



August 22, 2016

Genetically Engineered Mosquitoes: A Vector Control Technology for Reducing Zika Virus Transmission

Background

In February 2016, the World Health Organization (WHO) declared Zika virus a “public health emergency of international concern.” WHO defines such a public health emergency (1) to constitute a public health risk to other states through the international spread of disease, and (2) to potentially require a coordinated international response. This definition implies a situation that is serious, unusual, or unexpected; carries implications for public health beyond the affected state’s national border; and may require immediate international action. (See CRS Insight IN10433, *Zika Virus: Global Health Considerations*.)

While only about one out of five persons infected with Zika virus exhibit even the common symptoms of mild fever, rash, and joint pain, the U.S. Centers for Disease Control and Prevention (CDC) have confirmed that Zika-infected pregnant women are at risk for delivering babies with microcephaly, a birth defect of the cerebral cortex where a baby’s head is smaller than expected when compared to babies of the same sex and age. While research is limited, pregnant women are considered at risk for delivering babies with microcephaly no matter the stage of their pregnancy when they become infected with Zika virus. (See CRS Report R44368, *Zika Virus: Basics About the Disease*.)

Zika virus has now triggered outbreaks in 33 countries and territories, although confirmed cases linking Zika virus to babies with birth defects have thus far been seen in only Brazil and French Polynesia. Several countries have also reported a spike in cases of Guillain-Barré syndrome, a neurological syndrome, also believed to be an effect of the virus in some victims.

A Mosquito-Borne Virus

Zika virus (so named for the Zika forest in Uganda, where it was first identified in monkeys in 1947) is a mosquito-borne *flavivirus* that has rapidly infected human populations in Latin America and the Caribbean, including outbreaks in the U.S. territories of Puerto Rico, the U.S. Virgin Islands, and American Samoa. As of April 2016, over 400 cases in the United States have been confirmed, each acquired through either travel to areas where the mosquito vectors for Zika virus circulate or sexual contact with people who had traveled to such areas. No confirmed cases of local transmission have been confirmed in the contiguous United States as yet.

The first outbreak of Zika virus outside Africa, Asia, and the Pacific Islands occurred in Brazil in May 2015. The virus is spread predominantly by the female *Aedes aegypti* mosquito (and to a less effective extent by *Aedes albopictus*), an aggressive day-biter that is also a vector for

yellow fever, dengue, and chikungunya. *Aedes aegypti* mosquitoes are non-native to the United States. A model created by Toronto researchers found that approximately 63% of the U.S. population lives in areas where Zika virus might spread during seasonally warm months if mosquitoes in the United States were to become vectors of Zika virus. As much as 7% of Americans live in areas where the cold might not kill off the mosquito in the winter, leaving them vulnerable year round. (See CRS InFocus 10353, *Mosquitoes, Zika Virus, and Transmission Ecology*.)

No vaccine exists for Zika, and scientists have estimated that it could take two years or more to develop such a remedy. Mosquito control and bite prevention are the first lines of defense. Controlling *Aedes aegypti* by conventional methods such as truck and aerial spraying is only moderately effective in reducing mosquito populations—approximately 30%-50%—in part owing to the resistance the mosquitoes have developed to the more commonly used insecticides and to the limited area in which *Aedes aegypti* mosquitoes circulate (100-200 yards from where the larvae emerge). *Aedes aegypti* mosquitoes also tend to favor house interiors where spraying/fogging is not practical. Strategic placement of several low-cost autocidal gravid ovitraps (which mimic breeding sites) in house interiors can reduce the *Aedes aegypti* population by about 50%.

Further contributing to the urgency of the pandemic, the El Niño weather phenomenon in 2015-2016 brought warmer temperatures and moisture to the regions most affected by Zika virus, and with that weather pattern, a potential increase in the population of *Aedes aegypti* mosquitoes.

OX513A Genetically Engineered Mosquitoes

In this environment, the creation of a genetically engineered (GE) *Aedes aegypti* mosquito by the British firm Oxitec in 2002, known as OX513A, is generating significant interest among public health officials. Developed originally to suppress the incidence of dengue fever, OX513A is now regarded as a promising technology to reduce the incidence of Zika virus transmission by reducing the population of mosquitoes. Oxitec is owned by Maryland-based Intrexon Corporation.

Oxitec’s OX513A are mosquitoes that have been genetically engineered with a dominant transgene that produces a lethal protein that ties up the transcriptional machinery in the cells. The gene is passed on to the mosquito’s offspring so that they die before reaching adulthood. Each OX513A mosquito is also engineered with a fluorescent marker that permits effective monitoring of larvae to assess the effectiveness of control. The fluorescent marker is visible using a specialist microscope in all

OX5213A offspring. The OX513A male mosquitoes, which do not bite or spread the virus are reared in laboratories and then released to mate with wild *Aedes aegypti* female mosquitoes.

Since only the females bite, releasing millions of OX513A males to mate with wild females, who would then produce larvae that die, could reduce the population of *Aedes aegypti* mosquitoes and, thereby, reduce the risk of Zika virus transmission to humans. This approach targets only the *Aedes aegypti* mosquitoes that can spread disease, because the OX513A males produce offspring only with their own species.

OX513A mosquitoes can be bred for generations and multiplied. Adult males with Oxitec's lethal transgene survive in the environment for only about a week. The OX513A mosquitoes also have the advantage of repressing populations of *Aedes aegypti* mosquitoes that carry insecticide resistance genes. According to peer-reviewed studies, of the more than 150 million OX513A mosquitoes released to date in field trials, no effects on other species have been observed, no evolution of resistance to the lethal transgene has been seen, and there has been no mating with non-target mosquitoes detected.

According to peer-reviewed studies, releases of OX513A males in the Cayman Islands in 2010 led to 90% suppression of the wild *Aedes aegypti* population. Isolated field demonstrations in Brazil have also achieved similarly successful results after six to nine months. In 2011, Oxitec conducted a sustained series of OX513A field releases in Itaberaba, a suburb of Juazeiro in the semi-arid northeast region of Brazil. Normal mosquito control continued during the field study as public health agents continued to destroy breeding sites and treat homes with larvicide. According to peer-reviewed studies, the *Aedes aegypti* population was reduced by over 90% in a year based on data from multiple locations.

Brazil's National Biosafety Commission approved country-wide use of OX513A in 2014, making Brazil the first country to approve the commercial use of the OX513A mosquitoes. A year later, the OX513A mosquitoes were released in the Brazilian city of Piracicaba and, in January 2016, announced plans to scale up the program and expand their OX513A production capacity. Panama also field tested the OX513A mosquitoes in 2014.

In April 2016, Brazil's National Health Surveillance Agency announced that it would grant Oxitec a temporary registration to deploy the genetically engineered mosquitoes throughout the country. The agency is now developing new rules to provide Brazil with a regulatory framework to address the OX513A mosquitoes, as well as other genetically engineered insects that may be developed in the future. WHO has issued a positive recommendation in support of the OX513A mosquitoes. In addition, the Pan-American Health Organization has also announced that it will provide technical support for countries that wish to implement the OX513A mosquitoes.

Some researchers have raised questions about the OX513A mosquitoes' fitness for breeding, and whether the males could evolve resistance to the lethal gene. Males are mechanically sorted in the laboratory, resulting in less than

0.01% females accidentally released. This could lead to a small but temporary increase in the number of biting mosquitoes. A possible solution currently being explored by Oxitec and the University of California-Irvine is a genetic modification to make females unable to fly. If successful, this approach would make these 0.01% released females unable to mate or bite.

U.S. Environmental Assessment of GE Mosquitoes

Oxitec applied for a permit to field test the OX513A mosquitoes in the Florida Keys in 2011. On April 3, 2012, the Key West City Commission passed a resolution objecting to the release of the OX513A mosquitoes. The U.S. Food and Drug Administration Center for Veterinary Medicine (FDA-CVM) led an examination of OX513A under its Investigational New Animal Drug regulatory process. FDA's review team was comprised of experts from the CVM, the CDC, and the U.S. Environmental Protection Agency. On March 11, 2016, FDA published its Preliminary Finding of No Significant Impact (FONSI) for proposed field testing the OX513A mosquito in the Florida Keys. After a 60-day comment period, FDA published its final EA and associated FONSI on August 5, 2016, which allows Oxitec to begin field trials.

This review team examined Oxitec's and independent collaborators published evidence from their Brazil and Cayman Islands field trials and other data on safety studies. FDA found that the probability that the release of OX513A male mosquitoes would result in toxic or allergenic effects in humans or other animals is negligible. "Almost all of the OX513A mosquitoes released for the investigational field trial will be male, and male mosquitoes do not bite humans or other animals. They are therefore not expected to have any direct impacts on human or animal health." FDA also found that the "probability that the release or rearing of OX513A mosquitoes would have adverse impacts on the ecosystem is largely negligible" and that the "probability of OX513A mosquitoes and their progeny persisting and establishing at the proposed trial site or spreading beyond its boundaries is extremely unlikely."

With the FONSI, Oxitec plans to begin field testing in Key Haven, Florida, in collaboration with the Florida Keys Mosquito Control District. However, the Florida Keys Environmental Coalition and others have petitioned the Florida Commissioner of Agriculture and Consumer Services to halt any field testing of the OX513A mosquitoes in the state. As of August 2016, the Florida Keys Mosquito Control Board has not approved the trial release, instead putting it on the November ballot as a non-binding referendum. Oxitec has asked FDA to consider releasing the mosquitoes on an emergency basis elsewhere.

Congress has oversight of FDA regulations and appropriations. Annual appropriations for the CDC are also under congressional authority. If the United States supports stepped-up international efforts to reduce the incidence of Zika transmission, appropriations to the United States Agency for International Development could play an important role.

Tadlock Cowan, tcowan@crs.loc.gov, 7-7600

IF10401