Unitaid
SAVE LIVES FASTER

Genetically modified mosquitoes

Technology and access landscape report

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Foreword

The African continent bears the heaviest burden of malaria and other mosquito-borne illnesses in the world, and as such has embraced the leadership role in pioneering the solutions of tomorrow. The African Union Development Agency-NEPAD (AUDA-NEPAD), as mandated by the African Union Heads of States, has been championing policy decision-making, advocacy, social acceptance and regulatory capacity-building for science, technology and innovation across the continent – from advancing integrated vector management strategies to initiating horizon scanning for genetic-based vector control tools.

It is in this spirit of continental leadership and foresight that we welcome Unitaid's "Genetically modified mosquitoes (GMM) technology and access landscape" report, a timely resource to inform Africa's efforts to combat vector-borne diseases in an innovative, evidence-driven way.

African ownership, regional coordination, and scientific leadership are paramount as we explore novel technologies like GMMs. Our Union's high-level bodies have called for proactive engagement with these tools. In 2018, the African Union's High-Level Panel on Emerging Technologies identified gene drive mosquitoes as a promising option for malaria control as part of integrated vector management, a recommendation later endorsed by African Ministers and the AU Executive Council. In line with these directives, AUDA-NEPAD, together with regional partners such as the West African Health Organization has established platforms and frameworks to ensure readiness for GMM deployment.

The West Africa Integrated Vector Management programme, for example, brings together health, biosafety and environment regulators, ethics committees, and malaria control experts from multiple countries in a One Health, multi-sectoral regional governance approach. Through such initiatives, we are addressing regulatory and technical challenges ahead of time so that African countries can fully leverage the benefits of GMMs when they become available. This proactive work – from developing harmonized guidelines on biosafety, ethics, and risk assessment to strengthening institutional capacities – underscores Africa's commitment to regulatory readiness and shared responsibility in the age of genetic tools.

We also recognize the vital role of our global partners in catalysing health innovations. In particular, Unitaid has been instrumental in driving equitable innovation pathways and "access-oriented" initiatives. Unitaid's model – identifying groundbreaking health solutions and overcoming market barriers to reach those who need them most – has unlocked over 100 life-saving health products for low- and middle-income countries. By commissioning this GMM technology landscape, Unitaid continues to demonstrate its commitment to ensuring that new vector control tools like GMMs are developed and introduced with equity and access in mind. Since 2016, Unitaid has invested significantly in accelerating promising vector control innovations and mapping out the landscape of transformative solutions.

"This report reflects that focus: it is not just a survey of GMM technologies, but a roadmap for how they can be applied in the real world –safely, effectively, responsibly, affordably and sustainably – to serve public health goals."

As we look to the future of GMMs in Africa, we are guided by the principles of safety, inclusion, and anticipatory governance. Ensuring these technologies are safe and accepted requires engaging our communities at every step. AUDA-NEPAD firmly believes that community engagement and transparency are non-negotiable. We have learned that involving local stakeholders from the outset – listening to communities, addressing their concerns, and respecting indigenous knowledge – builds the trust and social license needed to make GMM interventions effective and sustainable. We are equally committed to policy coherence: aligning health, environmental, and agricultural policies across our Union so that novel tools complement existing interventions and regulatory frameworks work in harmony.

Our collaborative approach with Member States and Regional Economic Communities emphasizes consultation and consensus. Recognizing that mosquitoes do not respect borders, our response must be coordinated regionally and continentally. By investing in anticipatory governance – from early-stage risk assessments and ethical guidelines to legal preparedness – Africa is proactively shaping a future where GMM technologies can be safely and inclusively integrated into public health strategies. These efforts aim to ensure that GMMs, as they advance from research to field use, align with our public health priorities and ethical values every step of the way.

This landscape report comes at a pivotal moment. It offers a comprehensive view of the GMM field and highlights pathways to translate innovation into impact. African governments, funders, and research partners are encouraged to use this document as a platform for collaborative investment underscored by African-led action. Africa must leverage the insights here to drive coordinated efforts – from funding strategic research and development, to bolstering regulatory infrastructure, to preparing pilot deployments guided by evidence and community consent. By acting together, we can accelerate the development of these tools and ensure that Africa not only benefits from them but also guides their responsible use. Indeed, as Africa collectively advances in the battle against vector-borne diseases, broad collaboration among public and private stakeholders is a crucial step forward. The promise of GMMs will only be realized through partnership: between nations, between researchers and communities, and between Africa and its global allies.

This foreword reinforces AUDA-NEPAD's commitment to inclusive governance, development, and global partnership through evidence-based policymaking. The journey towards deploying genetically modified mosquitoes is emblematic of Africa's broader journey in science and innovation – one where we assert ownership of our solutions, work in unity, and engage the world on our own terms. With vision and vigilance, we will ensure that these novel vector control tools are used to save lives and secure the health of our people. Together, let us translate innovation into hope – and hope into lasting impact for Africa and beyond.

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Abbreviations

GMM	genetically modified mosquito
GMO	genetically modified organism
GVCR	"Global vector control response 2017–2030"
IRS	indoor residual spraying
ITN	insecticide-treated net
PPC	preferred product characteristics
SIT	sterile insect technique
TPoP	target policy profile
UCMI	University of California Malaria Initiative
WHO	World Health Organization

1. Introduction

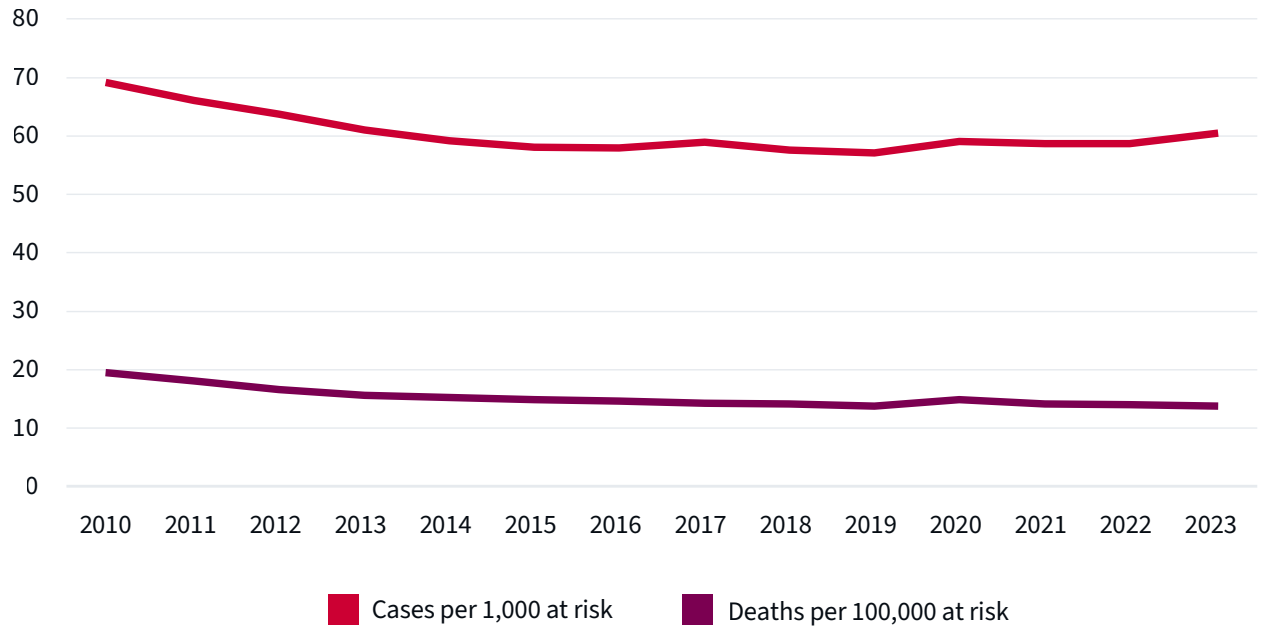
The mosquito is considered the world's deadliest animal, responsible for the transmission of a range of diseases that cause significant morbidity and mortality. Together, mosquito-borne diseases kill over 700,000 people each year, and a wide swath of the world is at risk of contracting one or more of these infections.[1]

Malaria is the best known of these mosquito-borne diseases. It kills roughly 600,000 people annually, most of whom are children under the age of 5.[2] However, other mosquito-borne diseases, such as dengue, Zika, chikungunya, filariasis, yellow fever and West Nile Virus, also cause serious and debilitating illnesses, some of which may persist for many years in the absence of effective treatment.[3]

Over the past decade, there have been major outbreaks of dengue, chikungunya, yellow fever and Zika[4]; meanwhile, progress in malaria control stalled around 2017 **(Figure 1)** and has been off-track ever since. An estimated 263 million malaria cases and 597,000 malaria deaths were reported in 2023.[5] By 2024, dengue had become the fastest growing mosquito-borne disease, with over 14 million cases and 9,000 deaths reported **(Figure 2)**.[6] It is now estimated that 4 billion people – just under 50% of the world's total population – live in areas at risk for dengue.[7]

1 "Fact Sheet: Vector Borne Diseases," World Health Organization, accessed 27 June 2025, https://www.who.int/news-room/fact-sheets/detail/vector-borne-diseases
2 World Health Organization, *World Malaria Report 2024*: Addressing Inequity in the Global Malaria Response (World Health Organization, 2024), https://iris.who.int/handle/10665/379751
3 World Health Organization and UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, *Global Vector Control Response 2017–2030* (World Health Organization, 2017), https://iris.who.int/handle/10665/259002
4 World Health Organization and UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, *Global Vector Control Response*
5 World Health Organization, *World Malaria Report 2024*
6 Najmul Haider et al., "Global Dengue Epidemic Worsens with Record 14 Million Cases and 9,000 Deaths Reported in 2024," *International Journal of Infectious Diseases* 158 (2025): 107940, https://doi.org/10.1016/j.ijid.2025.107940
7 "Fact Sheet: Dengue and Severe Dengue," World Health Organization, accessed 24 June 2025, https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue

Figure 1: Malaria incidence and mortality, 2010–2023



Source: World Malaria Report: https://www.who.int/teams/global-malaria-programme/reports/world-malaria-report-2024

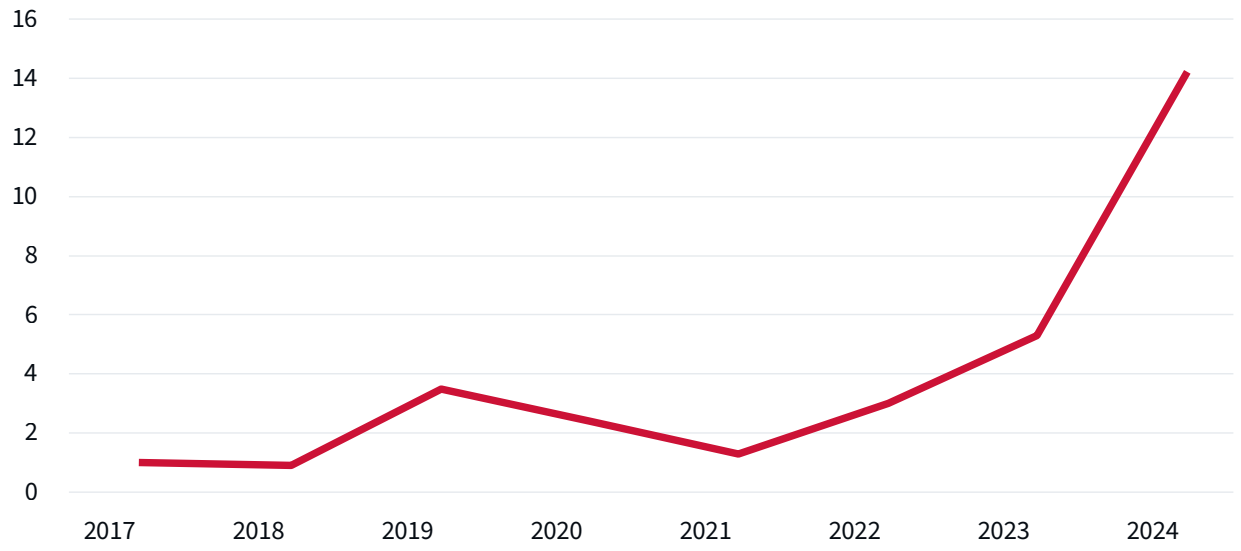
These figures point to a substantial and, in some areas, increasing global burden of mosquito-borne diseases. This challenge and the global policy failure to provide large-scale sustained control was formally recognized by the World Health Organization (WHO) during the Zika epidemic in 2016,[8] leading to the publication of the "Global vector control response 2017–2030" (GVCR) in 2017.[9] The GVCR points to a host of variables contributing to ongoing transmission and outbreaks, including the increasing spread and intensity of resistance to insecticides, rapid unplanned urbanization, climate and environmental change, and increased global travel and trade. In response, WHO developed a strategic approach to build effective, locally adapted and sustainable vector control. This approach seeks to tackle multiple vectors and diseases, and requires action across many sectors beyond health, including environment, urban planning and education. The GVCR also recognizes that continued investment and evaluation of innovative interventions, including genetically modified mosquitoes (GMMs), is essential if we are to succeed in controlling and, ultimately, eliminating vector-borne diseases.[10]

8 World Health Assembly 69, *Address by Dr Margaret Chan, Director-General, to the Sixty-ninth World Health Assembly* (World Health Organization, 2016), https://iris.who.int/handle/10665/252652

9 World Health Organization and UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases, *Global Vector Control Response*

10 Pedro Alonso et al., "Renewed Push to Strengthen Vector Control Globally," *Lancet* 389 (2017): 2270–71, https://doi.org/10.1016/S0140-6736(17)31376-4

Figure 2: Global dengue cases, 2017–2024 (in millions)



Source: WHO Global Dengue Surveillance: https://worldhealthorg.shinyapps.io/dengue_global/

By 2020, progress in the implementation of the GVCR had been slower than anticipated,[11] in part due to the lack of additional funding for the response; however, the slow pace of progress also reflects the inherent challenge in integrating a response across multiple diseases and sectors. Progress has since slowed further with recent cuts to overseas development aid, raising the question of whether we can still attain the original goals of reducing mortality from vector-borne diseases by at least 75% and incidence by at least 60% by 2030 (from a 2016 baseline).

In addition to the challenges identified in the GVCR and increasingly constrained funding, there has been growing recognition of the likely impact of climate change on mosquito-borne diseases. The current geographical range of mosquito species, such as *Aedes aegypti* – which is responsible for transmission of dengue, among other diseases – is constrained by a number of environmental factors, most importantly temperature. As a result of global warming, mosquito-borne diseases are anticipated to spread to new geographical areas, while transmission seasons may get longer in places where these diseases are already endemic.[12] Mathematical modeling suggests that, by 2050, the risk of *Aedes* transmission will expand significantly into temperate regions of North America, Europe and Asia, while the suitability for year-round transmission will spread in the tropics.[13] Similar potential increases in thermal transmission suitability

11 World Health Organization, *Global Vector Control Response: Progress in Planning and Implementation* (World Health Organization, 2020), https://iris.who.int/handle/10665/336658

12 Joacim Rocklöv and Robert Dubrow, "Climate Change: An Enduring Challenge for Vector-Borne Disease Prevention and Control," *Nature Immunology* 21 (2020):695, https://doi.org/10.1038/s41590-020-0648-y

13 Sadie J. Ryan et al., "Global Expansion and Redistribution of *Aedes*-Borne Virus Transmission Risk with Climate Change," *PLoS Neglected Tropical Diseases* 13 (2019): e0007213, https://doi.org/10.1371/journal.pntd.0007213

for malaria vectors have been identified, raising particular concerns over the further invasion and spread of highly adaptable and efficient vectors such as *Anopheles stephensi*.[14,15]

To tackle these threats, continuous improvements of existing tools and the development of new ones will be essential. Otherwise, we will be unable to maintain the gains made so far and make further advances toward the ultimate goal of eradication.[16] While existing interventions, such as insecticide-treated nets (ITNs) and indoor residual spraying (IRS), will continue to prevent millions of malaria cases over the coming years, these tools are mainly deployed indoors; furthermore, their effectiveness relies on changes in human behavior, such as adapting to sleeping under a net or allowing spray teams to enter houses to apply insecticides on at least an annual basis. These limitations paired with constrained funding have, in practice, meant that not all populations at risk of mosquito-borne diseases have had access to an ITN or IRS, and protection of at-risk populations has been incomplete, given that outdoor-biting mosquitoes are largely unaffected by these interventions.

A wide range of tools have been conceived to complement ITNs and IRS, or potentially replace them; these tools are at various stages of product development and evaluation.[17] Examples include attractive toxic sugar baits, endectocides, spatial repellents, eave tubes, sterile insect technique (SIT) using irradiation, and endosymbiont-based approaches, of which *Wolbachia* is the most well-known **(see Box 1)**. Since 2016, Unitaid has made significant investments in advancing market access to promising new vector control tools and continues to monitor the evolving landscape for truly transformative solutions. One such solution may be the use of GMMs. Genetic modification technology has been used across a range of sectors for many years, most prominently in agriculture to increase yields and develop more drought-resistant crops. By 2023, genetic modification technology was being used in 76 countries and regions globally, with the planting area of genetically modified crops accounting for about 13% of the total world farmland.[18] Countries that do not plant genetically modified crops are nonetheless often significant consumers of genetically modified crops, such as in the European Union, where the import of certain genetically modified crops for food and feed is authorized.[19]

14 Sadie J. Ryan et al., "Mapping Current and Future Thermal Limits to Suitability for Malaria Transmission by the Invasive Mosquito *Anopheles stephensi*," *Malaria Journal* 22 (2023): 104, https://doi.org/10.1186/s12936-023-04531-4

15 Qing Liu et al., "Possible Potential Spread of *Anopheles stephensi*, the Asian Malaria Vector," *BMC Infectious Diseases* 24 (2024): 333, https://doi.org/10.1186/s12879-024-09213-3

16 World Health Organization, *Malaria Eradication: Benefits, Future Scenarios and Feasibility. A Report of the Strategic Advisory Group on Malaria Eradication* (World Health Organization, 2020), https://iris.who.int/handle/10665/331795

17 The malERA Refresh Consultative Panel on Tools for Malaria Elimination, "malERA: An Updated Research Agenda for Malaria Elimination and Eradication," *PLoS Medicine* 14, no. 11 (2017): e1002456, https://doi.org/10.1371/journal.pmed.1002455

18 Xingru Cheng, "Trends in the Global Commercialization of Genetically Modified Crops in 2023," *Journal of Integrative Agriculture* 23, no. 12 (2024): 3943–52, https://doi.org/10.1016/j.jia.2024.09.012

19 The European Commission register for genetically modified crops compiles information on crops authorized for import or cultivation in the European Union. "Food and Feed Information Portal Database: Genetically Modified Organisms," European Commission, accessed 27 June 2025, https://ec.europa.eu/food/food-feed-portal/screen/gmo/search

Box 1: What is *Wolbachia*?

Wolbachia is a naturally occurring type of bacteria that is found in many insect species. When *Aedes* mosquitoes are infected with *Wolbachia*, their ability to reproduce or to transmit dengue, chikungunya and other diseases is affected. Several research groups have been working to leverage *Wolbachia* to develop new vector control technologies. This research has been largely focused on *Aedes* mosquitoes, in particular for dengue control. The World Mosquito Program is the largest project working on *Wolbachia*, with research taking place in 14 countries to date.[20]

Wolbachia infection can be used to both suppress the target population (as infected males mating with wild females will have no offspring) and/or stop transmission of the target disease through population modification (as infected individuals are no longer able to transmit the arboviruses responsible for many diseases such as dengue). [21]

"*Wolbachia* mosquitoes" are not genetically modified. The eggs are infected with the bacteria and bred. The infected mosquitoes pass the bacteria to their offspring through mating, making this approach self-sustaining; however, additional releases may be needed to maintain disease suppression levels. Since the bacteria are passed on through the population and can become established in that population, this method can also be described as a technology that "drives," not unlike the genetically modified "gene drive" approaches used by other researchers.[22,23]

While *Wolbachia* mosquitoes do not fall under the national regulations applicable to GMMs, their use is nonetheless subject to regulation by national authorities.

For decades, the potential use of GMMs to reduce disease burden has been under scientific investigation. Today, numerous evaluations of GMMs are under way and some products are beginning to reach the market, making this an opportune moment to distill the current technological advances in this area for a lay audience, outline the potential for products to become available in the near, medium and long term, describe market access barriers that lie ahead, and articulate possible solutions to these challenges to ensure broad access. In doing so, Unitaid's "Genetically modified mosquitoes technology and access landscape report" aims to provide a global public good, informing discussions and decisions among partners in the fight against mosquito-borne diseases. This information can help determine where and how to prioritize resources to accelerate potential pathways for GMM products to become part of national mosquito-borne disease control strategies.

This report is intended as a knowledge resource; it should not be interpreted as an endorsement of specific products or technologies by Unitaid, or as a committment to fund work on any specific product or technology.

20 "Our Work," World Mosquito Program, accessed 27 June 2025, https://www.worldmosquitoprogram.org/
21 World Health Organization, *Context and Background Materials in Support of the WHO Technical and Scientific Advisory Group with Respect to the Development of a Target Product Profile (TPP) for a Wolbachia Spp. Strain (Aedes aegypti Population Replacement Product)* (World Health Organization, 2022), https://cdn.who.int/media/docs/default-source/ntds/vector-ecology-mangement/context-background-materials-tpp-wolbachia-infected-aedes-aegypti.pdf?sfvrsn=6760a656_3
22 Diego Montenegro et al., "*Wolbachia*-Based Emerging Strategies for Control of Vector-Transmitted Disease," *Acta Tropica* 260 (2024), https://doi.org/10.1016/j.actatropica.2024.107410
23 Guan-Hong Wang et al., "Combating Mosquito-Borne Diseases Using Genetic Control Technologies," *Nature Communications* 12 (2021): 4388, https://doi.org/10.1038/s41467-021-24654-z

2. The potential contribution of GMMs

The concept of modifying organisms to select for desirable traits has been applied for thousands of years. Historically, it involved breeding plants and animals to achieve certain results. The development of genetic engineering in the 1970s opened up a new realm of possibilities for how to modify disease vectors.[24]

By the 1980s, two critical trends were coming into focus. First, major conceptual and technological advances in molecular biology and genetics were reshaping biomedical research,[25] pushing the boundaries of how genetic modification could one day be applied to insects. Second, mosquito-borne diseases were resurging in areas where they had previously been controlled, indicating that existing tools may not be up to the task of achieving and maintaining elimination of mosquito-borne diseases.

These technological and epidemiological developments paved the way for the establishment of the Vector Biology Network, a group funded by the MacArthur Foundation to adopt modern genetic techniques to combat vector-borne diseases. In January 1991, the Vector Biology Network held a seminal meeting on "Prospects for malaria control by genetic manipulation of its vectors" during which the group agreed that the use of molecular approaches to vector and disease control should be pursued as a real possibility and not as an impossible dream.[26] The meeting, sponsored by the Special Programme for Research and Training in Tropical Diseases, the MacArthur Foundation, and the University of Arizona, resulted in a 20-year plan for the development of GMMs. Concomitantly, the U.S. National Institute of Allergy and Infectious Diseases funded research on the genetic modification of mosquitoes and other insects.

In the decades since, there has been a great deal of progress toward realizing the goals established during that critical meeting, accelerated by the arrival of CRISPR-Cas9 gene editing technology. Scientists are now actively pursuing the genetic modification of mosquitoes to reduce the burden of malaria and *Aedes*-borne diseases such as dengue. A great number of strategies seek to leverage modern biotechnology tools to modify mosquitoes – from classic approaches involving sterilization of male mosquitoes to modifications that could persist in populations for extended periods of time.[27]

This landscape seeks to explore how GMMs could be scaled up in the future based on the current stage of research and market maturity. More technically detailed explanations of the subject can be found in the published literature, including the WHO publication "Guidance framework for testing genetically modified mosquitoes."

24 Luke S. Alphey et al., "Standardizing the Definition of Gene Drive," *Proceedings of the National Academy of Sciences of the United States of America* 117, no. 49 (2020):30864–67, https://doi.org/10.1073/pnas.2020417117

25 Barry J. Beaty et al., "From Tucson to Genomics and Transgenics: The Vector Biology Network and the Emergence of Modern Vector Biology," *PLoS Neglected Tropical Diseases* 3 (2009): e343, https://doi.org/10.1371/journal.pntd.0000343

26 Beaty et al., "From Tucson to Genomics and Transgenics"

27 There are also non-biotechnology approaches, such as *Wolbachia*, that share some characteristics with these biotechnology strategies (e.g., the "driving" factor)

Genetic modification of mosquitoes aims at reducing the burden of mosquito-borne diseases via one of two approaches (Figure 3). The first, population suppression (also called population reduction), reduces (suppresses) the size of the natural mosquito population to the extent that it can no longer sustain pathogen transmission.[28] This mode of action is analogous to conventional chemical control methods (e.g., larvicides) that also work by suppressing mosquito populations, but it is more targeted (i.e., species-specific). Population suppression could, however, face resistance to the modification over time and/or may result in empty breeding sites or niches that could be invaded by wild-type vectors of the same or possibly different species.

The second approach, population replacement (also known as population modification, population alteration or population conversion), targets vector competence with the aim of reducing the inherent ability of individual mosquitoes to transmit a given pathogen.[29] This approach could sidestep some perceived environmental concerns surrounding population suppression, as well as potential logistical issues of gene drive applications (e.g., the need for constant backcrossing). Modification drives, however, do not address overall biting rates, as they do not target mosquito density. They might also be vulnerable to the emergence of parasite resistance against the effector mechanism, and to mutational breakdown of the driver such that it loses its anti-parasitical effect.[30]

Although population suppression and population replacement are often presented as alternative approaches, they could be combined to reduce the shortcomings of each approach and to increase the magnitude and duration of impact. This combined approach has recently been explored successfully in caged populations and through mathematical modeling.[31]

A variety of approaches can be used to create GMMs for population suppression or population modification. These approaches can be differentiated mainly by how long the modification is likely to persist in the environment: from not at all in the case of male insects modified to be sterile, to potentially very long in the case of mosquitoes modified using gene drive approaches.

In the case of all GMM strategies, the genetic modification could impact the ability of the modified mosquito to compete against wild populations. Any genetic modification could impose such a "fitness cost" that would decrease the ability of the mosquito to survive or mate successfully, potentially affecting its competitivity against wild-type mosquitoes and its effectiveness as a vector control tool.[32,33]

28 World Health Organization, *Guidance Framework for Testing Genetically Modified Mosquitoes, Second Edition* (World Health Organization, 2021), https://iris.who.int/handle/10665/341370
29 World Health Organization, *Guidance Framework for Testing GMMs*
30 Andrea Beaghton et al., "Requirements for Driving Antipathogen Effector Genes into Populations of Disease Vectors by Homing," *Genetics* 205 (2017): 1587–96, https://doi.org/10.1534/genetics.116.197632
31 Sebald A. N. Verkuijl et al., "A Suppression-Modification Gene Drive for Malaria Control Targeting the Ultra-Conserved RNA Gene mir-184," Nature Communications 16 (2025): 3923, https://doi.org/10.1038/s41467-025-58954-5
32 Franck Adama Yao et al., "Mark-Release-Recapture Experiment in Burkina Faso Demonstrates Reduced Fitness and Dispersal of Genetically-Modified Sterile Malaria Mosquitoes," *Nature Communications* 13 (2022): 796, https://doi.org/10.1038/s41467-022-28419-0
33 William T. Garrood et al., "Driving Down Malaria Transmission with Engineered Gene Drives," *Frontiers in Genetics* 13 (2022), https://doi.org/10.3389/fgene.2022.891218

Figure 3: Characteristics of genetically modified, non-gene drive and gene drive products

Genetically modified, non-gene drive

Single generation

Uses genetic modification to make males and/or females sterile through mating. The modification lasts for one generation only and is not passed on to offspring.

Limited spread and persistence: The modification does not spread and does not persist. It requires repeated, frequent releases of large numbers of modified insects to significantly reduce the wild population of the target species.

Stability and resistance: Not a concern, since there is no expectation that the modification will spread or become established in the population.

Possible use: Could be best suited to species that are geographically concentrated – for example, in cities – and possibly seasonal.

Example: Synvect sterile male technology targets *Ae. aegypti,* the main vector of dengue and other diseases.

Suitable for suppression approaches only

Self-limiting

Uses genetic modification to introduce a gene that disrupts survival, fertility or other traits – for example, the ability to carry a parasite. The modified gene is only passed on to 50% of the progeny, so the trait will disappear over time.

Limited spread and persistence: Requires repeated releases of modified insects to maintain impact.

Stability and resistance: Stability of the modification and emerging resistance could impact efficacy over time.

Possible use: Could be best suited to species that are geographically concentrated – for example, in cities rather than large rural areas – and possibly seasonal. This will depend on target species behavior.

Example: Oxitec Friendly™ mosquitoes for the control of invasive *Ae. aegypti* in urban, dengue -impacted environments.

Suitable for both suppression & replacement approaches

Genetically modified, gene drive

Use genetic modification to introduce a gene that disrupts survival, fertility or other traits – for example, the ability to be infected by or transmit a parasite.

Self-limiting

The modification is inherited by up to 100% of the progeny. Self-limiting gene drive systems rely on constructs that are activated when two or more components are combined. These systems are time-limited, as they will stop working if one or more of the components become inactive or are lost from the construct.

Spread and persistence: The modification can become established and spread at a higher rate than non-driving elements but will eventually disappear. The geographical spread and persistence are less than for self-sustaining gene drives. The approach requires repeated releases of modified insects to maintain impact.

Stability and resistance: Stability of the modification and emerging resistance could impact efficacy over time.

Possible use: Suitable for controlling species that are specific to a particular area and for targeting specific subpopulations if these are geographically or otherwise isolated.

Example: Split drives.

Suitable for both suppression & replacement approaches

Self-sustaining

The modification is inherited by up to 100% of the progeny. As a result, the modification could remain present in the population for a long time at a rate high enough to sustain impact.

Spread and persistence: Designed to spread within a population and persist over time. Theoretically, one sufficiently large release of modified mosquitoes could suffice. However, factors affecting the rate of spread and persistence in the wild could necessitate additional releases over time.

Stability and resistance: Stability of the modification and emerging resistance could impact efficacy over time.

Possible use: Since the modification can become established and persist, this approach can offer long-term impact on diseases and species that are spread over wide or hard-to-access areas, which currently require intensive and logistically challenging interventions.

Examples: University of California Malaria Initiative (UCMI), Target Malaria, Transmission Zero.

Suitable for both suppression & replacement approaches

GMM methods may prove to be cost-effective and sustainable interventions to reduce mosquito-borne diseases. By targeting the root cause of mosquito-borne diseases, namely the mosquito, it is conceivable that single or infrequent releases of GMM constructs that are self-sustaining will be sufficient to achieve significant disease reduction, while frequent releases of self-limiting constructs would be required to achieve similar impact. In addition, as GMM methods do not require individual uptake or behavior change, particularly for self-sustaining approaches, they can also ensure that all populations benefit equally from the intervention, regardless of social status, gender or geographical location.

Efficiencies may be realized by developing GMM technologies that span multiple disease areas. For instance, *Ae. aegypti* is known to transmit dengue, yellow fever, chikungunya and Zika. A genetic modification that suppresses the population of this species could effectively reduce the transmission of any of these diseases, although the impact on each target disease still requires demonstration in the field.

Like all other technologies, the deployment of GMMs comes with a set of remaining challenges and some inherent limitations, meaning that some approaches are unlikely to be ready for routine field deployment for years to come. It also means that, once deployed, GMMs will not be a panacea for the control of all mosquito-borne diseases across all geographies. There will be a continued need for funding to support conventional forms of vector control in settings where GMMs do not provide sufficient impact or are not (yet) suitable. Moreover, GMMs will not be released in the environment without prior risk assessment and regulatory authorization; these processes are likely to extend the timeline to routine field deployment. As discussed in subsequent sections, other challenges, both technological and social, will need to be addressed as the research and market for these technologies mature.

Figure 4: GMM Technologies for population suppression or population replacement

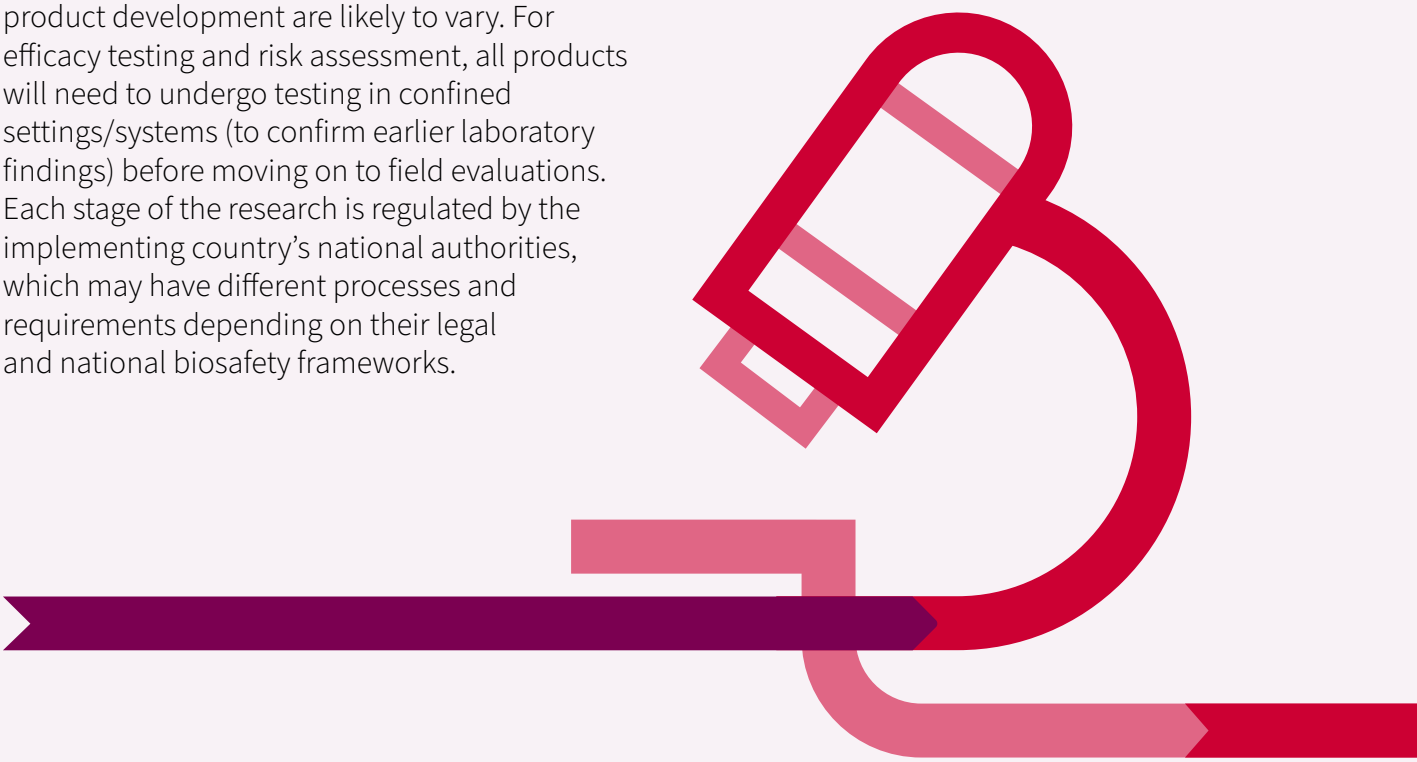
Adapted from: https://www.mdpi.com/2071-1050/13/10/5653

3. Current state of GMM research and market

While the concept of GMMs has been under development for decades, the opportunity to apply some of these technologies to advance public health goals is reaching a pivotal moment. One commercial entity has released GMMs targeting species that transmit dengue and malaria, with the latter currently undergoing entomological evaluation in Djibouti. Meanwhile, academic research groups are preparing for the first field trials of gene drive GMMs targeting malaria.

Development of GMMs follows the steps outlined in the WHO "Guidance framework for testing genetically modified mosquitoes."[34] However, depending on the product, the claim that developers intend to make and national regulatory requirements, the pathways for product development are likely to vary. For efficacy testing and risk assessment, all products will need to undergo testing in confined settings/systems (to confirm earlier laboratory findings) before moving on to field evaluations. Each stage of the research is regulated by the implementing country's national authorities, which may have different processes and requirements depending on their legal and national biosafety frameworks.

Given the broad spectrum of product maturity – from those already being released in the field to early-stage laboratory research – this landscape categorizes GMM projects into (1) "**first movers,**" which are commercial firms or research groups that have pioneered GMM efforts and reached Phase 2 or beyond in the research pipeline (Table 1), and (2) "**emerging technologies,**" which are in Phase 1, undergoing laboratory development or small-cage studies **(Table 2)**.



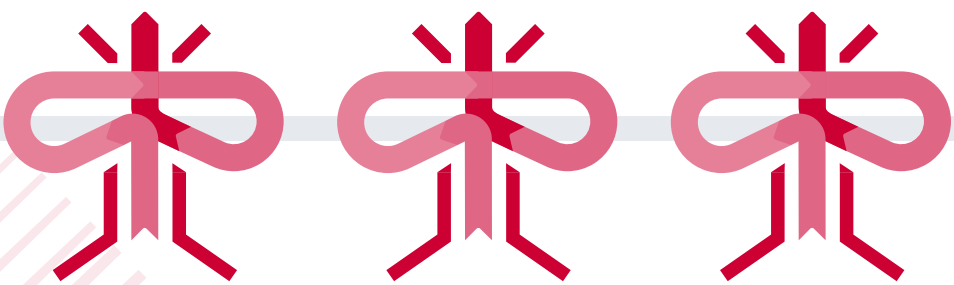
34 World Health Organization, *Guidance Framework for Testing GMMs*

3.1 GMM first movers

3.1.1 Commercial

While much of the research on gene drives has yet to be evaluated under field conditions, other types of GMMs are already being used or starting to be used. Most of the commercial products being developed target ***Ae. aegypti***, with the aim of reducing the burden of arboviral diseases such as Zika and dengue. Building on these experiences, development and evaluation of modified *Anopheles* strains is ongoing, with the aim of controlling malaria transmission. While the research groups listed below are working on self-sustaining gene drives for both population suppression and replacement, the commercial groups profiled below are focused on population suppression via non-gene drive, self-limiting approaches.

- **Oxitec:** Oxitec develops biological solutions to control pests that transmit diseases, destroy crops and harm livestock. In the public health space, Oxitec has historically focused on *Aedes* mosquitoes through its Friendly™ technology of self-limiting GMMs, which works through population suppression. Recently, Oxitec has begun to move into the genetic control of *An. stephensi* and *An. albimanus*, both of which are important invasive malaria vectors, along with *Ae. albopictus*, an important dengue vector.
- **Synvect:** Synvect aims to develop safe and economical biological solutions that eliminate disease-transmitting insects. The company is focused on introducing genetically modified sterile males into wild mosquito populations to reduce population density.



3.1.2 Non-commercial

Academic research groups are primarily focused on self-sustaining gene drive technologies. The appeal of such technologies lies in the possibility that relatively few mosquitoes would need to be released and that impact would be sustained over time. Consequently, such technologies would provide significantly higher cost-effectiveness and equitable access, while opening up use cases, such as coverage of large geographical areas, that go beyond those of other genetic modification approaches.

Current research is focused on preparing for the first field trials of gene drive mosquitoes to demonstrate impact on malaria. These trials will likely take place in the next few years. The research groups profiled below are all non-profits concentrating on malaria.

- **Target Malaria:** Target Malaria is a not-for-profit research consortium focused on developing gene drive for population suppression.
    - Includes the following partners: Imperial College London (United Kingdom of Great Britain and Northern Ireland [UK]), Institut de Recherche en Sciences de la Santé (Burkina Faso), Uganda Virus Research Institute (Uganda), Polo d'Innovazione di Genomica, Genetica e Biologia (Italy), CDC Foundation (United States of America [USA]), University of Ghana (Ghana), University of Oxford (UK), Liverpool School of Tropical Medicine (UK), Malaria Genetic Biocontrol Trust (UK), and Sya Innovation Centre (Burkina Faso).

- **Transmission Zero:** Transmission Zero is an international research program focused on gene drive for population replacement.
    - Includes the following partners: Ifakara Health Institute (United Republic of Tanzania), National Institute of Medical Research (United Republic of Tanzania), Imperial College London (UK), and Swiss Tropical and Public Health Institute (Switzerland).

- **University of California Malaria Initiative (UCMI):** UCMI is a not-for-profit research collaborative focused on gene drive for population replacement.
    - Includes the following partners: University of California Irvine (USA), University of California Davis (USA), University of California San Diego (USA), University of California Berkeley (USA) and Johns Hopkins University (USA).

3.1.3 Financing

To date, philanthropic funding has contributed the lion's share of support for GMM research and for product development by some commercial entities.

For research groups, the Gates Foundation has been the largest source of funding, contributing significant resources to Target Malaria and Transmission Zero. Open Philanthropy has also invested in GMMs, including the work of UCMI and Target Malaria. Wellcome and the European Union have also supported research activities that feed into GMM project work.

Commercial entities have raised funding from a blend of public and private sources. For example, Oxitec, which is privately owned, has received over US$40 million from the Gates Foundation for a portfolio of work on GMMs, as well as US$6.8 million from Wellcome, along with funding from a range of other sources across partnerships and development programs. Oxford Capital led early rounds of funding for Oxitec.

Synvect has raised US$1.3 million in commercial funds from Antler, Redbud and NuFund, and secured a US$1.7 million equity-free grant from the Gates Foundation.

Table 1: Current state of play of GMMs: first movers

Project / Institution(s)	Countries where research is taking place	Intended use countries	Type of organization or group (commercial or non-commercial)	Type of technology 1. non-driving (including single generation and multi-generation); 2. driving with 2.1 self-limiting / 2.2. self-sustaining; 3. other	Targeted disease	Species	Population suppression or population replacement
Oxitec	United Kingdom of Great Britain and Northern Ireland, Brazil, Djibouti, Australia, Panama, Marshall Islands, United States of America	Regions where dengue, malaria and other vector-borne diseases are present (United States of America, Latin America, Asia-Pacific, Europe, the Middle East, Oceania, Africa)	Commercial	Non-driving, multi-generation (1)	Dengue, Zika, chikungunya, malaria	*Ae. aegypti*, *An. stephensi*, *An. albimanus*, *Ae. albopictus* and more	Population suppression
Synvect	United States of America	Any region where dengue is present	Commercial	Non-driving, single generation (1)	Dengue, yellow fever, Zika, chikungunya	*Ae. aegypti*	Population suppression
Target Malaria	United Kingdom of Great Britain and Northern Ireland, Italy, Burkina Faso, Uganda, Ghana, United States of America	Sub-Saharan Africa	Non-commercial	Self-sustaining gene drive (2.2)	Malaria	*An. gambiae*, *An. coluzzii*, *An. arabiensis*, *An. funestus*	Population suppression
Transmission Zero	United Republic of Tanzania, United Kingdom of Great Britain and Northern Ireland	Sub-Saharan Africa	Non-commercial	Self-sustaining gene drive (2.2)	Malaria	*An. gambiae*, *An arabiensis*, *An. funestus*	Population replacement
UCMI	United States of America, Sao Tome and Principe	Sub-Saharan Africa	Non-commercial	Self-sustaining gene drive (2.2)	Malaria	*An. coluzzii*, *An. gambiae*	Population replacement

3.1.4 Regulatory status

Given that current research is largely focused on assessing genetic and entomological parameters and not yet disease impact, most organizations involved in the development of GMM products have yet to apply for approval through national regulatory agencies or submit documentation to inform an assessment by WHO.

The exceptions to this are as follows: (1) Target Malaria obtained national regulatory approval[35] for the first ever small-scale release of GMMs in Africa in 2019[36] and has applied to biosafety and environmental regulators for a release of its self-limiting strain. However, neither product is intended to be used as a malaria control tool.

(2) Oxitec received approval for field evaluation of GMMs in a number of countries, including Brazil, Cayman Islands (UK), Djibouti, Malaysia, Marshall Islands, Panama, and the United States of America.[37] (3) Synvect received approval from the U.S. Environmental Protection Agency for its first product, SEPARATOR. Pilot programs with government and mosquito control agencies are being launched in California, Florida, Texas and other high-risk areas.[38] All other projects are either in Phase 1 or 2 of research, as described below **(Figure 4)**.

35 As of August 2025, Target Malaria's research program in Burkina Faso has been suspended. https://www.bloomberg.com/news/articles/2025-08-23/burkina-faso-halts-gates-foundation-backed-anti-malaria-project

36 Yao et al., "Mark-Release-Recapture"

37 Approved for field evaluations in Florida (USA) by state and federal authorities (2020, extended 2022 (second-generation technology)); in Brazil by the National Biosafety Committee (2010 release approval (first-generation technology), 2020 commercial approval (second-generation technology)); in Djibouti by the national regulatory authority (2023 release approval (second-generation technology)); in Panama by the National Biosafety Committee and by the Ministries of Agricultural Development and Commerce and Industry (2014 release approval (first-generation technology)); in Cayman Islands (UK) by the national regulatory authority (2016 release approval (first-generation technology)); in Marshall Islands by the regulatory authorities (2023 release approval (second-generation technology)); in Malaysia by the national regulatory authorities (2010 release approval (first-generation technology)). No releases yet in India. Oxitec is in partnership with the Australian science agency, the Commonwealth Scientific and Industrial Research Organisation, and is in the application process for field releases in Australia. USA-wide commercialization approval is under review by the U.S. Environmental Protection Agency

38 "Synvect Secures $3M Seed Round to Combat Mosquito-Borne Diseases with CRISPR Technology," Business Wire, March 11, 2025, https://www.businesswire.com/news/home/20250305687057/en/Synvect-Secures-%243M-Seed-Round-to-Combat-Mosquito-Borne-Diseases-with-CRISPR-Technology

Figure 4: Research pipeline: first movers

Phase 1: Laboratory and small-cage studies	**Phase 2:** Large-cage studies or "semi-field testing"	**Phase 3:** Field evaluations and post-release monitoring	**Phase 4:** Approved and used as a public health tool
Oxitec: Pipeline of products in Phases 1, 2, 3 and 4			
Transmission Zero: Different components of its gene drive mosquito in Phase 1 and Phase 2			
	Target Malaria: Actively planning Phase 3 studies for its gene drive mosquito		
	Synvect: Conducting trials with *Ae. aegypti* next-generation SIT product		
	UCMI: Planning to conduct ecologically contained field trial with full drive on the island of Principe		

3.2 GMM emerging technologies

In addition to the group of "first movers" pioneering GMM research and market entry, there are a substantial number of organizations conducting Phase 1 research focused on laboratory development and/or small-cage studies. While these emerging technologies are at an earlier stage of research, they offer promising innovations targeting a broader range of diseases. With the exception of Biocentis, these technologies are being developed in university laboratory settings.

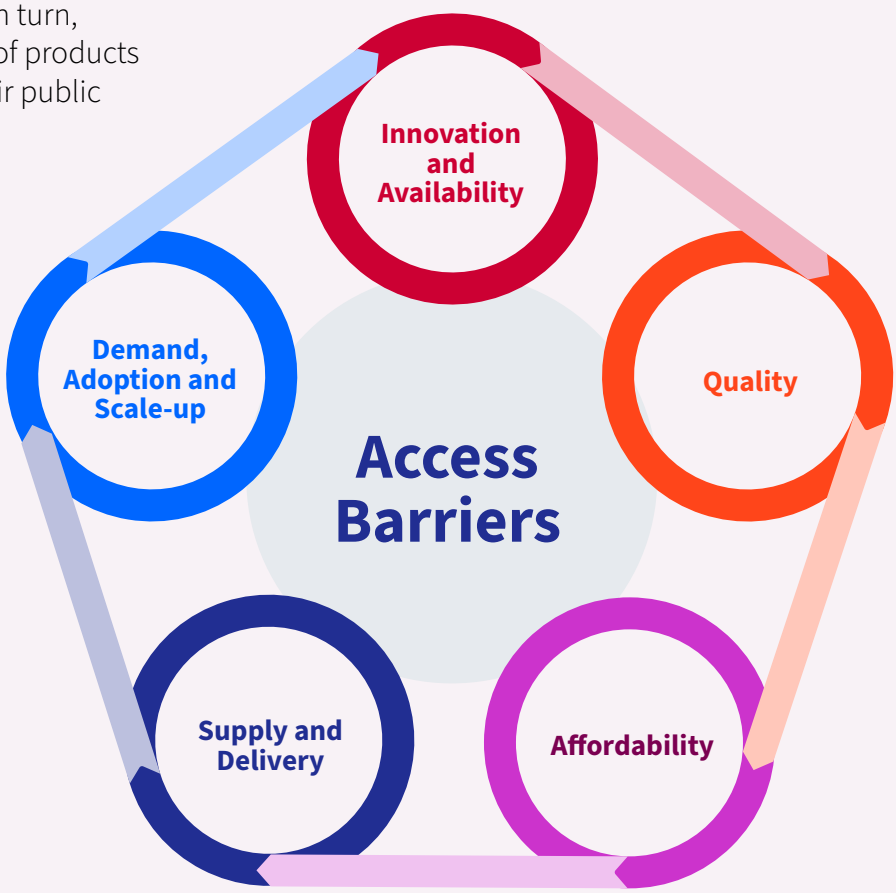
Table 2: Current state of play of GMMs: emerging technologies

Institution	Countries involved	Type of organization or group	Type of technology	Targeted disease	Species	Population suppression or population replacement
Biocentis	Italy	Commercial	Self-limiting	Dengue, yellow fever, Zika, chikungunya	*Ae. aegypti*	Population suppression
Commonwealth Scientific and Industrial Research Organisation	Australia and Asia-Pacific	Non-commercial/ government	Non-driving, multi-generation	Dengue, Zika, chikungunya	*Ae. aegypti*	Population replacement
Liverpool School of Tropical Medicine – Tony Nolan Lab	United Kingdom of Great Britain and Northern Ireland	Non-commercial	Driving, self-sustaining	Malaria	*An. gambiae, An. stephensi, An. funestus*	Both: Suppression *(An. gambiae)* and replacement (*An. funestus*)
Macquarie University	Australia	Non-commercial	Non-driving, "intragenerational," Allele Sail	To be determined	*Ae. aegypti*	Suppression
Peking University – Champer Lab	China	Non-commercial	Confined threshold-based and self-limiting drives	Malaria, dengue, chikungunya, yellow fever, Zika	*An. stephensi, Ae. aegypti, Culex quinquefasciatus*	Suppression and replacement
University of California San Diego – The Akbari Lab	United States of America	Non-commercial	Non-driving, multi-generation	Malaria, Zika, chikungunya	*Ae. aegypti, An. gambiae*	Suppression
University of Strasbourg / Institut National de la Recherche Médicale (Inserm)	France	Non-commercial	Not specified	Zika, malaria	*Ae. albopictus, An. gambiae*	Not specified
University of York – Luke Alphey Lab	United Kingdom of Great Britain and Northern Ireland	Non-commercial	Driving, self-limiting	Zika, dengue, chikungunya, yellow fever, malaria	*Ae. aegypti, An. stephensi*	Suppression and replacement
University of Queensland	Australia	Non-commercial	Driving, self-sustaining	Malaria	*An. farauti*	Replacement

4. Potential barriers to access

GMMs are a nascent technology from a product introduction perspective. While a few non-gene drive GMMs have reached the market, many products are still in Phase 1 of evaluation. In this context, it may seem premature to identify and evaluate the potential barriers to scaling up GMMs. For Unitaid, however, it should not be an afterthought to identify any barriers to market entry and scale-up of innovative interventions or products.[39] Given the unique nature of GMMs, we consider the in-depth assessment of potential barriers to be particularly important at the current stage of development, with a view to identifying and addressing such barriers as early as possible and, in turn, accelerating market introduction of products once they have demonstrated their public health value.

The potential access challenges below are organized according to Unitaid's Access Barrier Framework, which has been developed and refined over nearly two decades of supporting product introduction and scale-up. The framework spans five broad categories: innovation and availability; quality; affordability; supply and delivery; and demand, adoption and transition to scale-up.



39 "Access Is Not an Afterthought: Learnings and Opportunities for Equitable Access to Lifesaving Therapeutics in Future Pandemics," Unitaid, accessed 27 June 2025

4.1 Innovation and availability

Future availability of GMMs will depend on continued support for this area of innovation in the short and medium term to assess its potential public health value. Supportive action will need to include diversifying research products for other vector-borne diseases, broadening the funding base, supporting emerging technologies, and bringing greater institutional coordination to field evaluations.

- **Constrained product development pipeline:** While there is significant early-stage research on GMMs, the product development pipeline is relatively concentrated on malaria. In addition, there is an important gap between early movers and emerging technologies in terms of the level of advancement. Consequently, if some of the GMMs in the later stage of the pipeline do not make it through field evaluations, there will be few alternatives to be launched in the near to medium term.
    - Most of the research projects in the "first movers" category are focused on *Anopheles* malaria vectors. For dengue, there is little depth to the pipeline of genetic tools among the "first movers," besides Oxitec's work on non-gene drive, self-limiting mosquitoes. Although a number of projects in the "emerging technologies" category are working on *Aedes*, these are at a very early stage, and efforts to develop gene drive approaches for dengue have had limited success to date.[40]
    - Even in the *Anopheles* space, few of the research groups have the expertise required to move a product through registration and support its market entry. If one or more of the current innovations do not make it through the evaluation pathway, this may be a deterrent to other innovators or funders.
- **Limited sources of funding to support research:** Funding to develop GMMs is primarily coming from one philanthropic source, which leaves the field vulnerable and poses challenges to taking the resource-intensive steps toward market access, such as field trials.
- **Lack of institutional coordination to support field evaluations:** There is no existing support mechanism to convene the various actors that should be involved in implementing larger scale field evaluations.
    - Other product areas such as vaccines are often developed by large biomedical companies and benefit from groups such as Gavi, the Vaccine Alliance, to help foster partnerships to finance and implement field trials.
    - GMM developers are likely to face common challenges and questions. There are ongoing efforts through GeneConvene to support work around common technical issues affecting the lead research projects and to build scientific and regulatory capacity. However, each project will likely require a coalition of funders and implementing partners, many of which may not yet be active in this space.

40 Joshua XD Ang et al., "Synthetic Homing Endonuclease Gene Drives to Revolutionise Aedes aegypti Biocontrol: Game Changer or Pipe Dream?" *Current Opinion in Insect Science* 70 (2025), https://doi.org/10.1016/j.cois.2025.101373

4.2 Quality (and pathways to enable procurement)

At the global, regional and country levels, GMMs represent a new vector control intervention that will likely consist of a broad range of products. Therefore, novel approaches to quality assurance, regulation and approval will be required. This will have implications for how procurement agencies and regulatory authorities consider GMMs, adoption timelines and country procurement decisions.[41]

- **Unclear global and regional pathways to assess safety, quality and efficacy:** For developers seeking recommendation of their products as a public health intervention and associated prequalification, the WHO pathways for assessing genetically modified organisms (GMOs) are unclear. Similarly, while mechanisms such as the West Africa Integrated Vector Management platform have been established, it is not yet clear how subregional coordination for joint review or approval of products will work, particularly with respect to transboundary issues.
- **Uncertain country regulatory pathways:** Field evaluations of GMMs and broader deployment of GMMs will be subject to regulatory approval and registration in the country of use. These processes could involve several authorities in each country, including biosafety, environmental and health authorities, which would be a departure from other vector control tools and GMOs:
    - The novelty of regulating GMOs in most countries, in particular GMOs that are for health purposes (rather than for agriculture) and that may have a transboundary element, may present a new challenge for national regulators – with gaps in capacity and knowledge, and lack of clarity on regulatory requirements and pathways. For example, regulators may need to indicate what measures of efficacy they require to support registration of a product; these measures may be entomological or epidemiological, depending on the product claim. Some developers, such as Oxitec, have focused solely on entomological end-points to date. However, requirements could vary and evolve, particularly in the absence of clear global and regional pathways.
    - Countries may also require registration/approval through their health regulatory authorities, which are unlikely to have previous experience with regulating GMOs.
    - If countries choose to procure GMMs themselves (not via global procurement structures), it is unclear whether ministries of health will seek an alternative to currently established mechanisms, such as WHO recommendation and prequalification listing. For other health products, stringent regulatory authority (e.g., U.S. Food and Drug Administration) approvals have been considered a suitable substitute, but such approvals may not be relevant or appropriate in the case of technologies that would only be used in sub-Saharan Africa, such as gene drive mosquitoes for malaria control. National authorities may take different paths, and their level of experience in regulating other GMOs may influence their approach.

41 Stephanie L. James et al., "Regulatory and Policy Considerations for the Implementation of Gene Drive-Modified Mosquitoes to Prevent Malaria Transmission," *Transgenic Research* 32 (2023): 17–32, https://doi.org/10.1007/s11248-023-00335-z

4.3 Affordability

While an advantage of GMMs is thought to be their potential cost-effectiveness and sustainability, this has yet to be established. Field trials and use of GMMs may also require financial security mechanisms, such as liability insurance, which may impact the eventual cost of this intervention.

- **Lack of cost-effectiveness data:** GMMs are thought to be cost-effective, but data are currently insufficient with respect to both cost and effectiveness, including cost-effectiveness relative to alternative vector control interventions. This information will be crucial to inform prioritization analyses by countries and key procurers, as well as analyses of how to integrate GMMs into vector control and vector-borne disease prevention programs alongside other tools. Field testing provides an opportunity to start generating these essential insights. As the scale of deployment increases from trials to routine implementation, economies of scale are likely to arise that will need to be substantiated and quantified by means of additional cost and effectiveness data.
- **Financial security mechanisms:** Depending on national legislation, field trials and broader use of GMOs could be tied to insurance requirements in case of environmental or other damage.
    - Some obligations are laid out in international agreements, notably the Cartagena Protocol and the Nagoya-Kuala Lumpur Supplementary Protocol on liability and redress, to which many countries are Parties.
    - Exact requirements regarding insurance and liability will vary by country, and it is possible that countries will assume liability rather than requiring developers to do so. To date, this has been the case. If liability is carried by developers, the question of securing insurance will likely arise. This has been a challenge with other GMOs, as risks can be difficult for insurers to quantify, and could be a barrier to field evaluations and use.

4.4 Supply and delivery

Manufacturing facilities and supply chains to deliver GMMs will need to be designed from the ground up.

- **Scaled-up manufacturing facilities:** GMMs will require infrastructure to rear mosquitoes relatively close to where they will be released. This is particularly important for *Anopheles* mosquitoes, as their eggs are not drought-resistant and long-distance shipping currently poses considerable challenges. Rearing facilities will need to be constructed for field evaluations, particularly for the later phases. If products are validated as new vector control interventions, then the ability to quickly increase production beyond the scale required for field evaluations will be crucial.
    - Experience from SIT programs should be used to inform the supply and delivery of GMMs.
    - It is anticipated that there will be no major supply challenge when scaling up self-sustaining gene drives, as their releases will presumably be smaller than for more self-limiting tools.
    - Factors for determining optimal location of individual production facilities include logistical access, availability of necessary resources (e.g., power and water), enabling government environment, including regulatory frameworks for work on GMOs in containment, local acceptance, and skilled labor availability.[42]
    - Establishment of production lines will require adequately designed and equipped manufacturing facilities, including insectaries meeting biosafety standards, trained staff, and standard operating procedures for mosquito husbandry, biosafety compliance, quality management and documentation.[43]
- **Novel supply chain and delivery mechanisms needed:** Specific issues regarding permits, transport and post-release monitoring must be addressed if GMMs are to be transported over long distances or across borders.
    - There may be trade-offs to consider between the benefits of scaling up production and supply through regional hubs, and the benefits of more localized production facilities – for example, impact on mosquito fitness. Similar issues do, however, apply to other types of products and therefore do not present a unique barrier to the GMM supply chain.
    - Protocols for transporting GMMs, such as storage conditions, temperature monitoring, product integrity/quality, tracking, labeling, disposition of shipping materials, and record-keeping, will need to be prepared and tested in advance,[44] potentially during field evaluations.
    - When production facilities serve a broad geographical area (i.e., multinational), shipping GMOs across international borders involves regulatory permits, health inspection requirements, and containment and chain of custody issues, presenting possible compliance issues for the product.

42 James et al., "Regulatory and Policy Considerations"
43 Stephanie L. James et al., "Requirements for Market Entry of Gene Drive-Modified Mosquitoes for Control of Vector-Borne Diseases: Analogies to Other Biologic and Biotechnology Products," *Frontiers in Bioengineering and Biotechnology* 11 (2023): 1205865, https://doi.org/10.3389/fbioe.2023.1205865
44 James et al., "Requirements for Market Entry"

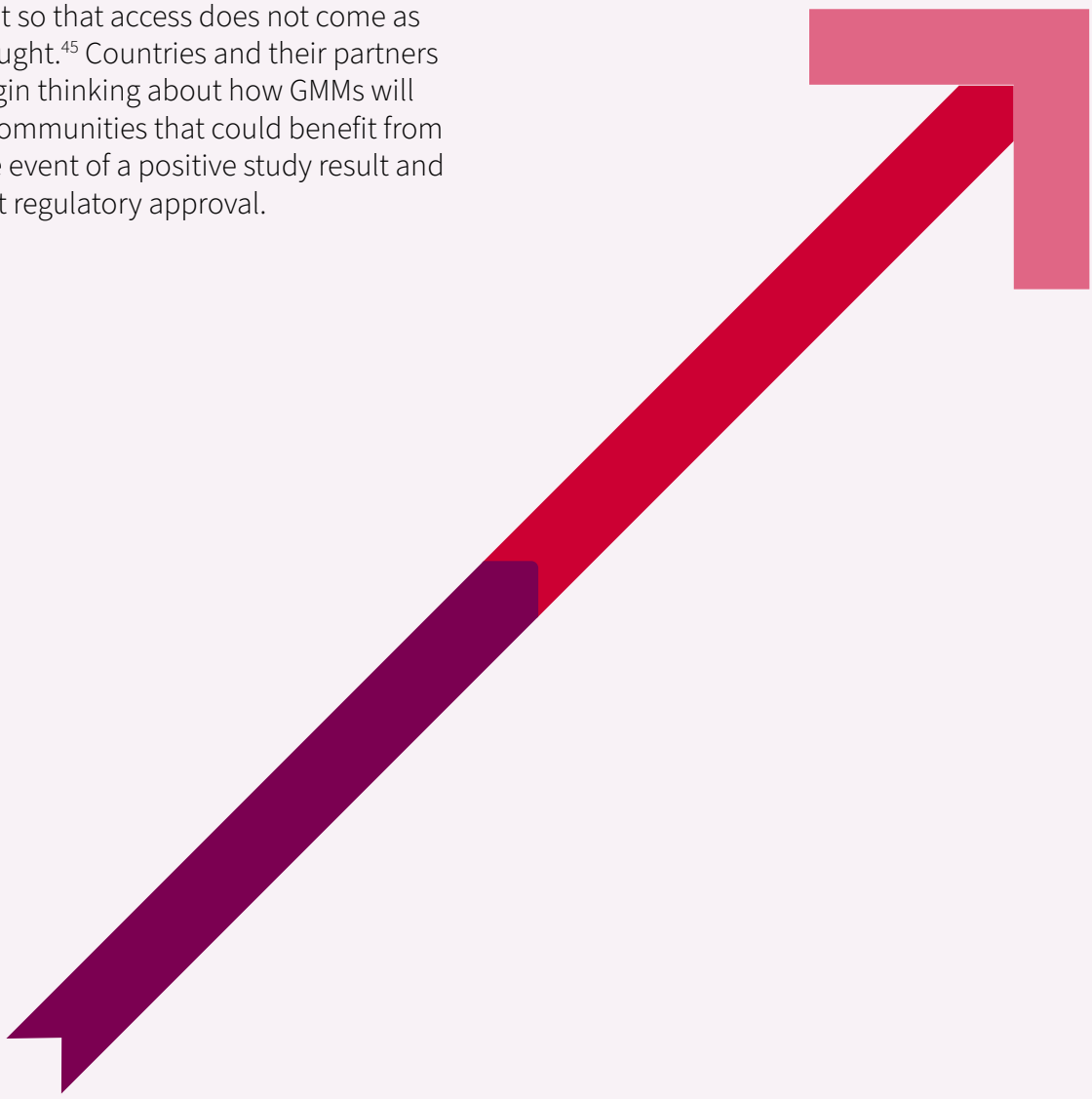
4.5 Demand, adoption and transition to scale-up

- **Long-term financing pathways not established:** Sustainable financing for the procurement of GMMs will depend on regulatory pathways as well as sufficient budget amid an increasingly competitive environment for global health products.
    - Establishing the criteria required to make GMM technologies eligible for procurement via the Global Fund or other donors and funding mechanisms will be key to supporting uptake. Considering how to facilitate procurement directly by malaria-endemic countries is also an important question.
    - Demand for GMMs will depend in part on product performance and cost-effectiveness data, which are not yet available. This evidence will be key to securing funding for GMM procurement, given that these technologies will, at least initially, need to be deployed in addition to existing vector control interventions and that they will be competing against an increasing number of other innovations (vaccines, other vector control products such as spatial repellents, diagnostics, treatments, etc.) for a limited and currently declining pool of malaria funding.
- **Public acceptance will affect demand:** Support for the use of GMMs may be affected by perceptions of genetic tools held by other researchers, experts, governments and funders. Perceptions of risk, competition or value-based considerations could limit support for GMM use. Although the efficacy of GMMs in controlling vector-borne diseases is likely to be less dependent on individual adoption and behavior change than is the case with ITNs and IRS, local communities' acceptance of the technology will also affect governments' interest in using these tools. Community-level agreement and engagement will be essential to facilitate implementation. Experience to date has shown that, at least in some communities, there are stigmas associated with GMOs, which are exacerbated by ongoing disinformation campaigns about the technology. However, these potential barriers have not hampered the introduction of Oxitec's Friendly™ mosquitoes.
    - Questions remain as to how much of the stigma related to genetically modified agricultural products will be transferred to GMMs and whether activist campaigns will dampen demand.
    - Experience from ongoing deployment of GMMs with regard to community sensitization and demand creation will need to be collated and disseminated to facilitate future introductions.

5. Opportunities for future scale

In the coming years, funders and investors supporting the scale-up of GMMs will encounter some familiar barriers to access, as well as novel challenges reflecting the nature of the product. The road to broad-based access will not look the same for every GMM product, as regulatory pathways will vary, and challenges linked to scale-up and rollout will depend on each product's characteristics. Despite these differences, mapping future access scenarios is important so that access does not come as an afterthought.[45] Countries and their partners need to begin thinking about how GMMs will reach the communities that could benefit from them in the event of a positive study result and subsequent regulatory approval.

By anticipating where future investments could make a difference, this final section of the landscape charts potential opportunities to accelerate access to GMMs in the near, medium and long term **(Figure 5)**.



45 Unitaid, "Access Is Not an Afterthought."

Figure 5: Opportunities for future scale

	Near Term (1–4 years)	Medium Term (5–8 years)	Long Term (8+ years)
Innovation & Availability	Develop preferred product characteristics and target policy profiles for different GMMs.	Build political coalitions to support GMM approaches within and across endemic countries.	
	Build capacity and contained facilities in endemic countries able to work with GMMs.		
		Convene possible funders and identify funding modalities to support later stage field evaluations.	
		Convene possible partners for implementation of larger scale field evaluations.	
Quality	Update information on the WHO evaluation processes for those who seek WHO prequalification and a recommendation in addition to national regulatory approvals.	Scale up mechanisms that support integrated vector control management in different regions.	Document and publish experiences with regulatory permit reviews and approvals.
	Facilitate or further invest in regional regulatory expert networks to support adaptation of existing biosafety and public health regulations for GMMs.	Create guidance on data transportability to support efficient and timely regulatory review.	
	Support capacity-building for health and environmental regulators, institutional and national biosafety committees, and ethics review boards.	Investigate the use of the WHO Expert Review Panel process to accelerate uptake.	
		Build capacity for post-release monitoring (staff, protocols, technologies, national reference laboratories).	
Affordability	Map liability and insurance requirements in countries where GMMs could be used.	Encourage national regulatory authorities to provide clarity on expectations regarding liability or insurance.	
	Map drivers of cost and demand factors based on initial evidence.	Integrate cost and impact data into models designed to compare the likely cost-effectiveness of malaria interventions to inform prioritization discussions.	
Supply & Delivery	For manufacturing capacity, map what exists, what is needed, where it could be developed, and how to balance economies of scale against localized manufacturing, learning from existing projects.	Explore financial mechanisms such as volume guarantees, concessional lending and other incentives to facilitate investment in production facilities.	
Demand, Adoption and Scale-Up	Support proactive information campaigns to counterbalance misinformation and intentional disinformation.		
	Encourage governments to undertake meaningful public consultations prior to regulatory decisions.		
	Map perceptions of GMMs among Global Fund contributors.		Update WHO consensus modeling with results from GMM field trials to support government decision-making on GMM use.
			Contributors to the Global Fund determine the criteria/ considerations for allocating funding to GMMs.

In the near term

Opportunities are mostly focused on building a supportive environment to guide and enable field evaluations (in particular larger scale evaluations for entomological and epidemiological outcomes), and conducting necessary implementation research to explore local barriers to uptake and scale-up. This entails setting out expectations for the role that GMMs can play in the control of different vector-borne diseases; building capacity of regulatory authorities and other bodies involved in the oversight of this research, such as national and institutional biosafety committees; and beginning to consider how to facilitate scale-up of evaluations and ultimately uptake of these new tools at scale.

1

Develop preferred product characteristics (PPCs) and target policy profiles (TPoPs) for different GMMs:

Building on work to define the efficacy and safety criteria for advancing GMMs to field testing,[46] outlining the PPCs of GMMs will help to prioritize research and available funding. Development of a PPC document for GMMs is already planned in the WHO "Global Malaria Programme operational strategy 2024–2030,"[47] but such PPCs could also be useful for other vector-borne diseases. In addition, the development of TPoPs should be considered as a means to analyze the nature of the evidence needed to affect the desired change in policy and practice, and the gaps in that evidence. TPoP development could also facilitate early and ongoing communication among researchers, policymakers and other global health stakeholders, such as manufacturers and regulators.[48]

2

Update information on the WHO evaluation processes for those who seek WHO prequalification and a recommendation in addition to national regulatory approvals:

While WHO prequalification and an associated disease-specific recommendation are not prerequisites for the use of GMMs or for other vector control interventions, these may be sought by national regulatory authorities that draw on WHO decisions to guide their regulatory decision-making processes for health products. At least in the near term, WHO assessments are therefore likely to be key elements – and potential barriers – in enabling GMM technologies to be procured by agencies that require these criteria to be met, such as the Global Fund. Clarity on WHO requirements and the process for evaluating GMMs will be needed to enable developers to seek prequalification and a recommendation, if needed by countries or procurers.

46 Stephanie L. James et al., "Toward the Definition of Efficacy and Safety Criteria for Advancing Gene Drive-Modified Mosquitoes to Field Testing," *Vector-Borne and Zoonotic Diseases* 20, no. 4 (2020): 237–51, https://doi.org/10.1089/vbz.2019.2606

47 World Health Organization, *Global Malaria Programme Operational Strategy 2024–2030* (World Health Organization, 2024), https://iris.who.int/handle/10665/376518

48 Gates Foundation, *Target Policy Profile (TPoP) Version 2 Design Analyze Communicate (DAC)* (Gates Foundation, 2023), https://dac-trials.org/wp-content/uploads/Target-Policy-Profile-V2.pdf

3

Facilitate or further invest in regional regulatory expert networks to support adaptation of existing biosafety and public health regulations for GMMs:

Existing initiatives to build capacity and facilitate regulatory cooperation, such as the West Africa Integrated Vector Management platform, are already working to address this barrier. However, continued and scaled-up efforts to proactively build expert networks and to review legal frameworks in countries and regions interested in GMMs could facilitate field evaluations and possibly adoption.

Currently, countries that are Party to the Cartagena Protocol should publish their regulatory decisions in a timely manner in the Biosafety Clearing-House, but significant delays are being observed. Furthermore, it is thought that faster publication of country regulatory decisions by countries that are Party to the Cartagena Protocol provides an immediate opportunity to enhance information sharing and to facilitate this area.

4

Support capacity-building for health and environmental regulators, institutional and national biosafety committees and ethics review boards:

Research on GMOs is a novelty for many institutions working on malaria or other vector-borne diseases. Many may not have the institutional framework required to supervise the research (institutional biosafety committees) and their institutional ethics review boards may be unfamiliar with this work. Absence of trained institutional biosafety committees and ethics review boards can slow down or stop research, in particular field evaluations. Similarly at the national level, in countries with little experience with GMOs and likely none with GMMs, training for national biosafety authorities and national ethics committees is key to enabling governments to make informed decisions and guide research.

5

Map liability and insurance requirements in countries where GMMs could be used:

Document how liability is handled for other types of vector control products and health technologies in the likely target countries, as well as how previous challenges around environmental liability have been addressed. Assess the impact of these requirements on field evaluations and on likely use to inform possible mechanisms to address liability and/or insurance where needed. In addition, encourage national regulatory authorities to provide clarity on expectations regarding liability or insurance as part of guidance to prospective applicants. Liability clauses and insurance requirements for field evaluations of GMMs will vary by country. While some countries may decide to take on the liability by granting permits and may not have specific insurance requirements, others may have. Understanding expectations and requirements can help to inform field trial designs and locations, and help research consortia to consider these elements in their (financial) planning.

6

Map drivers of cost and demand factors based on initial evidence:

Early evidence from the first field evaluations will yield essential information on effectiveness, use scenarios and costs. These inputs can be used to create initial models for understanding GMM technology value propositions.

7

For manufacturing capacity, map what exists, what is needed, where it could be developed, and how to balance economies of scale against localized manufacturing, learning from existing projects[49,50]:

Deploying GMMs at scale may present some logistical challenges, notably how to rear, transport and release modified mosquitoes, potentially of different species and in multiple locations/countries. While these challenges differ from the logistics associated with deploying current large-scale vector control interventions, namely ITNs and IRS, many are similar to those previously encountered for SIT programs. Learning from these and other similar experiences with rearing and releasing insects at scale will be essential. Mapping existing infrastructure and likely future needs should start as early as possible to inform infrastructure investments further down the line. Analyses will need to recognize that requirements may differ considerably depending on the type of GMM product to be deployed.

8

Map perceptions of GMMs among Global Fund contributors:

Eventually, procurers like the Global Fund may be involved in purchasing GMMs for deployment. It will be critical to understand the perception of GMMs among contributors to the Global Fund to provide the basis for further discussions on eligibility criteria that may differ from currently supported products.

49 World Health Organization, *Guidance Framework for Testing the Sterile Insect Technique as a Vector Control Tool Against Aedes-Borne Diseases* (World Health Organization, 2020), https://iris.who.int/handle/10665/331679

50 Victor A. Dyck et al., eds., *Sterile Insect Technique: Principles and Practice in Area-Wide Integrated Pest Management, Second Edition* (Taylor & Francis, 2021)

In the medium term

Funding should focus on the mechanisms that will support uptake. Given the complex regulatory landscape that GMMs face, there should be continued emphasis on establishing regulatory coordination mechanisms and technical guidance, while building political leadership to signify commitment to the full investigation of these new tools. In parallel, as more becomes known about how different GMMs perform in advanced laboratory studies and in the field, comparative analyses of the cost-effectiveness of different GMM technologies and how they may be combined with existing vector control tools will be critical. This information will feed back into further research and help to shape demand.

1

Build political coalitions to support GMM approaches within and across endemic countries:

Building high-level political support for evaluations of these new tools is key, as public acceptance of GMMs could be a deciding factor in whether they can be implemented at scale. Coalitions led by groups such as the African Union Development Agency – New Partnership for Africa's Development, the African Leaders Malaria Alliance, and the Asia Pacific Leaders Malaria Alliance, or an arrangement analogous to the E-2025 coalition in southern Africa could create political momentum and facilitate experience-sharing at the government level.

2

Convene possible funders and identify funding modalities to support later stage field evaluations:

Field evaluations are likely to be lengthy and expensive, and there are currently very few funders supporting GMM research. Identifying funding models, possible funders and other modalities would help speed up evaluations of new tools to generate the efficacy and cost data needed.

3

Convene possible partners for implementation of larger scale field evaluations:

In addition to the financial aspects of implementing field evaluations, involving other partners in the actual implementation of field trials could help incorporate lessons learned from other fields, complement the skills and knowledge of current GMM developers, and add capacity to the overall effort. Some existing convening platforms, such as GeneConvene, could be used for this purpose.

4

Scale up mechanisms that support integrated vector control management in different regions:

In some regions, organizations such as the Asia Pacific Malaria Elimination Network may offer platforms to build these expert networks and to provide advice to governments. In other regions, such mechanisms may need to be created. Facilitating learning from countries that have already regulated GMOs, in particular GMMs, such as Brazil, could also help countries update their regulatory processes and frameworks to increase readiness. Coordinated regulatory processes and political cooperation will be particularly relevant for GMMs that are likely to cross national borders.

5

Create guidance on data transportability to support efficient and timely regulatory review:

Regulatory processes for GMOs are onerous and time-consuming. To support adoption in multiple countries – which could increase the long-term effectiveness of some types of GMMs to prevent resurgence of disease transmission – it is important to facilitate quicker regulatory dossier reviews and reduce costs associated with each dossier. Regulatory authorities should set out which data can be reused from other dossiers, under what conditions, and which studies would need to be redone. Guidance from expert bodies and/or national authorities in advance of dossiers being prepared would help developers to plan effectively.

6

Investigate the use of the WHO Expert Review Panel process to accelerate uptake:

Depending on progress on a global pathway to review and recommend GMMs under WHO, other mechanisms to facilitate accelerated evaluation and procurement, such as the WHO Expert Review Panel process, should also be investigated, so that products can be made available quickly.

7

Build capacity for post-release monitoring (staff, protocols, technologies, national reference laboratories):

Post-release monitoring of GMMs is key to assessing dispersal and persistence, and is likely to be a regulatory requirement based on the potential environment impacts that may be flagged in risk assessments. To assess epidemiological impact, it will also be necessary to monitor cases of the target disease. For many countries, monitoring the presence of GMMs (or simply for the presence of a transgene) will be entirely novel, but will share some similarities with existing entomological surveillance. In some places, such surveillance already draws on polymerase chain reaction to identify mosquito alleles (e.g., species identification, insecticide resistance). Gene drive monitoring can be a complex task at scale. It will therefore be important to assess who should carry out the monitoring, how it could be integrated into existing entomological surveillance activities, what additional staff capacity needs to be built, and what technologies and tools can facilitate this exercise.

8

Encourage national regulatory authorities to provide clarity on expectations regarding liability or insurance:

Engage with national regulatory authorities based on previous mapping efforts to ensure that any liability and insurance requirements for future GMM deployments are clear. Where possible, encourage NRAs to develop public-facing policies for manufacturers.

9

Integrate cost and impact data into models designed to compare the likely cost-effectiveness of malaria interventions to inform prioritization discussions:

Building on initial modeling, utilize detailed field evaluation and release data to develop extensive cost-effectiveness analyses. These will include specific use case scenarios and comparisons with other vector control tools. Develop guidance on use of GMMs alongside or instead of other vector control interventions.

10

Explore financial mechanisms such as volume guarantees, concessional lending and other incentives to facilitate investment in production facilities:

In addition, building and operating these facilities may require substantial investments, at least at the start. Identifying the role of different actors and how investments can be de-risked will contribute to timely development of the supply chain infrastructure.

In the long term

Some GMMs may be deployed widely, particularly self-limiting approaches, while others may still be undergoing field evaluations. To reduce barriers to access, the focus should be on both overcoming logistical and financial procurement issues, and continuing to maintain a supportive environment for ongoing research on different GMM products. Once data on cost-effectiveness become available, WHO decision support tools for governments can be updated. GMMs that are eligible for Global Fund procurement will need to be integrated into countries' planning, and Global Fund criteria may need to be updated accordingly. At this stage, developing an effective infrastructure and process to manage the rearing, maintenance, shipping and release of multiple types of GMMs will be a priority.

1

Document and publish experiences with regulatory permit reviews and approvals:

In line with efforts to foster capacity-building and readiness, encouraging information-sharing around regulatory pathways and decisions can help developers as well as other regulatory authorities. As indicated under short-term opportunities, faster publication of regulatory decisions in the Biosafety Clearing House is an immediate step that should be taken now, but also present an opportunity to be continued into the future. The publication of these documents should ideally be complemented by studies or reports to provide lessons learned.

2

Update WHO consensus modeling with results from GMM field trials to support government decision-making on GMM use:

There could potentially be a suite of GMMs with different profiles available to governments. Understanding how they perform – with each other and alongside other vector control tools – will enable governments to make informed decisions for their national programs. Once data are available through field evaluations, updating the WHO malaria consensus modeling will support decision-making.

3

Contributors to the Global Fund and other pooled funding mechanisms may influence the criteria/considerations for allocating funding to GMMs:

Some GMMs may be recommended and prequalified by WHO and hence eligible for procurement through the Global Fund or other agencies that are reliant on WHO for guidance. However, not all contributors to pooled funding and procurement mechanisms will have the same views on GMOs and how they are regulated. Drawing on insights from previous mapping exercise, evidence-based engagement with diverse groups may be necessary to support GMMs though Global Fund grants.

Over the course of the next decade (near, medium, and long term)

Investing in building the capacity to do research with GMOs in endemic countries should be a priority, as it will help to sustain research and support public acceptance. Such investment should be accompanied by consistent efforts to share information, address misinformation and disinformation around GMOs, and support effective public consultations prior to decisions on GMM releases.

1

Build capacity and contained facilities in endemic countries able to work with GMMs:

While there is a fairly large number of groups investigating the use of genetic modification to control vector-borne diseases, they are primarily focused on malaria, and most are focused on research rather than development. Moving into development (and later delivery) will be a significant leap forward that may be a challenge for many university-based research programs. The product pipeline is noticeably constrained at that stage, though it is fairly robust in the earlier research phase. This challenge also partly stems from the lack of research teams in endemic settings with adequate facilities and skills to work with GMOs, and effective and supportive regulatory environments. These gaps constrain opportunities to initiate research from the start or become partners in broader collaborations to help move potential products through the development phase. More facilities with an appropriate level of containment and more know-how for genetic modification in endemic settings would enable more institutions to undertake research and development in situ, including field evaluations. Furthermore, institutions in endemic countries would be in the position to lead research, thereby reducing dependency on institutions in non-endemic settings.

2

Support proactive information campaigns to counterbalance misinformation and intentional disinformation

Enabling informed decision making by governments needs to be coupled with technology acceptance by residents where GMM may be used. Early information sharing campaigns and robust public consultations before permitting will be key to managing misinformation and encouraging public trust.

3

Encourage governments to undertake meaningful public consultations prior to regulatory decisions:

Enabling informed decision-making by governments needs to be coupled with technology acceptance by residents where GMMs may be deployed. As GMMs involve complex science and there may be negative perceptions of genetic modification, conducting early information-sharing campaigns and robust public consultations prior to any GMM releases will be key to managing misinformation and encouraging public trust.

While the activities laid out above represent an ambitious access agenda for a technology that has yet to prove broad effectiveness against mosquito-borne diseases, the current situation demands such forethought. As progress in reducing malaria burden stagnates and other mosquito-borne diseases surge, it is increasingly necessary to consider game-changing innovations. Unitaid supports the continued evaluation of GMMs as one such transformative solution.

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