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SHE: The Applications and Limitations of Genetically Modified *Aedes aegypti* Mosquitoes as a Way of Preventing the Spread of Mosquito-Borne Diseases

Introduction

Mosquito-borne diseases (MBD) such as West Nile virus, dengue, Zika, and yellow fever are the causes of more than one million deaths per year worldwide, infecting nearly seven-hundred million people (WMP, 2021). These diseases are mainly transmitted by the *Aedes aegypti* mosquito which originated in Africa and have spread to tropical and subtropical regions of the world (CDC, 2020). As female mosquitoes feed on blood to support egg development, pathogens found in the vertebrate's blood can infect the mosquito, allowing for transmission into other vertebrates. The control of MBDs mainly rely on health-control interventions such as vaccinations and drug treatments, and the control of vector populations via insecticides. (NIOSH, 2016). Genetic modification is a recent technology that is paving the way for the control of MBDs, modifying vectors to become resistant or sterile (Rosenberg and Beard, 2011). This report will discuss the applications and limitations of genetically modified Aedes aegypti mosquitoes.

Scientific Background

To combat these epidemics, researchers have developed two strategies using genetically modified mosquitoes (GMM). *Population replacement* replaces wild mosquitoes with GMMs. For example, the wMel strain of *Wolbachia pipientis*, a genus of bacteria, decreases the transmission of dengue in *A.aegypti* (Yen and Failloux, 2020). *Population suppression*, however, reduces the entire population by using gene drives of novel traits, which, as defined by the *Convention on Biological Diversity* (CBD, 2021), are characteristics which have been introduced to modify an organism, resulting in a genetic change. Gene drives do not have to be genes as every organism exists with not only their own genomes, but the genomes of their associated microorganisms, known as the "hologenome". This gene drive biases inheritance by increasing the prevalence of genetic elements, making the gene more likely to be passed on. The offspring of GMM matings inherit this trait and while females die, males survive and continue to pass on the trait.

Application + Impacts

The use of GMMs can reduce the spread of MBDs. *Wolbachia* infects nearly 70% of insect species, although harmless to humans and the environment. Many mosquitoes carry *Wolbachia,* however, *A.aegypti* mosquitoes do not. Researchers from the World Mosquito Program (WMP) discovered that the application of *Wolbachia* into *A.aegypti* results in the bacteria competing with MBD pathogens. The WMP have been breeding Wolbachia-carrying mosquitos and partnering with local communities, releasing them into areas most affected by MBDs. Since 2011, these modified mosquitoes have been released in North Queensland and, where high levels of them are present, no evidence of dengue transmission has been recorded (WMP, 2020). This is an example of the 'Population Replacement' approach and despite being marketed as a 'non-GM strategy', it is transferred from the fruit fly, whereby Wolbachia naturally infect, and into the mosquitoes. (Rasgon, 2018) By decreasing the number of susceptible vectors, fewer people contract the disease, meaning that other methods of mosquito-control will be needed less. This may impact the insecticide industry, however, GMM are not yet present in every

location where MBDs are. With a decrease in mosquito-borne disease cases, more people will be able to remain in their jobs, providing for themselves and families, as well as spending more time outside, without the concern of contracting a MBD. Countries with fewer absent workers due to MBDs ultimately lead to hospital facilities being more available, and a higher level of work efficiency. *Mosqguide* is a project funded by the WHO that guides the deployment of GMMs, having already developed risk assessments in the UK, Brazil, Thailand, and Kenya. This is to improve international communications to avoid cultural, social, and environmental concerns. (Mumford et al., 2009).

Oxitec, a biotechnology company, has created sterile mosquitoes which carry a gene that is safe for males but lethal to females, as males do not bite, therefore, cannot transmit diseases. These GMMs (OX513A) are altered to produce the protein tTAV which inhibits egg development (Strode, Beardsley and Bonetta, 2018). Larvae that produce the protein die before reaching maturity, however, if treated with the antibiotic tetracycline, they are able to develop normally. Ultimately, the offspring of GMM and wild mosquitoes will inherit the lethality gene which will then cause them to die in the absence of tetracycline. This was conducted in Brazil for a year and reduced the *A.aegypti* population by 96% (Evans et al., 2019), which meant that there were fewer cases of MBDs. This allowed civilians to remain in their occupations to support their families, whilst increasing the overall lifespan of Brazilians. (LaMotte, 2016). Since 2016, Oxitec's mosquito-breeding factory has been producing up to 60 million mosquitos per week in Piracicaba, after having achieved 83%-98% suppression in their 4-year program (Halliday, 2021). Since there is a lower number of mosquito population, the use of insecticides will be decreased, resulting in a positive impact on the environment as many sprays contain atrazine, malathion, and diazinon, which are harmful to the environment and other non-targeted organisms. Insecticides can contaminate water systems through its runoff, which can then be transported to other unintended locations. Soil that has been heavily treated with insecticides can cause beneficial soil microorganisms to degrade, similar to human overuse of antibiotics (Aktar, Sengupta and Chowdhury, 2009). Ultimately, the contamination of the environment can also produce both acute and chronic effects in humans such as diarrhoea, rashes, blindness, nausea, and death. (Nicolopoulous-Stamati et al., 2016))

Limitation

As with any GMO, there are often ethical concerns and controversies. A significant concern is the welfare of subjects who are not enrolled in the study during field trials. The insect's mobility allows for it to move out of target locations, which may cause unwanted interruptions in other locations. To combat this, field trials should be facilitated in isolated locations where the disease is a public health concern and that community members and leaders are in agreement to the trial (Resnik, 2014). Additionally, 4% of Oxitec's OX513A mosquitoes will survive despite the lack of tetracycline, which may raise concerns regarding the patent holders' power if the mosquitoes are to establish beyond the target area.

The new technology was also met with some resistance from communities. In 2016, Oxitec proposed a trial in the Florida Keys which resulted in over 155,000 signatures from people who were opposed to the release of the GMO. (Palmer, 2015) However, these perspectives, such as Key West resident Mila de Mier, derived from a lack of clear information. They expressed that their anxiety had stemmed from the unknown effects of a bite from a GMM although its likelihood is very low as only male GMMs were released, causing none of them to be capable of such transmission. Additionally, the self-limiting gene is

passed on through sexual reproduction, making it impossible for a bird, for example, to be affected by consuming the GMM.

The cost of the patented GMM also raises another ethical issue. Oxitec's two-year trial in Piracicaba, whose population was around 391,450, costed an estimate of approximately US$1.1 million. However, this estimate seems considerably low, in comparison to a recent suggestion that the cost for an urban population of 50,000 equates to US$1.9 million in the first year and US$394,000 for each year afterwards. (Boëte, 2018) Despite different situations, and severity of MBDs in the area, the discrepancy is concerning and may impact countries with restricted public health budgets.

Conclusion

Again, GMOs are still considered a recent technology which can cause unpredictable effects, although in the near future, it is likely that GMMs will be present in all countries affected by WBDs as thorough precautions would have already taken place. The GMO has already been shown effective through the thorough trialling process and proven safe. Resistance and potential concerns that the technology was initially met with were diminished by research and precautions that had taken place prior to the trialling process, including the GMM's ecological impact. By removing the amount of potential vectors, the transmission of disease is taken away, as well as the need for insecticides and funding for preventative measures.

Word Count: 1351

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