AUDA-NEPAD
AFRICAN UNION DEVELOPMENT AGENCY

Ethics Guidelines for the use of Genetically Modified Mosquitoes

West Africa Integrated Vector Management Programme

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About The AU, AUDA-NEPAD and WAHO

The African Union (AU)

The African Union (AU) is a body of 55 member states that make up the countries of the African Continent. It was officially launched in 2002 as a successor to the Organization of African Unity (OAU), which ran from 1963 to1999. The decision to re-launch Africa's pan-African organisation was the outcome of a consensus by African leaders that in order to realise Africa's potential, there was a need to re-focus attention from the fight for decolonisation and ridding the continent of apartheid hitherto pursued under the OAU, towards increased cooperation and integration of African states to drive Africa's growth and economic development. The AU is guided by its vision of *An integrated, prosperous and peaceful Africa, driven by its own citizens and representing a dynamic force in the global arena [1].*

To realise this vision, the Africa Union developed and adopted a 50-year strategic plan called Agenda 2063 [2]. Agenda 2063 is the continent's strategic framework that aims to deliver on its goal for inclusive and sustainable development and is a concrete manifestation of the pan-African drive for unity, self-determination, freedom, progress and collective prosperity pursued under Pan-Africanism and African Renaissance.

The AU has been steadfast in proposing more enabling and science-based approaches to the challenges of the continent. Its report on gene drives clearly embraces the technology as a realistic option for effective disease control. A constructive development along this path was witnessed at the 29th Ordinary Session of Heads of State and Government of the African Union in Addis Ababa, where pursuant to Decision *Assembly/AU/Dec.649 (XXIX),* the session embraced the gene drive technology as a realistic option for malaria control. The session, in its decision, requested the African Union Commission (AUC), West African Health Organization (WAHO) and African Union Development Agency-New Partnership for Africa's Development (AUDA-NEPAD) to collectively support the initiative [3].

In 2018, through recommendations of the African ministers responsible for science and technology *EX.CL/Dec. 987(XXXII),* the Executive Council of the African Union encouraged member states to harness emerging technologies, including gene drive, in their development initiatives [4].

The decisions above have offered solid policy statements for the continent regarding gene drives for human health purposes, which have impacted discussions in AU member states. It is a basis for a harmonised approach for Africa in the development of policy regulations and guidelines such as this to facilitate the responsible and safe application of the technologies for research and subsequent deployment.

The African Union Development Agency - NEPAD (AUDA-NEPAD)

At the 31st Ordinary Session of the Assembly of African Union Heads of State and Government held in Nouakchott, Mauritania from 25th June to 2nd July 2018, the Heads of State and Government approved the transformation of the New Partnership for Africa's Development (NEPAD) Planning and Coordinating Agency into the African Union Development Agency (AUDA) as the technical body of the African Union with its own legal identity, defined by its own statute [6]. The objectives of AUDA-NEPAD are to: a) coordinate and execute priority regional and continental projects to promote regional integration towards the accelerated realisation of Agenda 2063; b) strengthen capacity of African Union Member States and regional bodies; c) advance knowledge-based advisory support; d) undertake the full range of resource mobilisation; and e) serve as the continent's technical interface with all Africa's development stakeholders and development partners.

The West African Health Organization (WAHO)

The West African Health Organization (WAHO) was established in 1987 when the Heads of State and Government from all fifteen countries in the Economic Community of West African States (ECOWAS) adopted and thereafter ratified the protocol for its creation. WAHO has transcended linguistic borders and hurdles in the sub-region to serve all fifteen ECOWAS Member States. The protocol grants WAHO the status of a specialised agency of ECOWAS and, as guided by its mission statement, 'the attainment of the highest possible standard and protection."

The regional agency is charged with the responsibility of safeguarding the health of the peoples in the sub-region through initiation and harmonisation of relevant policies of Member States, pooling of resources, and in cooperation with one another, maintaining a collective and strategic focus on important health problems of the sub-region.

WAHO has, through its strategic programmes, undertaken measures to combat malaria, malnutrition, HIV/AIDS as well as maternal and infant mortality. It has also spearheaded the prevention of blindness, increased access to medicines and vaccines, epidemiological surveillance as well as training and health information management in the sub-region.

Through its second strategic plan, WAHO is currently implementing various cutting-edge programmes in the sub-region to improve the overall health systems, ensure high-quality health services, develop sustainable financing of health and support institutional development within WAHO itself.

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Abbreviations

AUDA-NEPAD	African Union Development Agency - New Partnership for Africa's Development
CBD	Convention on Biological Diversity
CIOMS	Council for International Organizations of Medical Sciences
ECOWAS	Economic Community of West African States
EIR	Entomological inoculation rate
GMM	Genetically modified mosquitoes
IRS	Indoor residual spraying
ITNs	Insecticide treated nets
LMO	Living modified organism
NEC	National Ethics Committee
NP	Nagoya Protocol
VBDs	Vector borne diseases
WAHO	West African Health Organization
WA-IVM	West Africa Integrated Vector Management
WHO	World Health Organisation

Foreword

Approximately 80% of the world's population is at risk of one or more vector-borne diseases (VBDs), which together are responsible for 17% of the global burden of disease [4, 5]. Considering the significance of these diseases, the Economic Community of West African States (ECOWAS) agreed to the establishment of a West Africa - Integrated Vector Management (WA-IVM) Programme. The purpose of this programme is to establish and operationalise a platform for the region to foster collaborations among member states on issues relevant to the effective control of vectors. Key thematic areas to be covered by this programme are biosafety, environment, ethics, regulatory oversight, health systems, among others. The WA-IVM platform also aims to equip and capacitate the region with innovative technologies and novel approaches for controlling vectors.

Malaria is the most important vector-borne disease in sub-Saharan Africa. According to the WHO 2020 report, there were 229 million cases and 409,000 deaths in 2019, 94% of which were in Africa [6]. The significance of Malaria as the most challenging vector-borne disease and the most widespread in Africa informs its choice by the WA-IVM programme as an important pathfinder disease for developing its platform activities.

Gene drive is a phenomenon of biased inheritance in which the prevalence of a genetic element (natural or synthetic) or specific alternate form of a gene (allele) is increased, even in the presence of some fitness cost [7]. This leads to the preferential increase of a specific genotype that may determine a specific phenotype from one generation to the next and potentially spread throughout a population. This process favours biased inheritance of certain genes from generation to generation and can alter wild populations of harmful mosquitoes, either by preventing them from transmitting pathogens or by suppressing the population towards elimination [8, 9]. Mathematical modelling suggests that successful development and deployment of this technology could, in combination with existing interventions, significantly improve and accelerate malaria control in various African settings [10, 11]. One model predicted that considerable suppression of vector populations could be achieved within just four years of using a female sterility gene but warned actual impact might likely vary over time and geography [11].

Despite the enormous potential anticipated, applying new technologies such as this will also create new ethical challenges that may need to be addressed. For example, since mosquitoes are mobile organisms, it will be difficult to conduct confined field trials in any country without raising transboundary concerns. Moreover, gene drive technologies could give rise to issues with anthropocentric or non-anthropocentric dimensions and therefore question current norms and values.

This document is part of a series of guidelines developed jointly by AUDA-NEPAD and WAHO, under the WA-IVM programme, to support regulation of both research on and the deployment of genetically modified mosquitoes in the region. The document provides a framework for addressing ethical considerations relevant to such projects.

Glossary

Alleles - different forms of the same gene.

Biosafety committee - a group responsible for implementing policies and guidelines related to the use of potentially hazardous biological agents, including but not limited to infectious agents, human materials, and recombinant DNA studies. This group ensures that research involving these agents does not endanger researchers, laboratory workers, human research subjects, the public or the environment.

Cartagena Protocol on Biosafety - an international agreement dealing with the safe handling, transport, and use of living modified organisms (LMOs) resulting from modern biotechnology. See: http://bch.cbd.int/protocol/

Clinical disease incidence - the number of new clinical cases per unit of time for the at-risk population. This is typically determined by voluntary reporting of symptoms or community-based active case detection followed by a laboratory diagnostic test.

Cluster randomised trials - trials that group individuals into clusters, such as residents of particular villages or urban neighbourhoods. Each cluster is assigned randomly an experimental treatment such as a placebo or drug, or, in the case of genetically modified mosquitoes (GMMs), releases may be in one set of clusters and not in another.

Community engagement - practices undertaken to inform stakeholders about the diseases and vectors of interest and goals of a proposed research study or intervention trial and to understand their perspectives and reaction.

Confinement - utilisation of measures that seek to prevent unplanned or uncontrolled release of organisms into the environment. This may involve physical confinement (sometimes termed "containment") within a large cage that simulates the disease-endemic setting while minimising the possibility of escape and/or ecological confinement by geographical/spatial and/or climatic isolation.

Data and Safety Monitoring Board - a committee of experts independent of the organisation conducting a clinical trial, which monitors trial progress, reviews safety and effectiveness data while the trial is ongoing and can recommend the trial be stopped early because of concerns about participant safety or because the research question has been answered.

Deployment - implementation of GMM technology as part of a national or regional programme for vector control.

Drive (also called gene drive) - a mechanism that increases the transmission of a transgene in a population above that which would be expected based on Mendelian inheritance. The increase is reflected in the excess proportion of progeny that carry the transgene.

Ecosystem - a biological system composed of a community of organisms and the non-living environment with which it interacts.

Endemic - a situation in which disease is present continuously at some level in an area.

Endpoint - an event or outcome that can be measured objectively to determine whether the intervention being studied has the desired effect.

Entomological inoculation rate (EIR) - a measure of the degree of infection risk that a human population is exposed to for a particular disease, as determined by assessing the vector mosquito population. It is described by the frequency of infectious mosquitoes feeding upon a person within some unit of time, such as per day or year.

Ethics - an activity or inquiry intended to shed light on the correctness or justifiability of a given course of conduct.

Ethics committee (also called institutional ethics committee, institutional review board or ethical review board) - a group charged with providing oversight of biomedical and behavioural research involving humans, with the aim to protect the rights and welfare of research subjects.

Fitness - description of the ability to both survive and reproduce, equal to the long-term average contribution to the gene pool by individuals having a particular genotype or phenotype. If differences between alleles of a given gene affect fitness, then the frequencies of the alleles will change over generations, with the alleles with higher fitness becoming more common.

Frequency - an expression of how common a particular gene variant is in the population.

Gene - a segment of DNA that contains information required by cells for the synthesis of a product.

Gene Drive (Process or Phenomenon) - a mechanism that increases the transmission of a transgene in a population, above that which would be expected based on Mendelian inheritance. The increase is reflected in the excess proportion of progeny that carry the transgene.

Gene Drive (Material object) - A gene drive is any genetic element able to bias its inheritance within a population.

Gene Drive (Intention) - A gene drive is a tool to effect certain changes in a population.

Engineered or Synthetic Gene Drive - A gene drive system that is created through recombinant DNA techniques.

Genetically Modified Mosquito (GMM) - also called genetically engineered mosquitoes or transgenic mosquitoes – mosquitoes that have heritable traits derived through the use of recombinant DNA technology, which alters the strain, line, or colony in a manner usually intended to result in the reduction of the transmission of mosquito-borne human diseases. GMM is also likely to be characterised by introduced heritable marker traits to facilitate monitoring upon release into the environment and, in some cases, may include only such markers, as for population biology studies.

Living modified organism (also called genetically modified organism) – any organism that has in its genome novel DNA of endogenous, exogenous, or mixed origin that was made using modern recombinant DNA technology. Although successive selective breeding of strains of organisms with naturally occurring allelic variations also results in strains with genotypes that differ from the natural population, these are excluded from this definition.

Genotype – the genetic constitution of an organism.

Hazard – an event, activity or other cause of a negative consequence or impact identified in a risk analysis.

Infection incidence – the rate at which new infections occur during a specific period of time.

Informed consent – the process intended to ensure that human subjects who will be observed or involved in a research activity are fully and explicitly advised of all risks, costs, or inconveniences they may bear as a result of participating as a research subject and voluntarily agree to accept or bear those risks and costs.

Integrated vector management (IVM) – rational decision-making for optimal use of resources for vector control. The aim is to improve the efficacy, cost-effectiveness, ecological soundness, and sustainability of vector control activities against vector-borne diseases.

Pathogen – an organism that causes disease. In dengue infection, the pathogen is a virus. In malaria infection, the pathogen is a unicellular parasite.

Phenotype – the observable characteristics of an organism based on genetic and environmental influences.

Prevalence of infection – the frequency of infection within a population at any given time.

Regulation – an official rule to manage the conduct of those to whom it applies, usually developed from legal interpretations of legislation, and implemented by government ministries or agencies.

Regulatory agency (also called regulatory authority, ministry, regulatory body, or regulator) – a public authority or government entity responsible for exercising authority over some area of activity in a supervisory capacity.

Risk – an objective measure of the product of the likelihood and consequences of a hazard, defined within a prescribed set of circumstances. Risk is often described as a probability distribution of a set of consequences over a defined time period.

Risk assessment – a methodological approach to define and characterise hazards and to estimate the exposure or likelihood of each hazard occurring, as well as the potential adverse impact of the hazard (harm).

Risk communication – the process through which risk concerns and risk tolerance are articulated by relevant stakeholders and the results of risk assessment and risk management are communicated to decision-makers and the public.

Risk management – the process of identifying and implementing measures that can be expected to reduce risk to an acceptable level.

Self-limiting – GMM approaches in which the genetic modification will not pass on indefinitely through subsequent generations.

Self-sustaining (also called self-propagating or self-perpetuating) – GMM approaches in which the heritable modification is spread and maintained indefinitely through the target population.

Spread – transmission of the genetic modification system to other individuals within an interbreeding population.

Traits – phenotypes that result from single or multiple genes and their interactions with the environment.

Transboundary movement – movement across national, state, or other political lines of demarcation.

Executive Summary

The West African Integrated Vector Management (WA-IVM) programme was established in August 2018 with the support of the AUDA-NEPAD Regional Office and the West African Health Organization (WAHO). The platform comprises Heads of National Biosafety Agencies, National Ethics Committees and National Medicines Regulatory Agencies, all within the ECOWAS sub-region. It was initiated to strengthen the control of disease vectors through a) improvement of existing interventions, b) better coordination and integrated actions of the various sectors, and c) exploring emerging technologies with the potential to improve or accelerate control of vector-borne diseases. The pilot phase rollout is to build a framework for responsible research on gene drive technology as a potentially complementary approach to malaria control and elimination efforts.

The present guidelines contribute to the WA-IVM platform by reflecting on key ethics requirements for any research on genetically modified mosquitoes to be respectful of human values. The guidelines take into account the different scenarios for the research into or deployment of genetically modified mosquitoes for disease control. They recognise the key challenges and complexities arising from the need to concomitantly consider different ethics domains, including ethics of research on human subjects, public health ethics, and environmental ethics. The underlying principles of these different ethics domains are highlighted, and the need to balance the potential benefits of engineered gene drives (in terms of public health) with potential risks to human, animal and environmental health is stated.

The main ethical issues raised by research on genetically modified mosquitoes are enumerated, and based on that, a framework is proposed to guide the diverse stakeholder groupings when addressing these issues. The resulting guidelines emphasise the importance of respect for human values as a core element when assessing and making a decision on engineered gene drive.

The issue of individual informed consent vs community authorisation is considered as dependent on the phase of the research. It is acknowledged that at certain stages of the research, individual informed consent may not be appropriate and that engaging communities would become the cornerstone for research on genetically modified mosquitoes. The guidelines also note that responsible research on gene drive technologies requires the parties involved to correctly evaluate and weigh the potential benefits and potential risks

Other aspects addressed by these guidelines include governance and decision-making processes, as well as the need for transparency and capacity building.

Introduction

Vector-borne diseases (VBDs) such as yellow fever, dengue, lymphatic filariasis, zika, malaria and chikungunya are a growing threat across the globe. About 80% of the world's population is at risk of one or more of the VBDs, which together are responsible for 17% of the global burden of disease [4, 5]. Malaria alone is responsible for 229 million cases and 409,000 deaths in 2019, nearly all of which is in Africa [6]. Other than malaria, Aedes borne diseases, particularly dengue and chikungunya, are also widespread in Africa. The world already has an effective vaccine against yellow fever, but not for the other diseases, for which the control is still heavily reliant on the actual control of the vectors and, in some cases, the effective diagnosis and treatment of individual cases.

Vector control has been particularly effective against malaria. For example, the use of insecticide-treated nets (ITNs) and indoor residual spraying (IRS) are estimated to have contributed to 78% of all the success against malaria since 2000 [12]. However, despite the successes chalked following the implementation of existing tools over several years, African countries still face various challenges, among them the rise of insecticide resistance, high costs of delivery and the sub-optimal use of the existing tools. It is now believed that malaria elimination will not be possible with just the current interventions and that new or improved tools are necessary to improve and accelerate progress.

The West Africa Integrated Vector Management (WA-IVM) Programme was established by AUDA-NEPAD and the West African Health Organization (WAHO) to spearhead the much-needed efforts to accelerate vector control initiatives. A key aspect of the programme is the adoption of integrated vector management as a way to overcome these challenges and achieve the goal of control or elimination of vector-borne diseases. Integrated Vector Management (IVM) calls for strengthened vector control measures globally through improved surveillance, increased capacity, better coordination, and integrated actions of the various sectors.

Recent reports from the African Union High-Level Panel on Emerging Technologies (APET) urged member states to harness emerging technologies for accelerated socio-economic transformation as well as overall improvements of the health and wellbeing of people on the continent. One of these reports focused on the potential applications of gene drive technology for malaria control and elimination [13]. The technology was identified by APET as a potential new option for accelerating the pace towards the achievement of the African Union Agenda 2063 [13]. AUDA-NEPAD is therefore spearheading the advancement of relevant engagements to create an enabling environment for exploring the potential of gene drives.

Starting with ECOWAS Member States, the West Africa Integrated Vector Management (WA-IVM) platform comprising ECOWAS Heads of National Biosafety Agencies, National Ethics Committees, and National Medicines Regulatory Agencies was established in August 2018. AUDA-NEPAD, in collaboration with the West African Health Organization (WAHO), serves as the secretariat. The rollout of the WA-IVM programme began by addressing malaria as a pathfinder disease and sought to specifically build a framework for investigating the gene drive technology as a tool to complement existing malaria interventions. This framework includes different guidelines for the research and development of this technology.

The present guideline addresses the domain of ethics of gene drive technology as a tool for the control or the elimination of malaria. It describes critical values and ethical issues arising from gene drive research and proposes a framework to address these issues.

Background

Malaria burden and its control

Malaria is a life-threatening disease caused by Plasmodium parasites and transmitted via bites of infected female Anopheles mosquitoes. There are five species of plasmodium (Plasmodium falciparum, Plasmodium ovale, Plasmodium malariae, Plasmodium vivax and Plasmodium knowlesi), but just P. falciparum accounts for ~99% of all malaria cases in sub-Saharan Africa. The main vectors in Africa include Anopheles gambiae, Anopheles coluzzi, Anopheles funestus and Anopheles arabiensis, but there are several other Anopheles species playing important roles in specific local settings [14]. In 2019, there were an estimated 229 million cases of malaria and 409,000 malaria-related deaths [6]. The WHO African region accounted for 94% of the burden.

Since the year 2000, nearly US$ 40 billion has been invested in the fight against malaria, about a third of which was contributed by malaria-endemic countries themselves [6]. In 2019 alone, total spending on this was US$ 3 billion, which was 45% less than the required US$ 5.6 billion budget. Annual malaria deaths in Africa declined from 680,000 in the year 2000 to 384,000 in 2019 [6], even though the overall population increased from ~800 million to 1.3 billion people. Most of the gains made against malaria was attributed to vector control interventions, notably ITNs and IRS [12], which currently form the backbone of malaria prevention in Africa. There have also been significant improvements in malaria case management and overall socio-economic development.

Unfortunately, despite the progress made so far, substantial transmission persists due to factors such as insecticide resistance, sub-optimal user compliance, high costs of interventions, general weaknesses in the health systems and other factors. With the advent of other challenges such as COVID-19, there is also a significant risk of reversing the gains made thus far [15]. The need for augmented and more sustainable approaches for malaria control has therefore been emphasised [16].

Gene drive technology as a potential tool for malaria control

Gene drives are systems of biased inheritance, in which the ability of a genetic element to pass from a parent to its offspring through sexual reproduction is enhanced. The emergence of this technology holds prospects for future deployment and to significantly improve control and possibly accelerate efforts towards elimination [17]. Current approaches can be used to either suppress malaria vector populations or to alter them such that they no longer transmit malaria [8, 9].

The gene drive approach is actively being developed in different laboratories, including in some African research institutions. The Target Malaria Programme is partnering with scientists in Burkina Faso, Ghana, Uganda, and Mali to co-develop and field-test a gene drive product for suppressing populations of dominant malaria vectors. This and other ongoing efforts still require further validation through various stages before eventual field deployment is considered. Moreover, the potential release of gene drive mosquitoes will present several ethical and regulatory challenges that need to be addressed carefully before reaching the field deployment stages.

Addressing ethical aspects related to the use of genetically modified mosquitoes to control and eradicate malaria

Since gene drive technologies have great potential against malaria-causing mosquitoes [18], it is important to closely examine the regulatory and ethical issues raised by this intervention at various stages of the testing. Other than the national, regional, and international regulations, there are also ethical issues that must be addressed, notably: a) the respect for and responsibilities towards host communities and b) safeguarding the health and environment biodiversity.

Different fields of application of ethics are involved when developing guidelines for the use of genetically modified vectors. These include research ethics, public health ethics, environmental ethics, and more globally bioethics, democratic principles governance. These should be considered in relation to certain values and principles as well as guidelines and international texts before developing a functional framework.

Addressing ethical considerations relevant to genetically modified mosquitoes requires that the different fields of application of ethics are tailored and mutually weighted.

Values and Principles in the Different Ethics Domains

Multiple authors have stressed the need to pay attention to the ethics of the application of gene drives and other innovative technologies and to do this considering multiple domains that address individual and communal values [19-21]. The current guidelines consider a wide spectrum of values:

- Societal values of importance to people and communities, and which should be preserved to the extent possible,
- Values associated with individual human subjects in research, or those that could impact their health or environment. Often, these values have been reflected in research ethics principles of common acceptance,
- Values that underpin public health interventions,
- Values associated with the environment.

Societal values

Human societies were built upon values that may differ from one society to another or may vary among groups in societies. What appears as an acceptable benefit to one society may be rejected or differently perceived by another society that gives prominence to a different set of values. Values give deep convictions to what should be done and what should be avoided. Occidental societies, for example, consider individual autonomy as intrinsically part of one's humanness and identity and as a pillar of democratic societies. In other societies, the individual finds strength and true identity through the community. Similarly, some societies consider humans as more valuable than other species, while others consider humans as part of the whole. These latter societies expect attention to be given to all, including other species and the environment.

These differing perspectives could lead to irreducible antagonisms that could only be attenuated if genuine attempts are made to understand the viewpoints and beliefs of others. That is particularly true when one party occupies a dominant position and has the power to impose decisions. When researchers enter into the community space, great attention should be given to the respect for the culture and beliefs of the communities. Efforts should also be made to know what matters to that community.

Research ethics principles

At the research stage, standard ethics guidelines for research involving humans have been based on internationally recognised principles, namely:

- Respect for individuals includes respect of the autonomy of the research participants, protection of persons lacking autonomy, respect for confidentiality concerning their data, respect for their privacy
- Beneficence: to do good to others by balancing benefits and risks.
- Non-maleficence: to not do harm to others (physical harm, social disadvantage, psychological distress, discomfort, or breach of confidentiality)
- Justice: equity in the selection of research participants, and in the distribution of burden and benefits,

Implementation of these principles means that various conditions must be present for the research to be ethical. These include:

1. The research should be scientifically well-designed.
2. The knowledge product from the research must be beneficial to society.
3. The risks to research participants and others directly impacted by the research should be minimised.
4. The risks must be reasonable in relation to the benefits to the research participants and the importance of the knowledge produced.
5. The selection of study participants should be fair.
6. Informed consent from the participants or their representatives should be obtained and appropriately documented.
7. Confidentiality and privacy should be protected.
8. Provisions should be in place to protect vulnerable research participants.

9. Provisions should be in place to avoid the exploitation of research participants or the community in which the research is taking place.
10. There should be an independent review and oversight of the research by an appropriate body,
11. Where appropriate, there should be data and safety monitoring to protect research participants and others.
12. Where appropriate, communities should be consulted about the research and have an opportunity to provide their input, approval, or disapproval

Public health ethics

Considering public health ethics implies that developers and researchers must take into account values that could be antagonistic to the individual perspectives. The following values are emphasised in public health ethics:

- Common good versus individual interest
- Population wellbeing
- Social justice and social responsibility
- Solidarity
- Equity
- Reciprocity
- Distributive justice (fair distribution of social goods)
- Procedural justice (fair process), participation, and transparency
- Respect for privacy and confidentiality
- Protection of subgroups from marginalisation and stigmatisation

Gene drive research will appeal to several of these values, but most important is the pre-eminence of the common good over individual interests. This requires that the different stakeholders should take social responsibility

Environmental ethics

Environmental ethics considers the moral and ethical relationships between humans and the environment. Environmental ethics can take two approaches, namely:

- Ecocentrism (where it is assumed that there is intrinsic value in all of nature and that humans are just one part of nature, alongside other forms of biodiversity), or
- Anthropocentrism (where the human species are considered more valuable than all other organisms).

Different international agreements address issues related to environmental ethics:

The Earth Charter (2000)

This Earth Charter was launched in 2000 after a decade of dialogue and was endorsed by over 6,000 organisations and governments [22]. It is defined as an ethical framework for building a more just, sustainable, and peaceful global society in the 21st century. The charter seeks to inspire in all peoples a sense of global interdependence and a shared responsibility for the wellbeing of the human family, the greater community of life, and future generations. It contains sixteen principles framed around four themes, namely: i) respect and care for the community of life, ii) ecological integrity, iii) social and economic justice, iv) democracy, non-violence, and peace. Several of these principles are relevant to genetically modified mosquitoes:

- **Principle 1:** Respect earth and life in all its diversity.
  a. Recognise that all beings are interdependent and that every form of life has value regardless of its worth to human beings
  b. Affirm faith in the inherent dignity of all human beings and in the intellectual, artistic, ethical, and spiritual potential of humanity.
- **Principle 2:** Care for the community of life with understanding, compassion, and love.
  a. Accept that with the right to own, manage, and use natural resources comes the duty to prevent environmental harm and to protect the rights of people.
  b. Affirm that with increased freedom, knowledge and power comes increased responsibility to promote the common good.
- **Principle 5:** Protect and restore the integrity of the earth's ecological systems, with special concern for biological diversity and the natural processes that sustain life.
  a. Adopt at all levels sustainable development plans and regulations that integrate environmental conservation and rehabilitation in all development initiatives.
  b. Establish and safeguard viable nature and biosphere reserves, including wild lands and marine areas, to protect the earth's life support systems, maintain biodiversity, and preserve our natural heritage.
  c. Promote the recovery of endangered species and ecosystems.
  d. Control and eradicate non-native or genetically modified organisms harmful to native species and the environment and prevent the introduction of such harmful organisms.
- **Principle 6:** Prevent harm as the best method of environmental protection and, when knowledge is limited, apply a precautionary approach.
  a. Take action to avoid the possibility of serious or irreversible environmental harm even when scientific knowledge is incomplete or inconclusive.
  b. Place the burden of proof on those who argue that a proposed activity will not cause significant harm and make the responsible parties liable for environmental harm.
  c. Ensure that decision making addresses the cumulative, long-term, indirect, long-distance, and global consequences of human activities.

Cartagena Protocol on Biosafety (2003)

The Cartagena Protocol on Biosafety has been in force since 11th September 2003 and was adopted as a complementary agreement to **the Convention on Biological Diversity** [23]. The Cartagena Protocol on Biosafety to the CBD is an international agreement that aims to ensure the safe transfer, handling, and use of living modified organisms (LMOs) resulting from modern biotechnology that may have adverse effects on biological diversity also taking into account risks to human health. The following five articles of the protocol are relevant when considering establishing an ethical framework for GMM technologies.

Article 15 - Risk assessment

Risk assessments undertaken pursuant to this Protocol shall be carried out in a scientifically sound manner, in accordance with Annex III and taking into account recognised risk assessment techniques. Such risk assessments shall be based, at a minimum, on information provided in accordance with Article 8 and other available scientific evidence in order to identify and evaluate the possible adverse effects of living modified organisms on the conservation and sustainable use of biological diversity, also taking into account risks to human health.

Article 16 - Risk Management

1. The Parties shall, taking into account Article 8 (g) of the Convention, establish and maintain appropriate mechanisms, measures, and strategies to regulate, manage and control risks identified in the risk assessment provisions of this Protocol associated with the use, handling, and transboundary movement of living modified organisms.

2. Measures based on risk assessment shall be imposed to the extent necessary to prevent adverse effects of the living modified organism on the conservation and sustainable use of biological diversity, also taking into account risks to human health within the territory of the Party of import.

3. Each Party shall take appropriate measures to prevent unintentional transboundary movements of living modified organisms, including such measures as requiring a risk assessment to be carried out prior to the first release of a living modified organism.

4. Without prejudice to paragraph 2 above, each Party shall endeavour to ensure that any living modified organism, whether imported or locally developed, has undergone an appropriate period of observation that is commensurate with its life cycle or generation time before it is put to its intended use.

Article 22 - Capacity Building

1. The Parties shall cooperate in the development and/or strengthening of human resources and institutional capacities in biosafety, including biotechnology to the extent that it is required for biosafety, for the purpose of the effective implementation of this Protocol, in developing country Parties, in particular, the Least Developed and Small Island Developing States among them, and in Parties with economies in transition, including through existing global, regional, subregional and national institutions and organisations and, as appropriate, through facilitating private sector involvement.

Article 23 - Public awareness and participation

1. The Parties shall:

   a. Promote and facilitate public awareness, education and participation concerning the safe transfer, handling, and use of living modified organisms in relation to the conservation and sustainable use of biological diversity, also taking into account risks to human health. In doing so, the parties shall cooperate, as appropriate, with other States and international bodies.

   b. Ensure that public awareness and education encompass access to information on living modified organisms identified in accordance with this Protocol that may be imported.

2. The Parties shall, in accordance with their respective laws and regulations, consult the public in the decision-making process regarding living modified organisms and shall make the results of such decisions available to the public while respecting confidential information in accordance with Article 21.

Article 26 - socio-economic considerations

1. The Parties, in reaching a decision on import under this Protocol or under its domestic measures implementing the Protocol, may take into account, consistent with their international obligations, socio-economic considerations arising from the impact of living modified organisms on the conservation and sustainable use of biological diversity, especially with regard to the value of biological diversity to indigenous and local communities.

2. The Parties are encouraged to cooperate on research and information exchange on any socio-economic impacts of living modified organisms, especially on indigenous and local communities.

Universal Declaration on Bioethics and Human Rights (2005)

Article 17 of this declaration is on the protection of the environment, the biosphere and biodiversity. It declares that:

"Due regard is to be given to the interconnection between human beings and other forms of life, to the importance of appropriate access and utilisation of biological and genetic resources, to respect for traditional knowledge and to the role of human beings in the protection of the environment, the biosphere and biodiversity."

Nagoya Protocol

The Nagoya Protocol on Access and Benefit Sharing of Genetic Resources (NP), adopted on 30th October 2010, is the instrument for the implementation of the access and benefit-sharing provisions of the Convention on Biological Diversity [24]. The Objective 1 of the Nagoya Protocol is "the fair and equitable sharing of the benefits arising from

the utilisation of genetic resources, including by appropriate access to genetic resources and by appropriate transfer of relevant technologies, taking into account all rights over those resources and to technologies, and by appropriate funding, thereby contributing to the conservation of biological diversity and the sustainable use of its components." The specific way to link GMMs to the Nagoya Protocol must be discussed among stakeholders.

There are several examples of international documents that should be considered for establishing guidelines for GMM research and GMM interventions.

The complexity of linking these different domains

The above principles should be intelligently applied so as to take into account the benefit/risk ratio in the fight against vector-borne diseases in Africa. This represents a challenging task as it means confronting conflicting values and interests of different nature that are not always easy to reconcile.

The African Union High-Level Panel on Emerging Technologies called for regulations that consider the weight of the potential health benefits when assessing potential risks [13]. AUDA-NEPAD already recognises that potential risks to the environment, especially with respect to its biodiversity component, will have to be assessed against improved public health as the expected benefit. Advocacy was made to consider the health value as the primary driver for decision-making for engineered gene drive applications taking into account potential risks to the environment. The difficulty will lie in the definition of the risks that are still unknown and unpredictable and those that would call for the application of the precautionary principle.

Malaria, with estimated global cases of 229 million and 409,000 deaths in 2019, and most of which were in Africa [6], is being considered as a pilot case for the reflection on the GMM research and potential applications of gene drive technology. Balancing between potential environmental risks and anticipated health benefits requires a thorough analysis of the ethics associated with the various stages of R&D and deployment.

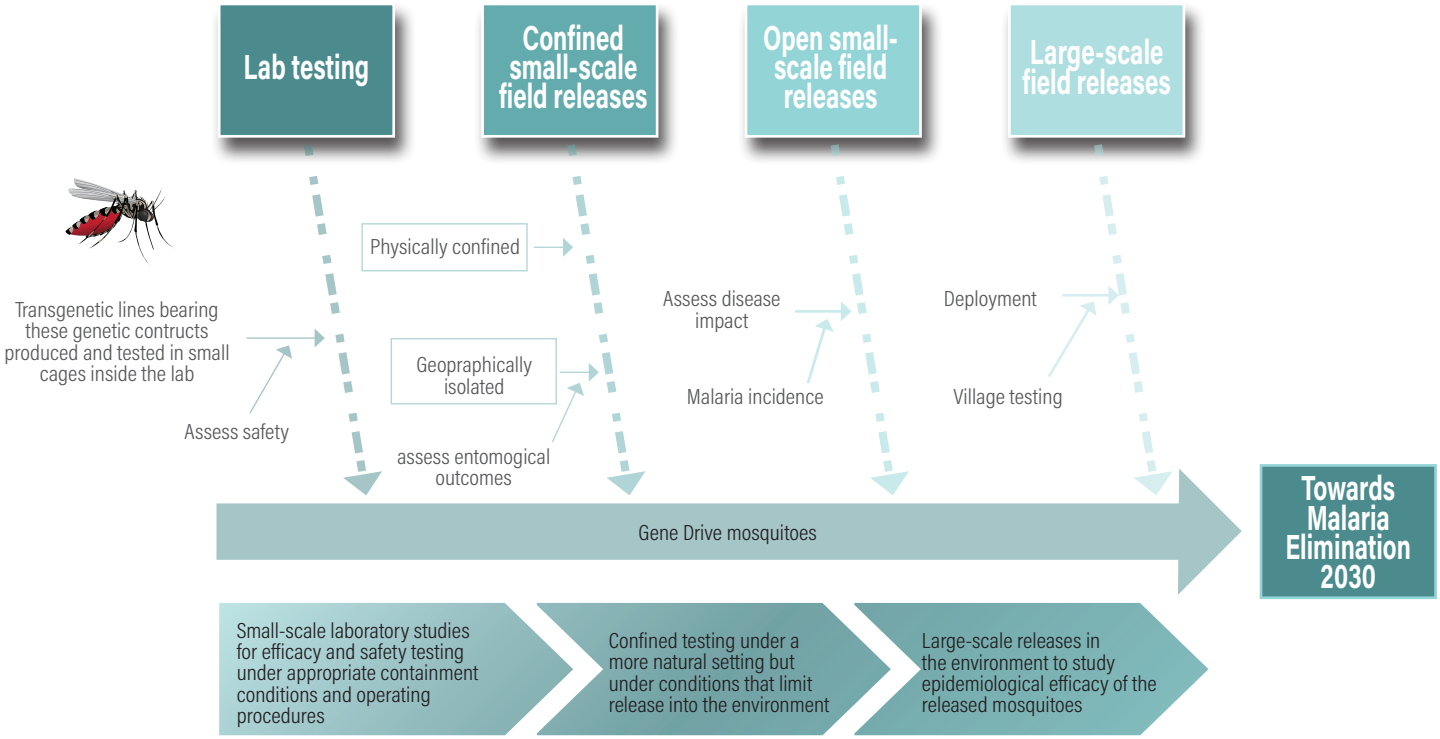
Ethical Issues Raised by GMM Research

GMM research is relevant to various fields of ethics, thus the need for a holistic approach to guide testing and implementation. In The Guidance Framework for testing genetically modified mosquitoes [25], experts recommended a phased testing pathway, in which new GMM products move from the laboratory to testing in more natural environments under confined conditions, and finally to open release trials, with each transition dependent upon satisfactory demonstration of efficacy and safety. The ethical concerns will be different depending on the stage of testing along the pathway. This does not mean that ethics should not be reflected concomitantly or from the beginning but instead acknowledges the possible escalation in complexity of the ethical issues along the pathway.

Ethics related to laboratory studies

At the laboratory stage, scientific integrity, biosafety, and potentially the use of animal subjects require attention to ethical requirements. That entails compliance with an effective set of biosafety procedures to protect research personnel and the environment. Procedures to reinforce the respect of scientific integrity are also required.

Pathway for malaria vectrol control via Gene Drive



(Credit: NEPAD Gene Drives for Malaria Control and Elimination in Africa)

Ethics related to the confined release

During the confined release, even if the release is on a small scale, environmental and public health impacts have to be considered in addition to the ethical issues from the laboratory stage. The environmental issues will depend on the actual technological approaches that are adopted (self-sustaining vs self-limiting changes, alteration vs suppression of a mosquito specie) and on the potential impact on other species.

Similarly, the biosafety procedures, particularly risk assessment and risk management, will be central in the reflections. The degree of isolation and likelihood of the modified mosquitoes spreading to neighbouring areas will require addressing the principle of non-maleficence. In other words, gathering additional knowledge while minimising the risk will be a central issue.

Ethics related to open releases

In open releases, further complexity is added to the aforementioned ethical issues. It is important to simultaneously address individual, communal and environmental ethics concerns. As illustrated by Lisa Lee in "A bridge back to the future: public health ethics, bioethics, and environmental ethics" [19], public health ethics can be used as a way to (re)connect biomedical research ethics and environmental ethics.

Ethical issues of balancing benefits and the risks

Public health issues related to the impact of GM mosquitoes on human health will have to be assessed and managed as the genetic modification could lead to non-expected and deleterious effects. These potential risks will have to be weighed against the potential public health benefits of malaria prevention. Two pitfalls should be avoided when conducting a risk/benefit analysis:

- Under-estimation of risks and overestimation of benefits could lead to exposing the population to unjustifiable harms.
- Overestimation of risks and underestimation of benefits that could block potentially highly beneficial research

Additional considerations beyond the scientific aspect of risk assessment and risk management are key in decision-making. These considerations may include economic factors, socio-cultural factors, as well as community values.

The definition of minimal risk could be challenging in using GMM as we have to ascertain that this risk is minimal compared to what any resistance within the organism or the environment would have been without it. And if we say the benefit is more, then we must consider the sustainability of these benefits and the beneficiaries, as well as the affordability and distribution.

Ethics issues related to informed consent

Informed consent is universally recognised in research ethics regulations and guidelines as a necessary protection for human research participants. However, in GMM research, informed consent could be a complex issue, and there exist conflicting presumptions about the role of informed consent [26].

The conflict is occasioned by the issue of who should be considered as a research participant when the research does not require the direct involvement of the individual. For research involving obtaining data on malaria incidence at the level of individuals, and which then will require direct involvement of participants (e.g., blood sampling, clinical follow-up and surveys), it is easy to conclude that individual informed consent is required as would be the case in any research, according to laws and guidelines and to standard research ethics. However, malaria incidence data could also be obtained by studying aggregated data from routine surveillance or alternatively, the research on resulting malaria transmission could be conducted via entomological studies. In both of these cases, there is no direct involvement with the individual other than potential exposure to the released modified mosquitoes. This means that it is the whole community that will be impacted by the research, and in which case the community represents the research participant. As a consequence, requiring researchers to obtain individual informed consents may render the research unfeasible.

Studies on ethics of cluster randomised trials address the subject of individuals that are not directly involved in research but could be impacted when the research is an intervention on the environment of the person. Some commentators consider that 'these people were deliberately intervened upon via manipulation of their environment and, hence, are human research subjects [27]. They proposed that researchers could request a waiver of consent from an ethics committee. Other commentators estimate that living in the vicinity of GMM release does not automatically render someone a research participant [26]. They acknowledge the challenge of conducting GMM trials under current regulations for clinical trials and conclude that there is a need to develop appropriate regulatory regimes and stakeholder engagement plans.

That leads to the path of community authorisation that could replace individual consent but then raises other issues such as the legitimacy of those speaking for the communities and the management of divergent voices. The last aspect would confront two values that are the respect of the rights and welfare of individuals versus the potential benefit for the community as a whole. That is the classical tension in the ethics of public health where a class of interventions may already be proven (or considered) as beneficial, while for GM research, it cannot be presumed that the actions taken for the research (release of GM mosquitoes) will be beneficial. Results and knowledge obtained in previous steps, level of malaria burden, and the quality of the collaboration with the communities will underpin the ethics reflection. Respect for communities through community engagement at an early stage of the research will depend on transparency, honesty, and fair participation of different actors in decision-making. This does not solve the controversial issues that should be tackled on a case-by-case basis, of defining the community, determining the authorised/legitimate voices of the community, and dealing with potential conflicts between the community and the wider public or between community leaders and segments of the community.

This crucial point of determining the pertinence of seeking or not seeking individual informed consent should not rest with researchers. Rather, the researchers should appeal to an ethics committee for a waiver of consent by demonstrating either the lack of necessity or the infeasibility of obtaining informed consent. This approach should not be conceived as a way to preclude the process of community engagement and obtaining community authorisation but as a way to combine the respect of laws and respect for communities.

Ethical issues related to risk analysis

The responsibility to anticipate and understand the potential for unwanted or adverse impact from the deployment of engineered gene drives is both legal and moral [20]. Risk assessment includes four interrelated aspects, namely: i) hazard identification, ii) exposure quantification, iii) risk management, and iv) risk communication.

Ethical perspectives extend the debate beyond the issue of outcomes on human health to those of intrinsic vs instrumental value of biodiversity and of potential misuse or dual use of technologies. Thompson (2017) also stressed the need to account for the "social amplification of risk", which goes beyond perception of risk [20]. That has ethical implications, for the estimation of the nature and extent of risk is influenced by social, cultural, historical factors. He stated that at this stage, ethics must be involved in making a judgement as to whether a third party's perception of risk is reasonable or unreasonable.

That leads to emphasise the need to build dynamics and framework that allows exchanges between different social groups and different actors of engineered gene drive research.

Ethics issues related to capacity building

New and innovative technologies often require the examination of ethical issues without the benefit of experience and a clear precedent. This requires examination of ethical issues using a multidisciplinary approach, taking into consideration expertise from fields as diverse as law, anthropology, sociology, psychology, science, medicine, economics, and philosophy. Reviewing protocols may then be challenging when it comes to new and emerging technologies, including engineered gene drives without sufficiently trained human resources.

Framework for Addressing Ethical Issues in Engineered Gene Drive Research

These guidelines are built upon 2014 WHO Guidance Framework for testing genetically modified mosquitoes [25], the 2016 gene drive report from the National Academies of Science, Engineering and Medicine [28], the 2018 publication on the development pathway for gene drive mosquitoes to control malaria in Africa [18], and other previous reports from working groups or individual analysis.

Human value

Human values are the virtues that guide us to take into account the human element when interacting with others. Individual values are forged by social systems, religions, culture, and family. Knowing others' values is the first step to understanding their behaviours or their position on specific subjects.

Acknowledging human values is not only an ethical feature but also a genuine way to build trust between different stakeholders of research. Human values will also be core elements to reflect on potential benefits and potential harms to other humans when making decisions about engineered gene drive technologies.

Scientific value

The engineered gene drive technology should be scientifically validated as that is one of the first ethical requirements for research. However, as with many innovative technologies, evaluating the validity may be challenging as knowledge in the field accumulates. Stakeholders and, in particular, the researchers must therefore base their work on the latest knowledge and continuously update their knowledge.

Informed consent, community authorisation

Informed consent is an ethical and legal requirement for recruiting an individual into research. In GMM research, the ethical committee will have to determine/define if an individual is a research participant by evaluating if he/she would be directly participating in the research (e.g., by providing biological samples, data, participating in surveys, giving access to his/her household etc.). In such cases, it is clear the researchers will have to fulfil the obligation of obtaining informed consent from each research participant.

However, in the final stages of GMM research, even the individuals not considered as research participants may not be able to avoid being potentially exposed to the GMM.

The Council for International Organizations of Medical Sciences (CIOMS) guideline 10 states that "Researchers must not initiate research involving humans without obtaining each participant's individual informed consent or that of a legally authorised representative unless researchers have received explicit approval to do so from a research ethics committee" [29]. A research ethics committee may approve a modification or waiver of informed consent to research if:

i. the research would not be feasible or practicable to carry out without the waiver or modification.

ii. the research has important social value; and

iii. the research poses no more than minimal risks to participants.

The issue with GMM research (as with numerous other research such as for drug trials) is that no one at the moment can assure that "there is no more than minimal risk". Indeed, in the perspective of releasing GMM, if the first and even the second conditions could be met, demonstrating that the research poses no more than minimal risk could be challenging. Ethical committees will have the task to evaluate the state of the knowledge at the time of the research and on the risk assessment information. Community authorisation is often suggested as an alternative when individual informed consent is judged to be infeasible.

Risks and benefits evaluation

The primary (and final) potential benefit of engineered gene drive mosquitos would be the improvement in human health and thus the need for efficacy data in decision-making. At each step, an evaluation of the risks and benefits is critical.

Nuffield Council on Bioethics has recommended, "comparison of the risks of the status quo with those posed by possible paths of action," recognising that "there can be dangers in inaction, or alternative courses of action, as well as in the adoption of a particular innovation" (Nuffield Council on Bioethics, 2014). Evaluation of the risks and benefits will take advantage of the risk assessment but should not stop there as they should be convinced that all aspects were taken into account beyond safety considerations. Other non-safety considerations such as economic as well as socio-cultural aspects and community values would be critical in decision-making.

Ecological and environmental considerations

Ecological and environmental aspects must be taken into account in the process of analysis and in-depth reflections. Engineered gene drive technologies require specific attention considering the intentionally invasive nature of the modifications, which have the theoretical potential to reach all individuals of a species in the environment, whether to eradicate or modify it. The release of GMMs may disrupt the ecosystem in different ways, including the potential formation of hybrids resulting from interbreeding with closely related species or the emergence of other pathogenic species. Resnick recommends that release sites be carefully selected in order to minimise the risk of interbreeding [21].

Another way of minimising the risk to the environment leading to lesser, if any, disruptions in ecosystems could be the use of technologies aiming at modifying mosquitoes resistant to disease or with the ability to host malaria parasites instead of those that lead to the elimination of a species.

Researchers and other stakeholders should integrate close scrutiny of what happens or could happen using different approaches, including entomological and molecular surveillance, as well as mathematical modelling.

Engaging communities, stakeholders, and the broader public

Community engagement is a process of continuous relationship-building in which those affected by a problem or issue are central to decision-making and the determination of appropriate responses. It requires the establishment of trust through early and ongoing communication, as well as mechanisms for coordination and collaboration between and among partners and stakeholders.

CIOMS 2016, guideline seven provides a solid rationale for reinforcing the crucial role of community engagement:

« Community engagement is also valuable for the contribution it can make to the successful conduct of research. In particular, community engagement is a means of ensuring the relevance of proposed research to the affected community, as well as its acceptance by the community. In addition, active community involvement helps to ensure the ethical and social value and outcome of the proposed research. »

Engaging communities should be started at the earliest stage and maintained as an ongoing mutually educative process between communities and researchers. Care should be taken to involve all segments of the community so as not to perpetuate inequities. Researchers and other stakeholders can build on the successful active process of community involvement. During the Eliminate Dengue Programme in Queensland, Australia [29], the success was dependent on four features, namely: i) enabling conditions (including support from sponsors who agree to fund community engagement activities); ii) internal leadership; iii) core commitments and guiding values that informed how the programme's approach to engagement was operationalised; and iv) formative social science research to provide key insights about the local context and about how the host communities wished to be engaged.

That is not to say that only one approach exists, but to illustrate that the community engagement process is more than a declaration of intent and is socially complex. Researchers should start by gaining a good knowledge of the communities they intend to engage with. Dada et al. [30] illuminate this point in reporting the lessons learnt from engaging communities for the Ebola vaccine trial in Sierra Leone. She reports that four main principles evolving from the discussions between team members and the community influenced the trust-building: i) reciprocity (reciprocal communication between the trial team and the community), ii) relatability (using relatable examples), iii) relationships (importance of interpersonal relationships) and iv) respect (for the people, their customs, and traditions). She also highlights the crucial role of interdisciplinarity that integrates the social sciences team with other scientific teams.

Listening and capturing all voices

Establishing project ethics advisory groups

Given the complex ethical and community engagement issues accompanying the engineered gene drive technology, an ethics advisory group comprising experts who are external to the project would be

an important mechanism to complement the input from community advisory boards or other community engagement activities. This group would advise the researchers on ethical issues that may arise along the course of the project.

Mechanisms should be established to allow this group to obtain relevant information on issues such as risk assessment, policy, engagement activities, and trial status from the project and other advisors.

It is recommended to establish an ethics advisory board that is external to the project team with in-country experts and the communities of interest, to advise the projects throughout the research and field-testing trajectory. This kind of ethics advisory is regularly required by funders of ethics for highly sensitive projects to enable them to anticipate problems and to help researchers avoid potential pitfalls.

This recommendation aligns with those in the WHO document The Guidance Framework for testing genetically modified mosquitoes that states, "the institution conducting the research are expected to have its own independent committees overseeing biosafety and the involvement of human subjects" [25].

Establishing a national ethics advisory committee

National authorities could envisage establishing a national ethics advisory committee to reflect and address controversial or sensitive issues and to provide a broader perspective. This committee would be distinct from the institutional review board or the national health research ethics committee, to which researchers must submit their proposed activities for review and approval.

This committee could include ethics and regulatory experts, civil society, social science experts, environment experts, health professionals, researchers, and members of communities to foster inclusive and multi-sectorial discussions on the questions related to GMM or to any kind of public health intervention. This would be an operational committee that could either receive requests from public research institutions or any other stakeholder or self-refer to give suggestions on interventions in progress.

Countries that have national bioethics committees can entrust these committees with the task of reflecting on ethical issues associated with GMM research. However, care should be taken to ensure that the national bioethics committees integrate all the different stakeholders, including communities and researchers. Some countries have established National Committees for Public Health that could be assigned this task with the same recommendation for inclusiveness in the membership.

Transparency

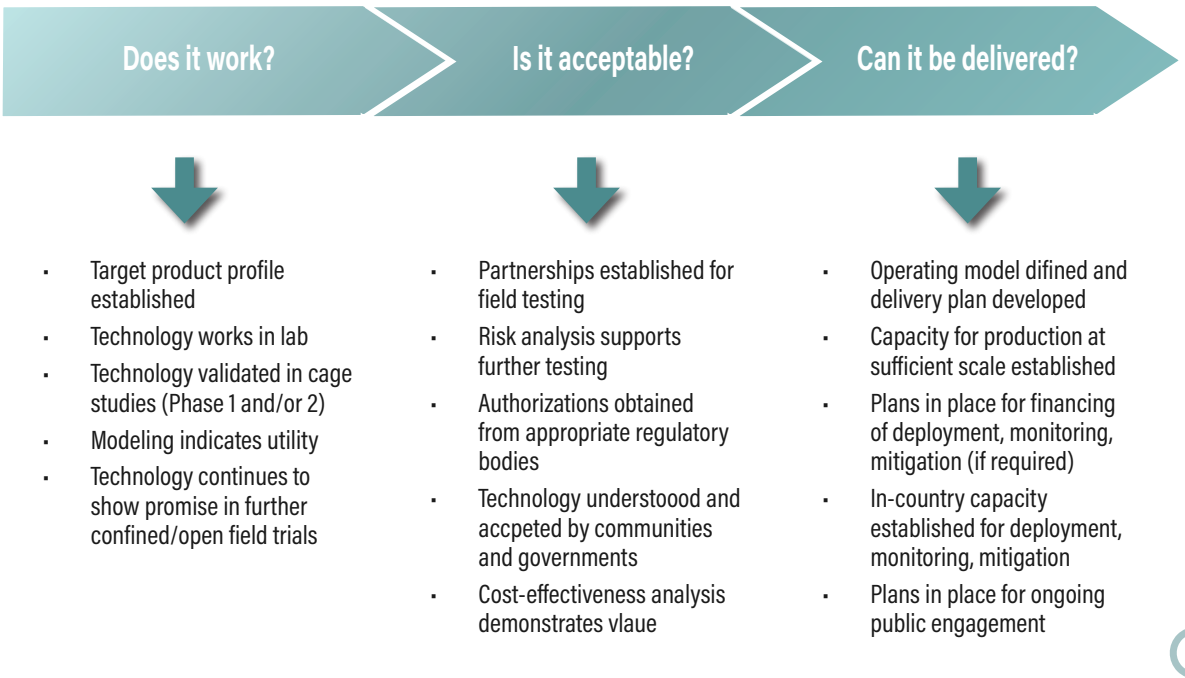
The development of engineered gene drive technology carries an obligation for transparency and accountability. Transparency includes but is not necessarily limited to keeping open and accessible records of any (accidental or intended) releases and a full description of the investigational product. Policies and mechanisms for inter-project coordination and broader data and information sharing are a necessity.

Decision making

The transition from one phase to the next will be subject to a "go/no-go" decision criterion, including efficacy and safety endpoints, regulatory and ethical approvals, social acceptance, proof of deliverability and efficacy when compared to other existing tools. For this, it is necessary to conduct a community consultation to obtain the informed opinions of different stakeholders. The Cost-effectiveness of the technology compared to other interventions may also influence the decision.

Efficacy evaluation

The ultimate goal of a GMM research and release programme is the reduction or elimination of Malaria in the highest-burden countries. In this regard, the efficacy of GMMs will require the measurement of epidemiological parameters such as infection incidence, clinical disease incidence or prevalence of infection in at-risk populations. This evaluation must integrate the other ongoing vector control interventions. Entomological parameters such as entomological inoculation rates



Development pathway for genetically modified mosquitoes. Source/Credit: WHO. Guidance Framework for testing genetically modified mosquitoes [25].

(EIRs) could also be a means of evaluation of the efficacy even if the relationship between malaria incidence and EIR is not linear.

However, in the first phases of GMM research (laboratory or confined Phase II experiments), the epidemiological endpoints or EIR cannot be used. At these early steps, efficacy evaluation will rely on the measurement of mosquito population characteristics such as the frequency of the genes of interest in offspring, competence for developing infections, survival, etc. The definition of key predictors of entomological efficacy criteria requires an inter-disciplinary and trans-disciplinary approach from a range of relevant fields through an ongoing process that has already led to some recommendations on the technical criteria to consider [18].

Ecological data will also be necessary during confined or small scale open-field release to provide accurate knowledge of the potential impact of testing GMMs in these localities. Mathematical modelling based on the data collected at these early steps will be critical for predicting potential outcomes in large scale open-field release and will therefore be important for decision-making [18].

Cost-benefit or cost effectiveness

Cost-effectiveness analysis is a critical step for decision-making about implementing GMM release programme as an additional or an alternative tool for vector control, especially in resource-constrained countries.

The thoroughness of economic evaluations beyond the monetary aspect will be crucial for weighing potential benefits against potential risks and in defining acceptable risk. Cost-benefit should integrate economics, health benefit, social impacts, and sustainability over time.

Proof of deliverability

Engineered gene drive technology implementation and GMM releases will need to demonstrate:

i. Proof of sufficient technical and logistical capacity for wide-scale deployment,

ii. Capacity for monitoring the efficacy and any adverse events or constraints,

iii. Ongoing political will,

iv. Financing capability and

v. Stakeholder engagement and support.

Regional and international collaboration

As mosquitoes do not obey administrative or political borders, regional collaboration is fundamental for harmonising positions and procedures for GMM research, as well as for sharing experiences.

International collaboration is also of tremendous importance to debate on these novel technology achievements as well as constraints, on the hope of possible positive effect on health and fears about the potential deleterious effect, on progress made in the understanding of mechanisms.

Responsibility and liability

A number of countries are Parties to the Nagoya Protocol and the Nagoya-Kuala Lumpur Supplementary Protocol [24]. The Supplementary Protocol applies to damage resulting from living modified organisms that find their origin in a transboundary movement as well as to damage within the limits of national jurisdictions. Damage is defined as an adverse effect on the conservation and sustainable use of biological diversity, also taking into account risks to human health that is measurable or otherwise observable, taking into account, wherever available, scientifically established baselines recognised by a competent authority that takes into account any other human-induced variation and natural variation, and is significant. The living modified organisms referred to are those: (a) intended for direct use as food or feed or for processing; (b) destined for contained use; (c) intended for intentional introduction into the environment.

The text determines the obligations of "Parties" that includes identifying the operator which had caused the damage, determining which response measures should be taken by the operator, taking appropriate response measures (restoration of biodiversity, for example) when the "operator" fails to do so.

The operator is defined as follows: "Operator" means any person in direct or indirect control of the living modified organism which could, as appropriate and as determined by domestic law, include, inter alia, the permit holder, the person who placed the living modified organism on the market, developer, producer, notifier, exporter, importer, carrier, or supplier.

In the context of GMM research, it will be challenging in all that chain of actors to designate the person/institution responsible for any damage that would occur as a result of the research. It is therefore recommended that regional and international deliberations are organised to address this issue and define how responsibilities would be shared as it is unrealistic that research groups would take entire responsibility and liability for damage such as loss of biodiversity or potential impact on entire communities.

Capacity building

Both the GMM research and GMM release programmes (if this step is reached) will require shared efforts for building capacities in various domains beyond those classically thought for vector control. If the needs for capacity building in emerging technologies seem obvious, other complementary expertise will be required. These may include molecular biology and genetics, computational modelling, environmental risks assessments, management and mitigation, vector biology etc.

In addition to the technical skills, capacities must be built for members of the ethics committees or regulatory agencies to effectively review GMM projects. Additional capacity building may be necessary for other researchers in various domains, as an ethical obligation in GMM research and as part of the community engagement processes.

Conclusion

These guidelines are developed based on the very recent reflections on the ethics of GMM as a tool to fight malaria. Many issues remain unresolved and will need further exploration by ethics experts as well as experts in other fields whose reflections should mutually cross-fertilise. These guidelines are therefore expected to be periodically revised and adapted in line with the advancement of knowledge.

The document is provided to guide stakeholders and will form a basis for putting into practice ethical intentions related to research on genetically modified mosquitoes. It is intended to support the required evaluation, which must balance the ethical and ecological implications with the potential benefits of the technology in terms of indicators such as health improvement, the number of lives saved and economic gains, all in consultation with the communities.

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