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The optimal socialization of modified mosquitoes to combat infectious disease

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The Optimal Socialization of Modified Mosquitoes to Combat Infectious Disease

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TABLE OF CONTENTS

INTRODUCTION

Female mosquitoes contribute heavily to global disease burden through their transmission of various illnesses, such as Zika Virus disease, dengue fever, and malaria. While these diseases continue to disproportionately affect marginalized countries at alarming rates, many of the current methods used to control these mosquito populations are failing. Indoor residual spraying has proven harmful to human, animal, and ecological health, while individuals who are provided with insecticide-treated bed nets often do not utilize them, for reasons including heat, discomfort, and feelings that net use is futile. These failures beg the introduction of a new, effective vector control method – biologically modified mosquitoes. There exist various mechanisms of modification; some of which prevent the disease agent from fully replicating within the mosquitoes, while others inhibit mosquito reproduction processes, thereby reducing mosquito populations. Regardless of the method used, the overarching biological modification process prevents human contraction of the disease carried by the respective mosquito.

While this alternative strategy has been researched for efficacy, there are evident social and ethical concerns regarding the release of these modified vectors. In many cases, communities lack a clear understanding of the technology, its scientific workings, and its known effects. Public perceptions oftentimes include concerns regarding unintended and unknown consequences. As said by James Lavery, an international leader in global health, "Stories trump data and relationships trump stories. Scientists... believe that their data should prevail at all times because it's science, but we know from policy that that's not the way it works." [1]If a technology

[1] Shastri, Devi. "Outbreak: Mosquito Battle Gets Political." *Projects Server Index - Milwaukee Journal Sentinel*, 5 October 2017.

is not accepted by the society that it is being implemented into, regardless of how lifesaving it may be, it cannot serve its intended function. Without being integrated into the preexisting structure of the target society, this technology can be undermined by innate beliefs and fears. For example, consider the atmosphere surrounding the anti-vaccine controversy. Despite the doctor behind the fraudulent vaccine-autism link losing his medical license and extensive scientific evidence denying the association, there are still people today who are against vaccinating their children due to an intrinsic fear of effects. In ways, this parallels the innate distaste that some individuals have against modifying entities, such as food or animals. In the wake of fear concerning the modification of living animals, how can this life-altering technology be socialized into communities that are heavily suffering from mosquito-borne diseases?

Because they are created by humans, modified mosquitoes can be classified as a form of artifact by the standards of Langdon Winner in *Do Artifacts Have Politics?* [2] In his work, he asserts that artifacts can not only have politics themselves but can also be strongly compatible with particular sociological systems. The socialization of these insects has proved to be compatible with networks that are able to effectively communicate information from higher to lower levels. In this way, individuals become appropriately informed about the vector technology, its purpose, and the possible realm of unintended consequences. For a technology to be desired within a society, it must fulfill four social requirements: alignment with a society's previous practices, addressing of problems felt by the target society, innovativeness, and societal norms.[3] Once a technology is desired by a community, its actual adoption into the society depends heavily on four main facets: the piece of technology itself, time, communication channels, and the larger

[2] Winner, Langdon. "Do Artifacts Have Politics?" 1980.
[3] Rogers, Everett M. *Diffusion of Innovations*. New York: Free Press, 2003.

social system. If these aspects are effectively in sync, the adoption process will begin. This takes place throughout a five-step procedure, consisting of knowledge, persuasion, decision, implementation, and confirmation stages. In the initial knowledge phase, individuals within the social system amass information concerning the technology.[4] These people form opinions in favor of, or against, the innovation, then, reaching the decision step, actively adopt or reject the technology at hand. The innovation is employed and utilized by the social system throughout implementation and is evaluated thoroughly during the final confirmation phase.

Rogers contends that the technology can be accepted in five social group stages. First, the new technology is accepted by the innovators (the initial 2.5% of the population), followed by the early adopters (13.5%), the early majority (34%), the late majority (34%), and finally, laggards (the remaining 16%). Though no technology will ever reach the entirety of a single society, once the innovation reaches the point of critical mass, it is able to successfully self-sustain. While a technology may fail during the societal adoption phase, it may always be later adopted.

Using the ideologies of both Winner and Rogers, this thesis analyzes the factors that have influenced the rejections and acceptances of modified mosquitoes released for combating disease in various settings. Various forms of modification embody slightly different politics, causing distinct issues in their obstacles for social acceptance. Despite these differences, any form of modified vector must be compatible with the social system to which they are being implemented. A given target society must not only feel a collective need for such an intervention, but also have the communication channels and social network for information regarding the technology to

[4] Rogers, Everett M. *Diffusion of Innovations*. New York: Free Press, 2003.

become widely spread. The effects of varying support levels, community engagement, and knowledge communication are examined through cases studies from the Cayman Islands, Australia, and Florida. This work analyzes these cases studies in order to create a strategical application for future socialization of the vectors. In its last chapter, this thesis provides an intricate strategy for optimally integrating modified mosquitoes into a society where citizens suffer greatly from mosquito-borne diseases but have limited knowledge or fear of modified insects. The approach is adapted specifically to the geographical, economic, social, and epidemiological landscape of Warri, Nigeria as the initial target setting for such a release.

CHRONOLOGICAL TIMELINE:

2009: First known global release of genetically modified mosquitoes in the Cayman Islands (OX513A strain by Oxitec), conducted without public knowledge

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2010: Oxitec's formal announcement of the Cayman Islands trial

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2011: Oxitec's risk assessment and results of the Cayman Islands trial released; Oxitec instigates another release without public knowledge in Malaysia

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2014: Successful release of Wolbachia-infected mosquitoes by the World Mosquito Program in North Queensland, Australia following a Public Acceptance Model

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2014: Oxitec release of OX513A strain in Panama; asserts to have fully engaged community without published evidence to back claim

•

2016: Release of Genetically Modified (OX513A strain) mosquitoes in Key West, Florida voted down by community members

CHAPTER 1: Mosquitoes, Mosquito-Borne Diseases, and Mosquito Modification as a Vector-Control Intervention Strategy

Although perhaps surprising, female mosquitoes are considered by many individuals to be the deadliest animal on the planet. The ability to efficiently transmit fatal diseases between people allows these mosquito-vectors to cause several million deaths and hundreds of millions of additional illnesses annually.[5] These vectors contribute to the global spread of infectious diseases such as Zika virus disease, dengue fever, and malaria. The burden of such diseases weighs disproportionally on less socially and economically developed nations, which often do not have sufficient economic capital, public health infrastructure, or community support to halt these epidemics. Many of the affected areas also provide the correct climate and environmental factors that accelerate mosquito reproduction. Higher temperatures provide not only suitable habitats for the carriers of these agents, the *Aedes aegypti* and *Anopheles gambiae* mosquitoes, but also support the replication of the viruses or parasites within their respective host. While the vectors hibernate through the winter in cooler climates, tropical regions allow year-long activity. The warmer conditions perpetuate the survival of these mosquitos, sustaining an alarmingly high incidence of various mosquito-borne diseases. Global climate change may create additional mosquito habitats, worsening potential disease threats if interventions are not made.

[5] "World Health Report: Executive Summary." *World Health Organization*. 2018.

I. Disease Profiles: Zika Virus Disease, Dengue Fever, and Malaria

Zika Virus Disease

The Zika virus disease (ZVD) is caused by a single-stranded RNA *Flavivirus*, a virus that is transmitted to humans via *A. aegypti* mosquito bites.[6] While most Zika virus infections are asymptotic, some cases may show acute fever, skin rashes, joint and muscle pain, and pink eye from two to seven days after infection. In most cases, these symptoms are mild, lasting between a few days and a week. The fatality rates of ZVD itself is low; however, it has severe implications for pregnant women and their children. ZVD is associated with many other severe neurological disorders and fetal defects. Guillain-Barré syndrome (GBS), a rare disorder affecting the nervous system, has been highly suspected to follow Zika infections. GBS causes an individual's immune system to misguidedly attack parts of the nervous system surrounding the brain and spinal cord, resulting in potentially irreversible nerve damage.[7] About 30% of individuals with GBS never fully recover, as its sudden onset results in severe pain, muscle weakness, and paralysis. Contracting ZVD during pregnancy is also a confirmed cause of various fetal brain developmental defects, including microcephaly. This lifelong, incurable condition prevents babies' brains from fully developing throughout pregnancy, which can contribute to other health complications such as seizures, hearing and vision issues, delays in child development, and intellectual disabilities.[8] Both of these conditions, stemming from contraction of the ZVD, can result in lifelong health complications and a lowered quality of life.

[6] U.S. Department of Health & Human Services. "Zika Virus." *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 13 December 2017.
[7] "Guillain-Barré Syndrome Fact Sheet." *National Institute of Neurological Disorders and Stroke*, U.S. Department of Health and Human Services, 6 July 2018.
[8] U.S. Department of Health & Human Services. "Facts about Microcephaly." *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 21 November 2017.

Once a human is infected with the Zika virus, female *A. aegypti* are able to harvest its agent through their bites. Eight to ten days after the vector has contracted the virus, new hosts can be infected with the disease.[9] Upon biting a different individual, the infected vector is able to transmit the agent through injecting saliva during its blood meals. While infected humans and *A. aegypti* are the primary carriers and transmitters of the virus, it has also been transmitted via sexual intercourse, perinatal transmission, and blood transfusions.[10] No effective vaccine, reactive treatment, or cure currently exists for ZVD, emphasizing the importance of preventing ZVD contraction. The Zika virus has asserted global presence in recent years, with 53 countries reporting first outbreaks only after 2015.[11] Because it is unlikely for the *A. aegypti* to live at altitudes exceeding 6,500 feet, areas across the globe with higher elevations are unlikely to experience ZVD. In 2018, the prevalence of ZVD is most prominent in the majority of Central and South America, central Africa, southern Asia, and the Pacific Islands.[12]

Dengue Fever

Dengue is the most common vector-borne viral disease, causing infection in human hosts by four virus serotypes – DENV 1, DENV 2, DENV 3, and DENV 4 – which are spread primarily by infected *A. aegypti*.[13] Similarly to the ZVD agent, these dengue viruses are also single-stranded RNA *Flaviviruses*.[14] While approximately half of dengue fever (DF) cases do not show symptoms, the symptomatic cases result in a fever between two and seven days after infection.

[9] "Zika Virus Transmission." *Zika Virus Net.* 2018.
[10] U.S. Department of Health & Human Services. "Zika Virus." *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 11 December 2018.
[11] "Emergencies: Zika Situation Report." *World Health Organization*. 25 August 2016.
[12] "World Map of Areas with Risk of Zika." *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 5 September 2018.
[13] "Epidemiology: Dengue." *Centers for Disease Control and Prevention*. 28 July 2010.
[14] U.S. Department of Health & Human Services. "Dengue." *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 6 September 2014.

The replication of the virus inside of the body during this time leads to high fevers and the development of other symptoms that resemble influenza, such as skin rashes, severe headaches, vomiting, and join and muscle pain.[15] These flu-like symptoms of DF should fade after a week. The onset of worse symptoms, such as intense migraines, persistent and bloody vomit, and excessive fatigue, may signal dengue hemorrhagic fever (DHF), a more severe form of the disease. DHF causes the leakage and accumulation of plasma, blood, and other fluids within the body, as well as internal bleeding and organ impairment that can lead to death.[16] Once symptoms begin to appear in an infected individual, the virus has replicated sufficiently for transmission.[17] Eight to twelve days after *A. aegypti* have contracted the dengue virus, incubation is finished, meaning that the virus has replicated enough to infect humans.[18] Infected *A. aegypti* are responsible for a vast majority of DF transmission, but the virus can also be spread on rare occasions through infected blood transfusions, infected organ and tissue transplants, and perinatal transmission. While one vaccine, Dengvaxia, protects against dengue virus contraction, the World Health Organization has warned against administering the vaccine to anyone who has not previously been infected with dengue.[19] There is no specific reactive treatment for DF or DHF once transmission has occurred.[20] However, contraction of one dengue virus serotypes results in lifelong immunity against the given serotype. Despite this limited immunity, a person is still susceptible to infection by the other variations of the virus. These significantly increase the chances of contracting severe DHF when the individual has already had a prior case of DF.

[15] "Dengue Control." *World Health Organization*, World Health Organization, 3 January 2017.
[16] Ibid.
[17] U.S. Department of Health & Human Services. "Clinical Guidance." *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 6 September 2014.
[18] "Dengue and Severe Dengue." *World Health Organization*. 13 September 2018.
[19] "WHO Advises Dengvaxia be used only in people previously infected with dengue." *Essential medicines and health products*, World Health Organization. 13 December 2017.
[20] "Dengue and Severe Dengue." *World Health Organization*. 13 September 2018.

Within the past three decades, many countries have reported their first outbreaks of dengue, while the global incidence of the disease has increased by over thirty times.[21] This disease burden has grown substantially since 1970, when only nine countries experienced dengue fever epidemics. In 2018, dengue is endemic in more than 100 countries, causing approximately 20 million cases a year, while threatening infection to over two and a half billion people.[22]

More than half of the human population lives in areas where *A. aegypti* exist, which spreads both the Zika virus and dengue virus. While coinfection of mosquitoes is rare, studies have shown the possibility of one vector to carry two viruses simultaneously.[23] Therefore, *A. aegypti* are capable of infecting humans with both Zika virus and dengue virus via one single blood meal. Once infected with either or both of the diseases, the vector remains a transmission threat to humans for the rest of its lifespan.[24] This species bites both during the day and at night, making it a constant threat to human health. Tropical areas often experience heightened risk periods of dengue, as seasonal bouts of rainfall provide prime conditions for vector reproduction.

Malaria

Five species of malaria parasites are capable of infecting humans and causing the disease - *Plasmodium vivax, Plasmodium ovale, Plasmodium malariae, Plasmodium knowlesi*, and the most threatening, *Plasmodium falciparum*.[25] Malaria can range between being completely asymptotic and being fatal. A typical case of malaria can cause the patient to undergo a cold

[21] "Mosquito-borne Diseases: Neglected Tropical Diseases, Vector Ecology and Management (VEM)." *World Health Organization*. 2018.
[22] "Dengue and Severe Dengue." *World Health Organization*. 13 September 2018.
[23] "Can a Mosquito Transmit More Than One Disease." *World Health Organization*. September 2016.
[24] "Dengue Transmission." *Scitable: Collaborative Learning Space for Science*. 2018.
[25] "Malaria: Malaria Parasites." *Centers for Disease Control and Prevention*. 29 March 2018.

stage, a hot stage that may include vomiting and seizures, and a final sweating stage for a six to ten-hour period.[26] If an infection becomes severe malaria, the patient may experience the failure of multiple organs, seizures or coma, and many other blood or metabolism-related complications. Even after symptoms fade, symptomatic relapses may continue for months or years.

Found across the world, *P. falciparum* is capable of rapid multiplication within the human bloodstream, inducing severe onsets of the disease. It is spread most effectively by *A. gambiae*, which has a longer lifespan than most other mosquito species, allowing for more full development of the parasite and associated increases in successful transmission rates.[27] Its proclivity for targeting humans, as opposed to animals, as blood meal sources, exacerbates this disease spread. Following the incubation period of at least seven days, the *A. gambiae* is capable of injecting malaria parasites into the next individual.[28] Similarly to dengue, malaria can also be spread through infected blood transfusions, infected organ and tissue transplants, and perinatal transmission on rare occasions. Utilizing antimalarial drugs can stifle reproduction of the parasite within the bloodstream, thereby preventing the development of malaria, but increasing resistance undermines the sustainability of this method. Artemisinin-based combination therapy, which combines two types of drugs and has minimal contributions to resistance, is available as a form of treatment for the *P. falciparum* strain of malaria.[29]

[26] U.S. Department of Health & Human Services. "Malaria: Disease" *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 8 January 2019.
[27] "Malaria: Key Facts." *World Health Organization*. 19 November 2018.
[28] U.S. Department of Health & Human Services. "Malaria: Frequently Asked Questions (FAQs)." *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 8 January 2019.
[29] "Malaria Treatment: Artemisinin-based Combination Therapy." *Malaria Consortium*. 2018.

Malaria is now endemic in over 90 countries, posing potential risk to approximately 40% of the world's population.[30] It caused about 445,000 deaths in 2016, which constitutes a large portion of all mosquito-borne disease-related deaths from the year.[31] Africa alone faces an overwhelming proportion of the disease's incidence, experiencing 90% of all global malaria cases and 91% of malaria-related deaths. Malaria transmission is seasonal in numerous regions around the globe, due to fluctuating environmental factors that influence *A. gambiae* populations.

II. Mosquito Transmission and Reproduction Mechanisms

Only female mosquitoes are capable of the transmission mechanism that spreads such diseases. The females of certain mosquito species are motivated to bite humans or animals as a method of obtaining protein and iron for the production of eggs.[32] Without the need to provide nutrients for offspring, males lack the double-tubed proboscis which allows females to bite into the host and extract blood meals, instead feeding on flower nectar.[33] Unique cpA neurons allow these female mosquitoes to find their next source of protein more efficiently than most other insects.[34] This cell has a receptor capable of detecting carbon dioxide in the atmosphere, allowing the vectors to efficiently scope out humans as they exhale. Natural human skin odor also attracts mosquitoes that are searching for blood meals, making humans very susceptible targets to disease transmission by this insect. Upon biting, the female injects saliva via one of the proboscis' tubes in order to slightly numb the prey's senses, as to not be detected and killed while feeding. This saliva contains active anticoagulant, which thins blood and allows it to flow freely into the

[30] "World Health Report: Executive Summary of Insect-borne Diseases." *World Health Organization*. 2018.
[31] "Malaria: Key Facts." *World Health Organization*. 19 November 2018.
[32] "How Do Mosquitoes Transmit Infectious Diseases?" *American Academy of Pediatrics*. 34-6. June 2013.
[33] "About Mosquitoes: Mosquito Bites." *Mosquito World*. 2018.
[34] "How Mosquitoes Detect People." *National Institutes of Health*. 16 December 2013.

insect. Given this human is infected with disease, the mosquito may contract any present viruses or parasites, which are transmitted to the next target via the same feeding process.

The egg production and laying commence once the female mosquito has acquired sufficient protein. Both the *A. aegypti* and *A. gambiae* mosquito life cycles require still-standing water as a site for egg-laying. These insects not only utilize large bodies of water, such as marshes and swamps, but can also capitalize on even tiny containers or puddles of collected rainwater. Because of this breeding phenomenon, these insects have often been characterized as 'urban mosquitoes', existing close to domestic households. Both genera lay eggs singly, rather than connected in float-like structures.[35] These generally hatch into larvae within 48 hours of being placed onto the water. From the larval stage onward, biological and ecological differences between the two species contribute to some differences in the reproduction cycle. Female *A. aegypti* mosquitoes lay around 100 eggs at once on the surface of the water. These can survive for up to eight months without the presence of water, even in colder climates.[36] When the laid eggs become covered with water, most generally from rainfall, the larvae emerge and begin consuming microorganisms from the water. Following three molts, the mosquito becomes a pupa, developing adult-like features. Adult *A. aegypti* travel only short distances, accumulating less than 500 meters throughout its life.[37] Without this traveling ability, they prefer to live in close proximity to humans, giving them efficient access to blood meals. While the life cycle normally lasts between eight and ten days, an adult lifetime can last between two weeks to a month, depending on the surrounding environment.

[35] "Mosquito Info: Life Cycle." *The American Mosquito Control Association*." 2018.
[36] "Mosquito Life Cycle: *Aedes Aegypti*." *Centers for Disease Control and Prevention*. PDF. 31 December 2013.
[37] "FAQ." *World Mosquito Program*. 2018.

Meanwhile, the female *A. gambiae* lays between fifty and 200 eggs at a time, which have unique 'floats' on either side to help the egg remain at the water's surface.[38] These eggs are susceptible to drying and can survive only two or three weeks in cooler environments without hatching. *Anopheles* larvae do not have the respiratory siphon that other mosquito larvae possess, which acts as a breathing tube, and therefore must regularly come to the surface in order to receive air through its abdominal segments. These larvae also feed on bacteria in the water. After becoming pupae, the mosquitoes develop into adults in 10 to 14 days. Males only survive for about a week, while the females do not usually live longer than two weeks. Like the *A. aegypti* genus, their survival relies on environmental conditions, such as temperature and relative humidity, as well as success in establishing a food source.

III. Past Disease Control Intervention Strategies and Introduction to Genetic Modification

Two major intervention strategies have been implemented in the past in order to combat the fatal spread of mosquito-borne illnesses. Currently, the most dominant method of preventing malaria contraction is insecticide-treated bed nets.[39] When changing environmental conditions and temperatures threaten to shorten mosquito lifespans, *A. aegypti* are able to find indoors spaces for resting and breeding purposes.[40] The *A. gambiae* species typically feeds from dusk until dawn, also commonly resting both indoor and outdoor.[41] This proclivity optimizes biting humans while they are asleep, indoors, at night. Therefore, structural barriers are necessary in order to protect

[38] "Malaria: *Anopheles* Mosquitoes." *Centers for Disease Control and Prevention*. 21 October 2015.
[39] Sexton, Alexis. "Best practices for an insecticide-treated bed net distribution program in sub-Saharan eastern Africa." *Malaria Journal*, 10:157. 8 June 2011.
[40] "Dengue Control: The Mosquito." *World Health Organization*. 2018.
[41] Dawaki, Salwa et al. "Is Nigeria Winning the Battle against Malaria? Prevalence, Risk Factors, and KAP Assessment among Hausa Communities in Kano State." *Malaria Journal* 15 (2016): 351. 8 October 2018.

families from possible disease transmission. The cost-effective nets, which cost only about two American dollars each, hang over beds to shield sleeping spaces and can be treated with insecticides to maximize effectiveness. However, studies have shown that when community households were given free access to nets, only 42% of families slept under them each night.[42] Because of substantial heat, fear of the insecticides used to treat nets, and doubts of effectiveness, a gap between access and use proves this practice relatively futile.

Similar insecticides have been utilized for indoor residual spraying, which involves spraying the inside of homes in order to interfere with such indoor resting and feeding habits. Although sprays that are approved should not pose harm to humans, as they are utilized in relatively small quantities, they can have severe environmental repercussions. Like the chemicals used to treat bed nets, these insecticides can be extremely toxic to certain aquatic organisms, insects, and other forms of wildlife through direct contact or contaminating runoff.[43] Along with this massive threat to biodiversity, the use of insecticides enables the possibility of resistance, which can significantly harm the goal of reducing mosquito-borne diseases in the long run. Further, neither of these strategies address the technical mechanisms of viral or parasitic reproduction and the already-infected mosquito population. These fail to address the mass of infected mosquitoes, and instead focus only on human incidence and avoidance of the vector. Without addressing and limiting the ability of mosquitoes to contract infectious agents, these agents will continue to exist in the surrounding environment. While this may provide temporary protection and relief, simply

[42] Aribodor, D.N. et al. "Survey of Indoor Adult Malaria Vectors and Challenges of Using Long Lasting Insecticide-Treated Nets in Malaria Control in Awka-Etiti, Anambra State, Southern Nigeria. *Nigerian Journal of Parasitology*, 32:163-167. 2011.
[43] "Pests in Gardens and Landscapes: Less Toxic Insecticides." *University of California Agriculture and Natural Resources Statewide Integrated Pest Management Program*. October 2017.

attempting to avoid its growing existence is unsustainable and ineffective in the longer term. Contrarily, influencing the population via genome editing can be perpetually self-sustaining.

The World Health Organization has asserted that focusing intervention on the vector is the primary and most effective strategy for interrupting the transmission of mosquito-borne diseases.[44] Cost analyses conducted in Africa have shown that intervening at the source of transmission is more cost-effective than using either insecticide-treated bed nets or indoor residual spraying.[45] This assertion also overlooks the potential pain and suffering that may be avoided by focusing on vector control, rather than treatment, for mosquito-borne diseases. Leading other alternative strategies in terms of economic efficiency, effectiveness, and human quality of life, vector control seems to be an undisputable route for public health efforts.

Various forms of vector control involve modifying mosquitoes' genetic make-ups. In 1973, scientists first delved into the research and development of genetically modifying living organisms.[46] In more recent years, this technology has been adapted into gene drives, a more specific technology whose purpose is to maintain the modified gene throughout generations of reproduction. This mandates directly manipulating an organism's genome in order to gain, or lose, the expression of a certain trait. Gene drives face only two limitations; they may only be successful in organisms that utilize sexual reproduction and they must be continually implemented in enough generations to significantly affect the larger population.[47]

[44] "Vector Control: Why Vector Control?" *World Health Organization*. 2019.
[45] Worrall, E, Fillinger, U. "Large-scale use of mosquito larval source management for malaria control in Africa: a cost analysis." *Malaria Journal*. 8 November 2011.
[46] Rangel, Gabriel. "From Corgis to Corn: A Brief Look at the Long History of GMO Technology." *Science in the News*, Harvard University, The Graduate School of Arts and Sciences, 9 August 2015.
[47] Oye, Kenneth et al. "Regulating Gene Drives." *Science*, American Association for the Advancement of Science, August 2014.

Historically, the World Health Organization formally defined genetic control as "the use of any condition of treatment that can reduce the reproductive potential of noxious forms [of an insect] by altering or replacing the hereditary material".[48] In 2014, the World Health Organization updated its description of genetically modified organisms to "plants, animals, or microorganisms in which the genetic material, DNA, has been altered in a way that does not occur naturally by mating and/or natural recombination".[49] Methods of population suppression and population modification, included under each of these definitions, are still the main goals of mosquito gene drive changes today. These are achieved through manipulating the genetic code by utilizing enzymes to add or delete certain genetic sequences, relocate sequences into a new area of the genome, or replicate part of the genome. While the end goal of suppression is to decrease a vector's population, modification attempts to reduce their ability to transmit diseases. Historically, population suppression has garnered more support than population modification due to the public lacking confidence in the technology's safety and efficacy.

IV. Modification Techniques that Reduce Mosquito Population Numbers

The use of sterile insect technique, utilized most heavily between the 1960s and 1980s, aims for population suppression through inducing sterility. This goal can be achieved with or without the use of actual genetic modification. Often, sterile insect technique involves mass rearing male mosquitoes, who are sterilized utilizing irradiation, such as gamma rays and X-rays.[50] When

[48] Macias, V., Ohm, J. R., Rasgon, J.L. "Gene Drive for Mosquito Control: Where Did It Come from and Where Are We Headed?" *International Junior Environmental Resources of Public Health*, 14:9. 2017.
[49] "Food Safety: Frequently Asked Questions on Genetically Modified Foods." *World Health Organization*. 2014.
[49] "FAQ: Wolbachia." *World Mosquito Program*. 2018.
[50] Lees, Rosemary et al. "Back to the future: the sterile insect technique against mosquito disease vectors." *Current Opinion in Insect Science*. 2015.

these sterile males are released, they remain sexually competitive and are able to successively induce sterility in wild females. By this process, the respective mosquito population will decline slowly over time. Levels of radiation can be adjusted over time without losing the ability to successfully sterilize mosquitoes. Because all male mosquitoes are rendered infertile by the random mutations and excessive gonad damage inflicted by irradiation, there is no significant risk of developing resistance. Since common vector control approaches, such as insecticide spraying, have started contributing to resistance, the possibility of introducing sterile insect technique has been again proposed.[51] Oftentimes, this form of vector control is employed alongside other forms of insect management, such as the Wolbachia approach, which is discussed in the following section, in order to maximize efficacy. However, the heavy reliance on irradiation for sterilizing mosquitoes began to taper out starting in the 1970s, largely due to public fear of the associated chemosterilants negatively affecting human health.[52]

The OX513A genetically-modified male strain of mosquitoes, created by the British company Oxitec, also exists as a form of sterile insect technique. However, this process relies on gene editing rather than irradiation. Oxitec's technique utilizes "synthetically created gene sequences" in order to suppress the *A. aegypti* populations.[53] This manufactured sequence is inserted into the insect to behave as a "self-limiting gene" which produces a tetracycline-controlled transactivator (tTAV) protein. The tTAV protein binds to a site on the self-limiting gene, creating a positive feedback cycle, in which the gene begins to produce even more of the tTAV proteins. High levels of the tTAV inhibit the mosquito's growth and development. Therefore, all of the

[51] Ibid.
[52] Helinksi, M. et al. "Radiation biology of mosquitoes." *Malaria Journal*. 16 November 2009.
[53] "Our Technology." *Oxitec*, Oxitec, 2018.

offspring related to the male will inherit this gene and be killed before maturation. These insects are also given a fluorescent genetic marker that allows simplified monitoring. This form of suppression relies on the mechanisms of sterile insect technique and requires repeated releases of sterile males. The technology's workings are explained in greater detail in the following chapter.

V. Modification Techniques that Alter Vector Properties

Infecting both male and female *A. aegypti* mosquitoes with Wolbachia, a naturally-occurring bacteria, has proved to be an effective method that involves both population suppression and modification. This strategy involves instigating the spread of a bacteria throughout the mosquito population but does not actually alter the genetic code of the mosquito. For this reason, the Wolbachia approach is not labeled as a form of *genetic* modification but nonetheless stands as another method of modifying mosquitoes' ability to transmit infectious disease. This bacterium makes disease contraction by mosquitoes more difficult by strengthening the insect's immune system and inhibiting viruses from multiplying sufficiently.[54] The bacteria also outcompete viruses for molecules, such as cholesterol, that they need to replicate. This infection can only be passed down maternally from the female. Infected males mating with uninfected females creates a sperm-egg conflict called cytoplasmic incompatibility, which causes the resulting eggs to die.[55] Conversely, uninfected males mating with infected females produces offspring which are all infected with Wolbachia. When both the female and male are infected, all of the resultant offspring will carry the bacteria. If a sufficient number of the vectors are released, the strategy should be self-sustaining, eventually fully overtaking the local population. If an insufficient quantity is released, the infection will not spread through the population, and will be lost.

[54] "FAQ: Wolbachia." *World Mosquito Program*. 2018.
[55] Jiggins, F.M. "The Spread of *Wolbachia* through Mosquito Populations." *PLOS Biology*. 1 June 2017.

In recent events, the modification of 'natural' organisms has been tested in an extreme degree. This technology targets the clustered regularly-interspaced short palindromic repeats (CRISPR) within bacterial DNA, which behave as an adaptive immune system responsible for the detection of infectious viruses.[56] Within this CRISPR system exists a CRISPR-associated protein 9, more commonly coined Cas9, which subsequently terminates infection by locating and cleaving the DNA of the given virus. The so-called 'gene knockout' function associated with CRISPR-Cas9 has been an ongoing development since the initial discovery of CRISPR in 1993.[57] Almost two decades later, in 2010, scientific researchers demonstrated its ability to recognize and cleave specific DNA segments. In 2012, American biochemist Jennifer Doudna and her colleagues uncovered an innovative method of harnessing this mechanism for genetic engineering.

Since its discovery, CRISPR gene editing has been utilized in various way for the modification of mosquitoes. Research conducted by the University of California, Irvine in 2011 successfully created the OX3604C strain of male *A. aegypti*, which prevented all resulting offspring from being able to fly.[58] These males mated with wild *A. aegypti*, passing the modification onto the offspring, rendering them unable to travel away from the hatching site and feed on humans, thereby reducing the threat of disease transmission. A 2013 study used CRISPR-Cas9 technology to remove the orco gene from *A. aegypti*, which accounts for half of the insect's sense of smell.[59] Removal of the single gene results in the loss of discrimination between non-human hosts and

[56] Doudna, Jennifer. "Transcript of "How CRISPR Lets Us Edit Our DNA."" *Ted Talk*. Ted Conference.
[57] "CRISPR: CRISPR Timeline." *Broad Institute*, 2019.
[58] De Valdez, Megan. "Genetic elimination of dengue vector mosquitoes." *Applied Biological Sciences* – 108(12):4772-4775. Proceedings of the National Academy of Sciences of the United States of America. 22 March 2018.
[59] DeGennaro, M, et al. "Orco Mutant Mosquitoes Lose Strong Preference for Humans and Are Not Repelled by Volatile DEET." *Current Neurology and Neuroscience Reports.*, U.S. National Library of Medicine, 27 June 2013.

human hosts, the mosquitoes' selective food source. The vectors no longer exhibited a strong preference for humans and also showed increased repelling to contact with diethyltoluamide, a commonly used insect repellant. While these modifications prevent the transmission of disease by genetically deterring female mosquitoes from biting human hosts, they do not address the initial ability of the vectors to contract infectious disease.

In March of 2018, researches utilized CRISPR-Cas9 in order to disallow *Anopheles* mosquitoes from developing malaria infections after contracting the parasite.[60] The technology is used to locate the FREP1 gene in the mosquitoes, which allows for the creation of specific immunity proteins that disallows the malaria parasite to persist in the insect's gut. Within the mosquito, the FREP1 gene develops into a form capable of infecting human hosts. By inactivating the FREP1 in the genomic sequence, the *P. falciparum* is unable to survive until maturation, diminishing the threat of transmission to human hosts. The modified insects show no evidence of sporozoites in their salivary glands, indicating that the parasite has not developed sufficiently to infect humans.

VI. Potential Environmental Impacts

Despite mosquitoes' deadly behaviors, ethical concerns and possible unintended outcomes still exist regarding the manipulation of mosquitoes. Public perceptions of this modification often include both misconceptions and valid uncertainties regarding unintended consequences. With certain forms of population suppression, there are concerns regarding biodiversity. Since mosquito larvae provide a food source for some aquatic insects and fish, some individuals worry that a loss of mosquitoes would create schisms in the food chain, potentially affecting many

[60] Dong, Yuemei, et al. "CRISPR/Cas9 -Mediated Gene Knockout of Anopheles Gambiae FREP1 Suppresses Malaria Parasite Infection." *PLOS ONE*, Public Library of Science, 8 March 2018.

other species. While their presence may be reduced in some locations, most vector control strategies do not aim for the complete elimination of mosquitoes. Therefore, their limited ecological roles are presumably unlikely to cause significant shifts in target areas or their biodiversity levels. However, with so little known about the role of mosquitoes within environments, there can be little assumption about possible effects of population suppression. Further, since mosquitoes' range cannot be limited, modified mosquitoes traveling outside of the target area is often mentioned as a concern. *A. aegypti* typically only travel 500 meters or less throughout its lifespan, while *A. gambiae* do not typically fly more than several miles.[61] While these restrictions mostly hinder the ability for these insects to influence locations outside of the intended area, there is still a possibility of the insects ending up outside of the target area by other organisms or shipments, like cargo. This poses a possible risk for locations in which the respective mosquitoes are not native, as invasive animals can disrupt foreign ecosystems.

While some modifications have not shown risks to human, animal, and environmental health, future unintended consequences cannot be fully eliminated. Individual and community rights, including informed consent, must be considered and weighed to ensure the ethical application of modern technology. Though no disease strain has yet shown resistance to measures such as Wolbachia infection, the possibility of future resistance cannot be fully disregarded.

VII. Controversial Atmosphere Surrounding the Modification of Living Organisms

Much controversy exists surrounding the production and use of modified living organisms. In many cases, the distaste for modification stems from the concept of psychological essentialism,

[61] "Transmission: Anopheles Mosquito." *Malaria Site*. 27 March 2015.

which explains the ways in which humans instinctually categorize and interpret worldly objects.[62] In this understanding, objects have a set of fixed characteristics that make them what they are. Changing these features morphs the entity into something foreign. This psychological tendency causes individuals to associate certain items with essentially-fixed properties that cannot be altered. Individuals that opposed modified organisms, such as the transgenic *A. aegypti*, often fear them due to the practice of altering what is considered to be 'natural'. This concept suggests that organisms which are modified from the way they exist naturally in the environment are 'unnatural' and to be feared.

Recent uses of CRISPR-Cas9 technology has stirred fear within many communities across the globe. Since its discovery, the method of gene editing has faced with ethical concerns regarding its use on animal and human subjects. While CRISPR-Cas9 applications have the potential to rid a wide array of potentially fatal diseases, Jennifer Doudna confirms the alternative possibility that technology could be used to enhance and design humans.[63] The ability to enhance children poses severe ethical and societal repercussions, making its use potentially alarming to individuals. While the United States Congress has annually renewed their ban on utilizing CRISPR-Cas9 for the modification of human embryos due to the possibility of harming other genes [64], CRISPR-Cas9 clinical trials have begun in multiple locations across the globe, but have only been conducted on adults to treat individual disease.[65] Because these adults have fully developed, the modifications are limited to the sole individual undergoing the trial, while sperm,

[62] Potter, Lisa M., et al. "Investigating Novice and Expert Conceptions of Genetically Modified Organisms." *CBE-Life Sciences Education*: 16(3), American Society for Cell Biology. 2017.
[63] Doudna, Jennifer. "Transcript of "How CRISPR Lets Us Edit Our DNA."" *Ted Talk*. Ted Conference.
[64] Regalado, Antonio. "Congress Is about to Renew Its Ban on Creating CRISPR Babies in the US." *MIT Technology Review*, MIT Technology Review, 11 January 2019.
[65] Schiefelbein, Mark. "Chinese Researcher Claims Birth of First Gene-Edited Babies." STAT News, November 2018.

eggs, or embryos changes can be passed onto offspring. In this way, the technology can alter what is naturally seen in the gene pool, raising societal concern through essentialist implications.

Despite vast concern associated with the modification of embryos, a Chinese scientist recently announced his use of the technology to modify the genomic sequences of twin embryos.[66] Amidst an international conference regarding gene edits, He Jiankui admitted to altering the genomic sequences of mice and monkeys, as well as the embryos of seven different couples in attempts to impart resistance to potential HIV infections. While other scientists have done this in embryos as well, there have not been any known births of children with edited genomes prior to this incident. The shady nature of the incident has caused international controversy, which can have larger effects on public perception of genetic engineering. Jiankui conducted this trial without adhering to crucial scientific research guidelines and without any prior experience in running human clinical trials. His research embodies numerous ethical complications. Review of his work showed gene editing to be incomplete, which allows for the possibility of HIV infection while still exposing the child to potential safety risks associated with genetic modification, such as unknown effects on other genes. Further, the project was only reported to the Chinese registry long after Jiankui had begun working on it. Consent documents identified the research as an "AIDS vaccine development" project, raising severe concerns as to whether recruited participants were truly informed of the research in which they had partaken.

Disapproval of the trial has been publicized through many media outlets. Many scientists have publicly denounced the prematurity of the experiment, calling it 'human experimentation'.

[66] Begley, Sharon. "The CRISPR shocker: How genome-editing scientist He Jiankui rose from obscurity to stun the world." *STAT News*. 17 December 2018.

Chinese investigators have declared the trials to be explicitly illegal, violating clear bans on the editing of human embryos for reproductive purposes.[67] Jiankui deliberately evaded the use of regulatory supervision and support personnel through his trials. Sensationalizing the illegal and dishonest nature of his work may feed concerns about the use of genetic engineering technology or modification of living organisms on a greater scale. These negative associations of CRISPR-Cas9 are likely to have strengthened some already-existing negative connotations of the given technology, making individuals less likely to support its use, even in different contexts. Especially because this technology can be utilized modifying mosquitoes in a multitude of ways, the genetically-modified twins' birth can cast societal mistrust in using CRISPR-Cas9 on these insects. As most common people do not understand the inner workings of editing techniques, it can become easy to perceive different techniques as virtually the same. If there are widespread negative connotations about any particular form of modification, it is undeniable that the processes of socializing and adopting modified mosquitoes can become infinitely more difficult.

Despite major disapproval towards Jiankui's trial, there are still various caveats in the public perception of different modification methods. Alternative strategies that do not utilize gene modification vary widely from one another in how much public acceptance, or backlash, they receive. For instance, although irradiation involves no form of gene editing, citizens still began to perceive this modification negatively due to fear of its effects on human health. The strategy became so heavily opposed that it was fused out of common use. It is both clear and reasonable that individuals may condemn scientific interventions that impact their own health negatively. On the contrary, some individuals are much more supportive of interventions like Wolbachia,

[67] Wang, Serenitie. "World's First Gene Edited Babies Were Illegal, Say Chinese Authorities." *CNS*, Cable News Network, 22 January 2019.

considering infection with the commonly-existing bacteria relatively safe and more natural than gene manipulation. While neither irradiation nor Wolbachia require genetic modification, public opinions on each strategy differ greatly. Such comparisons in community acceptance will be made later in this piece. While Jiankui's specific trial faced overwhelming disapproval because of its disregard for research standards, modification techniques still present much hope for public health efforts globally. With proper regulation and socialization of innovations, modern technology has the potential to greatly increase individuals' longevity and quality of life.

CHAPTER 2: Case Study – First Known Release of Genetically Modified Mosquitoes (Oxitec OX513A Strand), Cayman Islands

In 2009, Oxitec conducted the first known global release of genetically modified mosquitoes in the Cayman Islands, a British overseas territory. Until Oxitec's notice of the completed trial in 2010, the ongoing trial went undetected by Caymanian organizations, residents, and scientists across the world. Although the Cayman government approved the trial and no regulations existed concerning the release of the genetically modified organisms, the lack of public awareness and support sets a poor precedent for future releases. While many ethical concerns went unanswered by the company, the trial became the basis for regulatory approvals in foreign nations.

I. Oxitec OX513A Strain of *A. aegypti*

The OX513A strain of male *A. aegypti* mosquitoes were created by Oxitec, a biotechnology company focused on controlling insect populations via genetic modification. Gene sequences are "synthetically manufactured" and introduced into the genomes of male *A. aegypti* in order to prevent reproduction.[68] This method focuses on modifying only male mosquitoes, as their primary incentive is to find and breed with female counterparts. The gene sequences are based on the natural systems of bacteria but are modified to optimize function in the given mosquito. When added into the mosquito's genome, the sequence behaves as a 'self-limiting' gene, which can be inherited by any offspring stemming from the modified male.[69] This gene encodes the production of a tetracycline-controlled transactivator (tTAV) protein, which attaches back to a binding site on the self-limiting gene. A positive feedback loop then commences, in which

[68] "FAQ." *Oxitec*, Oxitec, 2018.
[69] "Our Technology." *Oxitec*, Oxitec, 2018.

additional tTAV proteins are created. High quantities of tTAV proteins prevent the expression of genes that are necessary for the *A. aegypti* development, killing offspring prior to maturation.

The modified mosquitoes are raised with tetracycline antibiotic, which the tTAV protein attaches to in place of the self-limiting gene binding site. In this method, the lack of positive feedback and the associated tTAV levels allow the bred insects to survive. When these male mosquitoes breed, the resulting offspring cannot obtain the tetracycline, as it does not exist environmentally in sufficient quantities, and therefore die before maturing. The *A. aegypti* are also given a fluorescent genetic marker, which leads to the expression of its abundant DsRe2 proteins. The protein, which is passed onto all offspring, glows under specialized light, creating a simple and effective method of monitoring the presence of OX513A mosquitoes, compared to the natural insects, in target areas. Once released, the modified vectors usually survive less than one week.

II. Ethical Concerns of the Cayman Islands Release

In 2009, Oxitec released three million mosquitoes from their *A. aegypti* OX513A strain in the Cayman Islands, carrying out the first known real-life application of genetically modified mosquitoes.[70] After obtaining approval from the Cayman government, Oxitec recruited the Mosquito Research and Control Unit to help implement this release by hatching modified egg shipments from Oxitec. Only on November 11, 2010, when the trial had fully completed, approximately one year after the first release, did Oxitec publicly announce that it had conducted such a trial.[71] Negligible public knowledge existed concerning this ongoing project until it had

[70] Nightingale, Katherine. "GM Mosquito Wild Release Takes Campaigners by Surprise." *Science and Development Network*, SciDev.Net, 11 November 2010.
[71] Enserink, Martin. "GM Mosquito Trial Strains Ties in Gates-Funded Project." *Science*, American Association for the Advancement of Science, 11 December 2017.

already ended. Though a grand majority of Cayman Islands citizens remained unaware of the release, the local Mosquito Research and Control Unit claimed to have sent information to a local newspaper and have posted a video on YouTube.[72] However, the video fails to indicate the genetically modified nature of these mosquitoes at any point. Shortly following the release, Oxitec failed to raise this agenda at the Parties to the Cartagena Protocol on Biosafety.[73] This international treaty has a particular focus on possible international safety issues concerning the movement of living modified organisms between countries.[74] Under the precautionary principle of the protocol, nations are meant to discuss the potential public health and economic consequences associated with such technologies. At the beginning of 2018, the association included 171 parties, including 168 states under the United Nations, Palestine, the South Pacific, and the European Union. Because there is no guarantee that mosquitoes will not infiltrate country borders, it was Oxitec's obligation to discuss this release at the convention. Avoiding the topic under the authority of the Biosafety Convention emphasizes the alarming secrecy and lack of transparency involved in the Cayman Island release. Researchers from the Action Group on Erosion, Technology, and Cooperation, a committee dedicated to socially responsible technology use, also claimed complete unawareness of the project. Despite being a smaller organization, it is focused on potential threats to biosecurity and has an international status for research and public policy changes.[75] Many members of the scientific community expressed grave concern about potential unintended consequences and denounced the secrecy of the trial, which greatly lacked any public knowledge and involvement. Oxitec's director of research claimed that while possible risks were considerably reviewed, there was reluctance to attract widespread attention to the trial

[72] Ibid.
[73] Nightingale, Katherine. "GM Mosquito Wild Release Takes Campaigners by Surprise." *Science and Development Network*, SciDev.Net, 11 November 2010.
[74] "About the Protocol." *The Cartagena Protocol*, Convention on Biological Diversity. 29 May 2012.
[75] "ETC Group." *Action Group in Erosion, Technology, and Cooperation*. 2019.

until its results were discovered. This risk assessment, along with statistical results of the experiment, were not available until the initiation of Oxitec's next release in Malaysia in 2011.[76]

Prior to any known transgenic organism release, communities of scientific researchers had emphasized the necessity of intensive education and public debate in order to gain consent from the human population of the target area.[77] Oxitec claims that the company did not engage in any local meetings or debates as part of a socialization process because the Cayman government itself had consented to the project and did not require this interaction with the community. At the time of release, no regulation existed concerning the release of genetically modified organisms into the environment.[78] Nonetheless, review of Oxitec's decision-making process has found the company to have severely lacked in transparency to the community, limiting the availability of project details. Prior to the public announcement of the trial in 2010, both the Cayman government and the Mosquito Research and Control Unit had no material concerning the study on their accessible internet webpages. Incomplete data emerged on these platforms following the Oxitec's announcement, but details such as the permit's applicant remained unclear.

III. Consequences of Cayman Islands Pilot Study

Following the release of their transgenic vectors, Oxitec researchers claimed that the released mosquitoes reduced local population by 80%, advertising that the project had been a "complete

[76] Reeves, R. Guy, et al. "Scientific Standards and the Regulation of Genetically Modified Insects." *PLOS ONE*, Public Library of Science, 31 January 2012.
[77] Enserink, Martin. "GM Mosquito Trial Strains Ties in Gates-Funded Project." *Science*, American Association for the Advancement of Science, 11 December 2017.
[78] Reeves, R. Guy, et al. "Scientific Standards and the Regulation of Genetically Modified Insects." *PLOS ONE*, Public Library of Science, 31 January 2012.

success." [79] Despite the limited availability of project details and abundant concerns with the ethics of Oxitec's actions, this trial became the precedent for regulation approvals globally.[80] Because of the epidemiological success, other locations began to implement the same technology without public knowledge, following the example of lacking transparency and consent. The Cayman Island pilot study behaved as a poor, and potentially dangerous, precedent for the future use of the modified *A. aegypti* strain. This not only instigates consequences in terms of further studies, but also magnifies the individuals that are stripped of their ability to consent to the trial. Most of the local residential population, given no education or debate opportunities by Oxitec and their government, was unaware and unable to consent to the ongoing release of vectors, over the course of a full year. Because Oxitec publicized the trial as a full success, other national government were inclined to test the technology, even without full access to information. Approximately one year after the Cayman Islands trial had concluded, in December of 2011, Oxitec released thousands of modified *A. aegypti* with the approval of the Malaysian government.[81] However, this followed the model shown in the Cayman Island study, with the public yet again unaware of their exposure to transgenic mosquitoes.

Following backlash, Oxitec's head researcher Luke Alphey publicly stated that since the study was conducted "by the Malaysian government in Malaysia... it was up to them to announce it." [82] Citizens were even blamed for their own lack of awareness, as the Oxitec representative tells that following governmental regulation approvals, it "seems predictable that the next step would be

[79] Enserink, Martin. "GM Mosquito Trial Strains Ties in Gates-Funded Project." *Science*, American Association for the Advancement of Science, 11 December 2017.
[80] Reeves, R. Guy, et al. "Scientific Standards and the Regulation of Genetically Modified Insects." *PLOS ONE*, Public Library of Science, 31 January 2012.
[81] Enserink, Martin. "GM Mosquito Release in Malaysia Surprises Opponents and Scientists-Again." *Science*, American Association for the Advancement of Science, 11 December 2017.
[82] Ibid.

the actual release," placing the responsibility on the residents to have anticipated the subsequent release. This displacement of blame identifies the governmental responsibility to educate the nation's population but overlooks the company's accountability. General principles suggest that Oxitec, as the creator with the greatest knowledge of the technology's workings, gives one a social responsibility to bind with the government to inform citizens properly. Despite the Malaysian trial being suspended due to severe protests, these events posed inadequate standards for the socialization of transgenic mosquitoes in other countries globally, undermining the necessity of government and company cooperation in educating the public for science and ethics.

Lack of community awareness also disallows the possibility of informed residential support and participation. Without transparency and project detail availability, other nations' access to crucial information is difficult. Without this access, government and citizen decisions about the applications of genetically modified organisms cannot be appropriately informed. Instead, these parties must rely on sources including media accounts, presentations, meetings, and limited documents, which may present unreliable data, in attempts to gain scientific information about the technology. In the Cayman Island trials, Oxitec and the national government excluded citizens from not only the decision-making process, but the implementation process as well. Without educating Caymanians, these parties eliminated the chance for residents to make informed decisions about, and possibly support, the use of modified mosquitoes. Further, while unaware, these individuals were unable to engage in acts that could support the research mission, such as offering households as release areas or actively aiding in the releases. Because the success of OX513A mosquitoes is dependent on reaching an extensive scope of area, overlooking citizen participation can be detrimental to full potential of the project.

Failure to acknowledge this lack of consent can foster future distrust of the government and of genetically modified organisms generally as a vector control intervention. Political trust has been deemed one of the requirements for just democratic ruling, contributing highly to efficiency and effectiveness of national developments.[83] When this method was once again proposed in 2016 in Grand Cayman, the largest section of the Cayman Islands region, legal actions were taken by residents that objected the initiative. [84] The opposition represents both continued wariness of the technology and sentiments of the government dishonesty. It is likely that the past dishonest and secretive nature of mosquito release contributed to this continued distrust in the government and use of Oxitec technology. Intrexon, Oxitec's holding company, reported that while the respective release was delayed by 14 days due to the legal objections, courts ruled that there was no substantial reason for the postponement, lifted the delay, and ruled for continuation of the release. Delaying or prematurely concluding trials can prohibit the mosquitoes from being released on large-enough scales for epidemiological success, resulting in wasted financial expenditures. These conflicts may further contribute to economic vulnerabilities by negatively influencing countries' tourism sectors. Following Oxitec's release, American citizens voiced their refusal to travel to the Cayman Islands due to transgenic mosquito opposition.[85] As a first documented release of this mosquito strain, this experiment could not only perpetuate this skepticism domestically, but in other foreign countries considering the method as well.

[83] van der Meer, Tom W. G. "Political Trust and the 'Crisis of Democracy.'" *Oxford Research Encyclopedias*, 15 June 2018.
[84] "GM Mosquito Release Commences in Grand Cayman." *Press Releases*, Intrexon: Better DNA. 28 July 2016.
[85] Glenza, Jessica. "Zika Virus: Floridians Fear 'Pandora's Box' of Genetically Altered Mosquitos." *The Guardian*, Guardian News and Media, 14 August 2016.

CHAPTER 3: Case Study – Release of Wolbachia-Infected Mosquitoes in North Queensland, Australia to Prevent the Transmission of ZVD and DF

In 2014, a successful release of Wolbachia-infected *A. aegypti* was conducted by the World Mosquito Program in North Queensland, Australia to combat the transmission of ZVD and DF. A specifically developed Public Acceptance Model, used to socialize the release of these modified vectors, led to the attainment of overall community consent. As a result, Wolbachia fully integrated into the mosquito populations within 28 months. There have been no detected cases of local Zika virus transmission in the area after the infected *A. aegypti* introduction, and DF infections reached a complete halt following this development as well, despite thirteen consecutive years of transmission prior to the mosquitoes' release.

I. North Queensland Disease Profile

While severe DHF cases have been historically uncommon in Queensland, the Australian state has faced major public health threats due to the more-common spread of DF via large *A. aegypti* populations. Since the beginning of the 1990s, the area experienced dengue virus epidemics growing in severity, frequency, and length.[86] The state encountered nine epidemics within just four years, beginning in 2005.[87] This pattern continued, with Queensland experiencing over 1,000 cases of locally transmitted dengue cases between 2008 and 2009, the largest recorded incidence in the state's history.[88] From 2010 until 2014, when Wolbachia-infected vectors were

[86] Viennet, Elvina, et al. "Public Health Responses to and Challenges for the Control of Dengue Transmission in High-Income Countries: Four Case Studies." *PLOS*, Public Library of Science, 19 Sept. 2016.
[87] Hanna, Jeffrey N et al. "Dengue in North Queensland, 2005–2008." *The Department of Health*, Australian Government Department of Health, 18 Sept. 2009.
[88] Viennet, Elvina, et al. "Public Health Responses to and Challenges for the Control of Dengue Transmission in High-Income Countries: Four Case Studies." *PLOS*, Public Library of Science, 19 Sept. 2016.

released, the area faced 1,603 additional cases, 580 of which were acquired locally.[89] Efforts to control these ongoing cases proved futile before the introduction of the infected mosquitoes.

II. Wolbachia Infections in *A. aegypti* Vectors

Wolbachia, a common and naturally-occurring bacterium, can be introduced to both male and female *A. aegypti* in order to diminish the transmission of mosquito-borne diseases. Although these bacteria exist in 60% of known insects, including certain mosquitoes, it has not been found naturally in the *A. aegypti* species, whose females are the primary carriers of both ZVD and DF. In order to introduce Wolbachia into the mosquitoes, the bacteria are taken from *Drosophila melanogaster* fruit flies, in which the bacteria already exist naturally.[90] This method does not utilize gene transfer but instead microinjects the bacteria into *A. aegypti* embryos.[91]

The bacteria transfer obstructs disease transmission by combining facets of both population modification and suppression. Wolbachia presence first modifies the mosquito's role in transmission by complicating disease contraction in two distinct ways. The bacteria itself rivals the given virus, often outcompeting it for molecules required for replication, such as cholesterol.[92] Its presence also strengthens the insect's immune system, prohibiting the virus from multiplying enough to cause infection. Because the disease-causing agent typically cannot fully develop in these circumstances, the vector is unable to transmit the disease to human hosts.

[89] Ibid.
[90] ACSH Staff. "Time to Embrace Genetically Modified Mosquitoes to End Their Disease Transmission." *American Council on Science on Health*, American Council on Science on Health, 20 Aug. 2018
[91] Hughes GL, Rasgon JL. Transinfection: a method to investigate Wolbachia-host interactions and control arthropod-borne disease. *Insect Molecular Biology* 23(2):141-51. 2013.
[92] "FAQ: Wolbachia." *World Mosquito Program*. 2018.

Wolbachia infections also significantly modify the results of the insect's sexual reproduction process. When both the mating male and female are infected with Wolbachia, all of the resulting offspring will hatch with the bacteria. Wolbachia can only be inherited in this method from mother to offspring and cannot be translated directly to other *A. aegypti* mosquitoes in the population. If only the female is infected, her offspring will still possess the bacteria; however, if only the male is infected, cytoplasmic incompatibility will occur.[93] Although the female will produce eggs, this phenomenon substantially reduces the percent of offspring that survive by disallowing most of the eggs to hatch. In this way, the *A. aegypti* reproduction mechanism is interrupted, contributing to suppression of the overall population quantity.

Once the Wolbachia infection reaches a threshold of between 20% and 30% of the native population, the intervention becomes self-sustaining.[94] At this level of infection, the bacteria will increase its prevalence without additional involvement, overtaking the local population. At any level lower than this threshold, the bacteria will not spread sufficiently through the *A. aegypti* and will eventually be lost completely. Since Wolbachia is already extremely common in the ecosystem, the bacterial overtake of the native population has extremely minimal effects on the health of the environment and exposed humans. As aforementioned, there are no significant consequences yet known associated with such decreases in mosquito populations.

Wolbachia-infected mosquitoes were created via collaboration between the World Mosquito Program (WMP) and Gates Open Research. The WMP, earlier entitled Eliminate Dengue, is

[93] O'Neill, Scott. "The Use of *Wolbachia* by the World Mosquito Program to Interrupt Transmission of Aedes Aegypti Transmitted Viruses" *Institute of Vector Borne-Disease*, Monash University. 2018.
[94] Jiggins, Francis M. "The Spread of Wolbachia through Mosquito Populations." *PLOS*, Public Library of Science, 1 June 2017.

responsible for the scientific research and development of the mosquitoes. Gates Open Research is a research branch of the Bill & Melinda Gates Foundation, the largest private foundation in the world which focuses on improving people's health and wellbeing in developing nations. The organization prioritizes an emphasis on combating the most burdensome infectious diseases with innovative approaches, such as the modified mosquito. A long-standing partnership against such illness exists between the prior entities, shown by the hundreds of millions Australian dollars that have been donated to the WMP by the Bill & Melinda Gates Foundation since 2010 for development of the Wolbachia-infection method.[95] Through financial donations from the Gates research branch, the World Mosquito Program had the capability to create these modified insects and carry out the release. The overarching study, including experimental factors such as public awareness and epidemiological success, was followed and published by Gates Open Research.

III. Implementation via the Public Acceptance Model

The large-scale trial in Townsville, the first of its kind, followed a much smaller scale trial in Cairns, another city in North Queensland. In this initial trial, consent for the modified mosquitoes was obtained from individual households; however, obtaining this form of individual consent is unfit for implementation on greater scales. To accommodate for the scale-up, Gates Open Research developed a Public Acceptance Model (PAM) for the end purpose of attaining overall community authorization of the project.[96] Its four central facets included heightening awareness, quantitative surveys, an issues management system, and a community reference group to socialize the Wolbachia-infected mosquitoes to the target population.

[95] "The WMP welcomes AUD $50m funding from the Gates Foundation and Wellcome Trust." *World Mosquito Program*. 28 August 2018.
[96] O'Neill, Scott. "The Use of *Wolbachia* by the World Mosquito Program to Interrupt Transmission of Aedes Aegypti Transmitted Viruses" *Institute of Vector Borne-Disease*, Monash University. 2018.

The PAM committed to educating both Townsville residents and the plan's key stakeholder groups. Information was distributed on an intimate level to citizens through environments catered to their preexisting habits. Information was purposefully circulated to provide a fundamental basis of the projects' objectives and characteristics.[97] This aspect of the PAM accounted for routine behaviors of Townsville citizens, creating billboards and information kiosks in heavily accessed public spaces, as well as creating educational stalls at frequently visited marketplaces. These have explicitly communicated the threat of mosquito-borne diseases, as well as the proven safety and efficacy of the altered mosquitoes. Media events were held in public spaces in order to attract support for the vectors. Oftentimes, trusted community organizations were engaged in community presentations in order to convey program information to residents. Data regarding the project's purpose, as well as frequent updates about the mosquitoes' deployment, were broadcasted using the city's popular communication networks, including newspaper, e-mail, and social media outlets. By using the communication systems that were most compatible to the Australian society, the city was able to widely circulate information throughout the city's population. Nonetheless, further efforts were made to ensure education at the individual level through personal meetings.

Focusing on not only generating community awareness of the project, but also on enabling active engagement, proved to be a vastly successful aspect of the campaign. A school outreach program was implemented, targeting college-level students, as well as younger grade-school students. Throughout the ongoing educational campaign, students were offered and encouraged to help

[97] Ibid.

raise and hatch the Wolbachia-infected mosquitoes via the use of Mozzie boxes.[98] Children received kits possessing the necessary materials to raise these mosquitoes for release in the environment as a part of the "Wolbachia Warriors" school program.[99] These small kits contain a strip of 100 female *A. aegypti* eggs, a source of nourishment, and simple breeding instructions. Public communication and engagement staff were responsible for giving presentations at targeted schools before distributing the kits. Residential houses and employees of large businesses throughout Townsville were also given this opportunity. When offered, over 6,000 Queensland households and 200 other individuals expressed interest in participation and contributed to successful rearing.[100] Since most public broadcasting and individual meetings are targeted towards older residents and parents, this system bridged the knowledge gap that otherwise would have left children unaware of ongoing current events. Encouraging this type of involvement throughout socialization helps further establish the prominence of Wolbachia-infected mosquitoes within the population while culturing enthusiasm for the modified vectors.

Quantitative surveys were implemented in order to assess how successfully the educational campaign increased awareness and influenced project acceptance and support. These were conducted by an external market research organization, beginning before the PAM was implemented and continuing throughout its employment at six months intervals.[101] Each survey interviewed between 200 and 600 individuals by phone, gathering data regarding increases in awareness due to media broadcasting and comfort levels regarding the research and releases.

[98] Braithwaite, Alyssa. "A Simple Breeding Kit Lets People Create Mutant Mozzies to Stop Zika." 3 June 2016.
[99] O'Neill, Scott L, et al. "Scaled Deployment of Wolbachia to Protect the Community from Aedes Transmitted Arboviruses." *Gates Open Research*, Gates Open Research, 1 Aug. 2018. PDF.
[100] Ibid.
[101] Ibid.

In order to create a relationship where citizens were comfortable enough to voice their questions and concerns about the project, community members were educated and trained as program staff for a specialized issues system. By preparing the program staff to effectively respond to any existing worries, individual awareness was greatly heightened and opposition to these mosquitoes' release oftentimes alleviated. However, most scientific research and local news outlets focus on the epidemiological success of the program, making it difficult to find initial opposition to the mosquitoes' release. With an efficient way to ask questions, voice concerns, and receive educated responses within one day, the PAM was able to alleviate many anxieties surrounding the project.[102] Through this system, individuals were also able to opt out of participating by offering their households as mosquito release sites.

A community reference group was composed in order to evaluate the system's outputs. This group included representative individuals from involved groups – local businesses and environmental groups, tourism and education divisions, indigenous communities, the Townsville City Council, and Queensland Health.[103] Together, these members were mainly responsible for ensuring that the activities carried out through the PAM adhered to the Public Participation Principles, by which the project's main goals were evaluated. The principles focused on qualitative aspects of the socialization process, including respect, inclusivity, transparency, responsivity, and honesty. Success in these categories was measured by how well residential concerns were validated and accommodated, the extent of people included by information communication, as well as the authenticity and transparency of project information.

[102] Ibid.
[103] Ibid.

IV. Social, Economic, and Epidemiological Success of the PAM

The PAM principles led to over 20% of residential households to willingly serve as mosquito release sites every two to three weeks during implementation until the Wolbachia's frequency reached above 50%. This participation allowed for the bacteria to cover the all areas of Townsville that provided appropriate habitats for the *A. aegypti* without leaving spatial gaps in the protective coverage. Utilizing the community deployments, in addition to the program's deployment measures, is considered the most suitable for large-scale procedures.[104] The "Wolbachia Warriors" program, while contributing to mosquito releases, was primarily advantageous for its role in amassing community participation. This process was done at the cost of fifteen Australian dollars per person in Townsville, which currently equates to just under eleven American dollars.[105] The potential deployments for larger-scale projects, the organization is targeting a goal cost of just one American dollar per person in the target area.

With engaged community support, the Wolbachia-infected mosquitoes were released throughout 28 months.[106] Local dengue transmission has occurred consistently in Townsville since 2001, due to the steady import of foreign acquired cases. Despite foreign-borne cases continuing after the deployment of Wolbachia-infected *A. aegypti* in 2014, only one locally contracted case had been identified in a Wolbachia established area in the subsequent four years.

[104] Ibid.
[105] "Long-Lasting Dengue Prevention Demonstrated for the First Time." *World Mosquito Program*, World Mosquito Program, 8 Jan. 2018.
[106] O'Neill, Scott et al. "Scaled Deployment of *Wolbachia* to Protect the Community from *Aedes* Transmitted Arboviruses." *Vector-Based Transmission of Control Discovery Research*, Global Health Initiative. 2018.

CHAPTER 4: Case Study – Failed Release of OX513A Mosquitoes in Key West, Florida

Oxitec failed to garner sufficient public support for the released OX513A strain of *A. aegypti* from the application's target population – Key West residents. While Oxitec technology met the original conditions needed for an innovation to be publicly adopted, as proposed by Everett Rogers, the subsequent procedure for the technology's diffusion failed due to its lack of fostering community awareness and public engagement. Without using heavily accessed social platforms to spread information about the technology and the release long enough before the decision-making period, the company could not gain public support.

I. Previous Key West Efforts to Combat *A. aegypti*

As of 2017, the Key West district was spending over one million dollars every year attempting to combat the *A. aegypti*.[107] Insecticidal methods by the Mosquito Control District became less effective due to strengthening resistance in the local mosquito population, only eliminating about half of the population. However, unless 90% of the insects are killed, disease will continue to spread. Oxitec was able to suppress the wild population of *A. aegypti* in Panama by 93% in comparison to untreated areas by releasing the OX513A strain in 2014.[108] Online, Oxitec notes that approval was granted from Panama's National Biosafety Committee, as well as the country's Ministries of Agricultural Development and Commerce and Industry. While the company claims to have carried out extensive community engagement on multiple occasions, the scientific report on the Panama release states only that Oxitec sought verbal consent from property owners to

[107] Shastri, Devi. "Outbreak: Mosquito Battle Gets Political." *Journal Sentinel*, Journal Sentinel, 5 October 2017.
[108] "Program: Panama." *Friendly Mosquitoes*, Oxitec. 2018.

place ovitraps and adult traps, both serving as means for vector *surveillance*.[109] The study fails to discuss community engagement or seeking consent for any facet of the initial release. While consent for the traps was obtained, a closer look shows that these traps were set on 30 properties, meaning that consent was only received from 30 different households. This quantity compromises a negligible proportion of the individuals that are exposed to the modified insects once they are released, showing little development in Oxitec's commitment to community engagement techniques following the Cayman Island trial.

The OX513A technique has numerous other advantages when compared to alternative vector control approaches. By suppressing mosquito populations rather than modifying their ability to contract certain viruses, the threat of contributing to resistant viruses is eliminated. Since there is no way of directly translating the gene between other mosquitoes naturally, the modified insects are not able to permanently establish themselves in the physical environment. Nonetheless, while present in the environment, they have posed no known threat to human or ecological health. Due to the *A. aegypti* producing strictly within their species, there is also no possibility of the gene interfering or harming other insects.[110]

II. Failures of the OX513A Strain Implementation in Key West, Florida

While Oxitec technology met Rogers' original conditions needed for an innovation to be publicly adopted, the subsequent procedure for the technology's diffusion failed. Genetically modified mosquitoes fulfilled the four social conditions required by its possible adoption – alignment with

[109] Gorman et al. "Short-term suppression of *Aedes aegypti* using genetic control does not facilitate *Aedes Albopictus.*" *Pest Management Science*, Society of Chemical Industry. 8 September 2015.
[110] "Our Technology." *Oxitec*, Oxitec, 2018.

previous practices, problems felt by the target society, innovativeness, and societal norms. The lack of individual action needed to sustain the impact of the modified vectors constituted one of its key benefits. Without requiring a need for individuals to adapt their routine behaviors, this technology could be physically employed into the surrounding environment easily. Over 93 Key West individuals had locally transmitted dengue between 2009 and 2010, the year the Oxitec vectors were first proposed in Florida, giving this innovation a critical social purpose.[111] While the Centers for Disease Control and Prevention recommends the use of permethrin, a common insecticide, for mosquito control in Florida, widespread permethrin resistance has been found in *A. aegypti* strains in the state.[112] As no other modified mosquito had been released in Florida when the Oxitec vectors were proposed, they constituted an innovative form of technology in Key West. Because of the prominence of these *A. aegypti*, combating the insects has become a societal norm in Florida, whether stemming from disease or nuisance related justifications.

Despite the vectors meeting the conditions for possible societal adoption, the stages needed for successful technology diffusion were unsuccessfully implemented. The five-step procedure theorized by Rogers identifies these phases as knowledge, persuasion, decision, implementation, and confirmation. The Florida district failed to implement the five-step procedure of knowledge, persuasion, implementation, and confirmation in a way that effectively disposed individuals to favor the technology. While the framework may not necessarily need to be intentionally implemented, it provides a theoretical structure for implementing community education processes, measuring their success, and obtaining truly informed consent for the project at hand.

[111] U.S. Department of Health & Human Services. "Locally Acquired Dengue - Key West, Florida, 2009-2010." *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 21 May 2010.
[112] Estep, Alden S., et al. "Quantification of Permethrin Resistance and Kdr Alleles in Florida Strains of Aedes Aegypti (L.) and Aedes Albopictus (Skuse)." *PLOS*, Public Library of Science, 24 Oct. 2018.

Lacking a thorough knowledge phase, the Floridian district provided insufficient information, failing to match the PAM used in North Queensland, Australia. A survey assessing residential knowledge about the trial two years after it was proposed by the Key West district found that 49.9% of participants had not even heard of the proposition prior to the study.[113] The information disseminated through public events and media announcements, such as public meetings and publicly-posted informational articles were insufficient for educating the public. While data was publicly posted, the lack of actual outreach to, and engagement with, community households may have limited the effectiveness of the actions taken. There seems to be no evidence that Oxitec aided in spreading awareness of the trial, potentially resembling their denial of accountability for public education seen in the Cayman Island case study.

A substantial percentage of those who had heard of the trial claimed neutrality, believing they did not possess enough information to make a well-informed decision. Even many of those who supported the plan conveyed a desire for more information or had unanswered concerns. The public release of information was not coupled with the necessary commitment to ensuring community awareness, easing concerns, and guaranteeing transparency regarding the project. There was a significant lack of timely communication at the community, household, and individual levels, as compared to the extensive efforts that were made in North Queensland. Giving the proposal without enough supporting evidence of its effectiveness and safety allowed for critics to dictate much of the initial public dialogue regarding the matter.

[113] Ernst, Kacey C. "Awareness and Support of Release of Genetically Modified 'Sterile' Mosquitoes, Key West, Florida, USA." *PubMed Central*, Emerging Infectious Diseases, Feb. 2015.

The knowledge phase of genetically engineered vectors is particularly crucial in American states, where there is substantial public controversy surrounding their release. Of the 2,649 notes submitted to the United States Food and Drug Administration in response to the proposed Oxitec trial in Key West, a majority (74.8%) were against the proposition.[114] Over half of all these oppositional comments identified a general aversion to genetically modified organisms (67.3%), potential harm to human (67.3%) and environmental health (51.2%), and governmental or industry mistrust (23.6%) as justification for their stances. Psychological essentialism has caused many individuals to oppose transgenic organisms, such as the modified *A. aegypti*, due to the practice of altering what is considered to be 'natural'. Certain modification types have been deemed more 'natural' and thus more acceptable by these standards. Following the extensive resistance to the Oxitec mosquitoes, the Key West district proposed utilizing an alternative company to release bacteria-infected mosquitoes. This was received with less controversy, as utilizing Wolbachia bacteria, which exists in many insects and the natural environment, is often considered more 'natural' than adding synthetically created genes to the insects. In this way, the given form of mosquito may have contributed to the society's resistance regarding the release. Society's mistrust of the government may have stemmed from prior trials, such as that conducted in the Cayman Islands. Knowledge about the lack of consent and choice of Caymanian residents could also have contributed to this concern of suspicious government activity.

Rogers proposes that the adoption of a new idea depends heavily on the piece of technology itself, time, communication channels, and the larger social system. While the technology was deemed practical for adoption by the criteria proposed by Rogers, the socialization of the Oxitec

[114] Bloss, Cinnamon S. "Public Response to a Field Trial of Genetically Engineered Mosquitoes." *JAMA*, American Medical Association, 15 Aug. 2017.

mosquitoes failed to appropriately fulfill and balance the remaining three components. In 2010, following the dengue fever outbreak, but prior to the federal review process completion of the Oxitec vectors, the Key West district first publicly announced a plan for the possible release of these OX513A *A. aegypti*.[115] This announcement neglected to incorporate critical aspects of the PAM model utilized in North Queensland, Australia. Without educational outreach prepared to commence immediately after this proposition, sudden controversy erupted throughout the society. The Key West district and Oxitec company failed to effectively engage with the public in a timely method, allowing the local, opposed groups to first insert information into heavily utilized communication channels. In such a dynamic, there is disconnect between which group has the most information about the given technology and which group dictates the social dialogue concerning its nature. Local organizations, community doctors, and individual residents took stances on both sides of the growing political debate.

While the research done by Oxitec negates many of the raised oppositional concerns, these resistant groups were able to spread political fear into parts of their community. The Florida Keys Environmental Coalition (FKEC) publicly expressed skepticism of Oxitec's new technology. By publishing accessible information online, the FKEC succeeded in instilling political mistrust throughout parts of the Florida community. In an online publication, the FKEC uses biased and accusatory phrases, asserting that Oxitec is "trying to use a loophole [to be approved by] the FDA" and "is a company with everything to gain by breaking into the U.S. market for GM mosquitoes".[116] The same publication attempts not only to undermine the

[115] Ernst, Kacey C. "Awareness and Support of Release of Genetically Modified 'Sterile' Mosquitoes, Key West, Florida, USA." *PubMed Central*, Emerging Infectious Diseases, Feb. 2015.
[116] de Mier, Mila. "Petitioning the U.S. Senate: Say No to Genetically Modified Mosquitoes Release in the Florida Keys." *Florida Keys Environmental Petition*.

credibility of the organization, but also to express the vulnerability of the residents. The FKEC stated that, despite public resistance, Oxitec could release "these mutant mosquitoes...at any point". Residential backyards were likened to test sites, while citizens were called the company's own "lab rats".[117] The organization also released pre-typed petitions addressed to the United Senate expressed strong disapproval of the plan, giving individuals an easy way of actively expressing their resistance. Utilizing this type of language heightens individuals' underlying fears about modified vectors. By strategically using this pathos in their publications regarding the mosquitoes, the coalition capitalized on general aversion to genetically modified organisms.

Appealing to the emotional vulnerabilities of Key West residents, this approach by the FKEC was followed by the rise of additional committees, households, and individuals announcing their disapproval to the transgenic vectors. Citizens for Safe Science, a community group in Key West opposing the vectors' release, also announced their opposition to Oxitec's plan, receiving thousands of dollars in support of its mission to stop the project.[118] Never Again, a non-profit foundation managed by citizens with the primary motivation of ensuring community wellbeing, began reaching out to individual residents via online platforms. Using platforms that are heavily visited and widely accessible in Key West, like Facebook and WordPress, the organization was able to influence many individuals with their selective publications. Protest signs began appearing outside of the Florida Keys Mosquito Control District, using political slogans to express outright disapproval.[119] The Mosquito Control District also received ongoing petitions from numerous local doctors, questioning the potential of antibiotic-resistant bacteria that could

[117] Ibid.
[118] Atkins, Katie. "Key West Group Fires Back at Oxitec." *FL Keys News*, FL Keys News, 15 Oct. 2016.
[119] Allen, Greg. "Florida Keys Approves Trial of Genetically Modified Mosquitoes to Fight Zika." *National Public Radio*, National Public Radio, 20 Nov. 2016.

evolve against the tetracycline injected into the mosquitoes.[120] One online petition had surpassed 230,000 thousand signatures in opposition to the trial.[121] Many journalism outlets covered the conflicting sides of the political battle, further circulating information throughout the society. Some promoted opposition by calling the technology "Jurassic Park mosquitoes", characterizing the approach as "science fiction".[122] At points the method is even discussed mockingly in the articles, one of which asserts that the vectors are "engineered to have two genes inserted into its DNA: one makes the insect glow, the other makes them self-destruct."

Published research negates the concerns raised by these parties. While some individuals resisting the plan claimed that Key West was unaffected by Zika and dengue, the continued release of Oxitec mosquitoes over time was also meant to help prevent future outbreaks. From 2009 to 2010, an outbreak of 90 Zika cases erupted in Key West, while five Florida counties experienced cases of dengue fever between 2010 and 2011.[123] These modified vectors also pose as a preventative measure to outbreaks such as that. At the time of the proposal, Oxitec had also shown that modified genes had not been capable of transmission into humans, other mosquitoes, or animals that ingested the mosquito.[124] The self-limiting mechanism used in the OX513A vectors also ensured that the gene responsible for population suppression would not maintain itself in the environment. After the federal review process was completed, Oxitec was able to confirm that the risk and possible negative effects associated of microbial resistance to

[120] Goodhue, David. "Oxitec's U.S. Owner Forms PAC to Promote GMO Mosquitoes before Vote Taken in Keys." *Miami Herald*, Miami Herald, 30 August 2016.
[121] "Sign the Petition." *Change.org*, www.change.org/p/tell-the-epa-no-to-gmo-mosquitoes.
[122] Shastri, Devi. "Outbreak: Mosquito Battle Gets Political." *Projects Server Index - Milwaukee Journal Sentinel*, 5 Oct. 2017.
[123] "Lessons Learned during Dengue Outbreaks in the United States, 2001–2011: 18(4) - Emerging Infectious Diseases Journal - CDC." *Centers for Disease Control and Prevention*, Centers for Disease Control and Prevention, 16 April 2012.
[124] "FAQ." *Oxitec*, Oxitec, 2018.

tetracycline were negligible.[125] Despite the method's eventually proven safety, the inability to communicate this information at the necessary time allowed a vast circulation of misinformation. Consequentially, results from the November ballot showed that 65% of Key West residents voted against the release of the mosquitoes.[126] However, the vote was given a non-binding nature, existing to primarily gauge public opinion rather than decide the fate of the release.

Not only was the timing of the proposal insufficient for easing public anxieties about the trial, but the district and company failed to be transparent about their actions. Many statements given regarding the safety of the OX513A mosquitoes were presented by Oxitec, possibly contributing to a conflict of interest. While the company has incentive to prove the safety and efficacy of their modified *A. aegypti*, publishing a majority of the studies from within the organization can foster corporate mistrust. Out of the aforementioned comments to the FDA regarding the mosquito release plan in Key West, 23.6% named mistrust of the government as a reason for their stance. Oxitec confirmed their posting of a Craigslist advertisement under a newly formed Florida Keys Safety Alliance on August 26, 2016, intended to recruit political campaigners.[127] These individuals were offered 15 American dollars per hour to visit households on foot, persuading citizens to vote in favor of the modified *A. aegypti* on the residential ballot. On the same day the advertisement was questioned by the Reporter news outlet, it was taken down from Craigslist and Safety Alliance publicly announced its full funding by Intrexon, a company owning Oxitec.

[125] "Environmental Assessment for Investigational Use of *Aedes Aegypti* OX513A." *Center for Veterinary Medicine*, United States Food and Drug Administration. 5 August 2016.
[126] "General 2016." *Summary Results - Election Night Reporting*, 8 Nov. 2016, enr.electionsfl.org/MON/Summary/1662/.
[127] Goodhue, David. "Oxitec's U.S. owner forms PAC to promote GMO mosquitoes before vote taken in Keys." *Miami Herald*. 30 August 2016.

Three days after the mosquito proposal was rejected, Never Again released documents confirming the active status of an Oxitec genetic modification laboratory for mosquitoes inside of the public Mosquito Control District headquarters.[128] Its construction had been complete since 2014, reaching full mosquito production by the beginning of 2015 without public awareness, despite Oxitec confirming that community notice was mandatory. This activity violated a 2012 resolution that guaranteed a halt in all genetic mosquito activity in Key West until additional tests were conducted and the public had voted again.[129] Because taxpayers support the costs of the public Mosquito Control headquarters building, this information generated societal backlash. Some residents saw this dynamic as a strategy for Oxitec to allocate the cost of their expenses to the public, possibly contributing to further resistance against their company.[130] The lack of transparency contributed the public to distrust aspects of the trial itself. Despite Oxitec declaring that female mosquitoes would not be released, community members feared that the company was falsely dismissing this possibility, potentially exposing residents to the bites of these vectors.[131]

III. Untapped Potential Success of Oxitec Mosquitoes in Key West, Florida

Oxitec project managers suggested that opposition to the trail stemmed partly from the lack of visibility surrounding the threat of A. aegypti in Key West.[132] However, in a study conducted two years after the trial's proposition, though 49.9% of participants had not heard of the proposition, a majority (57%) who had heard of the deployment supported or strongly supported

[128] "Secret Keys Lab Has Been Producing GMO Mosquitoes Since 2015." *Never Again*, WordPress. 18 November 2016.
[129] "Action Minutes – Final City Commission." *City Commission of Key West, Florida*, PDF. 3 April 2012.
[130] "Oxitec Secret Contract Hides Millions in Public Costs of GMO Mosquito Project." *Never Again*, WordPress. October 2016.
[131] Shastri, Devi. "Outbreak: Mosquito Battle Gets Political." *Projects Server Index - Milwaukee Journal Sentinel*, 5 October 2017.
[132] Bajak, Aleszu, et al. "In Florida, Managing Public Sentiments on GM Mosquitoes." *Undark*, 23 November 2016.

it.[133] These supporters conveyed a desire to take any measure required in order to eliminate mosquitoes, signifying that these individuals may have better realized the extent of mosquitoes' threats.[134] Most of the informed residents had positive outlooks regarding the trial; thereby, transparently informing the community members of the project's safety and efficacy with appropriate timing could have rallied further support for the project. However, awareness of the Key West trials was more frequent in white individuals, adults, and people earning over $50,000 annually. Historically, knowledge gaps have been regularly found in association with marginalized genders, races, and ethnicities, as well as lower education levels and age. Failure to adhere to principles set by the PAM allowed for the hierarchy to direct the communication of current events. The power structures of communication allow the perpetuation of social inequities. Because of their access to popular communication networks, these individuals are able to research the given technology, voice concerns, and dictate community decisions. Without widespread education, valuable society members will be left out of the disease management criticisms and choices in which, ethically, they should be involved.

Rogers theorizes that despite a certain technology facing rejection during the decision phase, it may later be adopted. In 2016, following the study's publication on the lack of public knowledge, the Florida Keys Safety Alliance began efforts to raise awareness supporting the mosquito campaign, sharing information about the technology and attempting to assuage resident concerns through one-on-one meetings with residents.[135] However, these efforts were conducted with only about two months until the ballot, before residents voted on the ballot, offering

[133] Ernst, Kacey C. "Awareness and Support of Release of Genetically Modified 'Sterile' Mosquitoes, Key West, Florida, USA." *PubMed Central*, Emerging Infectious Diseases, Feb. 2015.
[134] Ibid.
[135] Buzzacco-Foerster, Jenna. Florida Keys Safety Alliance launches to educate voters about genetically modified mosquitoes." *Florida Politics*. 31 August 2016.

insufficient time to fully educate and assure the target population of the OX513A strain. In recent years, significant changes made surrounding the mosquitoes are being utilized by Oxitec in attempts to restart the socialization process elsewhere in Florida. As of 2017, regulatory jurisdiction transferred Oxitec mosquitoes from the FDA to the Environmental Protection Agency (EPA), stating that "mosquito-related products [are]intended to function as pesticides..."[136] The company argues that defining their technology in such a way highlights the crucial role that the insects possess in combating infectious disease. The characterization may potentially appeal to humans who are already comfortable with the idea of utilizing pesticides as the company attempts to deploy the *A. aegypti* in another Floridian location.

If a technology is not accepted by the society that it is being implemented into, regardless of how lifesaving it may be, it cannot serve its intended function. Without being integrated into the preexisting structure of the target society, the technology will be undermined by innate beliefs and fears. As shown under Australian administration, the PAM design, committed to achieving high community awareness and engagement, as well as prioritizing the alleviation of concerns, allowed for the *A. aegypti* release. Arguments exist in the scientific community as to how much information should be released to the public when dealing with such complex technological vector control methods.[137] However, research asserts that public health associations must take scientific, stakeholder, and residential characteristics into account when determining specific thresholds for quantities of released information, as well as levels of engagement and support. In the case of Key West residents and the OX513A strain, insufficient information was released to

[136] "Transfer of Regulatory Jurisdiction for Oxitec's Self-Limiting Friendly™ Aedes in the United States." *Oxitec*, 24 April 2018.
[137] Ernst, Kacey C. "Awareness and Support of Release of Genetically Modified 'Sterile' Mosquitoes, Key West, Florida, USA." *PubMed Central*, Emerging Infectious Diseases, Feb. 2015.

the public, leading to public fear and panic. By failing to make assets of the project's nature available to the community, Oxitec was unable to introduce this disease-preventing technology.

CHAPTER 5: Optimal Socialization of Modified Mosquitoes for Combatting the High Incidence of Malaria throughout Nigeria

Nigeria possesses almost an entire quarter of all global malaria cases and malaria-related fatalities. The declining effectiveness of current vector control methods necessitates the use of Wolbachia-modified mosquitoes. Socializing their application would primarily follow the PAM introduced in Queensland, Australia, with changes made specifically towards the sentiments, daily life, and cultural context of Nigeria and its inhabitants.

I. Necessity for Genetically Modified Vectors in Nigeria

Despite decades of efforts to eradicate malaria, its annual incidence remains high throughout Nigeria, Africa's most populous country. Globally, Nigeria compromises 24% of global malaria cases and 24% of malaria-related fatalities.[138] Approximately three-quarters of Nigeria's 196 million people are presently living in areas with high risk of malaria transmission, signifying the detection of more than one case in every 1,000 individuals.[139] The high presence of *A. gambiae*, the most effective known transmitter of malaria, as well as *P. falciparum*, the deadliest of the human malaria parasites, contributes to 110 million diagnosed malaria cases and to at least 300,000 malaria-related deaths in the country each year.

Vector-borne disease have been shown to disproportionally affect human populations in tropical, underdeveloped nations. Nigeria's tropical climate has the rainfall needed to support the

[138] "Malaria." *World Health Organization*, 11 June 2018.
[139] "President's Malaria Initiative: Malaria Operational Plan FY 2018" *United States Agency of International Development*. PDF. 2018.

reproduction and survival of *A. gambiae* and *P. falciparum*. Dry seasons tend to last from December until March, whereas wet seasons occupy April through November.[140] Excess water produced by wet seasons provides breeding grounds for the mosquito, while seasonal fluctuations in temperature and rainfall correlate with the survival of mosquito and the maturation of the malaria parasite.[141] Underdeveloped nations like Nigeria often lack the human resources necessary for combatting these diseases. While Nigeria possesses a majority of the continent's natural resources, serving as an economic center for the African continent, it is subject to overwhelming poverty levels.[142] Incoming capital from this trade rarely reaches the public, contributing to a lack of public health infrastructure and maintenance. Without the foundation of these healthcare facilities, disease outbreak cannot be prevented.[143] In 2010, over 62% of Nigerians were found to be living in poverty, which considers the availability of basic human needs, including shelter, clothing, sanitation facilities, education, sufficient healthcare, and individual access to 3,000 calories of food each day.[144]

While poverty exists throughout the entirety of Nigeria, it is heavily amassed in the North, conveying a large divide between the North and South regions. Despite identical levels in each region as of 1980, the poverty disparity has since grown – reaching 73.9% of all Northern Nigerians and 53.9% of Southern Nigerians in 2010.[145] Southern Nigeria possesses substantially more universities, and therefore a much higher rate of adult literacy, than Northern Nigeria. The

[140] Eludoyin, O. et al. "Air temperature, relative humidity, climate regionalization, and thermal comfort of Nigeria." *International Journal of Climatology 34(6).* 4 October 2013.
[141] Bretscher, Hope. "Malaria and Climate Change." *Pulitzer Center*, Pulitzer Center.
[142] Felter, Claire, et al. "Nigeria's Battle with Boko Haram." *Council on Foreign Relations*. 8 August 2018.
[143] Sutherst, Robert W. "Global Change and Human Vulnerability to Vector-Borne Diseases." *Clinical Microbiology Reviews* – 17(1): 136-173l. American Society for Microbiology. January 2004.
[144] "National Poverty Rates for Nigeria: 2003-2004 (Revised) and 2009-2010." National Bureau of Statistics. 2019.
[145] Dapel, Zuhumnan. "Poverty in Nigeria: Understanding and Bridging the Divide between North and South." *Center for Global Development*, 6 April 2018.

southern region also has greater economic resources to spend on its citizens, spending more than double the amount per citizen than was spent by the northern counterpart in 2018.

Civil unrest has been associated with the failure of public health systems, contributing to the increased spread of vector-borne diseases; malaria, in particular.[146] In 2015, Boko Haram, an extreme Islamic militant group, was named the world's deadliest terrorist group, while Nigeria ranked as the third country most affected by terrorism throughout the world.[147] The organization is based in Northern Nigeria, which is inhabited by mainly Muslims, while Christians constitute most of Southern Nigeria.[148] Between 2013 and 2015, the group had killed over 12,000 individuals, primarily targeting private citizens through school destruction, village burning, abductions, and suicide bombings.[149] Researchers theorize that the group emerged as a result of political corruption. Following independence from the United Kingdom in 1960, the nation has been subject to long-term political violence, including the hiring of individuals to violently attack political opponents, post-election violence, military coups, and an induced famine during the 1966-1970 civil war. The threat of Boko Haram has reduced foreign investment in Nigeria, perpetuating a lack of financial resources.[150]

In Nigerian communities specifically, poorly structured homes, as well as misconceptions regarding malaria, its transmission, and major preventative actions further contribute to the high

[146] Sutherst, Robert W. "Global Change and Human Vulnerability to Vector-Borne Diseases." *Clinical Microbiology Reviews* – 17(1): 136-173l. American Society for Microbiology. January 2004.
[147] "Global Terrorism Index 2015." *Institute for Economics and Peace*, National Consortium for the Study of Terrorism and Responses to Terrorism. 2017. November 2015.
[148] Nigeria's Battle with Boko Haram." *Council on Foreign Relations*, Council on Foreign Relations. 8 August 2018.
[149] "Global Terrorism Index: Measuring and Understanding the Impact of Terrorism." *Institute for Economics and Peace*, National Consortium for the Study of Terrorism and Responses to Terrorism. 2017.
[150] Dapel, Zuhumnan. "Poverty in Nigeria: Understanding and Bridging the Divide between North and South." *Center for Global Development*, 6 April 2018.

incidence. Less wealthy individuals in Nigeria are likely to live in homes that lack proper ventilation screens or have doors that do not snugly fit into the walls, both of which fail to seal out the *A. gambiae* effectively.[151] Using mosquito nets, which can be treated with insecticides and last for a few years at a time, can effectively protect sleeping family members from transmission. However, despite the effectiveness and low cost of the nets, it has been found that households which possess at least one insecticide-treated net do not always use them, reflecting a disconnect between access and use. Even after supplying long-lasting insecticidal nets to 70 households throughout multiple villages in a Nigerian state, studies found that one year later, just 42% of those who received the nets slept under them each night, while only 52% used them to any degree.[152] In this study, those who failed to use the nets nightly identified the heat as a primary issue, reflecting hassle as a limiting factor. Others have misconceptions about the bed nets, fearing health risks from the chemicals used to treat them and doubting its effectiveness.

The Nigerian public health system faces an array of systematic issues that prevent individuals from receiving necessary malaria treatment. Primarily, a majority of public health infrastructure is poorly maintained, possessing inadequate treatment supplies.[153] Nigeria possesses an estimated 34,000 health facilities, but shortages of Nigerian health workers disallow many of these existing healthcare locations from functioning close to their full capacities. In these locations, many active health workers lack the appropriate knowledge or training to be able to treat unhealthy

[151] Musoke, D. et al. "Malaria Prevention Practices and Associated Environmental Risk Factors in a Rural Community in Wakiso District, Uganda." *Current Neurology & Neuroscience Reports*, US National Library of Medicine, October 2018.
[152] Aribodor, D.N. et al. "Survey of Indoor Adult Malaria Vectors and Challenges of Using Long Lasting Insecticide-Treated Nets in Malaria Control in Awka-Etiti, Anambra State, Southern Nigeria. *Nigerian Journal of Parasitology* 32(163-167). 2011.
[153] "Nigeria: President's Malaria Initiative." *Malaria Operational Plan FY 2018*, Centers for Disease Control and Prevention. 2017.

individuals. Because of these internal complications, many citizens are not able to access high quality healthcare, or healthcare at all.

Reducing the incidence of malaria is a crucial global objective, given that the disease can be deadly if left untreated. While most cases of malaria are curable, the cost of malaria treatment affects many Nigerian's ability to receive treatment after becoming infected. In Northern Ghana, malaria treatment was found to cost only 1% of the richest households' incomes and 34% of the poor groups' incomes.[154] Despite existing medical attention and treatment, some families cannot afford disease testing or other forms of clinical help, or even have access to health facilities nearby. For this reason, many children and pregnant women, who are highly susceptible to fatal malarial infections, often cannot obtain crucial medical services they need to survive.

This landscape of disease and infrastructure fulfill Rogers' first criteria for technological acceptance, addressing problems felt by a target society, while the innovativeness of modified mosquitoes as a vector control strategy has been previously discussed. Upcoming sections of this chapter describe how the technology can be aligned with previous social practices and norms.

II. Appropriate Modification Technique

The discussed case studies show the potential benefits and drawbacks of using each of the technological approaches – OX513A genetically-modified mosquitoes and Wolbachia-infected mosquitoes. While psychological essentialism can make the socialization of modified organisms difficult, the concept of genetic modification has often been seen as more drastic and 'unnatural'

[154] "The burden of malaria in Africa" *Against Malaria Foundation*. PDF.

than the process of infecting *A. aegypti* with Wolbachia bacteria. In the Cayman Islands, proposals to release the bacteria-infected mosquitoes was received with minimal controversy, even following the controversy of the genetically-modified mosquitoes' release. A key disparity between the two approaches is the nature of self-sustainability, or lack thereof. Because the Oxitec strain utilizes a self-limiting gene to instigate population suppression, there must be repeated releases in order sustain the desired effects. This provides stark contrast to the Wolbachia intervention, which is self-sustaining after overtaking a certain threshold of the wild mosquito population. The necessity for continual releases provides a form of 'opt-out' ability for the target society, in which the intervention is able to be halted if unexpected consequences were to occur. However, this benefit is accompanied by a substantial, continuous expenditure of resources. Not only must these genetically-modified mosquitoes be repeatedly reared in scientific laboratory settings, but factors such as community education must also be thoroughly upkept in order to ensure that each release is approved. In developing nations with unstable economic and political backgrounds, these abundant outputs can quickly place additional burdens on the target communities. In the case of Nigeria, the self-sustaining nature of the Wolbachia-infected mosquitoes poses as a significant benefit. Because the Wolbachia method is often seen as more 'natural' than genetic modification mechanisms and can continue its effects after one successful round of introduction, it stands as the most appropriate method to implement in Nigeria. The bacteria have been found to effectively prevent the mosquito-to-human disease transmission in not only *A. aegypti*, but also *A. gambiae*, the main carriers of malaria.[155]

[155] Rasgon JL, Ren X, Petridis M. Can Anopheles gambiae be infected with Wolbachia pipientis? Insights from an in vitro system. *Applied Environmental Microbiology*; 72(12):7718–7722. 2006.

Chauncey Starr, an American electrical engineer, asserted in his investigation of risk management and acceptability that "public acceptance of risk is more dependent on public confidence in risk management than on the quantitative estimate of risk consequences, probabilities, and magnitudes." [156] With respect to these modified vectors, this analysis suggests that target communities place more importance on the ability to combat potential problems associated with the insects' release rather than calculating the precise risks themselves. The potential to withdraw Wolbachia-infected mosquitoes from the target location if harmful consequences occur provides the highest degree of risk management possible. By ensuring target populations that the technology is revocable, much fear about potential harm can be eased.

Prior to 2015, Wolbachia detection in the *Anopheles* mosquito species had never been recorded. However, the bacteria were eventually found in a natural population of *A. gambiae* in Burkina Faso, a country in West Africa.[157] The infection had likely been transferred to the *Anopheles* species from *Aedes albopictus*, resulting in a perfect expression of cytoplasmic incompatibility. This discovery suggested that the *Anopheles* species was not resistant to the bacterial infection, making modification to hinder disease transmission possible. While there seems to be no company that currently manufactures these modified mosquitoes, like Oxitec creates the OX513A strain on a great scale, they have been created by scientists for various research studies. These modified vectors could now be created in large quantities for a release in Warri, Nigeria.

[156] Starr, Chauncey. Risk management, assessment, and acceptability. *Risk Analysis*; 5(2):97-102. 1985.
[157] Lees, Rosemary et al. "Back to the future: the sterile insect technique against mosquito disease vectors." *Current Opinion in Insect Science*. 2015.

III. Potential Social Barriers to the Technology

While the modified mosquito technology has proven its scientific efficacy, there are various potential social barriers to its acceptance. The historical context of colonialism acts as a primary obstacle to introducing the technology in Nigeria. British colonialism of the area in the eighteenth century forced Western culture into the lives of the local population. Under Western rule, Nigerians were required to adopt new ideals, including the English language, Christian beliefs, and the foundation of Western education.[158] The British attempted to utilize divide-and-rule strategies in order to avoid potential rioting and opposition, keeping native communities as geographically and socially separated as possible. In the 1920s, many Nigerians joined other foreign nations in the global Pan-Africanism movement, which focused on ending the European rule over black individuals. When faced with opposition, the British tried to simply foster greater representation for the colonized communities. While Nigeria became independent in 1960, this history contributed to the still-visible instability of the country's political and economic climate.

Because the technology was developed from outside of the intended target region, more specifically by Western scientists, its introduction can possess indications of colonialism or a white-savior complex. This complex refers to white people extending help to non-white people in a way supports one's own interests, rather than for altruistic reasons. Coupled with some of the negative perceptions of mosquito modification, this dynamic emphasizes the importance of ensuring that the target community truly needs this technology and that local community members and organizations are maximumly involved. Nigeria's current landscape of disease conveys the need for an innovative technology that can effectively halt the transmission of

[158] "Nigeria as a colony." *Britannica*, Encyclopedia Britannica. 2019.

malaria. Though the history and the nature of British colonialism have deeply-rooted, long-lasting effects that cannot be easily alleviated, maximum awareness and involvement of the native population can ease possible senses of foreign intrusion. Through education, consent, and participation, possible interpretations of self-serving interest can be effectively diminished.

IV. Practicality of Implementation in Nigeria

Practical implementation in Nigeria involves utilizing crucial aspects of the PAM in order to influence the community's standard way of thinking about vector control approaches. Indoor residual spraying and bed nets have comprised most of the current vector control strategies but are not sufficiently achieving a reduction in malaria prevalence. These methods are beginning to display their failures, with mosquitoes gaining resistance to heavily used insecticides and community's neglect of bed net use.[159] Solely utilizing these techniques will fail to curb the spread of malaria, emphasizing the need for a new, effective approach. The use of genetic modification technology presently represents an anomaly in mosquito control. Despite the proven effectiveness of modified mosquitoes, factors such as its innovative nature, fears of organism modification, and heightened concerns caused by recent controversial experiments require a thorough socialization process. By introducing Wolbachia-infected *A. gambiae* through the PAM, socialization can successfully occur, allowing for modified mosquitoes to be engulfed into the current scheme of vector control. Once the insects are socially accepted as a new norm for disease prevention, the insects can be ethically and effectively released across communities.

[159] Aderibigbe, S. et al. "Ownership and utilization of long-lasting insecticide-treated nets following free distribution campaign in South West Nigeria. *The Pan African Medical Journal*. 2014.

Due to economic practicalities, the city of Warri, located in the south Nigerian state of Delta, poses a suitable area to first implement Wolbachia-infected mosquitoes. The more stable political climate and greater economic expenditures per citizen in South Nigeria, as compared to the North, provides advantages for successful socialization and implementation processes. Throughout Queensland, Australia, the successful socialization and approval model cost around $13 USD per person. In more densely populated areas that utilized the same process, such as Brazil and Indonesia, costs were found to be less than $3 USD per capita.[160] Nigeria's average population density falls between those of Brazil and Indonesia, making the projected cost of the strategy in Nigeria also below $3 USD for each individual in the population.[161] Warri lies directly next to the Niger River delta, which behaves as a suitable environment for *A. gambiae* and *P. falciparum* survival.[162] It already behaves as a home to schools and federal hospitals, allowing for a simpler transition of the PAM into this southern Nigerian city.

Despite Warri possessing useful resources, internal structural and healthcare conflicts require the introduction of a new vector control method. A 2012 study found that, despite the prevalence of diseases such as malaria, only one primary healthcare center existed for the care of between twelve thousand and twenty-five thousand individuals living in Warri.[163] By standards set by the World Health Organization, this ratio was deemed insufficient for the goal of achieving stable health for all Nigerian citizens. The large imbalance between the population and its resources prevents affordable health treatment or optimal accessibility. While this necessitates additional

[160] Stone, Judy. "Mosquito Wars – Big Win in Australia Brings Hopeful News for Southern U.S." 3 August 2018.
[161] "Country Comparison: Australia vs. Nigeria." *Country Economy*. 2018.
[162] Britannica, The Editors of Encyclopaedia. "Warri." *Encyclopædia Britannica*, Encyclopædia Britannica, Inc., 26 May 2011.
[163] Agaja, S.A. "Spatial Distribution of Primary Health Care Centers in Ughelli South and Warri South Local Government Areas of Delta State, Nigeria. *International Journal of Science and Technology Research*, 1(9): 38-41. 9 October 2012.

functioning, accessible healthcare infrastructures throughout the southern state, it also highlights the current need for additional disease prevention measures.

Aspects of the PAM must recognize differences between the routines and social customs of their citizens in order to be successfully translated from Australia to other nations. The primary step of the community engagement process must cater to locations and activities that Warri citizens engage in frequently. Various media platforms constitute a large part of the middle-income class' entertainment. In Nigeria, television, radio, music, and movies have grown rapidly in popularity throughout the demographic, offering sufficient media channels to utilize for the spread of information.[164] Details concerning the threat of malaria, modification technology, the proven safety of its application to *A. gambiae*, and the implementation process can reach a large subset of the population in this manner. Informational kiosks and promotional posters can be placed in highly accessed areas, such as community markets and popular public locations that a majority of Warri's population is receiving information about the trial. Local organizations and community members must be involved in the communication and outreach stages of this process.

Using reliable society members, though also done in Queensland, is of even greater importance in developing nations. In these countries, like Nigeria, there commonly exist similar historical patterns of poor leadership, concentrated political and economic power, and governmental corruption that contribute to their failed development.[165] These dynamics can often cause a great mistrust of government figures. Possible sources of mistrust, such as Oxitec's conflict of interest,

[164] Kirk-Greene, Anthony Hamilton Millard, and Reuben Kenrick Udo. "Nigeria." *Encyclopædia Britannica*, Encyclopædia Britannica, Inc., 16 January 2019.
[165] Victor, Dike E. "'Why Nations Fail' to Develop: The Case of Nigeria." *Journal of Research in Crime and Delinquency*, 28 October 2015.

must be thoroughly minimized in order to foster the greatest sense of support possible. It is much more likely for technological innovations, such as the modified mosquitoes, to be accepted by citizens when proposed to them by their trusted leaders. These community leaders are local individuals who are largely involved with, and respected by, their fellow citizens. Oftentimes, they take on leadership roles within their area in order to improve community life or health, motivated by altruism rather than financial compensation.[166]

Stated by Dominique Brossard, a professor in the Department of Life Sciences Communication at the University of Wisconsin-Madison, "Trust matters more than knowledge." [167] Supporting this statement, Brossard's studies have shown that people are more likely to accept a message when they trust the person relaying the message. The form of necessary trust varies with respect to different agents that are involved in the introduction of technology. For example, citizens must believe that corporations prioritize their wellbeing, that advocacy groups are experts in their respective field, and that the government is transparent and honest. All of these facets apply to the socialization of modified mosquitoes in Nigeria. The scientific creators of the modified *A. gambiae* and the Nigerian government must actively collaborate to assure citizens that the introduction of modified vectors prioritizes community health and well-being, as opposed to profit alone. This sentiment can be conveyed most effectively through continuously updating the public on scientific research, government plans, the release, and epidemiological outcomes. Such information should be spread through the aforementioned methods, such as public posting and communication via media networks. Further revealed by Brossard, individuals are more likely to

[166] Ehrich, L. "Learning for Community Leaders." *Queensland University of Technology*. 2004.
[167] Sawyer, K. et al. "How People Think (about Genetically Modified Organisms)." *Public Engagement on Genetically Modified Organisms: When Science and Citizens Connect*." Washington, D.C. National Academies Press. 2015.

listen, understand, and approve of a position if it is presented to them by a person consistent with their own cultural outlook.[168] Otherwise, a person's views will most likely be dismissed. Hence, it is crucial that trusted community members are recruited to help advocate for the release. Because fellow citizens are expected to experience the same social, cultural, and epidemiological conditions as one another, they are more inclined to listen to, and trust, one another. Community members must be thoroughly educated about modified mosquitoes and their release by the mosquitoes' creators to assuage the concerns and gain the belief of their fellow citizens.

Following the failed trials in Key West, Florida, scientists stressed the importance of educational outreach targeting local groups with lower awareness of public health measures.[169] In order to reach these individuals in Warri, informative door-to-door visits and smaller public presentations can be held in areas of the city that do not receive, or utilize, enough electricity to be sufficiently informed of the trials through media outlets. These visits can be made by community leaders who are supported by government efforts to socialize the vectors, as well as local citizens who acknowledge the need for such technology and volunteer to help spread knowledge. As of December 2018, certain roads throughout Warri have been left without an electricity supply for over one full year.[170] Despite the Benin Electricity Distribution Company vowing to install new transformers in order to restore power along these roads, these measures have not yet been taken. The distribution or degree of utilizing these technologies, as well as other facets affecting access to information, must be considered in order to efficiently maximize the scope of education.

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[168] Sawyer, K. et al. "How People Think (about Genetically Modified Organisms)." *Public Engagement on Genetically Modified Organisms: When Science and Citizens Connect*." Washington, D.C. National Academies Press. 2015.
[169] Ernst, Kacey. "Awareness and Support of Release of Genetically Modified "Sterile" Mosquitoes, Key West, Florida, USA." *Emerging Infectious Diseases*, 21(2): 320-324. 21 February 2015.
[170] Falade, Faderera. "Warri Residents Protests Lack of Power Supply for Over A Year." *Naija News*, Naija News, 26 December 2018.

The city of Warri possesses numerous primary, secondary, and college-level institutions, which provide an optimal setting for beginning to foster active project participation from the surrounding community. In primary and secondary school settings, part of the curriculum can be shifted in order to educate students about the potential role of genetically modified mosquitoes in preventing the spread of infectious diseases. These students can be offered the opportunity to assist in rearing and releasing the insects, as were done in North Queensland communities. Nigeria's cultural emphasis on positive household relationships may further incline households to actively participate in the release process, which will subsequently contribute to both increasing general support for the modified vectors and slightly to reaching substantial prevalence in the environment.[171]Quantitative surveys should match the way in which they were conducted in the Queensland trial. An external market research company should be utilized in order to minimize bias in the strategy's outputs. Telephone surveys can be made at the same intervals, occurring approximately every six months, reaching the same audience of between 200 and 600 individuals per instance. This provides crucial information regarding how much Nigerian citizens' knowledge about the project has increased since the beginning of the process.

The issues management system must be composed of trusted Warri community members in order to create a dynamic in which citizens are comfortable voicing their questions and concerns about the mosquito trials. Individuals will feel more secure articulating their fears about the potential project with other community members to whom they feel they can relate. This dynamic can help foster a greater sense of trust – while residents will typically believe a fellow

[171] Labeodan, Morire. "The Family Lifestyle in Nigeria." *School of Statistics and Actuarial Science*, University of Witwatersrand.

local has their best interest in mind, they may not believe government officials possess the same interests and priorities. In this relationship, the community leaders represent a type of social deviancy, in which the individuals diverge from the norms of social thinking by welcoming the use of genetically modified organisms rather than bed nets and insecticides. The use of positive deviants is a proven approach to initiating social change to find improved public health solutions to societal problems, like the given prevalence of malaria.

By influencing peers to follow in this way of thinking, community leaders can effectively lead to the acceptance of the technology at hand. Their deviance in thinking can cause community leaders to be considered the innovators of the society, in terms used by Rogers, contributing to many others' latter acceptance and adoption. While the diffusion of innovation theory insinuates that acceptance of the new technology will never reach one hundred percent of the target audience, it is possible to reach a large majority of Warri citizens through this method. Because the PAM relies on community consent, rather than individual, the socialization process can lead to the approved use of the malaria-resistant vectors. In this way, the anomalous technology can be accepted by Warri citizens as a standard, effective method of vector control, creating a new overarching paradigm of thought on disease prevention.

As an evaluation measure, the community reference group noted in the PAM must include both these trusted group leaders and individuals from key stakeholder groups. In Warri, individuals appointed by the community, as well as representatives from Nigeria's Ministry of Health and the Ministry of Science and Technology should be present on this team. This group will review data regarding the socialization activities in Warri, ensuring that the strategy is actively carried

out through publicly and individually communicating information. The community members can relay their fellow inhabitants' opinions on the program and identify any possible changes that may need to occur to reach the elimination of malaria. As in Queensland, meetings should occur monthly before the beginning of releases, and at least bi-monthly following the initial release.

CONCLUSION

Globally, the suffering and fatality associated with mosquito-borne diseases remain unacceptably high, with illnesses such as Zika Virus disease, dengue fever, and malaria affecting marginalized countries at disproportionate rates. Prominent intervention methods continue to decrease in efficacy, with mosquitoes gaining resistance to residual spraying and individuals neglecting the use of insecticide-treated bed nets. This thesis has argued for the transition to modified mosquitoes as a primary form of vector control in order to combat various mosquito-borne illnesses. Despite existing concerns regarding the release of such insects, past models have shown that these worries can be effectively and morally alleviated. Analysis of the Cayman Islands case study discusses how dishonesty from both the Cayman government and Oxitec create a problematic social trade-off between epidemiological success and societal mistrust. The successful release of Wolbachia-infected mosquitoes in Australia is paralleled with a failed release in Key West to highlight not only the importance of fostering community engagement, but also how public perceptions of different modification techniques can differ greatly.

Utilizing analyses of the three case studies, this work created a strategy for implementing a new form of vector control into a much-needed public health context. Considering Winner's social requirements for technological acceptance, Warri, Nigeria was chosen as a practical, initial target setting for the release of such mosquitoes. Through contemplating the location, advocating for a specific form of modified vector, and modifying the social engagement model based on Warri's cultural context, this thesis produced an approach to socializing the modified mosquitoes and combatting the extremely high, ongoing prevalence of malaria.