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COMMENT

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Transforming malaria prevention and control: the prospects and challenges of gene drive technology for mosquito management

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ABSTRACT

Background: In the era of insecticides and anti-malarial drug resistance, gene drive technology holds considerable promise for malaria control. Gene drive technology deploys genetic modifications into mosquito populations to impede their ability to transmit the malaria parasite. This can be either through the disruption of an essential mosquito gene or the association of gene drive with a desirable effector gene. CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) is a gene editing tool that precisely modifies mosquito vector DNA sequences and curtails the rate of pathogen transmission.

Methods: A comprehensive search was conducted in the SCOPUS and MEDLINE databases (via PubMed) until October 2023. The keywords used were related to the principles and mechanisms of gene drive technology, its advantages, and disadvantages, and its ethical and regulatory considerations in sustainable malaria eradication.

Results: The development of gene drive enables the preferential inheritance of specific genes in targeted mosquitoes, potentially obstructing the transmission of the Plasmodium parasite. This technology was also studied for the control of other vector-borne diseases such as dengue and chikungunya viruses. Despite its experimental superiority over other traditional methods such as insecticide-treated nets and insecticide sprays, the long-term dynamic interplay of mutation and resistance poses challenges for gene drive efficiency in sustainable malaria control.

Conclusions: This commentary elucidates the underlying mechanisms and principles of gene drive technology, underscoring its promise and challenges as a novel strategy to curtail malaria prevalence. Although the release of such genetically modified mosquitoes into the natural environment would result in the eradication of the locally targeted species of mosquitoes, the complete eradication of the entire species remains questionable. Thus, the practical application raises significant ethical and regulatory concerns for further research and risk assessment, including the risk of gene drive spreading to nontarget species in the wider theatre of biodiverse species.

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Introduction

Despite intensive control efforts on malaria over the last two decades, this mosquito-borne disease remains an issue of major public health concern, placing a significant burden on morbidity and mortality in endemic regions throughout the world [1]. According to the World Malaria Report 2022, malaria is endemic in eighty-seven countries, and there were estimated 247 million malaria cases and 619,000 deaths globally in 2021, withSub-Saharan Africa accounting for 95% of new infections and 96% of deaths [2]. However, countries such as Nigeria (31%), the Democratic Republic of the Congo (13%), Niger (4%), and the United Republic of Tanzania (4%) accounted for more than half of the malaria cases in this region. Malaria is caused by the *Plasmodium* species parasite and is transmitted through the bite of female Anopheles mosquitoes (the vector) [2]. Vector control initiatives constitute a pivotal public health intervention in the battle against malaria. Nevertheless, the formidable challenge presented by

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Plasmodium falciparum, which accounts for the highest mortality rate, and *Plasmodium vivax*—the most extensively distributed causative agent of recurrent malaria in rural settings (estimated at 64% cases in isolation), is well documented [3, 4]. Generally, Vector control programs employed the use of long-lasting insecticide-treated bed nets and residual indoor spraying [3]. Unfortunately, the surge in insecticide resistance, including the growing resistance of vector mosquitoes to pyrethroids are undermining the advancement made in malaria control. Amidst these public health challenges, the exploration of molecular techniques, including gene drive- a genetic engineering methodology with the capacity to manipulate the population of targeted genes in mosquito vectors – has garnered attention as a potential avenue for revolutionizing malaria prevention in Sub-Saharan Africa and other endemic regions, thus, expanding the spectrum of possibilities for vector control. This paper provides an overview delineating the mechanisms underlying gene drive. Additionally, it examines the potential and associated challenges of employing gene-drive technology in malaria control, encompassing an exploration of the ethical and regulatory considerations related to the utilization of gene-drive -based genetic engineering methods for combating malaria infection.

Gene drive technology and its mechanism of action

In a bid to achieve sustainable malaria eradication, gene drive technology was proposed [5, 6]. This novel technique increases the probability of inherited specific traits from one generation to the next at a rate greater than 50% than observed through typical Mendelian inheritance in heterozygotes and results in the production of certain genes (either substantially higher or lower), thus modifying the frequency of their distribution in the targeted population [7]. This technology has gained significant attention in recent years as an important tool for the control of infectious diseases transmitted by arthropod vectors such as dengue fever, the chikungunya virus, and, more recently, malaria [4, 5, 8]. The mechanism behind the action of the gene drive lies in biased inheritance. To achieve this, a genetic element is introduced into the species of interest to allow rapid spread through the target population. The DNA nuclease-based gene drive has gained an overarching focus from researchers due to the easily programmable and cost-effective CRISPR-Cas9 gene editing technology [5, 7, 9]. CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) is a gene editing tool found in bacteria that can be used to precisely modify DNA sequences [9]. Cas9 is an RNA-guided endonuclease enzyme that acts as a molecular pair of scissors that can be used to cleave DNA at a specific target site specified by the guide RNA.

Gene drive for malaria control

In the development of a gene drive for mosquito control, a genetic system incorporating Cas9is employed to precisely cleave a designated site within the genome of the mosquito species.) This process is guided by the Ribonucleic acid (RNA) strand, and insertion of the Cas9 into the specific target site leading subsequently to genetic modification [5, 6, 10]. During this process, the gene drive is configured to remain active in the reproductive cells of the organism. In the case of species with two sets of chromosomes, i.e. diploids—where one of the chromosomes carries the gene drive and the other does not—a double-stranded break (DSB) is induced in the chromosome where the gene drive is lacking [5, 7]. The DSB can be repaired mainly by two processes: either by non-homologous end joining of the broken strands or through homology direct repair, which involves removing the DSB and making use of the intact strand as a template for synthesizing new strands [7]. For gene-drive homing mechanism, homology-directed repair stands out as the most efficient pathway due to its precision in modification and the easy conversion of heterozygotes to homozygotes. Subsequently, the gene drive utilizes this process to replicate information from the template strand (housing the gene drive) to the new introduced strand, thereby transforming a heterozygote organism (possessing one copy of the gene drive) into homozygote organisms (harbouring two copies of the gene drive). This alteration then proliferates within the population [10]. This process is known as homing, and to achieve a biased inheritance of the homing endonuclease gene, the occurrence of homing in the reproductive cell is the key [7]. Fortunately, should homing occur within the cells that become gametes, the heterozygous organism -with a single copy of the gene drive- will generate a large percentage of gametes carrying a copy of the endonuclease gene and its associated trait [4, 5, 7]. This can swift escalation in the frequency of gene drive within the target population across successive generations, thereby facilitating precise modifications to specific genes. An alternative strategy to gene-drive induced vector population modification is vector population suppression. This approach operates through

genetic-engineering technologies aimed at reducing the number of adult mosquito vectors to curtail the rate of pathogen transmission [11, 12]. This can be achieved by compromising the fitness or distorting sex ratios, inducing a drastic reduction in vector population in endemic regions. Studies have also reported proof-of-principle concepts for suppression in *An. gambiae*—an important vector of *Plasmodium falciparum* in Africa [11, 12]. Thus, vector population modification drives seek to alter specific traits in a population without reducing its numbers either through the introduction of genetic modifications to enhance certain traits, while population suppression seeks to decrease the vector population number by introducing non-viable, sterile offspring using the gene drive. Both approaches have their respective advantages and disadvantages, as comprehensively discussed in a review by Bier in 2022 [13].

It is imperative to recognize that, within mosquito control, the integration of a desirable trait with a gene drive follows two principal methodologies; the disruption of an essential mosquito gene or the association of gene drive with a desirable effector gene [14]. In the former approach, the gene drive induces a recessive phenotype, functioning akin to a genomic parasite. As the gene drive proliferates within the vector population, the heterozygous organism will remain viable, facilitating the transmit the gene drive [14]. However, in this situation, the homozygous organism is not viable and this would result in a decrease in the reproductive capacity of the targeted population. -an outcome substantiated by laboratory experiments. In a recent study conducted by Hammond et al. [15], the authors reported a close to 100% biased inheritance rate with CRISPR-based gene drive placed at three distinct genetic loci that result in rendering female mosquitoes infertile. While the release of such genetically modified mosquitoes into the natural environment would result in the eradication of the locally targeted species of mosquitoes, the complete eradication of the entire species remains questionable [10, 15, 16]. Furthermore, laboratory studies have revealed that the integration of the anti-*Plasmodium* effector with gene drive can disseminate within the mosquito population [17]. Beyond this, gene drive has exhibited the capability to deform the mouthparts of mosquitoes, thereby hindering their ability to bite and transmit the *Plasmodium* parasite.

Prospects of gene-drive technology in the control of malaria

Gene drive technology holds considerable promise for has malaria control, offering the prospect of deploying genetic modifications into mosquito populations to impede their ability to transmit the malaria parasite. Engineering mosquitoes with a gene drive causes a disruption in the life cycle of the malaria parasite development within the mosquito vector. This remains an important approach to rendering mosquitoes ineligible for transmission of malaria disease [5, 11]. Another approach is through the introduction of gene modification that increases the resistance of mosquitoes to the malaria parasite, making them less susceptible to infection and reducing their ability to transmit malaria to humans [11]. The potential of gene drive in the rapid distribution of these genetic modifications within the mosquito population can result in a significant decline in the transmission of malaria [15, 16]. Despite its experimental superiority over other traditional methods such as insecticide-treated nets and insecticide use in terms of long-term effectiveness for malaria eradication [7, 15], there are noteworthy challenges that must be addressed before deploying gene drives for malaria control.

Challenges of gene-drive technology in the control of malaria

As gene drives are designed to facilitate easy transmission and induce a suppressive effect on mosquito populations, a propensity exists to selection of resistance within each of mosquito species [14]. Research indicates the development of resistant alleles attributed to end-joining repair of the homologous strand, resulting in cleavage at the target site while inhibiting the function of the endonuclease [15]. The emergence of such alleles possesses a risk to the effectiveness of the gene drive. A key strategy to address this challenge involves designing a gene drive with multiple target sites [7, 11]. The approach's efficacy has been demonstrated in a study by Hammond et al. in 2017 [7]. Their investigation into the use of CRISPR-based gene drives for population suppression revealed a disruption in the haplosufficient gene i.e. AGAP007280crucial for fertility of female mosquitoes. Although the frequency of the gene drives initially increased significantly, reaching a peak of 72–77% by the sixth generation, only a modest reduction of less than 20% reduction was reported by the 25th generation [7]. Their finding underscores a dynamic interplay of mutation and resistance, as deep sequencing revealed deletions early generations, favoring short, in-frame deletions associated with resistance to the gene drive. The study also highlighted an increased generation rate of drive-resistance alleles due to the deposition of Cas9 nuclease during embryonic

development of mosquitoes. The documented resistance and the dynamic spread of mutations underscore the potential limitations of gene drive for mosquito population suppression [7, 11].

Ethical considerations involved with the use of gene drive

Despite the prospect of gene drive technology in mosquito control and the eradication of malaria, its practical utilization raises significant ethical concerns that warrant critical evaluation. key ethical considerations include [10]:

1-Safety concerns and unexpected consequences: gene drive has the potential to spread rapidly in the natural environment. The direct impact resulting from the eradication of mosquito species and the indirect effects through the cross-breeding approaches may give rise to unintended negative consequences for public health and environmental well-being, thereby raising substantial concerns regarding its use [17]. As such, there is a need for thorough risk assessment and evidence-based studies are imperative to evaluate potential health and environmental impacts, including the risk of gene drive spreading to non-target species in the wider theatre of biodiverse species.

2-Informed consent and community engagement: the implementation of gene drive technology for malaria control constitutes a sensitive decision with profound implications for vulnerable communities and indigenous people. Ensuring informed consent from stakeholders and fostering community engagement is a crucial step. This approach ensures the active participation of communities in the decision-making process, providing an effective means to their concerns and preferences.

3-Long-term consequences on biodiversity and reversibility: Through, Gene drive rapid spread can permanently introduce irreversible changes to biodiversity [4, 6]. This ethical concern must be addressed through an evaluation of the long-term consequences of gene drive and the implementation of measures to reverse the negative consequences of this molecular tool. Other ethical concerns about gene drive interventions, such as the equitable distribution of benefits and access, as well as the potential for inappropriate use or misuse, can be effectively tackled through a multidisciplinary approach, such as Planetary health [18]. Planetary health as a multidisciplinary framework involves collaborations between researchers, policymakers, affected communities and ethicists [18]. This can pave the way for the development of robust guidelines and protocols to navigate these ethical concerns, ensuring the sustainable beneficial use of gene drive technology.

Conclusion

In conclusion, malaria continues to pose a significant public health threat due to its high morbidity and mortality rate, coupled with a huge socioeconomic burden, particularly in the global South. While traditional method of malaria vector control has shown significant success over the years, the rising insecticides resistance is impeding this progress. Notably, the novel gene-drive technology presents a robust, cost-effective, and sustainable prospect for the control of malaria. The mechanism of action of this molecular tool, involving the dissemination of the gene of interest throughout the mosquito population, holds promise for a potentially sustainable approach to eradicating malaria. However, it is essential to acknowledge the challenges associated with gene drive implementation and address ethical considerations pertaining to public and environmental health. Recognizing that no intervention is without risk, it is recommended to adopt a multidisciplinary approach, such as planetary health in order to develop evidence-based measures with community and policy-makers involvement. A robust multidisciplinary framework that aims to maximize the potential benefit of this molecular tool while minimizing its risk and ensuring its justified use in the ongoing battle against malaria.

Authors contributions

Conceptualization, Y.A.T.; resources, Y. A. T., H.J.O.; data curation, Y.A.T., H.J.O., I.O.O., M.K.O., H.D.S., I. A; A.O.A., writing—original draft preparation, Y.A.T., H.J.O., M.K.O., A.O.A. writing—review and editing, Y.A.T., H.J.O., M.S.E.-S. All authors agreed to the final version of this manuscript.

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Data availability statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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