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The Ethical Implications of Population Suppression and the Irreversibility of Gene Drives

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Abstract: **Gene drive systems have the ability to eradicate human diseases through a gene editing technology called the CRISPR-Cas9. Malaria, which does not have any proven vaccines, is expected to affect half of the world's population. As such, scientists are considering the eradication of malaria-carrying mosquitos which has caused much debate and controversy. The irreversible nature of gene drives, particularly population suppression, has raised ethical concerns with increased tensions between scientific innovation and the protection of Earth's natural resources. Thus, this paper aims to examine the current situation by presenting important ethical arguments that include Chardin's principle of irreversibility and Weiss' beliefs on intergenerational equity, ideals upheld by the United Nations. To determine what is arguably more harmful to the ecosystem, human deaths by malaria or potentially dangerous modifications to the biosphere, remains a challenge and is expected to be an ongoing debate. Already the United States have administered field tests and Brazil is expected to legalize gene editing, therefore, it is pertinent to set appropriate regulations to minimize risks and promote safe practices in one of the most powerful scientific breakthroughs of our time.**

Keywords: **Gene editing, gene drive systems, CRISPR-Cas9, malaria, genetic engineering, population suppression.**

I. INTRODUCTION

The ability to change and modify genes in insects, plants, animals, and possibly humans beings has opened up a door of possibilities driving research to new heights. One of the most exciting findings is that insect-borne diseases such as malaria, the Zika virus, and the West Nile virus now have the potential to be completely wiped out through the use of gene editing tools such as the CRISPR-Cas9. However, with such potent technologies are hazards far too dangerous for scientists to release into the wild without thorough research. Currently, researchers are experimenting with the gene drive technology in highly controlled laboratories until it is considered safe enough for field tests. Although gene editing has been performed in the past, the idea of altering or terminating a whole species has raised a number of concerns. In fact, many critics wonder if scientists have the right to "play God" when humans being are so prone to err, and if the release of altered organisms can cause new viruses to spread in the ecosystem. In this paper, we examine both safety and ethical concerns surrounding the irreversibility of the CRISPR-cas9 technology and its gene drive systems, examining the eradication of malaria as a case sample.

II. WHAT ARE GENE DRIVES?

In order to understand the ethical implications of gene drives, it is important to understand what a gene drive system is. The inheritance of a gene or a set of genes, referred to the gene drive, can derive naturally or by gene editing. Natural forms of gene drive were first discovered in mice and fruit flies, which alerted scientists that the use of gene drive systems (GDS) could be used to control diseases as well as the population of a species. For decades, scientists have contemplated the possibility of creating a "perfect" GDS, a novel idea that could be used to wipe out whole species. To engineer such effects would require sophisticated gene editing tools which has not been possible until the recent discovery of the CRISPR-Cas9 technology. CRISPR, which stands for 'clustered regularly interspaced short palindromic repeats', is a

pattern found in bacteria first observed in 1987 (CDC). For years, scientists did not know what this pattern was until the mid-2000s when scientists discovered that it was in fact the bacteria's anti-defence system. A closer examination revealed that the DNA of a virus can the ability to form sections of bacteria using an enzyme known as 'Cas'. Cas was then used to create a CRISPR sequence which able to detect an attack on the virus. It was not until 2012 that a team of scientists at the University of California Berkeley, led by Jennifer Doudna and Emmanuelle Charpentier, discovered that this defence system could be used to 'cut and paste' gene sequences, the scientific breakthrough that researchers have been waiting for (CDC).

Today, the CRISPR-Cas9 has made it possible to cut almost any DNA sequence with the utmost accuracy through the use of a RNA design guide (Bull and Malik 2004). This is done by adding a CRISPR-Cas9 construct into a heterozygote diploid cell using the CRISPR-Cas9 technology itself to cut through the DNA sequence. The cell then repairs the cut ends of the "blank" chromosome site by copying the CRISPR-Cas9 bearing chromosome (Bull and Malik 2004). The once heterozygote cell now carries CRISPR-Cas9 constructs in both chromosomes of the GDS. As a result, the species will breed as a homozygote (no longer a heterozygote) producing germ cells with the CRISPR-Cas9 gene drive. If the drive activity only affects 1 sex (ie. males), then 50% of the population will be wiped out whereas if the drive affects both sexes then the whole population will be wiped out. The CRISPR-Cas9 also has the ability to eliminate specific genes, such as pathogens of a vector species, to potentially eradicate many other diseases.

III. WHY MALARIA SHOULD BE ERADICATED

About half the world's population is prone to getting infected by malaria. Malaria has been in existence for centuries, yet progress to find medication has been lackluster compared to other common diseases (i.e. the cold, flu, measles). There are antimalarial drugs such as amodiaquine and proguanil that are able to cure malaria but many of these medications are not as effective as expected. The world's first malaria vaccine, called the MosquirizTM, is only now ready to be applied in the country of Ghana (Aljazeera). The vaccine will act against plasmodium falciparum, one of the most fatal malaria parasites commonly found in Africa. Although it is difficult to know how successful the vaccine will be, in the case that it is, scientists should rethink if it is absolutely necessary to eradicate malaria parasites.

Still, many scientists could argue that such parasites should still be eradicated since vaccines are only available to those who have access to it. In the past, efforts to kill mosquitos (not eradicate) required a substantial amount of government funding, which many impoverished nations cannot afford, where malaria remains rampant. For instance, in 1945, the Venezuelan government started a program to kill mosquitos through a sticky substance called DDT which successfully killed thousands of mosquitoes instantly. By the end of the program, the mortality rate fell; unfortunately, as Venezuela's economy regressed so did their efforts to kill the mosquitos as mortality rates bounce back and new outbreaks spread throughout the region (Economist). Finally, even though UNICEF recently donated many antimalarial drugs, little progress has been made in containing the disease.

IV. HOW TO ERADICATE MALARIA

In 2015 alone, there were about 212 million malaria cases and 429,000 malaria deaths (WHO). In highly developed areas such as southern Europe and southern United States, malaria has been locally eradicated by controlling the transmission of the disease. Currently, there are only a few species that are able to carry the malaria parasite. To be specific, the parasite is transferred by female mosquitoes in species of the *Anopheles* genus. Researchers have been sequencing the genes, and thus, are able to identify key gene variants, such as parasite clearance or egg laying, that allow the insects to colonize human habitats (Nolan and Crisanti 2017). In essence, the research revealed that the genetic diversity of mosquitoes give light to the possibility for gene modification in favorable genes, however, preventing the spread of the gene drive to non-target mosquitos remains a challenge (Nolan and Crisanti 2017).

Thus far, scientists have come up with three key approaches to eradicate malaria. The first is to disrupt an endogenous mosquito gene; the second is to skew the sex ratio; the third is to add a cargo. The first strategy is to target a gene that is needed for female fertility, meaning mosquitos with one copy of the defective gene will be likely to transfer the gene to all of their gametes (Nolan and Cristanti 2017). This in turn will affect all of its offspring. Eventually the female mosquitoes will become sterile and over several generations, the targeted mosquito species will be resistant to the malaria parasite, eradicating malaria over time. Researchers have identified three necessary genes for mosquito reproduction which is also a viable option for gene drives (Nolan and Cristanti 2017). By placing the gene drive along with a germline

promoter within one of these genes, thus making the gene defective, nearly all of the carrier's gametes will carry the gene drive. Most of the carrier's offsprings, if any, will carry the gene drive as well. Therefore, when both female and male mosquitoes are carriers of the gene drive, reproduction will be challenged meaning this process will wipe out the targeted mosquitoes from the ecosystem (Nolan and Cristanti 2017).

The second strategy is to distort the sex ratio by eliminating all female mosquitoes, the carriers of the malaria parasite. Similar to the first approach, to skew the sex ratio, gene drive would be used to prevent X chromosomes in males from being carried down to its gametes (Nolan and Cristani 2017). By placing a gene drive in the Y chromosomes of male mosquitoes, the gene drive would bias all viable male gametes to carry the Y chromosome. A gene drive in the Y chromosome that damages the X chromosome would have been identified. The damaged X chromosome harms the development of sperms with it. A male mosquito with this gene drive has approximately 95% of its gametes carry the Y chromosome (Nolan and Cristanti 2017). Hence, 95% of the offsprings are male. Eventually, there would be a negligible amount of threat–malaria carrying female mosquitos (Nolan and Cristanti 2017).

The third strategy is to plant a cargo gene which fights the malaria parasite. Antimicrobial peptides have been recommended after the successful insemination of gene drives in the *Anopheles stephensi* (Nolan and Cristiani 2017). With a cargo, the desired effect is dependent on the makeup of the cargo itself rather than the location of the gene drive. Studies found that biased inheritance of the gene drive was possible in a single generation but has yet to be tested on a mosquito population. Some concerns regarding a cargo is that gene-drive elements of the cargo may be lost through mutation or recombination depending on the genetic backgrounds of the mosquito and *Plasmodium* strains in addition to environmental factors such as climate (Nolan and Cristiani 2017).

V. THE PROBLEM OF RESISTANCE ALLELES

It is important to note that gene drive research is still in its infancy stage. A few studies thus far have shown that the CRISPR gene drive construct is extremely vulnerable to resistance alleles, preventing the heterozygotes to become homozygotes in the GDS. Champer et al. found that the converted genes can be "misrepaired" into resistance alleles in the germ line of *Drosophila melanogaster* (a fruit fly). Similarly, the *Anopheles gambiae* (a mosquito) had low drive conversion rates. In fact, resistance alleles formations have been found in all CRISPR gene drive constructs tested thus far.

To understand this phenomenon, Champer et al. developed two CRISPR-Cas9 gene drive constructs in the model organism *D. melanogaster* measuring the rates of resistance allele formation and its drive efficiency (2017). One of the gene drives is based on a *nanos* promoter and the other is based on a *vasa* promoter, both revealing how resistance alleles are formed. Through this study, Champer et al. found that resistance alleles form in the germline prior to fertilization and post-fertilization in the embryo (Champer et al., 2017). The data also revealed that the *nanos* drive had a higher progeny inheritance and conversion rate of wild type alleles than the *vasa* drive. The *nanos* drive had an 81% inheritance in progeny and 62% conversion rate of wild type alleles; for the *vasa* drive, there was a 76% inheritance in progeny and 52% conversion rate of wild type alleles (Champer et al., 2017). Furthermore, the formation rates of resistance alleles varied depending on the genetic background of the flies.

VI. THE IRREVERSIBILITY OF GENE DRIVES

The application of CRISPR-Cas9 to a whole species and releasing them into the wild could have devastating effects. These unknown outcomes will not only permanently affect the ecosystem but inevitably human lives. Although epidemics solvable by gene drives go far beyond malaria, including dengue fever, chikungunya, the zika virus, and much more, resistance alleles present irrefutable doubts about the CRISPR-Cas9 gene drive construct. Although for diseases with no vaccines or viable treatments, such as Lassa fever, the gene drive may be the only feasible solution; nevertheless, gene drives raise important ethical concerns due to the irreversible nature of gene editing. Experimentation, thus, must be administered within strict parameters, laboratories with genetically diverse populations to be tested over generations before applying them in the wild and applying them to whole species.

French philosopher Pierre Teilhard de Chardin touches upon the notion of irreversibility and the idea of a 'New Earth', which human beings should construct instead of merely preserving it. However, in developing and constructing the Earth, Chardin does not mean dominion over the Earth but rather, responsibility towards it. He emphasizes three key ideas that human beings should reflect upon for the survival of all living creatures: irreversibility, proportionality, and foreseeability

(Cartolovni 2017). According to Chardin, gene editing would be considered inherently bad if it makes 'irreversible' changes to the environment. Some people would argue that one cannot assume gene editing will have such 'irreversible' effects without thorough research, thus scientists should pursue gene drive research in an effort to save humans from diseases. Still, examples from history have revealed that eradication of species can have harmful effects on the ecosystem. Oyster overfishing, for instance, has caused algal blooms leading to lower oxygen levels in which negatively impacts biodiversity. In regards to vector-borne diseases, the termination of one type of mosquito, such as the *Aedes aegypti*, does not mean the end of dengue fever or chikungunya because another mosquito species such as *Aedes albopictus* is also a vector for these diseases (Cartolovni 2017). In an effort to eradicate such diseases, it is important to ask how many species have to be eliminated to end a disease and in effect, how will the ecosystem be impacted.

Contrary to popular opinion, mosquitos are not without benefits to the environment; for instance, mosquitos are a food source to for birds, so much so that without their presence, the Earth may experience a 50% reduction in the bird population (Cartolovni 2017). The elimination of one species could mean the end of another which is why scientists should carefully consider the role of a species before terminating them. Furthermore, removing mosquitos may force other species to take its place, disrupting the biosphere and unintentionally affecting other species in the ecosystem. What's worse, the modified organisms could become carriers of other pathogens as they evolve throughout time or even jump to another species through a process called horizontal transfer (Cartolovni 2017). In an effort to suppress the population of one species, if the gene drive accidentally jumps to another species such as bees, this could have a detrimental effect on the biosphere as bees pollinate and produce honey. Further research is needed to determine if it will weaken the organism during the natural selection process or if it can lead to the unintended extinction of other species.

VII. HUMAN RESPONSIBILITY

While Chardin reflects on the idea of 'irreversibility' and human survival, it is important to note other moral arguments surrounding gene drives and the CRISPR-Cas9. Melanie Challenger, who reflects on the sanctity of life, questions whether or not it is intrinsically wrong to drive the extinction of a fellow species (Pugh 2016). She claims that scientists have shown excessive pride or hubris experimenting with the ecosystem as they please instead of accepting the environment in its original state (Pugh 2016). Challenger argues that all of life is precious therefore human beings have no right to harm it. However, her opponents argue that people kill and destroy life on a daily basis such as livestocks and plants for food, exotic creatures for furniture and clothes, millions of bacterias to avoid illnesses, and ecosystems for shelter and entertainment (Pugh 2016). If the general public permits all this slaughter, is there a valid moral argument against eradicating a species that have killed millions of human lives? Epidemics too are a natural occurrence that have wiped out whole populations, thus in this regard, it is the respect for human life that compels scientists to wipe out diseases such as malaria.

In one journal article titled, "Engineering the Wild: Gene Drives and Intergenerational Equity", Kuzma and Rawls (2016) present how discussions regarding the effects of gene drive on future generations has been lacking in influential scientific and policy organizations. The authors introduced the principles of intergenerational equity (IE), the act of present and future generations to responsibly maintain all necessary resources for all forms of life (Kuzma and Rawls 2016). In other words, every species must fulfill their role to sustain the ecosystem. Edith Brown Weiss describes IE as three basic principles: conservation of options, quality, and access. These three principles describe how each generation should conserve biodiversity, maintain the quality of the planet, and preserve the legacy of past generations thinking about the current and future generations (Weiss 1989). An intergenerational right of equitable access refers to each generation's right to use and benefit from the countless resources available on our planet. However, countries and people act on selfish measures, caring only for their descendants. (relate this to gene drive)

The idea of IE has been incorporated in other notable cases in recent history. In 1987, the Brundtland Commission of the United Nations was passed in which sustainable development was defined as development that "meets the needs of the present without compromising the ability of future generations to meet their own needs" (UN 1987). Similarly, the U.N. Commission on Environmental Development (UNCED) and the U.N. Framework Convention on Climate Change (UNFCCC) referenced concepts of IE in their preambles and body (Kuzma and Rawls 2016). Furthermore, the U.N. Educational Scientific and Cultural Organization (UNESCO) also incorporated the idea of IE, creating out a special declaration which outlined the responsibilities of the present generation for future generations; aligning to its IE roots, it stated that future generations should have the freedom to also choose their own economic, political, and social systems. IE has been a major leading force in ethics globally. The question of if a technology goes in line with IE has been asked continuously for many years.

VIII. INTERGENERATIONAL EQUITY

The IE requirements in the case of gene drives and human disease eradication is to make sure that the condition of the Earth, especially its natural resources, are not in a state worse than it is today. To determine what state is considered "worse" in regards to gene drives is difficult to determine because the technology offers both benefits and risks to the environment (Kuzma and Rawls 2016). The ability to wipe out malaria is hugely beneficial as millions of people will no longer be affected by the disease each year. Therefore, accordingly to IE requirements, gene drives will impact future generations in a better state than it is today in regards to malaria. On the other hand, gene drives also have the potential to permanently damage the Earth if the gene drive is horizontally transferred to another species that carry many environmental benefits (Kuzma and Rawls 2016). Other risks also include how the population suppression of the target species will negatively impact its predators and the possibility of another more dangerous species taking its place.

The challenge with field tests is that they are limited. To understand the impact of a full-scale release of GEOs is nearly impossible given the highly controlled nature of laboratories. Gene drives are still considered a novel concept since it was yet to be proven; therefore, the likelihood of something going wrong is quite definite. Thus, by eradicating whole species, gene drives would violate IE principles of 'conservation of access and options' since the species will no longer be available to the next generation (Kuzma and Rawls 2016). From an IE perspective, alternative ways to combat malaria may be recommended, such as the immunization of a vector species by weakening its ability to transmit the disease but still exist within the ecosystem. Outside of gene drives, alternative solutions to fight malaria would be to intensify vaccine research.

Currently, the debate continues in regards to IE as people argue that disease control using chemical pesticides is hazardous to the environment whereas gene drives have yet to be determined. In the case of the United States, genetically-engineered insects are already being released into the wild for population suppression (Kuzma and Rawls 2016). And the United States, who is not a signatory of the *United Nations Convention on Biological Diversity* or the *Living Modified Organisms through the Biosafety Protoco*l with IE being its preamble, the impact of GMOs on future generations does not appear to be a priority. Current decisions related to GMOs in the United States are based on direct environmental and human risks, which is regulated under the Coordinated Framework for the Regulation of Biotechnology and must abide by the National Environmental Policy Act (Comm on Gene Drive Research). An environmental assessment is required but does not need to be supported by quantitative or probabilistic estimates. For instance, Oxitec's proposal called the "Draft Environmental Assessment for Investigational Use of Aedes aegypti OX513A" was approved which only included a qualitative estimate regarding the risks of releasing genetically engineered mosquitoes in the Florida Keys to control dengue (Latham 2017). It was determined that hazardous effects on the environment, including animals and human beings were negligible. In the case that an environmental assessment of a particular GMO could have a negative impact on the environment, an EIS including a full report on the environmental, economical, and other societal implications of the proposed application of a gene drive must be approved (Latham 2017).

The current trend in the United States is that GMOs will continue to be released in the wild for field tests. GMO diamondback moths have also been already approved for field trials to reduce the population of pests in northeastern parts of America. With increasing number of proposals to release GMOs into the wild, particularly for population suppression, it is recommended that government leaders and scientists worldwide gather to discuss safe practices regarding gene drives. Edith Brown Weiss, an American lawyer and legal scholar, who wrote several scholarly journals about the concept of IE, suggests that today's children and youth should be consulted as the "first representatives of the future generations" in order to begin drafting appropriate policies surrounding gene drives (Kuzma and Rawls 2016).

IX. INTERNATIONAL REGULATIONS NEEDED

Regarding the *United Nations Convention on Biological Diversity*, its supplement called the *Cartagena Protocol* aims to discuss GMOs, to ensure that they do not cross international borders (Cartolovni 2017). Since GMOs are likely to take its own course, spreading across borders whether the countries like it or not. Those who oppose gene editing, such as the *Biological and Chemical Weapons Convention,* considers gene drives as 'biological weapons' and aims to prevent further research and development of the technology. Millions of farmers in Brazil are opposed to the legalization of gene editing technologies used to drive the extinction of a species, the largest rural movement in the history of the country. Farmers are opposed to the idea of biotechnology taking over their natural resources. The fight to control gene drives will be a challenge as gene drive research to combat malaria is generously funded by the Bill and Melinda Gates Foundation.

The advancement of GMOs appears to be an inevitable, and as such, it is critical to set appropriate standards today before more and more GMOs are released into the wild. The answer may not be to halt the development of gene drive research but rather, devise gene drive policies that requires scientists and environmental agencies to carefully assess the role of each specie within the ecosystem before terminating them. It is critical to determine the value of a species no matter how harmful it may be in the moment. Although it will require constant research over several generations to determine how the lack of one specie will impact another, continued efforts to understand the impact of the eradication of a specie is needed. Through international conferences and committee hearings, governments should set appropriate standards regarding the use of genetically engineered organisms to monitor its potential effects beyond state borders.

X. CONCLUSION

The responsible application of gene drive technologies must be closely monitored at every stage. Innovation has always required risks and uncertainties, but with such powerful and potent technology, it is critical that scientists proceed with proper regulations set in place. This is a matter that requires immense discussion and research due to the irreversible nature of gene editing. And instead of writing off gene drives as hazardous and unethical, government leaders and the scientific community at large may be able to find a way to perform research responsibility in the hope that genetic engineering can help humans leave the Earth in a state better than it was before.

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