World Health Organization

Evaluation of genetically modified mosquitoes for the control of vector-borne diseases

OCTOBER 2020

POSITION STATEMENT

EXECUTIVE SUMMARY

In accordance with its mandate to provide guidance to Member States on health policy, WHO is issuing this position statement to clarify its stance on the evaluation and use of genetically modified mosquitoes (GMMs) for the control of vector-borne diseases (VBDs). The main elements of WHO's position are summarized below.

1. VBDs cause more than 700 000 deaths annually and are responsible for 17% of the global burden of communicable diseases. Significant progress was made in the control of malaria until 2015, but progress has stalled in recent years. WHO recognizes the urgent need for development and testing of new tools to combat VBDs and supports investigation of all new potential control technologies, including GMMs.

2. In order to maintain the gains made so far and to advance further towards the elimination and eventual eradication of VBDs, the development and testing of new tools to control both the pathogens and the vectors are urgently needed. WHO actively encourages innovation in this field.

3. New technologies, including GMMs, may supplement or provide alternatives to existing interventions and may further reduce or even prevent disease transmission. Computer simulation modelling indicates that GMMs could be a valuable new tool in efforts to eliminate malaria and to control *Aedes*-borne VBDs. Use of GMMs, however, raises concerns about ethics, safety and governance and questions of affordability and cost–effectiveness, which must be addressed.

4. In the spirit of fostering innovation, WHO takes the position that all potentially beneficial new technologies, including GMMs, should be investigated to determine whether they could be useful in the continued fight against diseases of public health concern. Such research should be conducted in steps and be supported by clear governance mechanisms to evaluate the health, environmental and ecological implications.

5. Current mechanisms of governance and oversight, from global to national and institutional levels, must be adapted to the purpose rather than replaced. Existing governance mechanisms should be backed financially to ensure that they are effective.

6. Internationally recognized risk assessment tools and procedures should be used for evaluating safety. Decisions on evaluation of GMMs should account for the potential benefits to health in terms of disease control and not be limited to potential environmental risk.

7. Community engagement is essential in developing effective approaches to combating VBDs. Communities must be engaged in planning and conducting field trials before any new public health intervention is introduced. WHO considers that tools for engaging populations affected by VBDs are a priority in field research on GMMs.

INTRODUCTION

This WHO statement was prepared in response to enquiries from Member States and their implementing partners about the Organization's position on both research on and deployment of GMMs to reduce or prevent transmission of VBDs. Significant progress has been made in genetic modification of mosquito vectors to introduce physiological changes designed to either suppress local mosquito populations or to reduce their susceptibility to infection and their ability to transmit disease-causing pathogens. Scientists are now beginning to conduct research in endemic countries to explore the feasibility of deploying GMM approaches. These advances have led to an often-polarized debate on the benefits and risks of GMMs, in which the purpose of evaluating this new technology sometimes appears to be forgotten. In accordance with its mandate to provide guidance to Member States on matters concerning public health, WHO has therefore framed its position in this context and provides its views on the evaluation of GMMs as a potential tool in the fight against VBDs. This position statement is designed to support decision-making in Member States, although further support from WHO and other partners may be necessary in some countries, depending on developments in GMMs. Member States and their implementing partners are encouraged to contact WHO at geneticallymodifiedmosquitoes@who.int to pose any additional questions. On the basis of such feedback, WHO will post a question-and-answer document and may modify this position statement to provide additional clarity if necessary.

VECTOR-BORNE DISEASES: CURRENT BURDEN

VBDs pose a major threat to the health of people around the world. They are caused by parasites, viruses and bacteria transmitted to humans by mosquitoes, sandflies, triatomine bugs, blackflies, ticks, tsetse flies, mites, snails and lice. The major VBDs together account for around 17% of the estimated global burden of communicable diseases and claim more than 700 000 lives every year. The burden is highest in tropical and subtropical areas. More than 80% of the global population live in areas at risk of at least one major VBD, and more than half are at risk of two or more. VBDs exact an immense toll on economies and restrict both rural and urban development.

Mosquitoes transmit many important VBDs, including malaria, dengue, lymphatic filariasis, chikungunya, Zika virus disease, West Nile fever, yellow fever and Japanese

encephalitis. In 2018, there were an estimated 228 million cases of malaria worldwide, with 405 000 deaths. WHO has warned that malaria control work has stalled, especially in high-incidence regions, and malaria eradication cannot be achieved with current tools alone *(1, 2)*. Renewed calls have been made for investment in research and development of new tools to target anopheline vectors. *Aedes* mosquitoes are invasive species, and their geographical range has extended in the past few decades to over 128 countries, increasing the risk of transmission of pathogens that can cause viral and filarial diseases. *Culex* mosquitoes also transmit a variety of pathogens, affecting both humans and livestock. The risk of infection with certain viral pathogens is particularly high in towns and cities where *Aedes* and *Culex* mosquitoes exploit artificial habitats for breeding in close proximity to humans. The rates of morbidity and mortality caused by these mosquito-borne pathogens are disproportionately high among poorer populations, and people who survive these diseases may be left permanently disabled or disfigured, compounding their disadvantages. It is highly likely that the burden of VBDs will increase further as a result of the COVID-19 pandemic and the associated disruptions to health services and vector control programmes.

The dynamic, complex nature of vector-borne pathogens complicates predictions of the impact of existing, re-emerging or new diseases on human health. Nevertheless, it is reasonable to expect the emergence of new VBDs and further intensification of others, particularly those diseases transmitted by *Aedes* mosquitoes that are closely associated with urban areas. Such complexity and unpredictability indicate a critical need for adaptive, sustained approaches to prevent and reduce pathogen transmission and the disease burden and to explore new interventions.

GENETICALLY MODIFIED MOSQUITOES

GMMs – also known as "genetically engineered", "transgenic" or "living modified" mosquitoes – are defined as mosquitoes that have heritable traits introduced by recombinant DNA technology that alter the strain, line or colony in a manner usually intended to result in reduction of the transmission of mosquito-borne human diseases. GMMs are also likely to be characterized by introduced heritable marker traits that facilitate monitoring after their release into the environment. Field trials of some self-limiting GMM products have already obtained regulatory approval *(3–5)*; however, investigational GMM products are not expected to be ready for field testing for a number of years *(6)*.

Gene drive systems promote preferential (super-Mendelian) inheritance of the introduced genetic trait(s) within interbreeding mosquito populations. These systems can be designed to ensure that the effects are spatially and/or temporally restricted or that the introduced trait(s) is established and spread within the local population, with the phenotype of interest persisting in that population *(7)*. The promising characteristics of self-sustaining gene drive systems have raised hopes for durable, affordable protection against disease transmission *(3)*.

EVALUATION

A step-wise testing pathway is recommended for evaluation of GMMs as potential public health tools *(7, 8)*. Such a pathway moves from contained (physically confined) testing in a laboratory, insectary or indoor cage facility to physically or ecologically

confined field testing, before finally moving to staged field releases. The pathway accounts for the critical nature of the decision to move from contained indoor testing to confined field testing in disease-endemic regions, given the possibility that the escape of small numbers of mosquitoes that carry this form of drive could lead to establishment of the modification in the local target mosquito population *(9)*. The pathway also includes the recommendation that candidate GMMs considered for progression to any level of field testing should be assessed thoroughly for all possible hazards and demonstrate efficacy and fitness in the laboratory that are consistent with the desired disease reduction goal.

In the phased development and evaluation pathway, a candidate GMM product that obtains the necessary approvals for field testing will be released initially in the field only on a small scale in an area in which ecological barriers minimize the risk of spread. The success of early releases will be assessed primarily on the basis of entomological measures *(7, 9)*; however, as the benefit for health is the ultimate goal, the potential for measuring disease impact should be considered throughout product development and evaluation. Thus, it will be important to set entomological impact targets for the early releases that are likely to result in the desired reduction of clinical incidence in later, larger trials.

Safety

The phased development and evaluation pathway will include continuous consideration of product safety and quality, as well as efficacy. Investigational GMM products that meet the criteria for efficacy must also undergo extensive risk assessment and safety testing. Pertinent goals for broad protection that have been identified are human and animal health and biodiversity *(10, 11)*. The "go/no-go" safety criterion for advancing an investigational GMM product to field testing has been proposed as "will do no more harm to human health than wild-type mosquitoes of the same genetic background and no more harm to the ecosystem than other conventional vector control interventions" *(9)*. Thus, the appropriate comparator for adverse effects on health or the environment could be either unmodified *Anopheles gambiae* mosquitoes or insecticides (adulticides or larvicides) used locally for mosquito vector control.

Many issues of perceived risk can be examined with regard to containment. They include aspects of the introduced genetic construct, such as its locus of integration, that could affect the inter- or intra-generational stability of the genetic modification, potential genetic transmission to non-target organisms, the possibility of increased transmission of other diseases, allergenicity or toxicity, and biting behaviour *(6)*. It is important to remember that the intent of population suppression or replacement is to reduce the numbers of vector mosquitoes to a level insufficient to maintain transmission of the malaria pathogen, not to eliminate the vector. Recent modelling suggests that it is unlikely that population suppression strategies would completely eliminate the mosquito species under real-world conditions *(12)*. Safety for the environment must be examined throughout field testing. The possibility that another undesirable organism could invade the ecological niche vacated as a result of population suppression or replacement strategies is a concern that should be addressed by risk assessment and monitored after initial release.

Role of WHO in supporting Member State decisions

A number of mechanisms will be used to assist WHO in fulfilling its mandate of providing guidance to Member States on health policy matters, including the evaluation and potential deployment of GMMs. To improve the evaluation of all types

of vector control interventions, WHO revised its evaluation process in 2017. The process now consists of two separate but complementary pathways.

Interventions that fall into a class already covered by a WHO policy recommendation will be assigned to the "prequalification pathway", which is overseen by the WHO Prequalification Team for Vector Control Products (PQT-VCP). In this pathway, the safety, quality and entomological efficacy of interventions are assessed. No epidemiological trials are required, given that the intervention's impact on infection or disease – also termed "public health value" – has already been demonstrated in a "first-in-class" intervention that has received a WHO policy recommendation. Once the safety, quality and entomological efficacy of an intervention assigned to the prequalification pathway have been demonstrated, the intervention will be prequalified and will be added to the list of prequalified products by PQT-VCP.[1]

Interventions that belong to a class not covered by a WHO policy recommendation, including GMMs, are assigned to the "new intervention pathway" to validate whether they have public health value. This process is supported by the Vector Control Advisory Group (VCAG) (https://www.who.int/vector-control/vcag/en/), the role of which is to guide product developers, innovators and researchers in generating epidemiological data and choosing study designs that allow assessment of public health value. Once data from at least two studies with epidemiological end-points have been submitted to WHO, the VCAG assess the intervention's public health value and share this assessment with WHO where it will feed into the policy development process overseen by the Guidelines Review Committee *(13)*. In its assessment of the public health value of GMMs, VCAG would draw on the guidance framework of the WHO Special Programme for Research and Training in Tropical Diseases and the Foundation for the National Institutes of Health, first published in 2014 *(7)*. This framework is currently being revised, and the updated version will be available in late 2020. The VCAG assessment is complemented by an assessment of the product's quality, safety and entomological efficacy by PQT-VCP.

Once the public health value, safety, quality and entomological efficacy of a new intervention have been demonstrated, the findings will reviewed by a WHO guideline development group, which will then formulate WHO policy recommendations on use of the intervention by Member States and an associated "evidence-to-decision" table *(13)*. Before any new policy recommendations for vector control are published, they will be reviewed by the Malaria Policy Advisory Committee (https://www.who.int/malaria/mpac/en/) and/or the Strategic and Technical Advisory Group for Neglected Tropical Diseases (https://www.who.int/neglected_diseases/stag/en/), depending on the intended use patter on the intervention.