Using Gene Drive Technologies to Control Vector-Borne Infectious Diseases

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Abstract: After years of success in reducing the global malaria burden, the World Health Organization (WHO) recently reported that progress has stalled. Over 90% of malaria deaths world-wide occurred in the WHO African Region. New tools are needed to regain momentum and further decrease the burden of malaria. Gene drive, an emerging technology that can enhance the inheritance of beneficial genes, offers potentially transformative solutions for overcoming these challenges. Gene drives may decrease disease transmission by interfering with the growth of the malaria parasite in the mosquito vector or reducing mosquito reproductive capacity. Like other emerging technologies, development of gene drive products faces technical and non-technical challenges and uncertainties. In 2018, to begin addressing such challenges, a multidisciplinary group of international experts published comprehensive recommendations for responsible testing and implementation of gene drive-modified mosquitoes to combat malaria in Sub-Saharan Africa. Considering requirements for containment, efficacy and safety testing, monitoring, stakeholder engagement and authorization, as well as policy and regulatory issues, the group concluded that gene drive products for malaria can be tested safely and ethically, but that this will require substantial coordination, planning, and capacity development. The group emphasized the importance of co-development and co-ownership of products by in-country scientists.

Keywords: gene drive; mosquitoes; malaria; biocontrol; vector-borne infectious diseases; Africa

1. Introduction

Mosquitoes and several other invertebrate organisms are able to transmit (serve as vectors for) infectious pathogens that are responsible for tremendous global morbidity and mortality [1]. More than half the world’s population is at risk of contracting vector-borne diseases each year [2]. In particular, mosquitoes are recognized as one of the deadliest animals on earth, carrying malaria, as well as several debilitating arboviral and other diseases [3] (see Box 1).

Box 1. The Toll of Vector-borne Diseases [3].

- More than half the world population are at risk of vector-borne diseases each year
- Estimated 725,000 deaths annually from mosquito-borne diseases
- 216 million clinical cases of malaria infection
- 96 million clinical cases of dengue virus infection
- 84 countries with evidence of zika transmission
- 60 countries with evidence of chikungunya virus infection

It is widely recognized that new tools are required to combat vector-borne diseases. According to the World Health Organization (WHO), since 2014, major outbreaks of malaria, dengue, chikungunya,
yellow fever, and Zika have afflicted populations, claimed lives and overwhelmed health systems in many countries [1]. Despite an investment of US$2.7 billion on currently available control measures, malaria alone killed 445,000 people in 2016 [4]. In its World Malaria Reports for 2017 and 2018, the WHO acknowledged that after an unprecedented period of success in global malaria control, progress has stalled. In 2016, there were an estimated 216 million cases of malaria, an increase of about five million cases over 2015; this increased to 219 million cases in 2017 [5]. In the 2017 report, the Director-General of the WHO stated that “if we continue with a ‘business as usual’ approach—employing the same level of resources and the same interventions—we will face near-certain increases in malaria cases and deaths” and called for both “expanded access to effective interventions and greater investment in the research and development of new tools.”

The WHO African Region [6] accounted for 91% of all malaria deaths in 2016. Compared with 2016, an increase of approximately 3.5 million more malaria cases was reported in 2017 by the 10 highest burden African countries [5]. Malaria control has traditionally been most difficult to achieve and sustain in Africa. In many high-burden African countries, there has been a decrease in malaria funding per capita population at risk in recent years [4], emphasizing the impediments these countries experience in maintaining comprehensive malaria control and elimination initiatives and the resultant threat to recent hard-earned progress. The enormous area that malaria control measures must span, given the vast size of the continent [7] and region of malaria transmission [8], makes it easy to understand why Africa presents such challenges for sustained delivery of conventional chemotherapy and vector control tools. In addition, insecticide resistance is wide-spread, and drug resistance remains a perpetual threat. The WHO has made recommendations on priority actions to attempt to address this issue, identifying a need to change course and improve how we combat malaria, particularly in those countries with the highest burden [4,5].

2. Gene Drive Strategies

Gene drive systems offer a new and potentially transformative method for overcoming many challenges associated with controlling the transmission of vector-borne diseases. While this technology is being explored for other diseases carried by mosquitoes, the research has been most vigorously pursued to date in Anopheles mosquitoes responsible for transmitting malaria in Africa, since this is arguably where new solutions are most urgently needed. The species of Anopheles mosquitoes that are initially targeted, Anopheles gambiae sensu lato, have only been found in Africa [9]. Interest in exploring this possibility is reflected in the recommendation by the High-Level African Panel on Emerging Technologies in its recent report, Gene Drives for Malaria Control and Elimination in Africa, that “Africa should invest in the development and regulation of gene drive technology, whose greatest and most urgent application will be in malaria control and elimination” [10].

Gene drives are genetic systems that influence the frequency at which associated genes are passed on to subsequent generations, increasing the probability that they will be inherited. Observation of the many kinds of gene drives that occur naturally in plants and animals has helped scientists develop easily constructed systems that mimic their function [11]. The availability of new mechanisms for genetic engineering, including CRISPR/Cas9 and related systems, has provided unprecedented opportunities. For vector control, these systems can be used to promote the inheritance of genes that reduce mosquito reproductive capacity (thus decreasing numbers of malaria vectors) or interfere with the growth of the malaria parasite within the mosquito—either strategy is expected to reduce disease transmission [12]. Proof of principle for both strategies has been achieved in malaria vector mosquitoes in the laboratory. Examples include reducing inheritance of X chromosome to decrease numbers of female mosquitoes [13], inactivating specific genes required for reproduction in female mosquitoes [14], and introducing anti-Plasmodium falciparum effector genes into the mosquito genome [15].

For the gene drive systems demonstrated in these studies, the desired genetic modification will be passed on at high frequency to progeny resulting from the mating of a mosquito containing the modification with one that does not, and this will continue for many generations. This type
of gene drive is sometimes termed “self-sustaining” [16,17]. Computational modeling of a product employing this type of gene drive system predicts that release of only a few modified mosquitoes will initiate establishment and spread of the malaria transmission-reducing modification within the local population of targeted Anopheles gambiae mosquitoes and indicates great potential for reducing and preventing malaria transmission even under conditions that have proven most challenging for current mosquito control methods [12]. Such gene drive systems would in theory require only simple and infrequent delivery of low numbers of modified mosquitoes, suggesting this technology could provide cost effective and durable protection that would transform the fight against malaria in Africa [12].

3. Challenges of Gene Drive Strategies

Development of new products utilizing emerging technologies of any sort is generally marked by challenges and uncertainties. This is true for gene drive-modified products under development to control malaria (and other pathogens). Scientists are working to ensure the development of safe products and to address technical challenges in the optimization of efficacy. For example, research is being conducted to understand the role of the Anopheles vector in the African ecosystem, and other research efforts are looking at ways to postpone the appearance of resistance to the gene drive mechanism to prolong its protective effect, as well as ways to guarantee the specificity of the effect for its intended target and purpose.

As for many emerging innovative technologies, products employing gene drive systems also face non-technical challenges. These include: Establishing best practices and standards to ensure responsible research and development; strengthening regulatory capacity to provide for effective governance; and increasing public understanding and encouraging public dialogue to support informed decision making. Challenges associated with the development of gene drive technologies have been described in detail in a report by the National Academies of Science, Engineering and Medicine (NASEM) titled Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values [18], which recommended that the potential benefits of gene drives for basic and applied research justify proceeding with laboratory research and highly controlled field trials. The NASEM report advocated for a phased approach to testing, as well as additional studies to fill knowledge gaps. The report included recommendations for researchers, regulators, and funders. The need for case-by-case ecological risk assessment to inform decision making, the need for early attention to governance requirements, and the need for broad stakeholder engagement were noted. In response to NASEM recommendations directed to research funders, a group of prominent gene drive research sponsors and supporters have committed to several fundamental principles for the conduct of responsible research [19,20] (See Box 2).

**Box 2. Principles for Gene Drive Research [19].**

- Advance quality science to promote the public good;
- Demonstrate transparency and accountability;
- Engage thoughtfully with affected communities, stakeholders, and public; and
- Foster opportunities to strengthen capacity and education.

When the array of possible gene drive systems and applications is considered as a homogeneous category—as has been the case in much of the public discussion thus far—the uncertainties remaining at this early stage of research and development may be perceived as daunting. Some have argued for decades that the precautionary principle should be applied to any release of genetically modified organisms (for example [21]). The precautionary principle indicates that when human activities may lead to morally unacceptable harm that is scientifically plausible, but uncertain, actions shall be taken to avoid or diminish that harm [22]. Under the Convention on Biological Diversity, a multinational treaty addressing conservation of biodiversity [23], Principle 15 of the Rio Declaration on Environment
and Development states that “in order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities . . . ” [24]. With regard to gene drive, the characteristics that make it so potentially promising as a durable malaria control tool, the potential to persist and spread in the environment, have been cited as a reason for concern about possible adverse impact on biodiversity, generating calls for a precautionary approach to decisions about further research and field testing [25]. Others object to the notion that any uncertainty about the potential risks and benefits of using a novel biotechnology is a cause for not testing or using it, however, and note that viewing uncertainties associated with gene drive technologies as exceptional is inconsistent with the approach historically taken for other emerging innovative technologies that posed potential risks at the time of their initial deployment [26,27]. Indeed, it should be emphasized that continued research is the only way to decrease the uncertainties that underlie the perception of risk.

Considering that gene drive systems are being investigated for use in a spectrum of products, decision-making should not be at the level of gene drive technology as a whole. Rather, decisions should be made on a case-by-case basis to assess the relative benefits and risks of individual new gene drive-modified products. Such an approach would take into account the knowledge of the specific characteristics of each product, its intended function, and where it will be used. Already there has been a great deal of reflection on the requirements for development and testing of gene drive systems in mosquitoes. For example, experts have considered issues such as containment requirements [28,29], governance needs [30], and potential environmental interactions [31]. Notably, in 2014, the WHO published the Guidance framework for testing genetically modified mosquitoes [16] that describes a phased testing pathway analogous to the development pathway for other public health tools (drugs, vaccines and pesticides), with systematic assessment of safety and efficacy at each step.

4. Recommendations to Address Technical and Non-Technical Challenges

In 2018, an international multidisciplinary working group of experts published an update of this guidance specifically focused on self-sustaining gene drive systems as proposed for malaria control and elimination—Pathway to Deployment of Gene Drive Mosquitoes as a Potential Biocontrol Tool for Elimination of Malaria in Sub-Saharan Africa: Recommendations of a Scientific Working Group [17]. During the development of these recommendations, the working group considered two major aspects of the product development pathway: Proof of efficacy as determined through testing for entomological and epidemiological impact; and, evidence of acceptability as determined through biosafety, regulatory, ethics, and community and other stakeholder engagement activities. For gene drive-modified products developed outside malaria endemic regions where they may be field tested, the working group emphasized the critical role of in-country scientists and institutions in the product development process, and the importance of conducting the research in a spirit of co-ownership and co-development that recognizes the leadership of the in-country partners.

These working group recommendations for the development of gene drive-modified mosquito products as a potential biocontrol tool proposed a testing pathway (See Figure 1) that incorporates elements from established regulatory precedents.

![Figure 1. Recommended Pathway [17].](image)

As has been employed for testing of other biocontrol agents, the working group recommended extensive early testing in physical confinement (laboratory and insectary) with a definitive need for
assessing the safety of each individual product and establishing a ‘go/no-go’ decision gate for moving it to field testing. The recommended safety criterion for decision to enter into field testing is that the gene drive-modified mosquitoes will do no more harm to human health than wild type mosquitoes of the same genetic background (which are vectors of malaria and certain other tropical diseases) and no more harm to the ecosystem than other conventional vector control interventions (which currently include broad spectrum insecticides). The working group recommended that initial field testing of a gene drive-modified mosquito product be conducted under conditions that minimize environmental exposure, as is standardly the case for testing of genetically modified crops. While strict ecological confinement cannot be guaranteed in the field, the conduct of the trial in a geographically isolated site will reduce the possibility of outward migration of the product. At the stage of early small-scale releases, emphasis will be on testing whether the modified mosquitoes function the same way under natural conditions that they functioned under physical confinement and on monitoring for any unanticipated effects. Assuming that the first small scale release proceeds without evidence for adverse effects, testing may proceed through multiple additional small-scale releases to assess outcomes in different geographies, climates, ecologies, etc. as necessary to obtain the data required to plan for large-scale testing of the product’s impact on disease transmission. Large-scale product release(s) will be conducted according to regulatory procedures for clinical trials of drugs, vaccines or other vector control measures in the country hosting the study. Before this phase of testing is implemented, however, a regional coordination and authorization process should be established in response to the potential for transboundary movement of the gene drive-modified mosquitoes. At each point along the testing pathway, before moving forward to the next phase, decisions to expand to more extensive testing should be preceded by risk assessments that cover environmental and health risks, as well as social and economic risks, and will be contingent upon regulatory and ethical approvals, as well as continued authorization by the community(ies) hosting the trial(s).

The working group recognized that the decision to implement a gene drive-modified mosquito product as part of the overall strategy for controlling and eliminating malaria will be made by national governments. The working group considered the need for ongoing post-implementation monitoring in the context of current and planned mechanisms for monitoring for mosquito and malaria control as a component of malaria elimination efforts, recognizing that many of the monitoring needs and issues will be the same regardless of the nature of the control tools used. The group proposed that any required ongoing ecosystem monitoring should be case-specific, keeping plausibility and feasibility in mind and choosing endpoints for biological relevance specifically related to the potential to cause harm. Several specific resources were identified that should be created and/or provided for in preparation for field testing. These include developing improved monitoring tools, establishing mechanisms for regional decision-making, building quality management systems, and supporting non-technical aspects of development, such as stakeholder engagement.

5. Conclusions

It is expected to take several more years for a gene drive strategy to be ready for field testing. However, as gene drive and other genetic biotechnologies continue to emerge, it will be important to agree on consensus best practices for responsible development and testing that will lay the necessary groundwork. The recently published recommendations for the development of gene drive-modified mosquito products described above provide comprehensive guidance covering technical, regulatory and ethical aspects of research [17] that can serve as a framework for further planning and may be helpful as a model for other gene drive applications in public health, conservation, and agriculture. The authors found that moving the gene drive conversation toward specifics, rather than continuing to discuss the technology at a generic level, helped to address many uncertainties and concerns that have been raised. They concluded that low-threshold gene drive-modified products can be tested in a safe and ethical manner, although this will require significant advanced planning and coordination by researchers, funders, regulators, and policymakers. In determining the future of this technology,
decision-makers, including communities and other publics, must weigh concerns about the potential risks of gene drive-modified mosquito products against the potential benefit of their contribution toward ending the long and deadly history of malaria in Africa [10,32,33].

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