Rapid Response Brief
April 2019

What can research evidence tell us about:

Potential impacts of Genetic modification of mosquitoes in the control and prevention of malaria on individuals, community and ecology

Key messages

- Genetically modified mosquitoes (GMM) have been proposed as a potential malaria control strategy, but this has raised a lot of controversies.
- Much of the possible impact that the modification of mosquitoes can have on human health and ecology and evolution is still theoretical and has not yet been proven in scientific research.
- The release of genetically modified mosquitoes has a generated number of ethical considerations before releasing for field testing such as;
    - Possibility of the modified mosquitoes to cross geographical boundaries into other communities that are not under the trial,
    - Protection of humans in case of any untoward event through an existing law (Genetic Engineering Regulatory Act, 2019),
    - Complete elimination of an entire species on earth might have unintended consequences-
    - Seeking informed consent from the community (ensuring that the community understands the information and possible adverse effects of the intervention).
- The release of gene drive mosquitoes could have unpredictable ecological and health consequences.

Where did this Rapid Response come from?

This document was created in response to a specific question from a policy maker in Uganda in 2019.
It was prepared by the Center for Rapid Evidence Synthesis (ACRES), at the Uganda country node of the Regional East African Community Health (REACH) Policy Initiative.

Included:

- **Key findings** from research
- **Considerations about the relevance** of this research for health system decisions in Uganda

Not included:

- Recommendations
- Detailed descriptions

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Summary

Background:
Target Malaria is a not-for-profit research multi-national consortium in Africa and the United Kingdom that aims to develop and share technology for malaria control. In Uganda, the consortium partner is Uganda Virus research institute (UVRI) as an implementation partner and Uganda National Council of Science and Technology (UNCST) as a funding partner. Target malaria is involved in the testing of genetically modified (GM) mosquitoes as an intervention to eliminate malaria in local communities in Africa. Through UVRI, the group conducted an initial phase of the trial including collecting of mosquito species in three (3) villages in Mukono district but met resistance from one of the villages. On consulting the district leadership to seek community entry, the leadership requested for more consultations because of the controversy around GM mosquitoes, especially as alleged to have happened in other African countries such as in Burkina Faso.

Rapid Response Question:
What are the potential impacts of genetically modified mosquitoes in control and prevent the spread of malaria, on individuals, community and ecology and the ethical considerations?

Findings:
GM mosquitoes, like other GM organisms (GMOs) has generated a lot of controversies especially related to the ethical application of such technology in humans and communities. However, there is very limited information on the research evidence of the possible side effects of GM Mosquitoes both on the community and the individuals. Current information is majorly based on theories, rather than research evidence.

- Ethical considerations related to the release and application of GM mosquitoes in communities include:
    - Possibility of the modified mosquitoes to cross geographical boundaries into other communities that are not under the trial,
    - Protection of humans in case of any untoward event through an existing law (Genetic Engineering Regulatory Act, 2019),
    - Complete elimination of a complete species on earth might have unintended consequences- for some relating this to playing "God."
    - Seeking informed consent from the community (ensuring that the community understands the information and possible adverse effects of the intervention).

Conclusion:
There are few studies that have used GM Mosquitoes in the field and, therefore, very little is actually known about the effects/ impacts of the use of GM Mosquitoes in the control of the spread of malaria. Most of the field studies have been rejected or stopped due to local hostility from the host and global communities of anti- GM organisms making it untenable to assess for any impacts these technologies might have. There is therefore need to seek national as well local authority and community approval before any field trial is conducted. A comprehensive community engagement plan needs to be outlined and discussed with the stakeholders at the different phases of the study. The interest of the community needs to be considered in the planning and implementation of such an intervention during all the stages.

Background

> ### How this Rapid Response was prepared
> After clarifying the question being asked, we searched for systematic reviews, local or national evidence from Uganda, and other relevant research. The methods used by the SURE Rapid Response Service to find, select and assess research evidence are described here: www.evipnet.org/sure/rr/methods

Uganda has had substantial reduction in the number of malaria cases, by 28% from 408 cases per 1000 population in 2015/16 to 293 cases per 1000 population per year in 2017/2018 but malaria still remains a public health concern causing a total of over 11 million cases and 5000 deaths in 2017 despite several efforts to eliminate it (1, 2). This reduction is still short of the goal to reduce malaria burden by 80% set by the national malaria control program (3). There are currently several malaria control and prevention strategies in use in Uganda such as; long-lasting insecticide-treated mosquito Nets (LLINS), indoor residual spray (IRS), malaria case management strategy, intermittent preventive therapy (IPT) among the high-risk population like pregnant women and children under five years and Larval Source Management (LSM) as a complementary strategy (3). These strategies are applied according to a risk stratification according to the epidemiological profile of malaria burden in Uganda (3). However, despite the application of these strategies, malaria morbidity and mortality are still a public health concern.

The fight against malaria has been augmented by a number of innovations and application of smart new technologies globally, such as genetic modification (GM) of mosquitoes(4). Genetic modification of mosquitoes involves the editing of specific genes using a technic known as gene drive to influence the type and character of mosquitoes in the subsequent generations (5-7). The excitement around gene drives has currently been spurred by an innovative approach known as CRISPR method which has changed the rules of gene editing and at the same time drawn a lot of controversies (7, 8). With the controversy around CRISPR, a moratorium was passed by National institutes of health on the use of this technology in humans (9). Genes of specific species of mosquitoes have been edited to render them infertile or unable to transmit diseases such as malaria, zika and dengue fevers in South America and the United States but this has courted a lot of controversy such as unintended effects of exposing humans to unknown mutations through mosquito bites (10, 11). As such, a number of prominent scientists and regulatory bodies have advised that the use of GM Mosquitoes be rolled out in the following phases with safety a major consideration at each phase (6);

- Phase 0: Research preparation
- Phase 1: Laboratory-based research
- Phase 2: Field-based research
- Phase 3: Staged environmental release
- Phase 4: Post-release surveillance

Target Malaria is a not-for-profit research multi-national consortium in Africa and the United Kingdom that aims to develop and share technology for malaria control. In Uganda, the consortium partner is Uganda Virus research institute (UVRI) as an implementation partner and Uganda National Council of Science and Technology (UNCST) as a funding partner. Target malaria is involved in the testing of genetically modified (GM) mosquitoes as an intervention to eliminate malaria in local communities in Africa. The 'target malaria' group is using two major approaches; 1) reducing female fertility and 2) a modification of the male mosquitoes to ensure that females only breed males (12). Through UVRI, the group conducted an initial phase of the study that included collecting mosquito species in two (2) villages in Mukono district but met resistance from one of the villages. On consulting the district leadership to seek community entry, the leadership request for more consultations because of the controversy around GM mosquitoes especially as alleged to have happened in other African countries such as in Burkina Faso (13).

This rapid response brief, therefore, summarises the potential impacts of genetically modified mosquitoes in the control and prevent the spread of malaria, on individuals, community and ecology and the ethical considerations.

Summary of findings

In this rapid response brief, we have summarized the impact of GM mosquitoes in field trials on the health, socioeconomic effects of individuals and the community, ecology and evolution and the ethical considerations.

According to report from the National Academies of Sciences, Engineering, and Medicine (NASEM) there is a significant gap in knowledge on the potential impact of the basic and applied research of gene drives on humans, ecology and evolution (6). There are however, a lot of ethical considerations on the application of gene drive technology on organisms and in communities. This has made it challenging to justify proceedings from laboratory research to field trials as such that the National Academies of Sciences, Engineering and Medicine advise that only controlled field trials be considered (9).

Genetic engineering or modification applies gene drive technologies using the CRISPR method to edit DNA of organisms such as mosquitoes (14). CRISPR (clustered regularly interspersed short palindromic repeats) has generated a lot of excitement in the scientific community because it is faster, cheaper, more accurate, and more efficient than other gene-editing methods (5, 14). CRISPR uses enzymes to cut and insert targeted specific portions of DNA in organisms such as mosquitoes and plants (14).

Genetic modification has been applied in mosquitoes with the aim of supplementing the control and prevention of transmission of dangerous diseases such as malaria, zika and dengue fevers in Brazil and USA (7, 15). It is estimated that they are over 3000 species of mosquitoes, but only about five (5) are able to transmit malaria (16).

The female species of the mosquitoes are responsible for the transmission of malaria and, therefore, the target of genetic modification (GM) (4). The possibility of transmission is dependent on the lifespan and fertility of the female mosquitoes which varies with the environment- mosquitoes survive longer in a dry environment but reproduce more in wet conditions, stress- able to survive longer in stressful conditions without feeding and die earlier if they feed more on an infected host (17-19).

There are three major ways for which genetic engineering mosquitoes is used to prevent malaria;

1) Editing the gene of male mosquitoes to cut the X chromosome and induce an infertile gene in the next generation of female males when the modified mosquitoes mate with the wild female mosquitoes. It is expected that the GM mosquitoes will compete with the wild male mosquitoes to pass on the infertile gene to the next generation.
2) Editing the gene of mosquitoes to resist disease through changing the chromosome in the salivary glands to host the malaria parasite
3) Modifying the gene of mosquitoes so that they vaccinate humans against malaria by placing the vaccine in the mosquitoes (11).

Gene modification of mosquitoes is done with the aim of creating an imbalance in the male-female ratio so that there are more males than females which transmit the malaria plasmodium. This has raised one of the fears for the application of this technology, the possibility of the extinction of the anopheles mosquito as their reproductive capacity will be significantly impeded by the low numbers of female mosquitoes (11). This is because the male mosquito is expected to die within 3-5 days after mating, and the female mosquitoes will be unable to produce any females in the next generations.

The ‘target malaria’ group is reported to be using two major approaches:

1) reducing female fertility by editing the X chromosome of the male mosquitoes so that infertile gene is passed onto the next generation of female mosquitoes, thereby reducing the female: male ratio

2) a modification of the male mosquitoes to ensure that wild females are attracted to the modified breed and only mate with them (12).

Impact on human beings:

a) **Health effects;**

Very little has been studied or observed about the potential health effects of GM mosquitoes in individuals. However, current evidence is based on math models and theories that have to rely on certain idealistic environment assumptions such as steady-state population and distribution for accuracy, which is rare.

The summary of the health effects below is in theory and in no way exhaustive;

According to some scientists, in theory, individuals exposed to GM mosquitoes may be at risk of acquiring an enhanced or different parasite with unknown unintended consequences because;

1) There is a possibility that the genetic modifications might malfunction and as a result, this might reduce the efficacy of malaria control as the intended outcome is not achieved, or the mosquito might instead acquire new parasites other than plasmodium and transmit these
2) The mosquitoes that might instead carry a more virulent form of plasmodium parasite leading to severe disease (9, 11). From this possibility, it is crucial to closely and continuously monitor the individuals and provide free treatment for any mosquito-borne disease (11).

   Assumption

   - The parasite is able to mutate and acquires a new strain of virulence to be accommodated by the modified mosquito because the mosquito only becomes infected after a blood meal from an infected vertebrate. This has been shown in math models if the transmission is blocked for dengue fever in people with continued transmission (20).
   - The dynamics of parasite transmission remains stable, and the virulent strain is preferred to the wild type.
3) There is a possibility of loss of the partial immunity developed from the continuous exposure to Plasmodium parasites among individuals (21). This could lead to an epidemic in the event that mosquitoes from neighbouring communities carrying the plasmodium parasite migrate into an area where the mosquito population has significantly dropped.

   Assumption

- The mosquito is able to fly across geographical boundaries over a long distance. The maximum distance flight of mosquitoes is estimated to be about 5m to 50km, and this is dependent on the species. Most malaria-carrying species fly an average of 1.3km (22).

Socioeconomic effects

We did not find any information pertaining to the social-economic impact of GM mosquitoes. However, in theory, there is a possibility of destabilizing the eco-system where mosquitoes act as pollinators, and mosquito larvae are a source of food to fish. So, the reduction in number of mosquitoes could lead to reduced pollination and a lack of food for fish, thus reducing the fish population (7, 21).

Impact on the ecology and evolution

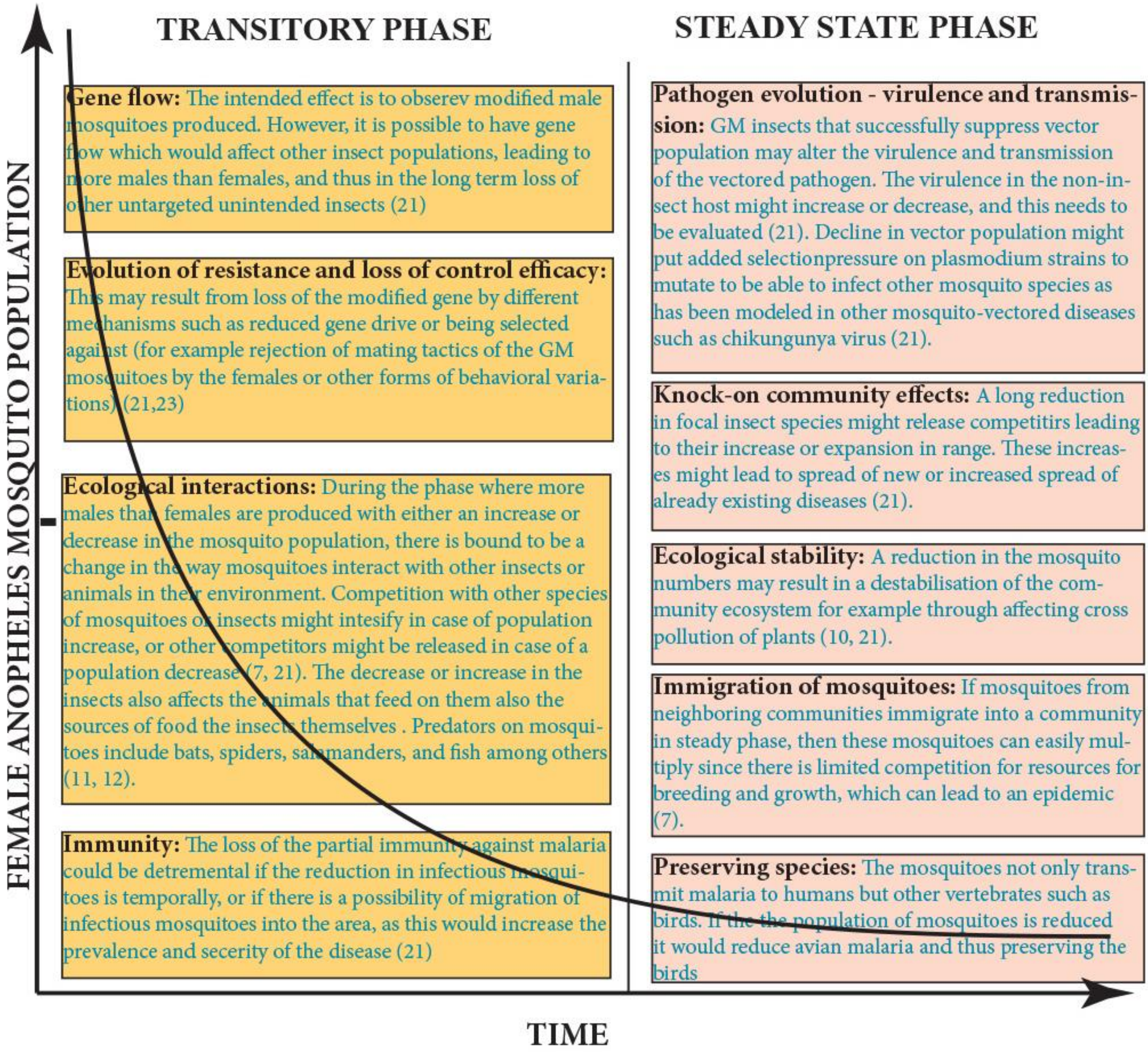
There is currently very scarce information on the ecological impact of GM insects. (5). The known information is based on a theory that indicates that ecological impact should be assessed on a case by case basis since it is dependent on; the type of genetic modification, the reproductive behaviour of the insect and the receiving environment (5).

The ecological effects can occur during the two phases of GM insect population perturbation (21);

1. Transitory phase: this is when the new breed of mosquitoes has been introduced into the community. The wild insect population changes relatively rapidly in density

2. Steady-state: After a number of cycles to release the new breed of mosquitoes a steady-state in the population dynamics of the insects is achieved. The wild insect population reaches a steady population density if the GM insect intervention is effective causing now awith suppressed population density of the wild mosquitoes.

However, some of the observed effects cut across the different phases as shown in the figure below



Ethical considerations:

It is quite clear that any GM technology to be used have to receive approval of the country in which they are to be applied and the communities to host the trials (23). Uganda has a supportive environment and legal framework for the development and research of genetically modified organisms (24). The Cartegana protocol on biosafety to the convention for which Uganda is a signatory is an international agreement governing the movements of living modified organisms (LMOs) resulting from modern biotechnology from one country to another (23). In addition, parliament passed the GMO bill known as the genetic engineering regulation act 2019 that provides a regulatory framework for biotechnology (25).

There are different ethical concerns and considerations that have been fronted pertaining to the field trials of GM mosquitoes. These are discussed in the below;

Possibility of eliminating a full species;

There are two counter opposing arguments to the value of eliminating a species of insects. The opponents of such a move are motivated by the argument that all life forms are sacred and humans should, therefore, play no part in eliminating them while proponents argue that mosquitoes are vectors of the dangerous parasites that cause eternal harm to humans and as such their elimination is beneficial to the health of humans as was done with diseases such as smallpox (10).

> R.L Metcalf wrote, '… *species should be regarded as sacred and man indeed has no right to destroy them.*'

Assumption

A particular species of anopheles mosquitoes will be completely eliminated, but field trials in Brazil showed that there was 80% reduction in a specific species of mosquitoes using sterile male mosquitoes.

Scientists try to act God by deciding which insect survives and gene to manipulate;

Intervention that alters the natural world are often criticized as playing God which might have a great deal of uncertainty pertaining to the unintended consequences that gene-drive technologies might have (10). This has been countered by the argument that all new technologies used could have unforeseen or unintended side effects on future generations, yet we use them.

Selection of site for research

The site for field trials must be geographically isolated to minimize potential environmental impacts by limiting the potential effects to a particular area (6, 11, 26). Geographical isolation has to consider the species of mosquitoes present in an area which might be related to their potential flight distance and geographical barriers.

GM mosquitoes to be used only when target disease is a significant public health problem and it is possible to prevent crossover between the intervention and control communities (11).

Community engagement and authorization;

This is crucial since the intervention can substantially impact the entire community. Obtaining the support of the local community is essential and a requirement for conducting GM insect field trials (6, 11, 16, 27, 28).

> Macer noted, ' *There is a need to engage the community and have a two-way communication between researchers, policymakers and local communities in order to find whether each particular community will want to have a field trial, the nature of the concerns they have, and the ways that can be designed to involve communities as partners in trials*.(29)'

There is always widespread opposition (public or institutional) to testing GM insects and this has to be anticipated (16). A comprehensive community engagement strategy needs to be outlined with the other stakeholders and implemented.

There is a possibility of the GM mosquitoes leaving the area where they have been released and impacts intended to be seen to other communities. To avoid a cross border dispute from different jurisdictions, it might be necessary to engage the neighboring communities as well before the release of the mosquitoes.

Resources;

There is need to have enough resources to carry out the trial successfully; the resources should be available and can be committed to the trial. This ranges from human resources to finances, logistics and collaborators (16).

Conclusion:

There are few studies that have used GM Mosquitoes in the field and, therefore, very little is actually known about the effects/ impacts of the use of GM Mosquitoes in the control of the spread of malaria. Most of the field studies have been rejected or stopped due to local hostility from the host and global communities of anti- GM organisms making it untenable to assess for any impacts these technologies might have. There is, therefore, need to seek national as well as local authority and community approval before any field trial is conducted. A comprehensive community engagement plan needs to be outlined and discussed with the stakeholders at the different phases of the study. The interest of the community needs to be considered in the planning and implementation of such an intervention during all the stages.

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Conflicts of interest
None known.

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What is a Rapid Response?

Rapid Responses address the needs of policymakers and managers for research evidence that has been appraised and contextualised in a matter of hours or days, if it is going to be of value to them. The Responses address questions about arrangements for organising, financing and governing health systems, and strategies for implementing changes.

What is ACRES?

ACRES – The Center for Rapid Evidence Synthesis (ACRES) is a center of excellence at Makerere University- in delivering timely evidence, building capacity and improving the understanding the effective, efficient and sustainable use of the rapid evidence syntheses for policy making in Africa. ACRES builds on and supports the Evidence-Informed Policy Network **(EVIPNet) in** Africa and the Regional East African Community Health **(REACH)** Policy Initiative (see back page). ACRES is funded by the Hewlett and Flora foundation. http://bit.do/eNQG6

SURE collaborators:

SURE Supporting the Use of Research Evidence

REACH Regional East African Community Health Policy Initiative

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Glossary

of terms used in this report:
www.evipnet.org/sure/rr/glossary