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Updated September 8, 2020

# Genetically Engineered Mosquitoes: A Vector Control Technology for Reducing 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.

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) confirmed that Zika-infected pregnant women were at risk for delivering babies with microcephaly, a birth defect of the cerebral cortex where a baby's head is smaller than expected based on sex and age.

Zika virus triggered outbreaks in 33 countries and territories, although confirmed cases linking Zika virus to babies with birth defects were initially seen in only Brazil and French Polynesia. Several countries 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 in the U.S. territories of Puerto Rico, the U.S. Virgin Islands, and American Samoa. In April 2016, over 400 cases in the United States were 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. As of 2019, no cases of local transmission of Zika virus have been confirmed in the contiguous United States and its territories.

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.

No vaccine exists for Zika, although the U.S. Food and Drug Administration (FDA) has approved several diagnostic tests for detecting Zika virus antibodies. Mosquito control and bite prevention are the first lines of defense. Conventional control methods such as truck and aerial spraying are only moderately effective (30%-50%) in reducing mosquito populations, in part owing to the resistance the mosquitoes have developed to common 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%.

## 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, generated significant interest among public health officials. Developed originally to suppress the incidence of dengue fever, OX513A was seen 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 mosquitoes were engineered with a synthetic genetic sequence encoding a tetracycline-repressible transcriptional activator (tTAV) that leads to the death of most of the mosquitoes carrying the trait. If tetracycline is present (as it is during the mosquito rearing in the laboratory), then tTAV is repressed and the larvae can develop and reach adulthood. When the gene is passed on to the mosquito's offspring, they die before reaching adulthood. Each mosquito is also engineered with a fluorescent marker permitting effective monitoring of larvae to assess the effectiveness of control. The fluorescent marker is visible in all OX5213A offspring using a special microscope. The 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 would then produce larvae that die. This would reduce the population of *Aedes aegypti* mosquitoes, thereby, reducing 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.

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 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, release of OX513A males in the Cayman Islands in 2010 led to 90% suppression of the wild *Aedes aegypti* population. Isolated field demonstrations in Brazil achieved similarly successful results after six to nine months. In 2011, Oxitec conducted a sustained series of OX513A field releases in Itaberaba, 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, Oxitec announced plans to scale up the program and expand its OX513A production capacity. Panama also field tested the OX513A mosquitoes in 2014.

In 2016, Brazil's National Health Surveillance Agency granted Oxitec a temporary registration to deploy the GE mosquitoes throughout the country. WHO issued a positive recommendation in support of the OX513A mosquitoes. In addition, the Pan-American Health Organization subsequently provided technical support for countries that wish to implement the OX513A mosquitoes.

Some researchers 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 accidently released. This could lead to a small but temporary increase in the number of biting mosquitoes.

## Environmental Assessment of GE Mosquitoes

Oxitec applied for an Experimental Use Permit (EUP) to field test the OX513A mosquitoes in the Florida Keys in 2011. In 2012, the Key West City Commission passed a resolution objecting to the release of the OX513A mosquitoes. The FDA Center for Veterinary Medicine conducted an Environmental Assessment of OX513A under its Investigational New Animal Drug regulatory process. In 2016, FDA published its Preliminary Finding of No Significant Impact (FONSI) for proposed field testing the OX513A. After a 60-day comment period, FDA published its final Environmental Assessment and associated FONSI, which allowed 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 the probability negligible that the release of OX513A male mosquitoes would result in toxic or allergenic effects in humans or other animals. "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 planned field testing in Key Haven, FL, in collaboration with the Florida Keys Mosquito Control District. However, the Florida Keys Environmental Coalition and others petitioned the Florida Commissioner of Agriculture and Consumer Services to halt any field testing of the OX513A mosquitoes in the state. The Florida Keys Mosquito Control Board did not approve the trial release, instead putting it on a November 2016 ballot as a non-binding referendum. The Key Haven neighborhood rejected the proposed release.

## Oxitec's Second-Generation GE Mosquito

With local opposition to the planned release, Oxitec withdrew its application for an EUP. Oxitec researchers subsequently developed a second-generation GE mosquito. EPA granted an EUP to Oxitec in May 2020 to test the efficacy of this second-generation GE mosquito expressing the tTAV-OX5034 protein. EPA regulates the GE mosquito as a biopesticide under the Federal Insecticide, Fungicide, and Rodenticide Act (7 U.S.C §136c).

Unlike the first-generation mosquito, eggs of the second-generation mosquito produce only males, thus reducing the risk of accidental female release. Instead of raising modified mosquitoes to adulthood before releasing them into the wild, the second-generation mosquitoes can be distributed as eggs in boxes. A box containing eggs can be placed in a back yard and filled with water, after which the males hatch. When the male mosquitoes emerge, they fly away into the neighborhood to mate. The previous proposed method required adult mosquitoes to be raised near the test site and then released via the use of a specially equipped van. With the first generation, released males mated with a female in the wild, and all of the offspring—male and female—would die. With the second generation, only the females are targeted. Male progeny survive, carrying the lethal gene to its offspring, which are male only.

In June, the Center for Food Safety (CFS) filed a notice of intent to sue unless EPA revokes Oxitec's EUP to test the second-generation mosquito in Monroe County, FL, and Harris County, TX. CFS's notice charges that the EUP is a violation of Section 7 of the Endangered Species Act.

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## Disclaimer