TAKSHASHILA INSTITUTION

Gene Drives and Vector-Borne Diseases

A Comparative Perspective Using Malaria as a Case Study

Saurabh Todi

Takshashila Discussion Document 2023-03
Version 1.0, February 2023

This document examines the viability of Gene Drives as a potential tool to eradicate vector-borne diseases using Malaria as a case study. It explains the technology, elaborates on the benefits and challenges associated with it, and then argues that Gene Drive technology is not a feasible tool to eradicate Malaria in India.

Recommended Citation:
Saurabh Todi, "Reducing Incidence of Vector-Borne Diseases in India through Gene Drives: A Comparative Perspective Using Malaria as a Case Study," Takshashila Discussion Document No. 2023-03, February 2023, The Takshashila Institution.

Executive Summary

Gene drives are an emerging technological application to reduce the prevalence of vector-borne diseases, crop pests, and non-native invasive species. This method for vector control is currently at the research stage, with parallel community engagement programmes being carried out in African countries to raise awareness for its adoption. Yet, the risks associated with using gene drives may go beyond the communities they are deployed in. Hence, it is critical for India to understand the relevance of gene drive application in India and its neighbouring countries to create effective policy measures for achieving control of vector-borne diseases.

Using malaria as a case study, we argue that India currently does not require the use of gene drives to achieve control of mosquito-borne diseases. However, India should invest in research for gene drives and vaccines, while continuing with current efforts to curb vector-borne diseases. Further, India will need strong data monitoring systems to identify if any gene drive mosquitoes deployed by other countries make their way to India.

This document has been formatted to be read conveniently on screens with landscape aspect ratios. Please print only if absolutely necessary.

Author
Saurabh Todi is a Research Analyst working with the High-Tech Geopolitics Programme at the Takshashila Institution. He tracks geopolitics of emerging technologies, especially in the field of biotechnology.

Acknowledgments
The author would like to thank his colleagues, Shambhavi Naik, and Aditya Ramanathan, for their valuable feedback and comments.

Table of Contents

I. Introduction

Gene drives are genetic elements of an organism that are transmitted to progeny at higher than mendelian frequencies (>50%). Gene editing techniques such as CRISPR–Cas9 have made gene drives extremely efficient in laboratory settings and have shown the potential to reduce the prevalence of vector-borne diseases, crop pests, and non-native invasive species[1]. Research in gene drives, especially on mosquitoes, is being carried out by scientists at the University of California, San Diego, Texas A&M University, and Massachusetts Institute of Technology, among others. A non-profit group, called Island Conservation is looking at the potential use of gene drive systems to eliminate invasive rodents from islands where they wreak havoc[2]. However, concerns have been raised regarding the potential unintended consequences, especially in terms of the ecological impact of gene-drive systems.

It is important to study the relative utility of traditional and new, biotechnology-based approaches in comparison to conventional approaches to control the prevalence of vector-borne diseases. Malaria is one of the leading vector-borne diseases globally. And in India, using malaria as a case study can be quite instructive to analyse the relative utility of these approaches for public health interventions.

Vector-borne Diseases

Vectors are living organisms such as bloodsucking insects that can transmit infectious pathogens between humans, or from animals to humans. These insects ingest disease-producing microorganisms when ingesting blood from an infected host (human or animal) and later transmit it to a new host. Often, once a vector becomes infectious, it can transmit the pathogen for the rest of its life during each subsequent bite/blood meal[3].

Vector-borne diseases are human illnesses caused by parasites, viruses and bacteria that are transmitted by vectors. Globally, they account for more than 17% of all infectious diseases, leading to more than 7,00,000 deaths annually from diseases such as malaria, dengue, human African trypanosomiasis, leishmaniasis, Chagas disease, yellow fever, and Japanese encephalitis, among others[4]. The burden of these diseases is highest in tropical and subtropical areas and disproportionately high on the poorest populations.

What are Gene Drives?

Reducing the incidence of vector-borne diseases has become a technology demonstrator for gene drive technology. Mosquitoes engineered with gene drive systems can pass specific genes to the next generation at higher than Mendelian inheritance rates (>50%). This ensures that the target gene spreads through the wild-type mosquito population, despite some associated fitness

costs (Figure 1)[5]. Currently, gene drive technology for vector control has not been commercialised and is under controlled trials in laboratory settings.

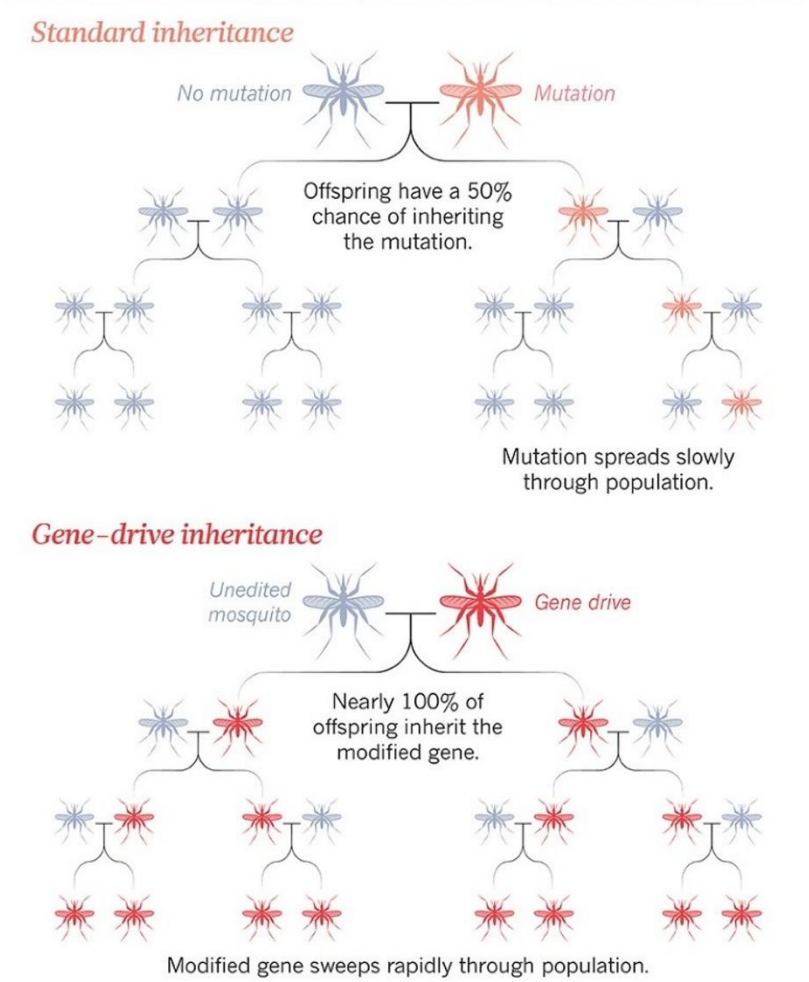

Figure 1 – Inheritance rates for gene drive mosquitoes (adapted from Megan Scudellari)

How Do Gene Drives Work?

Gene-drive mosquito techniques work in two major ways:

- They reduce the population of mosquitos (population suppression); or
- Modify (population replacement) a given vector population[6] (Figure 2).

Population suppression involves the release of modified male mosquitoes to suppress vector populations to a level which makes it difficult to sustain malaria transmission[7]. Traditionally, it is achieved by using the non-genetically modified Sterile Insect Technique (SIT) where sterile male mosquitoes are introduced into the wild population to mate with wild female mosquitoes. The resulting eggs do not hatch and over time, the number of mosquitoes being targeted in an area will decrease. One benefit of this technique is that when irradiated mosquitoes stop being released into an area, their numbers will slowly return to "normal levels[8]." But this technique is costly, time-consuming and requires the periodic introduction of irradiated mosquitoes.

Population suppression strategies are based on inactivation, or knock-out, of genes which aim to reduce fertility or production of female progeny or are biased towards higher production of male progeny (which do not bite). Scientists can also use gene drives to increase the efficiency of the transfer of

knockout genes to the next generation. In a small study, gene drive mosquitoes wiped out captive populations of mosquitoes in just eight to twelve generations[9].

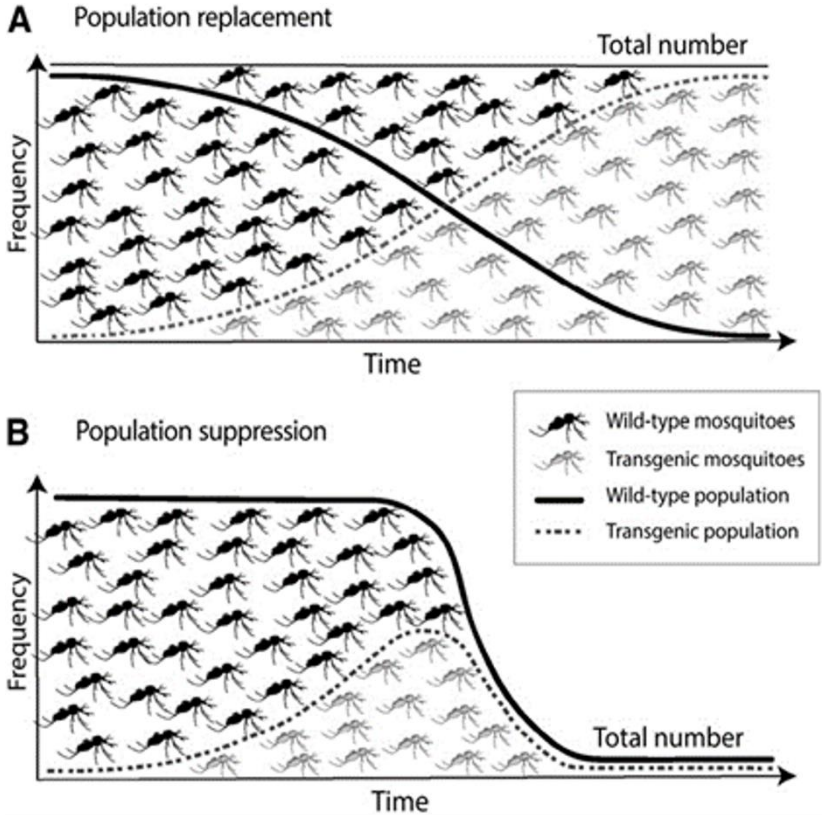

Figure 2 – Different population modification strategies (adapted from Stephanie J. et al)

In contrast, the population replacement method works differently. Population replacement aims to reduce the ability of a mosquito to transmit the malaria pathogen. Population replacement strategies are based on the

inactivation of genes that enable mosquitoes to be effective vectors. For example, many potential effector genes have been identified to impair the development of *Plasmodium* parasites (that cause malaria) by *Anopheles* mosquitoes (the vector). These include genes that code for immune system activators, peptides that neutralise *Plasmodium* parasites in the mosquito midgut or salivary glands, and antibodies that bind the surface of mosquito salivary glands and block the growth of *Plasmodium* parasites[10].

Effector genes regulate biological activity in such a way that can increase or decrease enzyme activity, gene expression, influence cell signalling, or other protein functions.

In order to sustain gene drive performance across generations, introduced genes must be carried into the mosquito genome in tight linkage with the gene drive mechanism, or else, natural mutation can occur that renders the gene-drives impotent[11]. Population replacement gene drive systems consist of a driver gene that copies both itself and an effector gene, which in turn confers desired phenotypic traits. The driver gene encodes a guide RNA and an endonuclease, such as Cas9, that together recognise and cut specific DNA sequences present in the wild-type mosquito population[12].

CRISPR/Cas9 gene-editing technology involves two essential components: a guide RNA that recognises a desired target gene, and Cas9, which is an endonuclease that causes a double-stranded DNA to break, allowing modifications to the genome.

Use of either population replacement or population suppression would depend on their relative strengths and challenges in the given situation. For example, population replacement can provide a level of environmental safety because it would not result in the elimination of an ecological niche that an opportunistic invasive species could occupy. However, it is a risky approach because the genetic modification will remain in the environment forever, increasing the likelihood of unintended consequences[13].

Scientists are trying to use these gene drive-based population modification strategies to eliminate dangerous vector-borne diseases. The gene drive technology to implement population modification strategies against mosquitoes of the *Anopheles* genus (vector for malaria) is at the most advanced stage. Target Malaria, a non-profit organisation is a research consortium seeking to use gene-drive mosquitoes for malaria control in Africa. Therefore, malaria is a good candidate to compare the utility of conventional and emerging technologies deployed in controlling vector-borne diseases.

II. Case Study: Malaria

Malaria is a life-threatening disease caused by parasites that are transmitted through the bites of infected female *Anopheles* mosquitoes. However, Malaria is preventable and curable. There are 5 parasite species that cause malaria in humans, and 2 of these species – *Plasmodium falciparum* and *Plasmodium vivax* – pose the greatest threat to human health[14]. Among various vector-borne diseases, Malaria is one of the most prevalent and deadly. It causes more than 200 million cases globally and results in more than 400,000 deaths every year[15]. This makes reducing the incidence of Malaria an urgent public health imperative.

Global Incidence of Malaria

In 2020, nearly half of the world's population was at risk of malaria. There were estimated 247 million cases of malaria in 2021, and the estimated number of malaria deaths stood at 619, 000[16]. Most cases and deaths occur in sub-Saharan Africa. The WHO African Region was home to 95% and 96% of malaria cases and deaths, respectively[17]. However, South-East Asia, Eastern Mediterranean, Western Pacific, and the Americas also report significant numbers of cases and deaths. Children under 5 years of age are the most vulnerable group affected by malaria; in 2021, they accounted for nearly 80% of all malaria deaths in the WHO African Region[18].

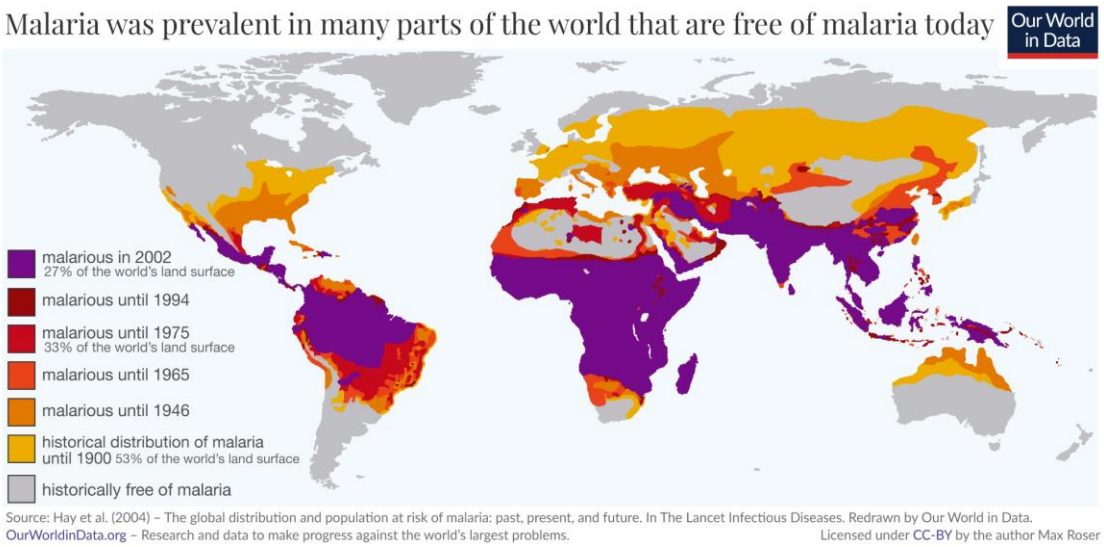

Figure 3 - Global prevalence of Malaria over time (adapted from Our World in Data)[19]

Existing Efforts Towards Malaria Eradication

Over the last few decades, several countries have achieved malaria-free status. The current caseload is concentrated primarily in WHO African region and South-East Asian region. The WHO Global Malaria Programme (GMP) is responsible for coordinating global efforts to control and eliminate malaria. Its work is guided by the "Global technical strategy for malaria 2016–2030" adopted by the World Health Assembly. The WHO recommends a multi-pronged approach to tackle the incidence of malaria. Specific interventions are prescribed for prevention, diagnosis, and treatment of the disease.

To prevent the spread of malaria vectors (i.e. mosquitoes), use of Insecticide-treated bed nets (ITNs) are recommended. ITNs are a form of personal protection. ITNs have been shown to reduce the death of children under 5 years from all causes by about 20%. As pregnant women in high-risk regions are especially vulnerable, they might be put on Intermittent Preventive Treatment of Malaria for Pregnant Women (IPTp) where a curative dose of an antimalarial drug is administered to all pregnant women without testing whether or not they are infected with the malaria parasite. Furthermore, use of surface insecticides is also recommended in some cases.

At the diagnostic stage, the World Health Organization recommends that all suspected cases of malaria be confirmed through microscopy or rapid diagnostic tests to make a definitive diagnosis of malaria. For treatment, use of antimalarial drugs is recommended. However, the development of resistance to drugs poses one of the greatest threats to malaria control and results in increased malaria morbidity and mortality.

Another WHO-approved method of case detection is the Reactive case detection (RACD) strategy which identifies and treats additional malaria infections (from an index case) in areas of low malaria transmission. RACD involves the investigation of passively-detected cases of malaria, like patients seeking care at their local clinic, to determine the suspected origin of infection and the potential risk for onward transmission of malaria[20].

Several countries have been able to either eradicate malaria or significantly reduce its incidence by developing strategies based on the WHO recommendations but tailored to local requirements.

Sri Lanka

In 2016, Sri Lanka was declared malaria-free, with the last case of indigenous P. vivax infection reported in 2012. P. vivax and P. falciparum were the most prevalent malarial parasites. Sri Lanka's strategy to eliminate malaria depended on a multi-pronged approach. It implemented the '1, 2, 3 approach' where confirmation was within 24 hours (1 day) of a malaria case by either a public or a private facility, investigation within 48 hours (2 days) and Rapid Case Detection (RACD) within 72 hours (3 days)[21]. It instituted extensive follow-up of up to one year to tackle the resurgence of malaria cases and prevention of relapse due to lack of treatment compliance. Other steps included mobile clinics and stringent vigilance on imported malaria through better surveillance and tracking once a case was identified as imported[22].

It is notable that despite facing a civil war, Sri Lanka was able to achieve the elimination of malaria. This further strengthens the argument that although malaria eradication is challenging, it can be achieved through sustained efforts.

China

In 2021, China was declared malaria-free after reporting the last indigenous malaria case in 2016. This reflected a culmination of efforts of over 70 years. P. vivax was the major parasite species of concern in China. The policies and strategies which became the cornerstone of the malaria elimination programme over the decades included 'the 523 project', which resulted in the discovery of the artemisinin group of highly effective antimalarial drugs in the 1960s, which are still the most potent antimalarial drugs in use[23]. China also implemented the strategy of environmental management as well as protective measures such as early distribution of anti-mosquito bed nets and indoor residual spray for vector control. In later years, the country adopted a local, tailor-made approach such as the '1-3-7' surveillance strategy, under which confirmed cases were reported within a day, and further investigation, treatment, and genome sequencing to distinguish imported and indigenous cases were to be done within 3 days, and RACD within 7 days to prevent further transmission[24].

III. Emerging Approaches

Malaria remains a significant health burden in the developing world, despite decades of efforts to eliminate the disease. However, since the early 2000s, the scale-up and mass deployment of long-lasting insecticidal nets, indoor residual spraying of insecticides, and anti-malarial drugs have drastically reduced malaria incidence. Despite these successes, these existing sets of tools are unlikely to bring about malaria eradication. This is because the development of natural drug and insecticide resistance has the potential to stall these malaria control efforts[25]. New strategies and technologies, therefore, are needed to achieve elimination, especially in high-incidence regions such as sub-Saharan Africa. Effective vaccines and the genetic engineering of mosquito populations are seen as promising new strategies to reinvigorate the fight against malaria and potentially lead to its elimination.

Vaccination

Vaccines use the body's natural defences to build resistance to specific infections and make the immune system stronger. Following vaccination, the body will now recognize the invading germ, such as the virus or bacteria and produce antibodies. Vaccinations have been extremely successful in reducing the incidence of several diseases such as Tuberculosis, polio, measles, hepatitis etc.

Antibodies are proteins produced naturally by the immune system to fight disease.

Despite several attempts over the last decades, scientists have struggled to produce an effective vaccine against malaria. The primary difficulty in developing an anti-malaria vaccine is that Malaria parasites are genetically complex and produce thousands of potential antigens. This makes narrowing down a specific antigen for vaccine development quite challenging. Furthermore, exposure to malaria parasites does not confer lifelong protection and individuals are prone to reinfection.

However, in 2021, the World Health Organization (WHO) recommended widespread use of the RTS,S/AS01 (RTS,S) malaria vaccine (brand name Mosquirix) among children in sub-Saharan Africa and in other regions with moderate to high P. falciparum malaria transmission. The recommendation was based on a pilot programme in Ghana, Kenya and Malawi. The vaccine is only moderately efficient as it prevents only about 30% of severe malaria cases after a series of four injections in children under the age of five[26]. But experts predict that it could still prevent the deaths of 23,000 children a year, making a significant dent in the tremendous toll of the disease[27]. Some studies show that even greater drops in hospitalisations and deaths can be achieved through tailored rollouts[28]. Vaccines are seen as the next frontier in anti-malaria strategy as there is increasing evidence of drug resistance developing against available antimalarial drugs[29].

Another vaccine candidate, the R21/Matrix-M during phase 3 trials have shown up to 80 per cent protection against malaria in children aged five to 17

months[30]. The vaccine, developed by scientists at the University of Oxford, is the first to meet the World Health Organization's (WHO) Malaria Vaccine Technology Roadmap goal of a vaccine with 75 per cent or greater efficiency over 12 months. After regulatory authorisation, the vaccine is expected to be manufactured by the India-based Serum Institute of India[31].

However, some public health experts also caution that excitement over a vaccine might overshadow existing malaria control measures that are already underfunded, such as insecticide programmes and functional health systems. Nevertheless, expanding the use of vaccines in malaria eradication programs can be considered, especially for high-risk countries.

Genetically Modified Mosquitoes

Another technology being considered to supplement the fight against malaria is the use of genetically modified (GM) mosquitoes. This technology is being broadly used in two different ways: the development of GM non-gene drive mosquitoes and GM gene drive mosquitoes.

GM non-gene drive mosquitoes are specially bred with special 'knock-out genes' which aim to reduce fertility or production of female progeny or are biased towards higher production of male progeny (which do not bite). These mosquitoes have undergone controlled field trials in several countries such as Brazil, Panama, the Cayman Islands and Malaysia[32]. These experiments have

been spearheaded by a biotechnology firm, Oxitec. In 2021, the company released GM mosquitoes into the open air in the United States, in the state of Florida for the first time[33]. In 2022, US Environmental Protection Agency (EPA) granted Oxitec permission to conduct similar trials in California, subject to local approvals[34].

GM gene drive mosquitoes, on the other hand, sustain performance across generations because introduced genes are carried into the mosquito genome in tight linkage with the gene drive mechanism. They can be used to implement both population suppression and population replacement strategies.

There is limited regulatory clarity regarding the use of genetically modified mosquitoes. Although some countries have allowed experimental trials of non-gene drive GM mosquitoes, approval has not been granted for any gene drive GM mosquitoes. However, in 2018, a 15-member scientific working group, under the aegis of the Foundation for the National Institutes of Health, put forward a series of recommendations for using gene-drive mosquitoes in sub-Saharan Africa[35]. The report stressed that governments, communities, and local scientists would need time to absorb the science and effectively regulate the technology.

The Foundation for the National Institutes of Health (FNIH) is a not-for-profit organisation established by the United States Congress in 1990. It raises private-sector funds and allies with public and private institutions in support of the mission of the United States National Institutes of Health (NIH).

IV. Benefits and Challenges of Gene Drives

Gene drive technology is a revolutionary tool which has the potential to significantly alter the odds in the fight against vector-borne diseases, especially malaria. However, the promise of this technology brings with it both enormous opportunities and significant challenges (Table 1).

Benefits of Gene Drives	Challenges with Gene Drives
Potential to fight anti-malaria drug resistance	Can speed up the emergence of resistant genes
Could help with the elimination of malaria, especially in high incidence regions	Ecological impact of population modification not known
	Possibility of misuse
	Changes can persist for generations within the environment

Table 1 - Benefits and challenges of gene drives

Benefits

Gene drive-based population modification strategies can provide sustainability to malaria elimination efforts by aiding the WHO-defined control, pre-elimination, elimination, and prevention-of-reintroduction phases of local malaria elimination[36]. These strategies would be quite effective if deployed in conjunction with other tools such as the use of prophylactic and therapeutic drugs that eliminate parasites, anti-malaria vaccines, and interventions such as insecticides, spatial repellents, and others that target the malarial vector.

Challenges

The gene drive population modification technology raises several questions that require further investigation. These include questions about the effectiveness of effector genes to deliver substantial reductions in malaria transmission, the effect of imperfect transmission-blocking traits on malaria elimination, and concerns about the efficacy of effector genes considering higher fitness costs for the vector[37].

A fitness cost is a measure of ecological competitive ability. This plays a key role in the evolutionary dynamic. In this example, as fitness of an organism is being artificially decreased, it is likely that the process of natural selection would generate selection against ability of vector to transmit effector genes.

The efficiency of the driver gene and gene drive system itself to achieve elimination must be examined. For example, the process of copying the effector gene from one chromosome to another is not always successful. DNA can undergo an alternative repair pathway, which has the potential to

generate "resistant" alleles that do not contain the desired drive or effector gene[38]. Furthermore, efforts to prevent mosquito reproduction through interference with fertility genes can impose a large selection pressure for resistance development in the mosquito[39]. The extent to which these factors affect the ability of gene-drive mosquitoes to eliminate malaria must be better examined.

An allele is one of two or more versions of DNA sequence at a given genomic location.

Gene editing can also lead to non-target mutations which may have adverse physiological effects. GM mosquitoes may become resistant to insecticide, may start harbouring other pathogens or may become ineffective at preventing the disease they were designed against. Both population suppression and replacement approaches have similar potentials of carrying non-target mutations[40].

The potential harms and possible ecological risks associated with releasing gene drive mosquitoes into the wild have not yet been well established. Therefore, community understanding, support, and buy-in are extremely crucial before gene drive mosquito releases can proceed, even at trial stage[41]. The ecological consequences of eliminating an organism, such as mosquitos from the environment have not been fully understood. The second and third-order effects on the ecosystem, livestock, agriculture, and human life is yet to be studied fully. Furthermore, given the complexity in ecosystem linkages, field trials would have to be conducted in several countries with variable climates, flora, and fauna to understand the consequences of eliminating

mosquitoes from the ecosystem. The process of environmental impact assessment would have to be extremely robust to account for the potential loss of ecological balance[42].

The example of Cane toads and Australia is illustrative of such ecological risks. Cane Toads are native to South and Central America. They are extremely hardy animals and are predators of insects and other small prey. These qualities led to their introduction into Australia as a pest-control measure against beetles in 1935. However, Cane toads themselves became pests after being introduced into Australia as they are capable of poisoning predators that try to eat them. Because of this, toads do not tend to hide. Several studies suggest that native animals such as crocodiles, turtles, and monitor lizards among others are greatly threatened by the invasion of the cane toad. They have also been linked to the decline and extinction of several native predator species in Australia[43].

Another potential risk with the gene drive technology is that the recall potential of the GM mosquito is extremely limited. Once released, the GM gene-drive mosquito would persist in the population for a long time. Furthermore, unlike the option to not buy GM foods if one is against the technology, the environmental release of GM mosquitoes does not confer the same freedom of choice to individuals. It would be virtually impossible to avoid coming in contact with a GM mosquito once they have become dominant in an area.

According to researchers at Imperial College London, there are at least 46 theoretical harms that could arise from the use of gene drives on mosquitoes[44]. These include potential downsides such as a reduction in pollinators, the development of allergic reactions to the bite of transgenic mosquitoes, or fish that would eat the larvae of transgenic mosquitoes.

Apart from technological and ecological challenges, gene-drive technology has the potential to be misused as well. For example, in an act of bioterrorism, someone could release a transgenic vector with harmful mutations in an area which can then potentially replace the wild-type population. This would have ramifications for a variety of domains, especially agriculture, public health, and food security. For this reason, specific types of reversible gene drives are being developed with built-in controls or external overrides which allow the original drive to be overwritten on command[45]. This effort is being funded by the US Defense Advanced Research Projects Agency (DARPA).

These new technologies are promising candidates for use in vector control. However, they are not silver bullets, and their benefits and risks need to be compared with existing measures to identify the best solution to curb disease prevalence. In the subsequent sections, we study India's existing efforts at malaria eradication and assess the relevance of gene drives in the Indian context.

V. Efforts at Malaria Eradication by India

The epidemiology of malaria in India is complex due to India's geographic and ecological diversity and the wide distribution of ten anopheline vectors. The most common malaria parasites in India are *Plasmodium falciparum* and *P. vivax* but both are unevenly distributed across India. Since its independence in 1947, India has instituted several programs to reduce the incidence of malaria. The Global Malaria Eradication Programme of the WHO, launched in the 1950s, was a huge success in India with the incidence of malaria dropping from an estimated 75 million cases and 8,00,000 deaths in 1947 to just 49,151 cases and no deaths in 1961[46].

However, several factors such as complacency, slow development of health infrastructure, inadequate surveillance, and issues such as vector resistance to the commonly used insecticide DDT and parasite resistance to chloroquine led to the reintroduction of malaria in India[47]. During the 1970s, reported cases increased to about 1.3 million in 1971 and then to 6.4 million in 1976. In response, the Modified Plan of Operations (MPO) was created, with a three-pronged strategy comprising government efforts, malaria research, and public participation. The programme was successful and malaria incidence decreased to approximately 2 million cases and 247 deaths by 1984. The program

underwent several iterations over the years and became the National Vector Borne Disease Control Programme (NVBDCP) in 2003.

In recent years, the National Strategic Plan (NSP) for Elimination of Malaria (2017-2022) has been developed under the National Vector Borne Disease Control Programme (NVBDCP) which envisages making India a malaria-free country by 2027 and eliminating the disease by 2030. It is designed based on the National Framework for Malaria Elimination (NFME) 2016 and the World Health Organization's Global Technical Strategy for Malaria (2016-2030). This framework provides a phased approach to elimination of Malaria and outlines priority areas based on district-level stratification of burden. States and districts are classified into four categories to eliminate malaria in a phased manner. A range of measures were deployed such as distribution of long-lasting insecticidal net (LLIN), indoor residual spray (IRS) and larval source management (LSM) strategies such as use of larvicides. Artemisinin-based combination therapy (ACT) and Rapid Diagnostic Tests (RDTs) were introduced with increased monitoring along international borders[48]. In 2019, India recorded a 60% reduction in reported cases compared to 2017 and a 46% reduction compared to 2018[49].

India's progress has been noted by the WHO World Malaria Report in 2018, 2019 and 2020, but the country must accelerate further malaria elimination activities at the district and peripheral levels to achieve the target of malaria elimination by 2030. Even though India is yet to achieve malaria-free status

for itself, countries like China and Sri Lanka have been able to eliminate malaria through conventional approaches and without using genetic editing methods.

Which Approach Works Best for India?

India is a major contributor to the global disease burden caused by Malaria. India accounted for 83% of estimated cases and about 82% of all malaria deaths in the WHO South-East Asia Region. Although the incidence and prevalence of malaria in India have come down in the last few years using conventional mitigation approaches, it is worth examining if emerging approaches can provide a fillip to India's efforts to eradicate malaria.

As a developing country, India needs to delicately balance its developmental imperatives and available financial resources. Therefore, a decision to adopt a new approach should account for economic viability, ease of introduction and public support, the quantum of decrease in disease burden, and available state capacity. One useful framework to approach this dilemma would be to assess the preventability and curability of disease (Figure 4). This decision matrix can also be used to assess available options for other uses of gene drive apart from for control of vector bounce diseases.

India has seen a consistent decline in malaria cases over the last few years and is believed to be on track to meet its goal to eradicate malaria by 2030. This

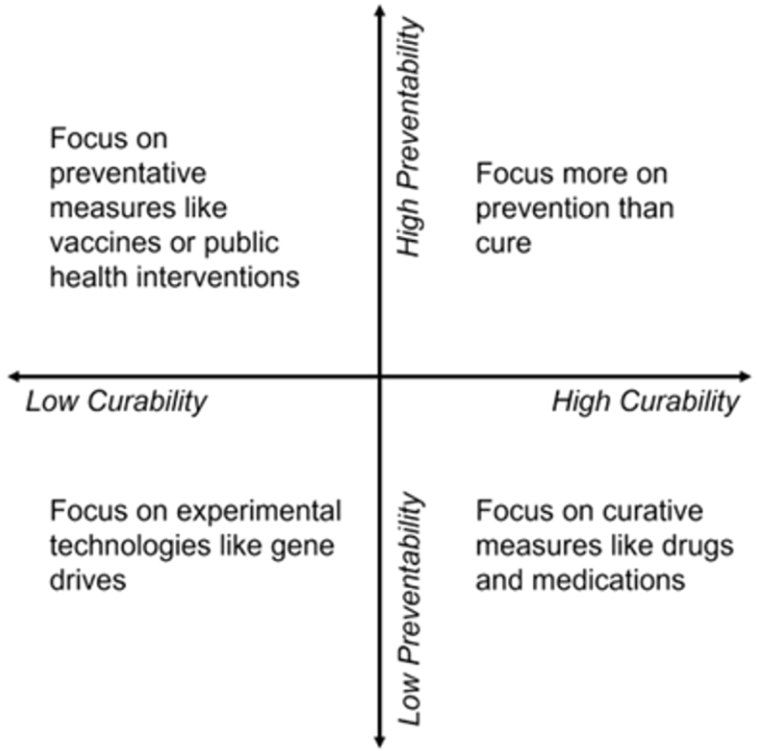

Figure 4 – Preventability and Curability matrix

indicates that the current conventional approach is working. However, there is always a risk of resurgence in high-risk areas so preventative measures need to be taken.

Vaccines may be considered an option for high-risk districts. An anti-malaria vaccine candidate from the UK has shown promise in phase 3 trials with an efficacy of >70%. The vaccine is expected to be manufactured by an Indian company as well. It would be easier to find public support for such a step as

the attitude of the Indian public towards vaccines, in general, has been quite positive, especially during the COVID-19 pandemic.[50] The inclusion of anti-Malaria vaccines would not be seen with suspicion as emerging approaches such as genetically modified mosquitoes might.

Despite GM mosquitos being a novel technology, regulatory experience for gene drive mosquitoes and non-gene drive mosquitoes has been quite different. In 2017, Oxitec announced the launch of outdoor caged trials in Jalna, Maharashtra to demonstrate the efficacy of its non-gene drive GM mosquitoes in suppressing the local *Aedes aegypti* population[51]. Results of the trials published in 2022 showed that the trial was successful in effectively suppressing the wild populations of the mosquito within 10 to 16 weeks of release[52]. However, in the same year in 2017, researchers at the University of California, San Diego proposed to conduct field trials of gene-drive mosquitoes in India under a $70 million grant from Tata Trusts[53]. Not much is known in the public domain regarding the current status of this project, suggesting the project did not receive appropriate regulatory approvals. Although gene-drive technology has developed further since then, the challenges associated with the mass adoption of such technology in India persist, especially as a method of eradicating vector-borne diseases such as malaria.

There are several unknowns about genetically modified mosquito technology, either with or without gene drives. Constant monitoring and

examination would be required to ensure that the gene drive mosquitoes don't lead to the development of gene-drive resistant genes in wild-type mosquito populations and *plasmodium* strains and complicate efforts to eradicate malaria. This will invariably necessitate the creation of additional ecological surveillance capabilities which adds to the cost and isn't an optimal option given the current disease burden.

Adoption of gene-drive GM mosquitoes would require significant buy-in from local communities[54]. This could be tricky considering the lack of adequate knowledge about genetic engineering techniques among the population and might even increase the chances of vested interests using misinformation and disinformation to flame the anti-GMO sentiment. This can jeopardise malaria elimination efforts by breeding suspicion of even non-gene drive approaches such as vaccination or anti-malarial drugs.

Lastly, given that the technology isn't ready for field trials yet, there is little clarity on how gene drive applications will be regulated, either globally or in India. Furthermore, the intellectual property associated with gene drive technology and its applications is not based in India. This creates a risk factor for India to be dependent on foreign technology to achieve its public health objectives.

All these challenges signal that it is not prudent to currently promote the use of gene drives or GM mosquitoes as a tool for malaria eradication. However, India's experience with almost eradicating malaria in the 1960s but witnessing

a resurgence in the 1970s, shows the risk of being complacent and underprepared to face unexpected challenges of drug and insecticide resistance. This makes research on emerging technologies and their evaluation for use in India critically important. Even if it is not prudent to deploy gene drive technology for malaria eradication in India currently, primary research in the gene drive technology should be encouraged to gain experience for possible future use. This technology could be useful in addressing other issues such as pest control for agriculture etc.

VI. Recommendations

Gene drive technology holds immense potential as a method to control vector-borne diseases. It is also likely that the technology would be mature enough to be deployed within a decade[55]. Therefore, it is worth considering the ecological, commercial, regulatory, and public health consequences of such a possibility.

It is not prudent for India to currently consider promoting gene drives as a tool to eradicate malaria due to technological challenges, regulatory uncertainty, ecological ramifications and comparatively less (and declining) burden of malaria itself. However, given the high incidence and persistence of malaria in several sub-Saharan countries, it is possible that an African country decides to deploy gene-drive GM mosquitos on a large scale in the next few years. The immense economic and developmental toll vector-borne

diseases inflict on vulnerable populations might make gene-drive GM mosquitos an attractive alternative. Even with some downsides to gene drives, the potential benefits for human health and economics may far outweigh the risks for some countries[56]. This would necessitate the formulation of regulations to ensure that cross-border flow between that country and India accounts for the possibility of transgenic mosquitoes finding their way to India. Similar issues would arise if any of India's immediate neighbours decide to deploy this technology as well.

As the gene drive technology develops and matures further, it is also likely that they would be used for a variety of purposes in addition to being a vector control mechanism. India should invest in cultivating domestic capabilities, both in primary research and manufacturing to take advantage of the potential of gene drives in future.

VII. Appendix

Comparative Analysis of Various anti-Malarial Strategies

	Conventional interventions based on WHO guidelines	Vaccines	Gene Drives
Situation in India	Significant success over the last few years. The economic cost of malaria for India is ~US$ 2 billion/year[57]	Not yet approved for use	Not yet approved for use
Situation globally and regionally	Primary method of disease eradication in South Asia, SEA and East Asia	After WHO approval in 2019, increasingly being used (paediatric use) in high incidence areas of Africa	Lab-based controlled trials show promise[58] but no field trials yet.

Success Stories	Eradication of malaria by Sri Lanka (regional peer) and China (demographic peer)	Success in sub-Saharan Africa[59]	
Public familiarity with tech		Relatively high familiarity of public with vaccines	Very low to non-existent familiarity of public/civil society with this tech
Relative need for public outreach programmes	Low need; comfort among public	Vaccine hesitancy not a big issue in general; existing awareness regarding malaria vaccines[60]	Need significant buy-in from public due to nature of technology and possibility of disinformation and rumours about the technology

Civil society/ environmental concerns		Not very high efficacy of approved anti-malaria vaccines yet[61]	Consequences for environment, ecology and second or third order effects on livestock and ecosystem as a whole
Current regulatory regime in India	Interventions by NVBDCP, MoHFW through National Framework for Malaria Elimination of 2016[62]	Not sanctioned for use in India yet but experts say it should be considered[63]; approved for limited use by WHO in high incidence countries[64]	No specific regulation but not allowed to even conduct trials yet; no international regulatory clarity[65]
Challenges	Low state capacity and fiscal constraints	Approved but low-efficacy vaccines may not be as suitable for Indian needs[66]; little indigenous research on anti-malaria	Not adequately commercialised; not an indigenous technology

		vaccines[67]	
Opportunities	Second order positive effects on health, infrastructure, state capacity and economy	Development of indigenous capabilities[68] in vaccine development[69]	Potential to help develop biotech industry

VIII. References

[1] Leung, Shirley, Nikolai Windbichler, Edward A Wenger, Caitlin A Bever, and Prashanth Selvaraj. "Population Replacement Gene Drive Characteristics for Malaria Elimination in a Range of Seasonal Transmission Settings: A Modelling Study." Malaria Journal 21, no. 1 (July 26, 2022): 226. https://doi.org/10.1186/s12936-022-04242-2.

[2] Scudellari, Megan. "Self-Destructing Mosquitoes and Sterilized Rodents: The Promise of Gene Drives." Nature 571, no. 7764 (July 9, 2019): 160–62. https://doi.org/10.1038/d41586-019-02087-5.

[3] "Vector-Borne Diseases." World Health Organisation, March 2, 2020. https://www.who.int/news-room/fact-sheets/detail/vector-borne-diseases.

[4] Ibid.

[5] Champer, Jackson, Anna Buchman, and Omar S. Akbari. "Cheating Evolution: Engineering Gene Drives to Manipulate the Fate of Wild Populations." Nature Reviews. Genetics 17, no. 3 (March 2016): 146–59. https://doi.org/10.1038/nrg.2015.34.

[6] Ibid

[7] Harris, Angela F., Andrew R. McKemey, Derric Nimmo, Zoe Curtis, Isaac Black, Siân A. Morgan, Marco Neira Oviedo, et al. "Successful Suppression of a Field Mosquito Population by Sustained Release of Engineered Male Mosquitoes." Nature Biotechnology 30, no. 9 (September 2012): 828–30. https://doi.org/10.1038/nbt.2350.

[8] CDC. "Irradiated Mosquitoes | CDC." Centers for Disease Control and Prevention, July 25, 2022. https://www.cdc.gov/mosquitoes/mosquito-control/community/emerging-methods/irradiated.html. .

[9] Kyrou, Kyros, Andrew M. Hammond, Roberto Galizi, Nace Kranjc, Austin Burt, Andrea K. Beaghton, Tony Nolan, and Andrea Crisanti. "A CRISPR–Cas9 Gene Drive Targeting Doublesex Causes Complete Population Suppression in Caged Anopheles Gambiae Mosquitoes." Nature Biotechnology 36, no. 11 (November 2018): 1062–66. https://doi.org/10.1038/nbt.4245.

[10] James, A. A., B. T. Beerntsen, M. de L. Capurro, C. J. Coates, J. Coleman, N. Jasinskiene, and A. U. Krettli. "Controlling Malaria Transmission with Genetically-Engineered, Plasmodium-Resistant Mosquitoes: Milestones in a Model System." Parassitologia 41, no. 1–3 (September 1999): 461–71.

[11] Scudellari, Megan. "Self-Destructing Mosquitoes and Sterilized Rodents: The Promise of Gene Drives." Nature 571, no. 7764 (July 9, 2019): 160–62. https://doi.org/10.1038/d41586-019-02087-5.

[12] Burt, Austin. "Site-Specific Selfish Genes as Tools for the Control and Genetic Engineering of Natural Populations." Proceedings. Biological Sciences 270, no. 1518 (May 7, 2003): 921–28. https://doi.org/10.1098/rspb.2002.2319.

[13] Naik, Shambhavi. "A Risk Assessment of the Potential Use of Gene Drives in Infectious Diseases." The Takshashila Institution; (2018). Available at: https://static1.squarespace.com/static/618a55c4cb03246776b68559/t/623966b6acef1a455e657191/1647929029899/TDS-Gene-Drives-Risk-Assessment-SN-2017-03.pdf

[14] "Malaria." World Health Organisation, April 6, 2022. https://www.who.int/news-room/questions-and-answers/item/malaria.

[15] Vector-Borne Diseases. World Health Organisation, 2 Mar. 2020, https://www.who.int/news-room/fact-sheets/detail/vector-borne-diseases.

[16] World Health Organization. World malaria report 2021. World Health Organization, 2021. https://www.who.int/publications/i/item/9789240040496

[17] World Health Organization. World malaria report 2022. World Health Organization, 2022. https://www.who.int/publications/i/item/9789240064898

[18] Ibid.

[19] Roser, Max and Hannah Ritchie. "Malaria". Published online at OurWorldInData.org. (2019). Retrieved from: https://ourworldindata.org/malaria

[20] Cotter, Chris, Prayuth Sudathip, Herdiana Herdiana, Yuanyuan Cao, Yaobao Liu, Alex Luo, Neil Ranasinghe, Adam Bennett, Jun Cao, and Roly D. Gosling. "Piloting a Programme Tool to Evaluate Malaria Case Investigation and Reactive Case Detection Activities: Results from 3 Settings in the Asia Pacific." Malaria Journal 16, no. 1 (December 2017): 347. https://doi.org/10.1186/s12936-017-1991-9. .

[21] Premaratne, Risintha, Rajitha Wickremasinghe, Dewanee Ranaweera, W. M. Kumudu T. de A. W. Gunasekera, Mihirini Hevawitharana, Lalanthika Pieris, Deepika Fernando, and Kamini Mendis. "Technical and Operational Underpinnings of Malaria Elimination from Sri Lanka." Malaria Journal 18, no. 1 (July 29, 2019): 256. https://doi.org/10.1186/s12936-019-2886-8.

[22] Ibid.

[23] Feng, Xinyu, Fang Huang, Jianhai Yin, Rubo Wang, and Zhigui Xia. "Key Takeaways from China's Success in Eliminating Malaria: Leveraging Existing Evidence for a Malaria-Free World." BMJ Global Health 7, no. 4 (April 1, 2022): e008351. https://doi.org/10.1136/bmjgh-2021-008351.

[24] Ibid.

[25] James, Stephanie, Frank H. Collins, Philip A. Welkhoff, Claudia Emerson, H. Charles J. Godfray, Michael Gottlieb, Brian Greenwood, et al. "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." The American Journal of Tropical Medicine and Hygiene 98, no. 6 Suppl (June 2018): 1–49. https://doi.org/10.4269/ajtmh.18-0083.

[26] RTS,S Clinical Trials Partnership. "Efficacy and Safety of RTS,S/AS01 Malaria Vaccine with or without a Booster Dose in Infants and Children in Africa: Final Results of a Phase 3, Individually Randomised, Controlled Trial." Lancet (London, England) 386, no. 9988 (July 4, 2015): 31–45. https://doi.org/10.1016/S0140-6736(15)60721-8.

[27] Maxmen, Amy. "Scientists Hail Historic Malaria Vaccine Approval — but Point to Challenges Ahead." Nature, October 8, 2021. https://doi.org/10.1038/d41586-021-02755-5.

[28] Chandramohan, Daniel, Issaka Zongo, Issaka Sagara, Matthew Cairns, Rakiswendé-Serge Yerbanga, Modibo Diarra, Frédéric Nikièma, et al. "Seasonal Malaria Vaccination with or without Seasonal Malaria Chemoprevention." The New England Journal of

Medicine 385, no. 11 (September 9, 2021): 1005–17. https://doi.org/10.1056/NEJMoa2026330.

[29] Kozlov, Max. "Resistance to Front-Line Malaria Drugs Confirmed in Africa." Nature 597, no. 7878 (September 23, 2021): 604–604. https://doi.org/10.1038/d41586-021-02592-6.

[30] Datoo, Mehreen S., Hamtandi Magloire Natama, Athanase Somé, Duncan Bellamy, Ousmane Traoré, Toussaint Rouamba, Marc Christian Tahita, et al. "Efficacy and Immunogenicity of R21/Matrix-M Vaccine against Clinical Malaria after 2 Years' Follow-up in Children in Burkina Faso: A Phase 1/2b Randomised Controlled Trial." The Lancet Infectious Diseases 22, no. 12 (December 1, 2022): 1728–36. https://doi.org/10.1016/S1473-3099(22)00442-X.

[31] The Economic Times. "Oxford, Serum Institute of India: New Anti-Malaria Vaccine Trial over, Authorization next Year," December 8, 2022. https://economictimes.indiatimes.com/news/new-updates/oxford-serum-institute-of-india-new-anti-malaria-vaccine-trial-over-authorization-next-year/articleshow/96080054.cms?from=mdr.

[32] Waltz, Emily. "First Genetically Modified Mosquitoes Released in the United States." Nature 593, no. 7858 (May 3, 2021): 175–76. https://doi.org/10.1038/d41586-021-01186-6.

[33] Ibid.

[34] Milius, Susan. "Genetically modified mosquitoes could be tested in California soon." Science News.9 March 2022. https://www.sciencenews.org/article/genetically-modified-mosquito-test-california-epa-oxitec.

[35] James, Stephanie, Frank H. Collins, Philip A. Welkhoff, Claudia Emerson, H. Charles J. Godfray, Michael Gottlieb, Brian Greenwood, et al. "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." The American Journal of Tropical Medicine and Hygiene 98, no. 6 Suppl (June 2018): 1–49. https://doi.org/10.4269/ajtmh.18-0083.

[36] Macias, Vanessa, and Anthony A. James. "Chapter 19 - Impact of Genetic Modification of Vector Populations on the Malaria Eradication Agenda." In Genetic Control of Malaria and Dengue, edited by Zach N. Adelman, 423–44. Boston: Academic Press, 2016. https://doi.org/10.1016/B978-0-12-800246-9.00019-3.

[37] Leung, Shirley, Nikolai Windbichler, Edward A Wenger, Caitlin A Bever, and Prashanth Selvaraj. "Population Replacement Gene Drive Characteristics for Malaria Elimination in a Range of Seasonal Transmission Settings: A Modelling Study." Malaria Journal 21, no. 1 (July 26, 2022): 226. https://doi.org/10.1186/s12936-022-04242-2.

[38] Hammond, Andrew M., Kyros Kyrou, Marco Bruttini, Ace North, Roberto Galizi, Xenia Karlsson, Nace Kranjc, et al. "The Creation and Selection of Mutations Resistant to a Gene Drive over Multiple Generations in the Malaria Mosquito." PLoS Genetics 13, no. 10 (October 2017): e1007039. https://doi.org/10.1371/journal.pgen.1007039.

[39] Padmanaban, G. "Can Gene Drive Wipe out All Mosquitoes?" The Hindu, November 11, 2017, sec. Science. https://www.thehindu.com/sci-tech/science/can-gene-drive-wipe-out-all-mosquitoes/article20218469.ece.

[40] Naik, Shambhavi. "A Risk Assessment of the Potential Use of Gene Drives in Infectious Diseases." The Takshashila Institution; (2018). Available at:

https://static1.squarespace.com/static/618a55c4cb03246776b68559/t/623966b6acef1a455e657191/1647929029899/TDS-Gene-Drives-Risk-Assessment-SN-2017-03.pdf

[41] Brossard, Dominique, Pam Belluck, Fred Gould, and Christopher D. Wirz. "Promises and Perils of Gene Drives: Navigating the Communication of Complex, Post-Normal Science." Proceedings of the National Academy of Sciences of the United States of America 116, no. 16 (April 16, 2019): 7692–97. https://doi.org/10.1073/pnas.1805874115.

[42] Committee on Gene Drive Research in Non-Human Organisms: Recommendations for Responsible Conduct; Board on Life Sciences; Division on Earth and Life Studies; National Academies of Sciences, Engineering, and Medicine. Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values. Washington (DC): National Academies Press (US); 2016 Jul 28. 6, Assessing Risks of Gene-Drive Modified Organisms. https://www.ncbi.nlm.nih.gov/books/NBK379271/

[43] "Cane Toads." NSW Environment and Heritage. Accessed January 24, 2023. http://www.environment.nsw.gov.au/topics/animals-and-plants/pest-animals-and-weeds/pest-animals/cane-toads.

[44] Connolly, John B., John D. Mumford, Silke Fuchs, Geoff Turner, Camilla Beech, Ace R. North, and Austin Burt. "Systematic Identification of Plausible Pathways to Potential Harm via Problem Formulation for Investigational Releases of a Population Suppression Gene Drive to Control the Human Malaria Vector Anopheles Gambiae in West Africa." Malaria Journal 20, no. 1 (March 29, 2021): 170. https://doi.org/10.1186/s12936-021-03674-6.

[45] Scudellari, Megan. "Self-Destructing Mosquitoes and Sterilized Rodents: The Promise of Gene Drives." Nature 571, no. 7764 (July 9, 2019): 160–62. https://doi.org/10.1038/d41586-019-02087-5.

[46] Ibid.

[47] Ibid.

[48] Ibid.

[49] Ibid.

[50] Lazarus, Jeffrey V., Katarzyna Wyka, Trenton M. White, Camila A. Picchio, Kenneth Rabin, Scott C. Ratzan, Jeanna Parsons Leigh, Jia Hu, and Ayman El-Mohandes. "Revisiting COVID-19 vaccine hesitancy around the world using data from 23 countries in 2021." Nature communications 13, no. 1 (2022): 3801.

[51] Oxitec. "Oxitec and Gbit Announce Launch of Friendly™ Aedes Project in India." Accessed January 24, 2023. https://www.oxitec.com/en/news/oxitec-and-gbit-announce-launch-of-friendly-aedes-project-in-india.

[52] Patil, Prabhakargouda B., Shaibal Kumar Dasgupta, Kevin Gorman, Angela Pickl-Herk, Mirel Puinean, Andrew McKemey, Bharat Char, Usha B. Zehr, and Shirish R. Barwale. "Elimination of a Closed Population of the Yellow Fever Mosquito, Aedes Aegypti, through Releases of Self-Limiting Male Mosquitoes." PLoS Neglected Tropical Diseases 16, no. 5 (May 16, 2022): e0010315. https://doi.org/10.1371/journal.pntd.0010315.

[53] UC Researchers to Test the Genetic Control of Mosquitoes in India. BioSpectrum, (21 Nov. 2017), https://www.biospectrumindia.com/news/58/9861/uc-researchers-to-test-the-genetic-control-of-mosquitoes-in-india.html.

[54] Kofler, Natalie, James P. Collins, Jennifer Kuzma, Emma Marris, Kevin Esvelt, Michael Paul Nelson, Andrew Newhouse, et al. "Editing Nature: Local Roots of Global

Governance." Science 362, no. 6414 (November 2, 2018): 527–29. https://doi.org/10.1126/science.aat4612.

[55] "What's next for Gene Drives That Fight Malaria-Carrying Mosquitoes? | Science News," June 3, 2022. https://www.sciencenews.org/article/gene-drives-mosquito-malaria-crispr-africa-public-outreach.

[56] Ibid.

[57] "India." Severe Malaria Observatory, https://www.severemalaria.org/countries/india-0.

[58] Champer, Jackson, Riona Reeves, Suh Yeon Oh, Chen Liu, Jingxian Liu, Andrew G. Clark, and Philipp W. Messer. "Novel CRISPR/Cas9 Gene Drive Constructs Reveal Insights into Mechanisms of Resistance Allele Formation and Drive Efficiency in Genetically Diverse Populations." PLoS Genetics 13, no. 7 (July 2017): e1006796. https://doi.org/10.1371/journal.pgen.1006796.

[59] "Over 1 Million African Children Protected by First Malaria Vaccine." World Health Organisation, April 21, 2022. https://www.who.int/news/item/21-04-2022-over-1-million-african-children-protected-by-first-malaria-vaccine.

[60] Singhal, Chinar, Taiwo O. Aremu, Pranjal Garg, Kunal Shah, and Olihe N. Okoro. "Awareness of the Malaria Vaccine in India." Cureus 14, no. 9 (September 15, 2022). https://doi.org/10.7759/cureus.29210.

[61] Chauhan, Virander. "New Hope for Malaria Vaccine: The Science, Challenges, Opportunity." The Indian Express, November 7, 2022.

https://indianexpress.com/article/explained/explained-health/new-hope-for-malaria-vaccine-the-science-challenges-opportunity-8253600/.

[62] Ministry of Health & Family Welfare, Government of India. National Framework for Malaria Elimination in India (2016-2030). https://nvbdcp.gov.in/WriteReadData/l892s/National-framework-for-malaria-elimination-in-India-2016%E2%80%932030.pdf

[63] Rahi, Manju, and Amit Sharma. "Should India Be Considering Deployment of the First Malaria Vaccine RTS,S/AS01?" BMJ Global Health 7, no. 1 (January 1, 2022): e007870. https://doi.org/10.1136/bmjgh-2021-007870.

[64] WHO Recommends Groundbreaking Malaria Vaccine for Children at Risk. World Health Orgnisation, 6 Oct. 2021, https://www.who.int/news/item/06-10-2021-who-recommends-groundbreaking-malaria-vaccine-for-children-at-risk.

[65] Callaway, Ewen. "UN Treaty Agrees to Limit Gene Drives but Rejects a Moratorium." Nature, November 29, 2018. https://doi.org/10.1038/d41586-018-07600-w.

[66] Dixit, Rekha. "Malaria Vaccine Mosquirix May Have Only Limited Impact in India, Say Experts." The Week, October 9, 2021. https://www.theweek.in/news/health/2021/10/09/malaria-vaccine-mosquirix-limited-pmact-india.html.

[67] Chauhan, Virander. "New Hope for Malaria Vaccine: The Science, Challenges, Opportunity." The Indian Express, November 7, 2022. https://indianexpress.com/article/explained/explained-health/new-hope-for-malaria-vaccine-the-science-challenges-opportunity-8253600/.

[68] Pillai, Sowmya. "Oxford, Serum Initiative: Anti-Malaria Vaccine's Phase 3 Trials Conclude." Hindustan Times, December 6, 2022. https://www.hindustantimes.com/india-news/oxford-serum-initiative-anti-malaria-vaccine-s-phase-3-trials-conclude-101670295509486.html.

[69] Ghosh, Abantika. "World Finally Gets a Malaria Vaccine and It Has an Indian Connection: Bharat Biotech." ThePrint (blog), October 7, 2021. https://theprint.in/health/the-india-connection-to-worlds-first-malaria-vaccine-now-approved-by-who/746683/.

The Takshashila Institution is an independent centre for research and education in public policy. It is a non-partisan, non-profit organisation that advocates the values of freedom, openness, tolerance, pluralism, and responsible citizenship. It seeks to transform India through better public policies, bridging the governance gap by developing better public servants, civil society leaders, professionals, and informed citizens.

Takshashila creates change by connecting good people, to good ideas and good networks. It produces independent policy research in a number of areas of governance, it grooms civic leaders through its online education programmes and engages in public discourse through its publications and digital media.