2ND EDITION REPORT

GENE DRIVES FOR MALARIA CONTROL AND ELIMINATION IN AFRICA

Scan to read document

https://au-apet.app/knowledge-products

AUDA - NEPAD
AFRICAN UNION DEVELOPMENT AGENCY

APET
African Union Panel on Emerging Technologies

EXECUTIVE SUMMARY

Malaria continues to impose a significant economic and public health burden on Africa. In 2021, the continent accounted for 95% of the global 247 million new malaria cases and 96% of the 619,000 malaria-related deaths. Notably, over three-quarters (77%) of these deaths occurred among children under the age of five. At present, ten countries—Burkina Faso, Cameroon, the Democratic Republic of the Congo, Ghana, Mali, Mozambique, Niger, Nigeria, Uganda, and the United Republic of Tanzania—have been classified as High Burden, High Impact (HBHI) nations, collectively contributing to 68% of all malaria cases and 70% of malaria-related fatalities globally. Furthermore, approximately 1,031,000,000 individuals across Africa are estimated to be at risk of contracting malaria.

Extensive studies have consistently demonstrated a strong correlation between economic development rates and the burden of malaria, underscoring malaria's role as a critical impediment to economic progress. The direct economic costs of malaria are substantial, placing immense strain on the limited resources of the affected African nations. Countries severely burdened by malaria exhibit Gross Domestic Products (GDPs) that are up to five times lower than those of malaria-free nations. The annual economic growth loss in endemic countries is estimated at 1.3%, equating to as much as US$12 billion in lost productivity. Moreover, malaria contributes to between 5-8% of school absenteeism among African children and causes an additional 2.4 to 6.5 days of absenteeism per student.

The costs associated with malaria prevention and treatment further highlight the economic challenge. The annual cost of protecting one individual against malaria ranges from US$1.18 to US$5.97 through vector control measures. Diagnosis costs have a median of US$6, while treatment costs for each case vary depending on severity, ranging from US$9 to US$89.93. As such, malaria remains the foremost public health priority in Africa, with the costs of treatment and disease prevention far exceeding the financial capacities of most African governments.

A further pressing concern is the recent introduction and establishment of Anopheles stephensi, a species of mosquito that poses a significant threat to the Horn of Africa and beyond. This invasive species, which tends to bite outdoors, could exacerbate the existing malaria burden and undermine the gains made in malaria control over the past two decades.

The global response to malaria control heavily relies on donor funding, which is currently only sufficient to meet half of the required global funding targets. This reliance on external financing is unsustainable and highly vulnerable to shifts in political priorities in donor countries. Approximately a quarter of the global malaria funding is directed to Africa for the provision of insecticide-treated nets, rapid diagnostic tests, and medicines, while national funding should cover the operating costs of the broader health sector.

Existing malaria control measures, including the use of Long-Lasting Insecticidal Nets (LLINs), Indoor Residual Spraying (IRS), and Larval Source Management (LSM), have demonstrated limited effectiveness, especially against the newly introduced invasive mosquito species. This underscores the necessity for the development and adoption of innovative mosquito control approaches, such as Attractive Targeted Sugar Bait (ATSB), Endocticides, Improved Housing, Sterile Insect Technique (SIT), and Paratransgenesis. Research into these methods is ongoing, and their potential for improving malaria control strategies is considerable.

To supplement existing malaria control efforts, innovative technologies like Gene Drive present promising long-term solutions to protect the most vulnerable populations and address the malaria burden in Africa. The African Union (AU) has recognised the potential of Gene Drive technology and has endorsed its development, with support from the African Union Development Agency (AUDA-NEPAD). This initiative aims to foster conducive environments for research, develop regulatory frameworks, and engage stakeholders across African Union Member States, ensuring a collaborative approach to the ongoing fight against malaria.

Phase II Recommendations

To advance gene drive technology and enhance malaria control efforts, the following strategic recommendations are proposed:

1. Case-by-Case Project Evaluation: Assess individual gene drive projects to ensure rigorous analysis of feasibility, risks, and alignment with malaria control goals. This approach will facilitate targeted resource allocation and enable tailored risk management strategies.
2. Sequential, Milestone-Driven Strategy: Implement a phased strategy to promote sustainable progress, building upon each milestone to strengthen adaptability, manage risks, and foster confidence among stakeholders. This structured approach will ensure the scalable development of gene drive applications.
3. Consortium-Led Framework Development: Establish a consortium comprising diverse AU Member States and stakeholders to create a cohesive framework for scaling and testing gene drive technology. This consortium should facilitate cross-sector collaboration and communication from controlled settings to broader field trials.
4. Enhance Regulatory and Financial Mechanisms: Work with AUDA-NEPAD to bolster regulatory frameworks and engage stakeholders effectively. Establish sustainable funding sources to support gene drive research and development, drawing on successful models from global initiatives.
5. Promote African-Led Commercialisation and Innovation: Develop Africa-centred entities to commercialise gene drive technology, utilising shareholding structures to attract investment from both the public and private sectors. Establish an incubator focused on transitioning gene drive research to market-ready applications, fostering leadership roles for African scientists.

6. Alignment with AU Agenda 2063 and SDGs: Ensure gene drive initiatives align with the African Union's Agenda 2063 and the United Nations' Sustainable Development Goals (notably Goals 3 and 17), focusing on sustainable malaria control, technology adoption, and capacity-building across Africa.
7. Institutional Capacity Building: Invest in capacity-building to enhance the technical and regulatory capabilities of African institutions. Support training programmes, develop comprehensive biosafety manuals, and engage communities to build trust and foster acceptance of gene drive technology.
8. Systematic Stakeholder Engagement: Maintain consistent engagement with communities, governments, and health sector partners to increase awareness of gene drive technology's potential benefits and address concerns. Transparent communication will be critical for fostering public understanding and support.
9. Risk Assessment and Regulatory Harmonisation: Ensure harmonisation of biosafety regulations across Africa to support the safe deployment of gene drive technology. Strengthen mechanisms for comprehensive risk assessments and post-deployment monitoring to maintain high safety standards.

By addressing these recommendations, APET believes that the AU can support an integrated vector management approach that leverages emerging gene drive technologies, aiming to reduce malaria transmission and improve economic and public health outcomes across Africa. This framework will also position Africa as a leader in innovative health solutions, promoting sustainable growth and resilience against vector-borne diseases.

TABLE OF CONTENTS

TABLE OF FIGURES

LIST OF TABLES

1

IMPACT OF MALARIA ON AFRICA'S DEVELOPMENT

1.1 SOCIO-ECONOMIC IMPACTS OF MALARIA

Malaria remains an economic and public health burden on Africa. Worldwide, 247 million new cases leading to 619,000 deaths have so far been recorded in the year 2021 with a high share of the burden (95% new cases and 96% Malaria deaths) in Africa (WHO Malaria Report, 2022). Out of the recorded deaths, 77% are children and the daily average deaths reported are about 1000 children under the age of 5. Currently, 10 African countries (Burkina Faso, Cameroon, the Democratic Republic of the Congo, Ghana, Mali, Mozambique, the Niger, Nigeria, Uganda and the United Republic of Tanzania) have been classified as High Burden, High Impact (HBHI) countries. They account for 68% of all malaria cases and 70% of malaria deaths reported. In 2021, the population at risk of malaria in Africa was estimated at 1,031,000,000 persons in 42 countries and the situation seems to be getting worse with the years. As reported by the WHO, between 2020 and 2021, malaria cases in HBHI countries increased from 163 million to 168 million people, an increase associated with disruption to services during the COVID-19 pandemic.

Several peer-reviewed studies have consistently shown a close correlation between the rate of economic development and the burden of malaria, indicating that malaria is an important constraint on economic progress. The direct financial costs of malaria are enormous and weigh heavily on the limited resources of affected African countries. Countries severely affected by malaria have up to five times lower Gross Domestic Product (GDP) than those without malaria. (Jobin, 2014). It is estimated that the annual growth loss in countries with endemic malaria is as high as 1.3 % and with up to US$12 billion in lost productivity. (Gallup and Sachs, 2001; Sachs and Malaney, 2002).

Other studies have shown that malaria contributes between 5% to 8% of absenteeism in school among African children (Halliday KE 2020) and is responsible for between 2.4 - 6.5 days of absenteeism from school (Akazili J 2007; Tawiah T 2015). In Kenya, malaria was reported by caregivers to account for over a third of school days missed (King N 2015). In addition, cerebral malaria in particular is known to have a direct impact on intellectual development in children through impaired attention and brain cognitive functions (Holding PA and Snow RW 2001).

The costs of malaria prevention and treatment in Africa reveal that the economic cost of protecting one person per year ranges from US$1:18 – US$ 5.97 with vector control, diagnosis with a median cost of US$6 and the treatment for each case depending on severity ranges from US$9 – US$89.93 Malaria is therefore, an urgent Africa public health priority as its cost of treatment and disease prevention are higher than what African governments can afford. As such, malaria is holding back Africa's economic development and demographic transition.

The current global interventions rely largely on donor funds that can only meet half of the global funding targets. This is deemed to be unsustainable and highly vulnerable to changing political priorities in donor countries. A quarter of this funding goes to Africa for insecticide-treated nets, rapid diagnostic tests and medicines leaving the national funding to cover operating expenditure in the general health sector. Augmenting the current vector control, case management and intermittent preventative treatments, with up-to-date technologies such as gene drive may present a sustainable attractive option to protect the most vulnerable populations.

1.2 IMPACT OF CLIMATE CHANGE ON MALARIA TRANSMISSION DYNAMICS

There has been a substantial burden of malaria on global health, based on data presented in the WHO Malaria Report 2023. This report illustrated that despite progress in combating the disease, malaria continues to pose a significant challenge, particularly in sub-Saharan Africa and Southeast Asia, where the majority of cases and deaths occur. The WHO data revealed that in 2022, there were an estimated 247 million cases of malaria worldwide, leading to over 600,000 deaths, with children under the age of five and pregnant women being the most vulnerable. These figures emphasise the urgency of implementing more effective strategies for prevention, control, and treatment to reduce the global malaria burden and achieve the goals outlined in the Global Technical Strategy for Malaria 2016–2030.

The report also underscored the influence of climate change on the transmission dynamics of malaria, emphasising how shifts in temperature, humidity, and rainfall patterns directly impact the behaviour and survival of malaria-carrying mosquitoes, particularly the Anopheles species. Temperature is a crucial factor affecting the development of the malaria parasite, Plasmodium, within mosquitoes, as well as the breeding cycle of the Anopheles mosquitoes themselves. Increased temperatures can shorten the extrinsic incubation period—the time it takes for the parasite to develop inside the mosquito—thus potentially increasing transmission rates in certain regions.

Changes in rainfall patterns are also critical, as rainfall creates breeding sites for mosquitoes in stagnant water sources. Excessive rainfall can lead to more standing water, thereby increasing the mosquito population, while droughts can limit breeding opportunities. However, irregular rainfall patterns, especially in regions not traditionally known for high malaria prevalence, can alter the geographical distribution of mosquitoes, extending the range of malaria to areas that were previously less affected. For example, higher altitudes that were once malaria-free due to cooler temperatures are now seeing an uptick in cases as temperatures rise.

Humidity levels play a role in mosquito survival, as higher humidity can extend their lifespan, giving them more opportunities to spread the disease. Low humidity, conversely, tends to reduce mosquito survival. As climate change alters these variables, regions may experience shifts in malaria transmission seasons, with some areas facing prolonged transmission periods or experiencing outbreaks at unexpected times of the year.

The interplay between climate change and malaria necessitates adaptable public health strategies that consider these evolving conditions. It calls for enhanced surveillance systems, vector control measures, and community-based interventions to mitigate the effects of climate change on malaria transmission. Additionally, climate-informed health planning is needed to anticipate and respond to shifts in malaria patterns, particularly in regions that might become newly susceptible to the disease.

1.3 GENDER CONSIDERATIONS

Women account for more than 52% of Africa's population and therefore, they need to be actively involved in malaria control strategies to substantially contribute to the achievement of the malaria elimination goal. In addition, women's vulnerability to malaria during pregnancy continues to carry substantial risks for the mother, her foetus and the newborn child. However, women should not solely be perceived as victims when addressing the malaria burden. Their often deep understanding of family and community thoughts on malaria, their involvement in the management of malaria cases and control tools, and their contribution to farming, forestry and fishery, make them valuable key stakeholders and agents of change at different levels of malaria control strategies to boost malaria elimination through the innovative technology like gene drive.

It is especially critical in the context of pregnancy, to prevent the transmission of malaria, where malaria can have severe consequences, such as maternal anaemia, low birth weight, premature birth, and even infant mortality. The risk to unborn children makes it crucial to prioritise malaria prevention and treatment among pregnant women, through measures such as intermittent preventive treatment in pregnancy (IPTp) and insecticide-treated bed nets (ITNs). The health of pregnant women directly affects the health of future generations, underscoring the need for targeted interventions in malaria control.

Women's involvement in vector control strategies is also pivotal, as they often play a central role in household-level decision-making related to health practices, childcare, and the use of preventive measures such as bed nets and indoor residual spraying. By actively engaging women in community-based malaria prevention programmes, Africa can harness their influence in promoting health-seeking behaviours and adopting vector control measures within their communities. This approach not only helps to reduce malaria transmission but also empowers women through participation in public health initiatives, fostering gender equality in health leadership.

However, it is equally important to acknowledge the economic influence and cultural decision-making roles of men in many African societies, particularly in decisions regarding resource allocation for vector control measures. Men often hold significant influence in household finances and community leadership, which can directly affect the availability and implementation of vector control strategies such as bed nets, spraying programmes, and healthcare access. Therefore, updated statistics and data analysis should also reflect how men's roles in financial decisions impact the success of malaria control interventions, highlighting the importance of engaging both men and women in holistic community-driven approaches to malaria eradication.

In addition to gender dynamics, the impact of war, civil unrest, and displacement on malaria control efforts presents another critical challenge, especially in conflict-affected AU Member States. In regions experiencing instability, health infrastructure is often compromised, leading to disruptions in malaria prevention programmes, supply chains, and health service delivery. Displacement of populations due to conflict often results in crowded living conditions with limited access to vector control measures, increasing the risk of malaria outbreaks. For instance, South Sudan and the Central African Republic have faced challenges in maintaining malaria control amidst conflict, leading to higher prevalence rates and increased mortality among displaced populations.

Statistics from these conflict-affected areas demonstrate a correlation between civil unrest and malaria resurgence, as disrupted health systems struggle to provide consistent preventive and curative services. For example, during conflicts, the distribution of bed nets and malaria medications often becomes irregular, leading to spikes in transmission. Additionally, displaced populations may lack access to clean water and sanitation, creating more breeding grounds for mosquitoes and worsening the situation. Addressing the impact of conflict on malaria control requires targeted international support and collaboration among African Union Member States to ensure that malaria prevention remains a priority even in humanitarian crises.

Therefore, an effective malaria strategy in Africa should address the interconnected challenges of gender, economic roles, and conflict. It should prioritise vulnerable populations such as pregnant women while ensuring that men's roles in decision-making are leveraged for better resource allocation. Furthermore, targeted interventions are needed in conflict-affected regions to maintain malaria control efforts and protect displaced populations. Through a comprehensive approach that considers these dimensions, Africa can make significant strides in reducing the burden of malaria and achieving health equity across the continent.

Since gene drive technology is independent of individual use, it provides extensive communal benefits regardless of the age or gender of individual members of the communities and a comparative advantage to the existing tools. This benefit can be increased by integrating a gender lens in the engagement principles for gene drive technology. Women have experience, expertise, perspectives and capacities that can contribute to effective behaviour change in family, community and decision-making processes regarding the knowledge building for informed decisions regarding gene drive research and deployment in Africa. Women at the community level and the decision-making arena, should be involved in gene drive debate on risks, benefits and governance. The use of gene drive technology for Africa should go through the gender-sensitive approach because malaria and its control tools are a domain for which gender specificity is needed. Besides, it enhances the sustainability of control efforts and African development processes and enhances the acceleration of the malaria elimination agenda through the combination of competencies between women and men. By considering gender norms, roles and relations between women and men and the way they affect malaria control strategies, it makes sense to target women and men-specific skills to support effective management of the gene drive technology.

1.4 THE MALARIA BURDEN IN WAR-RAVAGED INTERNAL DISPLACED AREAS

In the last couple of years, a dramatic escalation of terrorist attacks has occurred in several countries in Africa and when combined with the unending ethnic and religious conflicts, it has changed many African countries from being relatively peaceful nations to war-ravaged countries. In such countries, it is common to find several million people who are internally displaced and living under difficult conditions where they are vulnerable to exposure to malaria, especially women and children. In addition, a lot of constraints limit the implementation of conventional malaria control strategies. These include the proximity of people to each other, the nature of the houses and beds they sleep on, the poorly constructed community housing structures etc. all contributing to weaknesses in conventional malaria control measures. Gene drive technology for malaria control would help to circumvent challenges associated with malaria transmission in internally displaced areas.

1.5 ETHICAL CONSIDERATIONS IN THE MALARIAL BURDEN

In the Sub-Saharan African region, the gap between the need for funding and resources available to prevent and treat malaria has more than doubled since 2017, from $1.3 billion to $2.6 billion in 2019. The $3 billion invested in malaria in 2019 fell far short of what was needed to make progress towards global targets (WHO) The shortfall was associated with the COVID-19 crisis which devastated prevention and treatment programmes from 2020 to 2021 and rolled back the gains made. It is now recognised that the available resources for malaria control in Africa have never matched the need and while high-income countries spend trillions to manage the consequences of COVID-19, there is a need to rethink the ethical and world justice system for the malaria fight in Africa. Malaria kills a child every minute in Africa and this has gone on for decades compared to the overall mortality that was experienced with COVID-19. The malaria fight requires more attention, more funding and the use of transformative and innovative tools to complement existing tools like gene drive to tackle it.

Particularly, funding for malaria control, particularly from national and international organisations, involves ethical considerations that impact the equity, transparency, and effectiveness of resource allocation. While funding for malaria initiatives increased from US$1.7 billion to US$2.6 billion in 2019, this growth still falls short of the estimated US$6.8 billion needed annually to achieve global malaria targets, particularly in vector control research and programme implementation. The funding gap poses ethical questions about prioritisation and resource allocation among malaria-endemic regions, raising concerns about whether the most vulnerable populations receive adequate support.

Ethical funding mechanisms should ensure that resources are distributed equitably, with a particular focus on low-income countries that bear the highest malaria burden. The allocation of resources should aim to reach marginalised populations, including rural communities and conflict zones, where malaria prevalence is often highest. Failure to address these disparities can continue to perpetuate health inequities and undermine global efforts to eradicate malaria.

Transparency in fund disbursement and utilisation is crucial to ensure that malaria control programmes are effective. International donors, such as the Global Fund and WHO, and national governments should uphold accountability in how funds are used, avoiding mismanagement or corruption that could divert resources away from critical vector control and treatment initiatives. Effective monitoring and evaluation systems are needed to track the impact of funded projects and ensure that allocated funds directly contribute to malaria reduction goals.

The COVID-19 pandemic significantly disrupted global health funding, including resources allocated to malaria control. Many countries, faced with resource constraints due to the pandemic response, had to reallocate funds away from existing malaria programmes to address the emergency needs of the pandemic. This shift in funding priorities resulted in setbacks for malaria prevention and treatment, such as delays in bed net distribution, reduced vector control activities, and disruption of routine malaria services.

WHO estimates that malaria control programmes in some regions experienced up to a 50% reduction in funding during the peak of the pandemic. This decline in resources not only threatened progress toward malaria elimination but also led to a resurgence of cases in some areas, reversing gains made in previous years. The ethical challenge lies in balancing immediate pandemic response with the sustained support needed to address endemic diseases like malaria, which continue to claim thousands of lives, especially in Sub-Saharan Africa.

The development of malaria vaccines represents a critical advancement in the fight against malaria, but investment challenges persist. Despite the approval of the RTS, S/AS01 (Mosquirix) vaccine by the WHO, scaling up its production and distribution remains a challenge due to funding limitations. Ethical concerns arise over the affordability and availability of the vaccine to low-income countries most affected by malaria, ensuring that pricing strategies do not hinder accessibility for those in need.

Investment in new vaccines, such as the R21/Matrix-M vaccine, should consider the ethical implications of patent rights, technology transfer, and local production capabilities. Ensuring that African countries can manufacture and distribute these vaccines locally would address issues of vaccine equity and help overcome barriers to timely access.

The use of gene drive requires careful regulatory oversight and international cooperation to ensure that deployment is safe and responsible, particularly in regions where ecosystems are already vulnerable. Ethical frameworks should guide the research, testing, and deployment of gene drive technology, prioritizing safety and the long-term impact on both human health and environmental balance. Therefore, ethical considerations in funding mechanisms, vaccine development, vector control, and gene drive technology are crucial to advancing malaria control in Africa. Addressing these ethical dimensions will ensure that interventions are fair, equitable, and sustainable, enabling progress toward malaria eradication in a manner that respects community needs and protects vulnerable populations.

1.6 DOMINANT MALARIA VECTORS IN AFRICA AND INVASIVE SPECIES

There are more than 3,500 species of mosquitoes worldwide and of these, only about 100 species of Anopheles are known to transmit the human malaria parasite in Africa. Although there are important differences among these species that influence their role in malaria transmission, the dominant vector species for most malarial transmission come from the closely related species of the Anopheles gambiae complex (Anopheles arabiensis, Anopheles coluzzii, and Anopheles gambiae s.s.) and the Anopheles funestus complex (Anopheles funestus s.s.) (Battle et al., 2012; Sinka et al., 2012; Coetzee et al., 2013).

There are further three, highly anthropophilic dominant vector species in Africa, An. moucheti, An. nili, and An. coustani. Those from the gambiae and the funestus complex are undoubtedly the most important vectors transmitting both Plasmodium falciparum and Plasmodium vivax parasites to humans and contribute to the bulk of the global malaria burden in Africa (Sinka et al. 2010). Anopheles nili complex, (An. nili s.s., An. carnevalei, An. ovengensis), An. moucheti complex (An. moucheti moucheti, An. moucheti nigeriensis); and An. mascarensis is considered a secondary vector in Madagascar, Comoros, and Mayotte (Fontenille & Campbell, 1992; Fontenille et al., 2003; Marrama et al., 1999). Anopheles moucheti is also an important secondary vector in equatorial forests in Central and West Africa (Antonio-Nkondjio et al., 2002; Antonio-Nkondjio et al., 2008; Mattingly, 1949; Manga et al., 1995).

1.7 THREAT OF NEW MOSQUITO SPECIES (ANOPHELES STEPHENSI)

Among the invasive mosquitoes, Anopheles stephensi is a new major malaria vector with origins in South Asia and the Middle East, especially the Arabian Peninsula (Coetzee, M. 2020). The vector is known to transmit two major malaria parasite species: Plasmodium falciparum and P. vivax (Tadesse et al 2021; Balkew et al., 2020). An. stephensi was first reported in the Horn of Africa from Djibouti in 2012 and has now been found in many cities and towns in urban settings in Ethiopia (Carter et al., 2016; Balkew et al., 2021), Sudan (Ahmed et al., 2021a, 2021b) Somalia, and recently in Nigeria (Global Malaria Program 2022). There is a real risk of An. stephensi spreading further in the African cities. Africa has experienced rapid urbanization in recent years, rising from 31.5% of the population living in urban areas in 1990 to 42.5% in 2018. By 2050, approximately 60% of the population is expected to live in urban areas.

The recent invasion and establishment of Anopheles stephensi represent an imminent and substantial threat to the Horn of Africa and the wider African region and could jeopardise the two decades of gains in malaria control in Africa, especially to the continent's rapidly growing cities. The main mosquito-control interventions used in Africa, including the use of Long-Lasting Insecticidal Nets (LLINs), Indoor residual insecticide spray (IRS), and Larval source management (LSM) are not likely to work against the invasive mosquito species since they tend to bite people outdoors. Successes in reducing the malaria burden could be threatened by the recent detection of this invasive species in several countries in the Horn of Africa and its neighbours.

The threat of the new mosquito vector, An. stephensi, which has better adapted to large urban areas could make the situation worse. In Ethiopia, it is resistant to several classes of insecticides, most notably pyrethroids, carbamates, organochlorides, and organophosphates (Yared et al., 2020). However, it is not clear the mechanisms conferring resistance in An. stephensi in Ethiopia.

An. stephensi is found throughout South Asia, where it can transmit both Plasmodium falciparum and P. vivax parasites in a diverse set of habitats, from rural to highly urban settings (Subbarao et al. 2019). The success of this vector in urban locations is due to its ability to utilize water tanks, wells, and other artificial containers as larval habitats (Kumar et al. 1992; Gayan et al. 2017). Furthermore, it has shown substantial resistance to water pollution (Batra et al. 2001). In the last decade, Anopheles stephensi has been discovered outside of its traditional endemic region in Asia and was first detected in Djibouti in 2012 (Faulde et al. 2014). Anopheles stephensi species differs from the main dominant vector Anopheles gambiae in Africa in many respects as shown in Table 1 below.

Table 1
Ways in which Anopheles stephensi mosquito species differs from Africa's main dominant malaria vector Anopheles gambiae

Species Characteristics	Anopheles gambiae	Anopheles stephensi
Habitat	Mainly rural	Mainly urban
Egg laying niche	Natural water bodies, ponds, puddles and streams	Human water containers and natural water bodies
Peak biting period	Late nights so can be prevented by sleeping under a bed net	Evenings before bedtime so sleeping under bed nets is not effective.
Resting surface after biting	Rests on surfaces indoors, and is killed by indoor residual sprays	Rests outdoors and avoids contact with indoor residual sprayed surfaces.

2

OVERVIEW OF EXISTING, EMERGING AND RE-EMERGING INTERVENTIONS FOR MALARIA CONTROL

2.1 BACKGROUND

Malaria control involves strategies aimed at reducing the transmission, incidence, and impact of malaria through measures such as insecticide-treated nets (ITNs), indoor residual spraying (IRS), prompt diagnosis and treatment with artemisinin-based combination therapies (ACTs), and vaccination efforts like the RTS,S/AS01 vaccine in high-burden areas. For example, ITNs in Nigeria have reduced malaria incidence by up to 50%, while IRS in South Africa's KwaZulu-Natal province has helped significantly lower cases.

Malaria vector control, a key component of broader control efforts, specifically targets mosquito populations that transmit the disease. This includes using Indoor Residual Spraying (ITNs), Insecticide-Treated Nets (IRS), larval source management (LSM), and innovative gene drive technology, as seen in Burkina Faso. These approaches reduce mosquito populations and disrupt their ability to spread the malaria parasite. Together, these methods provide a comprehensive approach to mitigating malaria's impact, particularly in regions with high transmission rates.

2.2 EXISTING INTERVENTIONS FOR MALARIA CONTROL

The current malaria vector control tools, using long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) are critically important in malaria control and have saved many lives (Huho et al., 2013). These tools include (i) Insecticide-treated nets and indoor residual spraying (IRS) (ii) Drugs (treatment and prophylaxis) (iii) Malaria vaccines and (iv) Indigenous treatments.

Insecticide-treated nets and indoor residual spraying (IRS): The effectiveness of insecticide-treated nets and indoor residual spraying (IRS) in Africa is being threatened and undermined by insecticide resistance, residual transmission, and vector behaviour changes toward more early evening and outdoor biting malaria vectors. Malaria vectors exhibit different behavioural characteristics that mitigate the effectiveness of vector control strategies. For example, traditionally, An. gambiae s.s. has been regarded as a human-biting, late-night indoor-feeding and indoor-resting mosquito, while An. arabiensis is found more often in drier environments and is more zoophagic with outdoor biting and resting behaviours. Subsequently, shifts towards earlier evening biting by An.gambiae s.s. (before people enter houses to sleep under LLINs) and later biting by An. funestus (biting in the morning after sunrise are examples of behavioural plasticity enabling these species to avoid contact with the LLIN and IRS insecticides.

Drugs (Treatment and Prophylaxis): When it comes to the use of drugs for malaria treatment, early diagnosis and prompt, effective treatment of malaria is a key to good case management of malaria. In the absence of an effective vaccine worldwide deployed, the therapeutic use of antimalarial agents remains the only method for the management and prophylaxis of malaria in Africa. Thus, preventing or delaying resistance is essential for the success of the case management strategy. Thus, to help protect current and future antimalarial medicines, all episodes of malaria are now treated with at least two effective antimalarial medicines with different mechanisms of action. For uncomplicated malaria, WHO recommends the use of "Artemisinin Combination Therapies" (ACTs) for the treatment of adults and children (except pregnant women in their first trimester).

Malaria vaccine clinical development: One of the tools for combating malaria, is to have an effective and safe malaria vaccine (Peter D et al 2010; Gardner MJ et al 2002 and Florens L, et al 2002). Research and development on malaria immunization continues and is still very active. With the relative increase in research funds for the malaria vaccine development, notable advances are being made in this field where the complexity of the Plasmodium and its life cycle, antigenic variations and lack of knowledge of the interactions between the parasite and the immune system of the human host have made research on malaria vaccines very difficult. Malaria vaccine research should overcome its constraints to meet the three objectives focused on: (i) the induction of strong, long-lasting and strain-transcending immune responses; (ii) identification of protective antigens for stage-specific immunity; (iii) the successful combination of immunogenic antigens (Vasee S M et al 2004).

Indigenous treatments: Most of Africa's biodiversity plays major specific roles in the cultural evolution of human societies and plants have been an integral part of life in many indigenous communities. Many communities in Africa have much-elaborated plant knowledge (Barrow, 1996). Medicinal plants have played significant roles in the treatment of malaria and have been recommended in curbing resistance posed by Plasmodium parasites to conventional antimalarial drugs (Iwalokun et al., 2008; Adegbolagun et al., 2013). Traditionally, herbal medicine has remained the backbone for the treatment of malaria for thousands of years. Today, several plants have been used in the world as a treatment for malaria and presented in different forms as tea bags, blisters, solutions, capsules, tablets etc. The first antimalarial drug (quinine) was a herbal medicine isolated from the bark of the Cinchona tree, in the family of Rubiacea. In early 1632, an infusion of the Cinchona bark was used for the treatment of human malaria. Artemisia annua is another earliest millennial medicinal plant that was rediscovered in China from which artemisinin was isolated (Adebayo et al., 2011). From the foregoing, it becomes evident that for successful control of mosquitoes, a comprehensive approach using different interventions is necessary and none of the existing tools is satisfactory. A further review of the opportunities and challenges of these interventions is discussed in Box 1.

Box 1: Highlights of existing malaria control interventions

Insecticide-treated nets and indoor residual spraying (IRS)

LLINs and IRS specifically target indoor-biting and indoor-resting mosquitoes. However, the widespread scale-up of LLINs and IRSs has changed vectors' distributions and behaviours, with An. gambiae s.s. and An. funestus diminishing in abundance relative to An. arabiensis (Amek et al., 2012).

Drugs as treatment and/or prophylaxis

Several studies showed that the efficacies of most antimalarial agents are compromised by the emergency of drug-resistant malaria parasites (Dondorp AM, et al 2009; Noedl H, et al 2008; Ross LS et al 2018; Uwimana et al 2020). Resistance to artemisinin derivatives has arisen recently in P. falciparum in South-East Asia which has threatened control efforts. Some studies have shown high rates of treatments failures for ACTs in the treatment of malaria in Africa (Uwimana A. et al 2020; Gansané, A et al 2021; Moriarty LF,2021; Dimbu PR et al 2021). The sulfadoxine/pyrimethamine drug regimen is now no longer effective for intermittent preventive treatment in pregnancy and infancy in most of eastern Africa and parts of central Africa (Amimo F, Lambert B, Magit A, et al. 2020). The fact that resistance has been reported for nearly all available antimalarial agents reinforces the urgent need to develop new antimalarial agents (Menard D and Dondorp A 2017).

Drugs as treatment and/or prophylaxis

Several studies showed that the efficacies of most antimalarial agents are compromised by the emergency of drug-resistant malaria parasites (Dondorp AM, et al 2009; Noedl H, et al 2008; Ross LS et al 2018; Uwimana et al 2020). Resistance to artemisinin derivatives has arisen recently in P. falciparum in South-East Asia which has threatened control efforts. Some studies have shown high rates of treatments failures for ACTs in the treatment of malaria in Africa (Uwimana A. et al 2020; Gansané, A et al 2021; Moriarty LF,2021; Dimbu PR et al 2021). The sulfadoxine/pyrimethamine drug regimen is now no longer effective for intermittent preventive treatment in pregnancy and infancy in most of eastern Africa and parts of central Africa (Amimo F, Lambert B, Magit A, et al. 2020). The fact that resistance has been reported for nearly all available antimalarial agents reinforces the urgent need to develop new antimalarial agents (Menard D and Dondorp A 2017).

Malaria vaccine clinical development

In 2022, there were 89 candidate malaria vaccines in progress or having undergone clinical evaluation through 153 clinical trials on the WHO website. Only the RTS, S vaccine resulting from the collaboration between GSK and MVI has been prequalified and recommended for use by the WHO after 30 years of research and development. This vaccine has demonstrated efficacy of 30 to 50% in Phase III to the point of raising hope and good adaptation with EPI. In Burkina Faso, the R21/MM vaccine has shown good efficacy results in phase II trials.

Indigenous treatments
More than 2000 plant species from 160 families used to treat malaria or fever in Africa have been studied and dozens of plants with antimalarial activity discovered covering more than 175 antiplasmodial compounds extracted from plants. Satish and Kale, 2013 reported over one hundred thirty-nine medicinal plants for their use as antimalarials. A study by Willcox showed 1277 plant species from 160 families listed that have been used to treat malaria (Willcox, 2004). A large number of controlled trials of herbal preparations for uncomplicated malaria have been tested in Africa with promising results.

Figure 2 1: Box 1: Highlights of existing malaria control interventions

2.3 THE EMERGING AND RE-EMERGING INTERVENTIONS EMPLOYED AS MALARIA VECTOR CONTROL

Endocticides: In recent days, the use of systemic insecticides in veterinary, horticulture, and medical entomology (Yadav & Devi 2017) has shown that the development of resistance to these insecticides in pests is minimal (Abbas et al 2015; Bass et al 2015). Evaluation of Ivermectin, Fipronil, and Eprinomectin in humans/animals is now demonstrating that these endocticides could soon serve as novel malaria transmission control tools by reducing the longevity of Anopheles mosquitoes that feed on treated hosts, potentially decreasing Plasmodium parasite transmission when used as mass drug administration (MDA). Endectocides are drugs applied directly to hosts to kill endoparasites and ectoparasites, mainly blood-feeding arthropods (Yakob 2016). Although being used for the control of nematodes in humans and other vertebrates, endectocides can be toxic to Anopheles spp. When mosquitoes feed on a host that recently received these drugs (Foy et al 2011).

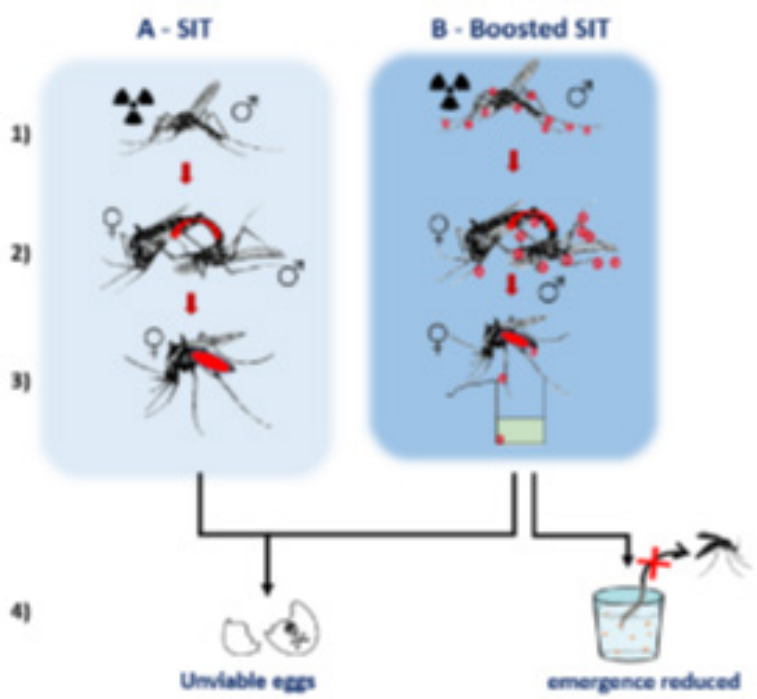
Attractive Targeted Sugar Bait (ATSB): The attractive-toxic sugar baits are a new vector control tool based on the "attract and kill" approach. The approach is based on the natural behaviour of the mosquitoes to feed on plant sugars as an energy source immediately after emergence and intermittently during their life history. It is a known fact that successful sugar feeding by mosquito adults helps in mosquitoes' high survival rate and reproductive fitness. The sugar-feeding behaviour of mosquitoes is being tapped to formulate ATSBs by combining a concentrated sugar-based food source, an olfaction stimulant to lure mosquitoes and a systemic insecticide to kill them. It is believed that the development of ATSBs may contribute to their localized control.

Improved/Innovative Housing: It has been observed that poor housing is associated with an increased risk of malaria incidence (Tusting et al., 2015). Anopheles gambiae s.i. The major African malaria vector, enters houses at night through open eaves, the gap between the top of the wall and the roof. The integration and installation of screening on doors, windows, and closing of eaves in houses can reduce vector density indoors, potentially reducing the incidence of malaria and other malaria-related complications (Lindsay et al., 2003; Kirby et al., 2008, 2009; Atieli et al., 2009; Massebo & Lindtjørn 2013; Ogoma 2010).

Sterile Insect Technique and Boosted SIT: The sterile insect technique (SIT) is one of several genetic control methods developed to control mosquitoes, such as Aedes and Anopheles. (Lees et al. 2015; Abraham et al. 2007). SIT is a species-specific and environmentally friendly pest population control method and consists of releasing male insects that are either sterilized using ionizing radiation or transformed to carry a lethal gene (Alphey 2014). In the former case, wild virgin females mated to these males will transmit lethal mutations to their offspring or genetic systems reducing their fitness (Dyck et al. 2021). The SIT has been successfully used throughout the world to suppress or eradicate field populations of several insect pest species such as fruit flies, moths, screwworm flies, mosquitoes and tsetse flies (Klassen et al. 2021; Lees et al. 2021). For the Aedes group, pilot trials showed the effectiveness of the SIT in suppressing natural populations (Bouyer et al. 2020; Lees et al. 2021; Gato et al. 2021).

SIT faces many technical and logistical constraints, particularly when it comes to treating insect populations over large areas (Cuisance et al. 1984). This is why a new control method called "boosted SIT" has been proposed to reinforce the SIT. It combines SIT and the self-dissemination of a biocide by the insect. (Bouyer et Lefrançois 2014). This approach consists of coating the sterile males with a thin layer of biocide that will then be carried to the breeding sites by mated females (Figure) (Bouyer et Lefrançois 2014; Mains et al. 2015). (credit drawing: L. Douchet). Studies on Aedes mosquitoes (Ae albopictus, aegypti) have shown that exposure to PP can reduce the reproductive capacity of mosquito females. (Ohba et al. 2013; Murtaza et al. 2022). Given the results on the Aedes mosquitoes, SIT and boosted SIT remains a potential technique that could be applied effectively in the control of the Anopheles mosquitoes.

Figure 2 2 A &B: Main principles of the SIT (A) and the Boosted SIT (B).



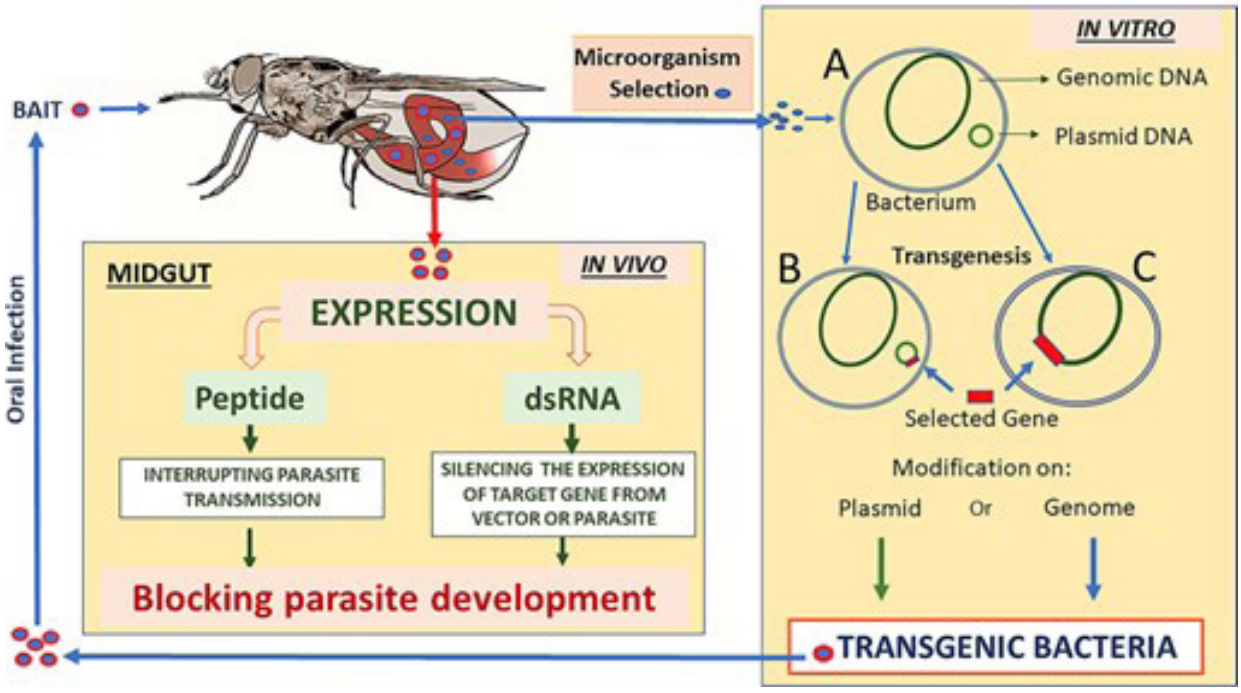
For SIT: 1) Irradiation to sterilize males, 2) mating with females to sterilize them, 3) blood-fed females lay sterile eggs into breeding sites, 4) no larvae

For Boosted SIT: 1) Coated sterile males with PPF, 2) transfer of PPF to females while mating, 3) blood-fed and contaminated females transfer the PPF to the breeding sites while laying sterile eggs, 4) contaminated breeding sites water induce larval mortality (credit drawing: L. Douchet)

Paratransgenesis: With the increased spread of many insect-vectored parasites and the arrival of newly emerging diseases, the need for effective control is vital. Control methods generally use several strategies and are focused either on preventing the vector from feeding upon the host and transmitting the disease, or on treating infected individuals with drugs. One of the most successful twentieth-century methods of controlling insect vectors, however, was the widespread use of insecticides. However, this strategy has limitations.

Recently, ingenious attempts to control insect vectors have turned to: i) genetic modification so that the vector competence to transmit pathogens is reduced or the insect is engineered with a lethal transgene causing death during development (Shaw et al., 2019).

Figure 2 3: Summary of the analysis and selection of bacteria from vector microbiota for cultivation and genetic modification in vitro The microorganism (A) is genetically modified by the insertion of an exogenous gene in a plasmid (B) or directly into the bacterial chromosome (C). The transgenic bacteria are offered to adult insects through an attractant bait. In the insect's digestive tract, the genetically modified microorganism expresses a peptide capable of interrupting the transmission of the parasite or a dsRNA that can silence genes in the parasite or the vector, if these are sensitive to RNA interference, thereby blocking parasite development. Abbreviations: dsRNA, Double-stranded RNA (Norman et al., 2022).



Population suppression/reduction: This is the Target Malaria technology in development based on principles of genetic control that involve the release of GM mosquitoes into the environment to ultimately suppress the population of wild mosquitoes through genetic means. Target Malaria work focuses on decreasing the number of female vector mosquitoes in a population because only females bite and their number usually determines future population size. The project is currently targeting only three very closely related species namely Anopheles gambiae, Anopheles coluzzii and Anopheles arabiensis. that are responsible for most transmission of malaria parasites in Africa.

The Oxitec technology uses the self-limiting gene approach as a pest control method where the Friendly™ males are planned to be released to reproduce with wild females, such that their offspring will inherit a copy of the self-limiting gene. This gene disrupts the proper functioning of the insects' cells by over-producing a protein, interfering with the cells' ability to produce other essential proteins needed for development. This will disrupt the insect's normal development and ability to survive to adulthood. This gene can be adjusted to function only in females, to enable large-scale and simple production of Friendly males only, and to target the pest female, which is frequently the most damaging. This self-limiting gene can be turned off with an antidote called tetracycline; allowing us to breed our Friendly™ males and females at a large scale without the need for any additional genetic engineering. Oxitec has initiated new projects in the fight against malaria, targeting Anopheles stephensi and Anopheles albimanus. A further review of these emerging and re-emerging interventions is discussed in Box 2.

BOX 2: HIGHLIGHTS OF EMERGING AND RE-EMERGING INTERVENTIONS FOR MALARIA CONTROL

Endocticides

Ivermectin and other endectocides could soon serve as novel malaria transmission control tools by reducing the longevity of Anopheles mosquitoes that feed on treated hosts, potentially decreasing Plasmodium parasite transmission when used as mass drug administration (MDA). Through the World Health Organization, an Ivermectin road map has been developed to scale up the use of MDA administration in humans and livestock. Currently, 3 large-scale trials are underway in Mozambique and Kenya to evaluate the epidemiological and entomological impact of ivermectin MDA on humans and livestock in Kenya and Mozambique to develop a complementary strategy for malaria elimination.

Attractive Targeted Sugar Bait (ATSB)

This method is suitable to be combined with any type of low-risk gut toxin, which makes it a potential and acceptable tool to fight rising resistance against conventional contact pesticides (Allan 2011). ATSB trials conducted in Mali against An. gambiae in an arid habitat with relatively little sugar source vegetation proved to be highly successful resulting in over 98% reduction in vector populations (Müller et al 2010; Beier et al 2012). Currently, Phase III large-scale trials are being conducted in Kenya, Zambia, and Mali to evaluate the efficacy, cost-effectiveness, and acceptability of ATSB for malaria burden reduction in Africa.

Improved/innovative Housing

Evidence shows that poor quality housing and neglected peri-domestic environments are risk factors for the transmission of malaria, and arboviral diseases (e.g. dengue, yellow fever, chikungunya, Zika and leishmaniasis). Housing interventions are essential for reducing morbidity, mortality, and human suffering, promoting economic growth, well-being and poverty reduction. There is a need to implement relevant vector control interventions that go beyond the health sector and strengthen multisectoral approaches – with housing being a key part of the African response.

Sterile Insect Technique and boosted SIT

For malaria vectors, significant progress has been made towards operationalizing the SIT technology for malaria control over the years. However, one of the main limitations being faced is the absence of an efficient genetic sexing system. The improvement of the SIT technology through boosted SIT facilitates the self-dissemination of a biocide that allows the horizontal transfer of the latter between two insects of the same species, for example, the male to the female through mating. (Wang et al. 2014) While laying sterile eggs. The contaminated breeding sites' water also induces larval mortality (as shown in the credit drawing by Douchet). The biocide here is an insect juvenile hormone mimic (Sullivan and Goh 2008) named pyriproxyfen which has extremely low toxicity effects on humans at doses recommended by the WHO (WHO 2009). Pyriproxyfen has traditionally been used in aquatic habitats to prevent mosquito larvae and pupae from developing into adults (Dhadialla et al. 1998; Hustedt et al. 2020). South Africa has planned to eliminate local malaria transmission by 2023 and use a SIT programme targeting Anopheles arabiensis (Ntoyi et al. 2022). The SIT has proven to be effective at the insular scale or in isolated populations of Aedes species (Zheng et al. 2019).

Biological Control using Wolbachia viruses

Biological control using Wolbachia viruses involves manipulating Wolbachia infections in mosquito populations to reduce disease transmission. This approach typically includes releasing Wolbachia-infected male mosquitoes into the wild, leading to the production of non-viable offspring. Recently, Wolbachia viruses, known as phage WO, have been utilized to enhance the effectiveness of these strategies. Field trials have shown promise in reducing mosquito populations and curbing diseases like dengue fever, but further research is needed to fully understand the long-term impact and ensure safety and sustainability.

Biological control using entomopathogenic fungi:

Biological control using entomopathogenic fungi involves using specific fungi to target and control insect populations. These fungi infect insects, causing disease and ultimately leading to their death. They can be applied as biopesticides and have shown effectiveness in various fields such as agriculture and public health. The method is advantageous due to its specificity and reduced impact on non-target organisms.

Paratransgenesis

Paratransgenesis is a promising and particularly ingenious strategy currently being developed for controlling vector-transmitted diseases (Fig. 1). It utilises the genetically manipulated native microbiome (mutualistic symbiotic and commensal bacteria, fungi and viruses) of the vector insect to inhibit or kill the disease pathogen (Marchesi et al., 2015). Native symbionts or commensals isolated from the vector are genetically transformed in vitro to produce antipathogen factors and then reintroduced to the insect to interrupt the life cycle of the disease organism. The great advantage of this method over genetically transformed mosquitoes is that the transformed bacteria/fungi/viruses used may have the ability to colonise a range of different insect vector strains and even species.

Population replacement

The "Transmission Zero" approach being undertaken by UC, Irvine seeks to develop and test transmission-blocking traits of transgenic malaria mosquitoes with the ultimate aim of eventually eliminating malaria transmission. Researchers have recently addressed the following key requirements for transgenic Anopheles mosquitoes that would render them suitable for a population suppression–based malaria control strategy: (i) effector transgenes that efficiently suppress Plasmodium infection; (ii) targeting of the malaria parasite with multiple independent effectors to potentiate suppression and minimize the probability for the development of resistance; (iii) spatiotemporal specificity in expressing these transgenes for effective targeting of different developmental stages of the parasite; and (iv) transgene selection to allow minimal fitness cost to the mosquitoes.

Population suppression/reduction

Target Malaria technologies in development are based on principles of genetic control which propose to involve the release of GM mosquitoes into the environment to ultimately suppress the population of wild mosquitoes through genetic means. Target Malaria developmental pathway is made of three phases. Subject to the approval of the relevant regulatory authorities, this plan proposes to include the phased release of different strains of genetically modified (GM) mosquitoes in different countries over several years.

The starting point involves the use of sterile male GM mosquitoes (denoted DSM=Dominant Sterile Male) which are not capable of producing viable offspring and thus are not intended to persist in the environment (i.e. "self-limiting") nor represent a means of vector control. The main objective of this phase is to enable the Target Malaria project to conduct controlled studies using GM mosquitoes in the field to assess various biological parameters and build local capacity with project partners.

The second phase is proposed to experimentally evaluate a second "self-limiting" strain of GM mosquitoes (denoted by the acronym PMB = Paternal Bias Male) which has been genetically modified to produce predominantly male offspring and is thus anticipated to persist in the environment for a slightly longer period than the DMS strain.

The PMB strain may have a local impact on population levels near release due to the anticipated effect of producing a male bias in future generations, but is not intended for mosquito vector control, and will serve only as a development phase to evaluate the experimental parameters. The final phase is expected to result in the release of a genetically modified mosquito capable of being self-sustaining and viable in the environment through a genetic strategy known as “gene drive".

It will be used for malaria vector control interventions. GM mosquitoes developed for “gene-drive" strategies will be evaluated in the later stages of Target Malaria's staged trial plan, following the evaluation of sterile and self-limiting strains in open-field trials. Laboratory work mainly takes place in Europe and Africa, where researchers are developing and evaluating mosquito strains. For each iteration, if laboratory assessments prove successful, the next step sees project partners in Africa reaching out to national governments to secure the necessary permits for small-scale release of the GM mosquitoes in selected village sites in Africa. This multi-phased pathway allows for the progressive development of scientific knowledge, operational awareness and skills development with a broad group of stakeholders, such as scientists, regulatory bodies, as well as policymakers and communities.

Figure 2 4: BOX 2: HIGHLIGHTS OF EMERGING AND RE-EMERGING INTERVENTIONS FOR MALARIA CONTROL

3

IMPLEMENTATION OF THE FIRST APET GENE DRIVE REPORT

3.1 AU DECISIONS ON THE FIRST GENE DRIVE REPORT

At the African Union Summit of Heads of State and Government of July 2017, African leaders committed to investing in the development and regulation of the gene drive technology as well as other innovations, including next-generation insecticides for indoor residual spray and LLIN, rapid diagnostic tests (RDT) and artemisinin-based combination therapy (ACT) for the elimination of malaria. The African Union High-Level Panel on Emerging Technologies (APET) has recommended gene drive as one of the technologies on the horizon that has the potential to contribute to the control and elimination of malaria on the continent. In 2018, through recommendations of the African ministers responsible for science and technology, the Executive Council of the African Union called upon Member States to harness emerging technologies, including gene drive, in their development initiatives. All these political pronouncements speak to the fact that the continent appreciates the economic gains that can be realised by eliminating malaria. The key African Union decisions on gene drive technology are highlighted below in Box C.

Box C: Key African Union Decisions on gene drive technology from the first APET report

- AU Decisions of 2016: The African Union Assembly through Assembly/AU/Dec.618 (XXVII) "Endorses" the request by the Technical Specialised Committee (STC) on Education, Science and Technology that the NEPAD Agency working with the AUC should advise Member States and RECs on matters of technology prospecting including regulatory and ethical requirements that need to be put in place for the continent to benefit from emerging technologies for economic development and environmental sustainability. Further directs the NEPAD Agency to establish a system for obtaining expert contributions on the matters of technology development, acquisition and deployment for economic development.

- AU Decisions of 2017: The African Union Assembly through the Assembly/AU/Dec.649(XXIX), "Commits" to sustain the gains made in the fight against Malaria and monitor antimalarial drug resistance and insecticide resistance; COMMITS ALSO to invest in the development and regulation of the gene-drive technology as well as other innovations including next generation insecticides for Indoor Residual Spraying and Long Lasting Insecticidal Nets, Rapid Diagnostic Tests and Artemisinin-based Combination Therapy for the elimination of malaria and REQUESTS the Commission, WHO and NEPAD Agency to support these initiatives."

- AU Decisions 2018: The African Union Executive Council through the EX.CL/ Dec.987(XXXII)R "Takes note" of the progress that the African Union High-Level Panel on Emerging Technologies (APET) has made since its inception and its analysis of the first three emerging technologies on Gene Drive for control and elimination of malaria; Drones in the horizon: transforming Africa's agriculture; and Micro-grid: empowering communities and enabling transformation in Africa. "Requests" the African Union and Member States to harness these emerging technologies for development initiatives.
- AU Decisions 2022: the 4th ordinary session of the specialized technical committee on education, science and technology (STF-EST 4) further directs APET to provide support in the establishment of an Africa Integrated Vector Management Platform, and to commence research and publishing of a supplementary report on the Panel's earlier report on gene drive technology.

Figure 3 1: Box C: Key African Union Decisions on gene drive technology from the first APET report

3.2 STATUS OF IMPLEMENTATION OF RECOMMENDATIONS BY AUDA-NEPAD

3.2.1 SCOPE AND APPROACH

Initially, the program took a regional approach, focusing on West Africa, and is currently expanding continentally. AUDA-NEPAD and the West Africa Health Organization (WAHO) collaborate with partners to strengthen the capacity of regulators and relevant stakeholders in Member States and RECs to ensure that countries can explore the potential of existing and new vector control approaches. Interventions include (i) developing appropriate guidelines for the various phases of product development; (ii) conducting capacity strengthening to deepen the understanding of regulators and relevant stakeholders; (iii) sensitising beneficiary communities and government officials; (iv) monitoring and evaluating the impact of interventions; and (v) using evidence from West Africa to advocate for the scale-up of the IVM programme to other regions.

The IVM Programme operationalises the APET recommendations by building the platform, using gene drive as a pathfinder approach among the technologies on the horizon. Due to the unique nature of the technology, the regulatory pathway being targeted forms a breakthrough model for other emerging technologies that need to be harnessed for economic development in future. For instance, Wolbachia-infested mosquitoes which control dengue have been released elsewhere but not yet in Africa. A key component of the platform is that regulators in agriculture, environment, health and other relevant stakeholders are best informed in order for them to make evidence-based decisions for the benefit of saving the African populations from the burden of malaria and vector-borne diseases. There is a need for a balance between ensuring the safety of the environment and human health without being so restrictive as to lose the potential health benefits of the various vector control approaches. This entails strong coordination between health and environmental regulators at national and regional levels.

3.2.2 STAKEHOLDER AND LANDSCAPE MAPPING

The programme is currently working to strengthen the development of an enabling regulatory environment for effective vector control tools in highly endemic African countries. AUDA-NEPAD is collaborating with AU Member States and RECs in Africa to strengthen the regulatory systems for vector control tools through integrated vector control platforms. AUDA-NEPAD's role is enhancing awareness, strengthening regulatory bodies, and building regulatory research capacity relating to vector control technologies across the African Union to ensure adequate capabilities to manage their deployment.

In the case of health applications, the regulation of emerging vector control technologies is a collective responsibility of both environmental and healthcare regulators. As these emerging vector control technologies have potential health benefits, it is important to create awareness among public health delivery system stakeholders. Introducing the technologies to such stakeholder groups facilitates eventual ownership of the technologies and creates awareness as to the pathways that will be followed to ensure the products reach the end-users. This requires building strong coordination between healthcare and environmental regulators at national, regional and continental levels. The stakeholders identified are as follows:

Table 2
Stakeholder engagements of the AUDA-NEPAD IVM Program

Identified sectors	Stakeholders engaged
Regulators	
• 21 National Academies of Sciences, E., & Medicine. (2016). Gene drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values: National Academies Press. • 22 National Academies of Sciences, E., & Medicine. (2016). Gene drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values: National Academies Press.	
Health, Agriculture and Environment	• National Medicines Regulatory Agencies (NMRAs)/ National Health Products Regulatory Agencies • Medicine regulation department • Clinical trials department including facilities inspection units • Product vigilance department • National ethics committees • National biosafety agencies • Environmental regulators • Expert groups (Environmental lawyers, ecologists, socio-economists, Agricultural experts)

National Disease Surveillance and Prevention Units	
National Malaria Programmes/ Neglected Tropical Diseases Programmes/Protection of Human Environment Programmes	• Malaria program leads (Epidemiologists, Entomologists, Laboratory technicians) • National malaria research and capacity strengthening centres - Ministry of Health • Research and development institutions – including academics and others under the Ministry of Health or scientific research or science and technology
Other Key Stakeholders	
African Union	• African Leaders Malaria Alliance (ALMA) • AIDS Watch Africa (AWA) • Pan-African Parliament • Africa Centers for Diseases Control and Prevention (Africa CDC)
United Nations	• World Health Organisation (WHO)
International Conventions	• Meetings of parties serving as conferences of parties (COP-MOP) to the Convention on Biological Diversity • Cartagena Protocol • Nagoya and Kuala Lumpur Protocols • International Union for the Conservation of Nature
Other Partners	• Roll Back Malaria Partnership • Eliminate 8 • Civil Society • Faith-based organisations • Organisation for Economic Community and Development (OECD) • Community Leaders • Media

3.2.3 IMPACT OF AU RECOMMENDATIONS

The Integrated Vector Management (IVM) programme has had a significant impact on African Union (AU) Member States, particularly in strengthening regulatory systems for vector control tools. The programme has supported seven countries, including Burkina Faso, Djibouti, Ghana, Mali, Nigeria, São Tomé and Príncipe, and Uganda. In these countries, the IVM programme has had a significant impact on strengthening regulatory systems for vector control tools in the AU Member States, leading to increased stakeholder engagement, enhanced capacity for risk assessment and decision-making, and greater awareness and understanding of gene drive potentials for malaria control. The programme has also facilitated transboundary discussions on the potential movement of GM mosquitoes and partnerships for gene drive product development, triggering investment in research and development. The impacts of the IVM programme in selected countries in Africa are discussed in Box 3 below.

Box 3: The impacts of the IVM programme in selected countries in Africa

Burkina Faso: The country has made good progress in contained studies of genetically modified (GM) mosquitoes and ecological data collection, thanks to the support of the IVM programme. The programme has facilitated stakeholder engagement both nationally and regionally, increasing the level of information and understanding on gene drive and preparing for the future field release of GM mosquitoes. As a result, the regulators have gained enhanced capacity for risk assessment and decision-making, while the stakeholders have increased their level of information on the potential of gene drive for malaria control.

Uganda: The IVM programme in Uganda has successfully reviewed the application for contained studies with GM mosquitoes, and multi-stakeholder sensitization on gene drive mosquitoes has been carried out. This has created greater awareness of gene drive among various groups of stakeholders, and transboundary discussions on the potential movement of GM mosquitoes have been initiated within the East African Community. The ongoing research activities at UVRI have been successful, and key stakeholders have been informed and sensitized on gene drive potentials and the new developments of the technology. The IVM programme has also facilitated policy dialogue on the potential transboundary movement of GM mosquitoes.

Mali: The IVM programme has supported the successful application review for PCR studies using non-viable GM mosquitoes. The ongoing ecological data collection on selected sites to baseline and stakeholder engagement to share outcomes of phase 1 have been possible due to the support of the programme. The IVM programme has also facilitated the process of finalising proposals for capacity building in the genetic transformation of mosquitoes, based on the changed strategy in Mali. This has led to stakeholder buy-in and public acceptance being secured. Regulators have gained enhanced capacity for risk assessment, and stakeholders have increased their level of information and understanding of the potential of gene drive for malaria control.

Nigeria: The country has officially requested regulatory capacity building on gene drive from the IVM programme, which is a testament to the valued support provided to other countries. The programme has also identified a potential partner for gene drive product development and triggered interest in investment in research and development on gene drives through engagements with member states. The IVM programme continues to facilitate partnership and strategically involve Nigeria fully in the regional consultations, providing support for leadership in tandem with Burkina Faso.

Ghana: The IVM programme has received an official request from Ghana for regulatory capacity building on gene drive. The University of Ghana is leading research studies on A. gambiae ecology, and an insectary has been newly established. The programme has identified a potential partner for gene drive product development and triggered interest in investment in research and development on gene drives. The IVM programme continues to support a greater role for Ghana in the regional consultations on transboundary considerations.

Figure 3 2: Box 3: The impacts of the IVM programme in selected countries in Africa

3.2.4 PROGRESS MADE THROUGH THE AUDA-NEPAD IVM PROGRAM

The AUDA-NEPAD IVM program is an important initiative that seeks to develop regulatory capacity for gene drive technologies aimed at controlling malaria. This program has made significant progress in several areas, including capacity building, stakeholder engagement, and the development of guidelines.

Capacity building on gene drives: One of the most significant innovations of the program is the capacity building and strengthening of regulators for risk assessment, dossier review, and decision-making for gene drives in malaria elimination. This initiative is the first of its kind globally on the African continent, and it serves as a pathfinder for other regions seeking to develop similar programmes. By building regulatory capacity, the program ensures that gene drive technologies are assessed and reviewed using rigorous scientific and ethical standards.

Stakeholder engagements on a transboundary technology: Another key innovation of the program is the engagement of stakeholders at various levels, nationally and regionally. This engagement is crucial for preparing for future field releases of genetically modified mosquitoes and advancing transboundary discussions, data transportability, and mutual recognition. Given that the technology is novel, these stakeholder engagements are also novel, and they ensure that the concerns and interests of different groups are considered in the development and implementation of gene drive technologies.

Voluntary guidelines for gene drives: Finally, the program has developed relevant voluntary guidelines and provided technical and material support to national stakeholders. These guidelines, developed by the West African region, are also novel and serve as a model for other regions seeking to develop similar guidelines. Other regions are now requesting support to replicate these guidelines, which demonstrates the impact and influence of the program.

Overall, the AUDA-NEPAD IVM program is a critical initiative that is making significant strides in developing regulatory capacity for gene drive technologies aimed at controlling malaria. In this regard, the key activities in the pipeline include:

1. Horizon scanning: a. Synthesize information on processes for broad and regular horizon scanning, monitoring, and assessments of the most recent technological developments in genetically based vector control (GBVC) tools. This will involve:
   a) Gathering data from various sources, conducting analyses, and generating comprehensive reports on the latest advancements in GBVC.
   b) Create a dashboard that tracks the usage of gene drives in Africa. The dashboard will provide real-time visualization and analysis of data related to the deployment and impact of gene drives, enabling stakeholders to monitor and evaluate their effectiveness.
   c) (c). Conduct a retrospective analysis of past work on GBVCs in Africa. This analysis will help inform future roadmaps for introducing new GBVC tools in candidate AU Member States.
   By reviewing previous experiences and lessons learned, the analysis will guide the selection of suitable strategies and approaches for successful implementation.

2. High-level transboundary engagements: a. Establish Africa's first continental platform for the regulation of genetically based vector control tools, employing integrated approaches. This platform will serve as a central hub for coordinating and harmonizing regulatory policies and guidelines across African countries. It will facilitate collaboration, information sharing, and decision-making processes to ensure safe and effective deployment of GBVC tools throughout the continent. b. Develop and disseminate voluntary guidelines to support stage 1, 2, and 3 releases of modified mosquitoes in both confined and open environments. These guidelines will provide a framework for conducting risk assessments, ensuring compliance with safety standards, and implementing responsible and transparent practices during the various stages of releasing modified mosquitoes. The guidelines will be designed to enhance public confidence, promote regulatory consistency, and facilitate the adoption of best practices in GBVC.

In conclusion, the use of genetically-based vector control tools, such as gene drives, holds significant potential for reducing the burden of vector-borne diseases in Africa. However, their deployment requires a careful and integrated approach that takes into account the regulatory, social, and ethical implications. The IVM program provides a useful framework for guiding the development and deployment of these tools, with a focus on effective governance, community engagement, and capacity building. By implementing the programme's objectives, AU Member States can ensure that genetically-based vector control tools are deployed in a safe and responsible manner that benefits both public health and the environment.

4

THE INTEGRATED VECTOR MANAGEMENT APPROACH OF AUDA-NEPAD

4.1 APPROACH TO INTEGRATED VECTOR MANAGEMENT

Integrated vector management (IVM) is commonly defined as a rational decision-making process to ensure the optimal use of resources to achieve efficient, cost-effective, and sustainable control of disease vectors. This could involve the use of several vector control methods to address a single disease or multiple diseases (WHO, 2009, 2012, 2019). In the context of the new vector control technologies, especially including those based on genetic modifications, AUDA-NEPAD promotes the integration among various sectors, and disciplines to address the complexity of considerations that are required to ensure full participation of stakeholders, their engagement in making informed decisions, and the acceptability of the final technology product.

Gene drive technology for instance, because of its potential for biased, preferential inheritance and its self-sustaining nature, may present potential challenges that relate, among others, to the prevention of the spread of the modified organisms beyond the intended geographical target areas, as well as how to limit its potential effects on the local non target organisms (WHO, 2019). Therefore, there is a need for effective integration amongst several sectors, notably ethics, environment and biodiversity, public health, and agriculture to ensure that decisions are made timely towards the elimination of target diseases. Thus, AUDA-NEPAD promotes IVM as an integrated platform where stakeholders from various sectors and disciplines, at national, regional, and continental levels can constructively engage and provide the necessary support for making decisions to allow the development and possible deployment of gene drive as a vector control tool, considering the scientific evidence on its efficacy and safety and in clearance with appropriate ethical values.

Recommendation 4.1: Considering that genetic manipulations of living organisms including mosquitos raise questions on the safety of the environment, biodiversity and have ethical considerations, we call on decision makers in the sectors of environment, agriculture, health to cooperate in making informed decision on the development and deployment of emerging genetically-based vector control tools.

4.2 THE NEED FOR HARMONISED APPROACHES AND REGULATION FOR GENE DRIVE

The development and deployment of genetically modified mosquitoes for vector control, involve a key regulatory component on environment and biodiversity which in nature calls for multilateral agreements and harmonization across borders and sectors. The specific potential of the gene drive elements to spread and establish in the environment, as well as the possibility of their misuse and/or for improper experiments, reaffirm the need for harmonizing relevant regulations at all levels. Therefore, AUDA-NEPAD calls researchers and developers to establish networks of scientists and developers with the aim to register their projects and studies, share information and experience, peer-review ongoing developments and field testing. The goal is to promote a culture and practices of self-regulation regarding the gene drive development.

> Recommendation 4.2: Considering the specific potential of the gene drive elements for integrated vector management to spread in the environment and persist in the target species, we call for the harmonization of relevant regulations at all levels, and researchers and developers to establish functional regulatory and institutional frameworks to register their projects, share information, to ensure transparency and self-regulation.

4.3 THE WEST AFRICA-IVM PLATFORM

In 2018, the African Union Development Agency – New Partnership for the Africa Development (AUDA-NEPAD), and the West Africa Health Organization (WAHO) jointly established the West Africa Integrated Vector Management (WA-IVM) platform to enable the region build strong collaboration between the health sector, and with other sectors to implement the integrated vector management strategy in the context of the new vector control technologies based on genetic modification. Considering that malaria is the most important vector-borne disease in the region, the WA-IVM platform has planned to use malaria as a pathfinder disease in developing its integrating interventions. Upon success of the designed model, it is expected that the template will be adapted to improve vector control for other diseases.

Priority interventions under the platform include (i) the development of appropriate guidelines and other technical documents to support the various phases of the gene drive product development; (ii) training to deepen the understanding of the scientific evidence pertinent to the efficacy and safety of the new technology, (iii) engagement with beneficiary communities, government officials and other relevant stakeholders to secure buy-in and social acceptance of the technology; (iv) regular update on progress in R&D along with challenges encountered and lessons learned, (v) monitor the impact of capacity strengthening interventions and (v) advocacy for the scale-up of the IVM programme to other regions and the continent, using evidence from the West Africa experience (AUDA-NEPAD, 2018).

Through the WA-IVM platform, regulators in agriculture, environment, health, and other relevant stakeholders are best informed and can make evidence-based decisions to the public health benefit. Stakeholders engaged in the IVM platform should ensure that there is a balance between the considerations for environmental safety and the public health benefit. It is critical therefore to avoid the establishment of overly restrictive regulations that could cause to lose the potential health benefits expected from the new vector control tools.

> Recommendation 4.3 To ensure effective implementation of the integrated vector management to harness emerging vector control technologies, policy makers should avoid developing overly restrictive regulations that could cause Africa to lose the expected potential health benefits, but rather ensure that there is a reasonable balance between environmental considerations and the public health benefits when developing regulatory policies.

4.4 APPROACH TO IMPLEMENTATION OF THE IVM CONCEPT

To implement the WA-IVM concept, key stakeholder groups in the ECOWAS region were identified, and a governance structure was established.

4.4.1 STAKEHOLDER MAPPING

Several groups of stakeholders were identified to implement IVM for the development of genetically based vector control technologies. These include (i) the health regulators, (ii) the environment and agriculture regulators, (iii) the national disease surveillance and prevention officers and (iv) representatives of various other relevant sectors.

The health regulators group is led by the National Medicines Regulatory Agencies (NMRAs) or National Health Products Regulatory Agencies which usually include several departments or units such as those in charge of Medicine regulation, clinical trials, and Product vigilance, respectively. National Ethics Committees is a critical component considering the growing importance of ethical considerations in decision making on genetically based vector control technologies.

Environment and agriculture regulators group is led by the National Biosafety Agencies established in countries based on the domestication of the Cartagena Protocol on Biosafety which is an international protocol under the Convention on Biological Diversity (CBD) that currently steers the global discussions on organisms modified with gene drive. Other environmental regulators and experts groups including environmental lawyers, ecologists, socio-economists, agricultural experts are represented in the platform.

The National Disease Surveillance and Prevention group is represented by the National Malaria Programme/Neglected Tropical Diseases, with the Malaria Control Programme and the National Malaria Research and Training Centre as the leading sub-groups. Research and development institutions including academics and others under ministries of health or scientific research or science and technology are also involved.

4.4.2 GOVERNANCE STRUCTURE OF WA-IVM

To operationalize the WA-IVM platform, a governance structure was established to respond to the need that vector control should be handled from an inter-sectoral perspective rather than being the single responsibility of the health sector. This is in line with the Global Vector Response's recommendations that Ministries of Health should collaborate with other ministries to efficiently implement a vector control programme.

The governance structure comprises of a steering committee, a secretariat and a number of technical working groups (TWGs). The Steering committee is formed of heads of the national biosafety agencies and the heads of the National Medicines Regulatory Agencies (NMRAs) (Fig. 1). Steering Committee is expected to report to the ECOWAS Council of Ministers of Health, which reports to the ECOWAS Summit of Heads of States and Government (Fig.1).

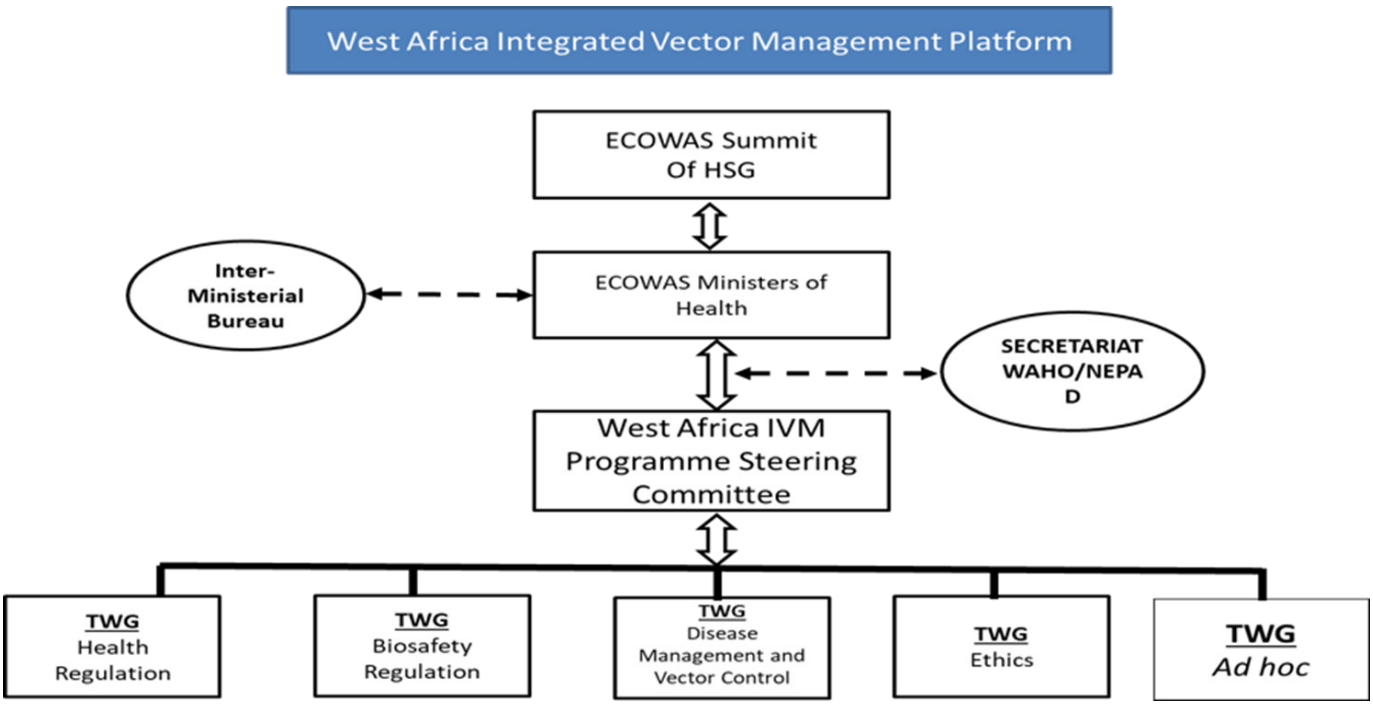


Figure 4 1:Governance structure of WA-IVM

Ultimately, the operationalization of the WA-IVM requires the establishment of a secretariat which is expected to be based at the WAHO, regional health organization, and is supported by AUDA-NEPAD. Technical working groups are composed of the various groups of experts identified through the stakeholders mapping and serve as the technical arm to the steering committee. Effective implementation of IVM on the ground requires the establishment in country, and operationalization of national platforms to provide opportunity to stakeholders to engage locally. It is then expected that lessons learned from national platforms will inform as needed, adjustments at the regional level and to improve other national IVM structures.

Recommendation 4.4: Considering that platforms play a critical role in fostering intersectoral and multi-disciplinary dialogue to achieve effective IVM, ensure buy-in and acceptance of emerging vector control tools, we recommend that resources are mobilized from all relevant sources including research projects and national malaria programmes to operationalize national and regional IVM platforms.

Box 4: Achievements of WA-IVM, Challenges and Lessons

Establishment and operationalization of the governance structure - The Steering Committee of the WA-IVM was inaugurated in September 2018 in Accra with the Minister of Environment, Science and Technology of the Republic of Ghana in the presence of officials from WAHO and the NEPAD Agency. All nominated members from the 15 ECOWAS Member States were in attendance and took an oath of service as members of the steering committee. TWGs were launched in May 2019 in Abidjan with the Minister of Environment of the Republic of Cote d'Ivoire in the presence of officials representing AUDA-NEPAD and WAHO. Six initial thematic working groups were established, namely TWGs for health regulation, biosafety regulation, disease management and vector control, and Ethics. Despite serious disruptions by the COVID-19 pandemic soon after the launch of the operational phase of the IVM program, the West Africa IVM platform has made breakthrough achievements that greatly advanced regulatory policy and R&D on the continent in the GBVC space.

Publication of technical guidelines - With support of AUDA-NEPAD as secretariat, WA-IVM developed and published, for the first time, a set of technical guidelines to support the regulatory capacity strengthening on gene drive in the continent. The publication of those guidelines has contributed to put the continent in a better position to leapfrog in the innovative vector control space, as is recommended in the APET report.

Technical regulatory capacity strengthening - WA-Africa IVM has provided support to the pioneer countries, Burkina Faso, Mali, and Uganda on various aspects, which has contributed to enhance the understanding of the new technology among the key stakeholders, enhance the technical capacities of regulators on risk assessment, risk management, risk communication, and decision-making processes. Tangible outcomes from those interventions translated to the submission of applications for stage 1 and 2, review of dossiers and decision-making in full compliance with international standards.

International engagement - Another major achievement of the WA-IVM platform is the support provided to the African group of negotiators at the international negotiations under the United Nations' Convention on Biological Diversity (CBD). Specifically, at the fourteen and fifteen Conference of Parties held respectively in Egypt and Montreal in 2018 and 2022, WA-IVM provided technical and material support to the delegates to build and strengthen a common position on the need for Africa to explore gene drive technology to accelerate the elimination of malaria on the continent. Such a support greatly contributed to avoid a global moratorium on the gene drive technology.

Challenges and lessons learned - Despite the enthusiasm and commitment demonstrated by stakeholders at national and regional levels, full operationalization of the platforms was challenged with the insufficient availability of financial resources. It is expected that resources are mobilized for IVM from all relevant sources and made available for the regional and national platforms. Research projects and national malaria programmes should consider allocating part of their stakeholder engagement budget to the IVM platforms to ensure regular convenings and all relevant integrating activities.

Figure 4 2: Achievements of WA-IVM, Challenges and Lessons

4.5 SCALING UP TO A CONTINENTAL IVM PLATFORM

Building on the regional West – Africa Integrated Vector Management platform experience and in pursuance of the political decisions and recommendations requesting that the IVM platform is scaled up to the continental level, AUDA-NEPAD is engaged to support the AU Member states and regional economic communities to establish the Africa-Integrated Vector Management Platform (Africa-IVM). Africa-IVM aims to provide a continental platform that is multi-ministerial and multi-discipline, involving at the forefront, ministries of health, environment, agriculture and science & technology, and various expert groups including regulators, entomologists, ethicists, social scientists, as well as major civil society groups.

The goal of the platform is to ensure that Africa can safely harness new and emerging vector control technologies to efficiently address high impact vector-borne diseases such as malaria which constrains the continent socio-economic development. This requires considering a balance between environmental safety and human health so that regulations are scientifically evidence-based to enable to safely harness the potential health benefits of genetically based vector control (GBVC). It is expected that Africa-IVM will assist African Union Member States and Regional economic communities to build regulatory systems that are flexible enough to avoid delays in decisions on innovative vector control technologies once these are proven efficacious, safe and cost-effective by appropriate institutions.

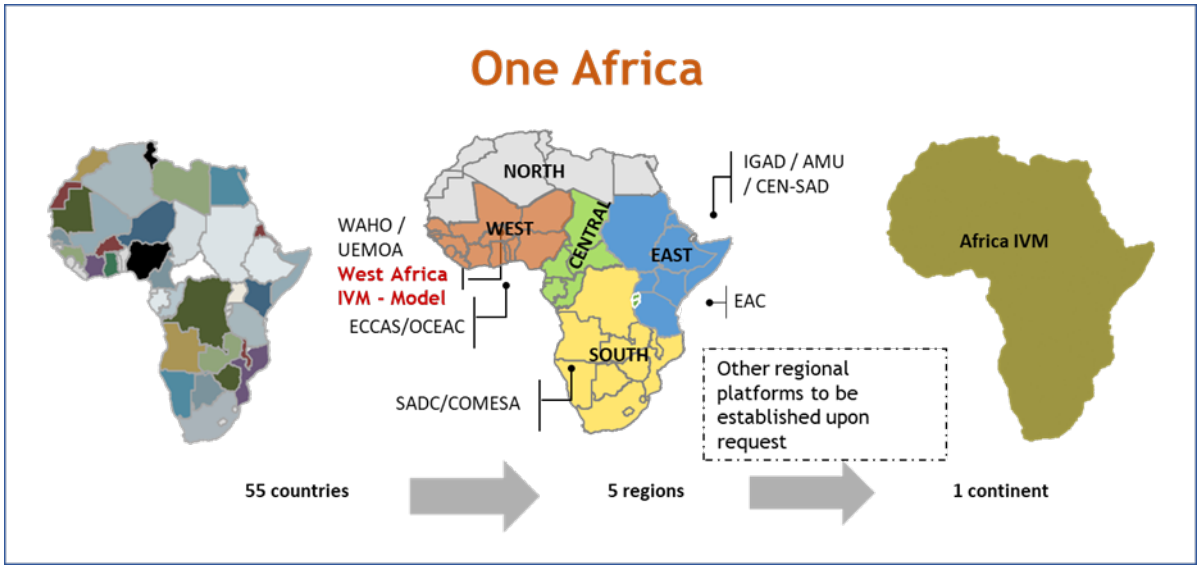


Figure 4 3: Africa IVM Vision

Africa-IVM, through its governance structure, will make recommendations, , and advise African Union, Regional Economic Communities, and the Member states, on the value of GBVC technologies. In essence, the Africa IVM will serve as the "Go to" platform for any GBVC that necessitates an African prior-informed decision. In the first place, Africa-IVM will focus on malaria as the pathfinder disease and on gene drive as the pathfinder technology but may gradually expand to cover other vector-borne diseases where GBVC are relevant. A governance structure is established to implement Africa-IVM, which comprises a steering committee, a secretariat, a panel of experts and several technical working groups (Figure 4 1)

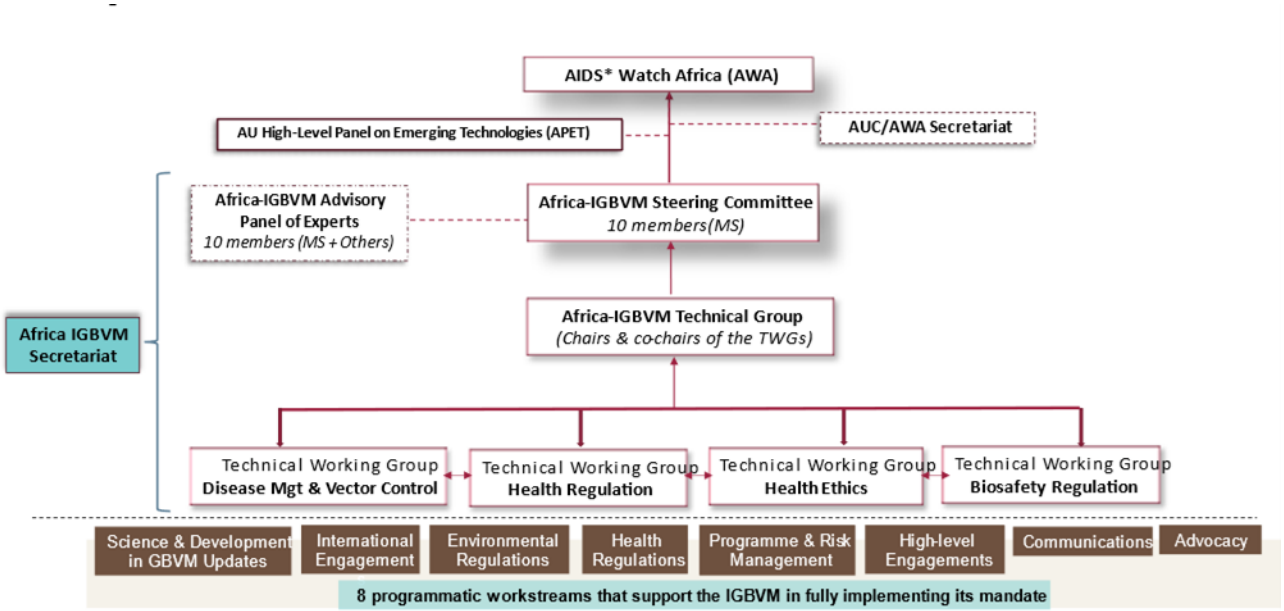


Figure 4 4: Africa IVM Organogram

5

PRODUCT DEVELOPMENT PATHWAYS AND TIMEFRAMES

5.1 BACKGROUND

Advances in research that focuses on genetically modified mosquitoes as a potential public health tool to control vector-borne diseases such as malaria and dengue indicate that the product development pathway has passed the initial steps of the proof of principle and laboratory experimentations. The question now is: when and how to move from the laboratory phase of testing to the field experiments and/or then to the implementation. Gene drive is a category of technology that cuts across disciplines. From the development of the genetic construct and testing in the laboratory to the implementation and deployment in the field, all the pieces of the puzzle need to fall in place. In addition to the scientific and technical components of the technology, other key elements should be engaged for proof of acceptability as well as proof of deliverability and sustainability (WHO 2021). There needs to be systematic communication, coordination and cooperation between the key players to allow the technology to advance.

5.2 THE POSITION OF THE AU HIGH-LEVEL PANEL ON EMERGING TECHNOLOGIES ON PRODUCT DEVELOPMENT PATHWAYS AND TIMEFRAMES

Advancing gene drive technology for mosquito control requires a clear pathway for testing that addresses acceptability, effectiveness, and long-term sustainability. This necessitates open communication, collaboration, and coordination among stakeholders. However, scaling up from controlled lab settings to real-world applications raises questions about proving the technology's long-term efficacy over large geographic areas.

Successful product development hinges on well-defined partnerships led by a consortium. This consortium should actively engage diverse stakeholders across AU Member States. The consortium's structure, goals, and operational processes need to be clearly defined. AUDA-NEPAD's critical role in strengthening regulatory environments and implementing IVM technology necessitates well-defined mechanisms for stakeholder engagement and identification to ensure long-term financial backing.

Securing sustainable funding is paramount for the long-term viability of this project, and successful global mega-projects can serve as valuable models. However, financial resources alone are not sufficient.

Greater recognition of African scientists within international collaborations is crucial, highlighting the importance of fostering intra-African recognition and leadership in product development and commercialisation.

APET advocates for a self-sustaining approach to gene drive technology. The high-level panel emphasises the importance of promoting indigenous knowledge and innovation, ultimately enhancing Africa's position in the research and development of emerging technologies. To achieve this goal, APET prioritises capacity building and infrastructural development, potentially through establishing African-owned companies or foundations dedicated to commercialisation. These entities would serve as a crucial bridge, connecting laboratory-based research and development to gene drive technology's successful innovation and commercialisation.

Recognising its limitations in establishing a for-profit entity, APET proposes collaboration with AUDA-NEPAD and other stakeholders to mobilise funding resources to create commercialisation initiatives for gene drive technology. This would enable the company to lead commercialisation efforts with AU's support for transformative impact.

The proposed commercialisation entities could incorporate a shareholding structure, allowing government representation through designated institutes or universities. This approach would attract private sector investment, crucial for overcoming commercialisation barriers. Additionally, establishing an incubator could shift the focus from purely scientific development to business promotion. This incubator would serve as a launchpad for promising technology concepts, thereby, facilitating product development. Once successful, the incubator could act as a springboard for scaling operations and achieving widespread commercialisation. APET believes that establishing a sustainable technology incubator can serve as a crucial step toward creating a shareholding company (foundation) to adopt the technology, attract funds, and drive the development of gene-drive technology products.

Achieving the targets outlined in the AU's Agenda 2063 and the UN's Sustainable Development Goals (SDGs) 2030, particularly Goal 3 (good health and well-being) and Goal 17 (partnerships for the Goals), within the next six years necessitates a strong focus on collaboration. Partnerships should prioritise promoting the adoption of relevant technologies, especially in emerging economies. This will directly address the significant challenge that malaria poses to development in the African region. Ideally, this initiative should be explicitly introduced in the report's introduction to ensure comprehensive alignment. Furthermore, it should integrate seamlessly with the AU's Agenda 2063 and national development goals across all sectors, creating a unified approach to achieving these critical sustainable objectives.

5.3 GENE DRIVE TESTING PATHWAYS

Conventional malaria control products including vaccines, drugs and insecticides have a predefined pathway of testing and market access strategy. The pathway is straightforward and is subdivided into incremental phases, starting with Phase 1 in the laboratory down to phase 4 with large-scale implementation. Different endpoint parameters are measured along the path and the transition from one phase to the next is conditional to satisfactory outcomes in the previous phase. The malaria community has a long-standing experience of several decades of testing these products and any new product that falls into one of these categories follows the same path with slight adjustments, owing to the nature and specificity of the incoming product.

When it comes to Gene Drive, there is no precedent to lean on though large-scale releases of Wolbachia infected Aedes have been conducted elsewhere to control dengue. It should be noted however that malaria mosquitoes are different and live in different ecological settings, making the technical approaches of generating the drive mechanism completely different, to an extent that the Wolbachia approach is not classified as "gene drive".

The pathway for testing gene drive is still under development and involves dealing with many challenges along the path including technical, legal, socio-economic and ethical framework, risk perception and public acceptance challenges. A series of pathway design exercises have been conducted over the past few years that has led to the publication of a genetically modified mosquitoes testing pathway in 2014 by WHO (WHO, 2014), clearly delineating the pathway into four phases. Phase 1 involves testing the efficacy and safety of the genetic construct under contained laboratory conditions, followed by a phase 2 whereby the interactions of the released mosquitoes with the wild counterpart are observed as well as the behavior of these mosquitoes in a natural setting. This phase requires a small scale, large outdoor or field release under ecological confinement. Phases 3 and 4 gradually increase the level of exposure of humans and the environment to the released mosquitoes. This design has been subsequently revised (Figure below) in 2021 by independent scientists and the WHO to accommodate the gene drive approach. In essence, the revised design underlined the persistence and spread of gene drive mosquitoes in the environment, characteristics that make it difficult to delineate distinct cut offs between Phases 2 through 4 (James et al., 2018). As such it is recommended that appropriate regulatory authorization be obtained prior to the conduct of the phase 2 studies since the guarantee of Phase 2 physical or ecological confinement becomes uncertain because the escape of small numbers of gene drive mosquitoes could lead to the establishment of the modification in a hospitable local mosquito population.

Different research groups involved in the development of the gene drive strategies adopted the precautionary stepwise testing approach whereby the genetic constructs harbouring the drive system will be released in the environment only at the later stage of the product development when efficacy and safety of the non-gene drive version of the same genetic construct have been previously evaluated in small scale field release. Target Malaria has completed its first phase by a small-scale field release of the non-gene drive sterile males in 2019 in Burkina Faso (Frank et al, 2022) and has now embarked on the next step with a non-gene drive male bias construct after obtaining appropriate regulatory authorization. Uganda has recently obtained regulatory approval to import the non-gene drive male bias construct for the contained studies. The gene drive version of the same construct, called Product 1 should be brought into the continent only after a rigorous risk assessment of both the non-gene drive and gene drive versions of the same construct in the laboratory, guided by mathematical modelling of the population dynamics. Continuous entomological and ecological data collection as well as regular epidemiological surveys by the Burkina Faso national health authority is ongoing and an environmental social and health impact assessment (ESHIA) is planned to be conducted at the release site to give more content to regulatory authorities for their decision-making process.

The Transmission Zero group will test the effector that impairs Plasmodium development in mosquitoes separately from the drive function in alignment with the incremental phased approach of the gene drive testing. While there is an urgent need to bring in innovative vector control tools that could significantly reduce/eliminate the malaria burden in Africa, gene drive releases in the field may be effective in years to come provided all the regulatory hurdles within and across borders are overcome and public acceptance is guaranteed.

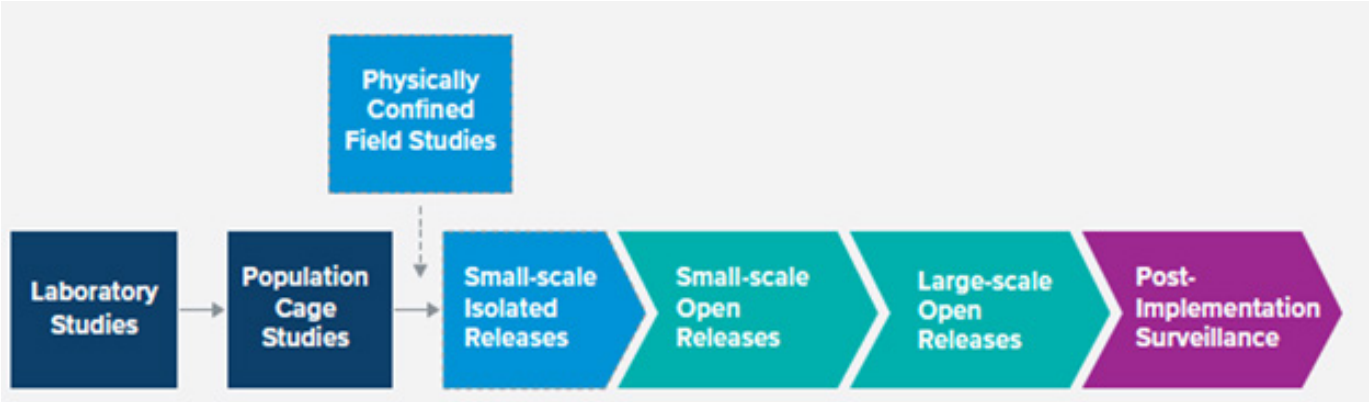


Figure 5 1: Phase testing pathway for genetically modified mosquitoes including low threshold gene drive considerations (WHO, 2021)

5.4 5.2 PARTNERSHIPS IN PRODUCT DEVELOPMENT

On the technical side of the product development, Target Malaria is the most advanced of the different research groups, having released in the field the first transgenic mosquitoes albeit non-gene drive (Frank et al, 2022). In this process, the consortium has engaged a wide range of stakeholders in each of the partner countries where it operates and built local capacity to handle and/or release mosquitoes in the field. Other groups such as Transmission zero and the University of California Irvine Malaria Initiative (UCMI), although adopting a different approach of gene drive could learn from Target Malaria and not reinvent the wheel and adjust approaches to their specific local context. For instance, although Target Malaria is operating in different geographic areas in West and East Africa with different cultures, there are common considerations that cut across geographic ranges and cultures when it comes to public acceptance. Transmission zero and the UCMI groups can learn from this experience to advance their product development.

Another critical element to address in the gene drive ecosystem is the transboundary movement. Although scientists are responsible for gathering evidence of the efficacy and safe use of the technology to inform the decision process, the regulation is an independent process which is out of their control. Africa is one continent but counts 55 countries. It will be difficult for the technology developers if they have to seek individual country authorization to implement gene drive. A robust regulatory and integrated system needs to be built across the continent to allow the technology to advance. AUDA-NEPAD on behalf of the African Union has an important role to play in building the regulatory capacity and facilitating the implementation of the technology on the continent.

Consistent and sustainable funding plans are required to support the technology development. The first gene drive project was funded to Austin Burt in 2005 by the Bill and Melinda Gates Foundation. The project was risky as it involved a lot of technical complexity. Seventeen years later and yet, only a few funders have clear funding schemes to support gene drive. A global effort of resource mobilization as described in Section 9 is needed to support the continuous effort and keep the momentum. Multinational consortia, public-private partnerships, not for-profit corporations, and other models for broadly supported funding may provide good precedents for GMM development (WHO 2021).

Recommendation 5.1: For developers engaged in projects involving the development of gene drive technology for integrated vector management, the key consideration to be made in the product development pathway is to:

1. Case-by-Case Project Evaluation: Assess each project individually to ensure a focused analysis of feasibility, risks, and alignment with strategic goals, allowing for efficient resource allocation and tailored risk management.
2. Step-by-Step Approach: Develop and implement a sequential, milestone-driven strategy that promotes sustainable progress, thereby, allowing each success to build on the last. This method enhances adaptability, supports risk management, and strengthens stakeholder confidence, fostering sustainable development and scalability.
3. Establish a Consortium-led Framework: Form a consortium with clear goals, structure, and operational processes, engaging diverse AU Member States and stakeholders. This framework should promote active communication and collaboration across sectors to facilitate the scaling and testing of gene drive technology from controlled settings to large geographic areas.
4. Strengthen Regulatory and Financial Mechanisms: Collaborate with AUDA-NEPAD to enhance regulatory frameworks, ensure effective stakeholder engagement, and secure sustainable funding for gene drive technology. Drawing on models from successful global mega-projects, establish reliable long-term financial backing and a self-sustaining funding strategy.
5. Promote African-led Commercialisation and Innovation: Develop African-owned companies or foundations for gene drive commercialisation, using shareholding structures to attract government and private sector investment. Establish an incubator focused on transitioning from research to market-ready products, acting as a bridge for African scientists in innovation and leadership roles.
6. Align with AU Agenda 2063 and SDGs: Align the consortium's initiatives with the AU's Agenda 2063 and SDGs (notably Goals 3 and 17) to ensure holistic and sustainable advancement in malaria control, technology adoption, and regional development goals, with an emphasis on partnership and capacity-building.

6

POLICY AND REGULATORY SYSTEMS AND APPROACHES

While characteristics unique to gene drives such as persistence and spreading offer great potential in areas as diverse as the control of disease vectors, invasive species, agricultural pests and predators of endangered species, they complicate decisions related to appropriate containment measures to be employed and pose potential challenge of unintended environmental risks. In this regard, considerable work is in progress at the International, African continental level, regional and national levels to develop enabling policies and regulatory systems to facilitate gene-drive research and development efforts in vector control. The science, guidance, regulatory approaches, and legislative frameworks for gene drive products are all evolving rapidly. Gene drive development and evaluation pathway requires separate regulatory science data sets, risk analysis and submissions for each strain. Consequently, each of the strains undergoes separate regulatory review and decision-making, consistent with the recommended case-by-case approach from guidance documents and established in-country regulatory processes.

In Burkina Faso, Mali, Uganda and Tanzania where gene-drive research is underway, regulatory efforts are geared at collecting the evidence base for gene-drive mosquito strain. The process has necessitated careful considerations and engagement amongst relevant stakeholders in government and standard-setting bodies, as well as the broader global regulatory science community. These activities will inevitably take time and resources to develop, although many will be transferable to other gene drive candidate strains in future.

Gene drives for malaria vector control or other purposes have yet to be assessed by regulators anywhere in the world, so there is no regulatory decision-making experience on which to develop either an analysis plan or risk assessments, or history of safe use on which to draw. Equally, risk communication for gene drives is essential for building trust, and this should be multifaceted and requires transparency, stakeholder engagement, and ethical consideration to ensure that the technology is developed and deployed responsibly.

In this regard, regulatory authorities in partner countries currently involved in gene drive research are continuing to evolve their administrative and regulatory processes as informed by national laws, as well as regional legislative initiatives and international obligations. Both international and regional guidance is also being advanced with new regulatory requirements and developers are making efforts to quickly adapt to new processes

6.2 RISK ASSESSMENT ON GENE DRIVE TECHNOLOGY

Risk assessments associated with gene drive technology play a crucial role in ensuring the safety and efficacy of these innovative biotechnological applications, particularly in the context of controlling vector-borne diseases such as malaria. Gene-drive technology employs genetic engineering to rapidly disseminate desired traits throughout populations, often aiming to reduce the prevalence of disease-carrying organisms. However, the speed at which these traits can spread poses significant ecological risks, necessitating comprehensive assessments that consider a wide range of potential outcomes. Such risk assessments should be thorough, addressing not only the direct impacts of gene-driven organisms but also their broader ecological implications.

A robust risk assessment framework for gene drive technology involves several key components. The first step is to identify potential risks, which may include unintended species knockouts, where the gene drive inadvertently affects non-target species or disrupts existing ecological dynamics. Additionally, there is the risk that the introduction of gene-driven organisms could lead to population increases in other species, either due to competitive advantages or unforeseen interactions within the ecosystem. Following this, an ecological impact analysis is conducted to examine how the introduction of gene-driven organisms might alter local ecosystems, focusing on changes in species interactions, biodiversity, and the overall functioning of ecosystem services.

The findings from these risk assessments should then inform corresponding regulatory measures to ensure the responsible implementation of gene drive technologies. Regulatory frameworks should establish clear guidelines for risk management, defining acceptable risk thresholds and necessary protocols for addressing identified risks, including contingency plans for unforeseen consequences such as the rapid proliferation of non-target species. Furthermore, mandatory environmental monitoring post-release should be implemented to track the ecological impact of gene drive organisms, ensuring ongoing evaluation of both the target organisms and potential non-target species affected by the gene drive.

The efficacy of regulatory measures is inherently linked to the quality of risk assessments conducted before the deployment of gene drive technologies. A comprehensive risk assessment not only identifies potential hazards but also evaluates their likelihood and impact, forming a solid foundation for regulatory development. By aligning regulatory frameworks with thorough risk assessments, authorities can better manage uncertainties, enhance public trust, and mitigate potential negative consequences of gene-drive technologies. This precautionary approach is essential for balancing the benefits of disease control with the need for environmental protection and public health safety, ultimately facilitating responsible innovation in biotechnology.

6.3 INTERNATIONAL FRAMEWORKS FOR GENE DRIVE BIOSAFETY PROTOCOLS

At the global level, several international governance instruments have continued to provide further guidance for the regulation and safe development of modern biotechnology involving gene drive technology. Key among these are the Convention for Biological Diversity (CBD) and its Cartagena Protocol on Biosafety (CPB), the World Health Organisation (WHO), the Organisations for Economic Cooperation and Development (OECD) and the International Union for the Conservation of Nature (IUCN).

6.3.1 THE CONVENTION ON BIOLOGICAL DIVERSITY AND CARTAGENA PROTOCOL ON BIOSAFETY

The Target Malaria project presents significant opportunities for advancing biosafety and gene drive research in Africa, particularly in the context of controlling malaria-transmitting mosquitoes. By establishing rigorous containment protocols and standardised risk assessment procedures, the project has created valuable frameworks that AU Member States can adopt to enhance their regulatory practices. Its focus on inclusive public engagement ensures community awareness and consent, addressing ethical considerations while promoting transparency and trust. Additionally, Target Malaria's collaborative approach fosters cross-border cooperation among nations, setting precedents for regulatory alignment and risk management in biotechnology across the continent.

Moreover, the project contributes to capacity building by training local scientists and regulatory personnel in advanced biotechnological practices, equipping AU Member States with the necessary expertise for effective governance of gene drive applications. Should the project move to open-environment trials, its commitment to extensive post-release environmental monitoring will provide a model for AU Member States to develop robust monitoring frameworks. By leveraging these practices and contributions, Target Malaria not only strengthens national biosafety frameworks but also positions Africa as a leader in the responsible use of biotechnology for public health innovation, particularly in the fight against malaria.

Thus, these are the principal international regulatory instruments for the regulation of living modified organisms. The Cartagena Protocol on Biosafety was originally conceived to deal with transboundary issues as a function of trade in genetically modified agricultural commodities. The implementation of the Protocol is of great importance in the management of risks linked to transboundary movements of "Living Modified Organisms (LMO)", such as gene drive mosquitoes. The national implementation of the provisions of the Cartagena protocol and the use of the Biosafety Clearing House (BCH), represent some of the tools to ensure that risks due to transboundary movement of any LMO can be managed within a regional and international context.

It will also be recalled that the Convention on Biological Diversity (CBD) Secretariat via Decision CBD/CP/MOP/DEC/9/134 established an online forum and Ad hoc Technical Expert Group to support countries on the suitability of current guidance for risk assessment of gene drive organisms. They concluded that the new guidance for risk assessment for engineered gene drives would be necessary.

Accordingly, at the recent meetings of the CBD in Montreal, including the Conference of the Parties (COP) serving as the Meeting of the Parties (MOP), a consensus was reached to have a new process involving the establishment of an Ad hoc Technical Expert Group to discuss the matter further. The outcomes of these deliberations at an international level are likely to influence the regulatory approach of individual countries that are signatories and may necessitate additional regulatory requirements.

The 15th and 16th Meeting of the Conference of the Parties to the Convention on Biological Diversity (CBD) serving as the 10th meeting of the parties to the Cartagena Protocol on Biosafety held in Montreal in 2022, and Cali, Colombia, 2024 also endorsed a Global Biodiversity Framework (GBF) 2020-2050 in which some landmark recommendations (Box 5) were made to guide future gene drive technology. Proceeding with an intentional release across borders of LMOs will require national regulatory approval in each country where the releases are meant to occur. The National Competent Authority for Biosafety in the territory where a gene drive mosquito or its offspring may be expected to disperse will define the relevant regulatory processes.

Box 5: Recent CBD COP/MOP recommendations with implications for gene drive technology

1. Appeal to Parties to enhance innovation and scientific research with emphasis on joint technology development, scientific cooperation and access to technologies as the priority areas of to focus for national and regional engagement.
2. Establishment of a "horizon scanning" process to develop "additional" and voluntary guidelines to support the risk assessment of gene drive organisms with gene drive mosquitoes.
3. Creation of interlinkages between biodiversity and health to facilitate and support the future work on the One Health approach.
4. The Global Action Plan on Health and Biodiversity was given the green light to start developing innovative tools for vector control, and more broadly IAS, in the context of CBD.
5. Recognition of a balanced language for biotechnology embracing both risks and benefits of the gene drive technology.
6. Development of mechanisms for risk assessment of the genetically modified gene drive mosquitoes through an AHTEG process.
7. Enhanced biosafety capacity-building efforts through the development of Training manuals
8. Adoption of Voluntary guidance documents for risk assessment involving gene drive mosquitoes
9. The Global plan of action was given light for synthetic biology developments

Figure 6 1: Box 5: Recent CBD COP/MOP recommendations with implications for gene drive technology

6.3.2 THE WORLD HEALTH ORGANISATION (WHO)

The WHO has also been at the forefront in providing technical guidance to gene drive technologies in the health sector. In 2021, WHO published a "Guidance framework for testing of genetically modified mosquitoes" which highlighted standards processes for developing, testing and regulating gene drive technologies to facilitate decision-making by countries interested in the potential use of GMMs as public health tools for the control of vector-borne diseases. Other guidance documents published by WHO relevant to gene drive research on mosquitoes include the *"WHO Laboratory Biosafety and Biosecurity Manual, 4th Edition, 2020", the "WHO Global Technical Strategy for Malaria 2016-2030", and the "WHO Preparing for certification of malaria elimination, 2nd edition, 2022" as well as the" Global Guidance framework for the responsible use of life sciences 2022".*

6.3.3 THE ORGANIZATION FOR ECONOMIC COOPERATION AND DEVELOPMENT (OECD)

The **OECD** which over the years has developed a track record for producing more than 30 biology consensus documents to promote harmonisation for risk/safety assessment of transgenic organisms, published a consensus document on the biology of *Aedes aegypti* mosquito in 2018. The OECD is now working to finalize another consensus document on the biology of *Anopheles gambiae* complex mosquitoes. These documents undoubtedly serve as key resources for technology developers, risk assessors and regulators to help them make informed decisions related to the potential use of genetically engineered mosquitoes.

6.3.4 THE INTERNATIONAL UNION FOR THE CONSERVATION OF NATURE (IUCN)

The IUCN, in 2019 commissioned an assessment of the state of science and policy around synthetic biology techniques, including gene drives, as they relate to biodiversity. In the ensuing report, IUCN observed that gene drive technology could potentially contribute positively is the saving of endangered species, reviving and restoring extinct species and controlling invasive species.

6.4 CONTINENTAL FRAMEWORKS

The regulatory frameworks and climate for biotechnology in Africa are largely driven by the implementation of the Cartagena Protocol on Biosafety (CPB). Implementation of CPB is therefore the de facto regulatory instrument for all LMOs not just gene drive organisms, in most of Africa, with limited technical or practical experience on which to draw. New laws, regulations and frameworks have been/are being put in place to varying degrees and with varying successes, to facilitate compliance with the requirements of CPB and some level of regional harmonisation for the evaluation of biosafety is currently enacted, but practical experience and implementation is still patchy across the continent

AUDA-NEPAD is working to strengthen the capacity of regulators in the region to assist countries in the review of gene drives and other novel vector control interventions, based on the model of the African Medicines Regulatory Harmonisation (AMRH) to establish and improve standards and requirements related to the regulation of medicines. In 2018, the African Union High-Level Panel on Emerging Technologies (APET) issued a report on Gene Drives for Malaria Control and Elimination in Africa, that recommends a risk-benefit approach and regional harmonisation of policy implementation of gene drive technologies, as well as early engagement with stakeholders.

National and regional authorities in the continent are actively working to facilitate discussion among neighbouring countries and develop regulatory processes and /or requirements for the evaluation of new vector control tools, such as gene drive mosquitoes. National sovereignty will still apply for the regulatory approval of the use of gene drive products, although a harmonized regional approach to data requirements and regulation would be highly desirable, particularly in the context of transboundary movement. For success to be achieved, national vector control programmes and health ministries will also need to be engaged for future deployment and operational use. Regular legal reviews of national legislations relevant for gene-drive vector control tools will also be sought from external providers to keep project information on compliance current.

These efforts have culminated in subsequent AU Summits in which gene drive mosquitoes was identified as a priority technology for malaria elimination by African Union's High-Level Panel on Emerging Technologies (APET). Since then, the AU has made tremendous progress in the development of a roadmap to guide its various organs and member states on how Africa should harness the emerging technologies for economic development and environmental sustainability. These landmarks summits include

The AU Summit of July 2016: Endorsed the request by the Technical Specialized Committee (STC) on Education, Science and Technology that the NEPAD Agency working together with the AU Commission, should advise Member States and the Regional Economic Communities (RECs) on matters of technology prospecting including regulatory and ethical requirements. AUDA NEPAD agency informed the meeting that the high burden of malaria in Africa has prompted Africa's leaders to prioritize the development of innovative tools for malaria prevention and control.

The AU Summit of July 2018: Embraced a report endorsing the development of the gene drive technology as well as "enabling legislation" for their deployment across its member states titled "Gene drives for malaria control and elimination in Africa"

The AU Summit Assembly Decisions /AU/Dec.649 (XXIX) and Executive Council Decision EX. CL/Dec. 987(XXXII): Embraced gene drive technology as a realistic option for malaria control. African leaders recommended that scientists and partners explore the possibility of developing and use innovative tools including Gene Drive Mosquitoes to accelerate malaria elimination and encourage African Ministers responsible for science and technology to harness emerging technologies including gene drive in their development initiatives.

The African Union High-Level Panel on Emerging Technologies (APET) in May 2020 issued a report on Gene Drives for Malaria Control and Elimination in Africa that recommended a risk-benefit approach and regional harmonisation of policy and implementation of gene drive technologies, as well as early engagement with stakeholders, amongst other recommendations. The scope of the APET key recommendations on gene drive technology included enhanced political support, consideration of risk/benefit approaches, harmonization and regional approach; ownership and responsibility; capacity building and early and continuous engagement with stakeholders. APET recommendations have received overwhelming support by African and international donors. Target Malaria will need to engage in discussions between neighbouring countries on risk management to address the potential for harmonisation of regional tools and strategies to manage the potential transboundary movement of gene drive mosquitoes and to explore if acceptable strategies can be developed to the satisfaction of all parties.

6.5 REGIONAL FRAMEWORKS

The Cartagena Protocol on Biosafety (CPB) encourages country parties to enter into bilateral, regional and multilateral agreements and arrangements regarding intentional transboundary movements of living modified organisms, consistent with the objective of the Protocol provided that such agreements and arrangements do not result in a lower level of protection than that provided for by the Protocol.

A key feature of gene drive technology is the potential for trans-boundary movement, which presumably calls for coordination in regulation among neighbouring countries. Therefore, ensuring early engagement and coordination among African leaders, policy makers and relevant stakeholders will be essential in ensuring strengthened capacity for regulation and evidence-based decision-making when gene-drive products are ready to be deployed. To this end, several African regional initiatives on Malaria control and gene drive technology have been unveiled in African regional economic centres as represented by the Economic Community of West African States (ECOWAS), in West Africa, the East African Community (EAC) in Eastern Africa and the Southern Africa Development Cooperation (SADC) in southern Africa.

The Economic Community of West African States (ECOWAS): Almost all countries in the ECOWAS region have developed and adopted Biosafety laws and are now moving towards the provisions of the CBD at a regional scale. Following recommendations from the APET Report on gene drives for the control and elimination of malaria, the countries have worked towards biosafety harmonisation and coordination of national policies, programmes, projects and activities in the sectors of health, science & technology as well as environmental protection, amongst others. A platform known as the "West African Integrated Vector Management Platform (WAIVM) was launched in 2018 as a pilot project to provide a foundation for the regulation of gene drives at regional level and foster collaboration and expertise in controlling vector-borne diseases with malaria as the first priority disease and gene drives as the pathfinder tool. Hosted by the West African Health Organization (WAHO), the platform has developed a set of technical guidelines to guide scientists in undertaking research activities with genetically modified mosquitos and regulators who may be reviewing such activities (Box 6).

ECOWAS is also involved in implementing other WHO initiatives on Malaria including the RBM Partnership to End Malaria has been launched as an inclusive, multi-sectoral response to control, eliminate and ultimately eradicate with a focus on fostering innovations and bringing them to scale.

Box 6: The ECOWAS WA-IVM Guidelines to support gene drive technology testing and development

1. Guidelines for the Use of Genetically Modified Mosquitoes
2. Guidelines for Risk Analysis for the Testing and Deployment of Genetically Modified Mosquitoes
3. Guidelines for Institutional Biosafety Committees (IBCs)
4. Guidelines for Importation, Exportation, Handling, Labelling and storage of Genetically Modified Mosquitoes
5. Guidelines for Containment Facilities for Testing of Genetically Modified Mosquitoes
6. Guidelines for Compliance Monitoring and Inspection of activities involving Genetically Modified Mosquitoes
7. Ethics Guidelines for the Use of Genetically Modified Mosquitoes.

The East African Community (EAC): The EAC has already laid the foundation for gene drive technology through its publication of a harmonized Biosafety Policy Framework for the East African Community (EAC) which was done in collaboration with the African Union in 2016.The EAC is now making deliberate efforts to chart a way forward on the regional legal and regulatory frameworks to guide research on genetically modified mosquitoes to solve the problem of malaria in the East African region. In November 2022, the first ever dialogue for legislators, policy makers, biotechnology/biosafety regulator, health experts and technology developers from the countries of the East African Community was convened in Dar es salaam. The meeting deliberated on the ongoing genetically modified mosquitoes research activities in Uganda and Tanzania and commended the countries for initiatives made so far in the development and testing of the genetically modified mosquitoes. A number of recommendations made at the workshop are summarised in Box 7.

Box 7 : The East Africa Community (EAC) Policy Dialogue Recommendations

1. Need for an enabling transboundary biosafety policy, legal and regulatory issues including intellectual property regimes to allow non-participating countries should also benefit from the technology as well
2. Need for enhanced biosafety policy harmonization in the East African Community region through a common approach for the biosafety and environmental assessment of the genetically modified mosquito before the release.
3. Need for research on safety and efficacy aspects of the technology and a robust stakeholder engagement to build trust and mitigate the negative publicity around GMOs in general.

4. Need for a greater cooperation and collaboration among the biosafety competent authorities, environmental protection agencies and civic organizations is urgently needed to facilitate better awareness raising, communication and decision making.
5. Requested NEPAD Agency to support policy implementation and strengthening of regulatory systems, facilitates the preparation of appropriate guidelines and support the fora for experts and regulators engagements at both national and regional levels

The Southern Africa Development Cooperation (SADC): In the SADC region, apart from Tanzania Ifakara's Research Institute where the gene drive research and development initiatives have gained traction, initiatives in the fight against Malaria in other countries of the region are still using the conventional approach in the fight against Malaria. These initiatives include the:

- Elimination Eight Initiative (E8).
- Southern Africa Roll Back Malaria Network (SARN).
- SADC Regional Roll Back Malaria (RBM) Partnership Programme.
- Windhoek Malaria Declaration.

6.6 NATIONAL FRAMEWORKS

Many African countries have established national biosafety frameworks that align with international guidelines, such as the Cartagena Protocol on Biosafety. The establishment of national biosafety frameworks in Africa has remained vital for maximising the benefits of modern biotechnology while safeguarding public health and environmental integrity. Through prioritising regulatory standards, comprehensive risk management, public engagement, capacity building, regional cooperation, and compliance monitoring, African countries can create a supportive environment for biotechnological innovation.

The last decade has seen many African countries developing their Biosafety frameworks under several initiatives, particularly under the aegis of the UNEP and the Global Environmental Facility (GEF). The development of national laws, regulations, guidelines or policies relating to biotechnology and biosafety continues to be an ongoing process in many African countries with mixed results. The process has been very strong in some countries such as Nigeria, South Africa, Kenya, Burkina Faso, Mali, and Ghana among others which have to operationalise their legislation with confined and contained research project activities.

The national biosafety frameworks of selected AU Member States active in biotechnology—specifically, South Africa, Nigeria, Kenya, Ghana, and Burkina Faso—warrant close examination regarding their containment measures, risk assessment procedures, and public engagement requirements. APET acknowledges that, while progress has been made toward aligning and harmonising these national regulatory frameworks, further efforts are necessary to achieve comprehensive harmonisation across jurisdictions.

6.6.1 SOUTH AFRICA'S LEGISLATIVE FRAMEWORK AND CONTAINMENT MEASURES

Legislative Framework: South Africa possesses one of the most comprehensive biosafety frameworks on the continent, underpinned by the Genetically Modified Organisms (GMO) Act of 1997, along with updated regulations. The Department of Agriculture, Forestry, and Fisheries (DAFF), in conjunction with the Advisory Committee on Genetic Modification, oversees research, import and export, and development of GMOs.

Containment Measures:

a. Stringency: South Africa enforces strict containment protocols, mandating that research involving GMOs or gene drive organisms is conducted within certified facilities, with regular inspections to ensure compliance.
b. Compliance: Laboratories are held to international standards, often in accordance with Cartagena Protocol guidelines, ensuring robust containment to minimise risks associated with accidental release.

Risk Assessment Procedures:

a. Scope: Risk assessments are obligatory across various stages of research, including laboratory trials, field testing, and commercial deployment, covering ecological, health, and socio-economic impacts.
b. Alignment with AU Recommendations: South Africa's risk assessments are generally in line with AUDA-NEPAD guidelines, with a strong emphasis on precautionary principles and rigorous public health safety thresholds.

Public Engagement Requirements:

a. Public Engagement: South Africa mandates public notifications and consultation periods ahead of project approvals; however, community representation remains limited, particularly in rural areas.
b. Alignment Gap: The country's formal mechanisms for public engagement could be improved to align with AU's emphasis on inclusive public participation, particularly among rural and directly impacted communities.

6.6.2 2. NIGERIA'S LEGISLATIVE FRAMEWORKS AND CONTAINMENT MEASURES

Legislative Framework: Nigeria's National Biosafety Management Agency Act (2015) provides a framework for GMO research, administered by the National Biosafety Management Agency (NBMA). The framework is relatively recent, and efforts to strengthen the agency's technical and administrative capacity are ongoing.

Containment Measures:

a. Stringency: The NBMA requires gene drive research to be conducted in high-standard containment facilities; however, containment protocols may lack the specificity and rigour evident in South Africa's approach.
b. Challenges: Resource constraints and limited advanced containment infrastructure hinder regular inspections and enforcement.

Risk Assessment Procedures:

a. Scope: Risk assessments are conducted on a project-by-project basis, although the NBMA's expertise in handling novel biotechnology, such as gene drives, is still under development.
b. Alignment with AU Recommendations: Nigeria's risk assessment procedures are improving but remain less comprehensive than those advised by AUDA-NEPAD, particularly in terms of public health and ecological risk considerations.

Public Engagement Requirements:

a. Public Engagement: Nigeria's approach includes stakeholder consultations and transparency in decision-making processes. Nonetheless, community outreach and civil society engagement could be expanded.
b. Alignment Gap: Nigeria could benefit from more structured public consent protocols, aligning more closely with AU standards for ethical and inclusive engagement.

6.6.3 KENYA'S LEGISLATIVE FRAMEWORKS AND CONTAINMENT MEASURES

Legislative Framework: Kenya's Biosafety Act of 2009 designates the National Biosafety Authority (NBA) as the regulatory body, responsible for GMO research and regulation of gene drives. The NBA has established risk assessment protocols and stakeholder consultations as part of its oversight.

Containment Measures:

a. Stringency: Kenya's approach requires high containment standards for experimental research, though enforcement in rural areas presents challenges.
b. Compliance: Research facilities handling gene drive organisms are expected to meet international containment standards, but limitations in monitoring adherence due to resource constraints remain.

Risk Assessment Procedures:

a. Scope: The NBA undertakes detailed risk assessments, considering both environmental and public health impacts, and is expanding its expertise in assessing gene drive technology.
b. Alignment with AU Recommendations: Kenya's protocols are broadly aligned with AUDA-NEPAD guidelines; however, additional capacity-building in technical assessments would enhance this alignment.

Public Engagement Requirements:

a. Public Engagement: NBA mandates public notifications and comment periods and has recently involved community leaders to address public concerns.
b. Alignment Gap: While Kenya demonstrates active public engagement, the inclusion of ongoing community feedback mechanisms could further align with AU recommendations.

6.6.4 GHANA'S LEGISLATIVE FRAMEWORKS AND CONTAINMENT MEASURES

Legislative Framework: The Biosafety Act of 2011 serves as Ghana's primary biosafety framework, administered by the National Biosafety Authority. Ghana is working to enhance its regulatory capacity for gene drive technologies and adheres to precautionary principles within its guidelines.

Containment Measures:

a. Stringency: Containment measures for gene drive research are required; however, Ghana's biosafety infrastructure is still in development.
b. Challenges: Resource constraints and limited infrastructure, particularly outside of major urban areas, present containment challenges.

Risk Assessment Procedures:

a. Scope: Ghana conducts risk assessments with a primary focus on ecological risks and an increasing emphasis on public health implications.
b. Alignment with AU Recommendations: Ghana aligns with AUDA-NEPAD's precautionary principles; however, expanding risk assessments to include socio-economic factors could achieve closer alignment.

Public Engagement Requirements:

a. Public Engagement: Ghana seeks public input in regulatory decisions; however, its engagement process is less formalised than in some other countries.
b. Alignment Gap: Establishing formal community consultation procedures, particularly for gene drive research, would better align with AU standards.

6.6.5 BURKINA FASO'S LEGISLATIVE FRAMEWORKS AND CONTAINMENT MEASURES

Legislative Framework: The Biosafety Law of 2006 governs GMO research in Burkina Faso, including gene drive studies under initiatives like the Target Malaria project. The National Biosafety Agency collaborates with regional and international bodies to build technical capacity.

Containment Measures:

a. Stringency: Burkina Faso mandates containment measures for gene drive research, although biosafety infrastructure remains limited, particularly in rural regions.
b. Compliance: Partnerships with international bodies support the implementation of containment protocols, although regular inspection is challenging due to limited resources.

Risk Assessment Procedures:

a. Scope: Risk assessments in Burkina Faso focus on environmental and public health impacts, supported by collaborations with organisations like Target Malaria.
b. Alignment with AU Recommendations: Burkina Faso aligns with AUDA-NEPAD's recommendations; however, it requires further capacity to perform independent, rigorous assessments.

Public Engagement Requirements:

a. Public Engagement: Community engagement is prioritised, especially where Target Malaria operates, though much of this engagement is externally driven.
b. Alignment Gap: More locally led and sustainable community engagement mechanisms could enhance alignment with AU standards, ensuring enduring public involvement.

Several key alignment gaps have been identified. The following comparative analysis highlights the primary areas of misalignment, summarised as follows:

1. Ensuring compliance with containment measures remains challenging. This is because most AU Member States face infrastructure and resource constraints in implementing effective containment, except South Africa. AU-supported capacity-building initiatives could bridge these gaps.

2. Risk assessment procedures exhibit variability in scope. The scope of risk assessments varies across AU Member States, with some prioritising ecological risks over socio-economic and public health impacts. Aligning risk assessment protocols with AUDA-NEPAD's comprehensive criteria would improve consistency.

3. Public engagement processes show variability in inclusivity. Currently, the public engagement mechanisms tend to be formal and may not reach rural communities effectively. Developing AU guidelines for community consent, particularly in rural areas, could improve alignment with continental standards.

APET observes that to address these gaps, AUDA-NEPAD could support investments in infrastructure, capacity-building, and the development of standardised AU-wide guidelines for public engagement and containment. These efforts would enhance the harmonisation of national biosafety frameworks across Africa, supporting the safe and responsible use of advanced biotechnology. Thus, AU Member States are encouraged to enhance mechanisms for comprehensive risk assessment and post-approval monitoring to ensure biotechnological products consistently meet safety standards throughout their lifecycle. Strengthening institutional capacities is essential for robust biosafety governance. This includes promoting effective risk communication, raising awareness, and engaging with stakeholders to build trust and foster community acceptance of biotechnological innovations.

Recommendation 6.1:

For developers engaged in projects involving the development of gene drive technology for integrated vector management, the key consideration to be made in the product development pathway is to:

1. Early Engagement with National Authorities: Gene drive developers should engage the national Competent Authority for Biosafety early on to ensure alignment with local legislative requirements, establishing clear communication channels for guidance and compliance.
2. Phased Compliance Approach: Developers should follow a stepwise regulatory process, submitting detailed documentation and approvals at each research phase to facilitate comprehensive biosafety assessments and align with national standards.
3. Transparent Public Engagement: Developers should actively build public trust by implementing community engagement initiatives, providing clear information, and involving local stakeholders to address concerns and ensure community awareness and support.
4. Comparative Analysis of National Frameworks: Identify discrepancies and align policies across key African nations.
5. Infrastructure and Capacity Building: A structured roadmap should be developed to strengthen national laboratory facilities and provide comprehensive training for regulators. This includes biosafety lab upgrades, monitoring tools, and skills development for regulatory personnel, ensuring they can effectively oversee gene drive technologies.
6. Regional Cross-Border Protocols: To address the movement of gene-drive organisms across national borders, formalized guidelines should be created. These protocols would outline notification processes, joint risk assessments, and mutual recognition agreements between countries, ensuring a coordinated approach to managing transboundary biosafety issues.
7. Stakeholder and Ethical Frameworks: Establish regional committees dedicated to ethical and inclusive stakeholder engagement. These committees would regularly consult with diverse groups—including indigenous communities, environmental advocates, and health experts—to gather input and foster transparency around gene drive projects.
8. Target Malaria as a Case Study: Target Malaria's practices should be examined as a model for biosafety. Key areas such as containment protocols, environmental impact assessments, and community engagement can provide valuable insights for other African countries looking to establish or improve gene drive frameworks.
9. Post-Release Environmental Monitoring: Implement mandatory guidelines for monitoring gene drive organisms after their release. Continuous ecological and health impact assessments will allow for adaptive management, adjusting policies based on real-world data and mitigating any unforeseen impacts.
10. Continental Biosafety Fund: Establish a dedicated fund to support biosafety activities across Africa, providing sustainable financing for lab infrastructure, personnel training, and long-term monitoring. The fund could attract international donor support to alleviate the financial burden on national governments.

11. Technical Harmonisation Taskforce: Form a taskforce to standardize biosafety protocols across African regions, ensuring alignment with the AU's continental vision. This taskforce would focus on harmonizing guidelines for risk assessment, containment measures, and compliance to facilitate cohesive and consistent biosafety practices continent-wide.
12. Enhancement of Risk Assessment: AU Member States should enhance mechanisms for comprehensive risk assessment and post-approval monitoring of biotechnological products to ensure these innovations consistently meet safety standards throughout their lifecycle.
13. Capacity of Institutional Capacities: Strengthening institutional capacities is crucial for effective biosafety governance. This includes promoting risk communication, raising awareness, and engaging stakeholders to build trust and foster community acceptance of biotechnological advancements.

6.7 INTELLECTUAL PROPERTY RIGHTS

Recent advances in modern biotechnology have exacerbated the need for a clear legal and public policy framework for biotechnological deliverables, particularly under the patent system. Patents represent the main type of intellectual property where their ownership confers the right to exclude others from benefitting from the tangible products of a proprietary subject matter.

For that matter, intellectual property issues for gene drive products should be handled in the context of their underlying legal requirements. The implications of other factors, such as international competition, research funding, and gene ownership, are also considered. The most advanced laboratories currently working on a gene drive for malaria vector control will implement partnerships with the Bill and Melinda Gates Foundation's Global access plan for intellectual property encouraging flexibility and low resource considerations for technology adoption. Nevertheless, institutions working on gene drive still need to address these challenges locally, while creating an enabling environment for the technology development to thrive. Projects should ensure that Intellectual property becomes a reality concerning sharing knowledge, ensuring access and responsible use as highlighted by the example set by the Target Malaria project Box 8.

Box 8 : Intellectual Property Rights Commitments by Target Malaria Project

Sharing Knowledge: Target Malaria has committed itself to regularly publish their findings in peer-reviewed journals and present at conferences and other expert gatherings. The publishing of its findings serves two purposes: the most direct is to share knowledge, contribute to the respective fields of research and allow others to use that knowledge to advance further. The second purpose is to establish the authors as the "inventors" or source of innovation in the public domain. Original findings published in the public domain are classified as "prior art" and therefore publishing builds a public record of innovation. This is important if someone else then seeks to obtain a patent on something the project considers to be one of its innovations. National and international intellectual property offices will look to publication records to establish whether the applicant was indeed the first to establish that novel finding. If someone else has published before them, their claim would not be deemed "novel". In addition, Target Malaria publications are under an open access agreement, which means that readers without a subscription to the journal can also read the publications.

Ensuring access to the technology: All Target Malaria collaborators are required to sign an agreement when joining the project specifying that any intellectual property derived from working on the project will remain available for use by the project in the pursuit of vector control tools for malaria. This will be in the form of a transferable, irrevocable, perpetual, non-exclusive, royalty-free license securing the use of any resulting IP for the Developing World for vector control for malaria. It also ensures that potential users of the technology, i.e. governments of malaria-affected countries, will not have to bear the cost of the research and development phase of any intellectual property should they want to use the technology.

Ensuring responsible use: Target Malaria has committed itself to ensure the technology being developed is used responsibly for its intended purpose. The project is committed to granting free licences to use the technology which is an important means for the technology developers to keep track of who is using the tools and to ensure it provides updates and support to those users and so maintain good stewardship of its technology. If a researcher is granted a patent or other form of intellectual property protection for an innovation that is necessary to Target Malaria's technology, and which was developed using funding from Target Malaria, free access and use of that component will be guaranteed by the collaborator agreement. This will holds regardless of where the researcher is based and regardless of whether the researcher is still at the collaborating institution. This ensures the viability of the technology and that Target Malaria's commitments can be fulfilled, even if researchers move on to other projects

Recommendation 6.2: Gene drive technology developers need to gather and leverage knowledge and skills from researchers in institutions around the world. Sharing that knowledge, ensuring fair access to the resulting technology and its responsible use should be mainstreamed in gene drive projects. This commitment should not only be limited to genetic technology but should also extends throughout the research process, so that all knowledge gained may contribute to the broader fields of vector control and genetics research.

6.8 STAKEHOLDER ENGAGEMENT

Gene drive technology for malaria elimination envisions to address a public health challenge with outcome in the environment. As such, it falls under several international oversight governance frameworks that either take into consideration its genetic modification specificity from a biosafety perspective (as is the case with the Cartagena Protocol and the UNECE Convention on Environmental Impact Assessment in a Transboundary Context, or its potential health impact (as is the case with WHO oversight); or the public right to information and involvement in the research process and the deployment of the technology (as espoused by the Convention on Biological Diversity, African Model Law on Biosafety, ECOWAS Biosafety regulation and AARHUS Convention).

Stakeholder engagement which broadly involves dialogue and collaboration between scientists and potential beneficiaries is necessary if science is to play a role a meaningful role in improving human welfare. It is critical for an innovative technology like gene drive which elicits questions from stakeholders with or without scientific background making it a mandatory requirement for gene drive development pathway to ensure the ownership of the technology by Africans.

Stakeholder engagement principles: Stakeholder engagement for gene drive technology faces a set of challenges – depending on whether it addresses area-wide vector control interventions, or some other interventions. These challenges include but are not limited to the identification of stakeholders, ensuring that the conversations and debates are brought closer to those who could benefit from the technology, finding the right balance between engaging proactively and not overpromising while the technology is still being developed, ensuring that decisions and discussions are informed, regardless of the complexity of the technology and maintaining an informed discussion on both the risks and the benefits.

Engagement for gene drive is founded on two-ways dialogue with relevant communities, stakeholders and the public (NASEM report) and should be started at the early stage of the research. The engagement is envisaged as an iterative process that adapts and evolves based on the context and values of the stakeholders, as well as new guidance and recommendations, and in turn can nourish the research process (Pare et al 2021; 2022). The literature on engagement for gene drive promotes the engagement through two perspectives: the *'utilitarian perspective'*, is where Interventions seek to involve communities in order to improve the effectiveness of the intervention (ref), or the *'social justice perspective'*, where "community members are empowered to determine for themselves the priorities and ways in which they want service resources to be deployed. The productive engagement of gene drive for malaria elimination should therefore reconcile the two perspectives by recognizing the need to empower potential beneficiaries and stakeholders to co- develop the approach, while recognizing that the engagement is also a way to improve the intervention and to build a dialogue to increase acceptance of the technology. The engagement should navigate between international guidance and the context study site meaning including national regulation, local priorities and governance landscape.

Prioritization of stakeholders: The stakeholder engagement strategy should be inclusive but should prioritize groups directly affected by research activities, including communities living in the site where field entomological studies and potential releases will be taking place. Beyond these affected communities, stakeholders not directly affected by the research activities should be engaged to ensure that their knowledge and perspectives are taken into consideration in the development of the technology and that their concerns are adequately addressed. Additionally, having publicly accessible communication channels and information will help foster a sense of transparency and build legitimacy for the wider public that may not be directly engaged.

Community consultation: The affected community should be consulted for the implementation of the research process. The model of consultation should be co-defined with the affected community and centred to this affected community by identifying the appropriate legitimate representatives who can express the decision of the community regarding proposed research activities.

Key operational challenges policy and regulatory for gene drive technologies are underpinned by three key elements:

1. The use of the problem formulation approach as a systematic, transparent, robust tool in risk assessment and study planning for the gene drive release, thereby enhancing risk communication and maximizing data portability.
2. The use of environmental impact assessments (EIA) to examine both risks and benefits in environmental, socio-economic and health contexts. These legally required instruments have a strong element of stakeholder engagement and communication of risk-benefit in the regulatory process. The strategic value of a programmatic strategic environmental assessment (SEA) to stimulate a permissive trans-national policy environment on the use of gene drive for vector control. This regulatory element also acts to de-risk the potential for trans-boundary movement liability on the ongoing projects and demonstrates due diligence based on high level pan-African engagement and consultation in policy decisions.

3. The centralized support for African project partners in managing regulatory consistency and compliance in a proactive manner to provide license to operate for the Project.
    - Despite this, there has been a lack of political commitment to implement the requirements of the Protocol through the development of national legislation.
    - Fragmented IP regulations at the regional level
    - Low funding and prioritization
    - Inadequate human capital development for the IP value chain
    - Inadequate utilization of the IP system
    - Lack of political will to elevate the status of IP as a key development priority and pillar.
    - Limited financial support for IP administration and enforcement.
    - Weak enforcement of IP legislation and associated high levels of counterfeiting and piracy.
    - Prohibitive cost of IP rights protection for inventors/innovators and creators.
    - Poor linkage and synergy between IP administration legal and licensing departments

6.9 POLICY RECOMMENDATIONS

The regulatory approach for gene drive is currently building on the incremental development of scientific knowledge, operational awareness and capacity building with a wide group of stakeholders such as scientists, regulators, policy makers and the communities concerned, based on a body of credible evidence generated through the phased developmental pathway and increasing knowledge of gene drives and their roles in malaria vector control. Consequently, the policy and regulatory environment will continue to be dynamic and constantly evolve when:

- Close interactions are fostered amongst relevant government ministries, departments and agencies, including the finance, Health, Environmental and Biosafety regulatory sectors and their legal frameworks. There will be high hurdles and burden of proof for the first in class products, especially in a pre-sensitized climate influenced by years of advocacy by special interest groups attempting to inoculate the public and policy makers with uncertainty over the safety of other genetically engineered/modified products in the environment.

- There will be a need for a horizon scanning for new developments in the area, and gene drive developers actively will need to involve themselves in policy, standard setting and techno-regulatory discussions in order to ensure project ideas are put forth in appropriate fora, and they have sight of evolving requirements.

- It is therefore incumbent upon the gene drive developers to present a highly credible evidence base, defensible to the global scientific and risk assessment community, serving to minimize levels of uncertainty in accordance with the tenets of the precautionary approach. In this regard, gene drive projects should be able to demonstrate an investigational product that maybe acceptable to decision makers and the community in the African context following appropriate review.

- There will also be a need for gene drive technology developers to commission a Strategic Environmental Impact Assessment for use of a gene drive population suppression in with a pan-African scope as well as prepare an environmental risk assessment using a problem formulation approach incorporating other risk assessment tools such as quantitative assessments to stimulate discussion on a permissive trans-national policy environment on the use of gene drive for malaria vector control.

- Techno-regulatory dialogue with international capacity building organizations and influencers will be essential to ensure that the latest thinking on the regulation of gene drive mosquitoes is incorporated into gene drive developers approach as well as keeping policy makers informed of progress in defining and generating the evidence base to support the release of the gene drive mosquitoes.

7

RISK AND BENEFIT ANALYSIS

The development and use of gene-drives, like other genetic technologies, is regulated by countries according to their national laws and governance structures. Such regulations are founded on legal frameworks that require specific information to be provided on the biology of the organism as well as the effect on human health, animal health and the environment where it will be released.

Appropriate risk analysis, comprising of risk assessment, management and communication, is an important basis for policy decision under these frameworks. While designing risk assessment and management measures however, care should be taken to ensure that they take into cognizance the implementing nation's health, environment and biodiversity protection goals as well as any community concerns. Furthermore, risk communication should employ key messages that ensure an enhanced understanding of stakeholders and encourage their inputs on identified risks and how they can be managed.

Since no GD GMM application for IVM has been submitted for regulatory approval in any jurisdiction globally, regulatory experience in terms of identification of potential hazards or risks, challenges for risk assessment as well as environmental monitoring are theoretical at best. Notwithstanding however, relevant experience gained from the deliberate releases of other GMOs, and existing risk assessment framework for genetically modified mosquitoes (GMMs) that do not contain engineered gene drives can serve as a foundation for risk analysis of GDMMs. It should be noted however, that while hazards associated with GD GMMs are expected to be similar to those of GMMs, the Risk Assessment should take into account the possibility of higher levels of environmental exposure due to persistence and spread.

Some characteristics of GD GMMs are novel when compared with naturally occurring gene drives, GMMs that do not contain engineered gene drives and other classical biological controls. These include the preferential inheritance of a transgenic construct, the intended spatial and temporal scale of spread of the genetic modification(s) of interest, and population modification strategies. An assessment on whether these novel characteristics present potential novel hazards, and thus may contribute to potential risks in some GDMMs, should be conducted on a case by-case basis as part of a specific problem formulation. For example, the potential persistence and sustained spread of some GD GMMs may result in the eventual spread of GDMMs across national borders necessitating considerations as to whether risk assessment be framed only by the specific protection goals recognised by national entities intending to conduct the deliberate release or address transboundary areas were GD GMMs may potentially spread.

The risk-benefit analysis of gene drives underscores their promise as transformative tools for addressing critical global health challenges. However, the inherent risks call for careful examination and the establishment of comprehensive regulatory frameworks. Policy guidance should prioritize rigorous risk assessments, robust public engagement, ethical reflection, and international cooperation to ensure that the use of gene drives remains safe, responsible, and reflective of societal values. Striking a balance between innovation and caution is essential for leveraging the potential of gene drives while managing associated risks effectively.

Box 9: Risk and Benefit Analsis Recommendations

Enhance Biosafety Research: Increase research focused on biosafety to deepen our understanding of ecological interactions and biodiversity implications of gene drives, promoting safe and environmentally responsible applications.

Strengthen Regional Collaboration: Facilitate regional dialogues on gene drive issues to encourage cooperative approaches in addressing the complex challenges related to gene drive technology.

Expand Capacity Building for Risk Assessment: Invest in capacity building, including sub-regional workshops, to improve skills in risk assessment and develop effective, context-sensitive responses to gene drive-related risks.

8

GENE DRIVE RESEARCH & DEVELOPMENT UPDATES

Gene drive Research and Development is currently under way in Africa with a handful of countries, such as Burkina Faso, Mali, Tanzania, Uganda, Sao Tome and Principe among others, having project teams involved in various technology research & development partnerships. Ghana is also involved in partnerships conducting supporting research to facilitate the deployment when ready. During the past several years, a number of critical technology development milestones have been attained. Key highlights include i) identification of some candidate target mosquito genes that could be modified to curb malaria transmission, and ii) success with gene drive demonstrative laboratory proof of principle experiments that have confirmed key preliminary research assumptions including their ability to suppress or make mosquito cage populations resistant to malaria parasite infection.

On-going initiatives in gene drive are mostly now focused on strengthening technical and infrastructural research capacity and bridging scientific knowledge gaps to better support further technology refinements, acquisition of operational experience handling genetically modified organisms, and readiness for future product evaluation. However several challenges with potential to affect product delivery timelines still remain, the main being limited funding prospects (diverse and long-term sources will be required) and establishment of robust regulatory frameworks to govern the development, testing and future uptake of this novel technology. Below is a brief account on the state of play of gene drive development in Africa, underlying challenges, and some recommendations on what could be done to better facilitate continued advancement of this important technology.

8.1 PAST ACHIEVEMENTS

To date, there have been considerable research advances in the development of genetically engineered mosquitoes including gene drive (Gantz et al, 2015; Hammond et al, 2016; Qsim et al, 2017; Kyrou et al 2018, Simoni et al, 2020; Adolfi et al, 2020; Carballar-Lejarazú et al, 2020; Chen et al, 2021) for controlling diseases such as malaria and dengue. Gene drive will be harnessed to enhance the spread of desired engineered traits in the control of malaria transmitting mosquito populations. The most advanced research initiatives are envisaging the application of genetic modification for malaria vector control via one of two control strategies- either population suppression (modifying in order to reduce the reproductive capacity of vector populations) or population replacement (modifying to introduce anti-parasite resistance in the wild mosquito populations). If successful either can contribute to the curbing of malaria transmission.

Presently, there is no gene drive product ready for deployment as the research in Africa is still in the early to intermediate stages of the development pathway with leading efforts mostly focused on either facility upgrades, or the development of genetically modified but non-driving mosquito strains for proof of principle and capacity building applications. In addition there are some on-going efforts looking into specific research questions where knowledge gaps still remain. In general the research is promising and findings from the on-going phases will further inform and refine the development and final deployment of gene drive versions. These advances have mostly focused on *Anopheles gambiae,* one of the most dangerous and wide-spread malaria vectors in Africa.

8.2 PRESENT ACHIEVEMENTS

In the last five years considerable advances have been made in the field of gene drive research on the major malaria vector, the Anopheles gambiae complex. After the first generations including high threshold drives, the second generation of low-threshold drive are currently under expansion. To date we could classify these into full gene drive (fGDs) and split gene drive (sGDs). Full gene drives (fGDs) systems have both the Cas9 and the guide RNA components in a single linked package. In contrast, in split drives (sGDs) systems the Cas9 and guide RNA components are separate and are inserted at different sites in the genome. sGDs are considered to offer possibilities to control and test the components carried by each of the elements separately or under conditions where they gradually amplify the frequency of the gRNA component. Researchers design the two elements to eventually reconnect in order to deliver the effects of a full gene drive (Terradas et al, 2021). All these fall under the two big umbrellas of population suppression and replacement. Population suppression includes but is not limited to approaches such as female sterility (e.g. double-sex drive - dsx) X-shredder (male bias), a composite of the former two (dsx-Shredder drive) (See in Ethan Bier, 2022). Population modification includes but is not limited to fitness-neutral modification drive, a clean drive.

In the effort to develop the gene drive approaches to spread genetic traits that will curb disease transmission, it is, also, necessary to explore possibilities for countering or neutralizing the drive in case the outcome do not go as planned. Recent studies have shown the possibility of having drive-neutralizing systems that either inactivate or delete and replace a gene drive (Xu et al, 2020, also see Ethan Bier, 2022).

8.3 CHALLENGES IN THE DEVELOPMENT OF GENE DRIVES

8.3.1 KNOWLEDGE GAPS

CRISPR/Cas9-based gene drive, which causes preferential inheritance of specific genetic elements, allowing them to spread through a population (Burt, 2003; Esvelt et al., 2014), has raised the prospects that malaria could be effectively controlled in Africa. Molecular biologists around the world have successfully developed and tested gene drive constructs in laboratories in the Northern hemisphere. However we do not yet have a solid understanding of how these genetic constructs will behave in the complex ecological systems in malaria endemic countries across Africa.

There are definitely knowledge gaps to address that are relevant to the safe and effective use of gene drives in the natural environment. Specifically, due to the reduced fitness of laboratory bred mosquitoes and the complex pattern of mosquito migration and mating, there is some apprehension that introduced genetic elements in the environment may not spread as expected (Dilani et al, 2022; Boëte C, Agusto FB, and Reeves RG, 2014; Zana et al, 2021). Large-scale genomic sequencing of An. gambiae complex mosquitoes across Africa (Miles et al. in 2017), (Anopheles gambiae 1000 Genomes, 2017) has recently reported relatively unrestricted gene flow between populations across countries. On the other hand , results also indicated strong isolation by distance among An. coluzzii populations, suggesting a lower range of dispersal in contradiction with mosquito long distance migration (Anopheles gambiae 1000 Genomes, 2020). While significant progress on our understanding of gene flow between and within An. gambiae populations have been made over the last years, sampling at different locations within countries is needed to amplify the 1000 Genome project database and give an in-depth understanding of the phenomenon.

Furthermore, the evolutionary processes similar to those that have led to selection for resistance to insecticides are likely to frustrate gene drive approaches (Champer et al, 2017). The most obvious source of failure is target site resistance, which can evolve due to mutations during the non-homologous end-joining repair or due to pre-existing mutations in the population. The former could be studied in the laboratory by the technology developers, but the latter can only be studied in the field with natural populations. Control strategies will need to anticipate and foil these adaptive responses. Potential research questions to consider, but not limited to, are:

- How will genetically modified mosquitoes compete for mating?
- How will transgenes spread in the complex genetic system of An. gambiae s.l.?
- What is the potential impact of gene drive on local ecosystems?
- Which sampling framework and tools are fit to track the spread of gene drive?
- How to mitigate the unintended effects of the gene drive release in the field?

As scientists are developing these genetic constructs and finding ways to test them in the field, risks identification and management should not be overlooked. It is thus imperative for safety and regulatory studies to be conducted to the best extent possible towards filling the gaps in knowledge for effective deployment. As a result several considerations including the following should be factored:

i. Systematic assessment of the potential for the technology to cause harm to humans, animals or the environment in general;
ii. Compliance to national regulations and known best practices including carrying out independent impact assessments and outlining potential mitigation measures;
iii. External expert advice and independent risk assessment should be sought in readiness of not to progress any further if evidence for potential harm is found;
iv. A step-wise approach should be adopted to ensure internationally recommended best practice for gene drive research;
v. Explore possibilities for countering or neutralizing the drive in case the outcome is undesirable. Recent studies have shown the possibility of having drive-neutralizing systems that either inactivate, or delete and replace a gene drive (Xu et al, 2020, also see Ethan Bier, 2022). [1]

8.3.2 HUMAN CAPITAL AND INSTITUTIONAL DEVELOPMENT

It is necessary that capacities are built in African institutions to allow effective participation of African scientists, regulators and other professionals in the development, use, and monitoring of these technologies. Enhanced African R&D capacity will reduce over-dependence on a small number of off-continent-based technology developers, while also facilitating innovation continuity for future sustainability. In addition, either home-grown or African-led scientific discovery and technology development project initiatives will enhance the uptake and ownership of these technologies in areas where they are needed the most. Some capacity building initiatives are laying the foundation- For example, Some technology developers (Target Malaria, UCMI) , the Pan-African Mosquito Association (PAMCA-a network of vector control professionals) and AUDA-NEPAD (High-level Africa Union technology policy advisors) have a running partnership, since 2017, organizing an annual 3-day theoretical course on gene drive technologies for African scientists and other professionals. The gene drive short course training series creates awareness and provides basic knowledge to African scientists and professionals about the potential of gene drive technologies for novel vector control.

The various pioneer technology developers have actively strengthened institutional research infrastructure at their African partner sites, in readiness for this work, through equipment upgrades and personnel training both for technical skills acquisition and higher academic qualifications at those facilities. Another initiative, Transmission Zero, is working in Tanzania for training and technology transfer. The World Bank has financed the establishment of the African Centre of Excellence in Biotechnology Innovations for Vector-Borne Diseases Elimination (ACE/ITECH-VBD). This is a collaborative regional center of excellence based in Burkina Faso offering quality graduate training and internship opportunities for technical and scientific skills acquisition.

In Mali, an initiative referred to as African Center for Excellence in Molecular Engineering (ACEME) is starting. The goal is to build the capacity and expertise of African scientists in molecular engineering, vector genetics and basic bioinformatics to enable them to play a leading role in designing and developing new tools for vector-borne diseases control. However, much more will be needed if Africa is to attain a critical mass of home-grown technology developers and Centers. Comprehensive human capital and institutional development required for further technology advancement and effective implementation of gene drive work in Africa also calls for the effective implications of subregional and regional organizations. AUDA-NEPAD, ECOWAS, AU and others should strongly encourage their member states towards this capacity building.

8.3.3 RESEARCH AND DEVELOPMENT FOCUS AND INFRASTRUCTURE

Working on emerging technologies such as gene drive for infectious diseases control requires an environment that meets a certain number of standards. This environment includes research and teaching facilities where best practices should be the rules. Safety being a key element in developing gene drive technology, biosafety and biosecurity standards should be met. Infrastructures meeting the required levels for developing and or handling gene drive organisms should be built in institutions working on the technology in Africa. Along with the infrastructures and the biosafety standards go the best documentation practices. All these preparedness could be termed as facility readiness (Quinlan et al, 2018) to having a safe, scientific, and technically sound environment to conduct research and or teaching activities involving gene drive technologies. Initial steps have been taken in a few countries, Mali, Burkina-Faso, Uganda and Tanzania under the funding of partners such as the Bill and Melinda Gates Foundation, Wellcome Trust, Open Philanthropy[MC1] .

8.3.4 FUNDING GAPS

International schemes: Research and development of gene drive technology is a huge capital intensive venture and funding remains a major challenge for Africa states. Institutions in countries presently involved in gene drive research and development receive core funding from International schemes such as the Bill and Melinda Gates Foundation, Open Philanthropy and the Wellcome Trust, mostly through partnerships with Western institutions. The need to broaden the funding base to bring on board other funders would accelerate the pace of development of the technology and help bridge the vast gaps in research, regulation, human capacity and infrastructure. To achieve this, member states have to create the enabling environment to facilitate the building of partnerships and collaborations between their home and western institutions to build the platform for research and development. Apart from the three international funding schemes earlier mentioned, several other development schemes that provide funding for health research and development could be approached and encouraged by the AU on behalf of member states to provide funding to African institutions. Funders may include international governmental development agencies like DANIDA, DFID, DAAD, etc, international organizations such as the World Bank, IMF, WHO and Philanthropic bodies like the Grand Challenges and other state actors like NIH of the United States of America could all play a role.

African states (AU, regional bodies, etc.): No single African state spends more than 0.9% of their GDP on research and development (R&D). With the exception of South Africa, Kenya, Egypt and Morocco, the rest of Africa spends less than 0.6% of their GDP on R&D, which partly underscore the reason why Africa lags behind the rest of the world in terms of technological advancement. Comparatively, countries described as technologically advanced such as Israel, South Korea, the United States, Japan, Germany and China spend as much as 5.44%, 4.81%, 3.40%, 3.27%, 3.13% and 2.40% respectively of their GDP on R&D. To catch up, African governments have to be committed to incrementally spend more, year on year, of their GDP on R&D (Anderson et al., 2023). With the gaps identified in research, regulatory framework, human capacity, and infrastructure, Africa could only assuage them by taking the lead in providing the seed funds.

The need for Africa to take ownership of its own gene drive technology would have enormous benefits and spin-offs for several sectors of its economy including biotechnology, health and agriculture as well as the public acceptability of the technology. It is thus incumbent on the AUDA-NEPAD to spearhead the drive for African countries to commit to providing support funding to African institutions towards research, development and deployment of the technology in controlling malaria on the continent.

8.3.5 REGULATORY GAPS

The development, testing and use of gene-drive mosquitoes in a given legal jurisdiction are currently regulated through relevant biosafety, environmental and health laws and regulations as well as biotechnology policies and guidelines. Of these legal instruments, only biosafety laws enacted from the domestication of the Cartagena Protocol on Biosafety (CPB) extends to governing transboundary movement, a key feature characterizing gene-drive mosquitoes.

In Africa, 23 countries have biosafety policies regulating modern biotechnology (process and/or product) in place, 28 countries have no biosafety policies but are party to the Cartagena Protocol on Biosafety (CPB) and 4 are not parties to the Protocol. Of the countries currently directly or indirectly involved in genetically modified mosquito research, only three (Mali, Ghana, Burkina Faso) have biosafety policies in place. This underscores the urgent need to build the necessary structures in member countries to ensure regulation of the technology keeps pace with its development and future deployment. Sao Tome and Principe, for example, are not signatory to the CPB. In terms of specific regulations on gene drives however, one country (Nigeria) has amended her biosafety law to include the regulation of gene drives, gene editing and synthetic biology and has further developed guidelines, together with Kenya, for gene editing, a technological component for gene drives. The current regulatory space across the African continent poses clear transboundary issues concerning the regulation and deployment of the technology.

Relevant regulatory agencies in each member state, including the health ministries, science/ environment/biodiversity ministries and national biosafety authorities, are expected to oversee the development, testing and use of GMMs at various stages. Within member countries, ministries, departments and agencies of concern should engage each other to build the necessary regulatory framework and facilitate the regulatory processes.

Indeed, all countries are encouraged to enact biosafety laws/ legal instruments to guide the process in a manner that is safe to human and animal health, as well as the environment. This is more so particularly for countries actively engaged in research and testing of gene drive products. The pressing need for a harmonised regulatory regime across the continent to minimise potential sources of transboundary disagreements cannot be underestimated. Regional bodies such as ECOWAS,EAC, ECCAS and SADC could all play a pivotal role in bringing about regulatory parity across member states.

8.3.6 LIMITATIONS IN THE CURRENT SCOPE FOR GENE DRIVES

Although no gene drives are ready for use as a vector control product at this point in time, results from the on-going work are promising, current advances indicate that we are not far from field testing of these technologies. Since Africa bears the bulk of the target diseases, it is more likely that it is there where field testing and actual control trials will happen. So far, the An. gambiae complex has been the main target species complex for malaria control purposes, but attention should be paid to other malaria vectors including the An. funestus group. In addition Anopheles stephensi, an invasive malaria vector species, is rapidly spreading across Africa (Sinka et al, 2020; Ahmed et al, 2021; Tadesse et al, 2021; Ali et al, 2022; Ochomo et al 2023) . This new entrant has the potential to change current malaria transmission trends, including the threat of increased malaria burden in urban areas, and so innovative initiatives to stop its spread will be needed (WHO 2022).

8.3.7 TECHNICAL COOPERATION AND TECHNOLOGY TRANSFER

No single institution on its own has the capability to develop genetically engineered insects, let alone those harnessing gene drive, through the entire technology innovation and evaluation pipeline. This requires diverse expertise coming from multi-disciplinary teams best assembled through technical cooperation. The leading gene drive technology development efforts are currently in countries with capacity built from collaborative endeavors. Countries like Burkina-Faso, Ghana, Mali and Uganda have built facilities and trained personnel on handling genetically engineering mosquitoes at institutions in collaboration with Target Malaria, which is funded by the Bill and Melinda Gates Foundation (BMGF) and the Open Philanthropy (OP). Tanzania's effort leading to establishment of transgenic capacities, is in collaboration with Transmission Zero, also funded by the BMGF. These examples are only in East and West Africa and should be multiplied at the regional level in a coordinated manner to ensure capacity is evenly built across Africa but at the same time avoiding unnecessary duplication. The AU ought to foster and or strengthen such technical cooperation, North-South and South-South to facilitate the urgently needed technology transfer. This terminology is used here to include both the process and the end-product.

Recommendation 8.1: Considering the above-mentioned challenges the following recommendations on the technical cooperation and technology transfer for gene drive technology for GMM come in light. These include:

1. Fill knowledge gaps in terms of sciences, regulations, ethics and legal issues by investing in training
2. Build institutional capacities in terms of policies, guidelines, SOPs, etc.
3. Extend the technology to other important malaria vectors (e.g. Anopheles funestus, Anopheles stephensi)
4. Increase awareness about the technology including the advantages and the challenges
5. Foster/strengthen North-South and South-South partnerships to accelerate the technology transfer (both the process and the end product).
6. Mobilize funds to support the research and capacity building in Africa; Encourage the AU member states to increase their financial support towards research

8.3 Future steps

The continued development and future deployment of gene drive technologies in Africa for disease control constitute the next phases. They will require strategic and careful scientific advancement, additional capacity building, long-term funding, navigating through uncertainties, and alignment with society's values. This calls for among others: (1) Establishing a conducive environment, including policies, for research and development (2) strengthening institutional capacities in terms of scientific and technical expertise (theoretical and hands-on training) for both technology development and regulatory oversight; this will provide qualified human resources to develop and handle the technologies in Africa, (3) building research? Infrastructures, (4) improved R & D financing and resource mobilization; (5) Closing knowledge gaps in areas requiring further research and (6) Fostering further technical cooperation to encourage technology transfer to Africa.

9

RESOURCE MOBILISATION

Science, technology and innovation (STI) are well recognized as having the potential to accelerate progress towards reducing poverty in Africa and raising the standards of living for people on the continent. Indeed, Africa's development blueprint, Agenda 2063, places STI at the centre of the continent's development as reflected in the STI Strategy for Africa 2024 (STISA 2024). The Science, Technology and Innovation Strategy for Africa 2024 (STISA) mission is to "Accelerate Africa's transition to innovation-led knowledge-based economies". Recognizes that for Africa to realize innovation-led knowledge-based economies, the continent should put in place a competitive research infrastructure base, strengthen technical and professional competencies, support innovation and entrepreneurship, and build a conducive policy environment for STI. This requires substantive and sustained investments. Yet, African governments' investments in research and development (R&D) remain low.

The 2006 commitment by African governments to raise investments in R&D to 1% of GDP has not been met; as of 2019, the average investment of African governments in R&D was 0.42% of GDP (REF). When you compare this to the global average of 1.7% of GDP investment in R&D (REF), it becomes clear that the continent lags behind the rest of the world in R&D investments. Olaoye and others (2021) demonstrated that increasing investments in R&D and ensuring good governance have the potential to drive sustainable economic development in Africa. This means that as long as investments in R&D by African countries remain low, achieving the continent's development goals and aspirations will remain a pipe dream.

The challenges that Africa faced in accessing COVID-19 vaccines made clear the urgent need for the continent to prioritize investments in R&D. This experience has set in place a positive momentum that member states should sustain and build on to fill the R&D gap on the continent. This momentum is evident from the initiatives that have emerged following the pandemic. For instance, the African Union Commission is currently setting up the African Education, Science, Technology and Innovation Fund (hosted by the African Development Bank) to "serve as a continental co-financing facility to help African countries build innovation-led and knowledge-based economies" (AFDB). There is also the recent establishment of the African Pharmaceutical Technology Foundation that will, among others, "build human and professional skills, the research and development ecosystem, and support the upgrading of manufacturing plant capacities and regulatory quality to meet World Health Organization standards" (AFDB). The success of these initiatives will depend on AU Member States' investments in them as well as investments from the private sector. This, and other emerging initiatives, point to the commendable growing political will and commitment to put R&D at the centre of the continent's development efforts.

9.1 HEALTH RESEARCH AND DEVELOPMENT IN AFRICA

Africa's limited investment in R&D is partly responsible for the fact that despite having only 15% of the global population, the continent accounts for 25% of the global disease burden (REF). Like other sectors, health R&D remains underdeveloped in Africa as a result of inadequate investments in R&D on the continent. As a result, weak or lacking infrastructure for research and innovation, inadequate numbers of highly skilled human capital to lead and manage research and innovation, inadequate research capacities, and lacking supportive institutional structures and processes for a conducive R&D environment, plague the sector.

In other parts of the world, the pharmaceutical industry is a major contributor to health R&D as part of product development. However, in Africa, the pharmaceutical industry is not well developed and cannot produce ingredients needed for the production of medicines, vaccines, and therapeutics. As a result, many pharmaceutical companies on the continent do not have R&D units.

Apart from addressing their financing gaps for health R&D, African governments should remove persisting barriers deterring private sector investments in the pharmaceutical industry that could spur investments in local R&D to support the development of medical products. These barriers include corruption, governance bottlenecks, and political instability.

9.2 THE CASE FOR INVESTING IN THE DEVELOPMENT, TESTING, AND DEPLOYMENT OF GENE DRIVES FOR MALARIA CONTROL IN AFRICA

The fact that Malaria continues to kill more than 600,000 people in Africa every year is the reason why African governments should shore up their investments in the development and testing of new innovative tools with the potential for Malaria elimination on the continent. The gene drives technology is one such tool with the potential to radically change the deadly story of Malaria on the continent. But for this potential to be realized, more investments should be made. The ongoing research mainly focused on developing and testing the deployment of gene drive tools for malaria control in Africa is highlighted in Box 9. These are good examples that demonstrate that minimal investments in development testing can go a long way in examining the ecological impacts of the vector suppression or replacement approach to using gene drives for Malaria control.

Box: 9. Projects investments in the development, testing, and deployment of gene drives for Malaria control in Africa

The case of Target Malaria: Target Malaria is one of the leading consortia that is developing collaboratively with partners in Africa the most advanced GD products targeting 3 subspecies of major malaria vectors in Africa. Between 2005 and 2025, Target Malaria will have received a total of US$173 million or an average of US$11.5 million per year in funding to advance research into the use of gene drive for malaria elimination. Funding has come from the Bill & Melinda Gates Foundation (US$155.5 million) and the Open Philanthropy Project Fund, an advised fund of the Silicon Valley Community Foundation (US$17.5 million). This funding has been supporting research at more than a dozen institutions since 2005, currently with more than 180 experts across three continents. The funding is not just for staff salaries, it also covers investments in facilities that could be used for other research in the future (in particular the renovation and construction of insectaries and research laboratories in Burkina Faso, Italy, Mali, and Uganda), equipment, and other costs. The building of local capacity is a significant direct impact of the project that has so far been supporting 35 PhDs, 55 MScs and 7 internships. It is a substantial investment in co-development between African, European and American scientific institutions. Individual teams have also received additional funding from a variety of sources to support their work, including:

The case of the University of California Malaria Initiative (UCMI): The University of California Malaria Initiative (UCMI); is a collaborative initiative comprising researchers from four University of California campuses (Irvine, Davis, San Diego, Berkeley) and Johns Hopkins University, who are dedicated to the elimination of malaria. UCMI researchers work to eliminate human malaria by modifying mosquito populations to prevent malaria transmission. It works in partnership and collaboration with local scientists, public health officials, government officials and communities ethically and transparently.

The case of Transmission Zero: The project seeks to develop and test transmission-blocking traits of transgenic malaria mosquitoes with the ultimate aim of eventually eliminating malaria transmission using mosquito population replacement. The project is centred on four activities that have been identified as having significant leads. The activities involve the: 1) construction of the MPL CL3 and its transportation to and installation at the Kingani site in Bagamoyo branch of the IHI, 2) Testing of the MPL CL3 as an infrastructure for conducting laboratory transmission studies using transgenic An. gambiae mosquitoes and P. falciparum parasites, 3) Identification of potential mosquitoes' release sites within a single release area, and 4) Stakeholder engagement at the national and local levels of these activities

There is a need for African governments to invest in generating: i) more research on the ecological effects; ii) research on socio-economic aspects of the gene drive technology for malaria control; and, iii) research on how the implementation of the tool will look like to generate insights that will be needed to roll out the tool if proven effective and safe; among others. Besides research, there is a need for investments in developing technical, institutional and infrastructural capacities needed to undertake gene drive research for malaria control. Importantly, if the technology is proven effective and safe, Africa will need to have technical, institutional and infrastructural capacities to produce, deploy, monitor, and regulate gene-drive solutions for Malaria control.

There is also a need for investments that expand awareness and understanding of the gene drives technology for Malaria control among communities in Africa. The complexity of this technology is one of the factors fanning fears, concerns and misconceptions around the tool, which partly underpin the opposition to the technology. Increasing the public's understanding of the technology is needed to reduce the fears and misconceptions around the tool. The fact that the gene drives technology can also be developed and tested for other vector-borne diseases such as dengue fever, chikungunya, etc. means that the investments in this technology will also facilitate the development of tools for dealing with other neglected, but persistent diseases in Africa.

9.3 RESOURCE MOBILISATION STRATEGIES

The AUDA-NEPAD is cognizant that considerable funding and HR capacity-building on a sustainable basis are essential to support a long-term research and development effort for biotechnological products to meet the health needs of most African countries riddled with malaria endemics. The agency can set up a sub-committee whose mission is to mobilise financial and human resources to support the research and innovation on GDT programmes in Africa through its policies. Currently, various and proven funding mechanisms exist that could be explored and leveraged by African researchers and decision-makers to raise funds to support R&D on GDT in Africa such as Science granting councils, Government programmes, Multinational and Bilateral Donors, International NGOs, Local Private Sector, Local NGOs and Others. Researchers and policy-makers should also be able to identify context-specific insights on how African countries can innovatively and sustainably finance research and innovation. Some of the current organisations that are funding GDT R&D are

9.4 POTENTIAL FINANCING SOURCES

Countries should own their research agendas, including promoting and prioritising the research agenda on emerging transformative technologies such as gene drives for Malaria control – increase investments in R&D. Governments should explore with private sector investors, the potential to increase private sector investment in research, innovation and entrepreneurship across the continent, including as part of their Social Impact Responsibility. Funding should also be directed in ways that promote capacity-building and technology transfer to the public and private sectors in developing countries.

We consider the following elements as fundamental for countries to implement for financial and resource mobilisation to harness the potential for gene drive technology in the elimination of malaria.

- Government Investment: It is essential to raise awareness and motivate African countries to invest in GDT implementation. Governments can allocate resources toward gene-drive testing and implementation programmes as part of a national health strategy. These resources can be used to fund research, development, and field testing of gene drive technologies. This would show the commitment of the government to the cause, and more resources could be expected to come from the international donor communities.
- Public-Private Partnerships: Collaboration between the public and private sector can provide essential funding for gene-drive testing and implementation programmes in Africa. Governments can partner with pharmaceutical companies, foundations, and other corporate organizations to mobilize financial resources to support the testing and implementation of gene-drive technologies in affected areas.
- International Donor Funding: International donor organizations can provide financial support for gene-drive testing and implementation programmes in Africa, in partnership with local and international organizations. The Bill and Melinda Gates Foundation, The Global Fund, The World Health Organization and others could be approached.
- Crowdfunding: Crowdfunding is becoming increasingly popular in Africa as a means of mobilizing resources for innovative health initiatives. A crowdfunding campaign could be launched to raise funds for gene-drive testing and implementation in Africa. This would be easier if a large segment of the population had been educated about the benefits of the technology.
- Philanthropic Initiatives: Philanthropic organizations can provide funding for gene-drive testing and implementation programmes in Africa. These organizations can fund research and development, support field testing initiatives or provide grants to development organizations that are working towards the elimination of malaria.
- Corporate Social Responsibility: Companies that operate in Africa can allocate resources toward gene-drive testing and implementation programmes in the regions where they operate as part of their corporate social responsibility initiatives.
- Fundraising Events: Fundraising events such as charity walks or runs can be organized to raise money for gene-drive testing and implementation programmes in Africa.
- Impact Investment: Impact investors can invest in organizations that are working towards gene-drive development and implementation in Africa. These organizations can use the investment to finance research, development, and field testing of gene drive technologies. Remove barriers deterring private sector investments, such as the local pharmaceutical industry, which could increase local R&D to support the development of products (diagnostics, therapeutics, etc.)
- Philanthropic funding: The majority of funds for research are derived from philanthropic donors or foundations. This is a historical source of funding research in Africa.

9.5 WORKFORCE BUILDING

The AUDA-NEPAD should focus on advancing best practices and informed decision-making for the development of genetic biocontrol technologies to improve public health. Existing research capacity in African countries (Burkina Faso, Mali, Uganda, Ghana, Kenya, Nigeria, Ethiopia, etc) should be leveraged to ensure gene drive technology implementation is based on Africa's cultural, social, and environmental contexts. Collaborative partnerships could offer technical information, advice, training, and coordination for research on gene drive and other genetic biocontrol technologies to ensure that genetic biocontrol research addresses important public health priorities ethically, safely, and effectively.

The availability and accessibility of quality research and implementing workforce, including a workforce for malaria vector and parasites genomic surveillance (e.g., field investigation and contact tracing teams, logisticians, laboratory personnel, vector biology experts, clinicians, communications and data managers, and experts in regulatory science and risk assessment, etc.) and early warning and awareness raising, is critical to building the resilience of communities and for the continuity of health services during an emergency. This priority requires investing in a well-educated, trained and appropriately compensated workforce, to ensure readiness for surges of workforce across sectors during public health emergencies. Training should be based on up-to-date curricula, common standards, and competencies, reflecting an interdisciplinary approach to pandemic prevention, preparedness and response.

Furthermore, establishing creative partnerships with the private sector aimed at sustained development of human capital & infrastructure for gene drives R&D for Malaria control and elimination is a technical area that needs capacity building including entomology, genetic transformation, modelling, bioinformatics, social science, risk management, science communication, stakeholder engagement, regulatory science. Building additional regional centres of expertise that can serve as hubs for education and training, as well as national and regional cadres of entomologists, public health specialists, malarialogists and other health workers, with the necessary training on genetic approach to control malaria and public health, could play a useful role.

The creation of Regional Centres of Excellence for hands-on training and gene drive technology development and provide funded-graduate studentships and internships tenable at those established Centers of Excellence. This Funding opportunity will solicit applications from students across Africa to 1) improve the understanding of malaria pathogenesis, epidemiology, and transmission; and 2) evaluate, optimize, and inform the development of genetic-based interventions to understand, control, eliminate, and eventually eradicate malaria. This program is intended to support gene drive research that is conducted primarily in countries in which centres already exist and should provide for significant involvement of local/regional researchers in study design, development, and execution.

The FNIH's GeneConvene Global Collaborative has identified field trial design and implementation for gene drive mosquitos as an area that requires further attention. Field trials are pivotal activities required for generating evidence to support key go-no-go decisions for gene drive candidate development. They provide critical information for regulators, policymakers, funders, implementers, communities, and decision influencers. Field trials, however, are complicated in that the parameter space for reasonable trial designs is large, with multiple design decisions. Given the importance, complexity, and unique nature of gene drive field trials, GeneConvene has assembled an international working group to identify some key technical questions, knowledge gaps, and potential solutions required for conducting safe, ethical, and efficacious gene drive field trial design. The working group consists of members from the three most advanced teams working on gene drive in mosquitos, Target Malaria, University of California Malaria Initiative (UCMI) and Transmission Zero. The findings will be published in an appropriate format.

9.6 RECOMMENDATIONS

In line with APET's recommendations, three countries namely Burkina Faso, Mali and Uganda have implemented research programmes on the use of Gene Drive technology. AUDA-NEPAD also provides financial and technical support to these countries and all West African countries within the framework of the West Africa IVM platform. These programmes benefit from the mobilization of human and financial resources at both national and regional levels. The limited scope of these programmes is related to insufficient financial and human resources. It is therefore essential that resource mobilization be conducted as a major task in this phase of implementation of these programmes throughout the African continent.

- AUDA-EPAD should build on its mandate to " undertake the full range of resource mobilization " and its role as a facilitator, technical capacity and convening power to lead resource mobilization and support African States in this activity. Historical trends show that the resources mobilized at the Agency's peak for every dollar mobilized by the Agency for programme coordination and implementation, at least $5 is dedicated to the implementation of projects in the country and the Regional Economic Communities (RECs).
- APET should take advantage of its international aura to provide the necessary support to AUDA-NEPAD to convince potential funders to financially support national, regional and continental programmes.
- African Union Member States and REC Commissions should invest more in human resources and deploy more vigorous strategies to mobilize financial resources.
- AUDA-NEPAD, APET, AU member states and RECS should adopt a concerted approach to rigorously sustain their traditional partners and also on-board new partners including the United Nations (UN) system, development finance institutions, multilateral organisations, and the private sector, foundations, and charities.

10

CONCLUSION

The persistent malaria burden due to the limited effectiveness of existing control and elimination strategies, besides the threat of a new invasive mosquito species, could translate to additional decades of limited economic growth and development as well as loss of lives in the continent. Augmenting the current malaria control and elimination strategies with innovative approaches and technologies such as Gene Drives presents an opportunity for Africa to bolster its efforts in the fight against malaria and meet its target as envisaged in the Agenda 2063. Despite the elaborated challenges in the research and development of Gene Drives, impressive steps have been taken and progress realized. The tremendous work put in by the AUDA-NEPAD through the Africa IVM Program is commendable and has laid a foundation for supporting the creation of a conducive environment for the research and development of novel technologies. Concerted efforts need to be put in place with multiple sectors to further support the research and development of Gene Drives as an intervention for control and elimination of Malaria. To this end, all AU Member States, African Union Commission, the African Union Development Agency – New Partnership for Africa's Development (AUDA-NEPAD), Regional Economic Communities (RECs), Gene Drive researchers and developers, Civil Societies, Local Communities as well as Development Partners, and the Private Sector have critical role to play concerning; Gene Drives' policy and regulatory frameworks, Information and knowledge sharing, partnerships and resource mobilization required, and lastly the development of human and institutional capacity.

11

ACKNOWLEDGMENT

AUTHORS

1. African Union High-Level Panel on Emerging Technologies; and
2. APET Secretariat

AFRICAN UNION HIGH-LEVEL PANEL ON EMERGING TECHNOLOGIES (APET) MEMBERS:

APET CHAIR:

Yaye Kène Gassama, Université Cheikh Anta Diop de Dakar, Senegal

APET MEMBERS:

1. **Prof Berhanu M. Abegaz**, Addis Ababa University, Ethiopia
2. **Prof Abdallah Daar,** University of Toronto, Canada
3. **Prof Francine Ntoumi,** Fondation Congolaise pour la Recherche Médicale, Congo-Brazzaville
4. **Prof Roseanne Diab,** University of Kwa-Zulu Natal, South Africa
5. **Prof Karim Maredia,** Michigan State University (MSU), East Lansing, Michigan, United States of America
6. **Dr Rachel Chikwamba,** Council for Scientific and Industrial Research (CSIR), South Africa
7. **Prof Shireen Assem,** The Agricultural Genetic Engineering and Biotechnology Research Institute (AGERI), Egypt
8. **Prof Abubakar Sambo,** Professor of Mechanical Engineering, former Director-General of the Energy Commission of Nigeria, Chairperson of the Nigerian Member Committee of the World Energy Council (WEC), Nigeria
9. **Dr William Wasswa,** Senior Lecturer, Department Head Biomedical Sciences & Engineering, Mbarara University of Science & Technology, Uganda

APET SECRETARIAT:

a. **Wiltshire Johnson** – AUDA-NEPAD
b. **Christopher Okonji** – AUDA-NEPAD
c. **Barbara Glover** – AUDA-NEPAD
d. **Chifundo Kungade** – AUDA-NEPAD
e. **Nhlawulo Shikwambane** – AUDA-NEPAD
f. **Gaokgakala Daniel Lemmenyane** – AUC
g. **Bhekani Mbuli,** University of Johannesburg, South Africa
h. **Maria Stella Namyalo,** AUDA-NEPAD

RESEARCHERS

Mamadou Coulibaly[the late] (Malaria Research and Training Center, Mali), **Charles M Mbogo** (Kenya Medical Research Institute, Kenya), **Lea PARE TOE** (Institut de Recherche en Sciences de la Santé, Burkina Faso), **Jonathan Kayondo** (Uganda Virus Research Institute, Uganda)., **Charles Mugoya** (Target Malaria, Uganda), **Josephine Amedu** (National Biosafety Management Agency, Nigeria)., **Soumaïla Pagabeleguem** (Insectarium de Bobo-Dioulasso/Université Daniel OUEZZIN COULIBALY, Burkina Faso)., **Charles Guissou** (Centre Muraz, Burkina Faso), Kwehangana Musa (AUDA-NEPAD), **Elizabeth Bandason** (Lilongwe University of Agriculture and Natural Resources, Malawi), **Tinga Jeremy OUEDRAOGO** (SafeBio Advisory Consulting, Burkina Faso), **Diabate Abdoulaye** (Institut de Recherche en Sciences de la Sante, Burkina Faso), **Justina Dugbazah** (Sahara Institute, Ghana), **Aggrey Ambali** (HDRAS, Malawi), **Rose Oronje** (AFIDEP, Kenya), **Richard Mukabana** (Kenya), **Fred Aboagye-Antwi** (University of Ghana, Ghana), **Moussa Savadogo** (Consultant - Wits Consortium, Burkina Faso), **Adama Gansané** (National Institute Of Public Health, Burkina Faso), **Brian Tarimo** (Ifakara Health Institute), **Barbara Glover** (AUDA-NEPAD).

REFERENCES

1. Active Genetic Neutralizing Elements for Halting or Deleting Gene Drives. Molecular Cell, Volume 80, Issue 2, 15 October 2020, Pages 246-262.e4 https://doi.org/10.1016/j.molcel.2020.09.003

2. Active Genetic Neutralizing Elements for Halting or Deleting Gene Drives. Molecular Cell, Volume 80, Issue 2, 15 October 2020, Pages 246-262.e4 https://doi.org/10.1016/j.molcel.2020.09.003

3. Adriana Adolfi, Valentino M. Gantz, Nijole Jasinskiene, Hsu-Feng Lee, Kristy Hwang, Gerard Terradas, Emily A. Bulger, Arunachalam Ramaiah, Jared B. Bennett, J. J. Emerson, John M. Marshall, Ethan Bier & Anthony A. James. Efficient population modification gene-drive rescue system in the malaria mosquito Anopheles stephensi. Nat Commun 11, 5553 (2020). https://doi.org/10.1038/s41467-020-19426-0

4. African Union Development Agency-New Partnership for African Development. (2018). West Africa Integrated Vector Management (WA-IVM) Programme Overview, August 2018.

5. Ahmed A, Pignatelli P, Elaagip A, Abdel Hamid MM, Alrahman OF, Weetman D. Invasive Malaria Vector Anopheles stephensi Mosquitoes in Sudan, 2016-2018. Emerg Infect Dis. 2021 Nov;27(11):2952-2954. doi: 10.3201/eid2711.210040. PMID: 34670658; PMCID: PMC8544976.

6. Ahmed A, Pignatelli P, Elaagip A, Abdel Hamid MM, Alrahman OF, Weetman D. Invasive Malaria Vector Anopheles stephensi Mosquitoes in Sudan, 2016-2018. Emerg Infect Dis. 2021 Nov;27(11):2952-2954. doi: 10.3201/eid2711.210040. PMID: 34670658; PMCID: PMC8544976.

7. Ali S., Jeanne N. Samake, Joseph Spear & Tamar E. Carter. 2022. Morphological identification and genetic characterization of Anopheles stephensi in Somaliland

8. Ali S., Jeanne N. Samake, Joseph Spear & Tamar E. Carter. 2022. Morphological identification and genetic characterization of Anopheles stephensi in Somaliland

9. Amato R, Pearson RD, Almagro-Garcia J, Amaratunga C, Lim P, Suon S, Sreng S, Drury E, Stalker J, Miotto O, Fairhurst RM, Kwiatkowski DP. Origins of the current outbreak of multidrug-resistant malaria in southeast Asia: a retrospective genetic study. Lancet Infect Dis. 2018 Mar;18(3):337-345.

10. Amato R, Pearson RD, Almagro-Garcia J, Amaratunga C, Lim P, Suon S, Sreng S, Drury E, Stalker J, Miotto O, Fairhurst RM, Kwiatkowski DP. Origins of the current outbreak of multidrug-resistant malaria in southeast Asia: a retrospective genetic study. Lancet Infect Dis. 2018 Mar;18(3):337-345.

11. Andrew Hammond, A, Roberto Galizi R, Kyros Kyrou, K Alekos Simoni, A Carla Siniscalchi, C Dimitris Katsanos, D Matthew Gribble, M Dean Baker, D Eric Marois, E Steven Russell, S, Austin Burt, A Nikolai Windbichler, N Andrea Crisanti A & Tony Nolan.T, 2016. A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector Anopheles gambiae. Nat Biotechnol 34: 78–83.

12. Anopheles gambiae 1000 Genomes Consortium et al. "Genetic diversity of the African malaria vector Anopheles gambiae." Nature vol. 552,7683 (2017): 96-100. doi:10.1038/nature24995

13. Anopheles gambiae 1000 Genomes Consortium. Genome variation and population structure among 1142 mosquitoes of the African malaria vector species Anopheles gambiae and Anopheles coluzzii. Genome Res. 2020;30(10):1533-1546. doi:10.1101/gr.262790.120

14. Bhatt S, Weiss DJ, Cameron L, Bisanzio D, Mappin B, Dalrymple U, et al. The effect of malaria control on Plasmodium falciparum in Africa between 2000 and 2015. Nature. 2015;526:207–11. doi:10.1038/nature15535.

15. Bier E. Gene drives gaining speed. 2022 Nature Reviews Genetics volume 23 January 2022 https://doi.org/10.1038/s41576-021-00386-0

16. Boëte C., F.B. Agusto, R.G. Reeves, Impact of mating behaviour on the success of malaria control through a single inundative release of transgenic mosquitoes, Journal of Theoretical Biology, Volume 347, 2014, Pages 33-43,

17. Burt A. Site-specific selfish genes as tools for the control and genetic engineering of natural populations. Proc Biol Sci. 2003 May 7;270(1518):921-8. doi: 10.1098/rspb.2002.2319. PMID: 12803906; PMCID: PMC1691325.

18. Carballar-Lejarazú Rebeca, Christian Ogaugwu, Taylor Tushar, Adam Kelsey, Thai Binh Pham, Jazmin Murphy, Hanno Schmidt, Yoosook Lee, Gregory C. Lanzaroc, and Anthony A. James. Next-generation gene drive for population modification of the malaria vector mosquito, Anopheles gambiae. PNAS | September 15, 2020 | vol. 117 | no. 37 | 22805–22814 https://doi.org/10.1073/pnas.2010214117

19. Carvalho D. O., Andrew R. McKemey, Luiza Garziera, Renaud Lacroix, Christl A. Donnelly, Luke Alphey, Aldo Malavasi, Margareth L. Capurro. 2015 Suppression of a Field Population of Aedes aegypti in Brazil by Sustained Release of Transgenic Male Mosquitoes. Published: July 2, 2015. https://doi.org/10.1371/journal.pntd.0003864

20. Champer J, Reeves Riona; Suh Yeon Oh, Chen Liu, Jingxian Liu, Andrew G. Clark and Philipp W. Messer (2017) Novel CRISPR/Cas9 gene drive constructs reveal insights into mechanisms of resistance allele formation and drive efficiency in genetically diverse populations. PLoS Genet 13(7): e1006796. https://doi.org/10.1371/journal.pager.1006796

21. Chen J, Luo J, Wang Y, Gurav AS, Li M, Akbari OS, Montell C. Suppression of female fertility in Aedes aegypti with a CRISPR-targeted male-sterile mutation. Proc Natl Acad Sci USA. 2021 Jun 1;118(22):e2105075118. doi: 10.1073/pnas.2105075118. PMID: 34031258; PMCID: PMC8179229.

22. Dimbu PR, Horth R, Candido ALM, Ferreira CM, Caquece F, Garcia LEA, et al. Continued low efficacy of artemether-lumefantrine in Angola in 2019. Antimicrob Agents Chemother. 2021;65:e01949-e2020.

23. Dondorp A. M., Nosten F., Yi P., Das D., Phyo A. P., Tarning J., et al. (2009). Artemisinin Resistance in Plasmodium Falciparum Malaria. N Engl. J. Med. 361 (5), 455–467.

24. EFSA GMO Panel (EFSA Panel on Genetically Modified Organisms), Naegeli, H., Bresson, J.-L., Dalmay, T., Dewhurst, I. C., Epstein, M. M., Guerche, P., Hejatko, J., Moreno, F. J., & Mullins, E. (2020). Scientific Opinion on the Adequacy and sufficiency evaluation of existing EFSA guidelines for the molecular characterisation, environmental risk assessment and post market environmental monitoring of genetically modified insects containing engineered gene drives. EFSA Journal, 18 (11), e06297. 90 pp. https://doi.org/10.2903/j.efsa.

25. Esvelt KM, Smidler AL, Catteruccia F, Church GM. Concerning RNA-guided gene drives for the alteration of wild populations. Elife. 2014 Jul 17;3:e03401. doi: 10.7554/eLife.03401. PMID: 25035423; PMCID: PMC4117217.

26. Fauldea M. K., Leopoldo M.Rueda, Bouh A.Khaireh. First record of the Asian malaria vector Anopheles stephensi and its possible role in the resurgence of malaria in Djibouti, Horn of Africa. Acta Tropica, Volume 139, November 2014, Pages 39-43

27. Franck Adama Yao, Abdoul-Azize Millogo, Patric Stephane Epopa, Ace North, Florian Noulin, Koulmaga Dao, Mouhamed Drabo, Charles Guissou, Souleymane Kekele, Moussa Namountougou, Robert Kossivi Ouedraogo, Lea Pare, Nourou Barry, Roger Sanou, Haida Wandaogo, Roch K. Dabire, Andrew McKemey, Frederic Tripet & Abdoulaye Diabaté. A mark-release-recapture experiment in Burkina Faso demonstrates reduced fitness and dispersal of genetically modified sterile malaria mosquitoes. Nat Commun 13, 796 (2022). https://doi.org/10.1038/s41467-022-28419-0

28. Gansané, A., Moriarty, L.F., Ménard, D. et al. Anti-malarial efficacy and resistance monitoring of artemether-lumefantrine and dihydroartemisinin-piperaquine show inadequate efficacy in children in Burkina Faso, 2017–2018. Malar J 20, 48 (2021)

29. Gantz VM, Jasinskiene N, Tatarenkova O, Fazekas A, Macias VM, Bier E, James AA, 2015. Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito Anopheles stephensi. Proc Natl Acad Sci USA 112:

30. Hamilton, W. L. et al. Evolution and expansion of multidrug-resistant malaria in Southeast Asia: a genomic epidemiology study. Lancet Infect. Dis. 19, 943–951 (2019)

31. Hammond A., Roberto Galizi, Kyros Kyrou, Alekos Simoni, Carla Siniscalchi, Dimitris Katsanos, Matthew Gribble, Dean Baker, Eric Marois, Steven Russell, Austin Burt, Nikolai Windbichler, Andrea Crisanti & Tony Nolan., 2016. A CRISPR-Cas9 gene drive system targeting female reproduction in the malaria mosquito vector Anopheles gambiae. Nat Biotechnol 34: 78–83.

32. James, S., Collins, F. H., Welkhoff, P. A., Emerson, C., Godfray, H. C. J., Gottlieb, M., Greenwood, B., Lindsay, S. W., Mbogo, C. M., & Okumu, F. O., Quemada, H., Savadogo, M., Singh, J. A., Tountas, K. H. and Toure, Y. T. (2018). Pathway to deployment of gene-drive mosquitoes as a potential biocontrol tool for elimination of malaria in sub-Saharan Africa: The American Journal of Tropical Medicine and Hygiene, 98(6 Suppl) 1.

33. John Marshal (2010). The Cartagena Protocol and Genetically Modified Mosquitoes. Correspondence, Nature Biotechnology: Vol 28 (9).pp 896 - 897

34. Kelsey A., Pham T., Stillinger D., Firth S., (2020). Global Governing Bodies: a Pathway for Gene Drive Governance for Vector Mosquito Control. The American Journal of Tropical Medicine and Hygiene: Vol 103 (3) pp 976 – 985

35. Kyros Kyrou, Andrew M Hammond, Roberto Galizi, Nace Kranjc, Austin Burt, Andrea K Beaghton, Tony Nolan & Andrea Crisanti., 2018 A CRISPR–Cas9 gene drive targeting doublesex causes complete population suppression in caged Anopheles gambiae mosquitoes. Nat Biotechnol 36, 1062–1066 (2018). https://doi.org/10.1038/nbt.4245

36. Moriarty LF, Nkoli PM, Likwela JL, Mulopo PM, Sompwe EM, Rika JM, et al. Therapeutic efficacy of artemisinin-based combination therapies in Democratic Republic of the Congo and investigation of molecular markers of antimalarial resistance. Am J Trop Med Hyg. 2021;105:1067–75

37. Noedl H., Se Y., Schaecher K., Smith B. L., Socheat D., Fukuda M. M. (2008). Evidence of Artemisinin-Resistant Malaria in Western Cambodia. N Engl. J. Med. 359 (24), 2619–2620.

38. Ochomo, Eric & Milanoi, Sylvia & Abongo, Bernard & Onyango, Brenda & Muchoki, Margaret & Omoke, Diana & Olanga, Evelyne & Njoroge, Laban & Juma, Elijah & Otieno, James & Matoke, Damaris & Kamau, Luna & Rafferty, Cristina & Gimnig, John & Shieshia, Mildred & Wacira, Daniel & Mwangangi, Joseph & Maia, Marta & Chege, Charles & Kariuki, Lenson. (2023). Molecular surveillance leads to the first detection of Anopheles stephensi in Kenya. 10.21203/rs.3.rs-2498485/v1. Preprint

39. Qsim M, Ashfaq UA, Yousaf MZ, Masoud MS, Rasul I, Noor N, Hussain A., 2017 Genetically Modified Aedes aegypti to Control Dengue: A Review. Crit Rev Eukaryot Gene Expr. 2017;27(4):331-340. doi: 10.1615/CritRevEukaryotGeneExpr.2017019937. PMID: 29283327.

40. Quinlan MM, Birungi J, Coulibaly MB, Diabaté A, Facchinelli L, Mukabana WR, Mutunga JM, Nolan T, Raymond P, Traoré SF. Containment Studies of Transgenic Mosquitoes in Disease Endemic Countries: The Broad Concept of Facilities Readiness. Vector-borne Zoonotic Dis. 2018 Jan;18(1):14-20. doi: 10.1089/vbz.2017.2189. PMID: 29337664; PMCID: PMC5770120.

41. Ross L. S., Dhingra S. K., Mok S., Yeo T., Wicht K. J., Kümpornsin K., et al. (2018). Emerging Southeast Asian Pfcrt Mutations Confer Plasmodium Falciparum Resistance to the First-Line Antimalarial Piperaquine. Nat. Commun. 9 (1), 3314.

42. Simoni A., Andrew M. Hammond, Andrea K. Beaghton, Roberto Galizi, Chrysanthi Taxiarchi, Kyros Kyrou, Dario Meacci, Matthew Gribble, Giulia Morselli, Austin Burt, Tony Nolan and Andrea Crisanti. A male-biased sex-distorter gene drive for the human malaria vector Anopheles gambiae. Nature Biotechnology | VOL 38 | September 2020 | 1054–1060 | https://doi.org/10.1038/s41587-020-0508-1 www.nature.com/naturebiotechnology

43. Sinka M. E., S. Pironon, N. C. Massey, J. Longbottom, J. Hemingway, C. L. Moyes, and K. J. Willis. A new malaria vector in Africa: Predicting the expansion range of Anopheles stephensi and identifying the urban populations at risk. 2020 | PNAS | 24900–24908 October 6, 2020 | vol. 117 | no. 40 www.pnas.org/cgi/doi/10.1073/pnas.2003976117

44. Tadesse FG, Ashine T, Teka H, Esayas E, Messenger LA, Chali W, Meerstein-Kessel L, Walker T, Wolde Behaksra S, Lanke K, Heutink R, Jeffries CL, Mekonnen DA, Hailemeskel E, Tebeje SK, Tafesse T, Gashaw A, Tsegaye T, Emiru T, Simon K, Bogale EA, Yohannes G, Kedir S, Shumie G, Sabir SA, Mumba P, Dengela D, Kolaczinski JH, Wilson A, Churcher TS, Chibsa S, Murphy M, Balkew M, Irish S, Drakeley C, Gadisa E, Bousema T. Anopheles stephensi Mosquitoes as Vectors of Plasmodium vivax and falciparum, Horn of Africa, 2019. Emerg Infect Dis. 2021 Feb;27(2):603-607. doi: 10.3201/eid2702.200019. PMID: 33496217; PMCID: PMC7853561.

45. Terradas G, Anna B. Buchman, Jared B. Bennett, Isaiah Shriner, John M. Marshall, Omar S. Akbari & Ethan Bier Inherently confinable split-drive systems in Drosophila. Nat Commun 12, 1480 (2021). https://doi.org/10.1038/s41467-021-21771-7

46. Thizy D, Coche I and de Vries J. Providing a policy framework for responsible gene drive research: an analysis of the existing governance landscape and priority areas for further research Welcome Open Research 2020, 5:173 https://doi.org/10.12688/wellcomeopenres.16023.1

47. Turner, G., Beech, C., & Roda, L. (2018). Means and ends of effective global risk assessments for genetic pest management. BMC Proceedings, 12 (8), 53–64.

48. Uwimana A., Legrand E., Stokes B. H., Ndikumana J. M., Warsame M., Umulisa N., et al. (2020). Emergence and Clonal Expansion of In Vitro Artemisinin-Resistant Plasmodium falciparum Kelch13 R561H Mutant Parasites in Rwanda. Nat. Med. 26, 1602–1608.

49. Van der Pluijm, R. W. et al. Determinants of dihydroartemisinin-piperaquine treatment failure in Plasmodium falciparum malaria in Cambodia, Thailand, and Vietnam: a prospective clinical, pharmacological, and genetic study. Lancet Infect. Dis. 19, 952–961 (2019)

50. WHO, 2014 Guidance framework for testing of genetically modified mosquitoes. ISBN 978 92 4 150748

51. WHO, 2020 Vector-borne diseases, key facts. https://www.who.int/news-room/fact-sheets/detail/vector-borne diseases#:~:text=Vector%2Dborne%20diseases%20account%20for,infection%20transmitted%20by%20Anopheline%20mosquitoes.

52. WHO, 2021 World Malaria Report. https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2021

53. World Health Organization, W. H. (2021). Guidance framework for testing genetically modified mosquitoes.

54. World Health Organization, WHO, 2019 - Guidelines for malaria vector control; https://creativecommons. org/licenses/by-nc-sa/3.0/igo .

55. World Health Organization, WHO. (2012). Handbook for integrated vector management, http://www.who.int/about/licensing/copyright_form/en/index.htm

56. World Health Organization. (2004). Global strategic framework for integrated vector management. http://whqlibdoc.who.int/hq/2004/WHO_CDS_CPE_PVC_2004_10.pdf.

57. World Health Organization. (2009). Vector Management and Delivery of Vector Control Services, National Library of Medicine, National Center for Biotechnology Information.

58. Xu X.R. S., Emily A. Bulger, Valentino M. Gantz, Carissa Klanseck, Stephanie R. Heimler, Ankush Auradkar, Jared B. Bennett, Lauren AshleyMiller, Sarah Leahy, Sara Sanz Juste, Anna Buchman, Omar S. Akbari, John M. Marshall and EthanBier. 2020 Parasites & Vectors volume 15, Article number: 247 (2022)

59. Xu X.R. S., Emily A. Bulger, Valentino M. Gantz, Carissa Klanseck, Stephanie R. Heimler, Ankush Auradkar, Jared B. Bennett, Lauren AshleyMiller, Sarah Leahy, Sara Sanz Juste, Anna Buchman, Omar S. Akbari, John M. Marshall and EthanBier. 2020

60. Zana L Sanogo, Alpha S Yaro, Adama Dao, Moussa Diallo, Ousman Yossi, Djibril Samaké, Benjamin J Krajacich, Roy Faiman, Tovi Lehmann, The Effects of High-Altitude Windborne Migration on Survival, Oviposition, and Blood-Feeding of the African Malaria Mosquito, Anopheles gambiae s.l. (Diptera: Culicidae), Journal of Medical Entomology, Volume 58, Issue 1, January 2021, Pages 343–349, https://doi.org/10.1093/jme/tjaa137