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 humanmade 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. aegyptiborne 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 locallyacquired 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 locallyacquired 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

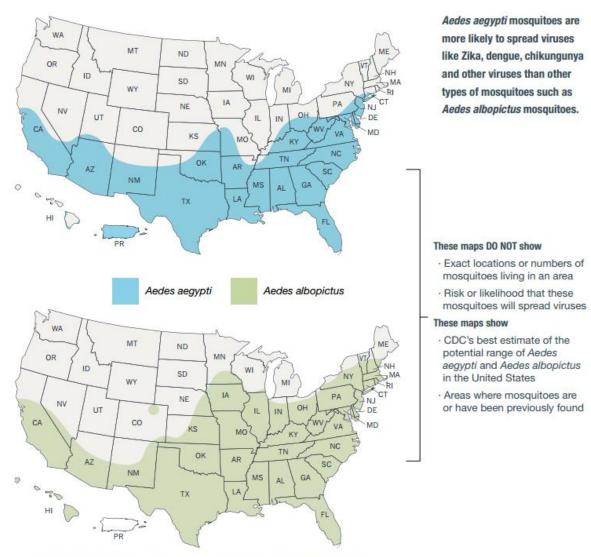
Our knowledge of *Ae. aegypti* (and *Ae. albopictus*) and our ability to assess present conditions or forecast upcoming risk of Zika transmission and related viruses in the continental United States is currently limited by our incomplete understanding of vector-virus-human interactions and our lack of 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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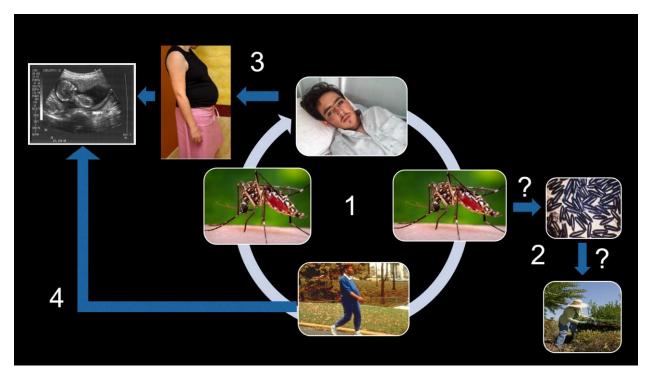
Figure 1. Estimated range of *Ae. aegypti* and *Ae. albopictus* in the United States in 2016.



* Maps have been updated from a variety of sources. These maps represent CDC's best estimate of the potential range of Aedes aegypti and Aedes albopictus in the United States. Maps are not meant to represent risk for spread of disease.

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).

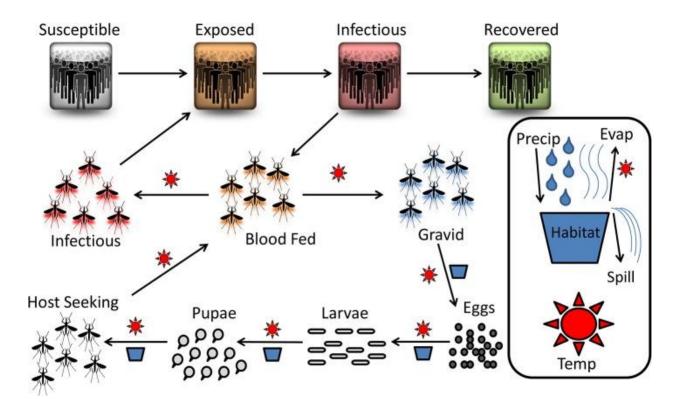


Figure 3. Complexities of modeling Ae. aegypti – borne viruses

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

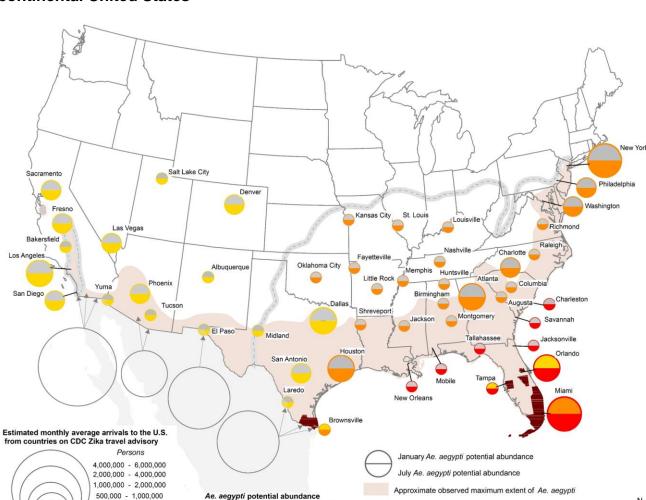


Figure 4. Map portraying key risk factors for Zika virus transmission in the continental United States

U.S. map showing 1) *Ae. aegypti* potential abundance for Jan/July (colored circles), 2) approximate maximum known range of *Ae. aegypti* (shaded regions) and *Ae. albopictus* (gray dashed lines), 3) monthly average number arrivals to the U.S. by air and land from countries on the CDC Zika travel advisory, and 4) counties that have had a previous history of arboviruses transmitted by *Ae. aegypti* (dengue and chikungunya)

High

Source: Monaghan et. al. 2016

100,000 - 500,000

10,000 - 100,000

< 10.000

None

Approximate observed maximum extent of Ae. albopictus

Counties with recent local dengue and/or chikungunya transmission