aspx) and *Biomeme, Inc.* (20 N 3rd St., Philadelphia, PA 19106 biomeme@biomeme.com), and are in the final planning stages. *COR Medical Technologies* operates the largest medical relational database in the world, and provides extensive reference resources for all known disease manifestations. The *COR* capability is designed as a comprehensive digital outcome support system for health care professionals and patients, with content and technology specifically designed for mobile use on *Apple* and *Android* devices, and with PC and MAC versions also intrinsic to the system. As of December, 2015, registrants utilizing *COR* services are located in all states in the United States of America and Canada, as well as in 47 other countries. In its current configuration *COR* is devoted primarily to diagnosis, surveillance, and reporting of acute, high risk medical disorders, including infections, toxins, cardiovascular diseases, and other life-threatening conditions.

Biomeme, Inc. has developed a smartphone-based DNA detection platform that is field deployable and does not require laboratory facilities. The *Biomeme* device is a real-time PCR thermocycler that attaches to an *iPhone SE* and enables one to perform gold-standard DNA analysis using sample preparation kits to isolate RNA/DNA from an environmental sample, add the sample to a specific test cartridge, and put it into the thermocycler. The *Biomeme* sample preparation system takes only 1-2 minutes and eliminates the need for common lab equipment such as pipettes, centrifuges and vortex machines, and fits on the end of a syringe to bind and clean DNA as you pipette up and down from reagent to reagent. Within 40-45 minutes an individual can determine the presence or absence of a series of specific molecular targets from a sample. PCR test results can be automatically tagged with GPS location and other metadata, and then synced to *Biomeme's* web portal for access by remote users and easy integration into public health and mosquito surveillance databases. The web portal is HIPAA-compliant and includes an API enabling external databases to easily share data.

Through my ongoing collaboration with *COR Medical Technologies* a collaborative research relationship with *Biomeme* has developed in which we are planning to conduct field trials in areas of Florida, Puerto Rico, and Central and South America to validate the accuracy of the *Biomeme* system for detecting Zika virus in *Ae. aegypti* and *Ae. albopictus*, as well as in other clinical samples such as blood, saliva, sputum, urine. Follow-on efforts may include validation of the system's effectiveness in testing for dengue virus and Chikungunya virus as well.

Conclusion

Historically in Texas, epidemics of dengue fever, malaria and yellow fever were relatively common. Less than 100 years ago, during 1922 and 1923, there were approximately 48,000 cases of malaria and 42,000 cases of dengue fever in Texas, respectively. There are numerous examples, both historic and contemporary, of outbreaks and epidemics of vector-borne diseases such as bubonic plague and St. Louis encephalitis. This rapidly evolving Zika virus threat in Texas and throughout the continental United States is just the most recent example of an emerging or resurgent arthropod-borne infectious disease to threaten the public health. I believe there is a common realization made apparent each time such a public health threat occurs, that being regardless of how modern medical and scientific technologies advance, protecting the public health from vector-borne disease threats requires both basic and applied understanding of the arthropod vector's biology, behavior and vulnerabilities.

Dr. Steve Presley is a Professor in the Department of Environmental Toxicology, and is the Director of the Biological Threat Research Laboratory at The Institute of Environmental and Human Health, Texas Tech University, Lubbock, Texas. He earned his Bachelor of Science in Animal Science from Texas Tech University (1982), his Master of Science (1985) and Doctorate of Philosophy (1987) in Entomology from Oklahoma State University. Before joining the faculty at Texas Tech University in 2002, he served on active duty in the U.S. Navy as a Medical Service Corps Officer and earned a Master of Military Studies (1996) from the United States Marine Corps University at Quantico, VA. Dr. Presley's professional career has focused upon zoonotic and vector-borne infectious diseases, with an emphasis on biological threat assessment and countermeasures to protect populations from infectious disease. His operational experiences include surveillance, prevention and control projects, including malaria control operations and research efforts in Africa, Asia and South America, as well as Rift Valley fever, Crimean Congo hemorrhagic fever, and cutaneous leishmaniasis studies in Africa and Asia. He has published more than 90 scientific and technical papers, co-edited two textbooks, authored and coauthored eleven book chapters in the fields of biological and chemical countermeasures, and diseases of wildlife. He has been the major advisor for 25 masters and doctoral-level graduate students, and he teaches an advanced graduate level course focused on biological threats in the environment. Dr. Presley is a past chairman and continues serve on the City of Lubbock, Texas Board of Health, and nationally serves as the Society for Vector Ecology Regional Director for the South Central Region of the United States, and as the Chairman of the Publications Committee for the American Mosquito Control Association.

Chairman SMITH. Thank you, Dr. Presley.
And Mr. Parry.

TESTIMONY OF MR. HADYN PARRY, CHIEF EXECUTIVE OFFICER, OXITEC

Mr. PARRY. Thank you, Chairman Smith, Ranking Member Johnson, Members of the Committee. Thank you for inviting me to testify today.

As the Chairman noted, we are facing an unprecedented challenge of mosquito-borne diseases today. Vector controlling the mosquito is actually our first line of defense, and it's an area we've sadly neglected over the past decades, and because of this, we have seen sharp rises in dengue, we have seen the introduction of chikungunya, and now we have the Zika emergency, and I'm sorry to say, but current insecticidal products are just not sufficient to control this mosquito in the urban environment.

So at Oxitec, we looked for and developed a new approach, and that was to use the mosquito against itself. So we have produced a genetically engineered Aedes aegypti strain, which we call LX–5138, and it carries two genes. It carries a self-limiting gene and a color marker. Now, the way this works is, we release males—males don't bite, they cannot bite—and they go out and they mate with females. The offspring will all inherit a copy of the self-limiting gene, and then they die before becoming adults, thereby reducing the wild population, and effectively, it's a numbers game. If we can put more of our males into the environment, the females cannot tell the difference and more will mate with our males, the offspring will die, and we'll bring the population crashing down.

The offspring also inherit this fluorescent marker you can see in the slide that you can't see with the naked eye but you can see under a light and a filter, and this provides a track-and-trace-type capability so we can see where our mosquitoes go, we can see what the effect is that we're having, and we can moderate the program as we go along in real time.

The releases are made from a truck driven by an operational plan, which we work out to make sure we cover the whole town, and we have a GPS system that helps us in terms of decision support.

The efficacy of this approach has actually been quite remarkable. In all the outdoor trials we have produced, every single one we have reduced the Aedes aegypti population in the urban environment by over 90 percent in about six months, and that is hugely more effectively than can be done with insecticides.

Now, safety and respect for the environment are obviously key factors, and again, in stark contrast to insecticides, we are just targeting the one mosquito species that is spreading the disease, so this is a species-specific approach.

Just as important, actually, I'd like to draw two points to your attention. Our insects do not persist or stay in the environment. The males we release will die. The offspring will die. It's a matter of days they will disappear. And also the marker system means actually that the whole process, the whole control program, is precision and metric-driven.

I'd also like to stress that in contrast to many other approaches that have been muted at the moment in response to Zika, we actually started this in 2002. Our product was developed in 2002 justified at that time by dengue, and it's all the more necessary now. And then we started doing outdoor evaluation in open field trials since 2009, so we have a very long body of evidence and data to back up both the efficacy and the environmental side. We've now received national biosafety approval in Brazil, and indeed, the World Health Organization has specifically recommended this product for operational use as part of their emergency responses to Zika. So these are ready to use now.

In the United States, the regulatory process is actually still ongoing but we opened a file with the FDA as far back as 2011 in order to conduct a small field trial, which is actually a very necessary part of the regulatory requirements. The FDA recently published a finding of no significant impact, but while we're waiting for the final review and final decision, we're not able to move forward. But in that same time frame, 2011 to today, in Brazil, we have filed similar applications. We've carried out several field trials. We've formed a company. We built a factory. We've got national biosafety release, and we're now in operational use.

Members of the Committee, I don't think time is on our side with Zika, and I think the utmost urgency is required in every area. I've come from Puerto Rico, and we could have a catastrophe on our hands if we're not careful. At any one time, there are 28,000 women pregnant, and that is a very salutary thought when you think that summer is coming up and we have active disease transmission.

So in view of that urgent health need, we'd urge your support actually to give the FDA all your support and encouragement so they can expedite approval of our application, and I would also urge consideration of an emergency use authorization actually, which is used sometimes to bring forward new medication or diagnostics, but I think the fact that we have such an urgent and pressing need means the FDA needs more tools at its disposal in order to help protect Americans. We want to make this technology available in the coming months rather than the coming years.

Thank you very much.

[The prepared statement of Mr. Parry follows:]

Statement of Mr. Hadyn Parry
Chief Executive Officer of Oxitec, Ltd

Testimony before the U.S. House of Representatives
Science, Space and Technology Committee

"Science of Zika: The DNA of an Epidemic"

May 25, 2016

Chairman Smith, Ranking Member Johnson, and members of the Committee thank you for inviting me to testify before your Committee today. My name is Hadyn Parry and since 2008, I have served as the CEO of Oxitec, a pioneer in using genetic engineering to control inspect pests that spread disease and damage crops. Oxitec was founded as a spinout from Oxford University and is a UK based subsidiary company of Intrexon Corporation, a New York Stock Exchange listed company which engineers biology to help solve some of the world's biggest problems.

Background

Oxitec Limited has pioneered the use of bioengineering to provide a solution for controlling the mosquito *Aedes aegypti* that spreads Zika virus. Oxitec developed its product OX513A, a self-limiting strain of *Aedes aegypti* in 2002 and since that date has conducted rigorous indoor and then outdoor evaluation and development. OX513A, therefore, has 14 years of data to support efficacy, environment and safety aspects. In all efficacy trials to date, Oxitec has demonstrated a reduction in the target *Aedes aegypti* population by over 90% in about six months. Over recent years, Oxitec has placed considerable focus and investment on its ability to scale up, supply and distribute its insects and OX513A should now be considered a fully operational solution, enabled to be deployed.

OX513A received a preliminary Finding of No Significant Impact (FONSI) from the Food and Drug Administration (FDA) in 2016 following an Investigational New Animal Drug (INAD) filing that was initiated in 2011. The public comment period ended on May 13, 2016 and a final opinion from the FDA is awaited before Oxitec has the regulatory approval to carry out a small trial in the Florida Keys as part of its application. We are hopeful that, in light of the public health need, FDA will act quickly to finalize its finding.

OX513A has national biosafety approval from the National Biosafety Technical Commission (CTNBio) for use in Brazil (April 2014) and Oxitec has been informed that we will shortly receive special registration from ANVISA, an agency within the Ministry of Health, to enable availability in Brazil.

OX513A has a specific recommendation from the World Health Organization (WHO) Vector Control Advisory Group for pilot deployment under operational conditions. WHO rarely recommends a specific product, but took this step as part of its emergency response and preparedness for the Zika virus.

Oxitec's bioengineering technology and status

a) *Aedes aegypti*

While the current urgent threat is the Zika virus, the real target is the mosquito that carries the disease. Despite the present and widespread use of insecticides, over the last 50 years, there has been a sharp increase in both incidence and number of diseases spread by *Aedes aegypti* across the world. Before 1970, only nine countries had experienced severe dengue epidemics. The disease is now endemic in more than 100 countries in the WHO regions of Africa, the Americas, the Eastern Mediterranean, South-East Asia and the Western Pacific. WHO reported an estimate of over 390 million dengue infections per year. Chikungunya came into the Caribbean in December 2013 and within one year, there were over one million cases across the Central America and Caribbean region.

By focusing on the mosquito, rather than the disease, Oxitec has accumulated years of development, well ahead of the Zika threat emerging. It also should be noted that it is unlikely that Zika will be the last disease transmitted by *Aedes aegypti.* It is clear that new tools are needed control this vector to guard against not only the current threat but also known threats such as dengue and Yellow Fever along with future, unidentified threats.

Aedes aegypti is the prime vector for Zika virus as well as for dengue, chikungunya and Yellow Fever. Understanding and then controlling the vector is key to controlling the spread of Zika or any other current or future virus transmitted by the mosquito. This mosquito species originated from Africa and has been spread around the world by human activities. This distribution has occurred via the transport of eggs, which are highly durable and easily carried in freight. Unlike many mosquito species which are adapted to the rural environment, this mosquito has adapted to be predominantly an urban one. It

bites humans by preference and lives in and around the home and other areas where people congregate. Its larvae and pupae develop in still water pools such as unused containers, birdbaths and blocked gutters. This mosquito can breed in as little as a bottle cap of water.

It is notoriously difficult to control with conventional insecticides not only because it has developed resistance to the most common insecticides but mainly because containers create multiple breeding sites in the urban setting that are often on private property and inaccessible to mosquito control staff. There are just too many dispersed inaccessible breeding sites that need to be continuously treated for this mosquito to be controlled through application of chemical insecticides.

Oxitec has used some key features of this mosquitoes' biology to design our solution. First, only females bite. Males cannot bite and, therefore, males represent no threat to humans.

Second, males are extremely effective at finding females. They tune in to the sound of the female wing beat to locate the female in order to mate. Once the female has mated successfully, she does not need to mate again and she will engage in a cycle of biting humans (to acquire blood), laying eggs, then biting again and will continue on this cycle. A single female can lay up to 500 eggs in her lifetime, which develop from egg to larvae to pupae to adult in a little over one month.

Third, it is important to note that neither male nor female mosquitoes have a significant spontaneous flight range. An adult mosquito will only fly up to about 200 yards in its lifetime.

b) Oxitec's approach

To control *Aedes aegypti*, Oxitec uses the mosquito against itself. We release males (that cannot bite) that mate with wild females. The offspring inherit self-limiting genes and die before becoming functional adults, thereby reducing the wild population. A male is biologically tuned to seek out females for mating purposes. The wild females cannot distinguish between an Oxitec OX513A male and a wild one, meaning that, provided sufficient Oxitec males are released across an urban area for a period of time, the population will rapidly decrease. In trials in several countries, we have shown that the population of *Aedes aegypti* may be reduced by over 90% in around six months. Moreover, as this species cannot fly far, the effect of the control can be highly specific to

the area of release. Specifically, we can treat broad urban areas by releasing in a pattern to cover a town or city, and we can modify the release rate to concentrate more on areas of higher mosquito population. Or we can even specifically target "hotspots". Once controlled, low level releases can be continued in areas of likely re-infestation to sustain the control over the longer term. Unlike chemical insecticides, the OX513A mosquito affects **only** the *Aedes aegypti* species, and has no measurable impact on other mosquito populations, or the overall insect population of the treated region.

c) Oxitec's technology

There are two key elements to the Oxitec bioengineering approach.

a) **A self-limiting gene.** Each released OX513A insect carries two alleles of the self-limiting gene meaning that each of its offspring inherits one copy. That single copy prevents the offspring from developing to become a functioning adult, so the offspring of a mating between an OX513A mosquito and a wild one die in early development. Oxitec uses the term self-limiting; meaning offspring will die before becoming functional adult. Therefore, these mosquitoes do not reproduce.

b) **A fluorescent biological marker.** In addition to inheriting the self-limiting gene, all of the offspring inherit a fluorescent marker. This gene allows us to identify all the larvae. When viewed under a filter, the larvae show a distinct red color and pattern. This color provides an unparalleled system for monitoring and tracing the Oxitec mosquito.

While the self-limiting gene is the mechanism to reduce the population of *Aedes aegypti* and, hence reduce the threat of transmission of Zika, the marker allows the program to be precise, efficient and cost-effective. Throughout a program, Oxitec collects eggs from the area of release and determines the proportion of the larvae that have an OX513A parent. More or fewer adult males then can be released in each area. The release rate is tailored to specific requirements and, as a result, overall control of the whole *Aedes aegypti* population is achieved as swiftly as possible.

d) Programs, results to date and status

An Oxitec program consists of the release of male mosquitoes from predetermined release points in a town or city each week. Global Positioning

System (GPS) release points are programmed into a release plan. Male OX513A mosquitoes are released from each GPS point from a moving van. The males then disperse and seek females. Eggs and larvae are collected each week from simple ovitraps (that are commonly used by most mosquito control teams) not only to show the level of *Aedes aegypti* population but also, using the marker, to adjust the release plan for the following weeks. The overall number of males used, the frequency of release and the number of release points are all determined at the commencement of the program and refined as it continues; the marker allowing for an unprecedented level of control and precision.

Oxitec has demonstrated over **90%** reduction in the *Aedes aegypti* population in about six months in all efficacy trials. Figure 1 shows the effect chronologically comparing an area of OX513A release (green line) against a site where no OX513A were released (a control area denoted by the orange line). Following first releases, the population starts to decline rapidly after about three months. As the population declines, releases continue but fewer OX513A males are used as they are not needed at the same level as when the wild population was higher. Even when the wet season starts, the wild *Aedes aegypti* do not recover in the release area with a continuing low level release. By contrast, the untreated area shows a reasonably consistent level of infestation throughout the year with a sharp seasonal rise in the wet season.

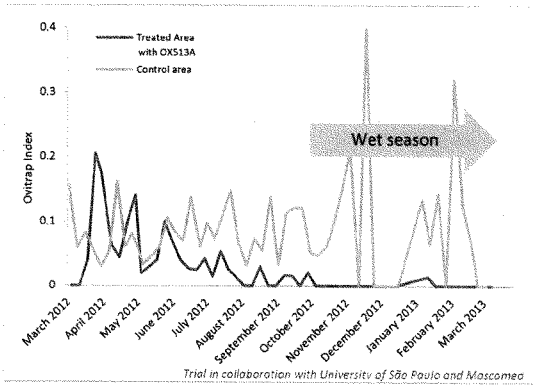


Figure 1. Oxitec's OX513A results in Mandacaru, Brazil suppressed *Aedes aegypti* by >90% and sustained control through rainy season

Oxitec has placed a major focus on operational preparedness. Oxitec has established permanent production units already in UK and Brazil and we are currently scaling up in Piracicaba, Brazil to a level to supply enough mosquitoes in the next phase to protect up to 1.5 million people. The supply chain can also use features of the mosquito biology to provide efficient logistics and quality control. Eggs can be produced at a central location for an entire country or region, from which they can be stored and distributed as required. More

locally, a production hub can receive eggs, rear to pupae, separate males from females and produce the males for release.

e) Safety and environment

Safety to environment and humans are key aspects of our approach. In stark contrast to insecticides (which will affect a broad array of insect life and respective food chains), Oxitec releases only affect the target mosquito so it is a species-specific approach. *Aedes aegypti* only mate and produce viable offspring with *Aedes aegypti*. Further, this species is an invasive or non-native one in all countries outside of Africa. From a historical perspective, it is a recent invader to the U.S. as well as an urban dweller so native ecosystems have not developed key dependencies. As a food source, it forms a very small part of the diet of other animals. For example, in the Florida Keys *Aedes aegypti* forms less than 1% of the biomass of all mosquitoes

But perhaps the most important environmental aspect of OX513A is that neither the released adults nor their offspring remain in the environment. Again, it is a self-limiting approach whereby the released males will die after a few days as will their offspring.

Over the last 14 years, Oxitec has conducted a broad array of studies on human safety and the environment and these studies have been used to inform regulatory decision making and these are publically available through the relevant country's regulatory mechanisms. Following the review of this data, the FDA's Center for Veterinary Medicine, working with experts from the Centers for Disease Control and Prevention (CDC) and the Environmental Protection Agency (EPA), has reached a preliminary Finding of No Significant Impact (FONSI). This finding corroborates that of the National Biosafety Technical Commission (CTNBio) in Brazil where OX513A has been approved for releases throughout the country.

Comparison to other forms of vector control

The main forms of vector control used today throughout the world are a combination of monitoring, good practice (through the prevention or removal of breeding sites though regular inspections and eliminating sources of standing water) and use of insecticides. While insecticides have been the mainstay of vector control products, insecticide resistance and the urban anthropophilic nature of *Aedes aegypti* mean that insecticides are not effective in controlling population of *Aedes aegypti* across an urban environment.

In addition to insecticides, there are a number of new innovations proposed that range from Oxitec's OX513A with proven efficacy along with over a decade of data, to those still in the research phase or suggested for future research. Perhaps the clearest way to differentiate these new innovations is based on

a) whether the released insects are designed to spread and persist in the environment, or not; and
b) field trial evidence and operational preparedness.

Spreading and persisting approaches (population replacement)

One school of thought relies on the concept of replacing the population of *Aedes aegypti* with a different, modified version. This could be achieved through genetic engineering or through other means. Using genetic engineering, genes may be introduced through the mosquito population (gene drive) with the intent of replacing the existing population in a biased or driven way that is less harmful. There are different early stage gene drive research programs investigating this approach.

Another approach is to try to achieve the same outcome (population replacement) by infecting the mosquito population with a bacterium. Wolbachia is an intracellular bacterium that is not naturally present in *Aedes aegypti* but, once infected with a specific wolbachia strain (wMel), investigators report a reduction in the viral load in the mosquito in laboratory experiments. To date, outdoor trials have concentrated on replacement of the wild *Aedes aegypti* population with the wolbachia (wMel) infected strain. Efficacy trials to examine the disease impact have not yet taken place.

Regardless of how these prototypes are developed, one needs to both replace the existing mosquito population with the modified version but also ensure that the new modified version is significantly less of a threat over the long term than the wild *Aedes aegypti* that it replaces. Both males and females will need to be released in order to allow the modified mosquito to replace the wild version. If the mechanism of action results in a reduction in virus rather than a complete block, then releasing biting females when virus is endemic may actually assist virus spread.

In practice, population replacement is more complex and a potentially riskier strategy than that of use of Oxitec's technology, since population replacement results in a new population of mosquitoes modified either by genetic means or

through infection with a bacterium. It is therefore essential to consider the long-term impact of the evolving mosquito combined with the bacteria and combined with virus. A particular focus for products that are designed to spread and persist in the environment is the potential long-term effects as by their nature there is no obvious ability to contain the spread or engage a product recall if this is required. Stewardship will also be a key issue.

Non-spreading and non-persisting (population reduction)

Population reduction approaches rest on using products that do not persist or spread in the environment. The product is used for as long as it is required and no longer. Some may argue that long-term control means ongoing releases but in effect we already have ongoing (but inadequate) vector control with chemical products. The ability to suppress populations of disease-carrying mosquitoes without ongoing consequences is a key advantage of these approaches.

Oxitec is a leading proponent of this approach with OX513A. Both the released males and their offspring die, meaning that there is no spreading in the environment and no persistency.

There is also significant precedent in this approach in agriculture through the Sterile Insect Technique (SIT) that was developed using radiation in the 1950's and 1960's. The use of radiation devices can impose limitation on deployment and the damaging nature of the radiation can weaken the mating fitness of the insects. Mosquitoes have been a key target for radiation driven SIT but have enjoyed mixed success over many years. *Aedes aegypti* radiation based programmes have been suggested as a response to Zika but no field trials have yet taken place so the applicability of radiation-based SIT to *Aedes aegypti* is not yet tested or proven.

Field trial evidence and operational preparedness

A key consideration is that Oxitec commenced its development in 2002. At that time Oxitec's core focus was *Aedes aegypti* due to the unmet need to control this vector with respect to dengue. Even since 2002 the geographic spread of dengue and the number of cases has risen alarmingly. To this has been added the Chikungunya epidemic and now Zika. But this singular focus on the vector has meant that Oxitec's OX513A has accumulated an extensive body of efficacy and other supporting data, especially since first outdoor trials in 2009. Ironically as a genetically engineered organism it has undergone arguably a far

higher standard of regulatory and independent scrutiny than non GE approaches.

Also, development has focused on operational practice, namely the development of methodologies, quality control and standards that have arisen as part of the maturation of the program. This level of data and operational use preparation sets OX513A apart from other approaches that are much earlier in research and development cycle.

Regulatory Status with a focus on the United States

The regulatory environment for all new approaches should be predictable, consistent and rigorous. The innovation that is needed in the area of vector control is stifled when regulatory delays occur. When serious diseases are involved, these delays can have life-altering consequences.

Oxitec's involvement in the United States began in 2009-10 when the Florida Keys experienced local transmission of dengue. The Florida Keys Mosquito Control District (FKMCD) determined that they needed new tools in order to protect their citizens from the mosquito that is the main disease vector: *Aedes aegypti.*

FKMCD sought the opportunity to evaluate Oxitec's technology, and it was agreed to conduct a small scale efficacy trial in a defined area in the Florida Keys to test our technology for the control of *Aedes aegypti.* Oxitec initially applied to USDA-Veterinary Services for permission to conduct the trial. In 2011, USDA-VS determined that it did not have regulatory authority over the Oxitec mosquitoes as it could envisage no risks to animal health from its use. Therefore, in the absence of another regulator, the FDA-CVM assumed regulatory responsibility by regulating OX513A under the new animal drug provisions of the Federal Food, Drug, and Cosmetic Act (FD&C Act). As set forth in FDA Guidance on Genetically Engineered Animals (referred to as "Guidance 187"), the agency regulates genetically engineered animals under its new animal drug authorities on the basis that the recombinant DNA construct introduced into the genome of the animal is intended to affect the "structure or function" of the animal and, thereby, meets the "drug" definition under the Act. As a result, genetically engineered animals are subject to mandatory pre-market approval by FDA.

In late 2011, Oxitec opened an investigational new animal drug (INAD) file with the FDA-CVM for a small scale efficacy trial in the Florida Keys, building on the promising efficacy results from Brazil and Cayman. While the recombinant

DNA introduced into Oxitec mosquitoes is regulated by FDA as a new animal drug, bacteria, such as wolbachia, that are introduced into mosquitoes as a form of vector control are regulated by the Environmental Protection Agency (EPA) as pesticides. The impact of this distinction in regulatory jurisdiction is substantial as there are significant procedural differences between FDA's and EPA's approval pathways. The FDA regulatory process for new animal drug approval is rigorous and multi-faceted. Companies seeking FDA approval generally must provide considerable and comprehensive data and information to establish safety and effectiveness, perform an in-depth assessment of environmental impacts, develop drug labeling for FDA approval, and otherwise comply with several pre- and post-market regulatory requirements. In order to assess environmental impacts, FDA-CVM brought together regulators from EPA and CDC as well as other experts for this evaluation - this took a considerable time to form the review team (6-9 months) as the agencies negotiated a memorandum of understanding to govern the interagency consultation. Meanwhile, Oxitec, as the regulated company, was prevented from moving forward with the efficacy trial in the Florida Keys.

FDA-CVM operates a modular dossier submission structure and Oxitec provided the first module in Dec 2013 and the last in Feb 2016, which was the final version of the sponsor-authored draft environmental assessment (EA) prepared in accordance with NEPA requirements and originally submitted to FDA in 2014. No items are outstanding from the FDA-CVM review for the efficacy trial and Oxitec has received letters of adequate response from FDA-CVM on modules submitted. Following this lengthy and time-consuming pre-trial process, FDA published on March 14th 2016 the draft Environmental Assessment (EA) for public comment along with a preliminary finding of no significant impact (FONSI) on human or environmental health. The public comment period was initially set for 30 days and the period was further extended for an additional 30 days at the request of non-governmental groups such as the Center for Food Safety. The public comment period finally closed on May 13th 2016, following the submission of over 2500 public comments. FDA-CVM is now required to review these comments for substantiveness and will prepare a final EA. Thereafter, Oxitec should be able to move forward with the efficacy trial in Florida. Given the urgency of moving forward, we hope that FDA will make the review of these comments one of its highest priorities and finalize their assessment quickly.

In the Keys, both the FKMCD and Oxitec have proceeded with a policy of transparency. The positive for this is that it allows for public information to accrue over a period of time. Interestingly, since 2013, there have been a

number of public surveys that -- despite the absence of recurring disease transmission in the Keys -- show a consistent level of strong support for the approach. A recent study by Purdue University reports 78% support respondents for the use of GE mosquitoes as part of the battle against Zika.

There will always be a divergence of opinion for any new intervention and there are those who are against the trial. The Florida Keys Mosquito Control Board has now agreed to hold a referendum in Monroe County to ascertain local opinion on the trial being carried out. This is likely to occur in August 2016.

In Brazil the first trial with the Oxitec mosquito, OX513A, was conducted in 2010 in Juazerio, Bahia, NE Brazil. This was followed by additional trials. These trials demonstrated no adverse effects resulting from the release of the Oxitec mosquitoes. Moreover, the trials generated sufficient data to submit a commercial application to the Brazilian National Biosafety Technical Commission (CTNBio) in July 2013. In April 2014, CTNBio approved Oxitec's application for use of the Oxitec mosquitoes throughout Brazil.

Oxitec has been informed that we will shortly receive special registration from ANVISA, the Health Agency within the Ministry of Health, to enable widespread availability in Brazil. Oxitec should therefore be able to bring OX513A into use throughout the country to support the fight against Zika.



Figure 2. Brazil press describe Oxitec solution as 'The Friendly Mosquito'

In Brazil, both dengue and Chikungunya are endemic and Zika has come into the public consciousness with alarm from 2015. Public support for the Oxitec approach has been at a high level – up to 96% support in Piracicaba; the first operational project. The Brazilian press has been almost uniformly supportive and indeed have given OX513A their own name describing it as *Aedes aegypti do Bem* or 'the friendly mosquito'.

Whilst at the time of writing there is no known local transmission of Zika on the United States mainland, local transmission is expected by many experts. However, there is already significant transmission in Puerto Rico and the first microcephaly case.

Considering it has already taken over 3 years due to a lack of clarity of the regulatory process for the analysis of a small scale efficacy trial we urge FDA to do the following:

a) expedite the final review of this dossier;
b) consider using its enforcement discretion to allow for rapid review of future environmental assessments, given the low risk profile of this product; and
c) given the current Zika crisis, grant emergency use or other expeditious regulatory solutions for the widespread approval of this promising vector control tool.

In conclusion, this technology has a very real potential of assisting in preventing and mitigating the Zika public health crisis. Here in the US and globally, I hope that we can work with the Congress and the Administration to expedite the approval and adoption of this promising technology. Our hope is that communities will have meaningful access to this technology in a timely manner as part of an integrated vector control approach. Mr. Chairman, Ranking Member Johnson, and members of the Committee, thank you for the opportunity to testify today and I look forward to answering your questions and working closely with you in the weeks ahead.

Hadyn Parry. CEO Oxitec



Hadyn Parry is the Chief Executive of Oxitec, a UK based company pioneering the use of genetic engineering to control of insects that spread disease and damage crops. Oxitec is a subsidiary of Intrexon, a NYSE listed company.

Hadyn has an extensive background in the Life Science sector. During his career at ICI Crop Protection/Zeneca/Syngenta he held various positions, including CEO of ICI Portugal, CEO of Societe Europeane de Semences, European Business Director and Global Head of R&D for Advanta, one of the world's largest seed companies, and General Manager of Zeneca Plant Sciences. More recently he has worked in the pharmaceutical sector prior to joining Oxitec.

Hadyn was also Chairman of Help for Heroes, a charity founded in 2007 to support wounded British soldiers, and now one of the UK's most recognised charities, from its foundation up until the end of 2103.

Chairman SMITH. Thank you, Mr. Parry.

Let me direct my first question to Dr. Presley, Dr. Ernst and Dr. Neafsey, and let me say initially, though, that we have two countries, Brazil and Colombia, where there are thousands of cases of individuals with the symptoms from Zika virus. We know that for every one who has a symptom, there are 20 others who are infected. We also know that over 99 percent of those in the United States who have become infected and have the symptoms contracted the Zika virus because of travel outside the country. So my question is this: Don't you feel that the Federal Government should issue a travel advisory that says that at the least, pregnant women and perhaps others, should avoid all nonessential travel to those two countries and perhaps others? Dr. Presley?

Dr. PRESLEY. Yes, sir, Mr. Chairman. I believe that the potential for people to travel to countries where the Zika virus transmission is actually occurring and then bring back an infection, they may be asymptomatic, but I believe stricter travel restrictions or advisories should be implemented.

Chairman SMITH. Okay. When you say that we should suggest that those traveling from the United States to other countries avoid all nonessential travel, are you talking about just women or a wider group?

Dr. PRESLEY. I'm talking about any nonessential travel from the standpoint of the few cases of sexual transmission were from male partners that came back, and I know at least one of the cases was a woman. A partner had become infected.

Chairman SMITH. So the government should issue a warning that says avoid all nonessential travel to Brazil, Colombia, anywhere else?

Dr. PRESLEY. I believe so, sir.

Chairman SMITH. Okay. Thank you.

And Dr. Ernst?

Dr. ERNST. I would say that definitely for pregnant women that it would be advisable to have them restrict nonessential travel but also to make sure that they understand if they are going to an area and they do choose to go to an area, that they look at the geography of the risk. So it is possible that in some of these countries where Zika virus is being transmitted that there are high-altitude locations and other locations within those countries that do not have Zika transmission or even the vector that is present so really trying to understand more specifically where they're going and working with their doctor to get advisement on whether or not it is important for them to——

Chairman SMITH. I think I saw a map, at least of Brazil, perhaps of Colombia, that showed over half the country was actually below the 6,000-foot altitude, so it seems to me—but you do agree at least for pregnant women that there should be an advisory to avoid all nonessential travel?

Dr. ERNST. Correct.

Chairman SMITH. Okay. Thank you.

And Dr. Neafsey?

Dr. NEAFSEY. Sure. I think this question probably falls closer to the expertise of my co-panelists, but I think it would be reasonable to advise caution, especially for pregnant women who might con-

sider traveling to a Zika-endemic area. But to echo what Dr. Ernst mentioned, beyond geographic considerations and altitude, there are also seasonal dynamics that really contribute to Zika transmission, so it's——

Chairman SMITH. What would be the most dangerous time of the year to travel?

Dr. NEAFSEY. Oh, I think the hot, wet time of the year.

Chairman SMITH. Summer?

Dr. NEAFSEY. Yes, but I think at this stage it's very difficult to quantify exactly what that represents.

Chairman SMITH. Okay. Thank you.

Second question to Dr. Presley and Mr. Parry, and that is, what are the best preventative measures that we in the United States could take to try to avoid contracting the virus?

Dr. PRESLEY. Because the biology and behavior of these vectors is completely different than the mosquito vectors of West Nile virus or other arboviruses, the immediate concern or the immediate action is, I believe prevention from the standpoint of educating the public. These mosquitoes are called backyard mosquitoes for a reason because they like to live around people and in their yards, so the pesticide application technologies and approaches that are used now are pretty much, at least throughout most of the country, is driving down the street in urban areas dispersing a fog or a spray or an ultra-low-volume insecticide that doesn't reach into the backyard, and so the control strategies with pesticides is going to take much more applied when you target an area where active transmission could be occurring, go in and kill the mosquitoes in the yard, and that may be a homeowner-driven——

Chairman SMITH. Almost on an individual basis?

Dr. PRESLEY. Yes, sir, become the individual homeowner until we have a technology like genetic modification like the sterile screw worm release

Chairman SMITH. Thank you, Dr. Presley.

Mr. Parry, my time has expired, so could you briefly respond?

Mr. PARRY. Yes. I think we can actually target the mosquito now and drive it down to a level where it can't transmit disease. I firmly believe that. I think it's an integrated approach. I wouldn't just rely on our technology but I think our technology provides the missing piece of the jigsaw, but really, we have now with our technology added in to what we have already a way of controlling this mosquito in urban environment and we should focus on the high-risk areas as a priority.

Chairman SMITH. Okay. Thank you, Mr. Parry.

The gentlewoman from Oregon, Ms. Bonamici, is recognized for her questions.

Ms. BONAMICI. Thank you very much, Mr. Chairman, and thank you for convening this expert panel of witnesses. It's been very enlightening. I have about 5 hours of questions but I only have 5 minutes, so I'm doing to start.

Dr. Ernst, you said in your written testimony that we don't know the complete distribution of the Aedes aegypti in the United States because surveillance for the mosquito is not consistent across jurisdictions and many don't have the resources to carry out the surveillance needed, and Dr. Neafsey, you talked about a different of map-

ping, the genomic mapping. So can you each address how close are we? Are we halfway there? Are we 25 percent there? And maybe just a mention of where we are in terms of resources as well, and then I want to have time for another question or two. Dr. Ernst?

Ms. ERNST. I will try and answer briefly. So I would say that it's very spotty where we have the surveillance data that is actually accurate and well collected. Some places do a great job and have a significant amount of resources. The majority of places do not. There are West Nile virus vector surveillance that is ongoing but the distribution, the way the ecological niche is for the Aedes aegypti mosquito, it's different, so you have to have different traps and different location of those traps. I would say at least 80 to 90 percent of the actual jurisdictions probably do not have active Aedes aegypti surveillance at this time.

Ms. BONAMICI. Thank you.

And Dr. Neafsey, on the mapping, how close are we, or how far are we, depending on how you look at it?

Mr. NEAFSEY. I think we're close. I think we're making good progress towards having a better genetic map, but I think having a better genetic map for the mosquito is a proximal goal and the goal of applying that map most fruitfully to studies, for example, of insecticide resistance and identifying those markers that are most useful in the field for maintaining the efficacy of the control measures we do have. That will take further application of the genome map and testing of more samples.

Ms. BONAMICI. Thank you. And many of you mentioned the urgency because of the summer weather that's approaching. It's almost June. Does anyone disagree that it's becoming more urgent as the weather is getting warmer across the country and the world? Anybody disagree with that?

So my next question is really for each of you. I was really surprised to learn that the Aedes aegypti mosquito can breed in a bottle cap of water. I don't think that this is what people think about when they're warned against keeping standing water around, and I know, Dr. Presley, you addressed this need for public health education, but what efforts are underway to educate people, and is there social science research about the most effective ways to communicate these kinds of messages? Are there—do we need more behavioral research on how to send the messages with urgency so that they'll be understood and acted upon? Dr. Presley, do you want to start and then I'd like to hear from the others as well.

Mr. PRESLEY. Yes, ma'am. There's efforts underway in Texas, I know for sure, to put out using social media and online resources. There's programs, there's web pages that CDC has. There's a lot of information out there.

I did a Zika virus search last week and found 91 million results so——

Ms. BONAMICI. I don't mean to interrupt, but maybe that gets to the heart of the question. Is somebody sees 91 million results, how do they know where to go to get something that's effective? Are there—is the CDC known as the reliable source and the others are—you know, everything we read on the internet isn't true so how do we get that message across in an urgent way?

Mr. PRESLEY. In Texas, in the local area I'm from, we're sending it out in utility—little flier, a pamphlet in utility bills, and they're going to do that—they started that in May and they're going to follow through the summer with that. That's really the only way that we found to make sure everybody at every level gets it.

Ms. BONAMICI. Okay. I know a lot of people pay their bills online so I just don't know if we're doing what we need to do to reach people to get the message across. I think people are thinking well, if I have a pond I'm in trouble but otherwise I'm not, so how do we communicate that?

Dr. Ernst, do you have thoughts on that?

Ms. ERNST. Sure. So we're doing a couple of things. One is try and engage people in social media but also to try and link that social media to whether or not it actually makes any kind of difference because there is a lot of advertising and there is a lot of information that's out there but whether or not that actually translates into action on a person's part is unknown. We are also developing a mobile application that people can subscribe to that has an educational component. I think that making sure that there is a cohesive on-the-ground network so in the area where I'm from, promotoras and community health workers can get that information out to areas where there are fewer resources and actually have one-on-one contact with most vulnerable communities.

Ms. BONAMICI. Terrific.

And Dr. Ernst, quickly, you mentioned that we don't know how different environments and different environmental conditions may change the feeding habits. If somebody researching that, and what would that research tell us if we could answer those questions? How would we use that information?

Ms. ERNST. Right. So in Phoenix where there's a fairly good vector surveillance and control program, they actually noted that the Aedes aegypti mosquito were altering their biting behavior and were biting as early as 3 or 4 in the morning. Now, that's anecdotal. They have not met published that information. But it seems like this is a very flexible mosquito, and it is able to modify its behavior in order to survive.

Ms. BONAMICI. Fascinating. Thank you, Mr. Chairman. I yield back.

Chairman SMITH. Thank you, Ms. Bonamici.

And the gentleman from Oklahoma, Mr. Lucas, is recognized for his questions.

Mr. LUCAS. Thank you, Mr. Chairman, and before I begin my questions, I would note that having known Dr. Presley since his graduate days at Oklahoma State, I have a little sense of co-ownership along with Congressman Neugebauer down there.

That said, Doc, let's turn to you for a couple of questions. Number one, in addressing the issues, and the panel's laid out very well today the challenges we face, the ultimate goal of what we try to do, but there's the short-term solution and there's the long-term solution. Talk for a moment about—and you discussed this earlier—about the mosquito control perspective for a homeowner, whether it's Lubbock or Stillwater or anywhere where this may be an issue. You've described how the traditional mass fogging systems going down the street won't get everywhere. I know historically in the

past, we've done aerial spraying in certain cases. As I talk to my constituents, the off-the-shelf products you're taking about, what kind of cost are we talking about for a homeowner to protect him or herself in their backyard? It's not particularly expensive, correct? It's the efforts involved?

Dr. PRESLEY. No, sir, you can buy a home thermal fogger, which creates a cloud, a smoke cloud, essentially, in your backyard that will penetrate vegetation and you can buy the pesticides. You can buy the thermal fogger for a couple hundred dollars, a very good one, and then the pesticides may be $20 or $30 a month to keep mosquitoes down in your yard.

The issue with these mosquitoes, albopictus and aegypti, is they stay pretty close to where they are hatched, about 200 yards, 300 yards in an area. The foggers that drive up and down the streets are really for mosquitoes like culex tarsalis that vectors West Nile virus, and that with restrictions and how we've refined pesticide application, you're relying on a small droplet of that insecticide impinging on the mosquito while in flight. That's effective for crepuscular biters, or mosquitoes that bite at night or between, you know, sunset and dusk and dawn, because with Aedes aegypti and Aedes albopictus, they're daytime biters primarily. So spraying with the fogger depends on before the thermal inversion occurs. When the sun comes up and the ground begins to heat, the currents are upwards, so these fogs, these clouds that you spray out of a ULV machine driving up and down the street will rise and dissipate. You're trying to get with these daytime biters treating early in the morning with a fogger or a thermal fogger or a spray, just a wand spray treating under the eaves of houses, around doors and windows and vegetation. It's a completely different strategy for vector control. It comes into private property issues, all of that.

The homeowner is going to be responsible for dumping that bottle cap full of water or that toy dump truck in the backyard or anything that can collect water is a good breeding site for these mosquitoes.

Mr. LUCAS. But our fellow citizens have the ability to protect themselves if they'll take action based on the right information?

Dr. PRESLEY. Yes, sir, and there are numerous over-the-counter, off-the-shelf products that can be bought at any big-box garden store or home improvement center.

Mr. LUCAS. Now let's go to the next step, Mr. Parry discussing an effort at a long-term solution. You mentioned the screw worm program so successful since the 1950s that most people don't even know it exists. Would you expand on the problem we face in the Southwest, in the South, for that matter, what the solution was and how it has continued to be effective since then?

Dr. PRESLEY. Oh, the sterile male release of screw worm flies. The primary screw worm, they're a blowfly. They would oviposit or larviposit their maggots into a wound, and that particular screw fly would eat living flesh. Other blowflies will——

Mr. LUCAS. And any cattleman 65 years or older in Texas or Oklahoma will tell you it was a horrible thing.

Dr. PRESLEY. And not only cattle, wildlife—whitetail deer, everything was affected. They came up with a sterile male screw fly release program where they irradiated the males and released them.

This particular species only bred once, the females, so it stopped the progression, and it essentially stopped——

Mr. LUCAS. For 50 years now.

Dr. PRESLEY. There still are cases but it's very controllable and managed on the Texas border now.

Mr. LUCAS. So we have a track record of using these type of technologies to make a real difference systematic in the long haul?

Dr. PRESLEY. Yes, sir.

Mr. LUCAS. Thank you, Doctor.

I yield back, Mr. Chairman.

Chairman SMITH. Thank you, Mr. Lucas.

And the gentleman from California, Mr. Bera, is recognized for questions.

Mr. BERA. Thank you, Mr. Chairman.

I'm going to put on my doctor cap here and public health perspective so with regards to travel advisory for those listening at home, just go to CDC's Zika Travel Advisory, and you'll get a lot of information and country-specific information.

Going back as far as February, the advice has been, if you're pregnant, do not travel to endemic areas. If you're of childbearing age, the advice is not to travel to endemic areas, but if you are going to travel, to take precautions—birth control, et cetera. We've also been working with global health agencies to increase access to birth control in endemic areas until we get ahead of Zika virus and we fully understand what's going on.

If you have to travel to these areas, obviously take mosquito precautions, you know, repellants, et cetera avoid going out at dusk or the times the mosquito's biting.

In addition, you know, back in February, we had a hearing. We had Dr. Frieden and Dr. Fauci come over from the National Institutes of Allergies and Infectious Disease. Dr. Fauci at that time was quite optimistic that by the end of the year we'd have a vaccine for clinical trials. I will be honest, I was skeptical that we'd be able to develop something as quickly as that.

You know, a few weeks ago I had a chance to go visit Dr. Fauci and his team at the National Institutes of Health. They will be ready for clinical trials, phase I trials, starting in September, and a very important aspect of our getting ahead of Zika is that vaccine development, and the science behind vaccine development. So, you know, September is still after mosquito season but we are moving fairly rapidly to get ahead of this and address it.

The bigger component here, though, and each of the witnesses touched on this, is two years ago we were talking about Ebola, we're talking about Zika this summer, and the world is a much smaller place right now, and vectors, infectious disease viruses move much more quickly. It's not as though we haven't known about Zika for, you know, years. We've known about this since the 1940s. And it's not that the virus has mutated. The virus has moved. It's now in a densely populated area and, you know, we are starting to see this pop up, and what we have to do is as a body is, provide adequate resources to the CDC, to the NIH to do the research but to understand that we are going to be battling these infectious diseases much more frequently, and we've got to support the science.

Dr. Ernst, I'll probably toss it over to you. With regards to both Zika—you know, certainly as we get a vaccine developed, disseminating that vaccine and making sure it's effective, but then also just more broadly as an epidemiologist and someone who studies this, you know, what we ought to be doing right now to prevent the next infectious disease and how we ought to be thinking about some of this.

Dr. ERNST. So you're talking more broadly, any infectious disease?

Mr. BERA. More broadly, yes.

Dr. ERNST. More broadly? I mean, I think some of the things that we can do is really understand where a lot of these infections are originating from. A lot of these are diseases of poverty. They're diseases where you have countries and places that have no infrastructure to be able to respond and control the epidemic in their own boundaries, and when you have something that is going on in another place and you have, as you said, a very globalized world, it doesn't take a lot for those viruses or bacteria to come over here.

So I think shoring up resources in other places to ensure that there's fewer pandemics in those areas as well is a critical step, and then also investing in research and understanding where those threats might be more likely to come from is also very important.

Mr. BERA. Wonderful. And again, I think for the public and for my colleagues in Congress, it is very important that we don't just fight the disease here, that we actually go to where these infections and these viruses are endemic and originating, and there's a reason why we fund global health, there's a reason why we, you know, fund the CDC to go do research and go to these endemic areas, and as we look at these fundings and we look at our budgets, it's really important for us, because if we don't get ahead of this in those endemic places where the virus is, they will certainly pop up here, and we've seen it time and time again with SARS, with, you know, various infectious diseases, and again, in a smaller world, we will see this more frequently.

You know, I'm running out of time. As Ms. Bonamici said, I could spend, you know, 5 hours asking questions, but we also have to then adequately fund the science as well so we can come up with those therapies to both control the vectors but then also to get ahead of this, and with that, Mr. Chairman, I'll yield back.

Chairman SMITH. Thank you, Mr. Bera.

The gentleman from Texas, Mr. Neugebauer, is recognized.

Mr. NEUGEBAUER. Thank you, Mr. Chairman.

The United States has been very lucky that many of the potential global health pandemics have not become epidemic in the United States. However, it's a little puzzling to me because you know, some of these things like Ebola and Zika have been around for a very long time, but what happens is, something kind of elevates their attention and then there's a call then for the Federal Government to come and spend billions of dollars to be in a reactive mode.

So I guess my first question to the panel this morning is, rather than being in a crisis mode on some of these things, what would be a better plan? Because I think what I always find is when we have crises, we don't spend money as efficiently as we do when we

spend money when we're planning for it, so kind of go down the panel, and in a perfect world, how can we get on the front of some of these rather than being in a reactive mode?

Dr. ERNST. So I would concur with that. I absolutely agree that the reactive mode that we seem to be in, in terms of pandemic response and planning, is not as efficient. I think we have made some strides towards trying to be more ahead of the curve. We had a lot of preparedness funding that has come through the health departments to try and set up some of these response plans in place, et cetera, but I think we can do more. I think that we need more investment in trying to understand where and when and forecast some of these risks and be able to quell them before they can even actually start taking off, and that means having really better surveillance systems globally as well as even improving our surveillance systems here domestically.

Dr. NEAFSEY. All right. So I second, you know, the importance of surveillance, and I can speak to work being done by one of my colleagues at the Broad Institute, Pardi Savetti, who was well positioned to apply DNA-based studies of the Ebola outbreak because she was establishing a research base in West Africa and starting to characterize fevers of unknown origin. There are many agents of infectious disease that result in symptoms and that are undiagnosable because we don't know what the agent is, and there are many of these, particularly in tropical parts of the world, any one of which could in principle emerge to cause an epidemic.

So I would advocate the importance of surveillance, the importance of catching new epidemics early, and the utility of DNA-based studies for getting an early characterization of perhaps the agent behind emerging outbreaks.

Dr. PRESLEY. I agree completely with what's been said. I'm much more applied in how I study vectors. It's more not at the genetic level, it's more transmission dynamics, how they behave, the ecology of the vectors. That is where I believe funding also needs to be focused. You're right, this "everybody panic and throw money at it" doesn't fix it, and I said it before. The Zika virus is just the latest of an emerging arthropod-borne threat, public health threat, in the United States. We had chikungunya last year, Valley fever before that, and we'll have more because there are viruses out there that we know or suspect are vector-borne but they're not in areas where we're really concerned right now. West Nile virus had never occurred in the real world until 1999. Zika virus wasn't in South America until last year, 2015. So viruses are moving around, and that's part of—whether it's climate change or global travel, speed of travel, they're moving around.

My basic belief is that we need to start at the applied level and train pest control operators. We saw a kneejerk response to Ebola where nurses and clinicians did not have the proper personal protective equipment, the most basic of supplies they need. I can draw a similar situation with vector control operators in mosquito control districts throughout the country right now. They don't have those basic supplies they need knowledge-wise and resource-wise to attack this issue.

Mr. PARRY. I think you have to look at the common element, and the common element is the mosquito. Control the mosquito, you

control all the diseases that it has spread, is spreading, and will spread.

When I say control, I mean giving yourselves the capacity, the tools, and the procedures to exercise that control. In some areas, some may wish to eliminate the mosquito. In other areas one may wish to have the ability to drive it down below a disease transmission threshold, which is not actually the same as elimination. But having that capacity, having that ability to do that to me is the absolute starting point of it.

Mr. NEUGEBAUER. Thank you, Mr. Chairman.

Chairman SMITH. Thank you, Mr. Neugebauer.

And the gentleman from California, Mr. Takano, is recognized for his questions.

Mr. TAKANO. Thank you, Mr. Chairman.

Mr. Parry, what you propose makes rational sense, statistically drive down the numbers of the mosquito control, the vector. Mr. Lucas mentioned the sterile—the sterilization of the male insect. Your process, though, is not sterilization, it's about a genetically modified mosquito, and there's some concerns of some environmental groups about the safety of this, and there's some rumors that this genetically modified mosquito actually transmits the virus. Can you just quickly clear that up? Because I have a lot of other questions I want to ask.

Mr. PARRY. Yes. I mean, our mosquito is modified in two ways. It can't reproduce, and it carries a color. It's no more or less capable of doing anything else than normal mosquitoes. There is no difference. In terms of the environment, actually I think our mosquito is far safer and softer on the environment than any other intervention. It's not a toxin. You're just taking out one insect. You're not affecting the rest of all the food chains.

I think it is a shame in many ways that there has been a concern over the words "genetic modification" in society. That's been there for several years now. And really, we need to be able to distinguish products by what they are, what they do, what the risk profile is, rather than assign a tag or a label.

But ultimately, with our product, it's like any other. It's—we provide the evidence to the actual arbiter. At the end of the day you go through the regulatory process. The evidence is weighed up and you have an outcome that's based on science and facts.

Mr. TAKANO. So with respect to Zika in this particular case, it seems controlling the vector is really important to keep what transmits the virus from doing that, and so reducing the numbers of mosquitoes is really important but also coming up with better technologies on repellants.

In my own district, the University of California Riverside, which is known as a great center of entomological research—I see a lot of nodding heads. Dr. Neafsey, are you familiar with Olfactor Laboratories, which is an attempt to monetize the research that was done in a laboratory by Dr. Anandasankar Ray, who is basically focused on trying to deal with the carbon dioxide receptors of the mosquito. You mentioned that some mosquitoes are able to distinguish between human and animals, but what's common is that they're kind of attracted to this carbon dioxide marker. Is that right?

Mr. NEAFSEY. So yes, that's right. I think there are a number of cues that lead mosquitoes to their host for a blood meal. Carbon dioxide is one such cue. What is amazing is that many mosquitoes, particularly those ones that are most culpable in transmitting human diseases, are very human specific so they're responding to carbon dioxide but they're also responding to other unique signatures of human odor. I think developing repellants, developing strategies that capitalize on our rapidly growing knowledge about the molecular biology and the neurobiological basis of how mosquitoes perceive these cues is a fantastic research direction and I think you've cited a good example of how it's actually translating into intervention measures of repellants.

Mr. TAKANO. This is a great example of how basic scientific research in a laboratory has these very practical effects and is being furthered by private-sector-funded efforts to monetize that research. I understand that they've developed a patch, something called a Kite patch, which can just be worn on clothing which interferes with the mosquito's ability to perceive these—what do you call them?—these markers or——

Mr. NEAFSEY. Cues.

Mr. TAKANO. Cues. The cues. The cues, the chemical cues. What's exciting about that is that it seems less—has less impact on the environment with the use of these pesticides. So this is a very promising line of research is what I perceive.

Mr. NEAFSEY. Absolutely. I think we're positioned now rather than to use sort of a random strategy for finding chemical repellants or other interventions, we can really use our knowledge to pursue these strategies with a rational basis, with a thorough understanding of the mosquito biology, and these have great potential.

Mr. TAKANO. Well, I hope that we can work together on both sides of the aisle to promote a number of strategies to deal with this vector.

Mr. Parry, you certainly propose, I think, a very rational strategy, and Dr. Neafsey, you've confirmed my excitement about what's going on in my own district on this research, and to the extent that we can buttress what's going out there—and Dr. Ernst, what you say about global poverty and making sure that we take care—that there can be no weak link. We can't allow any country to have a dysfunctional public health system. It comes back on us.

I yield back, Mr. Chairman.

Chairman SMITH. Thank you, Mr. Takano.

And the gentleman from Louisiana, Mr. Abraham, is recognized.

Mr. ABRAHAM. I thank you, Mr. Chairman. I think we certainly have a great panel here, and with your minds and minds out there working on this, we can probably cure this issue.

Going back to Congressman Neugebauer's argument of being reactive instead of proactive, the Federal Government is unfortunately often reactive, in my opinion, and it's like sending the Hindenburg to rescue the Titanic. We need to be better than that. We should be better than that at this stage of the game.

Mr. Parry, the CDC, I think in February, elevated Zika to a level one activation, and you can help me, but I think I recall that the only other time was Ebola was active one, H1N1, and being in Lou-

isiana, I remember post Katrina was a level one activation. So my question to you is, you've got evidently something that works here. You said you could get a 90 percent reduction in mosquito population in six months, which is, to me, a phenomenal feat. If CDC thinks this is so important, and I can assure you, it's very important—I've treated microencephaly and microencephalitic children, and it's a horrible, horrible thing for a child to undergo that, and their parents also—what is the FDA telling your company as to why it won't give you an emergency declaration? I mean, you've been after this since 2011 according to your testimony. We know this is bad. We don't want any child to be born with microcephaly or microencephaly. What's the answer FDA is giving you to why can't we do this now?

Mr. PARRY. The answer we have received is, it's complicated.

Mr. ABRAHAM. Well, come on. We've got wonderful scientists here including yourself that tells us we need to act now. We should have acted a year ago.

Mr. PARRY. I absolutely agree. We're being treated as an investigational animal drug as the sort of product class, if you like, because the genetic modification is a DNA insertion, which means that from the FDA perspective, they would have to approve an animal drug in order to provide a public health benefit.

Mr. ABRAHAM. But you've got objective data that says this works now.

Mr. PARRY. Exactly, and I think that's exactly the way we should go. We need to go down the emergency——

Mr. ABRAHAM. We've got to kill these mosquitoes. I mean, I understand, look, I think it's critically important what we've talked about, better repellants like Mr. Takano said, certainly spraying individually, but until we kill the mosquito, we can kill all we want to in our house but they're going to come back in. Mosquitoes are going to come from the islands, they're going to come up from the South. We've got to quit putting Band-Aids on this. We've got to go to the root cause. The root cause, like you alluded to, is a mosquito, and somebody asked about pandemics worldwide, and again, yellow fever, dengue, malaria, all these are vector-borne, and we've got to kill the source.

So, you know, I'm very frustrated as I am with many government agencies, unfortunately, but with the FDA in this instance, it's out there, we know it's here and we need to do something, but they're putting up blockages to your company and other companies like yours.

Mr. PARRY. I think we should encourage them to find the processes to make this happen.

Mr. ABRAHAM. Is the cost of your technology any more costly than spraying, traditional spraying?

Mr. PARRY. I think in terms of cost efficacy, ours will be streets better, to be honest.

Mr. ABRAHAM. Okay. And to the panel, I've just a couple of science questions. Is this an intracellular or an extracellular virus? Does it live in the RBC, the WBC or is it in the plasma? Where does it live in the human?

Mr. NEAFSEY. I think it replicates in cells, and I think work is underway on elaborating exactly which cell types are most favored

by the virus. I think there was this convincing work a few weeks ago with brain tissue organoids to establish its affinity for developing around the cells, but I would say that the preferences for the types of cells infected by the Zika virus are still being elaborated upon.

Mr. ABRAHAM. And Dr. Ernst, you said that certainly the mosquito vectors like the Aedes aegypti and the albopictus transmit not only Zika but other diseases such as dengue, yellow fever. When a mosquito that's infected with Zika and those other diseases bites somebody, are both viruses or more than one transmitted at the same time, or does Zika take precedent? Who wins that battle?

Dr. ERNST. That's a good question. I don't think we know that yet. There's certainly some evidence that mosquitoes can be co-infected with dengue and chikungunya but I'm not sure what the status of the research is right now on the interactions between dengue virus, for example, and Zika virus. I don't think we know that yet.

Mr. ABRAHAM. And one quick question. My time is out. After somebody's infected with Zika, is there antibodies built up? Can we test for antibodies in that person?

Dr. ERNST. Yes, we can test for antibodies for Zika but it's very difficult to disentangle if the person has had a previous dengue infection. Then when you try and test for antibodies, it becomes equivocal. The results become very difficult to interpret.

Mr. ABRAHAM. Well, Mr. Chairman, I have a thousand other questions also but my time is up so thank you very much for allowing me to go over.

Chairman SMITH. Thank you, Mr. Abraham, and the gentleman from Colorado, Mr. Perlmutter, is recognized.

Mr. PERLMUTTER. Thank you, Mr. Chair. This is a very fascinating hearing, and obviously—my question is going to be a little more parochial. I'm from Colorado. Looking at those maps that you presented to us, we're not really in the region that can anticipate Zika, the Zika mosquito, the egyptus or whatever it is.

So I'd like to start with you, Professor Presley, because you mentioned West Nile, which is something that we'll get a couple cases of West Nile in Colorado pretty much every year. Can you just for a layman like myself kind of explain the difference between the mosquito that delivers West Nile versus the mosquito that delivers the Zika virus? And then, you know, how are we managing West Nile mosquito versus the Zika mosquito?

Mr. PRESLEY. The West Nile vector is—and I'm not sure what part of Colorado you're talking about.

Mr. PERLMUTTER. Denver area.

Mr. PRESLEY. On the high plains?

Mr. PERLMUTTER. Yeah.

Mr. PRESLEY. It's culex tarsalis, and that mosquito breeds in pools and ponds, standing water, so we can survey for them. Their activity is primarily crepuscular, right after dark and right before sunrise. Contrast that to Aedes aegypti and Aedes albopictus that are vectors of Zika virus, and they like to—they're container breeders. It's fresher water typically in small containers in the axles of——

Mr. PERLMUTTER. When you say small containers, tell me what you mean by small containers. I'm trying to think. You ship them in boxes or what?

Mr. PRESLEY. A tuna can is more than—an empty tuna can is more than enough water. They will breed in the leaf axles of vermillion plants like in the house. You know, a comment was made about just outside. No, these mosquitoes will live in the house. They like to be in the house, hotel rooms. So just treating the outside doesn't control them. So these differences in where they breed and where they like to bite and rest are significantly different. You know, they're daytime biters, and it's really right after sunrise—typically right after sunrise. Then they rest during the heat of the day and they bite right before sunset when it cools back down. That's not a rule but that's generally.

Mr. PERLMUTTER. So in controlling them—and Mr. Parry, maybe I'll direct these questions to you for a second and then to the whole panel. So—and I don't know the Latin term but I'll call them the West Mile mosquito and the Zika mosquito. In your use of more or less a sterile male to defeat the virulent female or, you know, cause the death of the species, do you guys do any work on the West Nile mosquito?

Mr. PARRY. Not yet. So we've obviously developed aegypti. We can do anopheles, which is the malaria mosquito. We've actually done proof-of-concept work there. We're actually developing Aedes albopictus, which was also mentioned earlier, so that is actually coming through the R&D system and is a candidate product.

With the culex mosquitoes, the West Nile ones, we've looked at those. We think they're very tractable actually. We can do them. The research team is very confident but we haven't proven that yet.

Mr. PERLMUTTER. In Colorado, I think Professor Presley, we have up at Colorado State University, you know, studying the Zika virus and mosquitoes. Do we—I guess my question is, the symptoms of West Nile can make you—you get really sick. More negligible obvious symptoms with the Zika virus but the potential damage to the fetus or to the baby is tremendous. So I guess my question is similar to Mr. Abraham's, we ought to be allowing every possible defense whether it's using an insecticide or sterility, and I would—on the insecticide part of this, do we have any breakthroughs? It sounds like Mr. Parry has a good approach on the sterility. Do we have any breakthroughs on the insecticide piece of this against the Zika virus and the Zika mosquito?

Mr. PRESLEY. We do, Congressman. There are some very effective pesticides, but the whole insecticide resistance issue in these species is critical, and we don't know where resistant populations are. In the State of Texas, we're going to find out in Texas, but there needs to be, I think, a national effort where these mosquitoes are documented to occur to find out what insecticide resistance does exist in the population so we can knock them down immediately and then rely on long-term strategies to keep them numbers down.

And I would just add in that West Nile virus when it first occurred and during the first few years of its occurrence in the United States was considered to be West Nile fever predominantly, which was relatively mild symptoms. Now it's predominantly West

Nile neuroinvasive disease. The virus has changed over time. We don't know what Zika is going to do because it's only been in the new world in South America for a year. There's a lot of challenges there.

Mr. PERLMUTTER. Thank you, Mr. Chairman.

Mr. PARRY. I had a point.

Mr. PERLMUTTER. Oh, go ahead.

Mr. PARRY. Sorry. I know that's not done, but I'd just like to add a point.

The issue of insecticide resistance is a very real one, but when you get to the Aedes aegypti, which is the Zika transmitter, the biggest issue is private property actually because this mosquito lives in and around the home. For chemicals to be effective, you've got to have a public health authority coming into your house, your child's bedroom, your kitchen pretty much every week, and that doesn't work with modern society.

Mr. PERLMUTTER. Thank you.

Chairman SMITH. Thank you, Mr. Perlmutter.

And the gentleman from Alabama, Mr. Palmer, is recognized for his questions.

Mr. PALMER. Thank you, Mr. Chairman.

Dr. Presley, given that the symptoms of Zika virus in adults are associated with a host of other ailments, how likely is it that a general practitioner may not have seen a case of Zika and therefore be able to accurately diagnose it?

Dr. PRESLEY. Excellent question, Congressman. You know, we say the facts that are out there or the information out there is that only 20 percent are symptomatic with infections. Flu-like illness of influenza-like illness is so common in talking to my physician friends, how many infections are we saying, it looks like a virus, go home, rest, plenty of fluids, you'll be fine, and it never gets tested. So I think that these estimates of the number of infections in an area are way underestimated but there's no way that you can nail that down. It's like West Nile or flu, influenza.

Mr. PALMER. Do physicians have the necessary diagnostic tools? I mean, is there something out there that they could use to make sure they make a more accurate diagnosis?

Dr. PRESLEY. The current restrictions on human diagnostics, and my lab is one lab that does that but there's certain criteria both clinical and epidemiological criteria like have you traveled or been exposed to somebody that did travel in a Zika infectious area, and then the local public health authority has to authorize that test being performed. Those tests, diagnostic assays, can only be done at CDC LRN laboratories, and we've done a couple over the past few weeks, but it's a long administrative trail.

Mr. PALMER. It sounds like we need a kit, some——

Dr. PRESLEY. Yes, sir.

Mr. PALMER. —something like that. Let me move on. Thank you for your answer.

Dr. Ernst, in your testimony you described the Zika map that you helped developed to try to predict where Zika might spread in the United States. Have we stopped short of calling it a forecast because there's still too many unknowns? How would you improve your model to provide a better forecast for Zika or other vector-

borne diseases and what resources would a team need to provide a better forecast?

Ds. ERNST. So I think there are several key components that would be helpful to improve for model results. One is being able to have better validation. So we were lucky enough to find a couple of data sets to validate our model outputs, but as has been mentioned multiple times, having actual robust surveillance programs that allow us to test our results against the actual data is one step. Another step is having more information on the specifics of the host vector interactions, so critical are things like the extrinsic incubation period. We don't really know what that is. We don't know its temperature dependency. We do have some work that's going on in one of my collaborator's labs to identify that. And some other issues are really understanding the social side. So there are absolutely different factors like poverty, vector-human interaction that need to be incorporated into models in order to really predict that risk.

Mr. PALMER. I want to move to another question. Mr. Parry, we banned DDT, and by some estimates, there are 50 million people who have died from mosquito-borne diseases, and just in regard to the new science that we're trying to posit, what are the odds and potential consequences of the offspring of Oxitec genetically modified mosquitoes developing resistance or tolerance to the self-limiting gene they acquire?

Mr. PARRY. We haven't seen it. We've gone through over 200 generations now of our mosquito. We've seen no resistance developing at all. There are certain biological issues and also the way in which the technology is being done, so we're not expecting to see it, but any scientist will say you'll never say never.

I think the issue is, what does our product actually do. It stops the mosquito from breeding. So what happens if it doesn't work? Well, then the mosquito can breed, so it becomes a normal mosquito.

Mr. PALMER. Well——

Mr. PARRY. So effectively we would stop releasing.

Mr. PALMER. Looking at the situation from another angle, is there any chance that the Oxitec technology might eradicate the Aedes aegypti breed of mosquitoes?

Mr. PARRY. Mosquitoes only fly about 200 yards in their lifetime, so actually the effect when you're releasing our mosquito is in the area in which you're releasing it. So you actually have to be very deliberate about where you go, how you control it, and against all of the issues you've raised, we have the marker. We have something that no one's ever had, which is the ability to track and trace exactly what we're doing so we pick up that metric all the time.

Mr. PALMER. Well, I'm out of time. My last question is, one of our colleagues on the Committee talked about CO_2 as a marker apparently in the context of climate issues. Is it any of your recommendations that we breathe less?

I yield back.

Chairman SMITH. Thank you, Mr. Palmer.

The gentleman from New York, Mr. Tonko, is recognized.

Mr. TONKO. Thank you, Mr. Chair, and welcome to all of our experts for very valuable information.

Dr. Ernst, in your testimony, you discussed community-based surveillance activities including USDA's efforts to encourage participation by community members. There's no doubt that we need to invest more resources into surveillance. In particular, I'm encouraged by efforts to use crowdsourcing and citizen science methods within the Federal Government to advance and accelerated scientific research and literacy. One example of this is USDA's Invasive Mosquito Project, the IMP, which was launched recently as an initiative that pairs high school teachers and students with mosquito control and public health professionals. This partnered citizen science classroom project helps high school teachers meet the next-generation science standards and students learn about mosquitoes, public health, and safety. The project is aimed at monitoring invasive container inhabiting mosquito species across the United States. According to the project's description, by doing this monitoring, we can determine where the invasive mosquito species as well as the native species are distributed across the United States and define at-risk human and animal populations based on this distribution.

With all of that said, can you speak more about why projects like these can help with surveillance efforts as well as providing enhanced public education?

Ms. ERNST. Sure. So I think that these kinds of projects are great for a number of reasons. We've carried off some of these in Arizona specifically as well. We developed something called the Great Arizona Mosquito Hunt, and that engaged high school students to set out the ova position cups, which is a fairly sensitive measure of detecting whether or not there are mosquitoes present or not, and it allowed them to go through an educational module to teach them about the mosquitoes.

So I think these kinds of efforts not only can be broadly disseminated to a large group of people but it's also targeting young children as well as teachers who can pass that information on to their parents and really help be vigilant about mosquito control within their own household.

I think that there is some things that need to be ensured for these kinds of projects including standardization of the methods to ensure that when you do get a negative that it is because there is not a mosquito around. That's one of the things that's difficult to determine. We found a lot of negatives in the high schools where we placed traps in part because, as the gentlemen have said previously, it doesn't fly very far and school grounds are generally kept pretty clean. So really understanding some strategies to standardize this process to yield the best success are also important.

Mr. TONKO. Thank you. And to you also Dr. Ernst, in reading testimony for today, I was struck by how we do not have a good idea of where the mosquito that transmits the Zika virus lives. You have done research into modeling the geographic areas with higher potential risk for local Zika transmission. Can you please describe that study and how forecasting studies like yours could help decide where to invest our resources?

Ms. ERNST. Sure. So this was sort of a first cut, I think is what we basically have been stating, in trying to understand where the

Aedes aegypti might be present in the United States as well as the seasonality of the vector, and it really is based upon what we know about the dynamics of the mosquito and how it relates to climate and weather. So most of the stages of the mosquito are sensitive to temperature as well as precipitation for the aquatic stages of the mosquito so we can leverage information on sort of average—what we did was, we took average ten years. worth of data to look at if you had the weather that's sort of typical in these cities, when would you see Aedes aegypti abundance, and then we compared that to an area where we know there's fairly good conditions. We compared it to the numbers that we had in Miami. And so the map that we actually depict is relative abundance, so it's relative to sort of the high season in one of the most climatically suitable places, and we look to see how different that might be for the other 49 cities that were mapped and modeled.

I'm sorry. I can't remember the second part of your question.

Mr. TONKO. Well, it was just how we could best use that information to decide where to invest resources.

Ms. ERNST. Right. So, you know, some of the other layers that we have incorporated are related to travel introduction. So obviously without any local transmission at this point, it would have to come from somebody who had traveled outside the country and brought back the virus. And then as well needing to understand poverty and other factors that might facilitate more vector-human interaction.

Some of the things that you can use the data that we presented for are understanding when theoretically you're going to have a higher peak of mosquito activity within your jurisdiction if you're on the map as well as trying to look to see, has your jurisdiction actually had dengue or chikungunya in the past. That's another piece that we mapped into that study.

Mr. TONKO. Thank you very much. I sense, Mr. Chair, that there's a degree of urgency to invest here and invest wisely and deeply into this program.

If I might take the liberty, today is an opportunity for foster youth to shadow individual legislators, and if I might introduce right behind Congresswoman Clark, we have Steven Fallon, who is my shadow today as a foster youth, if you'll recognize Steven, please.

Chairman SMITH. Thank you, Mr. Tonko, and the gentleman from Michigan, Mr. Moolenaar, is recognized for his questions.

Mr. MOOLENAAR. Thank you, Mr. Chairman.

Dr. Ernst, in your testimony you identified some of the knowledge gap areas about the interaction between the Zika virus and the mosquito that spreads it.

I was also curious, Dr. Neafsey, the work you're doing to sequence and map the genome, is that going to help fill in some of the gaps in knowledge, and kind of where are we in that process, timelines, those kinds of things?

Dr. NEAFSEY. Sure. So I think I can attest to the value that genome sequences can have as a resource for informing precisely the kinds of parameters that make the types of models Dr. Ernst described accurate. In the malaria field, we've been using this kind of data to inform models of malaria transmission and malaria dis-

tribution. One example of the way these data can be used is a study that was published last year by investigators at Notre Dame, who did genetic profiling of Aedes mosquitoes from the Capitol Hill neighborhood, and used the genetic signature of these mosquito samples over the course of several years to determine that this was a year-round population, likely a year-round population, taking refuge in sewers and below ground during the cold winter months rather than a new population that was being refounded by genetically different sources with every successive warm season. So this is a small example of some of the resolution that DNA-based data can lend to some of the parameters that are useful for understanding the existing and maybe the prospective distribution of mosquitoes.

Mr. MOOLENAAR. I was reading a little bit about you're kind of communicating via Twitter and periodically getting together, like kind of work projects in place, and how do you monitor who's doing what and——

Dr. NEAFSEY. So Twitter is a fantastic scientific resource. I don't know if it's recognized outside of the scientific community but news travels so quickly. It is unparalleled for organizing people who are like-minded and who want to get behind a common cause.

So Twitter, I think, and a lament about the quality of the existing Aedes mosquito genome map was the genesis of this working group I alluded to. Since then we've had phone conversations, emails, but as yet no in-person meeting. As I mentioned, this is kind of a volunteer group, and we've been working catch as catch can to this point.

Mr. MOOLENAAR. I know you don't want to commit to a timetable of when, you know, the completion of the assembly of the DNA map but can you give us a rough ballpark?

Dr. NEAFSEY. I can say that we have efforts, parallel efforts, underway using several different new technologies that we hope will yield a better genome map on the order of a month or two. These are unproven but we're very optimistic given their performance with sequencing human genomes and assembling maps for human DNA. So I think we're optimistic that we won't have a perfect genome map by this fall but we will have a map that is significantly improved beyond the existing one.

Mr. MOOLENAAR. Thank you very much. I yield back, Mr. Chairman.

Chairman SMITH. Thank you, Mr. Moolenaar.

And the gentlewoman from Massachusetts, Ms. Clark, is recognized.

Ms. CLARK. Thank you, Mr. Chairman, and thanks to all the panelists, especially Dr. Ernst, thank you for making your decision to skip that milestone. We appreciate the information that you all are bringing to us today.

I wanted to start with something very specific and sort of move to the more general. The impact of this virus on a fetus is one of the most frightening aspects of a rapidly changing landscape but do we know now exactly how the virus causes birth defects like microcephaly and do we have an understanding of how exposure at different times of pregnancy can impact the fetus, or is this a gap in our research?

Mr. NEAFSEY. I don't think we have a virologist on the panel but I'm going to step slightly outside my comfort zone just to provide a basic answer and say that, you know, the general principles that determine what cells and what hosts a virus can infect often come down to the particular proteins or other attributes that are on the surface of those cells. The virus usually needs to recognize a doorway and be able to interact with it in a way that permits entry.

So some of the work that's been done to date has taken advantage of some of these fantastic new resources in a laboratory such as these brain organoids, very simple, very small, three-dimensional tissue replicas of what a developing brain might look like and the realization that that has led to is that there are, you know, particular cells at stages of brain development that are indeed susceptible to Zika infection. I think there's much work to be done to understand, as I mentioned previously, the spectrum of cell types that could be susceptible to Zika infection and the precise proteins and sort of molecular interplay that's responsible for Zika's ability to infect the cell types and the range of organisms that it does infect on the host side as well as, let me say, the mosquito side. Its ability to proliferate within mosquitoes and be injected into people that are bitten subsequently is another aspect of the molecular biology that I think we need to determine.

Ms. CLARK. Dr. Presley?

Mr. PRESLEY. If I could add, ma'am, there is so little known right now about how the Zika virus interacts in the body because we all looked at each other and shook our heads.

Ms. CLARK. Right.

Mr. PRESLEY. You know, something to consider, and it's another area that we're going to have to find out about is, you know, you may not be able to find it in a person's blood after they've recovered. A week or so after being viremic, you might not be able to find it in the blood, but they're finding it in semen 60 days after recovery or no more symptoms. The virus is going somewhere, hiding somewhere. There's a lot of viruses that do that, whether it's deep organ or whatever. I think there's a lot to learn. I think we can agree on that.

Ms. CLARK. And I think that brings me to a more general point that may be even harder to answer, especially in under 2 minutes, but as we have a discussion about how we react as Congress and in funding and when we get into pandemic mode, do we not make the most efficient choices, but here we are with this very frightening virus that is only one potential just mosquito-borne virus that has changed very quickly, spread very quickly around the globe and now in the United States, and we have very little understanding, and as I listened to your answers with the need for diagnostics, looking at resistance, mosquito control, dealing with issues of social behavior, private property, how we balance those, also looking at vaccines, understanding the genome, on and on, how do we approach these? And I have some concerns about the way we have funded our response by taking it from funding from other important diseases, and what is the better way?

One of the most terrifying conversations I ever had was at the Broad looking at antibiotic resistance and infections, so how can we

do a better job of funding basic science that allows you to do the applied science that can bring us some answers in 22 seconds?

Mr. NEAFSEY. I can speak briefly. I think what's important is to set up an infrastructure for collecting and pooling information. I think there are a lot of investigators collecting diverse forms of information, and I think there are opportunities to really rapidly advance our state of knowledge about Zika and other emerging epidemics on the horizon by organizing that information, creating communication channels, not just exclusively via Twitter but other media, and making sure that we are performing surveillance, that we're collecting the kind of information we need to in the short term limit the advance of these diseases and in the longer term understand them so that we can develop longer-term control measures.

Ms. CLARK. Thank you. I see I'm out of time. I yield back.

Chairman SMITH. Thank you, Ms. Clark.

The gentleman from California, Mr. Swalwell, is recognized.

Mr. SWALWELL. Thank you, Chair. Thank you to our panelists.

People at home are terrified about Zika, and for good reason. I've gone across the country with a group called Future Forum. It's 18 of the youngest members of our Democratic Caucus, and we've engaged with thousands of Millennials, young people who already are having financial difficulties, starting a family, and now I think Zika, from what we've heard, is an additional just health difficulty that has been posed as far as when it comes to travel and planning, for starting a family.

So my first question in light of that, does anyone on the panel disagree with the science behind the President's request for $1.9 billion for addressing this crisis?

Seeing that no one has answered, is anyone familiar with Ronald Klain's opinion piece in the Washington Post this weekend, "Zika is coming but we're far from ready"? Has everyone read that piece? In that thoughtful piece, Mr. Klain points out that the funding approved in the House for the Ebola—taking money from the Ebola crisis to address the Zika crisis is like sending all the fire trucks from one city to help fight a blaze in another. It's short-sighted and dangerous. He also suggests that we should look at—to plan for future crisis like this having a public health emergency management agency. Any thoughts from any of the panelists as far as having a separate agency similar to FEMA but focused on public health emergencies? Yes, Dr. Presley?

Mr. PRESLEY. I think one of the situations—and I don't know about California but Texas is a home-rule state, so everything—every emergency is handled at the local level until other support is needed, and this is mainly to your last comment. Making another federal agency to funnel down money and hope that a little bit finally gets to the bottom on the ground, I do not think works. I think that's part of the problem now is we don't have the on-the—the boots-on-the-ground support that's needed.

Mr. SWALWELL. Yes, Dr. Ernst?

Ms. ERNST. I'd just like to echo that. I also think that, you know, maybe something within one of the existing agencies, for example, the Centers for Disease Control, which has been leading a lot of the response in Puerto Rico, for example, but I also think trying to fig-

ure out a way where we can leverage other resources besides federal or state employees to respond would also be something that's useful. You know, every time that there's a crisis, there's a lot of volunteers, physicians and nurses and public health professionals who want to help, and we don't really have a good infrastructure in which they can be trained and deployed to help in these emergency situations. And so I think having some sort of infrastructure where people like myself and maybe some of the other panelists could use their expertise to help in the response would be really beneficial.

Mr. SWALWELL. Great. Thank you. And my perspective is that people at home and across the country, they don't care whether it's a Republican solution or a Democratic solution that solves this; they just want to see government act in a crisis and get it solved.

So thank you, Chairman. I yield back.

Chairman SMITH. Thank you, Mr. Swalwell.

And the gentlewoman from Maryland, Ms. Edwards, is recognized for her questions.

Ms. EDWARDS. Thank you, Mr. Chairman, and thank you very much to the witnesses today. I really appreciate your testimony.

Just a few weeks ago—I'm the Co-Chair of our Democratic Steering and Policy Committee—we held a hearing with Dr. Fauci, the Centers for Disease Control, the American Public Health Services, a mayor or so, about Zika, and one of the things that surprised me because I didn't know very much in looking at the maps, both the maps that we have here today but also other maps showing where the spheres of outbreaks are going to occur, it's pretty daunting, and especially if you look through the Gulf states, the South, and the Mid-Atlantic region.

And so my question actually has to do with the spread because although I understand there's a particular type of mosquito, I was surprised to know, and maybe I'm wrong about this, that whether the Aedes aegypti—is that how you pronounce it?—mosquito, once it transmits to a human host, then can another mosquito, the traditionally found Asian tiger mosquito in the East, then transmit infected blood to another human being, or is that something that we know? Because to me, that suggests that we have just, you know, much more potentially out-of-control circumstance. And I recognize there are a lot of things that we don't know, and this is tied to how we need to think about things like insecticide resistance and whether we then have the capacity for the boots on the ground to have the resources that they need to be able to respond should there—which I presume there will be a much wider spread or outbreak. If anybody has any thoughts on that, I'd appreciate it.

Mr. PRESLEY. On the transmission, if Aedes aegypti or Aedes albopictus—you mentioned the Asian tiger mosquito—it's not the blood, the infected blood, that they're moving. Dr. Ernst has talked about extrinsic incubation, and that's once the mosquito picks up that virus, that virus has to move through the mosquito's body into the salivary glands, where it can replicate, the traditional model. And so there's a period of time, up to a week, more information's needed. So it's not like the mosquito can feed on the person and immediately go bite another person and be infected.

Ms. EDWARDS. But then—I mean, the question gets—that I have is, does it really matter what type of mosquito then?

Mr. PARRY. Yes, it does. In this respect, Aedes aegypti, the way to think about it is, Aedes aegypti is public enemy number one responsible for far and away the greatest level of disease transmission, whether it's dengue or chikungunya and now actually Zika. So Aedes albopictus is a species which actually in its behavior it's quite aggressive. It's a nasty biter, worse actually then aegypti. You notice it worse. The bite is worse. But actually it's a very inefficient disease vector. So in an ideal world, one would tackle both, but if you're looking at disease transmission and how to make an impact, tackle Aedes aegypti.

Ms. EDWARDS. Got it.

And then if you could talk again about the incubation period, because I think part of the testimony that we've heard both here and today is, we don't know a lot about the incubation period, but there's a potential especially if there's a transmission through sexual contact that the incubation period could actually be much longer. So you might—one might, for example, in terms of public health advice, advise a woman who is of childbearing age that there could potentially be a year and a half during which you really should not engage in sexual contact. Is that true?

Ms. ERNST. Well, I think we don't really know exactly yet how long the virus can persist in semen. As Dr. Presley was saying, there has been some evidence up to 3 months after the infection was thought to occur. I would suggest that if possible—I know that the resources are really difficult—to follow up each individual man until he screens negative, but that's one potential possibility. The other possibility is that we do have some research that's ongoing that I have heard of that they are following cohorts of men who are return travelers to really identify what is sort of that average time frame in which they can harbor the virus in their semen.

Ms. EDWARDS. I guess, you know, if there's 3 months and then add to that a 9-month pregnancy, that is a long window of time, and so I think it begs the question of how it is that we're advising people of childbearing age who've traveled to those regions what they need to think about. I leave it at that.

Chairman SMITH. Thank you, Ms. Edwards.

That concludes our hearing today. We thank you for your expert testimony. This has been one of the more interesting hearings that we've had. You all are experts in certain areas and all of those areas were of interest to members of the Committee today. So thank you all again. We may be back in touch, and I should also say that members have two weeks to submit questions to you all. You heard the comments today, how many questions went unanswered, so you may get some more questions in the next couple of weeks.

Thank you all again, and we stand adjourned.

[Whereupon, at 12:15 p.m., the Committee was adjourned.]

Appendix I

Answers to Post-Hearing Questions

ANSWERS TO POST-HEARING QUESTIONS

Responses by Dr. Kacey Ernst

Responses to Congressional Questions from hearing "Science of Zika: The DNA of an Epidemic"

Kacey C. Ernst PhD, MPH
Associate Professor, College of Public Health, College of Geography, and College of Animal, and Comparative Biomedical Sciences, University of Arizona
Before the U.S. House of Representatives Committee on Science, Space, and Technology

July 5, 2016

1. **There seem to still be many unknowns about how exactly the mosquito transmits the Zika virus and about the habitat of the particular mosquito that carries it. And, as you stated in your testimony, we are still uncertain about whether or not other types of mosquitoes found in North America can effectively spread Zika. If you controlled the federal research budget, what are the top three questions you would invest federal resources in to help answer?**

   Response: There are several key questions that must be answered about potential mosquito vectors in North America to determine the potential geographic extent of transmission and the relative level of transmission that could occur. Focusing on solely the entomological aspects of transmission I would recommend that funding be put towards addressing these three fundamental questions.

   a. What is the adaptive capacity of *Ae. aegypti* and *Ae. albopictus* in terms of both physiological limits and behavior? The capacity of the mosquito vectors to adapt to new geophysical climates and to alter their behaviors is a significant unknown for Zika virus transmission and other arboviruses such as yellow fever, chikungunya and dengue viruses. For example, it had been thought that Ae. aegypti preferred clean water for laying their eggs but then they were identified in septic tanks in Puerto Rico (1) and biting patterns have been shown to shift from the typical morning and late afternoon/ early evening biting to include feeding at mid-day (2). Understanding both how adaptive these species can be and the factors that lead to adaptation are critically important in the United States. Most studies on the dynamics of these vectors have been carried out in tropical zones which have high levels of transmission. The continental United States is at the cool margins of *Aedes* habitat and dynamics may differ (3).

   b. Can the feeding patterns of *Ae. albopictus* support transmission of Zika virus? It is widely held that the more general feeding patterns of *Ae. albopictus* may prevent it from being a significant vector of arboviruses that are transmitted between human hosts. Several articles on *Ae. albopictus* blood feeding behavior in the United States have been published including one that found 90% of host blood meals in *Ae. albopictus* in the northeastern

United States were human (4) while in Raleigh, North Carolina a study indicated only 20% of host blood in the mosquito was human (5). Given the extended geographic range of *Ae. albopictus* a better understanding of factors that lead to higher feeding on humans is needed to understand the risk of transmission of Zika by this *Aedes* species.

c. What is the minimum infectious dose for Zika virus to *Aedes aegypti* and *Aedes albopictus* and can asymptomatic individuals successfully infect the mosquito vector? For each virus a minimum number of viral particles must be ingested by the mosquito to cause sufficient viral load for transmission. This level is not yet established for Zika virus. Additionally, the levels of virus in individuals who have asymptomatic Zika infection are not well quantified and it is not known if asymptomatic individuals can transmit the virus to mosquitoes. It appears that in sexual transmission the male may transmit the virus to his partner as long as three months beyond initial infection. Currently it is not known if the virus is sequestered in the reproductive organs or of there is a chance that viremia may occur at a later time and pass on to *Ae. aegypti* population.

2. In your testimony, you described the Zika map that you helped develop to try and predict where Zika might spread in the United States. However, you top short of calling it a forecast, because there are still too many unknowns. How would you improve your model to provide a better forecast for Zika or other vector-borne diseases? And what resources would a team need to provide a better forecast?

To create a forecast for a disease system that is highly accurate it is important to quantify the relationships between virus, vector, and human and non-human hosts. It is acknowledged that models of transmission will *always be imperfect* but they have reached a level of sophistication that would enable the provision of actionable information to public health and vector control decision makers about when cities will be at highest risk for virus transmission. Key information needed for models of *Aedes*-borne viruses specifically include 1) long-term year-round entomological surveillance data from multiple cities across the southern United States in different climatic zones, 2) a better understanding of the interactions among humans and *Ae. aegypti* and *Ae. albopictus*, 3) more accurate seasonal weather forecasts, 4) data on the potential distribution and impact of vector control resources and activities on mosquito abundance. Outside of the entomological components which I have focused on here, there is an urgent need to understand more about specific mosquito-virus interactions. These will facilitate incorporation of a viral component to the model.

a. **Entomological data:** As emphasized in my testimony, there is a lack of knowledge regarding the actual geographic distribution and seasonal patterns of *Ae. aegypti* and *Ae. albopictus* in the United States. Resources:

Investments in setting up surveillance specifically for *Aedes* species as they continue to be identified as key vectors for multiple emerging arboviruses. In addition, these data should be made publically and readily available for use by researchers and public health officials at spatial and temporal scales that allow in depth analyses. Year-round mosquito surveillance data would greatly enhance the ability to validate and cross-check forecast outputs for the entomological components of the models.

b. **Information on vector-human interactions:** While there is a fairly good understanding of the biological processes of *Ae. aegypti* and *Ae. albopictus* that can be included in forecasting efforts, the human-vector interaction components are still relatively under-studied, particularly in the United States. More information is needed on how frequently *Aedes* species feed on humans in different environments. In addition, understanding how to predict the density of containers and available habitat for *Aedes* species across large geographic regions requires further quantification of the relationship between human demographic factors and *Aedes aegypti* and *Aedes albopictus* indicators. Resources: This would require field studies and funding to be provided through grant mechanisms such as the NIH, NSF and NASA.

c. **Seasonal climate forecasts:** To achieve a timely but relatively accurate forecast, models must be driven by events that precede the onset of the event of interest, in this case disease transmission. Mosquito population dynamics are tightly linked to climate and weather and can be reliably estimated using known parameters of these relationships. To improve the accuracy of potential forecasts, ensembles of seasonal climate forecasts could be used to drive mosquito and virus transmission models to provide forecasts of potential mosquito abundance and virus transmission risk with up to 3 months of lead-time for cities across the United States. Issues to address, if such a forecast capability were to be implemented, would include ensuring sustained support (a necessity for any forecasting capability), determining the entity or entities that would operate it, and engaging the public health and vector control communities to maximize the forecast system's utility and iteratively improve it.

d. **Potential mitigation factors:** We need more information on the resources available for response and control of *Aedes* species across jurisdictions. To better predict actual risk of transmission, we must also have a better understanding of response capacity. There is sparse evidence publically available to develop an understanding of each community's resilience in the face of an outbreak of Zika virus or other mosquito-borne viruses. It is almost certain that many communities, particularly many of those at greatest risk,

have little capacity to respond. This information should be obtained in a standardized manner to allow incorporation into the modeling of transmission risk. Resources: Investment in a monitoring system as indicated in the entomological data section should include an annual assessment of response capacity.

e. **Key virus-vector relationship information:** Much like the human interactions with the vector need to be quantified, so do the virus- vector interactions. Three of the most important components for modeling any mosquito-borne system include; the time from when a mosquito becomes infected to when it becomes infectious to the next host, the minimum infectious dose of the virus that must be ingested before transmission can occur, and the duration of time that an infected individual can be infectious to mosquito populations.

3. **Every few years it seems that the United States is potentially under threat from a different vector-borne disease – from West Nile virus to Dengue Fever. How would you compare the threat of Zika to other vector-borne diseases?**

There are multiple ways of categorizing and comparing the different vector-borne diseases that are currently or have recently presented a threat to US populations. I will focus here on other mosquito-borne illnesses but acknowledge diseases from other classes of vectors such as ticks (Rocky Mountain Spotted Fever and Lyme Disease) and fleas (plague) that we have present in the United States. In comparing Zika to other diseases I will focus on the following characteristics:

a. **Potential level of transmission (i.e. number of cases):** The projected burden of illness is difficult to ascertain due to many unknowns as indicated in responses to question 1 and 2. Certainly the level of transmission has been high in areas where other *Aedes aegypti*-borne arboviruses have circulated and the asymptomatic nature of the disease makes it difficult to track. There have already been 934 travel-related cases in the continental United States and in US Territories local transmission is high, with 2020 confirmed locally-acquired cases as of June 29, 2016. These numbers likely grossly under-estimate the true number of infections. By comparison there were 2060 confirmed cases of locally-acquired West Nile Virus in 2015 with 119 deaths (CDC 2016). This is also likely an under-estimate given the mild symptomology of many West Nile Virus cases.
b. **Potential severity of illness (acute):** In most people Zika virus infection is milder than other arboviruses. Approximately 80% of individuals infected with Zika virus have no symptoms at all and has rarely been seen to cause mortality (6). This can be compared to 80% of individuals with chikungunya infection who have severe joint pain for several weeks and sometimes years

after infection but also relatively low mortality and dengue infection which can cause shock and hemorrhage and lead to death (CDC 2016).

c. **Potential long-term consequences of illness:** The greatest difference between Zika virus and the other mosquito-borne illnesses that have threatened the United States in the past is the extreme consequences for fetuses. Microcephaly is irreversible and there is no treatment for Zika infection that can reduce the course of development. It is estimated that between 1-13% of pregnant women who have Zika infection during the first trimester will go on to have babies with microcephaly (7). This does not include the burden of illness that could be caused by other neurological conditions that may be associated with Zika infection during pregnancy (8).
d. **Other unique aspects of Zika virus:** One of the key differences of Zika virus infection as compared to the other mosquito-borne illnesses is that there is an alternate mode of transmission, sexual transmission. This dual modality of transmission will require a broader engagement of partners across different disciplines. Currently these two response networks are relatively separate in public health. Considerable efforts will need to be made to join the knowledge and information from both which will require some investment in infrastructure to allow cross-referencing between data systems to track disease.

In summary, mosquito-borne illnesses have already been causing a significant burden of disease and investments in mosquito surveillance, control, and prevention would enhance not only protection from Zika virus but from other mosquito-borne illnesses that threaten the United States population. There are some aspects of Zika transmission that require an urgent need for more resources immediately. Emergency funding could provide resources that would enhance the nation's ability to prevent babies being born with catastrophic health outcomes and neurological problems in infected children and adults. Additionally, a more comprehensive view of resource enhancement for vector-borne diseases as an emerging threat to the health of U.S. citizens is warranted and longer term investments in surveillance, prevention, and control are needed.

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June 30th, 2016

Response to the following question submitted by Chairman Lamar Smith, Committee on Space, Science, and Technology, following the hearing "*Science of Zika: The DNA of an Epidemic*":

1. *Every few years it seems that the United States is potentially under threat from a different vector-borne disease-from West Nile virus to Dengue Fever. How would you compare the threat of Zika to other vector-borne diseases?*

Response:

The observation that new infectious disease epidemics are arising more frequently is accurate, and not hype. There have been two major changes to the world over the past several decades that have resulted in this shift:

1) **The world is increasingly urbanized.** Infectious diseases are more efficiently transmitted when people have contact with many other people during a window of contagiousness. As cities around the world grow, conditions improve for obscure or undescribed diseases to infect more people.

2) **The world is increasingly connected.** Air travel networks make it much easier for diseases to spread beyond national borders than in the past. A disease that first rises to public awareness in Hong Kong or Lagos can arrive in New York City or Los Angeles overnight.

As the most recent new epidemic of concern to US citizens, Zika joins a crowded field. As noted, we have all already heard warnings about the threat of other vector-borne diseases like Dengue Fever, Chikungunya, West Nile, Eastern Equine Encephalitis, etc. How to prioritize these threats?

Like some of the other mentioned diseases, Zika caused symptomless infections in most adults. The main mosquito vector of Zika, *Aedes aegypti*, has a geographic range that is smaller than the *Culex* mosquitoes that transmit West Nile, putting less of the U.S. population at risk. Zika is clearly not an existential threat to our society.

Currently, our ignorance about Zika is causing as much fear and apprehension as its known impacts. Here are some of the critical unanswered questions

requiring investigation in order to accurately assess and rank the threat posed by Zika relative to other vector-borne diseases:

1) Work from the CDC suggests that the risk of microcephaly is 1% in women infected by Zika during the first trimester of pregnancy[1]. **Does Zika induce less severe neurological defects in developing fetuses, children, or adults at a higher rate?** Impacts that are subclinical may nevertheless profoundly impact the course of lives.

2) Dengue Fever is transmitted by the same mosquito as Zika. Dengue outbreaks in the United States are rare and limited in scope, but unlike Dengue, Zika is also sexually transmitted. **How will sexual transmission impact Zika infection in the United States and around the world?**

3) Beyond their direct impact on infected individuals, epidemics take a toll on societies through secondary impacts. **How will Zika impact Americans indirectly, through effects on our health systems, fiscal and social costs of care for those with neurological symptoms, impacts on tourism and trade, etc.?**

In summary, Zika's impact on the U.S. will be smaller than its impact on much of Latin America, but we currently know too little about the disease to fully anticipate its effects. At this stage, it would be prudent to exercise appropriate mosquito control measures and build public awareness of practices to prevent the spread of traveller-imported cases, and to conduct critical basic research into the disease to inform the appropriate amplitude of response over the longer term.

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TEXAS TECH UNIVERSITY
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& Human Health
Reese Technology Center

30 June 2016

Representative Lamar Smith
Chairman
U.S. House Committee on Science, Space, and Technology
2321 Rayburn House Office Building
Washington, DC 20515-6301

Dear Chairman Smith:

Thank you for the opportunity to address the numerous and complex issues associated with the emerging public health threat from the Zika virus during the House Committee on Science, Space, and Technology hearing titled *"Science of Zika: The DNA of an Epidemic"* on 25 May 2016. I hope the information provided by the panel of witnesses was helpful in the committee's deliberation of the Zika virus public health threat and actions necessary to mitigate that threat.

I have attached a document with suggested edits to the verbatim transcript of my testimony and responses to member questions during the hearing. I have also attached a document with my responses to questions submitted to me on 21 June 2016, for the record from Members of the Committee.

Sincerely,

Steven M. Presley, Ph.D.
Professor and Director
Biological Threat Research Laboratory

copy to: K. Butts
M. Currier

RESPONSE TO QUESTIONS SUBMITTED TO DR. STEVEN M. PRESLEY BY MEMBERS OF THE HOUSE COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY ON 21 JUNE 2016

Question submitted by Chairman Lamar Smith

Every few years it seems that the United States is potentially under threat from a different vector-borne disease – from West Nile virus to Dengue Fever. How would you compare the threat of Zika to other vector-borne diseases?

As of 10 May 2016 there were 472 confirmed cases of Zika fever in the continental U.S., spread across 41 states and Washington D.C. By 01 June 2016 (three weeks) this number had increased by 31% to 618 cases. Within three weeks (01-22 June) Zika virus infections in the U.S. had increased by another 33% to 820 cases in 45 states; Florida having the highest number with 95 cases, New York has 89 Zika cases, California has 40 cases, and Texas has 30 confirmed cases. All confirmed Zika virus infections in the continental U.S. are reportedly directly or indirectly travel-associated. The CDC estimates 341 pregnant women in the U.S. have contracted Zika virus. Only one Zika virus infection in the U.S. has led to Guillain-Barré syndrome, so far. In the U.S. territories there are 1,114 cases of Zika fever, nearly all locally acquired and eight of which have led to Guillain-Barré syndrome.

Based upon these observations during the past months (i.e., increasing "travel-associated" cases, reports of sexual transmission after symptoms clear, and increasing numbers of infected pregnant women), I believe that at the national level the Zika virus threat is second only to the much more severe and longer term chronic health consequences posed by Chagas disease (American trypanosomiasis) vectored by triatomine bugs (kissing bugs). There are currently an estimated 300,000 to 600,000 human cases of Chagas disease in the United States – most in the U.S./Mexico border regions. However, I must qualify my response relative to the emerging Zika virus threat in the United States with two specific considerations, which are: (1) The as-of-yet uncertainty of the potential for Zika virus infection to cause microcephaly in infants and Guillain-Barré syndrome, and the unknown long-term sequelae of infection such as organ damage and recrudescence. (2) The likelihood of the establishment of local transmission (mosquito-human-mosquito) of the virus within specific areas of the United States where the mosquito vectors occur.

For most, if not the vast majority of people in the United States, the potential for Zika virus infection to result in severe, life-threatening illness is not any greater than infection by West Nile virus or dengue fever virus. However there are two specific scenarios associated with the establishment of Zika virus in the United States that make it more concerning to me, those being: (1) The potential ability of the virus to be "silently" introduced into an area/population through an individual that has apparently recovered from the virus, or was infected but was never symptomatic. Individuals infected with Zika virus are believed to be contagious for up to a two-week period, during which time they can potentially pass on the virus to mosquitoes that feed on their infective blood. And (2), the potential for indigenous, common mosquito species within the United States that vector other *Flaviviruses* (eg., West Nile virus) to be competent vectors of Zika virus. If either of these scenarios happens, Zika virus could become epidemic in the United States, especially during the summer season.

As I stated in my written testimony, "*This rapidly evolving Zika virus threat in Texas and throughout the continental United States is just the most recent example of an emerging or resurgent arthropod-borne infectious disease to threaten the public health. I believe there is a common realization made apparent*

each time such a public health threat occurs, that being regardless of how modern medical and scientific technologies advance, protecting the public health from vector-borne disease threats requires both basic and applied understanding of the arthropod vector's biology, behavior and vulnerabilities." Also, I recommend two directly relevant articles in the June 2016 Smithsonian Magazine, one by Jerry Adler, entitled *Kill All the Mosquitoes?!*, and the second by John R. McNeill entitled *How the Lowly Mosquito Helped America Win Independence*; both present a very informative perspective on mosquito-vectored diseases and public health.

Questions submitted by Representative Barbara Comstock

1. Will you explain in more detail why the human testing process is so limited at this time? Is it because of CDC protocol? Is the test so complex that the CDC is trying to avoid false positives or negatives?

Simply put, yes. Human sample testing for Zika virus is limited to qualified laboratories designated by the CDC that are equipped and certified to perform high-complexity tests, specifically Laboratory Response Network (LRN) system National or Reference laboratories that meet very rigid technical capabilities and regulatory quality control standards. Additionally, all of the LRN Reference labs maintain and utilize the same inventory (same make/model) of diagnostic equipment, as well as prescribed practices for handling samples and reporting. There are two types of human diagnostic testing that are/can be used for suspected Zika virus infections. The first is a serological assay to detect antibodies (IgM) in the serum of suspected patients called the CDC Zika IgM Antibody Capture Enzyme-Linked Immunosorbent Assay (*Zika MAC-ELISA*). The second type of testing detects nucleic acid and includes the *Trioplex rRT-PCR* assay to detect RNA of Zika, dengue and Chikungunya viruses in human samples, and the *Focus Diagnostics Zika Virus RNA Qualitative Real-time RT-PCR* assay which is for the detection of Zika RNA only. Both testing methods (i.e., serology and nucleic acid) are only authorized using specific protocols (including equipment) allowed under the FDA Emergency Use Authorization. Most diagnostic laboratories at hospitals, medical centers and clinics are considered "Sentinel laboratories" and do not have the equipment or technical capability to run the *Trioplex rRT-PCR* assay.

Or is it that the test is too expensive for mass production and use in hospitals?

Yes, both testing methods are expensive to perform relative to both labor and the supplies and equipment necessary to conduct the assays, and there is limited availability of materials and supplies for performing the testing. CDC reported on June 21, 2016 that they are working to expand diagnostic testing capacity with both public and commercial partners in the United States, so it is likely that there will soon be increased Zika virus testing capacity nationwide.

2. Might you be able to shed any light as to why this person did not receive a Zika test when they visited the hospital? Or, at minimum, can you explain why the person was not referred to a facility that is sanctioned to perform these tests?

I cannot explain, or even speculate why the person was not tested. My only guess is that there was some kind of miscommunication regarding her travel history or symptoms, or the attending physician was not aware of the sample submission criteria and protocols. Relevant to this, a friend of mine that is a local emergency medicine physician told me that he was never informed by the facility where he works of any criteria, procedures or protocol for submitting human samples for testing. He added that because of the hectic workload in emergency medicine facilities, such information received by the

hospital administration is often delayed or never trickles down to the ER docs. This anecdotal information suggests to me that there is a big "gap" in information flow and education for emergency room physicians.

3. Can you explain in further detail the hindrances to mass production of testing kits for human infection?

I cannot specifically address the hindrances to mass production, but speculate that it is because the tests only have FDA Emergency Use Authorization, and are only authorized for use by a very limited number of laboratories. However this may change due to increasing demand for testing, and volume of testing being performed. These limitations on facilities authorized to perform the tests are in-part due to biosafety considerations. Laboratories performing Zika virus diagnostic testing should, at a minimum, adhere to BSL-2 (biosafety level 2) precautions, but because a sample may contain a pathogen that requires BSL-3 precautions (e.g., chikungunya virus), more stringent biosafety requirements apply. Most hospitals, clinics and private medical practices do not have BSL-3 capabilities.

Responses by Dr. Daniel Neafsey

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June 30th, 2016

Response to the following question submitted by Chairman Lamar Smith, Committee on Space, Science, and Technology, following the hearing "*Science of Zika: The DNA of an Epidemic*":

1. *Every few years it seems that the United States is potentially under threat from a different vector-borne disease-from West Nile virus to Dengue Fever. How would you compare the threat of Zika to other vector-borne diseases?*

Response:

The observation that new infectious disease epidemics are arising more frequently is accurate, and not hype. There have been two major changes to the world over the past several decades that have resulted in this shift:

1) **The world is increasingly urbanized.** Infectious diseases are more efficiently transmitted when people have contact with many other people during a window of contagiousness. As cities around the world grow, conditions improve for obscure or undescribed diseases to infect more people.

2) **The world is increasingly connected.** Air travel networks make it much easier for diseases to spread beyond national borders than in the past. A disease that first rises to public awareness in Hong Kong or Lagos can arrive in New York City or Los Angeles overnight.

As the most recent new epidemic of concern to US citizens, Zika joins a crowded field. As noted, we have all already heard warnings about the threat of other vector-borne diseases like Dengue Fever, Chikungunya, West Nile, Eastern Equine Encephalitis, etc. How to prioritize these threats?

Like some of the other mentioned diseases, Zika caused symptomless infections in most adults. The main mosquito vector of Zika, *Aedes aegypti*, has a geographic range that is smaller than the *Culex* mosquitoes that transmit West Nile, putting less of the U.S. population at risk. Zika is clearly not an existential threat to our society.

Currently, our ignorance about Zika is causing as much fear and apprehension as its known impacts. Here are some of the critical unanswered questions

requiring investigation in order to accurately assess and rank the threat posed by Zika relative to other vector-borne diseases:

1) Work from the CDC suggests that the risk of microcephaly is 1% in women infected by Zika during the first trimester of pregnancy[1]. **Does Zika induce less severe neurological defects in developing fetuses, children, or adults at a higher rate?** Impacts that are subclinical may nevertheless profoundly impact the course of lives.

2) Dengue Fever is transmitted by the same mosquito as Zika. Dengue outbreaks in the United States are rare and limited in scope, but unlike Dengue, Zika is also sexually transmitted. **How will sexual transmission impact Zika infection in the United States and around the world?**

3) Beyond their direct impact on infected individuals, epidemics take a toll on societies through secondary impacts. **How will Zika impact Americans indirectly, through effects on our health systems, fiscal and social costs of care for those with neurological symptoms, impacts on tourism and trade, etc.?**

In summary, Zika's impact on the U.S. will be smaller than its impact on much of Latin America, but we currently know too little about the disease to fully anticipate its effects. At this stage, it would be prudent to exercise appropriate mosquito control measures and build public awareness of practices to prevent the spread of traveller-imported cases, and to conduct critical basic research into the disease to inform the appropriate amplitude of response over the longer term.

References

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Responses by Dr. Steven Presley

RESPONSE TO QUESTIONS SUBMITTED TO DR. STEVEN M. PRESLEY BY MEMBERS OF THE HOUSE COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY ON 21 JUNE 2016

Question submitted by Chairman Lamar Smith

Every few years it seems that the United States is potentially under threat from a different vector-borne disease – from West Nile virus to Dengue Fever. How would you compare the threat of Zika to other vector-borne diseases?

As of 10 May 2016 there were 472 confirmed cases of Zika fever in the continental U.S., spread across 41 states and Washington D.C. By 01 June 2016 (three weeks) this number had increased by 31% to 618 cases. Within three weeks (01-22 June) Zika virus infections in the U.S. had increased by another 33% to 820 cases in 45 states; Florida having the highest number with 95 cases, New York has 89 Zika cases, California has 40 cases, and Texas has 30 confirmed cases. All confirmed Zika virus infections in the continental U.S. are reportedly directly or indirectly travel-associated. The CDC estimates 341 pregnant women in the U.S. have contracted Zika virus. Only one Zika virus infection in the U.S. has led to Guillain-Barré syndrome, so far. In the U.S. territories there are 1,114 cases of Zika fever, nearly all locally acquired and eight of which have led to Guillain-Barré syndrome.

Based upon these observations during the past months (i.e., increasing "travel-associated" cases, reports of sexual transmission after symptoms clear, and increasing numbers of infected pregnant women), I believe that at the national level the Zika virus threat is second only to the much more severe and longer term chronic health consequences posed by Chagas disease (American trypanosomiasis) vectored by triatomine bugs (kissing bugs). There are currently an estimated 300,000 to 600,000 human cases of Chagas disease in the United States – most in the U.S./Mexico border regions. However, I must qualify my response relative to the emerging Zika virus threat in the United States with two specific considerations, which are: (1) The as-of-yet uncertainty of the potential for Zika virus infection to cause microcephaly in infants and Guillain-Barré syndrome, and the unknown long-term sequelae of infection such as organ damage and recrudescence. (2) The likelihood of the establishment of local transmission (mosquito-human-mosquito) of the virus within specific areas of the United States where the mosquito vectors occur.

For most, if not the vast majority of people in the United States, the potential for Zika virus infection to result in severe, life-threatening illness is not any greater than infection by West Nile virus or dengue fever virus. However there are two specific scenarios associated with the establishment of Zika virus in the United States that make it more concerning to me, those being: (1) The potential ability of the virus to be "silently" introduced into an area/population through an individual that has apparently recovered from the virus, or was infected but was never symptomatic. Individuals infected with Zika virus are believed to be contagious for up to a two-week period, during which time they can potentially pass on the virus to mosquitoes that feed on their infective blood. And (2), the potential for indigenous, common mosquito species within the United States that vector other *Flaviviruses* (eg., West Nile virus) to be competent vectors of Zika virus. If either of these scenarios happens, Zika virus could become epidemic in the United States, especially during the summer season.

As I stated in my written testimony, "*This rapidly evolving Zika virus threat in Texas and throughout the continental United States is just the most recent example of an emerging or resurgent arthropod-borne infectious disease to threaten the public health. I believe there is a common realization made apparent*

each time such a public health threat occurs, that being regardless of how modern medical and scientific technologies advance, protecting the public health from vector-borne disease threats requires both basic and applied understanding of the arthropod vector's biology, behavior and vulnerabilities." Also, I recommend two directly relevant articles in the June 2016 Smithsonian Magazine, one by Jerry Adler, entitled *Kill All the Mosquitoes?!*, and the second by John R. McNeill entitled *How the Lowly Mosquito Helped America Win Independence*; both present a very informative perspective on mosquito-vectored diseases and public health.

Questions submitted by Representative Barbara Comstock

1. Will you explain in more detail why the human testing process is so limited at this time? Is it because of CDC protocol? Is the test so complex that the CDC is trying to avoid false positives or negatives?

Simply put, yes. Human sample testing for Zika virus is limited to qualified laboratories designated by the CDC that are equipped and certified to perform high-complexity tests, specifically Laboratory Response Network (LRN) system National or Reference laboratories that meet very rigid technical capabilities and regulatory quality control standards. Additionally, all of the LRN Reference labs maintain and utilize the same inventory (same make/model) of diagnostic equipment, as well as prescribed practices for handling samples and reporting. There are two types of human diagnostic testing that are/can be used for suspected Zika virus infections. The first is a serological assay to detect antibodies (IgM) in the serum of suspected patients called the CDC Zika IgM Antibody Capture Enzyme-Linked Immunosorbent Assay (*Zika MAC-ELISA*). The second type of testing detects nucleic acid and includes the *Trioplex rRT-PCR* assay to detect RNA of Zika, dengue and Chikungunya viruses in human samples, and the *Focus Diagnostics Zika Virus RNA Qualitative Real-time RT-PCR* assay which is for the detection of Zika RNA only. Both testing methods (i.e., serology and nucleic acid) are only authorized using specific protocols (including equipment) allowed under the FDA Emergency Use Authorization. Most diagnostic laboratories at hospitals, medical centers and clinics are considered "Sentinel laboratories" and do not have the equipment or technical capability to run the *Trioplex rRT-PCR* assay.

Or is it that the test is too expensive for mass production and use in hospitals?

Yes, both testing methods are expensive to perform relative to both labor and the supplies and equipment necessary to conduct the assays, and there is limited availability of materials and supplies for performing the testing. CDC reported on June 21, 2016 that they are working to expand diagnostic testing capacity with both public and commercial partners in the United States, so it is likely that there will soon be increased Zika virus testing capacity nationwide.

2. Might you be able to shed any light as to why this person did not receive a Zika test when they visited the hospital? Or, at minimum, can you explain why the person was not referred to a facility that is sanctioned to perform these tests?

I cannot explain, or even speculate why the person was not tested. My only guess is that there was some kind of miscommunication regarding her travel history or symptoms, or the attending physician was not aware of the sample submission criteria and protocols. Relevant to this, a friend of mine that is a local emergency medicine physician told me that he was never informed by the facility where he works of any criteria, procedures or protocol for submitting human samples for testing. He added that because of the hectic workload in emergency medicine facilities, such information received by the

hospital administration is often delayed or never trickles down to the ER docs. This anecdotal information suggests to me that there is a big "gap" in information flow and education for emergency room physicians.

3. Can you explain in further detail the hindrances to mass production of testing kits for human infection?

I cannot specifically address the hindrances to mass production, but speculate that it is because the tests only have FDA Emergency Use Authorization, and are only authorized for use by a very limited number of laboratories. However this may change due to increasing demand for testing, and volume of testing being performed. These limitations on facilities authorized to perform the tests are in-part due to biosafety considerations. Laboratories performing Zika virus diagnostic testing should, at a minimum, adhere to BSL-2 (biosafety level 2) precautions, but because a sample may contain a pathogen that requires BSL-3 precautions (e.g., chikungunya virus), more stringent biosafety requirements apply. Most hospitals, clinics and private medical practices do not have BSL-3 capabilities.

Responses by Mr. Hadyn Parry

HOUSE COMMITTEE ON SCIENCE, SPACE, AND TECHNOLOGY

"Science of Zika: The DNA of an Epidemic"

Mr. Hadyn Parry, Chief Executive Officer, Oxitec Ltd.

Questions submitted by Chairman Lamar Smith

1. Every few years it seems that the United States is potentially under threat from a different vector-borne disease – from West Nile virus to Dengue Fever. How would you compare the threat of Zika to other vector-borne diseases?

The Zika virus is related to other flaviviruses, such as the West Nile virus, Yellow Fever and Dengue virus. Zika is transmitted by the *Aedes aegypti* mosquito species which is also the prime vector of Dengue and Chikungunya.

Zika virus has caused particular alarm due to the severity and indeed visibility of potential health impacts. Specifically, pregnant women with infections are at risk for miscarriages and their babies for congenital microcephaly and other birth defects. Zika has also been linked with other neurologic complications such as Guillain-Barré syndrome, myelitis, and meningoencephalitis.

Zika has one important distinction from other vector borne diseases which is that the nature and extent of health impacts are not yet fully understood. However, it should also be noted that the longer term impact of other flaviviruses may have been underestimated.

The alarming spread of the Zika virus is challenging public health authorities around the world and the U.S. In the continental U.S., more than 1,133 individuals have confirmed cases of Zika as of July 6th. The situation in Puerto Rico is especially dire, with 2,474 cases as of July 6th, mostly locally transmitted and including many pregnant women. CDC has estimated that 25 percent of residents of Puerto Rico may get infected with the Zika virus.

One of the main reasons that the United States comes under regular threat from mosquito borne diseases is that urban vector control has not received sufficient attention and funding over recent years. Essentially, the tools and methodology to combat mosquitoes have not significantly changed in decades.

As I have testified, it was an understanding of this need that drove Oxitec to develop a novel vector control technology that has been tested in 5 field trials and found to reduce *Aedes aegypti* populations in an urban environment by over 90% in each case.

The Oxitec solution harnesses the natural instincts of male mosquitoes to find females in the wild. Oxitec has used genetic engineering to create 'self-limiting' male insects which seek out and mate with females. After an Oxitec male mosquito has successfully mated with a wild female, the resulting offspring do not survive to adulthood, so the mosquito population declines.

The Oxitec Control Program is the system through which Oxitec mosquitoes are released and monitored over a predetermined and sustained period of time in an area with *Aedes aegypti*

mosquitoes. By applying the Oxitec Control Program to an area, the mosquito population in that area can be dramatically reduced or eliminated.

Unlike conventional insecticides or pesticides, which kill insects indiscriminately, the Oxitec approach is targeted at a single species. This means that, as well as being more effective, it is much better for the environment than conventional tools. In addition Oxitec's solution can be used an integrated manner with other control tools.

The Oxitec mosquito is now in use in Brazil and it has been recommended by the World Health Organization for pilot use as part of the WHO emergency response to Zika. In May, the Cayman Islands announced plans to roll out an island-wide eradication program with the Oxitec mosquito. In the U.S., Oxitec is seeking FDA approval for use of this technology to address the Zika public health crisis in areas already impacted, such as Puerto Rico, and areas at risk, including Florida and Texas.

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