GUIDANCE FRAMEWORK FOR TESTING **GENETICALLY MODIFIED MOSQUITOES**

Second edition

World Health Organization

TDR For research on diseases of poverty
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Foreword

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Vector-borne diseases are endemic in more than 100 countries and affect approximately half of the world's population *(1)*. Many types of arthropods may serve as disease vectors, but this guidance focuses particularly on mosquitoes. Mosquitoes transmit several diseases of major global public health importance, including malaria and dengue fever *(1)*. In fact, mosquitoes have been called the deadliest animal on earth *(2)*.

Malaria is still considered the world's most important parasitic infectious disease. Intensive deployment of currently available malaria control tools over the past two decades has greatly reduced malaria incidence *(3)*. However, this overall trend has slowed in recent years, and even reversed in some parts of Africa *(4, 5)*. The *Global technical strategy for malaria 2016–2030 (6)* sets a target of reducing global malaria incidence and mortality rates by at least 90% by 2030 (compared to 2015 levels). Yet, it is widely acknowledged that eliminating malaria in all countries, especially those with a high disease burden, will likely require new tools that are not available today *(6–8)*. Therefore, investing in research and development of innovative vector control tools has been identified as a priority *(9)*.

An estimated 2.5 billion people live in areas where dengue viruses can be transmitted. Dengue has been called the most important mosquito-borne viral disease with epidemic potential in the world, citing a 30-fold increase in the global incidence of dengue over the past 50 years, and recognizing that the human and economic costs are staggering. The number of cases reported increased from 2.2 million in 2010 to over 3.34 million in 2016 *(10)*. Outbreaks and epidemics of other viruses carried by the same mosquitoes that transmit dengue have occurred in Africa, the Americas, Asia and the Pacific *(1, 11)*.

Attacking mosquito vectors is one of the most effective ways to reduce the transmission of these diseases in endemic areas *(12)*. Application of mosquito population reduction methods was central to the successful elimination of malaria transmission in Italy and the United States of America in the early 20th century *(13)* and, transiently, of dengue in the Americas in the early 1960s *(14)*. Vector-targeted approaches remain a mainstay of current disease control practices. However, given the magnitude of ongoing malaria and dengue incidence, current efforts clearly are insufficient to meet the need. Moreover, dependence on a limited number of insecticides for vector control increases the risk that mosquitoes will develop resistance *(15)*, exacerbating the problem. Insecticide resistance is being reported in over three quarters of countries with ongoing malaria transmission, and such resistance affects all major vector species and classes of insecticide *(7)*. Resistance to all four classes of insecticide has also been reported in *Aedes* arbovirus vectors in the Americas, Asia and Africa *(16)*.

In considering the potential of new technologies to address the unmet needs of mosquito control, it is necessary to evaluate the benefits and risks in the context of the current situation. The potential public health benefit of practical and effective new tools to reduce or even eliminate diseases such as malaria and dengue is clear and widely recognized *(17)*. Both the risks incurred by testing new and unproven control strategies and the risks to human health and the environment posed by maintaining the status quo, which include ongoing health (morbidity and mortality), environmental (use of broad-spectrum insecticides) and economic *(18–20)* impacts, should be taken into account in decision-making.

For more than two decades, scientists have been working to harness the promise of molecular biology to develop genetically modified mosquitoes (GMMs) for use as public health tools to prevent the transmission of these diseases. The introduction of molecular biology techniques represents the next step in a progression that builds on the widespread success of programmes employing release of radiation-sterilized insects to control the Mediterranean fruit fly (Medfly) and other insect pests affecting plants and animals, a process known as the sterile insect technique (SIT) *(21)*. Radiation- and chemo-sterilization, sometimes in combination with biological sterilization methods, have been applied to mosquitoes *(22–24)*. However, genetic modification technologies offer additional options for specificity and durability of effect, as well as adaptability to different disease transmission conditions. Advances in the development of GMMs have raised hopes for the availability of new, potent and cost-effective tools to aid in the fight against malaria, dengue and other mosquito-borne pathogens. Data on which to base the evaluation of GMMs' protective potential can only be collected through testing, including testing under the natural conditions in which the technology would be utilized. Without the ability to conduct careful and rigorous testing, no new technology of any kind can be brought to fruition for the public good.

Some of these genetic technologies are now advancing to field testing. Field testing of GMMs began with releases of non-replicating male mosquitoes (which do not bite) *(25–27)*. The first field release of non-sterile, self-limiting GMMs was announced in 2019 *(28)*. To date, no gene drive-modified mosquitoes (GDMMs)[1] have been tested in the field. Given the novelty of GMMs, and particularly