A Strategy for Integrating Best Practices with New Science to Prevent Disease Transmission by Aedes Mosquito Vectors

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Dear Colleagues:

In late 2015, public health authorities globally became alerted to a new and rapidly spreading epidemic of Zika-virus infection associated with an elevated incidence of microcephaly—small head circumference and damaged brains—in newborns of mothers infected during pregnancy. An elevated incidence of Guillain-Barré Syndrome was also reported among infected adults; this syndrome is a rare neurological disorder characterized by advancing paralysis, generally reversible over time but sometimes requiring complex life-support.

The Zika virus is a member of the same family of viruses as dengue and yellow fever, predominantly transmitted through bites by some mosquitoes of the genus *Aedes*, most importantly *Ae. aegypti*, the yellow-fever mosquito, but also possibly in some circumstances *Ae. albopictus*, the Asian tiger mosquito. Zika can also be transmitted through sexual activity and contact with body fluids. The full health impacts of *in utero* Zika-virus infection are still being elucidated, but it's likely that they go beyond overt microcephaly at birth to include additional neurocognitive impacts in a proportion of newborns who were infected during gestation.

In response to this public-health emergency, President Obama directed Federal agencies to expedite the development of Zika diagnostics, therapeutics, and vaccines; implement vector-control actions; and provide international coordination and support for afflicted countries. OSTP was directed to coordinate Federal efforts to identify new science and technology (S&T) approaches to vector control to prevent Zika transmission.

The directive to OSTP was implemented through chartering the interagency Task Force on Science and Technology for Zika Vector Control under the National Science and Technology Council. The initial action of the Task Force, in early 2016, was to identify high-priority, near-term vector-control opportunities to assist in responding to the anticipated summer 2016 surge in Zika-transmission risk in the United States and its Territories. The enclosed Task Force Strategy builds on these initial actions by providing a more in-depth analysis of S&T needs, focusing on *Ae. aegypti* but also recognizing the expanding range of *Ae. albopictus* and remaining alert to the potential that other mosquitoes may be potential vectors.

The Strategy emphasizes the historical and ongoing central role of *Ae. aegypti* as the primary vector of the suite of viruses that cause yellow fever, dengue, chikungunya, and, most recently, this Zika epidemic. Without improved vector-control techniques that are affordable and acceptable to communities, *Ae. aegypti* will remain a threat capable of transmitting these viruses and, potentially, tfuture emerging viral illnesses. Although the recommendations in this Strategy are directed toward *Aedes*-vector control to prevent Zika transmission, the co-benefits flowing from increased mosquito vector-control research and workforce development will accrue across diverse mosquito species and mosquito-borne illnesses, including those yet to emerge.

Sincerely,

John P. Holdren
Assistant to the President for Science and Technology
Director, Office of Science and Technology Policy

About the National Science and Technology Council

The National Science and Technology Council (NSTC) is the principal means by which the Executive Branch coordinates science and technology policy across the diverse entities that make up the Federal research and development (R&D) enterprise. One of the NSTC's primary objectives is establishing clear national goals for Federal science and technology investments. The NSTC prepares R&D packages aimed at accomplishing multiple national goals. The NSTC's work is organized under five committees: Environment, Natural Resources, and Sustainability; Homeland and National Security; Science, Technology, Engineering, and Mathematics (STEM) Education; Science; and Technology. Each of these committees oversees subcommittees and working groups that are focused on different aspects of science and technology. More information is available at www.whitehouse.gov/ostp/nstc.

About the Office of Science and Technology Policy

The Office of Science and Technology Policy (OSTP) was established by the National Science and Technology Policy, Organization, and Priorities Act of 1976. OSTP's responsibilities include advising the President in policy formulation and budget development on questions in which science and technology are important elements; articulating the President's science and technology policy and programs; and fostering strong partnerships among Federal, state, and local governments, and the scientific communities in industry and academia. The Director of OSTP also serves as Assistant to the President for Science and Technology and manages the NSTC. More information is available at www.whitehouse.gov/ostp.

About the Task Force on Science and Technology for Zika Vector Control

The Federal Government has been monitoring the Zika virus and working with public-health partners to alert healthcare providers and the public about Zika, provide public-health laboratories with diagnostic tests, and detect and report cases both domestically and internationally. In order to support and strengthen capabilities for the part of Zika response that relates to the control of Zika vectors in the United States and abroad, this Task Force provides an interagency forum for communication, coordination, and collaboration on science and technology (S&T) activities aimed at understanding vector biology, ecology, monitoring, and control; viral diagnostics in the vector; and data sharing relevant to these topics.

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NATIONAL SCIENCE AND TECHNOLOGY COUNCIL
COMMITTEE ON SCIENCE
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Executive Summary

Zika is the latest—but likely not the last—of a series of microbial challenges to public health in the United States and across the globe. The Zika public-health emergency in the Americas first emerged in late 2015, with reports of elevated rates of microcephaly in newborn babies following Zika infection in mothers during pregnancy. The research community continues to evaluate the types, extent, rates, and factors contributing to the adverse outcomes that can occur following Zika infection, and to develop the necessary medical diagnostics, therapeutics, and vaccines. One constant in many recent infectious disease outbreaks—including Zika, dengue, and chikungunya in the United States and its territories, and yellow fever in Africa—is transmission of the viruses by mosquito vectors, most often *Aedes aegypti*, the yellow-fever mosquito, but possibly in some circumstances *Ae. albopictus*, the Asian tiger mosquito.

Humanity has successfully controlled mosquitoes in the past through rigorous interventions, but societies and environments have changed. Increasingly dense urban populations and waste produce more standing water in which mosquitoes can breed near housing, insecticide resistance and adaptive behaviors have reduced the effectiveness of standard vector-control practices, and there are higher community expectations for engagement and consultation on which strategies should be used to control these mosquitoes. Changes have also occurred through technological advances, including more targeted options for mosquito vector-control that raise the possibility of ending Zika and other disease transmission by mosquitoes, with reduced collateral risks to health and the environment. Whether implementing old or new mosquito-vector-control techniques, community education and engagement on the acceptability of interventions remains critical; without community support that allows the use of such techniques, mosquito-vectored endemic disease and sporadic epidemics will continue to occur.

The Zika Vector-Control Science and Technology (S&T) Strategy presented here was developed by a Federal Task Force chartered under the National Science and Technology Council (NSTC) in response to the President's direction to identify new S&T approaches to mosquito-vector control. Other concurrent activities implemented by Federal agencies under this Presidential directive include: development of Zika diagnostics, therapeutics, and vaccines; implementation of vector-control actions; and international coordination and support.

The first actions of the NSTC Task Force were to expeditiously prepare a landscape analysis of existing vector-control S&T research, from which high-priority, near-term opportunities were identified to assist in responding to the anticipated summer 2016 surge in Zika transmission. The Task-Force Strategy builds on these initial actions by providing a more in-depth analysis of short-, medium-, and long-term Zika vector-control S&T needs. The focus is on *Aedes aegypti (Ae. aegypti*) as the primary vector, but also recognizes the expanding range of *Aedes albopictus (Ae. albopictus)* in the continental United States and Hawaii. Notably, both of these mosquito species are invasive to the United States and do not occupy significant or beneficial ecological niches.

Recognizing the breadth, extent, and depth of research recommendations listed in the second half of the Strategy, the NSTC Task Force identified a short list of highest priorities for Zika vector-control research support. These are summarized as follows, accompanied by indications of whether agency experts consider them to be of potential short-, medium-, or long-term return-on-investment, albeit all warranting immediate support with available resources:

1. <u>Social/Behavioral Science for Community Engagement (short/medium):</u> *Ae. aegypti* has adapted to live and breed around human habitations and to feed on humans. Mosquito-control techniques for *Ae. aegypti* have worked in the past, and still can, through preventing even the smallest bodies of water, such as plastic lids, from serving as breeding sites. Such efforts are part of an integrated-vector-management (IVM) strategy that also includes larvicidal and adulticidal pesticides, physical-control measures to reduce breeding sites and prevent entry to homes, and personal protection. Successful implementation of these IVM practices requires community buy-in, education, and continual diligence, coupled with trust in a functioning and sufficiently resourced Mosquito Control District (MCD) or local health department. Recent experience with Zika vector-control activities to interrupt

disease outbreaks—and past experience with dengue and chikungunya—have revealed both successes and failures in *Aedes* control, highlighting the critical need to better understand what techniques work best to educate and elicit the necessary community engagement in vector-control interventions. This research should include community-level specificity in order to address the heterogeneity in social structures and circumstances. Research is also important on community engagement to adopt novel mosquito-control techniques. International experience has demonstrated that impacted communities will adopt new vector-control techniques, such as *Wolbachia* intracellular bacteria (which interfere with mosquito reproduction) and genetically-engineered (GE) sterile mosquitoes, but only after major and resource-intensive public education and engagement campaigns. Specific recommendations include expanding research on:

a. improving our understanding of citizen reactions to vector-borne diseases, and how to encourage citizens to optimize their own personal health-protection practices and engagement in community-wide public-health strategies, including overcoming social and economic impediments to implementing existing IVM strategies, and
b. how to engage and inform individuals and communities when Federally-approved, albeit novel, vector-control strategies offer the potential for improved mosquito and disease control with less risk to human-health and the environment, and yet these opportunities ultimately require understanding and acceptance by impacted communities, including their balancing of the risks from the disease against imputed (rightly or not) risks from the proposed intervention.

2. <u>Efficacy and Implementation Evaluation (short/medium):</u> Rigorous evaluation of vector-management strategies is essential, especially in field settings, against the ultimate metric of reducing disease transmission among humans. The necessary sequence of testing—from initial laboratory tests, to field trials to reduce mosquito numbers, to randomized-control trials at scale against human-disease indices—is expensive, time-consuming, and generally requires international collaboration. For example, field trials to reduce human-disease burden can only be conducted at locations where disease transmission is actively occurring. Support for efficacy evaluation is also an important adjunct to vector-control actions by MCDs and health departments in response to Zika outbreaks in the United States, including Puerto Rico and other territories. These S&T recommendations parallel and support the process and recommendations of the World Health Organization's Vector Control Assessment Group (VCAG), notably the March 2016 emergency-meeting recommendations regarding Zika vector control.[1] Specific recommendations include:
   a. maintaining active engagement internationally—bilaterally and multilaterally—to support the necessary field trials of novel vector-control strategies against measures of reducing *Aedes*-mosquito numbers and, ultimately, measures of reduced human-disease incidence, focused initially on those technologies closest to operational use—wMel *Wolbachia* to interrupt disease transmission and the GE mosquito (OX513A)—along with studies toward operational use of the various sterile-insect techniques for mosquitoes, *Aedes*-specific vector traps, and attractive toxic sugar baits (ATSB),
   b. supporting efficacy studies of existing and new vector-control practices as they are applied within regions of the United States, ideally in collaboration with MCDs and local public-health departments that are the ultimate practitioners of vector-control actions, including disseminating these results as updated guidance and best management practices for the control of public-health pests and pathogens, and
   c. improvements to *Aedes*-vector-surveillance equipment, coverage, and data-dissemination techniques, including improved traps that can reduce the burdensome (yet important) aspects of current surveillance practices, accompanied by incorporating latest technological advances in mosquito-species identification and pathogen detection, and more rapid ways to evaluate the extent of insecticide resistance among these mosquitoes.

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[1] http://www.who.int/neglected_diseases/news/mosquito_vector_control_response/en/

3. Developing New Vector-Control Techniques (medium/long): Current and anticipated *Aedes*-vector-control tools can be expensive to implement; require active, committed, and ongoing community engagement; and can elicit substantial social controversy. Locality-specific resistance of *Ae. aegypti* to pyrethroid and/or organophosphate pesticides offers a case in point, highlighting the need to develop new, active, pesticide ingredients—new classes and modes of action—and other control methods that are effective against mosquitoes yet safe for pregnant women and children. Open innovation and grand challenges offer a creative way to tackle the many, diverse, and evolving needs for new vector-control techniques, exemplified by the recently sponsored *Combating Zika and Future Threats: A Grand Challenge for Future Development* by the U.S. Agency for International Development.[2] Specific research recommendations include developing:
    a. new, improved, and cost-effective physical controls to prevent mosquito entry and breeding in buildings and infrastructure, and novel ways to remove mosquito larval-development sites;
    b. new core chemistries and classes of mosquito-larvicidal and -adulticidal insecticides, accompanied by a re-evaluation of existing pesticides for public-health uses and improved understanding of both mosquito resistance to insecticides and the potential risks posed by these insecticides to humans and non-target species,
    c. improved biological techniques to interrupt mosquito breeding or the ability of mosquitoes to transmit viruses, notably various sterile, incompatible, or genetically-engineered non-biting-male mosquitoes that can be grown *en masse* and released to overwhelm naturally-breeding mosquito populations, similar to past successful efforts to control screwworm and medfly infestations,
    d. better traps and lures that are more specific to *Aedes*-mosquito species and that are safe for use in and around homes, and
    e. improved personal-protection repellents and mosquito-bite-resistant, socially-acceptable, clothing.
4. Vector-Control Workforce Development (medium/long): Public-health programs and vector-control management are generally implemented at the local level, such as through MCDs, which vary greatly in expertise and resources. Many communities have no MCD. Much routine MCD activity relates to nuisance mosquito control, such as species that infest swamps and marshes, where intervention measures (e.g., marsh larviciding) differ from the actions necessary to control *Ae. aegypti*, which center more on urban and home environments requiring greater community engagement. Over the years, U.S. support for medical entomology and vector-control expertise has waned. The Task Force recommends that additional scientific and technical training and certification support be provided for public-health vector control, notably for:
    a. medical entomologists to improve the understanding of insects that cause or serve as vectors of human and animal disease and how to best address these threats,
    b. field technicians to implement integrated-vector-management strategies, potentially through an emphasis on community-college associate degrees and in collaboration with the American Mosquito Control Association and the Entomological Society of America,
    c. social and behavioral scientists with a focus on understanding and encouraging community and individual health practices for vector-control and disease prevention, and
    d. extension educators to work with local communities on their role in the management and control of vector-borne diseases.
5. Mosquito-Vector Biology and Ecology (long): Basic scientific research led to the discovery of the Zika virus in 1947, when Rockefeller Foundation researchers placed caged monkeys in the Zika Forest of Uganda to monitor for yellow-fever virus. Much of our initial evaluation of the emerging threat posed by *Aedes*-transmission of Zika also came from our existing biological and ecological understanding of this genus of mosquitoes and their potential to transmit related viruses. Many of the current and anticipated vector-control techniques also have their genesis in basic research, such as understanding the cryptic ecological locations where *Ae. aegypti* larvae can develop, how plants

[2] https://www.usaid.gov/grandchallenges/zika

defend against insects (e.g., chrysanthemum as the source of pyrethrum insecticides, which led to the development of their synthetic analogs, the pyrethroids), and the impact of intracellular infection by *Wolbachia* species on insect reproduction and virus transmission. In the urgency to address short-term crises related to disease outbreaks, continued support remains critical to expand the underlying knowledge of vector and disease biology and ecology relevant to Zika and potential future viruses, and on the insects that transmit these diseases. Research emphases should include evaluation of:

a. vector competency, the ability of a mosquito to transmit a pathogen between humans, both the applied side of evaluating which mosquito species can transmit Zika and other viruses, along with an improved understanding of the biology underlying vector competency and the extent to which viruses can be passed from female mosquitoes, through eggs, to offspring,
b. the potential for Zika transmission to be maintained in animal reservoirs and serve as a prolonged source of human-disease-outbreak risk, which can be evaluated by conducting serum-virus and -antibody surveys of farm livestock and other animals to look for ongoing host-vector pathogen transmission, and
c. habitat suitability and modeling to address knowledge gaps on the extent of, and factors influencing, the geographic range of *Aedes* occurrence and the processes that drive the evolution of competent vectors, including climate-change impacts and shifts in vector ranges.

The *Aedes aegypti* mosquito is the primary vector of the viruses that cause yellow fever, dengue, chikungunya, and most recently Zika disease epidemics. Without improved vector-control techniques that are affordable and acceptable to communities, *Ae. aegypti* will remain a threat capable of transmitting the next emerging viral illness. *Ae. aegypti* is not alone in posing threats to public health, with other mosquitoes also potentially transmitting Zika (*Aedes* spp.), not to mention other mosquito-transmitted diseases from West Nile virus (*Culex* spp.) in the United States to the continuing scourge of malaria (*Anopheles* spp.) across the globe. Although the recommendations in this Strategy are directed toward Zika prevention through *Aedes* vector-control, the co-benefits flowing from increased mosquito vector-control research and workforce development will accrue across mosquito species, against various mosquito-borne illnesses, and in anticipation of the next, as yet unknown, vector-borne outbreak in our crowded, interconnected, and rapidly mobile world.

Introduction

In late summer 1793, President George Washington left the interim United States Capital of Philadelphia as yet another yellow-fever epidemic scourged an American seaport city, a legacy of death to rich and poor alike that is still recalled in historic home tours along the Eastern seaboard and Gulf Coast. It was not until 1900 that the U.S. Army's Major Walter Reed and colleagues confirmed that the bite of a particular mosquito, *Aedes aegypti (Ae. aegypti)*, was transmitting the yellow-fever virus between humans, ushering in a new era of mosquito control for public-health protection. Yet, *Ae. aegypti* still lives with us, infecting people in the Americas anew with Zika virus, adding to its repertoire of transmitting yellow fever, dengue, and chikungunya. Zika is the latest, but likely not the last, illness caused by a pathogen transmitted by *Aedes* mosquito species. Zika virus causes mild or no overt illness in most people, but can have devastating impacts on unborn babies through damage to growing nervous tissue, leading to microcephaly, developmental abnormalities, and possibly other neurocognitive deficits that will come to the fore as more is learned about this new public-health emergency—same mosquito, same virus family, same ability to propagate epidemics of human disease.

Public health and vector-control experts know this enemy, the *Aedes aegypti* mosquito, how difficult it is to control, and that it has been defeated in the past in the Americas. Times have changed, though, and approaches need to be adapted to address new challenges and new opportunities. There are many more people now, crowded into cities, sometimes poor, with much urban waste (e.g., tires, plastic containers, etc.) that provides ideal *Aede*s larval-development habitat, along with citizens who have access to information from multiple sources, some more reliable than others. Meanwhile, as temperatures rise from climate change, the range of the *Aedes*-mosquito vector expands and mosquito season is extended in some areas.[3] Conversely, vector-control experts know what has worked in the past to suppress and eradicate *Ae. aegypti*, and most communities in the United States are, or can be, well protected by screens and air conditioning, supported by mosquito control districts (MCDs). A suite of new technologies are also coming available that can supplement the old, but proven, ways with more targeted approaches to find *Ae. aegypti* in its cryptic breeding sites and impact disease transmission in those areas where other controls have proven insufficient.

This Zika Vector-Control Science and Technology Strategy (Strategy) is directed toward identifying and advancing these new vector-control technologies, with the objective of preparing the scientific, technical, and social foundation for preventing the transmission of Zika and other viruses by *Aede*s mosquitoes in the United States and its Territories. This may be achieved by locally eliminating the *Aedes* vector species, reducing the ability of *Aedes* vectors to transmit viruses, or creating effective, early-response, vector-control options to suppress disease outbreaks. Operationally, Federal agencies can advance these objectives through:

- Implementing policy frameworks conducive to expeditiously advancing vector-control research and innovation in the private sector, consistent with regulatory oversight responsibilities;
- Supporting vector-control research across Federal agencies, in partnership with the private sector/academia/philanthropy through grants, cooperative agreements, and contractual mechanisms;
- Fostering coordination among Federal agencies and state and local vector-control agencies in the field—in the United States and internationally—to conduct the necessary efficacy testing against mosquito indices and epidemiological endpoints to determine and refine the performance and safety of existing and new technologies; and
- Educating and engaging local communities in the deployment of vector-control tactics.

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[3] Monahan AJ, Sampson KM, Steinhoff DF *et al.* 2016. The potential impacts of 21st century climatic and population changes on human exposure to the virus vector mosquito *Aedes aegypti*. Climatic Change. http://link.springer.com/article/10.1007/s10584-016-1679-0

The Strategy emphasizes supporting and studying local-scale efforts to prevent the transmission of Zika and other viruses by *Ae. aegypti* in the United States, as a foundation for large-scale efforts and emergency response to disease outbreaks. The Strategy highlights promising new technologies, while also recognizing that technological innovation alone is unlikely to achieve control of *Ae. aegypti*. Effective tools exist, but, like novel approaches, they must be applied appropriately. This requires the support of communities and adequate resources at the local level to implement these measures. The Strategy therefore highlights the need for social and behavioral research to guide community engagement as an essential component of S&T for *Ae. aegypti* control. Many of these actions will be relevant to other mosquito species, both in the United States and internationally, and to other viruses transmitted by these mosquitoes. Continuing research is also needed on control specifics for the Asian tiger mosquito, *Ae. albopictus,* across the large regions of the United States where it occurs.

The Zika vector-control S&T Strategy was developed as a collaboration among Federal agencies, under the aegis of the National Science and Technology Council (NSTC) and convened by the White House Office of Science and Technology Policy (OSTP). The vector-control S&T Strategy was tasked to the NSTC as a complement to other urgent Zika efforts, led by consortia of Federal agencies under the general oversight of the White House and the Office of the Assistant Secretary for Prevention and Response (ASPR) in the Department of Health and Human Services (HHS). Other activities in this coordinated Federal effort include: vector-control implementation under the leadership of the Centers for Disease Control and Prevention (CDC); Zika-vaccine development coordinated by the HHS National Institute of Allergy and Infectious Disease (NIAID); Zika diagnostics and therapeutics with engagement from a number of Federal agencies including the HHS Biomedical Advanced Research and Development Authority (BARDA); and international activities coordinated through the Department of State and the U.S. Agency for International Development (USAID).

Background

1. Zika and the History of *Aedes aegypti*-Transmitted Viral Disease

Zika virus (ZIKV) is a member of the family of flaviviruses, as are yellow fever, dengue, and West Nile viruses, among others.[4] ZIKV was first discovered in 1947 when Rockefeller Foundation scientists exposed monkeys to hitherto unknown viruses in the Zika Forest of Uganda.[5] In the ensuing years, Zika was considered to be a mild disease characterized by fever, rash, red eyes, and joint pains, with nearly 80 percent of those infected reporting no symptoms at all. Following several Zika epidemics on Pacific islands, disturbing reports began to surface from Brazil in 2015 of a large increase in microcephalic babies born several months after the onset of a Zika epidemic. The link between Zika infection during pregnancy and severe adverse birth outcomes has since been confirmed,[6] although the full suite of contributing factors and the extent to which less overt neurological damage may also be occurring following these infections are still unknown. Zika is one of a small but devastating group of infectious illnesses that can cross the placental barrier to cause fetal impacts, sharing this characteristic with cytomegalovirus and rubella (German measles). Zika has also been associated with Guillain-Barré Syndrome in adults,[7] a rare neurological disorder characterized by advancing paralysis, generally

[4] Centers for Disease Control and Prevention. Zika Website. http://www.cdc.gov/zika/index.html

[5] Dick GW, Kitchen SF, Haddow AJ. 1952. Zika virus. I. Isolations and serological specificity. Trans R Soc Trop Med Hyg. 46(5):509-20.

[6] Rasmussen SA, Jamieson DJ, Honein MA *et al.* 2016. Zika Virus and Birth Defects--Reviewing the Evidence for Causality. NEJM 374(20):1981-7.

de Araujo TV, Rodrigues LC, de Alencar Ximines RA *et al.* 2016. Association between Zika virus infection and microcephaly in Brazil, January to May, 2016: preliminary report of a case-control study. Lancet Infect Dis. 2016 Sep 15. pii: S1473-3099(16)30318-8. doi: 10.1016/S1473-3099(16)30318-8. [Epub ahead of print]

[7] Dirlikov E, Major CG, Mayshack M *et al.* 2016. Guillain-Barré Syndrome During Ongoing Zika Virus Transmission — Puerto Rico, January 1–July 31, 2016. MMWR Morb Mortal Wkly Rep;65:910–914. DOI: http://dx.doi.org/10.15585/mmwr.mm6534e1

reversible over time but sometimes requiring complex plasma-exchange therapies and temporary life-support, such as mechanical ventilation, to maintain breathing.

Zika virus is primarily transmitted through the bite of an infected mosquito, as well as through sexual transmission between humans, and via bodily fluids, including blood, tears, saliva, and semen.[8] *Ae. aegypti* is the primary mosquito vector for the current Zika outbreak in the Americas, as it is for yellow fever, dengue, and chikungunya viruses. Laboratory studies show that *Ae. albopictus* can also serve as a vector of the Zika virus, and this mosquito species has been implicated in an urban outbreak of Zika in Gabon.[9] A number of other *Aedes* species, particularly within the *Stegomyia* sub-genus, may contribute to Zika outbreaks, commencing with the original forest-dwelling *Ae. africanus* in the Zika forest. Other mosquito species have also been postulated as potential vectors for Zika.

It is difficult to overstate the devastation that mosquito-borne illnesses have wrought on humanity, past and present. In 2014, the World Health Organization (WHO) estimated the global health burden of several important vector-borne diseases.[10] Malaria, transmitted predominantly by *Anopheles* mosquitoes, is estimated to cause 207 million illnesses and 627,000 deaths per year. Regarding illnesses associated with *Aedes* mosquitoes, forty percent of all people in the world—2.5 billion—are at risk of dengue, with an estimated 100 million dengue infections worldwide per year, 500,000 of whom develop dengue hemorrhagic fever, and about 12,500 of whom die. Yellow fever affects approximately 200,000 people each year and there are 30,000 deaths, even in the presence of an effective and affordable vaccine. Meanwhile, chikungunya now has become widespread with an estimated 1.3 billion people living in areas at risk for chikungunya transmission.[11]

Associated with this rise in global illness are increasingly urban human populations and the potential for disease transmission by *Ae. aegypti*. Yellow fever is now enzootic in South America, maintained in forest-dwelling monkeys and transmitted by *Haemagogus* mosquito species, thereby posing a continuing threat to human populations. Dengue and chikungunya are endemic in Puerto Rico and cause intermittent epidemics. External sources of dengue have led to viral transmission in Texas, Florida, and Hawaii by *Aedes* spp. The full scale, impacts, and future of Zika are still being elucidated as we learn from and respond to the current epidemic.

Investments made to control mosquitoes that carry the Zika virus will also pay dividends with other mosquito-borne diseases. While vaccine and medical-therapeutic development will continue to play an important role in managing outbreaks of mosquito-borne diseases, it is not practical to maintain a complete arsenal of vaccines and drugs for every known or emerging pathogen. It is also impossible to fully anticipate the emergence of new pathogens. There are many other potential arboviruses (viruses transmitted by the bite of mosquitoes, ticks, or other arthropods) that may pose a risk to humans, many of which are transmitted by *Ae. aegypti* and other mosquitoes. Currently, the Centers for Disease Control and Prevention's list of arboviruses and related zoonotic viruses encompasses more than 600 known arboviruses, over 80 of which are known human pathogens.[12]

2. The *Aedes* Species Mosquito Vectors

Both *Ae. aegypti* and *Ae. albopictus* (Figure 1) were originally forest dwellers that evolved to inhabit tree holes but now thrive in human-inhabited landscapes where pools of standing water are often available,

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[8] http://www.cdc.gov/zika/transmission/

[9] Grard G, Caron M, Mombo IM *et al.* 2014. Zika Virus in Gabon (Central Africa) – 2007: A New Threat from Aedes albopictus? PLoS Negl Trop Dis 8(2): e2681. doi:10.1371/journal.pntd.0002681

[10] World Health Organization. 2014. A global brief on vector-borne diseases. WHO/DCO/WHG/2014.1 http://www.who.int/campaigns/world-health-day/2014/global-brief/en/

[11] Nsoesie EP, Kraemer MU, Golding N *et al.* 2016. Global Distribution and Environmental Suitability for Chikungunya virus, 1952-2015. Eurosurveillance 21(20) DOI: http://dx.doi.org/10.2807/1560-7917.ES.2016.21.20.30234

[12] Conway MJ, Colpitts TM, Fikrig E. 2014. Role of the Vector in Arbovirus Transmission. Ann. Review of Virology 1:71-88: http://www.annualreviews.org/doi/full/10.1146/annurev-virology-031413-085513

Figure 1 a. *Aedes aegypti*

Credit: James Gathany/CDC

Figure 1 b. *Aedes albopictus*

Credit: James Gathany/CDC

providing habitats for egg laying and larval development. Eggs can survive desiccation for many months but require a 7-to-10-day development cycle in water to mature into adult mosquitoes. *Ae. aegypti* is particularly problematic. In hot climates, it develops rapidly in any small water container or standing source left in or around human housing for a few days after rain—old tires, clogged gutters and drains, discarded rubbish and plastic containers, houseplant saucers, birdbaths, water storage containers, abandoned swimming pools and hot tubs, sand-box toys, and cryptic places like sewers, drain pipes, or even indoor shower drains and toilet cisterns in houses without screens and air conditioning. It rests indoors or outdoors in hidden locations, bites during the daytime, bites primarily humans, can probe and bite multiple people sequentially, and can locally be resistant to a number of common insecticides. In many locations, *Ae. aegypti* is not numerically common compared to the large swarms of nuisance mosquitoes that breed in marshes and swamps, but it lives in close association with humans and specifically targets humans for blood meals. *Ae. albopictus* (the Asian tiger mosquito) shares many of these traits, but spends more of its time outdoors and will feed on many mammalian and bird species, not just humans.[13] It will also use natural sites, such as tree holes, to lay its eggs. *Ae. aegypti* and *Ae. albopictus* are invasive species to the United States, and they do not occupy an ecological niche necessary to support any native species. Appendix A maps the estimated ranges[14] and reported occurrences[15] of these mosquitoes in the United States.

Adults of both sexes of all mosquito species feed on nectar and plant juices and, in most species, the female also requires a blood meal to develop eggs. Pathogen transmission is determined by a composite of (1) the intrinsic ability of the insect to carry and replicate a pathogen, (2) the behavior of the insect and its vertebrate host(s), and (3) environmental conditions. Transmission of a pathogen to and between humans starts with vector competency, which is the result of an insect's ability to acquire the virus or other pathogen by biting a human or other animal, support the growth of the pathogen internally, and then transmit it to another animal or human. There are several barriers within the insect that must be overcome for transmission to occur, notably barriers to viral spread within the mosquito from the mid-gut to the salivary glands.

While internal barriers determine the inherent ability of each mosquito species to transmit a given virus, whether transmission occurs is due to other factors including the behavior of both the mosquito and the vertebrate host: e.g., whether the mosquito prefers living in and around human houses (*Ae. aegypti*), near human houses (*Ae. albopictus*), or in forest treetops, and whether it preferentially feeds on humans (*Ae. aegypti*) or will feed on any vertebrate host (*Ae. albopictus*). These differences explain why certain mosquitoes are particularly problematic as competent vectors all of the time (*Ae. aegypti*), while others remain a concern and can come to the fore under particular circumstances, such as when there is a high density of both mosquito and human populations, poor housing conditions, and hot temperatures. Similar transmission-risk evaluations are necessary in locations where other *Aedes* species are prevalent that may transmit Zika, such as *Ae. polynesiensis* and *Ae. hensilli* on Pacific Islands and *Ae. luteocephalus*, *Ae. vittatus,* and *Ae. furcifer* in Africa.

3. Past *Aedes aegypti*-Elimination Efforts

During a previous fever outbreak in Philadelphia, President Washington's colleague and physician, Dr. Benjamin Rush, had noted that: "The mosquitoes were uncommonly numerous during the autumn. A

[13] Faraji A, Egizi A, Fonseca DM *et al.* 2014. Comparative host feeding patterns of the Asian tiger mosquito, Aedes albopictus, in urban and suburban northeastern USA and implications for disease transmission. PLoS Neglected Tropical Diseases 8(8): e3037. http://www.ncbi.nlm.nih.gov/pubmed/25101969

[14] Centers for Disease Control and Prevention. 2016. Estimated range of Aedes albopictus and Aedes aegypti in the United States, 2016. http://www.cdc.gov/zika/vector/range.html

[15] Hahn MB, Eisen RJ, Eisen L *et al.* 2016. Reported Distribution of Aedes (Stegomyia) aegypti and Aedes (Stegomyia) albopictus in the United States, 1995-2016 (Diptera: Culicidae). J. Med. Entomology. 53(5):1169-1175. http://jme.oxfordjournals.org/content/53/5/1169

certain sign (says Dr. Lind) of an unwholesome atmosphere."[16] Dr. Rush's insight was noted by Dr. Carlos Finlay as contributing to his theory in 1881 that *Ae. aegypti* mosquitoes were transmitting yellow fever,[17] confirmation of which was provided by the U.S. Army Yellow Fever Commission of 1900. U.S. Army engagement was again instrumental through the leadership of Major William Gorgas (later Army Surgeon General) in Florida, Havana, and during construction of the Panama Canal to reduce the transmission of yellow fever and malaria by controlling mosquitoes. Use of these fundamental mosquito-control techniques was expanded to Brazil by Oswaldo Cruz and then the Rockefeller Foundation in the 1930s under the leadership of Dr. Fred Soper, focusing on chemical treatments with insecticides and the elimination of mosquito foci by destroying abandoned containers. A yellow-fever vaccine produced at the Rockefeller Institute was introduced in 1937 and has been used internationally ever since, reducing disease concerns domestically in the United States.

Engagement in mosquito control by the Pan American Health Organization (PAHO) was stimulated by the success of these interventions and the advent of the insecticide DDT (dichlorodiphenyl-trichloroethane), leading to approval in 1947 of the Continental *Ae. aegypti* eradication plan, initially directed at urban yellow fever. By 1962, 18 nations in the Americas had eliminated *Ae. aegypti*, along with a number of Caribbean islands. Despite these efforts, the mosquito had not been eradicated from Cuba, the United States, Venezuela, and several Caribbean countries.[18] In 1963, the United States Congress appropriated funds to begin limited eradication operations, commencing in 1964 with the activation of the *Aedes aegypti* Eradication Branch in the Communicable Disease Center (now the Centers for Disease Control and Prevention) in Atlanta.[19] The CDC itself had been established from the Office of Malaria Control in War Areas, initiated by President Roosevelt in 1942, and thus CDC has been from its inception a renowned vector-control organization. Many of the procedures in use by the Public Health Service in the 1960s remain valid 50 years later, as was their understanding of the difficulty in dealing with this mosquito, including its more-widespread range than anticipated, re-emergence of trash dumps after clean-up, cryptic larval-development sites, and developing resistance to DDT.[20] Across the Americas, reinfestations began to occur in previously cleared regions from the 1970s, thought to be the result of declining political will, decreased surveillance efforts capable of detecting and rapidly responding to small reinfestations, insufficient environmental sanitation in rapidly growing urban centers, insect resistance to organochlorine insecticides, expanding travel opportunities, high cost, insufficient community participation, and unwillingness of some governments to join in simultaneous programs.[18]

The promise and early benefits of DDT offer a cautionary example of the limitations of heavy reliance on chemical vector control. DDT was once widely and effectively used in the United States to reduce pest and disease impacts, and it is still used for indoor residual spraying (IRS) in some developing countries. The extent of DDT use eventually led to widespread insect resistance, including in Puerto Rico and the Virgin Islands in the early 1960s,[21] requiring substitution with malathion. The persistence of DDT

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[16] Benjamin Rush. Medical inquiries and observations. Vol. 1. Philadelphia. https://archive.org/stream/2569001R.nlm.nih.gov/2569001R_djvu.txt

The specific viral cause of this outbreak in 1780 remains uncertain. The symptoms reported by Dr. Rush—"bilious remitting fever"… "exquisitely severe [pains] in the head, back, and limbs" … "the break-bone fever"—are consistent with dengue fever, also transmitted by *Ae. aegypti*. Dr. James Lind was a noted British naval hygienist of the time.

[17] Charles Finlay. 1881. The mosquito hypothetically considered as an agent in the transmission of yellow fever poison. Extract from the Annals of the Royal Academy of Sciences of Havana. The New Orleans Medical and Surgical Journal. 9:601-161 https://books.google.com/books?id=Qd9DAQAAIAAJ&pg=PA601#v=onepage&q&f=false

[18] Braithwaite-Dick O, San Martin JL, Montoya RH *et al.* 2012. Review: The history of dengue outbreaks in the Americas. Am. J. Top. Med. Hyg 87(4):584-593.

[19] Schliessman, DJ. 1967. Aedes aegypti eradication program of the United States—progress report 1965. AJPH. 57(3):460-465

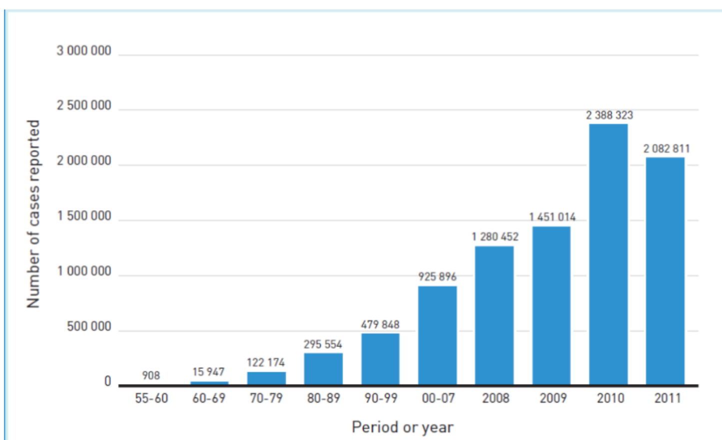
[20] U.S. Department of Health, Education, and Welfare, Public Health Service. 1966. The Aedes aegypti eradication program. Atlanda GA. https://stacks.cdc.gov/view/cdc/20798 *Aedes*-control practices summarized as: engagement with state agencies, sanitation and waste removal, draining standing water, household screens, insecticide application, community engagement and campaigns, testing for pesticide resistance, staff training, and diligent follow-up.

[21] U.S. DHEW, PHS. 1966. The Aedes aegypti eradication program. Atlanda GA. https://stacks.cdc.gov/view/cdc/20798

residues was also found to cause egg-shell thinning that threatened the virtual extirpation of many large bird species (e.g., bald eagle, brown pelican) from the lower 48 United States. These considerations led the United States to cancel the DDT pesticide registration in 1972.

The deployment of an effective vaccine reduced the burden of yellow fever, but the incidence of dengue has risen dramatically over recent decades (Figure 2). This highlights the critical and expanding role of *Ae. aegypti* in magnifying illness rates in the absence of an effective vaccine program. Dengue is a member of the same flaviviridae family as Zika and yellow fever viruses, and is characterized by high fever, severe headache, and muscle, joint, and bone pain; in its most severe, potentially deadly, form it presents as dengue hemorrhagic fever. A safe and effective vaccine against all four dengue serotypes has recently been licensed, but is in limited early stage use and evaluation by only six nations. Dengue had once been repeatedly epidemic along the U.S. Eastern seaboard, but after epidemics in Puerto Rico and Louisiana in 1945 became quiescent for over a decade. Epidemics of dengue fever began to recur in the 1960s in locations that had not eradicated *Ae. aegypti*, beginning in Jamaica and then Puerto Rico and beyond. Dengue is now endemic in Puerto Rico, amplified through sporadic epidemic outbreaks, a pattern followed by chikungunya, also transmitted by *Aedes* spp. Localized dengue outbreaks have occurred in Florida, Texas, and Hawaii. These outbreaks in the continental United States and Hawaii have taken months to years to suppress.

Studies of vector-control efforts to reduce dengue provide an initial guide to the extent of mosquito control necessary to impact Zika transmission among humans. This is a critical consideration when evaluating the efficacy of vector-control interventions, underpinning the importance of measuring both impacts on mosquito abundance and, ultimately, whether efforts have impacted disease transmission. Studies in Brazil and Taiwan have demonstrated that source-reduction measures that suppress *Aedes* vector infestations to less than 1 percent of houses with positive traps effectively averted outbreaks of dengue. Outreach levels below 100 percent household coverage were associated with resurgence of disease (Figure 3).[22] In developed nations, the relationship between mosquito numbers and human disease is attenuated by housing features, such as the aforementioned air conditioning and screen barriers, which prevent easy access of mosquitoes into homes.



Average number of cases of dengue and severe dengue reported to WHO annually during 1955–2007 compared with the number of cases reported during 2008–2011 [9]

Figure 2. Dengue World-Wide Incidence[23]

[22] Pontes R, Freeman J, Oliviera-Lima JW *et al.* 2000. Vector densities that potentiate Dengue outbreaks in a Brazilian city. American Journal of Tropical Medicine and Hygiene 62:378-383. http://www.ajtmh.org/content/62/3/378.long
Chang FS, Tseng YT, Hsu PS *et al.* 2015. Re-assess Vector Indices Threshold as an Early Warning Tool for Predicting Dengue Epidemic in a Dengue Non-endemic Country. PLoS Negl Trop Dis. 14;9(9):e0004043. doi: 10.1371/journal.pntd.0004043

[23] WHO. 2014. A global brief on vector-borne diseases. WHO/DCO/WHG/2014.1 http://www.who.int/campaigns/world-health-day/2014/global-brief/en/

The World Health Organization (WHO) and its regional affiliate, the Pan American Health Organization, continue to provide international coordination and support for vector-control implementation, in addition to reviewing the science behind proposed new interventions. The WHO Vector Control Advisory Group (VCAG) was tasked in 2013 with providing international guidance on policies and practices related to public-health vector control.[24] VCAG's functions are to review and assess the public-health value (epidemiological impact, ideally through randomized-control trials) of new tools, approaches, and technologies, and how these may fit in the context of integrated vector management (IVM) in multi-disease settings. In March 2016, VCAG met in Geneva to provide recommendations for emergency response and preparedness for Zika virus. It validated the use of existing integrated vector management tools for the control of *Aedes* vector mosquitoes, and recommended expedited evaluation of five new tools: (1) microbial control of human pathogens in adult vectors, e.g., *Wolbachia* Mel; (2) mosquito-population reduction through genetic manipulation, e.g., OX513A; (3) sterile-insect techniques; (4) vector traps for disease management; and (5) attractive toxic sugar baits.[25] All are discussed in more detail below.

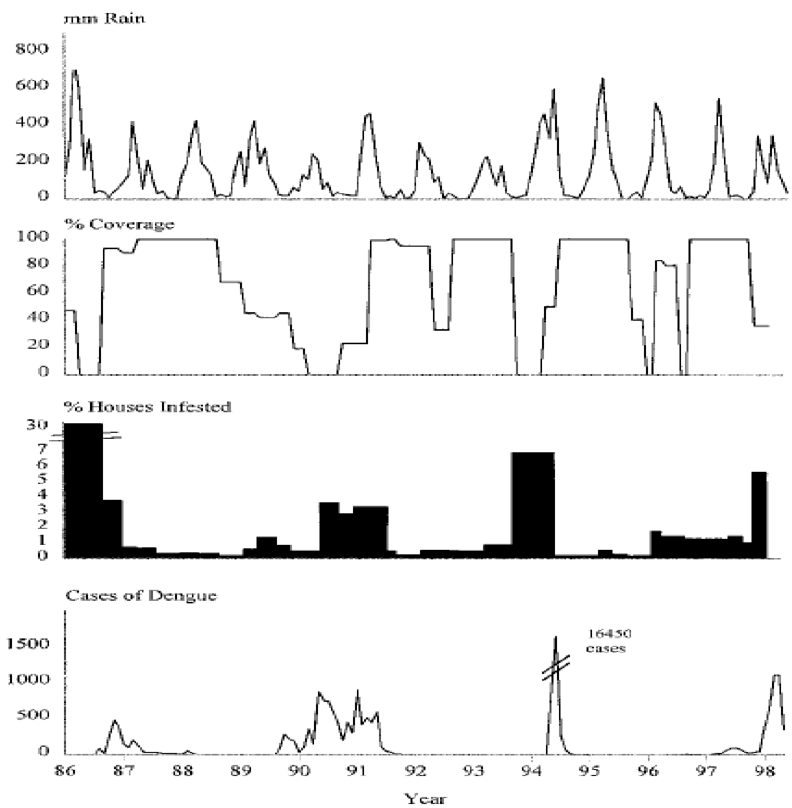


Figure 3. Pontes et al. (2000) demonstrated the relationship between vector-control outreach and disease incidence in Forteleza, Brazil, concluding that source-reduction measures that suppress Aedes infestations to less than 1 percent of houses (Household Index, HI) effectively avert outbreaks of dengue, an initial proxy for Zika. Outreach levels below 100 percent of houses were associated with resurgence of disease. Similar results were reported from Taiwan, with the following container Aedes threshold values for dengue transmission of: HI=1 percent, CI=1.8 percent, and BI= 1.2 (Chang et al. 2015).

[24] http://www.who.int/neglected_diseases/vector_ecology/VCAG/en/

[25] http://www.who.int/neglected_diseases/news/mosquito_vector_control_response/en/

4. Current Vector-Control Practices

Mosquito control in the United States is generally vested with state and local governments implemented, for example, through Mosquito Control Districts (MCD), which are generally under the purview of the relevant state or local health department or as independent government entities. MCDs are central to a number of the recommendations in this Federal research strategy through their role as the implementation arm in mosquito control. Much of the routine work of MCDs is directed toward control of nuisance mosquitoes, with additional public-health responsibilities depending on locale, such as monitoring to prevent West Nile virus outbreaks transmitted by *Culex* mosquitoes.

The resources and expertise available to individual MCDs varies greatly, depending on the yearly extent of nuisance and public-health impacts of mosquitoes, and the concern and wealth of the affected communities under their jurisdiction. At the upper end, a MCD will have highly trained and expert staff dealing with public education; mosquito surveillance; test laboratories; larvicide and adulticide delivery mechanisms, including aerial; and outreach staff to engage the community in the rigorous trash removal necessary to address *Aedes* vectors on a house-by-house basis, through community clean-up events, and on abandoned properties. Yet, even these expert and resourced MCDs have experienced difficulties in terminating *Aedes*-transmitted outbreaks of dengue in the past, with similar concerns expressed regarding Zika. At the other end of the spectrum, many communities do not have an MCD, or it is part-time and substantially under-resourced.

Mosquito-control practices are based on the concept of integrated vector management (IVM), a decision-making process, based on egg, larval, and adult monitoring, to optimize the use of a suite of vector-control resources by improving the efficacy, cost effectiveness, ecological soundness, and sustainability of complementary interventions. Application of IVM to *Aedes* species is based on understanding the specific ecology of these vector species, notably that *Ae. aegypti* has adapted to human settlements, breeds in open containers near houses, and rests and feeds during the day inside or near human dwellings. These behaviors are distinct from those of marsh and swamp mosquitoes. The application of IVM strategies, along with robust public-health surveillance, has proven effective in controlling outbreaks of mosquito-borne diseases, but it requires sustained and diligent human and financial resources, broad public and government engagement, public education, and established infrastructure, such as MCDs.

The subsections that follow summarize the basic IVM strategies of monitoring, physical controls, chemical treatment, biological interventions, and personal protection as they apply to mosquitoes, particularly *Ae. aegypti* and *Ae. albopictus.* Additional details on current vector-control practices are available from the CDC,[26] World Health Organization,[27] American Mosquito Control Association,[28] and often from local MCDs, such as the Florida Keys MCD.[29]

a. Mosquito Surveillance

Surveillance of mosquito populations is crucial to providing a baseline assessment of their presence and abundance, targeting interventions to key larval-development sites, determining the efficacy of control strategies, and designing and evaluating new strategies for control. Mosquito surveillance can be undertaken for all mosquito life stages—through egg collection (usually in a trap), larvae and pupae counts and indices (such as the proportion of houses in which these immature life-stages are detected), and collection of adult females. Capturing adult mosquitoes is particularly useful as they can be readily identified to species and tested for the presence of disease agents, such as viral genetic sequences using laboratory polymerase chain reaction (PCR) testing. The DoD has developed field-test kits that are available for dengue and West Nile viruses, and a Zika virus field-test kit is under expedited development.

[26] http://www.cdc.gov/zika/vector/

[27] http://www.who.int/csr/resources/publications/zika/vector-control/en/

[28] http://www.mosquito.org/

[29] http://keysmosquito.org/

The surveillance of mosquito populations should be accompanied by evaluation of insecticide-resistance patterns. To improve surveillance for *Ae. aegypti* and *Ae. albopictus* in the United States, including their presence and abundance as well as susceptibility to commonly-used insecticides, CDC has provided additional funding to state and local jurisdictions via the Epidemiology and Laboratory Capacity for Infectious Diseases (ELC) Cooperative Agreement,[30] and launched MosquitoNET[31] to capture collected-surveillance data at the national scale.

b. Physical Control

Physical-control strategies are a primary component of IVM because they provide sustained protection against vectors, despite being initially labor intensive and requiring a high level of citizen and community education and participation. Physical-control measures include: removal of all sources of standing water, such as plastic containers, old tires, and other outdoor waste; drainage of blocked overhead gutters and water drains; and well-fitted and intact screens on all house doors and windows. Peculiarities of *Ae. aegypti* behavior, however, make some of these methods either difficult to implement or less effective against this particular species. Specifically:

- *Ae. aegypti* larvae can develop in small pools of water (as small as one tablespoon under certain conditions), meaning exceptional diligence is required throughout the entire community to eliminate this mosquito's breeding habitat. *Ae. aegypti* eradication campaigns have been most successful where governments have mandated elimination of mosquito habitat and have enforced compliance through house-to-house inspections. This approach is challenging to implement and maintain throughout the mosquito season (which can be year-round in hotter regions) while maintaining privacy and property rights in a democratic society.
- *Ae. aegypti* feeds during the day, making bed nets an ineffective means for reducing human exposure to this mosquito. The daytime-feeding behavior of *Ae. aegypti* also means that protection must extend to buildings beyond the home, as well as personal protection outdoors (such as wearing long pants and long sleeves, and using repellents).

Physical-control strategies also offer long-term benefits in managing *Ae. albopictus*. The habits of *Ae. albopictus* often make it less of a risk to humans than *Ae. aegypti*—its primary residence is outside houses and it feeds on other vertebrates as well as humans—thereby reducing the opportunity for the human-vector-human cycle of virus transmission.

c. Chemical Control

Chemical control with EPA-registered insecticides remains a critical component in reducing mosquito populations, particularly in preventing and responding to disease outbreaks. The chemical approach is best applied selectively and in combination with other IVM measures, as over-reliance on chemical control can lead to the evolution of insecticide-resistant mosquitoes. Chemical-control methods can cover larval and adult-mosquito stages of life (Table 1). Larvicides control mosquito larvae in outdoor breeding sites. Adulticides are available to kill mosquitoes both outdoors and indoors. Insecticides can be applied using many techniques including, but not limited to, aerial- and ground-application methods, fogging or spraying with hand-held equipment, or in solid form, depending on the target location and life stage of the mosquito. The success of these chemical strategies in reducing mosquito populations depends on the location of breeding sites and the extent of air penetration into homes and cryptic locations. The ecology of *Ae. aegypti*, residing part-time indoors, reduces, but does not eliminate, the efficacy of aerial and

[30] http://www.cdc.gov/ncezid/dpei/epidemiology-laboratory-capacity.html

[31] http://www.cdc.gov/zika/vector/vector-control.html

ground spraying as a control strategy, as demonstrated during recent local Zika-transmission episodes in Miami.[32]

Indoor residual spraying (IRS) involves application of a pesticide that remains active for weeks to the inside walls of human dwellings. The family of pyrethroid insecticides now constitute the majority of household insecticides. Pyrethroids act by disrupting sodium channels in nerve axons, leaving them permanently depolarized and paralyzing the insect. Pyrethroid toxicity is highly specific to arthropods, but unfortunately this includes beneficial species such as bees and dragonflies, and aquatic arthropods that serve as the base of the food chain in lakes and rivers.

Table 1. Chemical Control of Mosquitoes

Approach	Use Categories and Examples
Larvicides (outdoor)	- Biologically-derived insect toxins, such as spinosad - Insect growth regulators, such as pyriproxyfen and methoprene - Organophosphate pesticides, such as temephos, which is now limited to the use of existing stocks in the United States following registration cancellation - Monomolecular films and oils that suffocate immature mosquitoes
Adulticides (indoor/outdoor)	- Household pyrethroid sprays that are widely available over-the-counter - Ultra-low volume or thermal fogging with various EPA-registered insecticides, such as pyrethroids (permethrin, bifenthrin, Duet®) and organophosphates (malathion, naled®) - Aerial application of insecticides, such as naled® (organophosphate, dimethyl 1,2-dibromo-2,2-dichloroethylphosphate) or Duet® (a combination of two pyrethroids, pralethrin and sumithrin)
Traps (indoor)	- Autocidal Gravid Ovitrap (AGO), developed by the CDC as a safe, low-cost, device for indoor use to lure gravid (pregnant) mosquitoes and capture them on a non-toxic adhesive—now commercially available.
Indoor Residual Spraying	- Indoor spraying with a synthetic pyrethoid, such as deltamethrin
Baited traps (outdoor)	- Traps to lure and kill mosquitoes, such as Trap-N-Kill® with slow release of the organophosphate, dichlorvos, and the Gravid Aedes Trap (GAT) with canola oil as a localized insecticide. - Attractive toxic sugar baits (ATSB), to disseminate low-risk insecticides, such as dinotefuran, boric acid, spinosad, or natural, active ingredients, such as eugenol and garlic
Targeted autodissemination (outdoor)	- Traps, such as In2Care®, which lure gravid mosquitoes, kill their larvae with pyriproxyfen, and infect the adults with a delayed-lethal fungus *Beauveria bassiana*
Repellents (indoor/outdoor)	- Personal repellents, such as DEET and picaridin, available over-the-counter - Clothing repellents, widely available using impregnated permethrin - Spatial repellents, including citronella candles and mosquito coils, currently being augmented with active-repellent properties of the pyrethroids, metofluthrin and allethrin

IRS has proven effective in controlling mosquito populations and disease outbreaks, but it has raised concerns because of the prolonged human exposure to the pesticide. In Puerto Rico, CDC and the Puerto Rican Government initially focused efforts on protecting the houses of pregnant women against Zika virus transmission by offering IRS with the pyrethroid adulticide deltamethrin, which is approved by the

[32] Likos A, Griffin I, Bingham AM *et al.* 2016. Local Mosquito-Borne Transmission of Zika Virus — Miami-Dade and Broward Counties, Florida, June–August 2016. MMWR ePub: 23 September 2016. DOI: http://dx.doi.org/10.15585/mmwr.mm6538e1

U.S. Environmental Protection Agency (EPA) for this use and has not been shown to cause cancer, birth defects, or other reproductive harm.

Organophosphate insecticides are most often used as adulticides. These chemicals (such as naled®) inhibit cholinesterase action, causing accumulation of acetylcholine in nerves and continuous neuronal firing that leads to muscle dysfunction. Organophosphates can affect all animals, including mammals, and must therefore be carefully applied according to recommendations so as not to overexpose humans and ecologically-important species. Organophosphates break down very quickly in the environment, which means that their effectiveness, and their risks, are limited to a few days after application.

Recent insecticide developments include more targeted approaches that rely on understanding mosquito behavior, such as luring mosquitoes into contact with growth-retardant larvicides during feeding, mating, or egg laying, enabling the larvicide to be carried to subsequent, often hidden, breeding sites. Advances also include the development of insect-growth regulators (IGR), which are synthetic homologs, analogs, or inhibitors of insect hormones and interrupt or inhibit the life cycle of a specific pest. Pyriproxifen and methoprene are IGRs that are used as larvicides for mosquitoes.

Effective larval and adult-mosquito control requires an appropriate arsenal of larvicides and adulticides with different modes of action to prevent insecticide resistance, targeted formulations for application in varied settings and by different equipment types, and different intended residual characteristics.

Managing insecticide resistance is a key consideration in any chemical program for vector control, and resistance levels need to be assessed before implementing insecticide programs and routinely thereafter. Mosquito resistance to pyrethroids and other insecticides has been widely reported in *Aedes* species in Latin America and the Caribbean, including Puerto Rico. Both CDC and WHO have kits and procedures available for evaluating insect resistance.

d. Biological Control

Current biological strategies for controlling mosquito populations center on the use of bacteria or fungi that can infect and kill mosquitoes at the larval stage or as adults, or produce biological toxins that can be applied as insecticides. The most commonly used is *Bacillus thuringiensis* var. *israelensis* (Bti), a bacterium that produces a toxin that kills mosquito larvae when they eat it. Bti is relatively uncommon in nature, but can be cultured at an industrial scale, formulated in various ways, and shipped worldwide without compromising efficacy. The entire collection of *Bacillus thuringiensis* (Bt) pesticides—Bti and several other varieties—represent the largest bio-pesticide market worldwide. Bti is commonly applied to reduce mosquito-larva populations in standing water, often killing between 60 and 95 percent of the larvae and remaining active for 2 to 4 weeks.[33] Efficacy is influenced by the turbidity of the water, presence of algae, and other physical factors (including temperature and solar radiation). Bti is highly selective for mosquitoes, so effects on plants, animals (including honey bees and most other insects), and humans are minimal. For more than 60 years, other Bt subspecies and beneficial bacteria (e.g., *Lysinibacillus sphaericus*) have been used in agriculture, forestry, and home gardening, and have been found safe for human contact. Another bacterium, *Saccharopolyspora spinosa*, produces natural toxins that are active by contact and ingestion against a variety of insects, including mosquitoes. A combination of two of these natural toxins is commercially registered as Spinosad®.

e. Baits and Traps

Baits and traps have the potential to bring together physical, chemical, and biological components in targeted approaches to reduce indoor- and outdoor-*Aedes* vector populations. They take advantage of specific reproductive and feeding preferences of these mosquitoes. Gravid (i.e., pregnant) *Ae. aegypti* females lay their eggs in small containers of water in dark locations in or near houses. This preference can be simulated in trap construction and enhanced by lures that attract the mosquitoes. Inside houses,

[33] Boyce R, Lenhart A, Kroeger A *et al.* 2013. Bacillus thuringiensis israelensis (Bti) for the control of dengue vectors: systematic literature review. Trop. Med. Int. Health. 18(5):564-577 http://onlinelibrary.wiley.com/doi/10.1111/tmi.12087/pdf

adult mosquitoes can be killed (and counted) as they get stuck to sticky surfaces, as done in the CDC's Autocidal Gravid Ovitrap (AGO), which is inexpensive, contains no pesticides, and is safe for indoor use with pregnant women and children. In Puerto Rico, communities with AGOs had lower mosquito density and reduced human infection with chikungunya virus during the widespread outbreak that began in 2014.[34] Adding a slow-release pesticide to a low-cost design, such as the Trap N'Kill™ ovitrap, attracts and kills gravid *Aedes* mosquitoes outdoors. EPA has also recently granted a Section 18 emergency registration in Zika-transmission areas to a mosquito trap (In2Care® Mosquito Trap) that uses a combination of chemical larvicide and fungal adulticide. On contacting the trap, the larvicide is deposited on the gravid mosquito and then conveyed by her to the next egg laying sites. Microscopic spores of the parasitic fungus *Beauveria bassiana* are also in the trap, and these adhere to, germinate, and kill the female mosquito within a few days, but not until she has delivered the larvicide to additional breeding sites. The WHO VCAG (2016) recommends that priority be given to additional testing of the large-scale use of vector traps to determine their performance and efficacy in *Aedes*-vector control and their impact on disease transmission.

Increasing emphasis is being placed on use of Attractive Toxic Sugar Baits (ATSB), which take advantage of mosquitoes' need for plant sugars as a food source. ATSBs use attractants accompanied by a range of registered, low-risk, active insecticides, such as dinotefuran, boric acid, spinosad, or natural active ingredients, including eugenol and garlic. When sprayed on leafy vegetation around homes, but not flowering plants, ATSBs can be targeted toward mosquitoes without killing beneficial pollinating insects.[35] An ATSB using fruit sugars and microencapsulated garlic is commercially available in the United States. The WHO VCAG (2016) recommends further trials on the efficacy of ATSB technologies against entomological- and human-disease metrics.

f. Personal Protection

Personal protection against mosquito bites combines both physical and chemical controls as an important adjunct to direct mosquito-reduction efforts. Physical personal-protection barriers include long-sleeved shirts, long pants, hats, and clothing nets. These can be supplemented with chemical repellents impregnated into the clothing or topically applied to the person, such as permethrin and DEET, respectively. Repellents can also be used on a spatial scale inside buildings and in outdoor environments, spanning the commonly available burning coils for the patio and garden to pyrethroid spatial-repellents that can be connected to electrical outlets or passively released in homes based on their vapor-pressure characteristics. Personal-protection actions benefit from being within the empowered control of an individual and functional outside of their home environment. This is particularly important for protection against day-biting *Aedes* vector species as it provides protection during the conduct of necessary life-activities during the daytime, either outdoors or in built environments.

5. New Vector-Control Practices Under Development and Evaluation

A continuum exists between the current mosquito-control practices summarized in the preceding sections and new technologies on the horizon, with the new technologies often building on past experience in both design and implementation. Building on the conclusions and recommendations of the March 2016 WHO VCAG review, a variety of cytoplasmic incompatibility (CI) and sterile-insect techniques (SIT) have moved beyond basic research and into the pilot-testing phase of field application. These techniques are particularly appealing as they specifically target *Ae. aegypti* and *Ae. albopictus*, even into cryptic breeding locations, supplementing other existing and new IVM practices to reduce or locally eliminate

[34] Lorenzi OD, Major C, Acevedo V *et al.* 2016. Reduced incidence of chikungunya virus infection in communities with ongoing Aedes aegypti mosquito trap intervention studies—Salinas and Guayama, Puerto Rico, November 2015-February 2016. MMWR:65. http://www.cdc.gov/mmwr/volumes/65/wr/mm6518e3.htm

[35] Qualls WA, Muller GC, Revay EE *et al.* 2014. Evaluation of attractive toxic sugar bait (ATSB)—barrier for control of vector and nuisance mosquitoes and its effect on non-target organisms in sub-tropical environments in Florida. Acta Trop. 131:104-110. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3944220/

mosquito populations or virus transmission, while minimizing collateral risks to humans and impacts on other species.

a. Sterile-Insect Technique

Sterile-Insect Technique (SIT) is a method of biological control where sterile insects, usually male, are released to the wild. Male mosquitoes cannot bite or transmit pathogens to humans. Sterile males will compete with wild males to mate with female mosquitoes, producing no offspring and reducing the next generation. SIT has been successfully used to eradicate the screwworm fly in areas of North America and to control fruit flies. Critical to the success of SIT is the ability of the sterile males to overwhelm the mating capacity of wild males. This is achieved through a combination of the reproductive fitness of the sterile male mosquitoes in competition with their wild counterparts, and the ratio of sterile to wild males, the latter being increased by a combination of the number of sterile males released and sequencing SIT to follow other IVM actions to reduce wild mosquito numbers. SIT techniques require ongoing release of relatively large numbers of sterile males. Hence, the economics of mass rearing, sex separation (to prevent the release of female mosquitoes), transportation, and release are critical challenges to the viability of programs.

There are a variety of means under consideration to sterilize mosquitoes, including radiation, chemicals, or more recently using ds-RNA to induce sterility. A primary consideration is to achieve the maximum proportion of sterility among males with the minimum impact on their reproductive competitiveness to mate with female mosquitoes. Radiation has been the preferred sterilization technique for screwworm and fruit-fly SIT, but has proven challenging for *Aedes* mosquitoes as the dose necessary to induce a high rate of male sterility is close to the dose that adversely affects mating competitiveness. Reducing the radiation dose to increase competitive performance can be associated with the release of a small percentage of residually-fertile males, which may be coupled with the inadvertent release of females through inadequate sex sorting. The risk of releasing active-breeding and biting *Aedes* populations can be addressed by concomitant use of cytoplasmic-incompatibility techniques (see below) to bolster overall sterility.[36] Successful demonstration of radiation SIT for mosquitoes would offer numerous benefits, notably the inability of mosquitoes to develop resistance to radiation-induced sterility, a history of public acceptability of this technique, and no need for regulatory approval. Radiation SIT can be implemented using X-rays, reducing security concerns regarding transporting gamma-ray sources to remote locations. Irradiation SIT is being advanced with support of the International Atomic Energy Agency (IAEA),[37] and is one of the vector-control techniques recommended by the WHO VCAG (2016) for pilot studies to generate entomological and epidemiological evidence.

b. Cytoplasmic-Incompatibility-Insect Technique

Cytoplasmic incompatibility (CI) is similar in application to SIT, where large numbers of artificially raised males infected with *Wolbachia* intracellular bacteria are released to compete with wild males for females, but cannot produce viable offspring. *Wolbachia* are only able to grow and reproduce inside the cells of an insect or nematode host. These bacteria are passed on to insect progeny by the mother, becoming a permanent part of the insect line. Although most insect species have natural associations with *Wolbachia*, it has not been found in *Ae. aegypti* in nature. Males from mosquito lines that are artificially infected with *Wolbachia* cannot reproduce with female mosquitoes that do not have *Wolbachia*, or that have a different strain of *Wolbachia*. Similar to SIT, this technique relies on the fitness and numbers of the released *Wolbachia*-infected male mosquitoes to overwhelm the reproductive capacity of the wild males. Releases need to be for a prolonged period of time, and hence the efficiency and economics of production, distribution, and release are again critical challenges to the success of this technique. Sex-

[36] Zhang D, Zheng Z, Xi Z *et al.* 2016. Combining the Sterile Insect Technique with the Incompatible Insect Technique: III-Robust Mating Competitiveness of Irradiated Triple Wolbachia-Infected Aedes albopictus Males under Semi-Field Conditions. PLoS One. 2016 Mar 18;11(3):e0151864. doi: 10.1371/journal.pone.0151864 http://www.ncbi.nlm.nih.gov/pubmed/26990981

[37] https://www.iaea.org/sites/default/files/gov-2016-12-derestricted-c.pdf

separation in the production facility is particularly important, as inadvertent release of *Wolbachia*-infected females has the potential to "flip" the wild population into a *Wolbachia*-infected breeding population (see below for the alternative use of *Wolbachia* to prevent virus transmission). *Wolbachia* cytoplasmic incompatibility is been field tested in the United States under an EPA Experimental Use Permit,[38] and a registration package has been submitted to, and is under review by, the EPA.

c. Genetic Techniques and Late-Lethal Mortality

One company has recently engineered a "late lethal" male *Ae. aegypti* mosquito, which mates with wild females and produces offspring that die before they emerge as an adult or mate. This transgenic strain of *Ae. aegypti* carries a dominant, non-sex-specific, late-acting, lethal, self-limiting gene. The lethal gene can be suppressed by tetracycline in the laboratory, allowing the mosquito to be bred in large numbers, but all offspring will die in the wild when the tetracycline suppression ends. A fluorescent marker gene is also added to the mosquito, allowing field technicians using ultraviolet light to count the number of late-lethal larvae compared to wild larvae, thereby monitoring the success of interventions. There have been open-field release tests in several countries, including the Cayman Islands, Panama, and three test sites in Brazil, in which each six-month trial has reduced the local *Ae. aegypti* population by more than 90 percent. The WHO VCAG (2016) recommended that pilot deployment under operational conditions be studied against epidemiological outcomes to build evidence for routine deployment. On August 5, 2016, the U.S. Food and Drug Administration issued a finding that a proposed field test of this mosquito in the Florida Keys will not have significant impacts on the environment. Implementation of the field test is under active discussion between the Florida Keys MCD and local community. A non-binding referendum was held in the Florida Keys on November 8, 2016, with a majority of residents of Key Haven, where the trial would take place, not supporting the field test, whereas residents of the surrounding Monroe County voted to approve.

As with SIT, this late-lethal genetic method to suppress populations over time requires repeated releases of engineered mosquitoes to reduce populations permanently, since the "late lethal" traits are not passed on to future generations. In the above-mentioned field trials, wild *Aedes* mosquito populations started returning to pre-trial levels within six months of the end of a trial. This recovery characteristic translates into high costs of carrying out the approach at scale although, as noted above, the radiation-induced "sterile male" approach, which shows similar potential for population recovery, has been used successfully on a large scale on the screwworm, fruit fly, and tsetse fly.

Last year, scientists demonstrated that a "gene drive"[39] can be used to facilitate passing certain genetic modifications of mosquitoes on to subsequent generations. In November 2015, scientists in California reported that they had developed a gene drive that would propagate *Anopheles stephensi* mosquitoes (which transmit malaria in India) engineered to be resistant to infection by the malaria pathogen.[40] In December 2015, scientists in London reported they had engineered *Anopheles gambiae* mosquitoes—which are responsible for more than 100 million cases of malaria each year—to selectively pass on genes that cause infertility in female offspring.[41] In theory, similar gene drives could be developed for the

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[38] https://www.epa.gov/pesticides/epa-grants-extension-experimental-use-permit-wolbachia-mosquito EUP expansion for testing in California and Florida.

[39] Gene drives are systems of genetic elements, usually comprising multiple genes and associated regulatory genetic material, that can spread through a population of sexually-reproducing organisms, even if these elements reduce the fitness of individual organisms. Gene drives accomplish this by ensuring that they will be inherited by most, rather than only half, of the offspring of the engineered organisms, thereby driving the genes to fixation.

[40] Gantz VO, Jasinskiene J, Tatarenkova O *et al.* 2015. Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito Anopheles stephensi. Proc Natl Acad Sci USA. Dec 8;112(49):E6736-43. doi: 10.1073/pnas.1521077112 http://www.ncbi.nlm.nih.gov/pubmed/26598698

[41] Hammond A, Galizi R, Kyrou K *et al.* 2016. A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector Anopheles gambiae. Nat Biotechnol. 2016 Jan;34(1):78-83. doi: 10.1038/nbt.3439. Epub 2015 Dec 7. http://www.ncbi.nlm.nih.gov/pubmed/26641531

mosquito species that carry the Zika virus. There is still work to be done to better understand efficacy and safety, however, before the gene-drive approach is pursued outside of the laboratory.

d. Microbial Control of Human Pathogens in Adult Mosquitoes

In a second application of symbiotic intracellular *Wolbachia* (see the previous cytoplasmic-incompatibility section), evidence indicates that infection of *Ae. aegypti* females with the *Wolbachia* Mel (wMel) strain substantially reduces the mosquito's ability to transmit dengue and Zika viruses.[42] *Wolbachia* infection reduces viral replication and eliminates or substantially delays passage of the virus from the midgut to the saliva, hence reducing virus-transmission risk. The strategy to introduce wMel into wild populations relies on cytoplasmic incompatibility, where wMel-infected *Ae. aegypti* females are able to produce offspring with non-infected and infected males, but non-infected females can only breed with non-infected males. This creates a reproductive advantage toward wMel, and the wMel-infected populations cannot coexist with wild wMel-negative populations. After introduction of the wMel-infected strain of *Ae. aegypti* in Australian field trials in 2011, resident non-infected *Ae. aegypti* were overwhelmed, and the wMel-infected *Ae. aegypti* reached and maintained a frequency of more than 90 percent.[43] wMel-infected mosquitoes collected from these experiments show markedly reduced dengue virus infection and viral replication after experimental exposure, suggesting reduced capacity to transmit dengue compared to the native-*Ae. aegypti* populations. Recent data indicate that a similar effect is possible with Zika virus.[44]

This application of *Wolbachia* has several important features that make it potentially an ecologically-sound control measure. In contrast to SIT and cytoplasmic incompatibility as "sterile" insect techniques (see previous sections), wMel does not seek to eradicate or reduce the *Ae. aegypti* population, but rather to prevent virus transmission in the mosquitoes that remain. wMel infections are persistent and heritable, so the bacterium does not need to be reintroduced into every generation of mosquitoes, suggesting that it could be a lower-cost, long-term solution to preventing outbreaks of dengue, Zika, and other viruses. The program can be easily implemented and sustained through distribution of small cartons containing wMel *Aedes* eggs—just add water and place outside. *Wolbachia spp.* are already present in many insect species, including bees, butterflies, and other mosquitoes, mitigating public concern about ecological risk. With support from the Bill and Melinda Gates Foundation, *Wolbachia* trials are currently underway in Indonesia and Vietnam, with pilot studies planned in Brazil and Colombia. WHO VCAG (2016) recommended pilot deployment under field conditions and planning for randomized-control trials (RCTs) with epidemiological outcomes to build evidence for routine programmatic use.

e. Regulatory-Review Frameworks for Vector-Control Technologies in the United States

Many of the vector-control approaches that rely on application of emerging technologies must be evaluated by Federal agencies for their safety (and in some cases efficacy) prior to commercial use. The regulatory framework for evaluation in the United States has developed pursuant to a number of Congressional mandates, regulatory actions, and judicial interpretations. Outlining the details of this regulatory structure is beyond the purview of this Strategy. Indeed, in a number of cases, identifying the specific agency with regulatory oversight will depend on the specifics of the individual application or registration claim, such as whether the claim is to kill mosquitoes, to protect livestock, or to directly impact disease transmission. Consistent with their legal requirements, Federal agencies—including the U.S. Environmental Protection Agency (EPA), Food and Drug Administration (FDA), and USDA Animal

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[42] Aliota MT, Peinado SA, Dario-Velez I *et al.* 2016. The wMel strain of Wolbachia Reduces Transmission of Zika virus by *Aedes aegypti*. Sci Rep. 2016 Jul 1;6:28792. doi: 10.1038/srep28792

[43] Hoffmann AA, Montgomery BL, Popovici J *et al.* 2011. Successful establishment of Wolbachia in Aedes populations to suppress dengue transmission. Nature 476: 454–457. https://www.ncbi.nlm.nih.gov/pubmed/21866160

Hoffmann AA, Iturbe-Ormaetxe I, Callahan AG *et al.* 2014. Stability of the wMel Wolbachia infection following invasion into Aedes aegypti populations. PLoS Negl Trop Dis.8(9):e3115. https://www.ncbi.nlm.nih.gov/pubmed/25211492

[44] Dutra HL, Rocha MN, Dias FB *et al.* 2016. Wolbachia Blocks Currently Circulating Zika Virus Isolates in Brazilian Aedes aegypti Mosquitoes. Cell Host Microbe. 19(6): 771–774. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4906366/

and Plant Health Inspection Service (APHIS)—coordinate on regulatory applications where jurisdictional coverage may be unclear in order to avoid duplication of effort and delays. For more information on the regulatory system for biotechnology products, including vector-control approaches that utilize biotechnology products, the U.S. Government has recently proposed an Updated Coordinated Framework for the Regulation of Biotechnology, along with a *National Strategy for Modernizing the Regulatory System for Biotechnology Products*.[45]

Many of the existing products to control vector mosquitoes contain active ingredients that are registered as pesticides by the EPA. A pesticide includes "any substance or mixture of substances intended for preventing, destroying, repelling, or mitigating any pest." Because pesticides are often designed to kill animals and plants, they pose a potential risk to human health and the environment if overused or not used in accordance with the labelling instructions. Pesticides are primarily regulated by the EPA under the Federal Insecticide Fungicide and Rodenticide Act (FIFRA), the Food Quality Protection Act (FQPA), and the Pesticide Registration Improvement Act (PRIA). To make registration decisions allowing new uses of pesticides and new active ingredients, EPA must review data and information on the potential risks to human health and the environment. If the proposed pesticide will not pose unreasonable adverse effects, and there is a reasonable certainty of no harm to human health from any dietary exposure, EPA may register the pesticide use. There are a number of general agency terminologies and processes that are particularly pertinent to understanding the regulatory-review pathways and timelines applicable to new Zika interventions. For example, some of the required testing for pesticide registration is necessarily done under open-field conditions and involves use of an unregistered product, in which case EPA must first authorize an experimental-use permit (EUP) under FIFRA Section 5. Certain pesticide registrations and amendments can be expedited in response to the threat posed by Zika. PRIA (2003) created a fee system for applications for specific pesticide registrations and amendments, under which EPA is required to meet decision-review time periods that result in a more predictable evaluation process and a shorter decision-review period for reduced-risk registration applications. In emergencies, FIFRA Section 18 authorizes the EPA to allow an unregistered use of a pesticide for one year if the Agency determines that a serious pest problem jeopardizes agricultural production or public health.

6. Community Acceptance and Social and Behavioral Science

The importance of social and behavioral science to guide engagement of communities in *Aedes* control cannot be overstated. The effectiveness of public-health interventions hinges on the extent to which control practices are implemented in communities and on the knowledge and perception of residents. For example, a recent trial in New Jersey showed a significant reduction of mosquito-container habitats in neighborhoods where volunteers provided active peer education, compared to control areas.[46] Experience has shown that advancing social and behavioral science for *Aedes*-vector control should be accorded the same level of priority as potentially game-changing new technologies. This is not a new insight, with the importance of community and homeowner relations having been identified from the earliest days of mosquito-control efforts.

Social science needs relate to both implementing current IVM practices and the acceptability of new technologies. Current IVM practices depend on household participation to clean up larval-development sites in yard waste, adequately screen houses, apply pesticides, wear protective clothing and repellents, and be aware of the community nature of virus-transmission risks to other people's homes, families, and babies. For new technologies, such as SIT, *Wolbachia*, and late-lethal genetically-engineered (GE)

[45] https://www.whitehouse.gov/sites/default/files/microsites/ostp/biotech_coordinated_framework.pdf
https://www.whitehouse.gov/blog/2016/09/16/building-30-years-experience-prepare-future-biotechnology

[46] Healy K, Hamilton G, Crepeau T *et al.* 2014. Integrating the public in mosquito management: active education by community peers can lead to significant reduction in peridomestic container mosquito habitats. PLoS One. 9(9):e108504. http://www.ncbi.nlm.nih.gov/pubmed/25255027

mosquitoes, social acceptability is critical to the ability of MCDs to implement new vector-management practices, even after evaluation by Federal agencies to determine safety and efficacy.

A number of aspects of Zika make it a particular social challenge. For most people, the disease is mild or completely asymptomatic. If a laboratory-diagnostic test is sought, it can take days to weeks for confirmation, by which time the symptoms, concerns, and ability to respond have passed into memory. Many of the most affected regions have been tolerating household mosquitoes, dengue, and chikungunya for years, and have other pressing concerns. The predominant major impacts of Zika are to the fetuses of a proportion of pregnant women, many of whom may not be aware of their pregnancy until well into the first trimester. Any adverse effects on the fetuses and babies may not be evident for many months, offering a false sense of normality to mother and community alike. As the serious effects of Zika are not immediately evident to a community, it has proven difficult to rally communities around mosquito-control efforts.

Against this under-perceived risk of Zika are the misinformation, rumors, and conspiracy theories that can circulate regarding vector-control practices. Already with Zika, unsubstantiated rumors have given rise to the idea that the rise in microcephaly cases resulted from release of the late-lethal GE mosquito or the use of chemical pesticides in the region, and that the GE mosquito and Zika are being used as bioweapons.[47] Damaging misinformation has even come from supposedly respectable sources, picked up by the media and persisting in public discourse despite having been discredited by health authorities.[48, 49]

Encouragingly, there is a theoretical literature, supported by successful examples, where accurate information has been conveyed to communities to facilitate the introduction of new *Aedes*-control technologies. Behavioral-science literature highlights the importance of framing public-awareness campaigns, early and active engagement with the community, and financial motivation through incentives backed by enforcement mechanisms. Public-awareness campaigns can harness concerns surrounding Zika-related birth defects, encouraging feelings of altruism for babies and, in turn, adherence to *Aedes*-control recommendations. Zika risks and remedial actions can be messaged through informing trusted sources, such as local family-healthcare providers, and by recruiting celebrities to improve visibility and facilitate the dissemination of accurate information across social networks. The upfront commitment of substantial personnel and financial resources has proven central to successful community-outreach programs.

In northern Australia, the successful introduction of *Wolbachia*-infected *Ae. aegypti* for dengue control was supported by the involvement and active engagement of host communities and other stakeholders. Community-engagement frameworks were tailored to local concerns and expectations. The host community's acceptance of the trials was facilitated by four components: internal leadership prioritizing community engagement, research into the perspectives of stakeholders regarding the technology, adherence to the core commitments and guiding values identified by those stakeholders, as well as the continuous presence and accessibility of the vector-control team in the host community. More than a quarter of the dollars allocated for implementation were devoted to community engagement, the success of which is evident now in the "Wolbachia Warriors" School Program.

In Brazil, community engagement in preparing for release of the late-lethal GE mosquito was supported by community-education campaigns branded as the Friendly™ Aedes mosquito. Technicians familiar with the mosquito, supported by the Secretary of Health, engaged over several months with local citizens to explain what the Friendly™ Aedes is and how it works. This was accompanied by an advertising campaign in newspapers, billboards, and bus-door posters, followed by radio spots and an information kiosk in the largest shopping mall. The message was that the Friendly™ Aedes is a male mosquito that is unable to bite and transmit diseases, as demonstrated by placing hands in cages of these insects. The

[47] http://www.infowars.com/top-expert-zika-virus-a-bioweapon/

[48] http://www.huffingtonpost.com/entry/zika-monsanto-pyriproxyfen-microcephaly_us_56c2712de4b0b40245c79f7c

[49] http://www.who.int/emergencies/zika-virus/articles/rumours/en/

impact of the public engagement was monitored through market-research surveys. Again, over a quarter of the initial implementation funding was devoted to public outreach.

Community engagement and leadership were also central to the successful response to dengue in Key West, Florida, in 2009-2010. Comprehensive communication between the MCD teams and the public was necessary to engender the trust, knowledge, and outreach necessary to facilitate the elimination of containers with standing water that were serving as *Ae. aegypti* larval-development sites, and the acceptance of insecticide applications.

Research Recommendations

The large and expanding geographic scope and scale of *Aedes*-transmitted human pathogens highlights the need to prioritize and improve coordination of research on *Aedes* vector species and ways to control them. Our inability to adequately control *Aedes* vector species is the core reason that we continue to experience dengue and chikungunya illness and epidemics in the United States and its Territories, and now Zika. Even with an effective vaccine, yellow-fever epidemics still occur in developing countries, transmitted by this mosquito. Globally, with more people crowding into cities, many with inadequate housing, there is an urgency to undertake the research necessary to counter this ubiquitous and dangerous pest species that lives with us, feeds on us, and transmits disease among us. *Ae. aegypti*-mosquito research will help to address the millions of dengue, chikungunya, yellow-fever, and Zika infections that already occur globally, and may help to prevent a future epidemic from an as-yet-unidentified viral threat, where diseases that start on different continents don't stay there.

The research recommendations listed below are broad in nature, covering the spectrum of *Aedes* vector research needs, but also accord particular emphasis to the importance of behavioral science and rigorously evaluating the efficacy of vector-control interventions. There are many means and possible collaboration opportunities to get this research done. These include Federal support through grants, cooperative agreements, and contracts, but also opportunities through new collaborations with philanthropies, universities, and MCDs to monitor and evaluate vector-control activities in the field, as well as to enlist novel means such as open innovation, grand challenges, and citizen science. The urgency is not just in the face of today's Zika outbreak, but to act while public attention is high and not allow a hiatus of interest to occur until the next epidemic unfolds.

1. Vector Control

Within the overall construct of Integrated Vector Management (IVM), there are a number of individual "paradigms" that represent typical vector-control practices that have been demonstrated, or are under review, as effective in reducing vector numbers and/or impacting human-disease transmission (VCAG 2014). Examples of these paradigms for *Ae. aegypti* include larval-source management, indoor-wall spraying with adulticides, attractive toxic sugar baits (ATSBs), spatial repellents, vector traps, and microbial control of human pathogens. Paradigms are not restricted to an individual chemical, technology, or company, but are conceptual in nature and amenable to improvement through better products and technologies, the objective of many of the research opportunities outlined below.

a. Physical Control – New and Improved Technologies

The risk of exposure to *Aedes*-transmitted viruses is strongly mitigated over much of the United States by the presence of physical barriers, notably window and door screens on a background of air conditioning, demonstrating the long-term benefits (albeit expensive) of "hard" infrastructure. Especially for the hotter and island regions of the United States within the range of *Ae. aegypti* and *Ae. albopictus*, opportunities exist to identify new materials and practices to improve vector control through physical barriers by developing new, affordable (in the U.S., regional, and territorial context), and culturally-appropriate technologies for:

- Buildings, such as culturally-appropriate, appealing, and affordable impregnated curtains, window screens, frames, doors, eaves, and closed water-storage containers;
- Infrastructure, such as modifications to water meters, drainage locations, septic tanks and sewers that make them less conducive as larval-development sites; and
- Removing or eliminating objects that retain water and serve as *Aedes*-larval development sites, such as tire and plastic-container removal and recycling technologies, practices, or incentives.

b. Chemical Control – New and Improved Technologies

Chemical-control technologies have proven instrumental in responding to past vector-borne-disease outbreaks. Overreliance on these insecticides has led to the development of resistance by mosquitoes, with an early history of resistance developing to DDT, organochlorines, and organophosphates, and now becoming more widespread with the pyrethroids. Against this increasing backdrop of insecticide resistance is the relative dearth of new public-health insecticides being brought onto the market, the loss of current pesticides due to lowering of risk tolerance, and the need to stimulate and accelerate this pipeline for new insecticide development. Research advances are needed related to:

- Insecticide development, including developing new core chemistries and newer classes for larvicides and adulticides, and insecticides that target particular species;
- Re-evaluation of existing pesticides for public-health uses, such as expanded testing of existing insecticides (e.g., isoxazoline) against mosquito vectors, and potential Federal-agency sponsorship of the necessary studies and regulatory submission in support of orphan public-health insecticide registrations and production;
- Vector resistance, characterizing the extent and pattern of insecticide resistance within and among populations of *Aedes* vectors, the physiological and genetic basis for this resistance and potential countermeasures, and the development of an insecticide-resistance strategy to potentially increase the susceptibility of *Aedes spp.* to available insecticides, based on lessons learned from agricultural pest-management strategies;
- Dispersion and application technologies to improve on current equipment and application and targeting practices, noting the potential for incremental improvement to existing methods and through innovative new application paradigms, particularly for ultra-low-volume and peridomestic spraying; and
- Exposure and risk associated with current and proposed chemical-control agents, for both humans (including sensitive subpopulations) and non-target species (including endangered species and pollinating insects), to refine risk assessments that support pesticide-registration decision-making.

c. Biological Control – New and Improved Technologies

Many of the most promising biological-vector-control opportunities have been discussed previously in this Strategy. The research opportunities highlighted below focus on conducting supplementary studies that may not be routinely conducted as part of the standard regulatory-review packages prepared by sponsoring organizations. Many of these recommendations parallel those of the WHO VCAG (2016) to rigorously test the most promising technologies against vector and disease outcome measures.

- Sterile-, Incompatible-, and Genetic-Engineered-Insect Techniques are grouped together here for expediency, most of which have moved beyond the laboratory into field-testing and are an overarching priority for support. These technologies include *Wolbachia* ZAP strain; radiation, chemical, and ds-RNA SIT; and late-lethal gene modification. Additional research could be considered to: optimize competitive reproductive performance for the male mosquitoes under each technology; test and evaluate the risk of transfer of bacterial or genetic-active ingredients to non-target organisms; characterize and reduce the capital and maintenance costs; and explore factors conducive to the scalability of the technologies.
- Mass-rearing technologies are critical to all SIT, CI, and GE technologies, which can benefit from improvements to the commercial and industrial processes and economics of rearing, sex separation, distribution, release, and sustained maintenance of large numbers of insects.
- Disease-Transmission Interruption can be advanced by field studies on *Wolbachia* Mel in a variety of locations and against Zika-virus transmission, as well as dengue virus. Studies could also evaluate the extent and duration of virus-transmission interruption by *Wolbachia*, and the prevalence, potential transfer, and impacts of *Wolbachia* strains on other insects and animals.
- Gene-drive mechanisms should be advanced through laboratory studies, paying particular attention to designs and study protocols that address the novel risks posed by this technology, recognizing that these technologies will ultimately be subject to considerable public and regulatory scrutiny prior to release into commercial use.
- Microbial pathogens should be further evaluated for insecticidal properties, building on the successful history of looking to natural processes for agents to counter human-disease threats,

including advancing research on *Bacillus thuringiensis* variants, testing other microbial pathogens, e.g., C*hromobacterium* and *Lysinibacillus sphaericus*, and other microbial toxins, e.g., *Saccharopolyspora spinosa*.

d. Traps and Bait Stations — New and Improved Technologies

Baits and traps offer long-term, low-risk solutions to indoor and outdoor control of *Aedes* vectors, with research and testing recommended for large-scale application against vector and human-disease outcome measures. Options include:

- Lethal ovitraps, through the development and testing of additional low-cost, easy-to-produce and -maintain ovitrap variants for indoor use;
- Autodissemination ovitraps and bait stations, advancing the combination of new lures, chemicals, and biological agents that rely on inducing female mosquitoes to carry toxins to their next egg-laying sites, especially cryptic or hard-to-access locations; and
- Attractive toxic sugar baits (ATSB), seeking new baits and low-toxicity substances that enhance target specificity and efficacy against mosquitoes.

e. Personal Protection — New and Improved Technologies

Personal protection against mosquitoes offers advantages of being within the control of an individual and providing protection during the daytime and outside the home environment. Research opportunities include:

- New repellent chemicals for personal use, clothing impregnation, and as building and outdoor-spatial repellents. All compounds should be tested for safety to pregnant women. Clothing additives should remain active over months of normal washing, and not suffer from mosquito resistance, as is increasingly being experienced with permethrin impregnation.
- New mosquito bite-resistant clothing that physically prevents bites through the fabric and is fashionable and appealing to affected communities, especially pregnant women of a variety of ethnicities living in hot climates, and linked to behavioral studies regarding the acceptability of these designs.

2. Social and Behavioral Science

As discussed previously, this Strategy recommends that social- and behavioral-science studies be prioritized in conjunction with vector-control operations that engage citizens in both the planning and operational stages. Cooperative Extension Service educators also need to be provided resources to adapt scientific knowledge and create community education and engagement programming. Beyond these applied needs, studies specifically oriented toward public-risk perception, communication strategies, receptivity to differing vector-control practices, and inducements for improved public-health practices warrant highlighting under this research theme.

a. Existing Vector-Control Techniques – Social and Behavioral Science

Much can be done to improve our understanding of citizen reactions to vector-borne diseases, and how to encourage citizens to optimize their own personal health-protection practices and engagement in community-wide public-health strategies. Research opportunities include:

- Social and behavioral theory applied to vector-control efforts, bringing the broad theoretical knowledge and field experience with public-health campaigns to *Aedes* vector- and Zika virus-control interventions. Themes may include, *inter alia*, message framing and response to concerns, community and leader engagement, trusted messengers, and motivation through incentives and penalties;
- Community risk awareness and generating the social concern and cohesion necessary to respond to Zika and *Aedes* vectors at the community level, noting that Zika risks are heavily weighted toward pregnant women and their babies, the adverse effects are delayed many months, the disease is otherwise mild or unnoticed, and the virus can be transmitted between sexual partners. Research is needed to better understand how to develop the communication, outreach, and

marketing strategies to accurately inform and engage communities to allow, and hopefully assist, vector-control practices oriented toward this relatively uncommon mosquito species in people's homes, as distinct from the swarms of nuisance mosquitoes more evident and overtly disturbing at other locations;

- Overcoming impediments to implementation of existing vector-control strategies, and ways to identify these challenges, interpret cultural differences and needs, and develop response strategies, such as communication, outreach, inducement, and potential social disapproval and penalties for non-compliance. Challenges include socioeconomic circumstances and lifestyle choices that lead to outdoor living and open windows with no screens, reticence to permanently clean yard wastes, resistance to truck and aerial application of pesticides in *Aedes*-vectored disease-transmission areas, and distrust of government agencies and staff;
- Economic considerations, with a particular focus on the preferences and financial abilities of different socioeconomic groups in the United States to address *Aedes* risks, as distinct from studies in developing countries where low to zero cost is a controlling factor; and
- Best-management practices, including Integrated Vector Management guidelines, for effective vector-control outreach in the United States, bringing together social and behavioral understanding and experience to guide vector-control-implementation efforts.

b. New Vector-Control Techniques – Social Acceptability through Behavioral Science

As noted previously, there are successful examples of the introduction of new technologies to combat vector-borne disease, all of which relied on extensively resourced, early and ongoing public engagement. Research should evaluate and build on this foundation, with particular focus on:

- Application of social or behavioral theory to facilitate novel sterile-insect techniques (SIT), genetic engineering (GE), and cytoplasmic-incompatibility (CI) implementation;
- Evaluation of community awareness, including comparative risks posed by the disease compared to standard IVM techniques and the novel options under consideration, and of impediments to the use of new technologies and ways to incentivize or "nudge" beneficial behaviors and adoption;
- Prioritization and targeting of research and outreach to address community concerns identified in social-science studies;
- Efficacy evaluation of social and behavioral engagement in new technology applications;
- Economic considerations in SIT/GE/CI implementation; and
- Best-management practices for community engagement in new SIT/GE/CI applications.

3. Efficacy Testing and Monitoring

In conjunction with social and behavioral science, efficacy testing of vector-control strategies—individually and integrated—is essential to prepare a rigorous foundation for countering the increase in *Aedes*-vectored Zika, dengue, chikungunya, and yellow fever. From the Federal perspective, coordination of activities across agencies and budget lines is central to effective use of resources. Success also requires a vigorous effort to expand contact and collaboration with organizations and technicians implementing control technologies in the field, especially where these interventions are occurring in the presence of active disease transmission. Needs include:

a. International, Collaborative Research

The spread of the Zika epidemic across islands, then continents, and now to the continental United States highlights again the international nature of epidemic illnesses, whether to U.S. citizens residing abroad, to travelers returning home from overseas, or from transmission occurring across U.S. States and Territories. International collaboration and the pooling of resources offers the potential to benefit all participating nations, researchers, and citizens, including protecting U.S. citizens who choose to stay at home. Intervention-efficacy research against epidemiological outcome measures—the gold standard—can only be conducted in locations where active disease transmission is occurring on a wide-scale (e.g., Zika is currently occurring in South and Central America, and some U.S. Territories). Although there is now local transmission of Zika virus in the continental United States, it is unlikely to occur at a large scale.

Working with international teams also provides U.S. researchers with the opportunity to supplement international-study protocols to cover topics of particular relevance to the United States, such as information potentially supportive of U.S. regulatory-study requirements or responsive to domestic public concerns, real or rumored (e.g., social acceptability and human and/or ecological impacts of SIT/GE/CI mosquitoes; rumored pesticide-impact claims). Research collaborations can be made:

- Multilaterally, where working with the WHO, PAHO, and VCAG facilitates coordination of resources and international access to impacted populations in locations where current IVM or new technologies are being implemented in existing-disease hot spots. For instance, VCAG (2016) recommendations include pilot deployment through randomized-control trials for wMel and the GE mosquito (OX513A) against epidemiological endpoints, and advancing studies for SIT, vector traps, and ATSB toward operational use; or
- Bilaterally, working with governments, university researchers, and other institutions in Latin America and the Caribbean to support mutually beneficial research (e.g., through existing global-health collaborations of CDC, NIH, DoD, USDA, and other Federal agencies).

b. Efficacy of *Aedes*-Control Technologies

In addition to collaborating internationally, Federal agencies can support efficacy studies of existing and new vector-control practices within the United States, predominantly against vector-outcome measures as proxies for human-disease control. These studies can be conducted through universities, with Federal agencies that have building-management and community responsibilities, and ideally in collaboration with U.S. MCDs and local public-health departments that are the ultimate practitioners of vector-control actions. Technologies could include all options noted previously (physical, chemical, biological, traps, SIT/GE/CI, social science, and best management practices). These vector-control practices can be studied individually and as part of IVM programs. With specific emphasis on working with MCDs, activities could include:

- Engaging MCD input in research planning, either directly or through university affiliations;
- Supplementing vector-control field operations conducted by resource-constrained MCDs by providing additional research expertise and resources to generate information that can guide future control actions, essentially "instrumenting" the efficacy of existing vector-control practices in collaboration with the MCDs;
- Fostering long-term, collaborative partnerships among public-health agencies, MCDs, and research communities to promote the sustained integration of research results into practice;
- Developing tools to assist decision-making for vector and pathogen management, including updated guidance and best management practices for the integrated vector control of public-health pests and pathogens; and
- Optimizing *Ae. Aegypti*-control approaches locally, in collaboration with MCDs, because the mosquitoes adapt to local environments, and communities differ in social, economic, and physical respects that may impact mosquito control. The set of interventions that works well in one area may not be as affective in another.

4. Vector Biology and Ecology

Much remains to be learned across a broad suite of biological and ecological aspects of *Aedes* vectors. Research needs range from understanding intracellular mechanisms that impact viral propagation and immune response to population dynamics among different vector species and higher-order ecological relationships impacting the geographic scale and timing of human-disease risk, including the impacts of climate change on vector distribution and abundance.[50,51,52] Examples of these research needs include:

a. Vector competency, the ability of a mosquito to transmit a pathogen, which is a complex interplay among the immune defenses of the host mosquito, its genotype and phenotype, the virus, and environmental parameters (e.g., temperature). Advances are needed on:
   - Biology of competency and virus transmission, including the infective dose to the mosquito in relation to pre- and subclinical Zika-viremia levels, and new and expanded options for interceding in the midgut, salivary gland, and other barriers to prevent virus dissemination or transmission.
   - Mosquito species' competency to determine the ability of different mosquito species and their regional strains to transmit Zika-virus strains of different geographic origin. A secondary goal could be to examine the potential for transmission by other blood-feeding arthropods.
   - Vertical-transmission potential, evaluating whether Zika virus can be transmitted across generations of mosquitoes through eggs to offspring, and whether such vertical transmission might be a significant factor in disease propagation; and
   - Multiple-virus-transmission potential, recognizing the ability of *Aedes* vector species to transmit multiple viruses to a particular host, the overlapping geographic distributions of the viral diseases, and potential interaction effects on transmission potential and disease consequence.

b. Animal reservoirs, which are species that maintain a continuing cycle of host-vector pathogen transmission and may serve as a prolonged source of potential human-disease outbreaks. Monkeys that maintain the forest (sylvatic) cycle of yellow-fever virus transmission are an example of an "enzootic" disease reservoir. The concern is that Zika virus may set up an enzootic cycle in a domestic or wild-animal species in North America, thereby greatly complicating and prolonging attempts to eradicate the virus. Additional research can be undertaken on:
   - Surveillance for virus and antibodies in animals in high Zika virus-transmission areas, especially mammals that have shown evidence of Zika-virus exposure (e.g., bats, rodents, ungulates), domesticated species in direct or indirect association with humans (e.g., farm livestock, such as cows and goats), and non-human primates elsewhere in Central and South America and the Caribbean; and
   - Laboratory-pathogenicity testing in potential animal-reservoir hosts susceptible to Zika virus and vectors, including the widely distributed *Ae. albopictus*, to evaluate whether animal species can host and transmit Zika virus to mosquitoes, along with the potential for enzootic cycles.

c. Habitat suitability and modeling, spanning knowledge gaps on the extent of, and factors influencing, the geographic range of *Aedes* occurrence (down to an understanding of micro- and cryptic-breeding sites) and the processes that drive the evolution of competent vectors in order to better inform human populations at risk, target interventions, and undertake predictive modeling. Climate change and subsequent shifts in vector ranges add urgency to these efforts. Additional work is needed on:
   - Habitat prediction and modeling, evaluating species and environmental factors conducive to *Aedes* colonization, including biological competition for breeding sites, climate and weather, cryptic or overwintering sites, domestic- and community-container availability and preferences, and migratory distances and rates of range expansion and recovery after control interventions.

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[50] Rochlin I, Ninivaggi DV, Hutchinson ML, Farajollahi A. 2013. Climate Change and Range Expansion of the Asian Tiger Mosquito (Aedes albopictus) in Northeastern USA: Implications for Public Health Practitioners. PLoS ONE 8(4): e60874. doi:10.1371/journal.pone.0060874

[51] Rueda LM, Patel KJ, Axtell RC, Stinner RE. 1990. Temperature-dependent development and survival rates of Culex quinquefasciatus and Aedes aegypti (Diptera, Culicidae). J Med Entomol 27:892–898.

[52] Kraemer MU, Sinka ME, Duda KA *et al.* 2015. The global distribution of the arbovirus vectors Aedes aegypti and Ae. albopictus. eLife, 4, e08347. http://doi.org/10.7554/eLife.08347

Models should also incorporate human-behavior variables to highlight risk areas where critical interventions should be targeted.

5. Vector Surveillance, Data Management, and Modeling

Surveillance data are critical, yet often under-resourced, to provide baseline information on location-specific vector abundance and pesticide resistance; to inform intervention targeting, timing, and efficacy studies; and to update managers and the public through data collation and dissemination. Mosquito surveillance is currently cumbersome, time consuming, and resource intensive, especially when seeking details on *Aedes* species identification, geographic distribution, pesticide sensitivity, and carriage of viral pathogens, offering considerable opportunities to supplement, automate, and expedite data collection and delivery.

a. Traps, lures, and monitors are the basic tools for vector surveillance. In the case of *Ae. aegypti and Ae. albopictus,* surveillance is currently centered on the BG Sentinel™ trap which costs approximately $200 per trap, requires daily maintenance, and relies on laboratory-technician expertise to sort and identify collected mosquitoes. Notably, because they feed in the daytime, *Ae. aegypti* and *Ae. albopictus* are not attracted by light but rather by carbon dioxide and human scents for feeding. They prefer to live in dark, moist locations inside or near houses, and their short flight range complicates trap placement for effective surveillance.

- Improved lures and traps need to be developed and tested for *Ae. aegypti* and *Ae. albopictus* that are cheaper, more portable, and more effective than existing options to collect these mosquitoes.
- Mosquito quantification needs to be streamlined to specifically identify species and count mosquitoes, currently a manual process that may be improved through the development and testing of automated, remote techniques, such as acoustic sensing to distinguish between the wingbeat frequencies of males and females of different mosquito species.

b. Surveillance is the ongoing systematic collection, analysis, interpretation, and dissemination of data. This Strategy is focused on *Ae. aegypti* and *Ae. albopictus* surveillance, and is linked in the broader sense to Zika-disease surveillance in the human population.

- Expanded mosquito surveillance is needed to generate more widespread, expedited, and accessible data on the location-specific presence and abundance of *Ae. aegypti* and *Ae. albopictus* in the United States. This should also include studies to determine the effectiveness of different surveillance trap options (for eggs and adults) and to define optimal and acceptable schemes for trap numbers and trap placement in the surveillance program.
- Improved pathogen detection in vectors can supplement human-disease surveillance, recognizing that approximately 80 percent of human Zika is subclinical and may not be detected during routine monitoring of human populations. The significance of detecting a virus in mosquitoes is tempered by the understanding that detection is not synonymous with transmission, as the mosquito may have fed on infected blood but not be able, or have had the opportunity, to transmit the virus. Zika virus surveillance in vectors is currently conducted using laboratory polymerase chain reaction (PCR) tests on pooled batches of wild-caught mosquitoes. The Department of Defense is currently supporting expedited development of a Zika dip-stick field-test kit, similar to the Dengue Detection Test Kit. More cost-effective and multi-pathogen kits would be valuable, especially if linked to automated traps.
- Evaluating insecticide resistance is an often overlooked, but essential predicate for vector-control interventions because *Aedes* vectors can develop resistance to common insecticides and this resistance can be very locale-specific. Insecticide-resistance testing is currently based on CDC and WHO protocols that require a substantial number of adult mosquitoes of the correct species and locale to be tested in bottles under technician supervision over a few hours. In addition to expanding our understanding of the extent and patterns of insecticide resistance using existing test protocols, resistance testing could be expedited through the development of new, affordable, rapid, insecticide-resistance-identification technologies. In addition, a central repository for

academia, MCDs, and extension agents to submit verified resistance data using GPS coordinates could help advance understanding of how resistance spreads, ultimately leading to more rapid success in pest control.

- Citizen science projects are underway for *Aedes* vectors, notably the Invasive Mosquito Project, and can be expanded to engage members of the general public in the collection and analysis of data on mosquitoes, under the guidance of professional entomologists. Citizen-science efforts can amplify the resources and reach of Federal-agency, university, and MCD activities, including engagement through community organizations, such as 4-H, to educate children and increase awareness in their families and communities.
- Data dissemination, vector mapping, and vector or disease modeling can be improved by taking advantage of new communication, mapping, and modeling technologies, and social-media networks for both information collection and dissemination. Modeling also is valuable as a means to determine optimal ways to integrate and target surveillance and IVM approaches. Care must be taken to ensure the quality of the data underlying the mapping and modeling efforts.
- Advance-outbreak prediction brings together much of the above data collection and analysis of vector and virus to provide additional predictive-modeling capacity to inform advance decision-making. Predictive modeling is relevant to estimating the time-course, location, and scale of epidemic risks from known viral pathogens (e.g., Zika virus), and to as-yet-uncharacterized arboviruses that could also be vectored by *Aedes* mosquitoes.

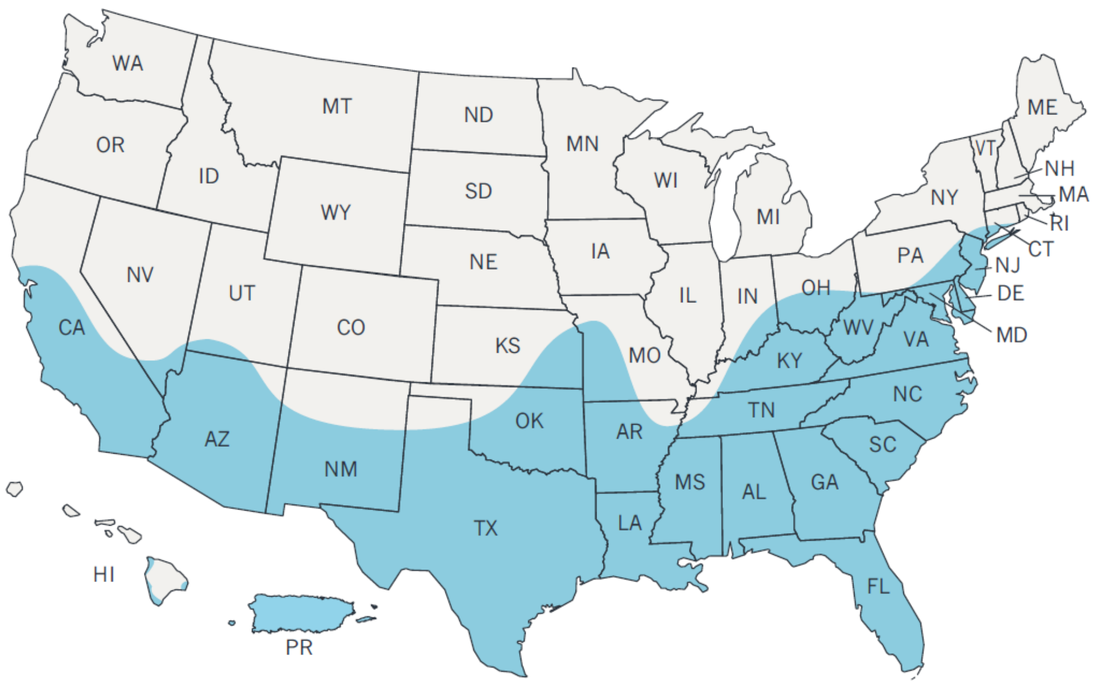
6. Training and Certification

Household-pest and mosquito control in the United States is generally conducted by the private sector and oriented toward nuisance control, as are many of the routine activities of MCDs. The risk posed by, and control of, transmissible human-disease pathogens engenders inherently community-based protection needs and heightened oversight by state and local health departments and MCDs. In notable instances, particularly in mosquito-prone areas, these health departments and MCDs have highly-trained staff and laboratory capacity to conduct public-`health interventions, supported by their state health departments and the Federal Centers for Disease Control and Prevention. History has shown, however, that mosquito-borne disease outbreaks can stress the capacities of even well-resourced MCDs, and overwhelm less-resourced counties or counties that might only rarely experience such outbreaks. The availability of staff with vector-control expertise — research, laboratory, or operational — is also nationally under-resourced in comparison to the scale of nuisance control and the risks posed by vector-borne-disease outbreaks, warranting additional consideration for training and certification support in the following skill sets:

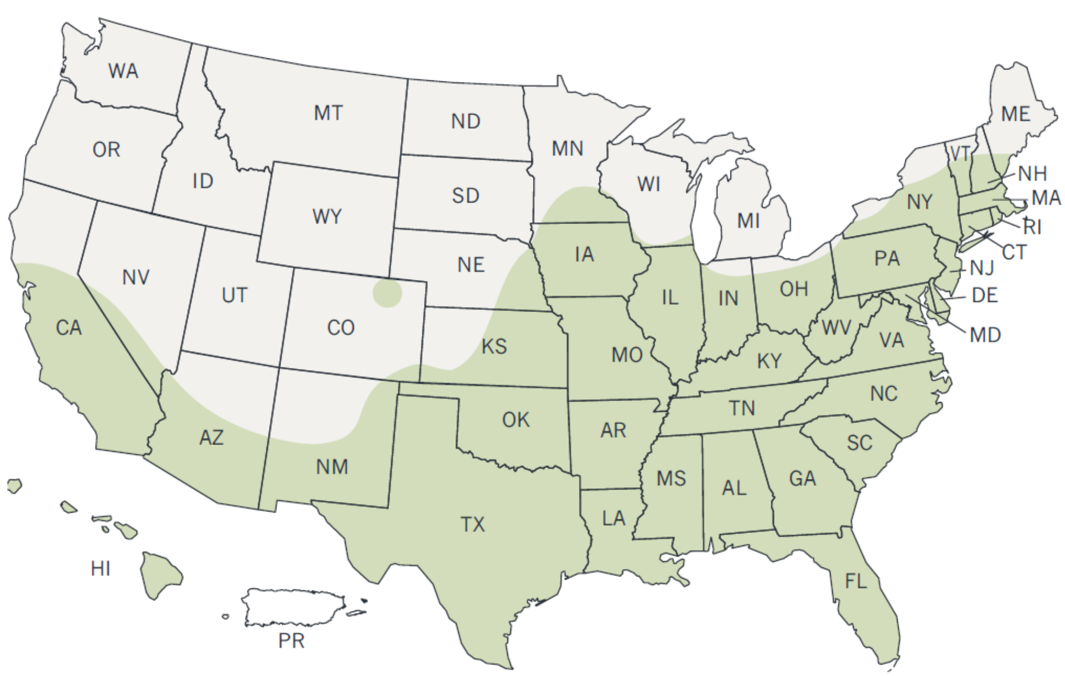
- Medical entomology, the branch of science dealing with insects that cause disease or that serve as vectors of organisms that cause disease in humans, and linked to veterinary entomology since animal diseases can become a human-health threat;
- Integrated Vector Management field technicians who directly engage in mosquito-control activities, in collaboration with the American Mosquito Control Association and the Entomological Society of America;
- Social and behavioral scientists with a focus on understanding and encouraging health practices for vector-control and disease prevention; and
- Extension educators with a focus on developing extension capabilities in local communities related to vector-borne diseases and their management and control.

Appendix A: Estimated Range of *Ae. aegypti* and *Ae. albopictus* in the United States, 2016. Centers for Disease Control and Prevention.[53]

Aedes aegypti



Aedes albopictus



[53] http://www.cdc.gov/zika/vector/range.html