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Eradicating Mosquitoes? The Promise and Peril of Gene Drive Technologies

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Abstract

This paper discusses the ethical issues associated with genetic modification of mosquito species that are human disease vectors. The Oxitec genetically changed mosquito—a variant of a species called *Aedes aegypti*, OX513A, is taken as an example. The benefits and risks are discussed, and questions need to be discussed in public prior to release of this gene drive system.

Introduction

Mosquitoes are high-impact disease vectors with the capacity to transmit pathogen agents that cause diseases such as malaria, yellow fever, chikungunya, dengue, and most recently Zika (Overcash 2015). Mosquitoes kill an average of 725,000 people every year. Since scientists first made the connection between malaria and mosquito bites, the mosquito has been the subject of important research, and also the vector of at least a dozen fatal diseases (Dawson 2016).

There are as many as 3,500 different mosquito species, of which 30 spread malaria, which kills more than 400,000 people, mostly children, every year. Zika virus, closely associated with birth defects and severe neurological symptoms, has

spread to dozens of countries. If species such as *Anopheles gambiae*, a major malaria vector and *Aedes aegypti* , a Zika virus vector could be eradicated, the world would surely be relieved from the deadly diseases (Economist 2016). The most common manners in which to target the mosquito are familiar. Nets, spray repellant, and insecticides are used worldwide to keep mosquitoes away and to reduce population density. But more recently, genetically-modified mosquitoes have been developed, which could potentially be used to reduce mosquito populations. A British company named Oxitec has developed a genetically changed mosquito—a variant of a species called *Aedes aegypti*. This mosquito, called OX513A, is a sterile male, modified so that when a male OX513A mates with a wild female, the resultant eggs will not be viable. They will never hatch. These male *A. aegypti* mosquitoes have been released in Brazil, and sought approval to release the male OX513A mosquitoes in Florida, as a way to combat the spread of the Zika virus (Wolf 2016).

While there is no vaccine for Zika virus, many people are so excited at using genetic engineering to kill off mosquitoes. However, no one yet knows if this method is an effective solution (Plumer 2016).

Gene drive

A tool called gene drive may be even more effective than Oxitec's GM mosquito. Unlike an ordinary gene, which is passed on to just half of all offspring, a gene drive construct could be passed on to virtually all offspring (Adelman 2016). By combining a revolutionary new technology called CRISPR-Cas9 with gene drive, eradicating the mosquito has become reality. CRISPR (an acronym for "clustered regularly interspaced short palindromic repeats") refers to bits of viral DNA that bacteria have incorporated into their own genomes. With assistance from the splitting enzyme known as Cas9, CRISPRs help bacteria defend themselves against viruses. In 2012, researchers modified the CRISPR system into a gene-editing tool to cut and paste any gene in any organism (Saey 2015). Guide RNA helps the Cas9 enzyme to find and cut the pre-selected location in double DNA. As the cell moves to repair the cut strand of DNA, it replaces it with DNA that matches the selected DNA. It inserts a pre-selected gene sequence precisely where researchers want to put it.

Because the CRISPR-Cas9 tool can be made of DNA (that code single guide RNA and Cas9 protein), it is possible to use CRISPR to insert it into the target organism. Whenever the cells divide, the CRISPR-Cas9 tool is spliced into each genome, and brings with it whatever genetic sequence researchers select. In this way, a genetic sequence can be inserted into every wild-type DNA sequence with which it is paired. This mechanism is called a "gene drive," because it can be used to drive a selected genetic sequence into a population so that, eventually, if the genes function as expected, every descendent organism will possess the phenotypic trait associated with the selected sequence (Wolf 2016).

Gene-drive technology essentially creates genetically modified organisms to stimulate the inheritance of certain genes combating malaria throughout entire populations. Last year, a research team at Imperial College successfully modified *Anopheles gambiae* mosquitoes to have 95% male offspring (Hammond et al. 2015); this sex ratio bias was further inherited by the modified offspring. The long-term effect of this modification would be the eradication of this mosquito species.

The research team of the University of California, San Diego and Irvine campuses reported that they successfully modified the mosquitoes to carry genes for antibodies that target the *Plasmodium* parasite (Gantz et al. 2015). The anti-malarial gene was inherited by 99.5% of the modified offspring. These mosquitoes would then mate with non-modified mosquitoes in the wild and pass the anti-malarial genes on to their offspring, ideally leading to all future generations being resistant to the malaria parasite.

As noted above, a trait is a genetically determined characteristic of an organism. In normal sexual reproduction, a trait generally has only a 50% chance of being expressed. With a gene drive, however, that trait is "driven" into the organism's reproductive cycle so that every single offspring always carries and expresses the specified trait (SynBio Watch 2016).

The promise

The implications are huge, with both tremendous potential and risks. Among the possibilities, gene drive could be used to spread genes that reduce the ability of mosquitoes to transmit parasites or that produce mostly male mosquitoes to twist the sex ratio. Such systems could stop mosquito-borne deadly diseases, including malaria, Zika, and dengue (Otto 2016).

Gene-drive-based approaches differ from traditional vector control methods such as insecticides and removing breeding sites. With a gene-drive system, the population of the target species could be massively disrupted, without directly affecting any other species.

The development of gene drive approaches, combined with current mosquito control practices, holds the promise of reversing this trend and bringing us closer to the goal of eradication of a

mosquito species and the terrible pathogens that depend on it (Adelman 2016). Some researchers even contend that the eradication of deadly mosquito is our moral duty (Meador 2016).

The risks

Many people including some researchers are uncomfortable with the idea of gene drives that have the potential to eradicate an entire species. Though we might assume that mosquito lack significant moral status, we can distinguish killing of individual organisms from the eradication of a whole species. For example, Holmes Rolston III argues that to kill a species is the "super killing" of a whole pattern of life, and as such is less acceptable than the killing of an individual organism. Although species lack moral agency, self-awareness, sentience or individuality, Rolston's contention is that species lines are individual systems, whose parts are individual organisms. The argument for species-level respect might be to accept the traditional deontological view that a duty requires a moral agent, while denying that this agent must be a person or an individual organism (Jebari 2015).

Yet, there has been a degree of moral concern about eradicating mosquitoes. it seems ridiculous to claim that humans were overly bold in eradicating the mosquitoes responsible for malaria or Zika transmission through the development of gene drive, and even more problematic to claim that such boldness was morally wrong; the wrong of the supposed bold attitude here is surely morally outweighed by the value of the many human lives that were saved by eradicating mosquitoes (Pugh 2016).

On the other hand, the risks of gene drive following release can be also huge. Driven genes could spread beyond the intended area. Applying gene drive to reduce or eliminate the species may have unintended side effects (Otto 2016). Gene drive might act in unexpected ways and cause a variety of environmental harms, while not deliver the promised benefits. And, it's impossible to predict the ecological consequences of such a rapid, massive, and unprecedented disruption (SynBio Watch 2016).

Mosquitoes might play key roles in ecosystems, such as providing food for bats and other insectivores, and "scientists have minimal experience engineering biological systems for evolutionary robustness". It's possible that a gene drive might not distribute the intended trait throughout a target population, or might find its work blocked by a naturally occurring mutation, or might spread the trait to non-targeted species. It's also possible that a gene drive could stimulate other unforeseen evolutionary responses over a longer term in both target and non-target species. And, again, the ability to redress any of these unintended consequences could be sharply limited by the lack of reliable reversal mechanisms (Meador 2016).

However, many scientists who research mosquito biology and ecology are skeptical that the eradication of mosquitoes would have particularly bad ecological consequences.

> *"Mosquitoes don't occupy an assailable niche in the environment. If we eradicated them tomorrow, the ecosystems where they are active will hiccup and then get on with life. Something better or worse would take over (Fang 2010)."*

Scientists are unclear whether gene drives could spread to closely related species. Eight species known as the *Anopheles gambiae* complex of mosquitoes in Africa came from common ancestors less than 5 million years ago, and they sometimes still interbreed, producing fertile hybrids. Gene drives might transfer from one species to another by this interbreeding. But given that almost all species can carry malaria, transfer from one species into another might even be desirable (Saey 2015). In contrast, the eradication of a mosquito lets another mosquito occupy the same niche, making things even worse. Once *Aedes aegypti* is gone, *Aedes albopictus* might move in and serve as a Zika vector (Adelman 2016).

Conclusion

The ethical, ecological and societal implications of gene drives are especially complex and challenging. Activists and even some experts in the field are on alert against this powerful technology. This raises the basic question: Who will benefit from this technology and who decides how it will be used? How would anyone be able to assess the risks of gene drives? Would the public be informed and have a say in how they would be used? And if an accident were to occur, given that the damage would be massive and irreversible, who would be held accountable (Civil Society Working Group 2016)?

Until recently, such questions are exclusively in the hands of scientists, who promise to regulate themselves so as to push their research to the limit (Akbari et al. 2015). As attractive as the promise of eradicating mosquitoes and halting the advance of malaria and Zika using CRISPR-Cas9 gene drives may be, we need a deliberation on the risks of gene drive technologies. We need to have a genuinely inclusive debate about the issues raised by this new technology, addressing the ethical, legal, and social implications of gene drive (Dawson 2016).

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Better Humans and evolutionary nudge

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Abstract

Gene therapy especially newly developed CRISPR gene editing spawns complex conversations, ethically, emotionally, politically, and economically, within and among countries. As new technology makes its way through the experimental development, assessment, refinement and application, it is not too soon to begin the policy and ethical dialogues about how and when and for what purpose it is used. Certainly experiments should continue to assess whether CRISPR is the long sought for means to effective gene therapy. It will probably be used in somatic cell gene therapy trials sooner than later. Policy and ethical discussions ought to precede its use at the germline stage.

Introduction

The recent discovery and application of clustered irregularly interspaced short palindromic repeats (CRISPR) Cas9 editing of DNA has generated great optimism for its potential to correct harmful genetic traits. Eliminating all "genetic diseases" stretches the imagination and posits an objective that may be feasible in theory while doubtful in application. New applications, tests, and successes with CRISPR/Cas9 saturate the scientific literature. So prevalent are such reports that the faculty in the Biomedical Sciences Master of Science program at Hood College offered a special topic graduate course on "Gene Editing" in summer 2017. The course had three units: (i) the science of editing, how the guide RNA matches the target DNA to specify where to cut and repair the genetic

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