GENE DRIVES

FOR MALARIA CONTROL AND ELIMINATION IN AFRICA

African Union

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About the AU and NEPAD

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Members of the High-Level African Panel on Emerging Technologies

Co-chairs

Calestous Juma, John F. Kennedy School of Government, Harvard University, USA (Deceased)

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

Panel Members

Abdallah Daar, University of Toronto, Canada

Berhanu M. Abegaz, African Academy of Sciences, Ethiopia

Francine Ntoumi, Fondation Congolaise pour la Recherche Médicale, Congo-Brazzaville

Karim Maredia, Michigan State University (MSU), East Lansing, Michigan, USA

Oye Ibidapo-Obe, Federal University Ndufu Alike, Ikwo (FUNAI), Nigeria

Rachel Chikwamba, Council for Scientific and Industrial Research (CSIR), South Africa

Roseanne Diab, Academy of Science of South Africa (ASSAf), South Africa

Shireen Assem, the Agricultural Genetic Engineering and Biotechnology Research Institute (AGERI), Egypt

Secretariat

Aggrey Ambali (Coordinator) – NEPAD Agency

Diran Makinde – NEPAD Agency

Towela Nyirenda-Jere – NEPAD Agency

Jeremy Ouedraogo – NEPAD Agency

Hlazo Mkandawire – NEPAD Agency

Hudu Mogtari – NEPAD Agency

Justina Dugbazah – NEPAD Agency

Margaret Mahlomuza – NEPAD Agency

Barbara Glover – NEPAD Agency

Mahama Ouedraogo – African Union Commission

Monica Edinoba – Africa Union Commission

Hambani Masheleni – Africa Union Commission

Kate Bauer – Harvard University

Research

Fredros Okumu (Ifakara Health Institute), **Leonard Kamwanja** (Lake Malawi Anglican University), **Walter Alhassan** (Biotechnology and Stewardship for Sustainable Agriculture in West Africa), **Aggrey Ambali** (NEPAD Agency), **Hudu Mogtari** (NEPAD Agency), **Justina Dugbazah** (NEPAD Agency), **Barbara Glover** (NEPAD Agency), **Moussa Savadogo** (NEPAD Agency) **Olalekan Akinbo** (NEPAD Agency) **Jeremy T. Ouédraogo** (NEPAD Agency) **Sunday Igu Rocks** (NEPAD Agency)

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ABI	African Biosciences Initiative
ABNE	African Biosafety Network of Expertise
ACTs	Artemisinin-based Combination Therapies
AMRH	African Medicines Regulatory Harmonisation
AU	African Union
AUC	African Union Commission
CBD	Convention on Biological Diversity
CFT	Confined Field Trials
COMESA	Common Market for Eastern and Southern Africa
COP-MOP	Conference of the Parties serving as the Meeting of the Parties to the Protocol
GM	Genetically Modified / Genetic modification
IBC	Institutional Biosafety Committees
IPTp	Intermittent Preventive Treatment in Pregnancy
IRS	Indoor Residual Spraying
IRSS	Institut de Recherche en Sciences de la Santé
IT	Information Technology
LLIN	Long Lasting Insecticide Nets
LMO	Living Modified Organisms
MRH	Medicines Registration Harmonization
NAS	United States of America's National Academies of Sciences, Engineering and Medicine
NECs	National Ethics Committees
NEPAD	New Partnership for Africa's Development

NMRA	National Medicines Regulatory Agencies
RA	Risk Assessment
REC	Regional Economic Community
RM	Risk Management
SADC	Southern African Development Community
STISA	Science, Technology and Innovation Strategy for Africa
WHO	World Health Organization

Executive Summary

This document examines the use of gene drive technology for the control and elimination of malaria in Africa. It begins by examining the burden of malaria; the gains so far accrued from existing interventions notably vector control, and the need for complementary tools. Gene drive technology has been identified as a potential new option to augment existing interventions in pursuance of achieving the African Union Agenda 2063. This document provides an overview of gene drive as a technology, its readiness for implementation, as well as essential testing pathways and implementation strategies at both country and regional levels, taking into consideration all the possible socio-cultural and ethical issues. Given that there may be potential risks associated with the use of genetic modification technologies, a risk analysis and risk management system has been proposed, mindful of the overwhelming health benefits to be derived from the technology. To ensure safety and the appropriate deployment of this technology, recommendations have been made with regard to policy regulatory systems.

The African continent is the most affected by malaria, with 90% of the world's 216 million cases in 2016 recorded in sub-Saharan Africa (WHO, 2017). The disease causes extensive economic losses, with recent estimates suggesting that countries which are severely affected by malaria have up to five times lower Gross Domestic Product (GDP) than those without malaria (Jobin, 2014). There has been significant progress against the disease in the past decade and a half, mostly due to the scale-up of long-lasting insecticide treated bed nets (LLINs), indoor residual spraying (IRS), and artemisinin-based combination therapies (ACTs). Between the years 2000 and 2015, an estimated 663 million malaria cases were prevented, with insecticidal bed nets and IRS together contributing 78% towards these gains (Bhatt et al., 2015).

Despite these successes, residual levels of malaria transmission still persist in several areas across the continent, even in places where coverage with existing interventions already exceeds 80%. Complete elimination of malaria remains a challenging goal across most sub-Saharan Africa settings due to factors such as insecticide and drug resistance, low funding which affects compliance to current best practices, sub-optimal strategies and poor living conditions. Other factors include human activities and mosquito behavioural adaptations. For example, although LLINs and IRS have effectively tackled mosquitoes that bite humans inside houses, they may not adequately control mosquitoes that bite outdoors or early in the evenings (Durnez & Coosemans, 2013; Elliott, 1972; Pates & Curtis, 2005). Experts now believe that without additional complementary interventions, the Africa Union target for malaria elimination by 2030 will not be achieved. Hence the need to explore emerging technologies such as gene drive technology for malaria control and elimination.

Gene drive techniques have already been demonstrated in laboratories to effectively alter *Anopheles* mosquito populations so that they can no longer transmit malaria parasites (Gantz et al., 2015), and also to introduce lethal gene sequences that suppress and rapidly crash entire mosquito populations in laboratories (Hammond et al., 2016). Mathematical evaluations of these approaches indicate that, if combined with existing interventions like LLINs, these technologies can effectively eliminate malaria in several African settings within a few years after the initial releases of even small numbers of modified mosquitoes (Eckhoff, Wenger, Godfray, & Burt, 2016). It is particularly important to emphasize that the use of transgenic mosquitoes of any kind, as with any other vector control tool, should be considered as just one component of an integrated approach, rather than as stand-alone technology (Marshall & Taylor, 2009).

Given the potential of this technology *vis a vis* the threat of malaria to human health and development, it is imperative to

comprehensively examine the technology, so as to guide further development and adoption in African countries. Although still in early development stage, gene drives present realistic options for effective disease control. It will certainly take many years before actual outcomes are ready for field deployment, but potential benefits for African countries against malaria will almost certainly be extensive. Moreover, this or related technologies could potentially be adapted to tackle other vector-borne diseases.

While existing interventions have significantly reduced the burden of malaria across Africa, complementary new interventions are required to drive the residual burden towards zero, and to eventually achieve malaria elimination on the continent. Africa should invest in the development and regulation of gene drive technology, whose greatest and most urgent application will be in malaria control and elimination. The High Level Panel recommends that the AU, RECs, Member States and their partners should consider the following:

- Given the potential for rapid developments in this technology space and the potential for misuse and improper trials, researchers and developers should establish a network of Africa-based scientists and developers to register their studies, self-regulate, share information regarding their technology, and peer-review all ongoing developments and field testing of the technology on the continent. They should also adopt a 'co-development' approach that emphasises collaboration between the partners in the teams, from research design to the creation of standard operating procedures.

- Regulation of gene drive products should take into account the value proposition and potential risks. Thus, regulators should facilitate and adapt essential guidelines and frameworks and where necessary, enact enabling legislation for the development and adjudication of the technology. They should encourage interaction between different agencies mandated to regulate emerging technologies, including genetically modified organisms and related technologies. AU Agencies and RECs should facilitate development, coordination and harmonization of regulations and guidelines for regulating the development, approval and use of the final product.

- Member States should obtain support for Private-Public-Partnerships, funding, laboratory infrastructure and international partnerships and ensure budgetary support for research, development and public engagement.

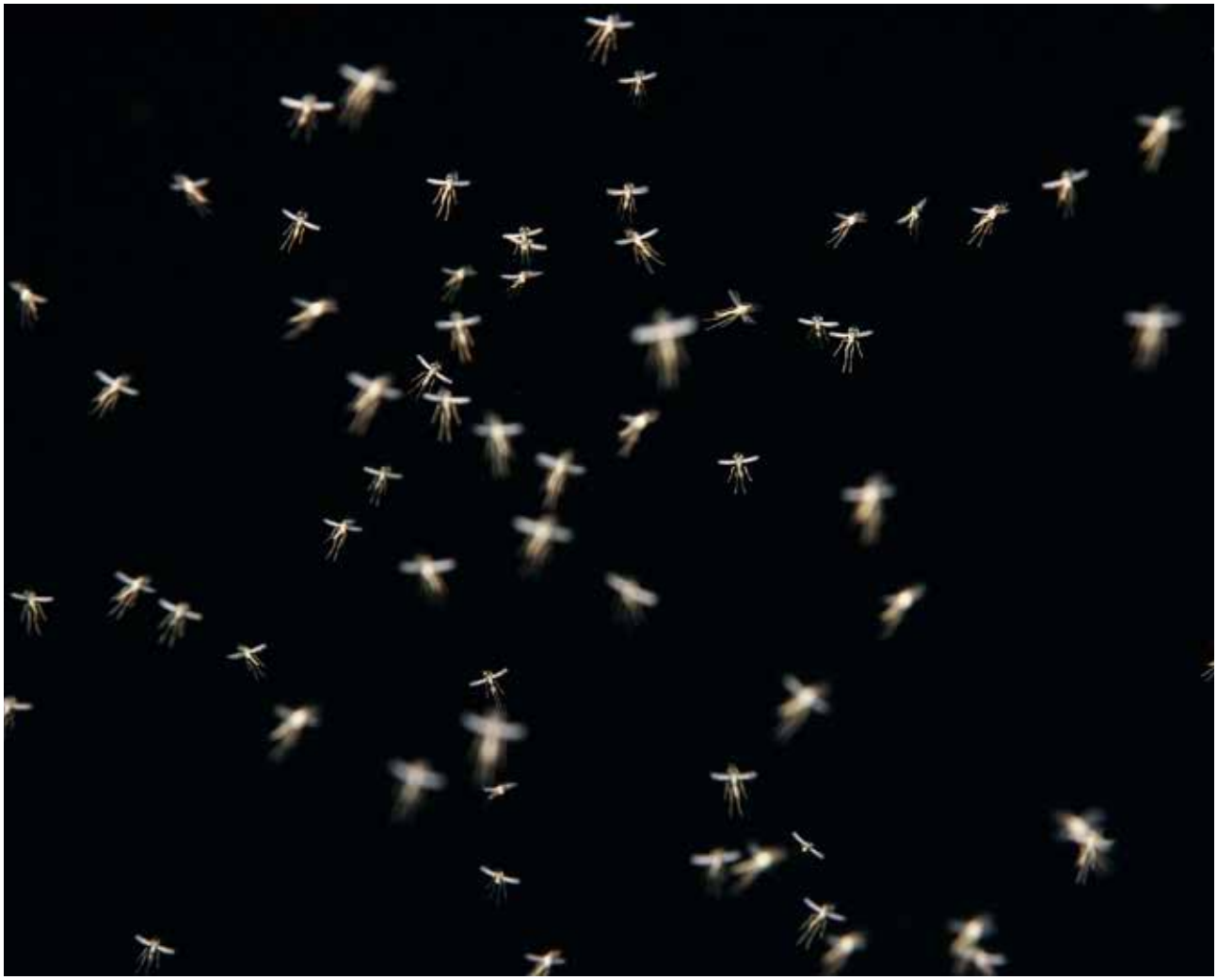
- Researchers and developers, member states and the AU, NEPAD Agency and Regional Economic Communities should adopt a regional approach to the harmonization of policies and implementation of the gene drive technologies across countries.

- Member states should provide support for the conduct of laboratory, field and semi-field studies to verify the potential of the technology for various African settings; and to support essential research for optimization of the technology. These studies should include the modelling of potential risks of gene-drive technology and mitigation of same.

- Support for bio-banking and data archiving, as well as the safeguarding of intellectual property associated with all trials on gene drive, is essential to maximize local impact and help expedite future evaluation and approvals.

- Governments have a central role to play in harnessing emerging technologies for Africa's development. In addition, the Panel calls for a more proactive involvement of financial institutions, foundations and private sector investors, as well as philanthropic associations, to name a few examples. Banks and other financial institutions are generally profit oriented; however, they want to see the products developed as well as profits generated.

- The Panel calls for the development of strategies that should address the challenges of the availability of African skills, the issue of regulation and ethics, education and awareness creation to prepare young people for their future role as decision-makers.
- Early engagement with stakeholders is critical for the development of emerging technologies, in order to ensure that technologies meet their expectations, and therefore, have great chance to be accepted and supported.
- Last but not least, the Panel calls for advocacy and support of policy makers for emerging technologies for economic development. For instance, the panel suggests to liaise with ministers of health in the field of gene drive against malaria.



1

Introduction

Malaria is caused by parasites of the *Plasmodium* genus and is transmitted to humans primarily through the bite of infected female *Anopheles* mosquitoes. In 2016, the disease affected approximately 216 million and killed 445,000 people worldwide, most of them African children under the age of five years (WHO, 2017). Of concern is the consistent marginal increase of cases "with 216 million cases in 2016, 5 million more cases than in 2015, which marks a return to 2012 levels" (Alonso & Noor, 2017). If untreated, the infection, in its most severe form, can lead to permanent learning disabilities, coma, and death. There are ~3500 species of mosquitoes, including ~400 *Anopheles* species, of which ~70 can transmit malaria to varying degrees (Centers for Diseases Control and Prevention, 2017). In Africa however, most malaria transmission is done by three closely related species in the *Anopheles gambiae* complex (namely, *Anopheles gambiae sensu stricto*, *Anopheles coluzzii* and *Anopheles arabiensis*), and also by *Anopheles funestus*, which now dominates many transmission settings in the east and southern Africa regions (Sinka et al., 2010).

Vector control is the most common and most effective way to control malaria transmission and is widely implemented in the form of long-lasting insecticide-treated mosquito nets (LLINs) and indoor residual spraying (IRS). Other vector control methods, such as larval source management (Tusting et al., 2013) and improved housing (Tusting et al., 2015) are also used, though on a far smaller scale than LLINS and IRS. Over a decade and a half, there have been major increases in coverage of insecticide-treated nets in Africa. By 2016, 54% of the sub-Saharan population had access to bed nets (WHO, 2017), compared to less than 2% in 2000, when African Heads of State and Government released the Abuja Declaration (WHO, 2000). Another 3.1% of the population at risk of malaria in Africa lived in households protected by IRS (WHO, 2016).

The extensive scale-up of vector control programmes has clearly paid off, as about 663 million cases of malaria were averted in sub-Saharan Africa between 2000 and 2015, nearly 78% of these gains coming from bed nets and IRS (Bhatt et al., 2015). Treatment with artemisinin combination therapy (ACT), which has also been widely scaled up in Africa, contributed another 21% of the gains (Bhatt et al., 2015). ACT treatment courses procured from manufacturers peaked at 393 million in 2013, with 98% of the deliveries going to Africa, subsequently fell to 311 million in 2015 (WHO, 2016) but then increased to an estimated 409 million treatment courses in 2016 (WHO, 2017).

The 2015 World Health Assembly adopted the Global Technical Strategy (GTS) for Malaria 2016-2030, to guide and support regional and country programmes in their malaria control and elimination efforts (World Health Organization, 2015). This strategy boldly outlined major targets to be achieved by 2030, including, a) reducing malaria case incidence by at least 90%; b) reducing malaria mortality rates by at least 90%; c) eliminating malaria in at least 35 countries; and d) preventing a resurgence of malaria in all countries that are currently malaria-free (World Health Organization, 2015). These global targets are perfectly in line with the Africa Union Agenda 2063 target, which is also to achieve malaria elimination by 2030 (African Union, 2016).

A core component of the efforts towards both WHO targets and AU targets is the need to ensure universal access to malaria prevention, diagnosis and treatment. Unfortunately, while significant progress has been made against malaria, residual levels of transmission still persist even in places where coverage with existing intervention tools is already very high (WHO, 2017). In many countries, progress in malaria control has been threatened by the rapid spread of resistance to antimalarial drugs and insecticides commonly used for LLINs and IRS. Today, resistance to public health insecticides has been reported in nearly 100 countries worldwide, including all countries in sub-Saharan Africa.

Other challenges include sub-optimal coverage and use of existing interventions, poor compliance among users of current interventions and behavioural shifts in mosquito species including the tendency to bite more outdoors and to survive on non-human hosts (The malERA Consultative Group on Vector Control, 2011). Therefore, new complementary technologies are required, which can be used alongside current intervention tools to address these existing gaps and challenges. The use of genetic manipulation, as a complementary tool, has been proposed as one that offers new opportunities for high impact, well-organized and large-scale malaria control campaigns against dominant malaria vectors.

This report provides an overview of the gene drive technology and its potential applications in malaria control and elimination in Africa. It addresses major developments so far accomplished, the current state of the technology, and approaches necessary to determine potential risks and benefits. Various opportunities for future research and development are highlighted. The report outlines the need for risk assessments and the role that governments, funding partners and developers should play. It refers to various preceding documents and outlines suggestions of a testing pathway for the technology within the African context. Finally, a set of recommendations is proposed for consideration in any future developments and applications of the technology.

While existing interventions have significantly reduced the burden of malaria across Africa, complementary new interventions are required to drive the residual burden towards zero, and to eventually achieve malaria elimination on the continent

2

Relevance of the problem to Africa's development

The Malarial Burden

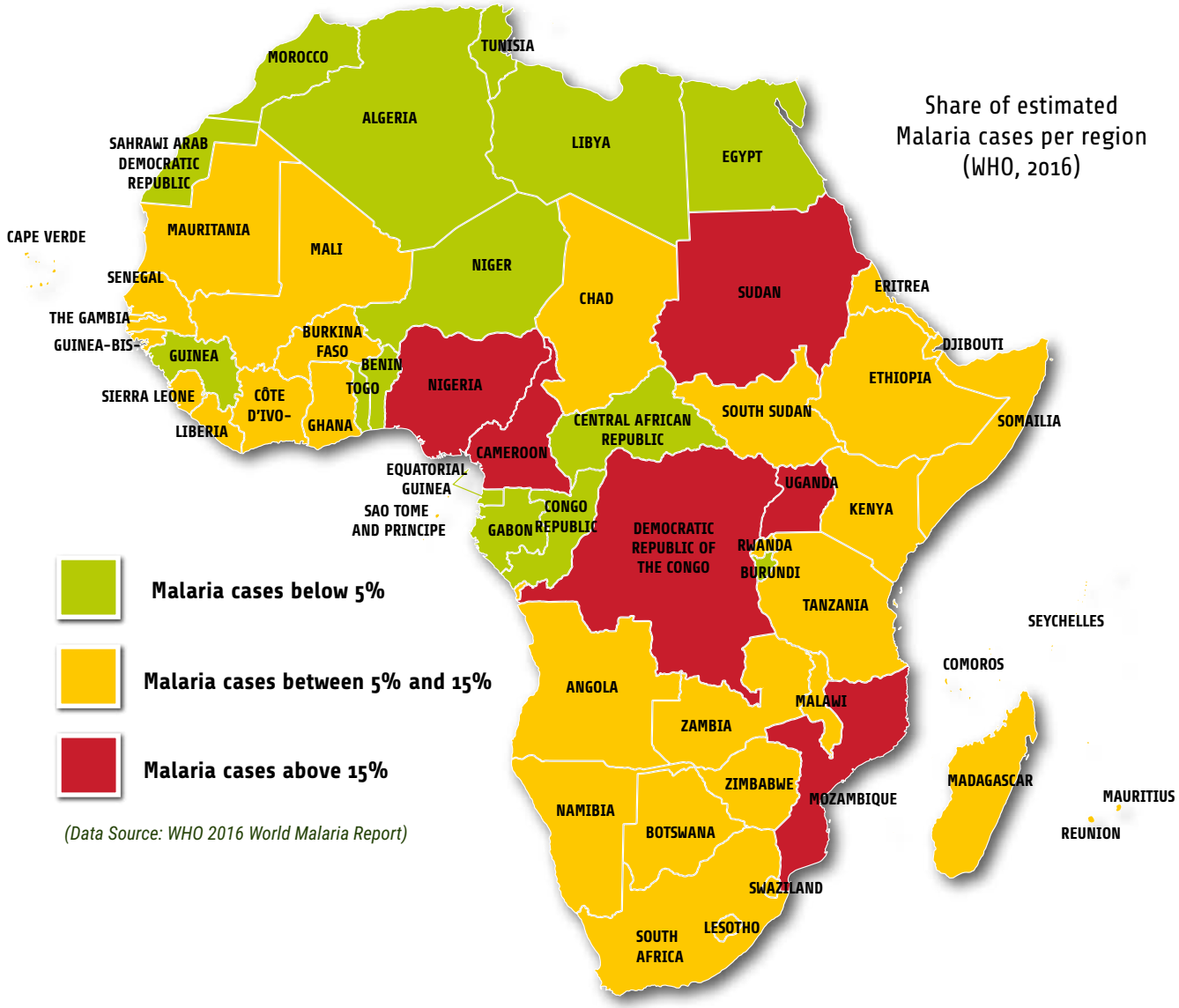
According to the latest estimates from WHO, there were 216 million new malaria cases and 445,000 deaths worldwide in 2016, with Africa accounting for 90% of the cases and 91% of the deaths (WHO, 2017). Children under five years of age are the most affected. In 2016, the global burden of malaria remained heavily concentrated in 14 African countries, which together accounted for 80% of global malaria cases and deaths. Today, the Democratic Republic of Congo and Nigeria alone constitute 40% of the global malaria deaths (WHO, 2016). Data collected by WHO indicate that these two countries, together with Mozambique, Cameroon, Uganda, Tanzania, Kenya and Somalia have the highest prevalence rates, accounting for about half of the global malaria burden (Figure 1). In 2015, about 291 million people in 8 out of the 21 countries in the WHO EMRO Region were at some risk of malaria, with 111 million at high risk. Three African countries: Djibouti, Somalia and Sudan are part of these countries, which have areas of high malaria transmission. While significant progress has been made in recent years, these high-burden countries performed worse (32% reduction since 2000) than the global average (53% reduction since 2000) (WHO, 2017).

Malaria in Africa is widely recognized as both a cause and consequence of poverty. Though no recent comprehensive figures exist, the malaria-related losses were estimated to cost up to 1.3 % of Africa's GDP, and about US$12 billion per year in direct costs, as of 2002 (Gallup & Sachs, 2001; Sachs & Malaney, 2002). At country level, these economic losses varied from 0.41% of GDP in Ghana to 8.9% of GDP in Chad. More recent estimates, using data collected between 2007 and 2011, indicate that countries severely affected by malaria have up to five times lower Gross Domestic Product (GDP) than those without malaria (Jobin, 2014).

In the WHO/RBM Action and Investment Plan to defeat malaria, which was also adopted by the WHO General Assembly in 2015, it was estimated that if malaria were eliminated, the return on investment for Africa would be as high as 60:1, effectively unlocking extensive human and economic development on the continent (WHO/RBM, 2015). Suppressing or modifying vector populations to eliminate malaria will therefore, clearly offer enormous health benefits to Africa. Public health delivery systems will be the major primary beneficiaries of the technology.

The end goal for malaria has been clearly defined by the African Union, with 2030 as the target date for elimination (African Union, 2016). It is therefore, important for decision makers to objectively review new technologies with potentially high impact, such as gene drive, and determine a suitable pathway for future development and deployment.

Figure 1: Malaria burden in African countries



(Data Source: WHO 2016 World Malaria Report)

3

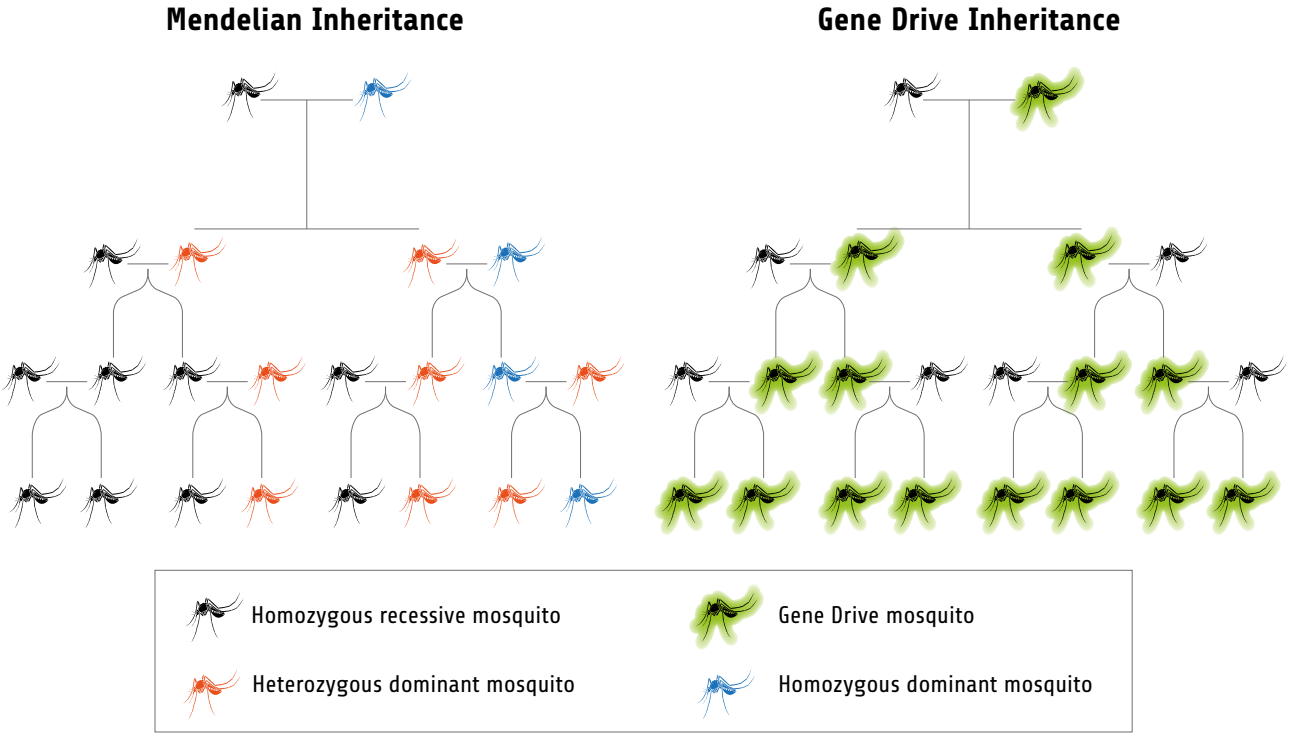
Gene Drive Technology in Malaria Control

Gene drives are systems of biased inheritance in which the ability of a genetic element to pass from a parent to its offspring through sexual reproduction is enhanced (National Academies of Sciences & Medicine, 2016; Sinkins & Gould, 2006). Gene drives are therefore, an exception to conventional rules of inheritance as originally described by Gregor Mendel (Mendelian inheritance) where offspring have on average a 50% chance of inheriting a gene (Figure 2). Offspring of sexually reproducing organisms with a gene drive element will almost always receive the targeted genetic element, creating a preferential increase of specifically desired genotypes. The technology can increase the frequency of a desired gene, despite any fitness costs, an attribute that is particularly key to the effectiveness against vector populations. Under optimal conditions, the targeted genetic element is eventually present in all or nearly all of the population (James, 2005; National Academies of Sciences & Medicine, 2016). This technology has multiple potential applications, including control of disease vectors, agricultural pests, and invasive species, as well as reclamation of threatened species (National Academies of Sciences & Medicine, 2016). For Africa however, perhaps its greatest application will be in malaria control and elimination, as described below.

There are many naturally-occurring gene drive systems in animals and microbes that have been studied for decades (Hurst & Werren, 2001; Sinkins & Gould, 2006). However, only in the last few years has it been possible to make synthetic drive systems that could be useful in organisms of applied interest. Through this process of "biased inheritance", a gene can increase rapidly in frequency in a population over multiple generations. This is the key differentiating characteristic from other forms of genetic modification

which is applied either only to one generation or eventually selected out, if disadvantageous, over a few generations. This quality makes gene drive approaches particularly interesting to tackle disease vectors, and perhaps other pests where conventional forms of genetic modification are not sufficient to bring the desired change in the target population. That is, the gene drives can increase frequencies of specific genes, despite any associated fitness costs, which is a key attribute for application of this strategy to achieve vector population suppression. In the case of disease vectors, such as certain species of mosquitoes, gene drive offers the only practicable way to introduce traits into the entire population that would reduce their capacity for disease transmission.

Figure 2: Illustration of the gene drive concept, compared to normal Mendelian inheritance



Different laboratories are using various molecular strategies to develop synthetic gene drive systems. The main alternative strategies include: (i) the use of sequence-specific DNA-cutting enzymes ("endonucleases"); (ii) using systems of toxins and antidotes to promote certain genetic traits; or (iii) chromosomal translocations. Of the three, progress has been most rapid with the DNA-cutting enzymes, particularly since the advent of CRISPR/Cas9 gene-editing technology (Doudna & Charpentier, 2014), which signals a new wave of developments based on gene-drive. CRISPR stands for Clustered Regularly-Interspaced Short Palindromic Repeats. The functions of CRISPR and CRISPR-associated (Cas) genes are essential in adaptive immunity in select bacteria and archaea, enabling the organisms to respond to and eliminate invading genetic material. The advent of synthetic CRISPR/Cas9 based gene drive systems allows very specific gene editing in the mosquito, as well as validation of genes expected to be essential in processes of interest for malaria control, such as reproductive capacity, mate-seeking behaviour, immunity against parasites and sex determination.

For Africa, perhaps the greatest and most urgent application of gene drive technologies will be in malaria control and elimination. It is therefore, important that we develop essential expertise to create, test, and evaluate the technology and its associated health application

3.1 Technology options: population suppression and population alteration

Gene drives can take two different forms for malaria control, namely population suppression or population alteration. In population suppression, the artificial gene introduced into the vector population disrupts reproduction by either distorting sex chromosome inheritance such that most progenies are males, or by knocking out female fertility genes such that they no longer lay eggs. Over time, the resulting population dwindles. Gene drive constructs, in this case, are not expected to persist in the environment. Nucleases, including CRISPR/Cas9 systems, can be adapted to distort inheritance and generate gene drive in malaria mosquitoes. In one example, the UK-based scientists demonstrated close to 100% inheritance of the Y (male-determining) chromosome after cleavage of the X chromosome (Galizi et al., 2014; Galizi et al., 2016), and close to 100% inheritance of a CRISPR-based gene drive element at three different genetic loci that cause disruption of female fertility (Hammond et al., 2016).

In population alteration on the other hand, the gene constructs introduced are those that reduce organisms' ability to transmit specific pathogens. For example, specific genetic segments that code for parasite binding proteins in the mosquito are altered so that malaria parasites can no longer bind to these receptors, effectively making the progeny incapable of carrying malaria pathogens. Unlike in the population suppression systems, the artificial gene constructs are intended to spread throughout the vector population and persist. In a pioneering example of this approach, scientists in California have created a highly efficient CRISPR/Cas-9 mediated gene drive, which achieved 98% modification of a laboratory population of Anopheles stephensi such that it could no longer transmit the malaria parasite, Plasmodium falciparum (Gantz et al., 2015). This approach therefore equally lends itself to use in large-scale malaria elimination efforts with potentially high impact over short durations (Eckhoff et al., 2016).

The existing demonstrations of gene drive in malaria mosquitoes, though only initial proofs of principle are important milestones in gene drive research. The studies offer real confidence that these technologies are indeed technically and scientifically feasible. Mathematical evaluations of both the population suppression and population alteration approaches to gene drive have demonstrated the potential to contribute to malaria elimination within just a few years after initial release (Akbari et al., 2013; Eckhoff et al., 2016).

3.2 Strength of gene drives

Gene drive strategies differ in 'strength' and have different thresholds beyond which they would continue to spread unassisted in nature. Weaker drive systems, sometimes also referred to as high threshold systems, are slower to increase in frequency in a target population, less likely to spread to neighbouring populations and require a higher number of releases to be effective. On the other hand, current technologies proposed for malaria elimination are strong drives, also referred to as low threshold gene drives, in which releases of even a small number of individual gene-drive mosquitoes can lead to an extensive spread in populations. Because of this high probability of spread, such low-threshold gene drives also carry significant potential for malaria control. It is estimated that even releases in less than 10% of the wild population of mosquitoes, given optimal conditions, could spread sufficiently and lead to malaria eradication within a few years (Eckhoff et al., 2016).

3.3 Readiness of technology for implementation

Currently gene-drive technologies to suppress or alter malaria-transmitting mosquitoes with potential field applications in Africa, are actively being developed in different laboratories. There are at least two research groups whose initial work on gene drive has been presented to the WHO Vector Control Advisory Group (VCAG) for evaluation (WHO Vector Control Advisory Group, 2017), but several other groups are also working on gene drives for malaria control. Already, the principle of using the technology for malaria control has been proven. Gene drive mosquitoes have been produced in laboratories (Gantz et al., 2015; Hammond et al., 2016) and are expected to be eventually tested in the field in Africa.

A small number of African institutions and scientists are also engaging actively in these developments and regulatory processes. Recently, scientists in Burkina Faso have obtained authorization from their National Biosafety Agency to import "sterile male" transgenic mosquitoes without any gene-drive, for purposes of capacity building, public engagement and strengthening of internal regulatory processes. The eggs have been received and the mosquitoes are being maintained in a contained facility at Institut de Recherche en Sciences de la Santé (IRSS) in Bobo Dioulasso, southwestern Burkina Faso. The Mali team has recently submitted its application for contained trials to the regulatory body and are awaiting their feedback.

As for Uganda, a contained facility laboratory will be constructed and the team will proceed with the application for contained trials once the facility is ready. All this progress will ensure other countries that come on board that they can circumvent any challenges and benefit from the experiences of Burkina Faso, Uganda and Mali. Mathematical models suggest that introducing gene-drive for vector control could lead to malaria elimination, either by suppressing Anopheles populations or by modifying the mosquitoes so that they cannot carry malaria parasites (Eckhoff et al., 2016). Most of the work however, is still in the early stages and will require further validation and field-testing. It is likely that the technology will take several years (estimated to be ~10 years) before actual field-deployable gene-drive approaches are ready. However, it is likely that most of this delay will be because of the need to adequately engage with stakeholders, and time required to effectively address regulatory requirements, and only minimally due to technology development reasons.

Already, the principle of using the technology for malaria control has been proven. Gene drive mosquitos have been produced in laboratories (Gantz et al., 2015; Hammond et al., 2016) and are expected to be eventually tested in the field in Africa.

The release of genetically modified mosquitoes will present several challenges, which may not necessarily be unique but probably not pursued with other vector control interventions, including biological control agents without genetic modification. For example, the likelihood of mosquitoes crossing national boundaries will require information sharing between countries. Besides, fears of disturbing biodiversity will require risk assessments and mitigation plans. In addition to assessments conducted by the developers and regulators, independent risk assessments may be essential to improve perception of non-bias among stakeholders and should be conducted at the different stages of development. Data from these assessments should then be made publicly available to improve transparency and compliance from all parties involved. Moreover, regulatory systems across the continent, including those already available for regulations of genetically modified crops, may need to be adjusted to effectively regulate gene drive mosquitoes. Nonetheless, several efforts are underway to ensure conditions are created that would enable the deployment of the technology as soon as it is eventually ready.

WHO already has a set of guidelines on field-testing of genetically modified mosquitoes (World Health Organization, 2014) and efforts are underway to update them, taking into consideration the properties of gene drive constructs. While many African countries are still relying on the biosafety regulations previously developed for genetically modified crops, some countries, such as Kenya, already have draft guidelines for the containment of genetically modified arthropods.

Previous research on gene drives for malaria vector control involved *An. stephensi* (Gantz et al., 2015) a species found in Asia and *An. gambiae sensu stricto* (Hammond et al., 2016), which was historically the most notorious malaria vector in Africa, and is still widespread in many communities. *Anopheles gambiae s.s.* is a member of the *An. gambiae* complex, which has seven other sibling species with varying capacities to transmit malaria (Sinka et al., 2010). There is an underlying assumption that resultant genetic constructs from ongoing work on *An. gambiae s.s.* will be readily introduced into related sibling species of the *An. gambiae* complex, i.e. *An. arabiensis* and *An. coluzzii*. These two species are increasingly important malaria vectors, with the *An. coluzzii* being particularly important and widespread in West Africa. *An. arabiensis* on the other hand, given its tendency to readily bite non-human hosts in the absence of actual humans, and its ability to bite early in the evenings and outdoors, has become an important contributor to ongoing residual malaria transmission in Africa (Durnez & Coosemans, 2013). Experts believe that the gene drive constructs being developed for *An. gambiae* can indeed be readily introduced into *An. arabiensis*, which would then be effectively targeted by gene drive.

The future elimination agenda however, will need to also aggressively target An. funestus, which is increasingly the dominant malaria vector in east and southern Africa, but also in some west and central African communities (Coetzee & Koekemoer, 2013; Kaindoa et al., 2017). This species is particularly challenging to study and has remained elusive, even though evidence suggests that, in places such as southeastern Tanzania, it now mediates 80-90% of the persisting malaria transmission (Kaindoa et al., 2017). Failure to develop gene drive constructs for this species, and to understand its ecology well enough to be able to colonize it in the laboratory, may signal limited impact of the gene drive technology for malaria elimination. To date, there are only two laboratories with the capability to colonize *Anopheles funestus,* the first being at the University of the Witwatersrand, South Africa (Hunt, Brooke, Pillay, Koekemoer, & Coetzee, 2005) and the other at the Centre National de Recherche et de Formation sur le Paludisme (CNRFP) in Burkina Faso. Detailed ecological studies are required to comprehensively understand the biology, ecology and genetic diversity of this vector, and to enable colonization in laboratories, so that the deployment of genetic control techniques can be most effective. Fortunately, efforts are already underway to comprehensively tackle some of these challenges, a process that should be encouraged and supported across multiple laboratories in Africa.

Existing gene drive proofs of principal have been done using *An. stephensi* and *An. gambiae*, with the assumption that the *An. gambiae* constructs can be easily introgressed into sibling species such as *An. arabiensis* and *An. coluzzii*. However, for elimination purposes, the development efforts should also focus on other major malaria vectors such as *An. funestus,* which now dominate malaria transmission in east and southern Africa region.

3.4 Opportunities for leap-frogging

Gene editing and, in particular, gene drive, are relatively new fields of research. There are no existing gene drive technologies already deployed anywhere in the world today. As a result, opportunities for technological 'leap-frogging' are minimal, as the African region is entering this field at nearly the same time as all other regions. While malaria mosquitoes that carry gene drive constructs have already been developed in laboratories in USA and Europe, they are expected to eventually undergo field-testing in Africa, where the technology would achieve maximum impact. In this regard, the technology is being developed with a specific focus on the African region as the major beneficiary, rather than being adapted from previously developed technologies in use elsewhere. The knowledge and expertise generated through this process and the associated research can indeed be applied to new applications. Since this is a new technology and malaria control in Africa likely to be among the first usages, African scientists, regulators, etc. will end up with world-class expertise that people in other parts of the world will look to them for advice, etc.

The region can also benefit from the capacity building and technology transfer that takes place as part of the research process. In this case, it will also have to look at how research teams are structured and how research proceeds will influence the capacity building and technology transfer benefits. A 'co-development' approach that emphasises collaboration between the partners in the teams, from research design to the creation of standard operating procedures is recommended.

In future, the three countries (Burkina Faso, Mali and Uganda) that will build capacity for the initial stages of gene drive work via the Target Malaria program (Box 1) may present multiple opportunities for leapfrogging whereby other member states can benefit from the expertise and resources of these countries without having to repeat some of the developmental and evaluation stages. Indeed, approval to test self-limiting versions of genetically modified mosquitoes, (bearing no gene drive), inside contained facilities has been granted by Burkina Faso, while Mali and Uganda will be pursuing similar approvals. The regulatory aspects will also offer opportunities for leapfrogging, where countries could learn from neighbours and select to forgo some of the intermediate evaluations if the product is already deemed adequately efficacious and safe for scale-up.

There are also related technologies that already exist for control of mosquito-borne diseases, but which do not use gene drive systems (Box 2 & 3). Examples include the large-scale rollout of *Wolbachia*-infected *Aedes* mosquitoes for control of dengue and Zika in Brazil, Australia, Colombia and Indonesia (Hoffmann et al., 2011). Another is the development of sterile *Aedes* male mosquitoes, which are already being deployed across cities in Brazil, Cayman Islands and USA (Harris et al., 2011). While these

BOX 1

Target Malaria is a not-for-profit research consortium that aims to develop and share gene drive technology for malaria control.

The consortium has adopted a staged approach to its research and development, gradually moving from genetically modified sterile males *An. gambiae* (that are not gene drive-based) through to a self-sustaining modified *An. gambiae* based on gene drive

http://www.targetmalaria.org
http://targetmalaria.org/who-we-are/

examples do not involve gene drive, their implementation requires field releases of large numbers of laboratory-reared mosquitoes, that are either sustained in the environment (*Wolbachia*-infected mosquitoes) or are self-limiting (sterile male mosquitoes). Beyond vector control, genetically modified crops, such as Bt cotton (Vitale, Glick, Greenplate, Abdennadher, & Traoré, 2008) and drought-tolerant maize (Fisher et al., 2015) have been experimented in some African countries in the recent past. There are therefore, clear learning opportunities that the African scientists, developers and regulators can benefit from in the years ahead.

BOX 2

Eliminate Dengue: Eliminate Dengue uses naturally occurring bacteria - called *Wolbachia* - to reduce the ability of mosquitoes to transmit harmful human viruses such as dengue, chikungunya, and Zika. They have shown their approach works when they introduce *Wolbachia* into mosquitoes in the laboratory, and have been conducting open trials with dengue-affected communities since 2011.

Wolbachia bacteria can be used in a number of ways, including to suppress mosquito populations. However, the Eliminate Dengue Program's *Wolbachia* method is unique because it uses the bacteria to stop viruses from growing inside the mosquito and being transmitted between people. The method is self-sustaining and has the potential to transform the fight against life-threatening viral diseases.

http://www.eliminatedengue.com/program/

BOX 3

OXITEC: Oxitec is a pioneer in controlling insects that spread disease and damage crops.

Oxitec uses advanced genetics to insert a self-limiting gene into its mosquitoes. The gene is passed onto the insect's offspring, so when male Oxitec engineered mosquitoes are released into the wild and mate with wild females, their offspring inherit the self-limiting trait. The resulting offspring will die before reaching adulthood, and the local mosquito population will decline.

They control vectors for dengue, Zika, chikungunya and yellow fever by controlling populations of *Aedes aegypti.* They have programmes using self-limiting mosquito in Brazil, USA, Cayman, Panama and India

http://www.oxitec.com/programmes/

Three African countries, namely, Burkina Faso, Mali and Uganda are already actively building technical, regulatory and institutional capacities for gene drive work, and should provide learning opportunities for other countries on the continent.

4

Testing and implementation strategies

4.1 Phased testing approaches for gene drive mosquitoes

Both the WHO guidelines for testing genetically modified mosquitoes (World Health Organization, 2014), and the US National Academies for Sciences, Engineering and Mathematics report (National Academies of Sciences & Medicine, 2016) emphasize the need for a phased-testing pathway (a stepwise approach to guide the preparation for and conduct of research that begins in the laboratory and continues through, if applicable, environmental monitoring). A comprehensive approach to the development and governance of gene-drive modified organisms will need to go beyond considerations for public health and the environment. It must also consider the benefits of technological innovation, implications for intellectual property arrangements, public engagement, and economics, among other valued societal commitments. The WHO and US Academies reports have provided a set of recommendations for researchers, developers, funders and policymakers, with relevance to African Union institutions on the development and regulation of gene drive technology for Africa's economic development.

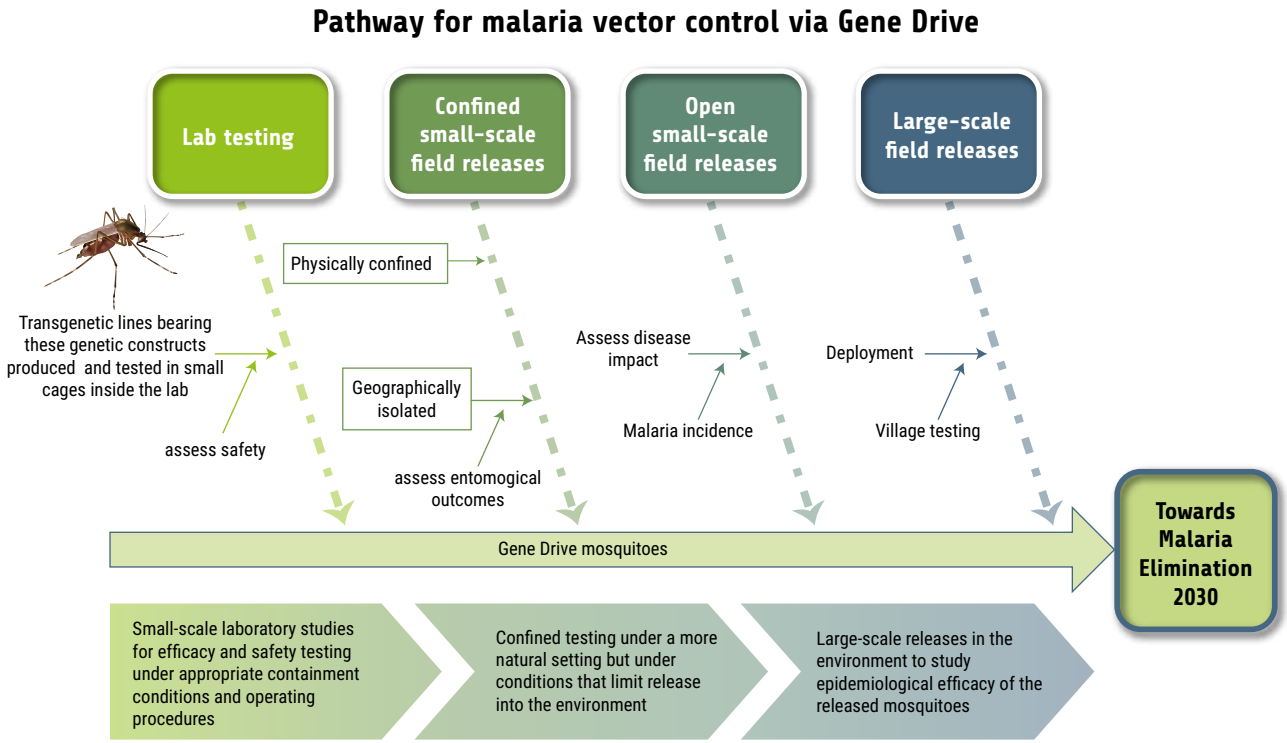
The three main stages of testing gene drives as currently envisioned (though these may change or overlap as the technology develops) are as follows (Figure 3):

i. Laboratory development and assessments to determine safety and efficacy in small-scale laboratory cages;

ii. Small-scale studies, beginning with testing under physically contained field cages, to assess stability, genetic flow, various entomological outcomes, possible implementation strategies and likelihood of development of adverse mutations that could prevent the spread of the drive. This is followed by additional small-scale studies where gene drive mosquitoes are released, first in ecologically-confined areas such as islands, to assess field efficacy and stability, genetic flow, acceptance by human communities in target areas, reproductive fitness of the mosquitoes, various entomological outcomes, potential implementation strategies and also the likelihood of resistance to the drives; and

iii. Large-scale controlled field releases to assess the impact of the intervention in clinical parameters of the disease, such as malaria incidence in a defined human population, and to monitor key entomological indicators, such as vector densities and vectorial capacities.

Figure 3: Stages in the testing approach to gene drive mosquitoes for malaria elimination



Along the process will be independent risk management procedures to identify any potential risks, allay any stake holder fears and identify specific mitigation measures should need be. Regulatory approval will also be sought for each phase.

Unlike in the phased-development of drugs or vaccines, the stages of gene drive development will likely overlap. For example, once the gene drive mosquitoes are released in small scale at stage two, successful outcome may mean that they spread beyond the initial areas of release, and would effectively transform into a large-scale release. It is also envisioned that after the large-scale trials, further assessments will include post-deployment surveillance to monitor the ongoing performance of the interventions in the field. The risk assessments already mentioned above should be performed in parallel as the technology moves through the different stages to identify potential risks and mitigation strategies, and allow for opportunities of different stakeholders to raise any concerns that need to be addressed before proceeding.

Development of the gene drive technology should follow a stepwise approach, starting from laboratory development to full field releases, where efficacy and safety are adequately monitored alongside risk assessments to guide decision-making and implementation

4.2 Implementation at country level

Specific implementation strategies will depend on the final gene drive product and its estimated potential in each setting. However, experts so far have recommended that the technology should be rolled out as a complementary tool, rather than a replacement of existing interventions. It is envisioned that implementation would be led by existing malaria control programmes, in close consultation with other agencies, depending on local set-ups. The technology is intended to reduce malaria transmission, which should in turn reduce the levels of coverage required for other methods. The decision to implement the technology, as well as an actual modality of implementation would, therefore, be the remit of the National Malaria Control/Elimination programme in each country. Moreover, such decisions should consider the epidemiological profile of malaria in the country, taking into consideration local evidence on the magnitude and characteristics of the actual residual transmission. All implementation targets should be in line with the indicators set in health sector frameworks for individual countries. Lastly, the actual implementation should be planned and incorporated into national strategies to ensure wider engagement with other sectors, and effective fundraising for long-term sustainability. However, because of the potential for transboundary movement, decision-making on the implementation of gene drive mosquitoes will need to take place in a regional context (see below).

From a regulatory standpoint, the uniqueness of gene-drive technology may necessitate that different arms of governments take different roles as developer, evaluator, implementer and regulator. Aspects such as continuous independent assessments during development and implementation may be contracted out to independent experts, but the processes will still need to be managed by government agencies. Given the primary application for malaria control, countries should seek guidance from WHO on questions of implementation. In some African countries, there is already a National Biosafety Agency, which acts as a central coordinator of all reviews of genetically modified organisms. It should, however, be noted that there are other reviews, such as efficacy, and product deployment approval, that might not be the remit of the National Biosafety Agencies. Coordination of these agencies and a clear roadmap should therefore, be developed at country level. The WHO guidelines will also provide a crucial reference for countries wishing to develop their own guidelines, as far as the utilization of this technology for health is concerned.

There should be early engagement and capacity building efforts with programs like the National Malaria Control/ Elimination in focus

From a regulatory standpoint, the uniqueness of gene-drive technology may necessitate that different arms of governments take different roles, as developer, evaluator, implementer and regulator.

4.3 Implementation at regional level

Border issues constitute one of the greatest impediments to African Science, Technology and Innovation (STI) and economic development. These boundaries limit the movement of researchers, materials and equipment across borders. They discourage collaboration and promote costly and ineffective duplication of effort. This is especially significant as many of the challenges and issues that research needs to deal with occur across boundaries, and yet few countries have all the expertise and facilities to single-handedly and independently deal with key STI issues. On the other hand, there have been some excellent examples of cross-border collaborations, which are proving quite productive and effective, in particular, the efforts of the NEPAD Agency's African Biosciences Initiative (ABI) networks. Without broader policy and programme harmonization the hope for countries in moving towards knowledge-based economies will not be feasible.

For countries where the reviews of factors such as the efficacy and product deployment approval of genetically modified organisms might not be the remit of the National Biosafety Agency, coordination of these agencies and a clear roadmap should be developed.

Collaboration in STI can be risky when adopting new technologies. However, in many cases, potential risks are significantly outweighed by the potential benefits when there exists a proper legal and regulatory environment that takes account of technical, societal and ethical aspects. The challenges that African researchers and entrepreneurs face are compounded by having to manage technological risks through a highly fragmented system in several countries. This presents a strong barrier to regional collaboration and integration. STISA 2024 promotes responsible use of intellectual property rights. It pays due attention to environmental protection, biodiversity, human health and public interests while ensuring that the society derives maximum benefits from science, technology and innovations.

In this regard, the NEPAD Agency will be promoting and supporting legal and regulatory systems that enable STI to be stimulated at the national and regional levels. Regional Economic Communities (RECs) offer an opportunity for rationalizing and harmonizing the regulatory environment for the application of new technologies. Besides, the AU/NEPAD Planning and Coordinating Agency is working with various regional bodies on the continent to improve the capacity of African Biosafety Agencies and NMRAs in different countries so that they are ready and capable of regulating the products.

Given the rapid developments in this technology space and the potential for misuse or mistrials, researchers and developers should establish a network of Africa-based scientists and developers to register their studies, self-regulate, share information regarding their technology, and peer-review all ongoing developments and field trials of the technology.

The current malaria control agenda is mostly implemented by individual countries based on independent national strategies. However, there is at least one platform where eight southern-Africa countries (Botswana, Mozambique, Namibia, South Africa, Swaziland, Zambia, Angola and Zimbabwe) have come together to pursue the goal of malaria elimination by 2030 under the Elimination Eight (E8) umbrella (Southern African Development Corporation, 2016) (Box 4). It is foreseeable that such cross-border partnerships will become the norm as more countries move towards malaria elimination. The strategy pursued by the E8 program focuses on five key pillars, namely regional coordination and dialogue, political prioritisation, policy harmonization and knowledge management, containment of cross-border transmission and sustainable financing, all of which will be particularly attractive for incorporation of gene-drive approaches (Box 4).

BOX 4

Eight countries – Angola, Botswana, Mozambique, Namibia, South Africa, Swaziland, Zambia, and Zimbabwe have formed a partnership, the Elimination 8, to collaborate across borders for the attainment of a bold goal by 2030. These eight countries are leading the way for the African continent, demonstrating that elimination of malaria is possible in continental sub-Saharan Africa.

The E8 Technical Committee comprises the senior malaria leads in each of the E8 member states, along with a range of thought partners from academic, non-profit think tanks, civil society groups, and private foundations. The Technical Committee deliberates on the technical and strategic elements of collaboration, guiding policy standards, and bringing new evidence and operational approaches to improve national and regional elimination strategies.

https://malariaelimination8.org/about-us/

Being organisms that are mobile and that the transgenic construct will spread through interbreeding populations, which cannot be contained within a single country, transboundary issues have to be taken into consideration in the regulation and deployment of transgenic insects. In this case, a regional regulatory approach will be relevant instead of only having independent national regulatory systems as has been the case with GM crops. A regional approach is also required because the spread of malaria cuts across several countries in a REC and yet it will be practically impossible to conduct confined trials in each of the malaria-infested countries. Implementation of such technologies would have more impact if done at regional level than just in one country. This will require building strong collaborations among countries and harmonizing technical requirements and processes for regulating transgenic insects, the most practical being at the regional level.

There is also a strong need for self-regulation, as well as peer reviews and audits among technology developers and scientists to avoid unwarranted outcomes. As a result of these features, RECs, with unified regulation and decision making on the subject may provide opportunities for large-scale trials as well as to implement the technology across multiple countries. Such unified approaches may also be necessary for authorization of the large-scale trials as well, since these may be difficult to restrict to a single country. These regional platforms would have advantages. For example, resolutions could be achieved more rapidly if there is sufficient motivation amongst the concerned countries and expected solutions that are developed by those countries, thus assuring policies that are more tailored to the African context.

There are already various precedents on this space, notably in the African Medicines Regulatory Harmonization (AMRH) that is being coordinated across the continent, and clinical trials which require advance vetting and registration internationally. Guidelines for implementation of gene drive would be drawn and harmonized across African regional networks. On technology development side, there is a need for the creation of an Africa-wide network of researchers and technology developers working on gene drive. Among other things, the objectives of such a network will include the following: a) self-regulation of the development and testing processes, b) data & knowledge sharing on gene drive across the continent, c) technology transfer between countries, and d) overall capacity building on development, field-testing, utilization and regulation of gene drive across the continent. Here, the Pan African Mosquito Control Association (PAMCA) offers a known platform upon which such a network could be established and supported (Box 5).

BOX 5

The Pan-Africa Mosquito Control Association (PAMCA) is a professional body comprised of mosquito control and research professionals from Africa and beyond.

The overall objective of the Organization is to promote control of and research on mosquitoes and to disseminate information on the bionomics of mosquitoes and related subjects across Africa and worldwide

http://www.pamca.org/about/

Development of gene drive technologies, like other interventions, will require coordinated and extensive stakeholder engagement, not only to understand public concerns but also to engage potential beneficiary communities. Such engagement should begin early and where appropriate, should include a co-development approach to enhance ownership of the technology in user communities

4.4 Consideration in Addressing Socio-cultural and Ethical issues

4.4.1 Social-cultural

The development of new technologies such as gene drive should entail extensive stakeholder engagement, not only to understand public concerns but also to engage potential beneficiary communities. Stakeholder perceptions of risk can inform the risk assessment process. Substantive stakeholder engagement can help ensure that the developed technologies respond to the needs of those who will potentially benefit, and ensuring that the technologies have the best chance of acceptance and support. Research using gene drive should be guided by the same principles that apply to other research, such as respect, integrity, fairness, and proportionality in weighing risk against benefit. The questions raised about gene drive technology, notably concerns about minimizing risk and maximizing benefit, individual and community informed consent, public acceptance, equality in access, transparency, accountability, mitigation and redress and so forth, are in many ways similar to those raised regarding other technologies.

The novelty of gene drive science can however, raise previously unknown challenges, thus it is important to plan for and implement effective engagement from early stages. The importance of this aspect is clearly emphasised in the current WHO guidelines for genetically modified mosquitoes (World Health Organization, 2014), by fifth meeting of the WHO/VCAG panel (WHO Vector Control Advisory Group, 2017) and also the US Academies of Sciences report on gene drives (National Academies of Sciences & Medicine, 2016). Of particular interest is the US Academy recommendation Nos. 7.1: "Research plans to develop gene drives should include a thoughtful engagement plan that considers relevant communities, stakeholders and the public throughout the process of research, from proposal development through if applicable, the release and monitoring of gene-drive modified organisms in the environment"; and 7.2: "Because engagement can contribute to defining the values and preferences of communities, stakeholders, and the public about gene drive technologies, researchers and risk assessors should integrate engagement into the construction of risk assessment models. In turn, the outputs of risk assessments should feed back into engagement efforts". Early engagement ensures that enough time is available for a meaningful dialogue and a genuine co-development of the technology. This co-development aspect is critical to ensure ownership and future adoption of the technology.

4.4.2 Ethics

Most countries already have strong institutional national ethics committees with the capacity to assess research related to the development and field-testing of novel vector control programmes, including gene drive mosquitoes. Beyond the existing in-country ethics regulations, there will be a need to share the data on the review process with scientists or implementers working in other countries, in order to make the processes more efficient in the next iterations. All researchers working on the programme should be conversant with important ethical concepts for protecting human participants in health research, such as provided by the National Institutes of Health (NIH) (National Institutes of Health, 2014). Key principles of ethics should be adhered to in the conduct of all such research, notably justice, respect and beneficence.

4.4.3 Gender impact

Unlike long-lasting insecticide-treated bed nets, which primarily offer personal, in addition to marginal communal protection, gene drive approaches are envisioned to provide mostly communal protection. LLINs can be used by individuals and, depending on household characteristics or cultural practices, their use may occasionally be biased against certain demographics based on gender or age groups. For example, men and young adults are sometimes left out of regular bed net coverage as campaigns have traditionally focused on young children and pregnant women (Garley, Ivanovich, Eckert, Negroustoueva, & Ye, 2013). Elsewhere, women may in some cases have compromised decision-making roles when choosing which members of the households should or should not use available bed nets. Gene drive on the other hand, would not be dependent on individual use or compliance and would instead provide extensive communal benefits regardless of age or gender of individual members of the communities. This way, most challenges associated with gender would be circumvented.

Already, many African countries are making significant efforts towards safeguarding the needs of women and children. In particular, since malaria infection during pregnancy carries substantial risks for the mother, her fetus and the newborn child, proportions of women who receive intermittent preventive treatment during pregnancy (IPTp) for malaria have been increasing over time, though levels remain below national targets. In 2014, an estimated 15 million of the 28 million pregnant women at risk of malaria did not receive a single dose of IPTp. Progress in adopting and rolling out preventive therapies for children have been even slower. As of 2014, 6 of the 15 countries where WHO recommends preventive therapies for children under five years have adopted the treatment as a national policy. Only one country Chad, had adopted the recommended preventive therapy for infants by 2015 (WHO, 2015). It is expected that the benefits of gene drive if used as a complementary tool against malaria, would be accrued by both children and adults of both sexes equally.

5

Risk analysis and management

In the course of development and implementation of gene drive technologies it will be essential that risk assessments are undertaken at different stages to: i) identify any potential risks that may arise in relation to the technology, ii) allay any stakeholder fears in relation to potential negative impacts of the technology, and iii) identify specific mitigation measures to address any negative impacts that may arise during development or implementation of the technology. Nonetheless, risk assessments should always be conducted from the perspective of the accrued benefits versus potential risks, ensuring to not overemphasize one over the other

Evaluations of related but not identical technologies such as the use of sterile or *Wolbachia*-infected *Ae. aegypti* mosquitoes for control of Dengue and Zika (see Boxes 2& 3) may offer insights into such risk evaluations. In these specific examples, the regulatory agencies have determined that the genetically modified *Aedes* mosquitoes pose no more harm to the environment than the natural wild mosquito populations and are therefore, safe for release. Where there is a clear value of disease reduction such as would be the case in the use of gene drive for malaria elimination, relevant information should be assessed vis a vis any potential risks associated with short and long term risks of releasing the mosquitoes.

It is reasonable to expect that the "first-in-class" products will undergo the most stringent risk assessment processes, as there is still a relatively high level of uncertainty in this technology space. However, once there is at least one candidate product being used, follow-on products will likely have multiple opportunities to leapfrog beyond some of the risk assessment processes. All stakeholders should make efforts to assure that subsequent technology versions maximize upon experiences of the "first-in-class" versions. The experience with genetically-modified crops indicated that in some situations, greater experience by regulators resulted in the expansion of questions and increased data requirements, thus resulting in greater delays. Such precautionary practices need to be balanced by the evidence-based risk evaluations and the potential benefits of the technology. Different perspectives on environmental protection and human health goals, with diverse moral or ethical considerations for use of gene drive technology, will likely arise when the gene drive mosquitoes are evaluated and deployed for malaria control or elimination. In such circumstances, it will be important to use existing environmental and human health goals as a baseline for consideration.

There has been at least one problem-formulation process completed in relation to risk assessments for malaria control using gene drive *An. gambiae* mosquitoes in Africa (Roberts et al., 2017). Here, the Foundation of the US National Institutes of Health (FNIH) convened a problem-formulation exercise with various stakeholders where potential effects of gene drive constructs on human health, animal health, environmental health and biodiversity were assessed (Roberts et al., 2017). The group determined that human health considerations related to disease transmission are important for analysis in the context of the risk assessment for gene drive mosquitoes. On the other hand, they also determined that harm to livestock health is unlikely, though the potential for altered pathogen transmission remains a relevant endpoint for assessment in that regard. Thirdly, the group also determined that although harmful impacts to biodiversity are unlikely to arise after suppression or alteration of *An. gambiae* populations, important

ecological interactions should be adequately considered in specific risk assessments.

A summary of the key aspects relating to the specific protection goals from this analysis are highlighted in Box 6. Overall, no major risks are foreseen that cannot be mitigated, and the potential benefits associated with malaria elimination (see chapter 3) will almost certainly outweigh any minor risks observed. Nonetheless, developers and regulators must remain vigilant, and independent assessments should be conducted at different stages to update available information on the state of development, risks and benefits of the technology.

Expert views currently indicate that no major risks are foreseen that cannot be mitigated in the application of gene drive technology for malaria elimination, and that the potential benefits will almost certainly outweigh any minor risks observed. However, developers, regulators and any risk assessors must remain vigilant and should update available information on the state of development, risks and benefits of the technology

BOX 6

Results from the Workshop "Problem Formulation for the Use of "Gene Drive in Mosquitoes"

Human Health

- The relevant interaction for human health are mosquito bites
- Incidental exposure through inhalation and ingestion are unlikely to cause significant levels of exposure leading to harm to human health
- Proteins introduced into *An. gambiae*, including components of the gene drive and markers should be considered with respect to toxicity and allergenicity potential
- Horizontal gene flow to humans is extremely unlikely to occur
- Because *An. gambiae* is an important disease vector, consideration should be given to potential alterations in disease transmission
- Altered *P. falciparum* transmission or virulence, other human malarial transmission as well as altered transmission of other diseases must be considered important

Animal Health

- Potential harm could result from altered pathogen transmission dynamics to livestock
- Harm resulting from other mechanisms, including toxicity from introduced proteins are unlikely

Biodiversity

- *An. gambiae* is not a "keystone" species in the environment and is not known to provide any non-redundant ecosystem services
- Changes in population size or even elimination of *An. gambiae* from a particular environment are unlikely to harm biodiversity or ecosystem services. This is based on existing knowledge and experience with vector control programmes
- *An. gambiae* interacts with other species by feeding on them, being consumed, or competing with them
- These interactions may require consideration for species of relevance to the assessment such as threatened, endangered, or valued species; Incidental contact between organisms and *An. gambiae* carrying gene drives is not likely to lead to harm those organisms, compared to interactions with other *A. gambiae*.
- *An. gambiae* is not known to be the sole or primary food source for any organism, with the possible exception of a few species of spider known to prefer Anophelines
- Removing *A. gambiae* from the environment is unlikely to harm species that feed on it due to the availability of other prey, including Anophelines
- Consideration should be given to any proteins introduced into *An. gambiae* (including gene drive components or markers) for toxicity to other species
- Gene flow to other species within the *An. gambiae* s.l. complex through hybridization is likely, and does not create additional pathways to harm
- Horizontal gene transfer is not likely to occur to other organisms on any relevant time scale and is not a pertinent pathway to harm

Other considerations

- The use of gene drive in *An. gambiae* should be considered as a complementary strategy to other vector control methods and malaria mitigation strategies
- The potential harm identified for the use of gene drive in *An. gambiae* should be considered in the context of other vector control methods and malaria mitigation strategies
- Failure to sustain a successful malaria vector control strategy can have harmful effects on malaria incidence. This is not unique to gene drive, and would be the same for other malaria control or eradication techniques; the ability to control disease resurgence needs to be sustained and availability of effective additional control methods assured
- Stakeholder engagement and capacity building of senior policy-makers and decision-makers are very critical for the successful implementation of the technology

Source: Roberts, A., De Andrade, P.P., Okumu, F., Quemada, H., Savadogo, M., Singh, J.A. and James, S., 2017. Results from the Workshop "Problem Formulation for the Use of Gene Drive in Mosquitoes". *The American journal of tropical medicine and hygiene*, 96(3), pp.530-53

6

Policy and Regulatory systems

Favourable policy support by governments at the national and regional levels, as well as appropriate regulatory systems can help enable and support research in areas of interest to African governments. As noted earlier, policies to support education and capacity building opportunities are an important consideration in equipping African scientists to lead in this innovative field of gene drive technology for the benefit of the continent. While gene drive technology offers potential to improve human health, there could also be potential ecological risks. There is therefore, need for a balance between ensuring the safety of the environment and human health without being so restrictive as to lose the potential health benefits of the technology. Gene drives are being developed for application in a diverse range of sectors, hence its regulation cannot just fall within the powers of a single body. In the case of health applications, regulations of gene drive need to be a collective responsibility of regulators in environment and health sectors.

In this regard, the WHO and the CBD are collaborating at the global level by acknowledging that health-biodiversity linkages are related to the Agenda 2063 and Sustainable Development Goals (SDGs). The CBD has urged member states to evaluate the linkages with a view to maximising health benefits, addressing trade-offs, and where possible, addressing common drivers for health risks and biodiversity loss (CBD/COP/DEC/XIII/6 December 2016). While the Cartagena Protocol provides for Regulation of safety and a trans-border approach, the WHO Guidance Framework for Testing of Genetically modified Mosquitoes serves as a blueprint for countries and regional groupings to develop guidelines for evaluating the efficacy, product approval and licensure as well as for post-licensure activities.

A key feature of gene drive approaches is the potential for trans-boundary movement, which presumably calls for coordination among neighbouring countries. Conventional biological control programmes may offer a useful precedent in this regard. Ensuring early engagement and coordination among African leaders and decision-makers will be essential to guarantee that they are ready to evaluate proposals for the use of gene-drive based technologies when these are sufficiently advanced.

Member states should customize and incorporate regulatory processes to harness gene drive technology within the national and regional agenda

Going by the current trends, it is likely that the first product from gene-drive technology will be for suppressing or altering populations of malaria-transmitting mosquito in sub-Saharan Africa. The product has health benefits, hence it is important to create awareness early enough among stakeholders who are involved in public health delivery systems. Introducing the product to such a stakeholder group early will facilitate eventual ownership of the technology and create awareness as to the pathways that will be followed for

the product to reach the end users. There will therefore, be need to build strong coordination between health and environmental regulators at national and regional levels.

Regulation of gene drive technology is unique because it needs to translate from transgenic insects for vector control directly into reducing mortality through the elimination of malaria in Africa. The regulatory process needs to consider multiple aspects, ranging from technologies initiated by agricultural genetic modification processes, through transgenic insect vector control, to health value propositions. This will require bridging from agriculture to health and the regulatory pathway being targeted will form a break-through model for other emerging technologies that need to be harnessed for economic development in future. A key component of it will also require that the regulators in agriculture, environment and health be best informed in order for them to make evidence-based decisions for the benefit of saving the African populations from the burden of malaria. Consequently, the NEPAD Agency, through ABNE and AMRH (Box 7&8) and by virtue of its position in the African Union, REC and national systems, should, therefore, play an enabling role by coordinating processes and programmes at all these levels.

BOX 7

The African Biosafety Network of Expertise (ABNE) is a programme of the African Union/NEPAD Agency. ABNE was conceptualized under AU's Science and Technology Consolidated Plan of Action and fulfils the recommendation of the High-Level African Panel on Modern Biotechnology - Freedom to Innovate.

The overall goal of the ABNE service network is to build functional regulatory systems in Africa. ABNE biosafety services include information resources; training and education (workshops, short courses, on-line courses, internships, and regulatory study tours); technical support, networking. These are aimed at empowering African regulators with science-based information, targeting the National Competent Authority/Focal Points, including members of National Biosafety Committees(NBCs), Institutional Biosafety Committees (IBCs), and Plant Quarantine Officers (PQs) so that they can make informed decisions on biotechnology.

BOX 8

The African Medicines Regulatory Harmonization (AMRH) programme is implemented within the framework of the Pharmaceutical Manufacturing Plan for Africa (PMPA), the AU Roadmap on Shared Responsibility and Global Solidarity on AIDS, TB and Malaria Response in Africa (2015-2030). The programme is aimed at increasing access to quality, safe and efficacious essential medical products to the African populations, by accelerating and deepening medicines regulatory harmonization on the continent.

AMRH supports Regional Economic Communities (RECs) and regional organizations (ROs) to develop and implement programmes for harmonizing standards, operating procedures, and related policies and legislation on medical products regulation. It is envisaged that harmonization of regulation of medical products will remove barriers to scientific research and innovation, and will facilitate easy procurement of and access to essential medical products.

In addition, the NEPAD Agency will be required to provide the appropriate fora for both technology development experts and regulators where they will exchange information and implement a shared and co-owned strategy. This would facilitate greater understanding of the technology, identification of the risks and opportunities in the context of malaria elimination so that informed objective decisions can be made. The various actors will learn from each other. In terms of regulatory pathways, assessment of transgenic insects for vector control will mostly be based on a Risk-Benefit Analysis (RBA) model, focusing on both risks and benefits of the technology. The risks will mostly be environmental while benefits will be for human health and development value.

Member states should facilitate capacity building for scientists and regulators on gene-drive technology for the eradication of malaria

It is therefore recommended that the NEPAD Agency should support policy implementation and strengthening of regulatory systems, facilitates the preparation of appropriate guidelines and support the fora for experts and regulators engagements at both national and regional levels. It is also important, therefore, that countries formulating guidelines for assessment of the development of the technology should also consider the rigorous evaluations already being conducted by WHO VCAG (Box 9) on this and other vector control tools.

BOX 9

Vector Control Advisory Group (VCAG) guides innovators in data and documentation requirements, and advises WHO on the public health value of new tools, technologies and approaches. This advisory group was jointly established by the Global Malaria Programme and the Department of Control of Neglected Tropical Diseases

For each new product class or variant not yet recognized by WHO and for which there is no WHO policy recommendation, VCAG provides a recommendation to WHO on the evidence required to substantiate the claim(s) and advises on the evaluation methods needed to generate these data. VCAG's role depends on how advanced the evidence is to support a new vector control tool, technology or approach.

http://www.who.int/neglected_diseases/vector_ecology/VCAG/en/

During the 67th Session of the WHO Regional Committee for Africa, held in Zimbabwe between August 29th and September 1st 2017, various important recommendations were made regarding clinical trials across the continent (WHO Office for Africa, 2017a, 2017b). Many of these recommendations could be adopted by members states as a guiding principle to support these regional efforts. Key among them were:

1. Member states should strengthen capacity for clinical trials within the continent
2. Member states should take ownership of the trials; this would be particularly important in cases of gene drive trials where the levels of uncertainty are still unknown, and where no single sponsor would be readily willing to bear the costs of aspects such as trial insurance
3. Member states should establish systems to improve governance and transparency. This would compliment the self-regulation efforts by scientists and developers, so that all stakeholders readily have access to important information about the trials, as is already being done for clinical trials of drugs and vaccines
4. Member states should provide support for bio-banking and data archiving, as well as safeguarding intellectual property associated with all trials on gene drive, to maximize local impact, and help expedite future evaluations and approvals; and lastly,
5. Member states should encourage and support harmonization of monitoring, regulating and approvals.

7

Research & Development

7.1 Research and Development Focus and Infrastructure

The powerful gene-editing tool, CRISPR/Cas-9, and the application of gene drive technology for modification of malaria mosquitoes are both in their infancy. The approach could offer high potential but there is still a significant body of knowledge that must be generated in order to determine actual feasibility and effectiveness. Final decisions on whether to adopt the technology will require inputs from a wide range of research fields examining different aspects of the technology. Indeed, beyond the proof of principle already achieved in the laboratories, the technology still requires a series of validation and optimization studies to be conducted rigorously in safe and secure laboratories. Research on appropriate strategies for moving from contained laboratory trials to semi-confined and eventually unconfined environments are also required. Examples of some of the key research studies necessary should include among others, the following;

- Investigations into how the gene drive technology will interact with existing interventions such as LLINs, IRS, ACTs and Vaccines.
- Investigations into the potential for selection or evolution of resistance to the genetic transformations as well as examination of the stability and spread of the gene drive under conditions of potential mutations in the targeted alleles. Undertake studies to determine fitness of the gene drive mosquito, including survival, fecundity and fertility in a laboratory environment and semi-field or open environments.
- Investigations into the effects of resistance to insecticides currently used for malaria control. This should include strategies for introducing gene drive mosquitoes in communities with insecticide-resistant wild mosquitoes.
- Investigations into the ecology and gene flow within various populations of dominant malaria-transmitting mosquitoes of different species. Data from such studies should be made available to developers of the technology so that more effective versions of the gene constructs can be created to target the dominant malaria vectors in various settings.
- Sociological, anthropological and human behaviour studies on how stakeholders and beneficiary communities would respond to the implementation of gene drive for malaria mosquitoes.
- Economic evaluations to determine the potential gains and opportunities for synergy associated with the implementation of gene drive, in the context of other interventions.
- Profiling of the malaria transmission patterns, including contributions of the different malaria vector species across settings. These studies should include both entomological and epidemiological assessments to understand the

potential of gene drive in different settings, but also to improve decision making on deployment.

- Health, social and environmental impact assessments to identify any potential negative impact and mitigation strategies.
- Ethical and legal considerations: research using gene drive should be guided by the same principles that apply to other research such as respect, integrity, fairness, and proportionality in weighing risk against benefit. The questions raised by genome editing technologies, notably concerns about minimizing risk and maximizing benefit, informed consent, community acceptance, equality in access, transparency, accountability, redress and so forth, are the same questions raised by many other technologies.

7.2 Human Capital and Institutional Development

Africa should benefit from the capacity building and technology transfer that will take place as part of the research process. In this case, how research teams are structured and how research proceeds will influence the capacity building and technology transfer benefits. The need for a 'co-development' approach that emphasises collaboration between the partners in the teams, from research design to the creation of standard operating procedures. The work on gene drive will involve investment in new or upgraded research facilities at participating institutions in Africa. Though the initial investments necessary to support such endeavours may be high, the economic and human health gains associated with such efforts would most likely outweigh these investments and lead to positive returns in the long term. WHO estimates suggest a 60:1 return on investment ratio, which puts malaria elimination among the most cost-effective ventures in the long-term.

Stakeholders should adopt a 'co-development' approach that emphasises collaboration between the partners in the teams, from research design to the creation of standard operating procedures

7.3 Intellectual Property (IP)

Ownership of the IP for gene drive is an issue of concern that needs to be addressed and will need to be resolved as the technology develops, especially for humanitarian applications like malaria elimination. Competing patents for the CRISPR Cas9 gene have been reported, but these are unlikely to affect its application for malaria elimination in Africa. Given their funding sources, the most advanced laboratories currently working on gene drive for malaria vector control will likely be signatories to the Bill and Melinda Gates Foundation's Global access plan for intellectual property. This requires that the products from Gates-funded research are made available at reasonable cost to the communities that need them most, and that the results are published on open access platforms. The Target Malaria Programme (Box 1) under which the most advanced African initiatives on gene drive for malaria control are working, is already transformed into a non-profit entity. It has a mission to solve global health challenges through co-developed technology. Nevertheless, institutions working on gene drive still need to address these challenges locally, while creating an enabling environment for the technology development to thrive.

8

Recommendations

The AU High Level Panel on Emerging Technologies notes that while existing interventions have significantly reduced the burden of malaria across Africa, complementary new interventions are required to drive the residual burden towards zero, and eventually achieve malaria elimination on the continent. Africa should invest in the development and regulation of gene drive technology, whose greatest and most urgent application will be in malaria control and elimination. The Panel recommends that the AU, RECs, Member States and their partners should consider the following:

- Given the potential for rapid developments in this technology space and the potential for misuse and improper trials, researchers and developers should establish a network of Africa-based scientists and developers to register their studies, self-regulate, share information regarding their technology, and peer-review all ongoing developments

and field testing of the technology on the continent. They should also adopt a 'co-development' approach that emphasises collaboration between the partners in the teams, from research design to the creation of standard operating procedures.

- Regulation of gene drive technology should take into account the value propositions and potential risks. Thus, regulators should facilitate and adopt essential guidelines and frameworks and, where necessary, enact enabling legislation for the development and adjudication of the technology.
- Member states should encourage interaction between different agencies mandated to regulate emerging technologies including genetically modified organisms and related technologies.
- AU Agenda and RECs should facilitate development, coordination and harmonization of regulations and guidelines for regulating the development, approval and use of the final product.
- Member States should obtain support for Public-Private-Partnerships, funding, laboratory infrastructure and international partnerships and ensure they provide budgetary support to research, development and public engagements.
- Researchers and developers, member states and the AU, NEPAD Agency and RECs should adopt a regional approach to the harmonization of policies and implementation of the gene drive technology across African countries.
- Member states should provide support for the conduct of laboratory, field and semi-field studies to verify the potential of the technology for various African settings; and to support essential research for optimization of the technology. These studies should include the modelling of potential risks of gene-drive technology and mitigation of same.
- Support for bio-banking and data archiving, as well as the safeguarding of intellectual property associated with all trials on gene drive is essential to maximize local impact and help expedite future evaluations and approvals.
- Governments have a central role to play in harnessing emerging technologies for Africa's development. In addition, the AU High Level Panel calls for a more proactive involvement of financial institutions, Foundations and private sector investors, as well as philanthropic associations, to name but a few examples. Banks and other financial institutions are generally profit oriented; however, they want to see the products developed as well as the profits generated.
- The Panel calls for the development of strategies that should address challenges of availability of African skills, the issue of regulation and ethics, education and awareness creation for the public, targeting young people, in order to prepare them for their future role as decision-makers.
- Early engagement with stakeholders is critical for the development of emerging technologies in order to ensure that the technologies meet their expectations and therefore, have great chance to be accepted and supported.
- The Panel calls for advocacy and support of policy makers for emerging technologies for economic development for instance, liaising with Ministers of Health in the field of gene drive against malaria.

9

Conclusion

Malaria elimination, which it is envisaged to be achieved by 2030, is a key target for the African Union. Estimates indicate that the return on investment could be as high as 60:1, making malaria elimination among the best investments in the long-term for the continent. This report has provided a general overview of the gene drive technology and its potential for malaria control and elimination in Africa. It has highlighted major developments which have already been achieved and the opportunities offered by the revolutionary CRISPR/Cas-9 gene-editing tools. Various opportunities for future research and development, as well as the essential regulatory needs within countries and in regional economic communities are highlighted. A set of key recommendations are proposed for consideration in the future development and application of the technology. It is concluded that though gene drive for malaria elimination is still in early development phase, it present realistic options to achieve high-impact, well-organized and large-scale malaria control and elimination. It may take many years before actual products are ready for field deployment, but the potential benefits for African countries against malaria will most likely be extensive.

10

Acknowledgment

The AU Summit of July 2016 endorsed the request by the Technical Specialized Committee (STC) on Education, Science and Technology that the NEPAD Agency working together with the AU Commission, should advise Member States and the Regional Economic Communities (RECs) on matters of technology prospecting including regulatory and ethical requirements. These need to be put in place in order for the continent to benefit from emerging technologies for economic development and environmental sustainability. In response to the above resolutions and decisions, the Chairperson of the AU Commission appointed a ten-member High-Level African Panel on Emerging Technologies (APET) to advise the Union, its various organs and Member States on how Africa should harness Emerging Technologies.

The Panel carefully selected ten technologies in it's first round, beyond which the panel identified a set of three technologies that it has processed which includes the application of gene drive for the control and elimination of malaria. However, with the new initiatives there is need for consultations to either establish new regulatory frameworks or align these new developments with the existing ones to create an enabling environment. The AU authorized the NEPAD Agency to roll out consultations prior to building the required consensus before the implementation of these technologies.

Thus the consultation meetings held in Accra-Ghana (16-19 October, 2016), Nairobi-Kenya (19-22 June, 2017) Gaborone-Botswana (25-28 June, 2017), and Libreville-Gabon (19-22 February, 2018) aimed at building consensus among participants hailing from countries of the Regional Economic Communities on the continent.

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NEPAD

230, 15th Road, Randjespark

Midrand, Gauteng

South Africa

Telephone +27 (0) 11 256 3600

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