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FACTSHEET

Gene Drives for Malaria Control and Elimination

What are gene drives?

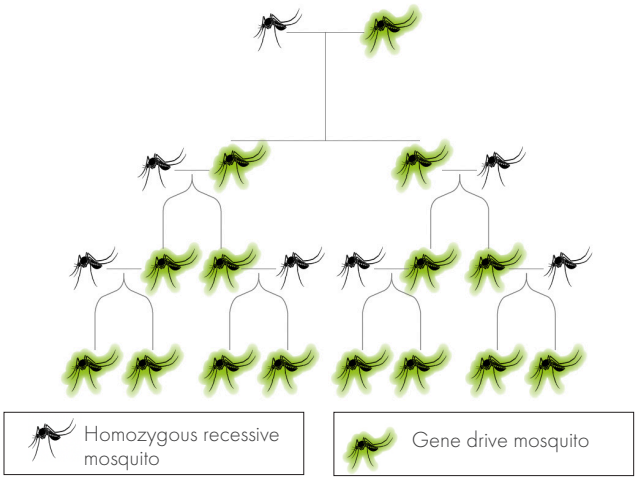
Gene drive can be defined as a technology where genetic materials are transferred from parents to unusually high numbers of their offspring due to biased inheritance (sometimes referred to as the possession of "selfish" genetic materials). There are different ways of achieving this biased inheritance needed for a drive, but the shared outcome is one where the offspring of a parent carrying a certain genetic variant has over a 50% likelihood of inheriting it.

Malaria-transmitting mosquitoes modified with gene drive systems are being proposed as new tools that will complement current practices aimed at reducing or preventing transmission of vector-borne diseases such as malaria[1]. Gene drive systems have the potential to spread new genetic traits through interbreeding populations of malaria mosquitoes from low initial introductions, and the constructed genes could persist in those mosquitoes indefinitely or until the target mosquito population is locally eliminated.

How do gene drives work?

Gene drives dramatically increase the likelihood that a particular suite of genes will be passed onto the next generation, allowing the genes to rapidly spread through a population and onto the next generation, allowing the genes to rapidly spread through a population and override natural selection[2].

Illustration of the gene drive concept



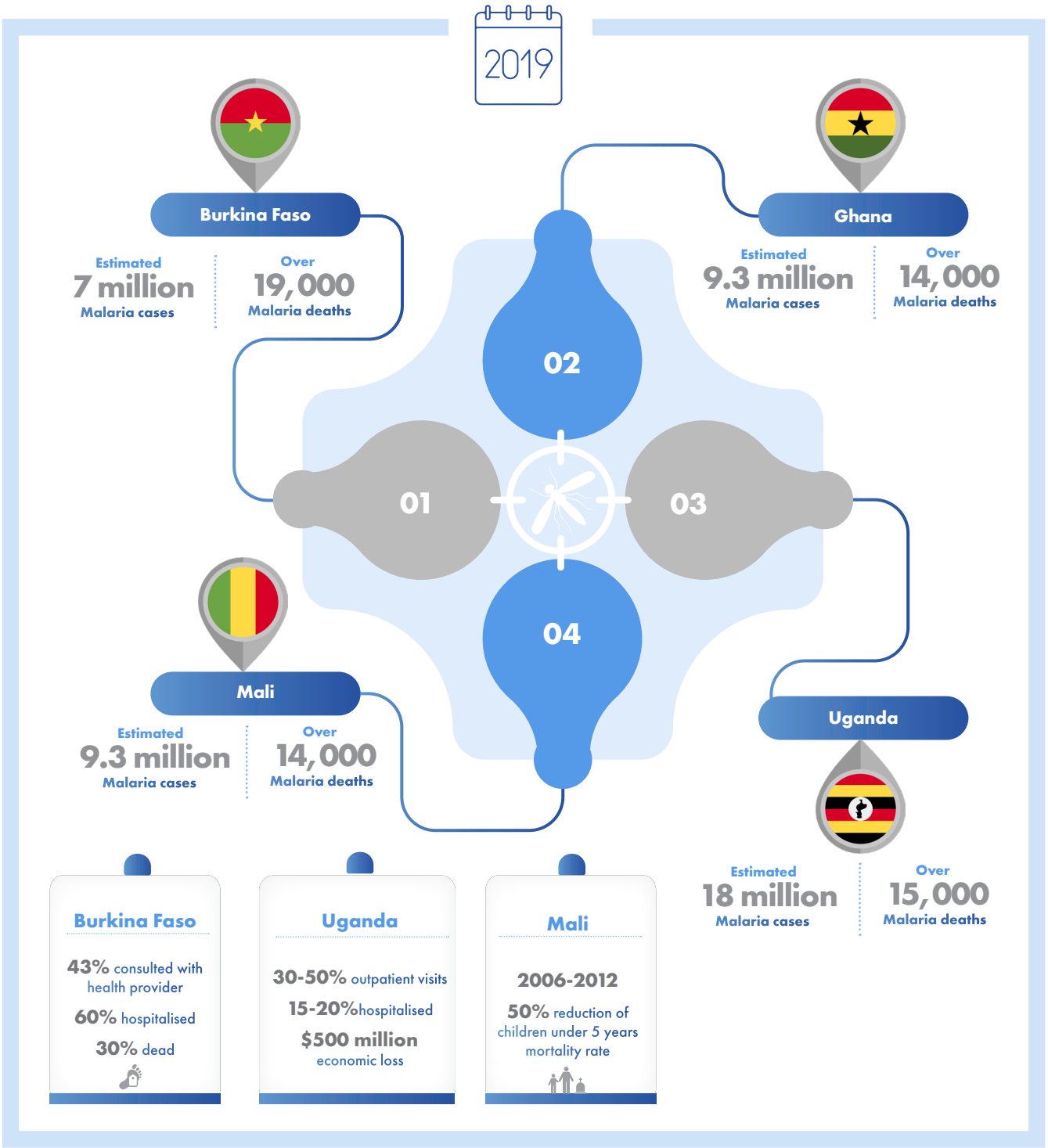
What are the two types of gene drives?

Gene drives technology can take two different forms, namely population suppression or population alteration[3].

i) Self-Limiting

In population suppression, the artificial gene introduced into the vector population disrupts reproduction by either distorting sex chromosome inheritance such that most progenies are males, or by knocking out female fertility genes such that they no longer lay eggs. Over time, the

[1]https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5993454/
[2]https://www.livescience.com/gene-drive.html
[3]https://www.nepad.org/publication/gene-drives-malaria-control-and-elimination-africa



Source: World Health Organisation

resulting population dwindles. Gene drive constructs, in this case, are not expected to persist in the environment.

ii) Self-Sustaining

In population alteration on the other hand, the gene constructs introduced are those that reduce organisms' ability to transmit specific pathogens. For example, specific genetic segments that code for parasite binding proteins in the mosquito are altered so that malaria parasites can no longer bind to these receptors, effectively making the progeny incapable of carrying malaria pathogens. Unlike in the population suppression systems, the artificial gene constructs are intended to spread throughout the vector population and persist[4]. In a pioneering example of this approach, scientists in California have created a highly efficient mediated gene drive, which achieved 98% modification of a

[4]https://www.nepad.org/publication/gene-drives-malaria-control-and-elimination-africa

laboratory population of *Anopheles stephensi* such that it could no longer transmit the malaria parasite. This approach therefore equally lends itself to use in large-scale malaria elimination efforts with potentially high impact over short durations.

State of research on the technology – laboratory testing, no field-testing has been done so far

The principle of using the gene drive technology for malaria control has been proven in the laboratory. Gene drive mosquitoes have been produced in laboratories (Gantz et al., 2015; Hammond et al., 2016) and are expected to be eventually tested in the field in Africa (NEPAD 2018). African institutions and scientists are engaging actively in these technology development efforts as well as the regulatory processes. Exploratory research on gene drive is currently ongoing in Burkina Faso, Ghana, Mali, Uganda, led by the Target Malaria Consortium in partnership with local research institutions as described below.

Research on gene drive for malaria control and elimination in Africa

Burkina Faso

Burkina Faso in West Africa, is among ten countries with the highest incidence of malaria in the world[5]. According to the national Ministry of Health, the disease accounts for 43% of consultations with a health provider, over 60% of hospitalisations and 30% of deaths. In 2019, WHO noted[6] that there were an estimated 7 million malaria cases in the country, and over 19,000 estimated malaria associated deaths.

Initiated in 2012, Target Malaria's exploratory gene drive research in Burkina Faso is led by the Institut de Recherche en Sciences de la Santé (IRSS) in Bobo-Dioulasso. The research has focused on collection of baseline entomology data to better understand what species of mosquitoes are present, their seasonal dynamics and behaviour in the natural environment. Target Malaria has completed what the project refers to as "Facilities Readiness" for its insectary at IRSS, ensuring compliance with international Arthropod Containment Level 2 (ACL) guidelines. It has also engaged with the different stakeholders to keep them informed of what the project is doing and future plans.

In 2019, the team achieved a milestone when they released genetically modified sterile male mosquitoes in Bana village[7]. The mosquitoes were genetically-modified to be sterile, which means they died without any offspring; and being male mosquitoes, they did not bite people since male mosquitoes do not bite. These were not gene drive mosquitoes, and their release was not to test these as a vector control tool. The release was meant to help the Target Malaria team to work closely with the stakeholders and the regulatory authorities; provide information regarding the behaviour of modified mosquitoes in the field, and serve as a capacity-building opportunity for the team on how to import, rear, transport and release and monitor non-gene drive genetically modified mosquitoes[8].

Ghana

Malaria is both endemic and perennial throughout Ghana, putting the entire population at risk. In 2019, WHO estimated that there were an estimated 6.7 million malaria cases with 11,800 estimated deaths recorded. The team in Ghana joined Target Malaria in 2018 and is based at the University of Ghana, Legon, an institution with a renowned track record in malaria research.

In Ghana, there is no plan to test gene drive mosquitoes; rather, the focus is on studying mosquito behavior and the impact of reducing Malaria-transmitting mosquitoes on the ecology. Their work is currently focused on two main activities:

- *Anopheles gambiae* ecological observatory that will aid in making predictions regarding the impact of eliminating or reducing this species on the rest of the ecosystem[9].
- Mosquito rearing and male fitness studies of *Anopheles gambiae* complex that will develop protocols for rearing,

[5]https://www.severemalaria.org/countries/burkina-faso#3
[6]https://www.who.int/publications/i/item/9789240015791
[7]https://targetmalaria.org/results-from-months-of-monitoring-following-the-first-release-of-non-gene-drive-genetically-modified-mosquitoes-in-africa/
[8]https://targetmalaria.org/results-from-months-of-monitoring-following-the-first-release-of-non-gene-drive-genetically-modified-mosquitoes-in-africa/
[9]https://targetmalaria.org/where-we-operate/ghana/

transporting, and releasing mosquitoes. These will ensure that in the future, gene drives constructs developed by Target Malaria will get introduced into the natural *Anopheles gambiae* populations in an efficient manner.

Mali

Malaria is the primary cause of morbidity and mortality in Mali, particularly among children under five. Household surveys indicate a nearly 50% reduction of children under-five mortality rates from 2006 to 2012. However, in 2019 alone, WHO noted that there were an estimated 9.3 million malaria cases and over 14,000 estimated deaths across the country.

Initiated in 2012, Target Malaria research in Mali is led the Malaria Research and Training Center (MRTC) of the Faculty of Medicine, Pharmacy and Odontostomatology (FMPOS) of the University of Science Techniques and Technologies in Bamako. The team has an insectary and has been working on non-gene drive genetically modified sterile male mosquitoes - the initial stage of a stepwise approach to develop Target Malaria's genetic-based technologies for malaria vector control. These studies aim to strengthen the teams' capacities in operations and containment measures. They also help understand regulatory processes and improve the dialogue with stakeholders[10]. Engagement activities with communities include visitation to the insectary and field sites to understand Target Malaria's work.

Uganda

Uganda has one of the highest global burden of malaria cases, with over 90% of the population at risk, malaria remains Uganda's leading cause of death, especially in children. The disease causes immense detrimental health effects and is responsible for 30 to 50% of outpatient visits and 15 to 20% of hospital admissions. The average economic loss in Uganda due to malaria annually is over $500 million. In 2019, WHO reported that there were an estimated 18 million malaria cases and over 15,000 estimated deaths in the country.

Initiated in 2018, Target Malaria's work in Uganda is led by the Uganda Virus Research Institute (UVRI)[11]. The work in Uganda is still in early stages, focusing on entomological mosquito collections from field sites on islands within Lake Victoria and mainland sites. The entomology team has already collected baseline data for two years to enable studies on mosquito dynamics and behaviour.

Stakeholder engagement is ongoing involving dialogues with communities and other stakeholders to create awareness on the work, seek their consent and inputs. A major milestone for the project was the construction and inauguration of a new insectary at the UVRI in Entebbe. Since it was opened in July 2019, the team has been conducting experiments with local wild mosquitoes. In the future, it will be used for genetically modified mosquito experiments following regulatory approval.

Experts' recommendations for gene drive research for malaria control in sub-Saharan Africa

Experts have opined that the gene drive technology offers the promise for a high-impact, cost-effective, and durable method to control malaria transmission that would make a significant contribution to elimination. Gene drive systems, such as those based on clustered regularly interspaced short palindromic repeats (CRISPR)/CRISPR associated protein, have the potential to spread beneficial traits through interbreeding populations of malaria mosquitoes[12].

Gene drive techniques have already been demonstrated in laboratories to effectively alter *Anopheles* mosquito populations so that they can no longer transmit malaria parasites (Gantz et al., 2015), and also to introduce lethal gene sequences that suppress and rapidly crash entire mosquito populations in laboratories (Hammond et al., 2016). Mathematical evaluations of these approaches indicate that, if combined with existing interventions like LLINs, these technologies can effectively eliminate malaria in several African settings within a few years after the initial releases of even small numbers of modified mosquitoes (Eckhoff, Wenger, Godfray, & Burt, 2016). It is particularly important to emphasize that the use of transgenic mosquitoes of any kind, as with any other vector control tool, should be considered as just one component of an integrated approach, rather than as stand-alone technology (Marshall & Taylor, 2009)[13].

Genetic modification technologies offer additional options for specificity and durability of effect, as well as adaptability to different disease transmission conditions. Advances in the development of genetically modified mosquitoes have raised hopes for the availability of new, potent and cost-effective tools to aid in the fight against malaria, dengue and other mosquito-borne pathogens[14].

Gene drive regulatory efforts

From a regulatory standpoint, the uniqueness of gene-drive technology may necessitate that different arms of governments take different roles as developer, evaluator, implementer and regulator. Aspects such as continuous independent assessments during development and implementation may

[10] https://targetmalaria.org/where-we-operate/mali/
[11] https://targetmalaria.org/where-we-operate/uganda/
[12] https://pubmed.ncbi.nlm.nih.gov/29882508/
[13] https://www.nepad.org/publication/gene-drives-malaria-control-and-elimination-africa
[14] http://apps.who.int/iris/bitstream/handle/10665/341370/9789240025233-eng.pdf?sequence=1&isAllowed=y

be contracted out to independent experts, but the processes will still need to be managed by government agencies. Given the primary application for malaria control, countries should seek guidance from WHO on questions of implementation. In some African countries, there is already a National Biosafety Agency, which acts as a central coordinator of all reviews of genetically modified organisms[15].

It should, however, be noted that there are other reviews, such as efficacy, and product deployment approval, that might not be the remit of the National Biosafety Agencies. Coordination of these agencies and a clear roadmap should therefore, be developed at country level. The WHO guidelines will also provide a crucial reference for countries wishing to develop their own guidelines, as far as the utilization of this technology for health is concerned.

Concerns with the gene drives technology

The characteristics of this technology have raised concerns that necessitate careful consideration of the product development pathway. A multidisciplinary working group considered the implications of low-threshold gene drive systems on the development pathway described in the World Health Organization *Guidance Framework for testing genetically modified (GM) mosquitoes*, focusing on reduction of malaria transmission by *Anopheles gambiae s.l.* mosquitoes in Africa as a case study. The most recent study[16] models mosquito populations at more than 40,000 settlements in Burkina Faso and surrounding countries. It takes into account rivers, lakes and rainfall, as well as field data on mosquito movement. The results[17] show that repeated introduction, rather than a single

There are many ways to utilise the ability of gene drives to suppress or spread a trait through a population

- Both gene drive technologies and its implementation are vital and cost-effective component of malaria control program.
- Gene drives can also be used for human health purposes, particular for the control of vector-borne diseases including malaria vector control/elimination:
    - To suppress populations of species so that the population is no longer large enough to effectively spread disease, plant or animal, that cause agricultural damage, reducing the need to use pesticides or herbicides.
    - To remove populations of invasive species that cause damage to ecosystems or economies.
    - To complement current integrated vector control efforts in accelerating malaria elimination in SSA.
    - To increase the coverage of existing malaria interventions mainly combination of ITNs (impregnated bednets), RDT (rapid diagnostic test) and ACT (artemisinin combination therapy).
    - To increase the coverage of existing malaria interventions mainly combination of ITNs (impregnated bednets), RDT (rapid diagnostic test) and ACT (artemisinin combination therapy).
    - To boost the long-term cost-effectiveness of national and regional malaria interventions.
- Also, gene drives could be used to target weeds, spreading a trait that would reverse their evolved resistance to non-toxic herbicides. This could reduce the need to use newer and more toxic herbicides, which could have both cost-saving and environmental benefits.
- To spread a specific (engineered) trait throughout the population so that the trait prevents organisms in the population from being disease vectors, yet the uncertainties about genetically modified anopheles vectors behavior and abundance/competence.

[15]https://www.nepad.org/publication/gene-drives-malaria-control-and-elimination-africa
[16]https://www.nature.com/articles/d41586-019-02087-5#ref-CR11
[17]https://www.nature.com/articles/d41586-019-02087-5#ref-CR11

release, of modified mosquitoes over a few years across villages will be needed to reduce the insects' overall numbers.

"The theory says that, in principle, if you release once it would spread continent-wide. The reality is that would happen very slowly," says population biologist Charles Godfray at the University of Oxford, UK, a collaborator with Target Malaria and the study's lead researcher.

Another concern is that gene drives have the potential to alter entire populations and therefore entire ecosystems. They could also, in theory, negatively affect human health by causing the malaria parasite to evolve to be more virulent or to be carried by another host, says molecular biologist and bioethicist Natalie Kofler. She is the founding director of the Editing Nature group at Yale University in New Haven, Connecticut, which aims to address environmental genetic technologies worldwide. "This technology has the potential to be immensely powerful and to change the course of things that we may not be able to predict," says Kofler.

In 2014, geneticist at Harvard Medical School simultaneously built a reversal drive to overwrite the original drive on command[18].

The rest of the field has followed suit, developing gene drives with built-in controls, external overrides or both. US research teams are studying how to control, counter and reverse gene drives. Researches are developing gene drives that should be unable to spread beyond a target population of mosquitoes or flies. One such drive requires continual release for many generations. When those releases stop, it becomes diluted with wild-type versions of the gene and wipes itself out within four years. That might be long enough to eliminate a virus such as Zika or dengue from a mosquito population but safer and effective.

WHO's guidance on efficacy evaluation, safety evaluation, and ethical considerations

Efficacy evaluation

Both entomological and epidemiological endpoints may be used to test the efficacy of GMMs that are intended to reduce morbidity and mortality from vector-borne diseases. The entomological endpoint is a reflection of the likelihood of disease transmission due to mosquito population characteristics and will be the predominant outcome measure in early small-scale releases. Since this is difficult to measure directly, surrogate indicators may be chosen, which could include GMM fitness, frequency of the transgenics construct,

Ghana Health Project-supriyaam-Flickr.jpg

[18]https://www.nature.com/articles/d41586-019-02087-5#ref-CR8

vector population size and or ability to support pathogen replication. The epidemiological endpoint is a measurable reduction in the incidence of infection or disease in human populations, which can be assessed in later large-scale releases. Testing for epidemiological efficacy should be conducted according to accepted standards for clinical trials.

Safety evaluation

Safety in the development of genetically modified mechanisms (GMM's) focuses on reducing any possible adverse effects on health and the environment to acceptable levels, keeping in mind the known and ongoing adverse impact of vector-borne diseases. Risk analysis, a multi-stage process for identifying and managing potential hazards and mechanisms of harmful impact on the receiving environment, human or animal health; the likelihood and magnitude of that harmful impact and the levels and consequences of uncertainity associated with these effects. RM should provide appropriate measures to reduce risk to an acceptable level. Both RA and RM should be grounded in a country's health, environmental and biodiversity protection goal, also taking into account any additional community concerns.

Ethical considerations

The development, testing and introduction of GMM's for the control of vector-borne diseases raises ethical and governance issues that warrant careful deliberation, particularly for GMM's with gene drives designed to spread and persist in the environment. Researchers must consider the motivation for conducting the research and its purported social value; the relationship; and how the risks and benefits of GMM research will be assessed, managed and discussed with communities, stakeholders and publics.

Researchers should ensure that coordination and communication with communities is fair and culturally appropriate, and that community values and concerns are taken into account in research plans at all stages. Ethical GMM research will attend to considerations of justice and equity, and fulfil obligations of transparency, capacity strengthening, benefit sharing and ongoing stewardship.

Respect for communities should be an overarching ethical goal in GMM trials.

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