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Genetic Modification of Malarious Mosquitoes: Biological, Bioethical, and Biopolitical Considerations

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***Abstract*: Accounting for roughly 400,000 deaths and 300 million infections each year, malaria is one of the toughest and most important global health challenges for scientists and public health policymakers. In order to reduce malaria morbidity and illness, policymakers have implemented numerous antimalarial interventions in endemic areas, such as indoor residual spraying and the distribution of bednets. A novel control method that more directly targets the disease-transmitting vectors entails the genetic modification of mosquitoes and the release of these modified mosquitoes into malaria endemic environments. In order to gain a clearer understanding of this novel malaria control method, this paper thoroughly reviews the growing body of literature pertaining to developments and issues in transgenic mosquito research. This paper finds that to date, scientists have approached transgenic malaria research from two distinct angles. While some have attempted to induce female sterility traits in mosquito populations, others have focused on spreading refractory genes into mosquito populations. Although both research approaches have been demonstrated to have remarkable success, there are several bioethical and public health considerations that must be taken into account before either method can be implemented in the field. Most importantly, field implementation will require additional research on the population dynamics of mosquitoes in endemic settings and a more thorough assessment of public consent in malarious communities. Once researchers gain a more complete understanding of the biological, bioethical, and biopolitical facets of genetically modified mosquitoes, genetic malaria control may become a reality.**

***Keywords*: Bioethics, Genetically Modified Mosquitoes, Malaria, Public Health.**

I. INTRODUCTION

Globally, malaria is an infectious disease that results in more than 400,000 deaths and 300 million infections each year [1]. Approximately half of the world's population lives at risk of malaria, making malaria one of the toughest and most important global health issues for researchers and public health policymakers. In order to reduce morbidity and illness, numerous antimalarial interventions have been implemented in regions where populations are at risk of malaria. Common interventions in malaria endemic communities include indoor residual spraying, the dispensation of antimalarial drugs, and the distribution of malaria bednets, among others [2,3,4]. Although these three interventions have greatly reduced malaria-related deaths and infections in the past decade, these interventions alone are unlikely to completely eradicate malaria at the international level. This is due, in large part, to the severe economic conditions in malarious areas, which reduce availability and accessibility of antimalarial resources to the millions of people who require these resources [5]. Several studies have reported that in order to eliminate malaria, researchers will need to more directly target the vectors that transmit malaria infections [6,7,8].

As a result of relatively recent technological developments, the most direct way to target malarial vectors may be the genetic modification and manipulation of disease-transmitting mosquitoes. The rationale behind this novel malaria control method is that if mosquitoes are genetically transformed and rendered refractory against malaria infection, these genetically engineered mosquitoes can be released into the natural environment. As a result, over several generations, mosquito populations would become increasingly incapable of transmitting malaria, thereby reducing the global burden of malaria to the point of disease eradication [9,10,11]. In theoretical terms, this novel malaria control method appears promising and has therefore garnered the attention and interest of parasitology researchers and global health strategists.

In order to better understand the nature of genetically modified mosquitoes, this paper aims to expound on the findings and technological advancements that have been made by researchers to date. Additionally, by virtue of a thorough literature search using Google Scholar, this paper considers the bioethical and public health concerns that have surfaced in response to the idea of genetically modified mosquitoes.

II. DISCOVERIES AND DEVELOPMENTS THUS FAR

The idea of genetically manipulating mosquitoes as a malaria control method was first proposed in 1968 by Professor C.F. Curtis at the London School of Hygiene and Tropical Medicine [12]. After major advances in the molecular manipulation of *Drosophila melanogaster* during the 1980s, the World Health Organization released a document that enumerated three research aims that would have to be fulfilled before field research on a malaria genetic control method could commence [13]. These research aims were the development of tools that could be utilized for genetically engineering malaria vectors, the identification of specific effector genes that could inhibit parasite transmission, and the invention of methods to effectively drive these specific genes to fixation in wild mosquito populations [13]. In 2002, a report explained that while the first two aims had been met, the third aim was still in the developmental stages [14].

In the last five years, as a result of the novel CRISPR-Cas9 technology, researchers have been able to accomplish the third objective that was issued by the World Health Organization. The CRISPR-Cas9 gene-editing tool, which first emerged in 2012, enables scientists to cut a desired fragment of DNA and accurately modify or remove genetic sequences in a target organism [15]. Moreover, the CRISPR-Cas9 gene-editing tool is remarkably inexpensive, costing only 30 United States dollars per sequence. For these reasons, this powerful new technology has biomedical implications not only for malaria, but also for sickle cell anemia, HIV/AIDS, cancers, and several other human diseases [16]. The implementation of the CRISPR-Cas9 technology for diseases such as malaria, however, depends on innovative “gene drive” systems. First proposed more than 10 years ago, synthetic gene drive systems use site-specific endonucleases to spread hereditary traits throughout a population over the course of a few generations. Most importantly, the gene drive system ensures that the gene of interest is passed down to all of an individual’s offspring, rather than the expected 50 percent, even if the gene renders the offspring less fit [17]. For this reason, in a relatively short period of time, gene drive systems that enable this type of super-Mendelian inheritance could transform the entire genetic makeup of mosquitoes in a way that might eliminate their malaria-transmitting capabilities.

In 2015, using this notion as a basis, a team led by researchers at Imperial College London made an important discovery that momentously advanced the potential of gene drives to eradicate malaria. In order to test the previously theoretical gene drive, the researchers first identified three genes (*AGAP005958, AGAP011377* and *AGAP007280*) that confer a recessive female-sterility phenotype. Into each locus, the team inserted specific CRISPR-Cas9 gene drive constructs that were designed to target and edit each gene. The paper, published in *Nature Biotechnology*, reported that at each targeted locus, transmission rates of female-sterility genes from parent to offspring ranged from 91.4% to 99.6% [18]. The team also found that one gene in particular (*AGAP007280*) met the established minimum requirement for a gene drive targeting female reproduction in an insect population, suggesting that if this gene were to be inserted into a few individual mosquitoes, an entire population of mosquitoes could acquire the gene within just a few generations. As a result, the mosquito population would be soon characterized by universal female sterility, and the entire mosquito population could be eliminated shortly thereafter. These findings highlight the promising potential of gene drives to accelerate the global reduction of malaria transmission.

In contrast, another genetic solution to malaria focuses not on female sterility traits, but on malaria resistance traits. Among several innovative technologies proposed to reduce malaria prevalence is the introgression refractory genes into mosquito populations [19]. Such genes, if introduced into mosquito populations, would interfere with the vectors’ ability to transmit the disease-causing pathogens to humans. Accordingly, a team of researchers from the University of California at Irvine and the University of California at San Diego investigated the potential of this novel method last year. Using the Asian malaria vector *Anopheles stephensi*, the team developed a highly efficient gene drive system that can rapidly spread antimalarial genes into a target vector population. The study, published in the *Proceedings of the National Academy of Sciences*, reported that following outcrosses of transgenic lines to wild-type mosquitoes, the antimalarial genes were successfully introgressed into 99.5% of the progeny [20]. These findings suggest that engineered refractory genes can be rapidly spread into a population of mosquitoes, thereby rendering the entire population unable to transmit malaria infections.

Therefore, scientists have made momentous strides towards the development of technologies that manipulate the genes of mosquitoes as a means to substantially reduce malaria transmission. To date, researchers have approached genetic engineering of mosquitoes from two distinct angles. While some have focused on inducing female sterility in mosquito populations, others have concentrated their efforts on spreading refractory genes that would maintain the existence of mosquitoes, but prevent the transmission of pathogens from mosquitoes to humans. Interestingly, both methods have been demonstrated to have remarkable efficacy as potential malaria control measures.

III. BIOETHICAL AND PUBLIC HEALTH CONCERNS

Despite the promising potential reported in recent studies, however, these novel genetic control strategies have spawned bioethical and public health concerns that ought to be duly considered before genetic mosquito control can be implemented in field settings.

Prior to the release of genetically modified mosquitoes into the field, researchers will need to develop a stronger understanding of the ecological and population genetic aspects of genetic malaria control. In order to establish reasonable goals and procedures for the release of genetically modified mosquitoes in field trials, researchers must first study the dynamics of the natural populations of mosquitoes, as well as their prey and predators. A firm understanding of population dynamics will enable researchers to more accurately assess the feasibility of specific release strains and potential release timelines [14]. Population genetics studies, such as one that examined gene flow among populations of the vector *Anopheles gambiae* in Mali, will enable policymakers to more effectively plan the logistics of field trials, which will be essential to the success of transgenic mosquito releases in natural field settings [21]. Without proper planning and without sufficient knowledge on the ecology and population dynamics of natural mosquito populations in malaria endemic settings, releases of genetically modified mosquitoes may be unsuccessful, thereby weakening public trust and confidence in the potential of genetic malaria control [14]. Therefore, researchers must thoroughly study the ecological aspects of transgenic mosquito releases prior to the implementation of large-scale field trials.

Moreover, concerns have been raised by bioethicists. The most important ethical consideration is the informed consent of the public in communities where genetically modified mosquitoes may be released. Proper authorization and consent from the community is a paramount ethical requirement that must be met before sites can be chosen for field research on genetic malaria control [22]. Currently, the best way to assess public consent is most likely the implementation of large-scale surveys that qualitatively or quantitatively evaluate participants' knowledge, attitudes, and opinions about genetically modified mosquitoes [23]. One such survey investigated the perspectives of people in Mali towards the idea of releasing transgenic mosquitoes for malaria control [24]. The authors of this study found that although the majority of participants supported genetic malaria control in their communities, they nonetheless wanted scientists to be sure of the potential environmental and health consequences prior to releasing transgenic mosquitoes in field trials. These findings underscore the importance of gaining and verifying public acceptance before testing transgenic mosquitoes in natural field settings.

Although the aforementioned issues represent the primary ecological and bioethical concerns, there are still many more points that public health researchers and strategists must consider. For example, although modern global health interventions rely heavily on community engagement and public consent, the notion of a community remains poorly defined because there is no standard scientific definition of a "community" or "community engagement" [25]. In other words, there is no standardized procedure for obtaining a community's consent for field research. Moreover, in developing nations where transgenic organisms have historically had unintended consequences, political leaders may be averse to the notion of releasing transgenic mosquitoes into the natural environment [26]. Thus, controlling malaria by

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means of transgenic mosquitoes is a multifaceted issue. There are a myriad of biological, bioethical, and biopolitical considerations that must be taken into account before genetic malaria control can become a reality.

IV. CONCLUSIONS

By virtue of a thorough literature review, this paper examined the growing body of research on transgenic mosquitoes as a novel malaria control method. Thus far, researchers have successfully developed techniques to rapidly spread female sterility and refractory genes into mosquito populations. However, before these techniques can be implemented in field trials, several ecological and bioethical considerations must be taken into account. Specifically, the implementation of field trials will require additional research on the population dynamics of wild mosquito populations in endemic areas and a more thorough analysis of public and political perspectives on genetic malaria control in developing countries. Only once the various scientific, ethical, and political facets of transgenic mosquitoes are given full consideration will researchers be able to proceed to large-scale field research on genetically modified mosquitoes.

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