

FIFTH MEETING OF THE VECTOR CONTROL ADVISORY GROUP

VCAAG



GENEVA, SWITZERLAND
2-4 NOVEMBER 2016



**World Health
Organization**

The support provided by the Bill and Melinda Gates Foundation (Grant No OPP1032376) for the work of Vector Control Advisory Group is gratefully acknowledged.

This report was produced by the Vector Ecology and Management Unit, Department of Control of Neglected Tropical Diseases, and the Vector Control Unit of the Global Malaria Programme of the World Health Organization.

Design & Layout: Patrick Tissot WHO/HTM/NTD

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Printed in France.

WHO/HTM/NTD/VEM/2017.02

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ABBREVIATIONS AND GLOSSARY

Effectiveness	Estimates the effect of an intervention under programmatic or real-life conditions (e.g. delivery of the intervention under routine conditions to maximize the relevance of the findings for policy and practice)
Efficacy	Estimates the effect of an intervention under highly controlled conditions (e.g. maximal coverage of the target population and adherence to the intervention)
IAEA	International Atomic Energy Agency
FAO	Food and Agriculture Organization of the United Nations
GMP	Global Malaria Programme
IIT	incompatible insect technique
IRS	indoor residual spraying
LLIN	long-lasting insecticidal net
NTD	neglected tropical disease
PQ	Prequalification Programme
Product class	For vector control, a category of intervention that shares a common entomological mechanism of action to reduce infection and/or disease
SIT	sterile insect technique
TDR	Special Programme for Research and Training in Tropical Diseases
TPP	target product profile
VCAG	Vector Control Advisory Group
VEM	Vector Ecology and Management unit
WHO	World Health Organization
WHOPES	WHO Pesticide Evaluation Scheme

DECLARATIONS OF INTEREST

All invited experts completed a declaration of interests form for WHO experts before the meeting, which was submitted to and assessed by the WHO Secretariat. On review of the completed forms, the following expert declared interests that required further consideration and discussion with the Office of Compliance, Risk Management and Ethics:

- Professor Immo Kleinschmidt

Further to a meeting with the Office of Compliance, Risk Management and Ethics, the technical units sought additional information from the expert regarding their respective disclosed interests:

Professor Immo Kleinschmidt is a Professor of Epidemiology at the London School of Hygiene & Tropical Medicine. In his declaration, he noted that his Research Unit receives institutional research funding from the Bill & Melinda Gates Foundation via Penn State University to assist in the development of the Eaves Tubes Trial methodology. This information was shared with the Office of Compliance, Risk Management and Ethics.

Conclusion

Upon receipt and review of the additional information, it was determined that this interest was potentially significant as it relates directly to the subject of activity for one session of this meeting (eave tubes). Due to this interest, Professor Kleinschmidt did not participate in the drafting and finalization of the recommendations on eave tubes: partial exclusion.

The reported interest was publicly disclosed to other meeting participants and recorded during the meeting. Participants were notified that interests will be disclosed in the report of the meeting and relevant publications or work products.

1. SUMMARY

The World Health Organization's (WHO) Vector Control Advisory Group (VCAG) held its fifth annual meeting on 2–4 November 2016 at WHO headquarters in Geneva, Switzerland. The objectives of were to review new potential vector control approaches to target malaria and other *Aedes*-borne diseases and to finalize recommendations to WHO on evidence-based policy pathways for new tools and approaches. Participants reviewed evidence on three new approaches: (i) combined sterile insect technique (SIT) and incompatible insect technique (IIT) to reduce vector populations and control *Aedes*-borne disease transmission; (ii) genetic manipulation of mosquitoes through gene-drive technology to reduce vector populations and malaria transmission; and (iii) genetic manipulation of mosquitoes through gene-drive technology to introduce *Plasmodium*-refractory genes into wild mosquito populations to reduce malaria transmission.

The main conclusions of the meeting are summarized below.

1. Clarification on policy for new products

A product class in vector control is a category of intervention that shares a common entomological mechanism of action to reduce infection and/or disease. A WHO policy recommendation of a product class is based on evidence that substantiates public health value, e.g. proven impact on infection and/or disease in humans. Each product class is defined through a target product profile (TPP).

VCAG will continue to provide recommendations to WHO on the evidence required to substantiate public health value of the product and advise on the evaluation methods needed to generate these data. Validation of the claims will require the availability of sufficient evidence from across different settings to demonstrate the efficacy of the new product in reducing infection and/or disease in human populations and to support evidence-based guidance for deployment.

2. Major conclusions on public health value of new products reviewed

VCAG concluded that the combined SIT/IIT technology has potential for long-term control of *Ae. aegypti* and *Ae. albopictus* mosquitoes. It strongly recommends that further entomological and epidemiological field trials be conducted to validate the use of this intervention and its claims of efficacy against infection and/or disease.

VCAG encourages further development of tools utilizing gene-drive-based technologies (gene drive for population reduction and gene drive for population modification), while recognizing that these strategies are still in the early phases of development, and that important challenges lie ahead for their development and deployment. Both submissions require more evidence from laboratory-based studies before semi-field or open field-testing should be undertaken.

2. BACKGROUND AND OPENING REMARKS

The fifth annual meeting of the World Health Organization (WHO) Vector Control Advisory Group (VCAG) was organized by WHO in Geneva, Switzerland on 2–4 November 2016. The objectives of the meeting were to review three new potential vector control approaches to target malaria and *Aedes*-borne diseases, and to finalize recommendations to WHO on optimal pathways for evaluating new vector control interventions, including expected evaluation methods, data requirements and efficacy indicators.

Dr Pedro Alonso, Director, WHO Global Malaria Programme, opened the meeting by reflecting on the importance of vector control and the gains made against malaria in recent years. He detailed the initiation of a WHO draft Global Vector Control Response, led by the Department of Control of Neglected Tropical Diseases, the Global Malaria Programme and the Special Programme for Research and Training in Tropical Diseases. The plateau in funding for vector control has limited the resources available to deploy tools for maximum benefit. A number of technologies are in development. WHO recommendations must be data driven and science-based in order to provide countries with the best possible outcomes against malaria and other vector-borne diseases.

Dr Dirk Engels, Director, WHO Department of Control of Neglected Tropical Diseases, reiterated the need for novel tools to address current challenges in control and elimination of vector-borne neglected tropical diseases (NTDs). Vector control is a core public health intervention. VCAG plays an important role in advising WHO on the efficacy of new products with which to reduce vector-borne infection and disease and the evidence needed to guide deployment.

Dr Raman Velayudhan, Coordinator, Vector Ecology and Management, WHO Department of Control of Neglected Tropical Diseases, welcomed participants and reviewed the meeting's objectives. Dr Thomas Scott, Chair of the VCAG, was appointed as Chair, and Dr Anna Drexler, Vector Ecology and Management, and Emmanuel Temu, Global Malaria Programme, as the Rapporteurs. Participants introduced themselves with a tour de table.

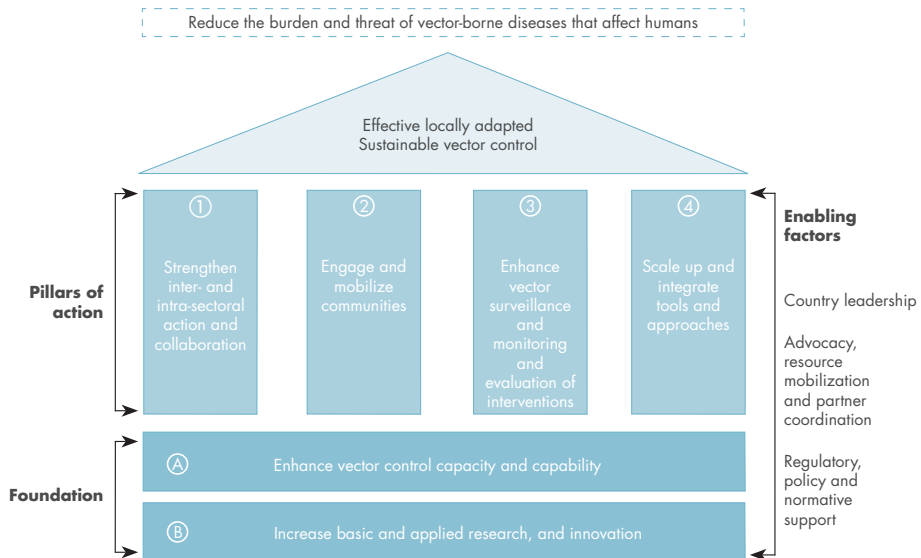
The meeting was convened in open and closed plenary sessions and in working groups (**Annex 1**: Agenda). It was attended by VCAG members, invited temporary experts, stakeholders, representatives of the Bill & Melinda Gates Foundation, the United States President's Malaria Initiative and members of the WHO Secretariat (**Annex 2**: List of participants).

The Chair invited comments from participants for amending the agenda; no comments or requests were received, so the agenda was adopted.

2.1 UPDATE ON WHO DRAFT GLOBAL VECTOR CONTROL RESPONSE

Professor Steve Lindsay briefed the meeting on the preparation of a WHO draft Global Vector Control Response 2017–2030 (**Box 1**) for submission to the 140th session of the Executive Board (Geneva, 23 January – 1 February 2017). Vector-borne diseases represent a large proportion of infectious and emerging diseases, and new investments are therefore needed to boost capacity to address them in the face of changing transmission patterns and emerging disease threats. The Response was drafted jointly by the WHO Global Malaria Programme, the Department for Control of Neglected Tropical Diseases and the Special Programme for Research and Training in Tropical Diseases. The development process, which spanned 7 months, was guided by steering committee meetings and consultations with national programmes, research

Box 1. Framework for the Global Vector Control Response



and academia, and regional vector control focal points. Further information is available from the WHO website.

Participants expressed broad support for the initiative. Vector control is integral to targeting disease and should be well integrated into public health programmes as a core intervention for disease control. The Response draws attention to the importance of vector control in this context, but countries will also need support in its future implementation. The Zika virus disease global public health emergency highlighted the need for new tools, particularly against *Aedes*-borne diseases. In response, several new vector control products were

¹ Draft Global vector control response 2010–2030. Geneva: World Health Organization; 2016 (<http://www.who.int/malaria/global-vector-control-response/en/>, accessed May 2017).

fast-tracked for pilot deployment, opening new routes to generate evidence on disease impact and considerations for use. Increased basic and applied research is critical, and evidence-based science has a fundamental role to play in the overall success of the Response. Furthermore, career pathways and capacity at all levels must be strengthened to improve vector control. This will take commitment of time and resources, but is essential to provide effective and sustainable vector control programmes.

2.2 BRIEFING ON MULTI-COUNTRY STUDY ON INSECTICIDE RESISTANCE

Professor Immo Kleinschmidt presented the outcomes of a multi-country study on insecticide resistance. From the analysis of prevalence of infection, a major conclusion of the study was that sleeping under long-lasting insecticidal nets (LLINs) continues to protect users from malaria. No evidence of an increase in disease burden with insecticide resistance was seen. However, there was some indication that in higher resistance areas, the rate of active case detection in children was higher for non-users than LLIN users; this was not seen in the lower resistance areas. There was an observed trend of increasing resistance in the mosquito populations studied, and some evidence of the benefits of LLIN coverage combined with indoor residual spraying (IRS) of insecticides where different insecticide classes were used. Generally, resistance was heterogeneous, pointing to the difficulty of using sentinel sites to characterize national resistance status. Detailed information on this study and its outcomes has been published by WHO's Global Malaria Programme.¹

2.3 OVERVIEW OF TERMS OF REFERENCE OF THE GROUP

Dr Emmanuel Temu, Technical Officer, WHO Entomology and Vector Control, introduced the purpose, functions and role in WHO policy development of the Vector Control Advisory Group, and reviewed the revised terms of reference (**Annex 3**). WHO develops global policies and strategies for the prevention, control and elimination of major vector-borne diseases. Vector control is a key strategy to target malaria and vector-borne NTDs including *Aedes*-borne viral diseases (dengue, chikungunya, Zika virus disease and yellow fever). Developing policies, strategies and technical guidance for vector control is a cross-cutting area of work between WHO's Global Malaria Programme and Department of Control of Neglected Tropical Diseases. WHO has, therefore, established VCAG – a standing expert group – to advise the Organization on new products proposed for control of vector-borne diseases.

¹ Implications of insecticide resistance for malaria vector control. Geneva; World Health Organization; 2016 (WHO/HTM/GMP/2016.8.rev, <http://www.who.int/malaria/publications/atoz/insecticide-resistance-implications/en/>).

The Group comprises a maximum of 15 individuals, including core members (7) and ad hoc experts (maximum 8). Core members are appointed for a 3-year term and are eligible for a single re-appointment term. Ad hoc experts are invited to provide specific knowledge tailored to the topics under review in a given meeting. All experts are chosen according to their distribution of expertise as well as geographical and gender representation. Expertise in practical vector control and product development is emphasized in the choice of experts and includes, but is not restricted to, vector biology, ecology, population biology, insecticides, epidemiology of vector-borne diseases, study design, statistics, product development and management of control programmes.

As per WHO procedures, this committee has no executive or regulatory function; rather, it provides advice and recommendations to the Director-General of WHO, which may include providing expertise for urgent public health issues related to the efficacy of new intervention concepts in vector control. Members have a responsibility to provide high-quality, well-considered, evidence-informed advice, as described in the *VCAG Operational procedures*.¹ Furthermore, members play a critical role in ensuring the reputation of the Group as an internationally recognized expert advisory committee.

Meetings are held in two types of working sessions. General topics are discussed in **open sessions**, where selected observers may be allowed to attend. Recommendations and advice to WHO are made within **closed sessions**, which are restricted to members of the Group and the WHO Secretariat. Closed sessions may also discuss confidential information.

Policy setting for new products in vector control is described in detail in the operational procedures¹. In brief, the Group advises WHO on the evidence supporting a TPP (**Box 2**) and considers the parameters listed in **Table 1** in assessing the claims of a new vector control product. Examples of the types of evidence required are provided in **Table 1** and detailed in the operational procedures. **Table 2** summarizes the product classes, epidemiological and entomological modes of action and products under review by the Group prior to November 2016, and **Table 3** the submissions considered by the Group at the present meeting. Further details are given in **Annex 4**.

Box 2. Target product profile (TPP)

- Gives a detailed technical description that defines the ideal end goals for a product and guides the development process.
- Summarizes essential and desirable characteristics as well as the specific studies that will supply the evidence for each conclusion about the product.

¹ Vector Control Advisory Group: operational procedures (http://www.who.int/neglected_diseases/vector_ecology/Operational_procedures_for_VCAG.pdf, accessed May 2017).

Discussion

- A single assessment pipeline that progresses stepwise through data generation from laboratory-based proof of concept to entomological and epidemiological efficacy is needed for new tools.
- Tools are placed in similar categories depending on what data will be required to demonstrate safety and efficacy and for making policy decisions. For example, the microbial control of pathogens in vectors via *Wolbachia* is considered a separate category from gene-drive technologies because the transfer of bacteria, rather than mosquito genetic material, is the mechanism of action of this intervention.

Table 1. Parameters and types of evidence required for policy review

Parameter	Examples of evidence required
Entomology	Key measurements for entomological impact; key results from laboratory, semi-field and small-scale field trials
Epidemiology	Detailed plans, studies in progress or studies completed to demonstrate epidemiological efficacy
Economics	expected cost of protection per person (at scale)
Technology development	Technical feasibility of making the prototype
Manufacturability and sustainability	Intellectual property issues addressed
User compliance and acceptability	Defined target user groups and expected mode(s) of application
Delivery and feasibility of implementation	How the intervention is applied at scale and monitored
Regulatory, safety, ethical and environmental impact	Safety, health and environmental risk assessments

Table 2. Overview of product classes, modes of action and products under review by the Group (prior to November 2016)

Product class	Description of entomological and epidemiological mode of action	Prototype/product
1. New product class – chemical / biological (i.e. no existing policy)		
Attract-and-kill baits	Uses an olfactory attractant, a sugar solution feeding stimulant and an oral toxin to kill the target vectors. These baits aim to effectively suppress vector populations and reduce insect-borne disease transmission.	Attractive toxic sugar baits
Genetic manipulation of mosquitoes for disease control	Reduction or alteration of vector populations through genetic manipulation. This approach aims to reduce vector populations and disease.	Oxitec OX513A
lethal house lures	The concept exploits vector behaviour using occupants of a house to lure vectors to material treated with a bioagent that kills the vector, having a negative overall effect on vectorial capacity, and reducing infection or disease in humans.	Eave tubes
Microbial control of human pathogens in adult vectors	Introduction of microorganisms into vectors to prevent biological transmission of the pathogen to humans.	wMel strain <i>Wolbachia</i> in <i>Aedes aegypti</i>
Systemic insecticides	Systemic insecticide given to animal reservoirs of human disease to control or prevent human arthropod-borne pathogens transmitted by zoophilic vectors. This approach aims to kill vectors that feed on non-human hosts that consumed the systemic insecticide.	Rodent bait for control of vectors of zoonotic cutaneous leishmaniasis
Spatial repellents	Spatial repellents interrupt human–vector contact through vector behaviour modification induced by airborne chemicals, offering protection (personal and/or community) from bites from medically important vectors and nuisance pests.	Transfluthrin and metfluthrin passive emanators
Vector traps for disease management	Vector traps for disease management are devices designed to attract mosquitoes in order to reduce mosquito abundance, resulting in decreased infection and disease in humans. Current products are designed to capture and/or kill female mosquitoes attempting to lay eggs.	Adulticidal oviposition traps (ALOT, AGO, TNK) and auto-dissemination traps (In2Trap)
2. Extending claims of existing product class to a different vector target population (e.g. species, insecticide resistance)		
Resistance-targeting products	Products claim to impact vectorial capacity and reduce infection and /or disease in humans in areas where local vectors have substantive resistance to certain classes of insecticide, such as pyrethroids. Proposed product extends LUN claims to include impact on insecticide-resistant populations.	Permanet® 3.0, Interceptor G2, SmartPatch
3. Extending claims of an existing product class to a different use/approach		
House screening	This concept extends the claim of a pyrethroid insecticide-treated net to encompass using pyrethroid treated netting for full house protection.	Pyrethroid-insecticide-treated netting applied to eaves, windows and doors of houses for full house protection
Insecticide-treated materials for specific at risk-populations	Insecticide-impregnated materials to protect specific at-risk populations (nomads, displaced populations, disaster situations) in situations where use of conventional tools (e.g. LUNs, IRS) is not feasible. The intervention protects against outdoor transmission but is not expected to provide a community effect.	Skintex MR111 – durable synthetic blanket treated with microencapsulated permethrin
External residual spraying	This concept extends the claim of products for IRS to target outdoor resting <i>Aedes</i> vector mosquitoes via residual spraying of external surfaces, such as verandas or terraces.	Deltamethrin-based formulation for extended residual activity on sprayed surfaces

3. WHO PATHWAYS FOR NEW TOOLS

*Dr Raman Velayudhan briefed the Group on the outcomes of a September 2016 expert meeting held to review and refine policy development processes for new vector control tools, with focus on those tools for which the product class or claim is not yet recognized by WHO and for which there is no WHO policy recommendation. The topic was discussed in open plenary after which the meeting was closed to observers in order to formulate recommendations to WHO and finalize the document. A full version of the final Pathways for Vector Control Tools is given in **Annex 5**.*

The Vector Control Advisory Group was constituted in 2013 by WHO to advise on the efficacy of new tools, technologies and approaches for public health vector control.^{1,2} It issues advice to WHO to inform policy recommendations as well as to innovators of new vector control interventions to guide product development. To date, VCAG has assessed a number of new product classes³ for vector control with diverse entomological modes of action, which aim to reduce transmission and burden of vector-borne diseases in humans. Full information is contained in VCAG meeting reports available on the WHO website.⁴

Reforms in the WHO process for evaluating vector control interventions began in 2015. In order to define the optimal pathway for the evaluation of new vector control interventions, including expected evaluation methods, data requirements and efficacy indicators, WHO convened a special expert meeting on 19 September 2016. The draft conclusions of that meeting were subsequently reviewed and revised at the VCAG meeting convened on 2–4 November 2016.

The finalized conclusions from those two meetings are summarized below.

1. A product class in vector control is a category of intervention that shares a common entomological mechanism of action to reduce infection and/or disease. WHO policy recommendation of a product class is based on the evidence of epidemiological efficacy that substantiates public health value, i.e. proven impact on infection and/or disease in humans. Each product class is defined through a TPP.
2. In any given product class there could be products with one or several specific product claims. WHO recognition of each product claim, which constitutes a WHO recommendation, requires evidence of epidemiological efficacy that substantiates public health value, i.e. proven impact on infection and/or disease in humans.

¹ Further information can be found in “The evaluation process for vector control products”, which details the comprehensive process within WHO. <http://www.who.int/malaria/publications/atoz/evaluation-process-vector-control-products/en/>

² For further information, the VCAG website should be consulted at http://www.who.int/neglected_diseases/vector_ecology/VCAG/en/.

³ “Product class” replaces the word “paradigm” in this document.

⁴ WHO Neglected tropical diseases: VCAG documents and publications (http://www.who.int/neglected_diseases/vector_ecology/VCAG_resources/, accessed May 2017).

3. For each new product class or claim not yet recognized by WHO and for which there is no WHO policy recommendation, validation of the claims will require sufficient evidence from across different settings to demonstrate the efficacy of the new product in reducing infection and/or disease in human populations and to support evidence-based guidance for deployment. For guidance, at least two randomized controlled trials with epidemiological end-points would be needed, with entomological end-points to include one season baseline and two seasons post-intervention follow up.
4. For each new product class or claim not yet recognized by WHO and for which there is no WHO policy recommendation, VCAG will provide a recommendation to WHO on the evidence required to substantiate the product claim(s) and will advise on the evaluation methods needed to generate these data. Once these data are available (i.e. the completed product data package containing the full evidence requested is submitted for review by WHO), VCAG will assess whether the evidence provided validates the product claim(s). WHO will then consider the validation by VCAG in order to recognize the product claim.
5. VCAG advice on new interventions will include:
 - Early interaction with investigators on the submission to clarify if it constitutes a new product class and/or product claim.
 - VCAG initial concept review and determination of data generation required in order to substantiate a new product class or product claim; VCAG will provide periodic review as requested by WHO or by investigators.
 - VCAG final review of evidence, including (i) in the case of a new product class, completion of the TPP and (ii) in the case of a new product claim, validation of that claim.
6. Once VCAG validates a new product class or claim, the following additional policy steps are anticipated:
 - After a policy recommendation is issued by the WHO disease-specific programme for a new product class or claim, responsibility for further assessment of that product and subsequent products within that class or claim will thereafter be assumed by WHO's prequalification programme.
 - The relevant WHO disease-specific programmes (i.e. Global Malaria Programme or Department of Control of Neglected Tropical Diseases) will assess the situations and conditions appropriate for programmatic use of the intervention with the support of relevant expert groups (e.g. Malaria Policy Advisory Committee, Malaria Vector Control Technical Expert Group, Strategic and Technical Advisory Group for Neglected Tropical Diseases) and may issue policy recommendations or other guidance for deployment.
 - Specific variations within a product class (e.g. nets having combinations of insecticides at different dosages and varying patterns of distribution) will be reviewed by WHO to clarify if these constitute new claims for which no current WHO policy recommendation applies.

The following points were discussed prior to finalization of recommendations to WHO

- **Predictability in data generation.** Clarity in the data requirements will assist investigators to predict the costs and timelines for product development and streamline data generation.
- **Harmonizing pathways for different kinds of products.** Testing pathways, including efficacy, effectiveness, stability and safety described in VCAG's operational procedures and other relevant WHO documents (e.g. Guidance Framework for testing genetically modified mosquitoes) should be reviewed and a broad consistent policy developed for data generation. However, in some cases methodologies and test requirements may need to be tailored to the specific intervention, for example small-scale contained field trials may not apply to gene-drive based technologies. Ethical issues need careful consideration given the potential to result in protocol differences between sites.
- **Interim recommendations and pilot deployment.** For LLINs, after laboratory and small-scale field efficacy studies are done, WHO has in the past issued an interim recommendation to enable procurement of LLINs. While this is beneficial in providing access to new products, it has also resulted in a system whereby a product can be distributed without full consideration of its quality or effectiveness and in some cases causing an unacceptable increased risk for disease. Recommendations for pilot operational deployment by VCAG during the Zika virus disease Public Health Emergency of International Concern were discussed in this context. The systems for product recommendations by WHO must also ensure that sufficient evidence is available to support the public health use of new products, and mechanisms are built in to reduce risks for communities and individuals exposed.
- **Numbers of trials.** A single trial can provide evidence to support a recommendation that is based only on the outcomes of that trial. In most cases, these data will not be generalizable to other eco-epidemiological settings. Furthermore, there is a risk that product underperformance in one setting could cause rejection of a tool which may be useful in another context. Under current WHO processes, data are requested from three large-scale trials in different settings to provide an evidence-based recommendation targeted to the different settings and sufficient data to allow a recommendation to be made if the product's performance differs between the settings. A careful balance is needed between the level of data required and sufficient evidence to support a strong recommendation.
- **Product claims.** Determining the novelty of a product claim is not always straightforward. VCAG encourages manufacturers to develop clear product claims, which can be demonstrated with existing data or data from planned trials. Use of the term "paradigm" was broadly discussed, but the term "product class" was considered more appropriate and useful in policy development.

- **Data requirements.** In order to determine data requirements for medicines, clear evidence is needed for registration and policy decisions. Currently, less data are required for vector control interventions than for medical interventions to support global policies. Disease control programmes consider vector control to be a core, life-saving public health intervention, and WHO must align the standards of evidence needed for vector-control interventions to those required for medical interventions. For medicines that claim to target malaria parasites, either a validated surrogate test or clinical trials are needed that demonstrate impact on disease to support global policies on use of these interventions. Similar standards should be required for products that claim to target mosquitoes, requiring either a validated surrogate (currently not available) or evidence for reduction in disease. Product development for public health is a long process, regardless of the field (e.g. 30+ years for vaccines). Clear guidance and predictable pathways will be helpful for manufacturers.
- **Sources of funding for vector control trials.** The need for a “global fund” to support vector control trials was identified to help support innovation and fast-track new vector control tools, similar to existing funding mechanisms that support global health trials for medicines or vaccines in other countries (e.g. UK).

Table 3. Overview of submissions for review at the fifth annual meeting of the Group: 2–4 November 2016

Manufacturer/ developer	Proposed product	Summary points
Joint FAO/IAEA Division of Nuclear Techniques in Food and Agriculture (Insect Pest Control Subprogramme)	Combined SIT/ IIT approach	<p>Combined sterile insect technique (SIT) and incompatible insect technique (IIT) approach for controlling mosquito populations.</p> <p>A combined approach targeting populations of <i>Ae. aegypti</i> and <i>Ae. albopictus</i> that could in principle be used against several other mosquito vector populations if properly developed and implemented. The main goal of this intervention is to suppress the target mosquito populations in pilot projects in urban and suburban environments, ideally below the density required to sustain transmission of pathogens.</p>
Imperial College of Science, Technology and Medicine Target Malaria Consortium	Reducing vector populations through genetic manipulation	<p>Mosquito population alteration strains for reducing malaria transmission.</p> <p>An intervention using <i>Anopheles</i> spp. mosquitoes that express gene-drive constructs to significantly reduce mosquito numbers and thereby reduce vectorial capacity for malaria.</p> <p>A target with focus on reducing malaria transmission in Africa, where mosquitoes in the <i>Anopheles gambiae</i> and <i>An. funestus</i> complexes are responsible for most malaria transmission.</p> <p>The goal is to provide a novel, cost-effective biological intervention that will contribute to the elimination of malaria in Africa.</p>
University of California, Irvine Anthony A. James	Population alteration of malaria vector mosquitoes	<p>Mosquito population alteration strains for controlling malaria transmission.</p> <p>Development of genetic tools to assist eradication of malaria by providing low-cost, effective and sustainable regional malaria elimination. Implicit in these claims are that molecular genetic and transgenesis technologies can be used to generate population-alteration strains of mosquitoes that will achieve the principal public health claims.</p> <p>The approach currently focuses on <i>Anopheles</i> species where the technology could have the greatest impact in contributing to local elimination of malaria.</p> <p>The technology aims to achieve prevention of transmission and regional, sustainable malaria elimination. It also is expected to contribute to sustainable prevention of re-introduction of malaria.</p>

4. COMBINED STERILE INSECT TECHNIQUE AND INCOMPATIBLE INSECT TECHNIQUE FOR MOSQUITO POPULATION CONTROL

4.1 OVERVIEW OF THE INTERVENTION CONCEPT¹

4.1.1 BACKGROUND SUMMARY

Ae. aegypti and *Ae. albopictus* are the vectors of many globally important human pathogenic viruses including dengue, chikungunya and Zika. Dengue and chikungunya are still major human public health problems in over 100 countries, and Zika virus disease has now spread to more than 70 countries and territories and has been associated with microcephaly, other central nervous system malformations and Guillain-Barré syndrome (www.who.int; www.paho.org). WHO announced on 1 February 2016 that Zika virus disease is a potential threat for the entire world. The economic impact of mosquito-transmitted diseases is enormous with respect to health care, lost working days and productivity.

In the absence of efficient, safe and inexpensive medicines and/or vaccines to control dengue, chikungunya and Zika virus disease, population control of the insect vector is considered the most effective way of managing these diseases. Most vector control strategies are insecticide-based and their expanded use is resulting in growing resistance to all major groups of insecticides. Based on the above, and the difficulty in eliminating larval breeding sites throughout urban and suburban areas, there is an urgent need for novel, sustainable and environmentally friendly approaches for controlling populations of *Aedes* mosquitoes.

The proposed intervention uses a combined sterile insect technique (SIT) and incompatible insect technique (IIT) approach, as a component of a stakeholder-driven integrated vector management strategy, to effectively control *Aedes* mosquito populations below the densities required for disease transmission. The approach combines irradiation and *Wolbachia*-based tools, providing a responsible strategy for suppression of mosquito populations in the absence of a 100% efficient, robust and cost-effective sex separation methods. This combined approach has been developed for *Ae. aegypti* and *Ae. albopictus*. Studies to support proof-of-concept have been done in the laboratory and in small-scale pilot trials examining suppression of mosquito populations.

The combined SIT/IIT approach claims to address major safety, health and environmental risks. Notably, it does not release fertile female mosquitoes and the few females that might be released are fully sterile; therefore, there is no genetic or other footprint in the environment. Also, the few females that might be released are infected with *Wolbachia*, thereby eliminating or drastically reducing the chance of pathogen transmission. Finally, the risk of resistance developing with this strategy is estimated by the applicants to be very low, mitigating unpredictable and unforeseen safety, health and environmental consequences.

¹ Information in this section was provided by the applicant.

The mandate of the Joint FAO/IAEA Division's Insect Pest Control Subprogramme is to develop, refine, validate and transfer methods, protocols, tools, equipment (prototypes) and strains in support of the SIT to be used as a component of integrated pest/vector management for the population control of insect species of agricultural, veterinary and human health importance. The combined SIT/IIT approach is part of these research and development (R&D) efforts for the population control of mosquito vector species transmitting major human pathogens, including *Ae. aegypti* and *Ae. albopictus*.

The R&D programme is implemented in response to FAO and IAEA Member State requests. All tools, protocols, methods and strains developed in the FAO/IAEA laboratories are freely available to Member States, and transferred cost-free through the IAEA's Technical Cooperation Programme. Scientists and experts provide their support and expertise for the implementation of small-scale pilot trials and/or large-scale operational programmes. However, these trials and programmes are owned and managed by the Member States, not by the Joint FAO/IAEA Division's Insect Pest Control Subprogramme or the IAEA's Technical Cooperation Programme.

4.1.2 DESCRIPTION OF THE INTERVENTION CONCEPT

Target vector and human population

The combined SIT/IIT approach proposed will target populations of *Ae. aegypti* and *Ae. albopictus*. The main goal of this intervention is to suppress the target mosquito populations in pilot projects in urban and suburban environments below the densities required for disease transmission.

Detailed description of the intervention proposed

The SIT relies on the mass-rearing of a target species, the separation of sexes in the case of disease vectors, the sterilization of males through ionizing irradiation, and the handling, transport and release of sterile males in target areas where they compete with wild males for mating with wild females. Because the released males are sterile, these matings should not result in any viable offspring. Over time, and through the systematic and continuous releases of sterile males, the targeted population will diminish and be suppressed. In other words, the SIT is a type of "insect birth control".

SIT was conceived by Edward Knippling, a scientist from the United States Department of Agriculture (USDA), and was first developed and applied against the New World screwworm fly in the 1950s and 1960s. Due to this early success and the environmental friendliness of the method, and in response to requests by IAEA and FAO Member States, IPCL has supported the development, refinement and application of the SIT for use in Member States against major crops and livestock pest insects for over 50 years. More than a decade ago, IAEA Member States requested the initiation of a project to develop the SIT for key mosquito species that transmit diseases. It should be noted, however, that the first SIT release pilot project against a mosquito vector (*An. albimanus*) was implemented in El Salvador in the 1970s. During the past decade, the Insect Pest Control Laboratory (IPCL) has developed basics of the SIT package against several major mosquito vector species, including *Ae. aegypti* and *Ae. albopictus*.

IPCL and collaborators have developed protocols and equipment for the mass-rearing of both *Aedes* species, including inexpensive and effective diets, a tray and rack system for the rearing of larval and pupal stages, and mass-rearing cages for blood-feeding, mating and egg-laying of adult mosquitoes. In addition, methods have been developed for: (i) storage of *Ae. aegypti* and *Ae. albopictus* eggs; (ii) quantification of eggs of *Ae. aegypti* and *Ae. albopictus*; (iii) optimal hatching of stored eggs that enables trays to be loaded with the desired number of eggs to give a predictable larval density; and (iv) volumetric pupal quantification to load cages with the desired number of adults. All of the above steps are crucial for the development and optimization of a cost-effective mass-rearing platform which is a prerequisite of any SIT-based application. The IPCL has also designed a spreadsheet to facilitate the construction and equipment of mosquito mass-rearing facilities based on experience gained from the successful large-scale operational SIT programmes against fruit flies, moths and tsetse flies.

Protocols are available for irradiating both *Ae. aegypti* and *Ae. albopictus* to induce complete sterility without significantly reducing the males' performance. Competitiveness assays in large cages, semi-field settings and in the field have demonstrated that, following release, sterilized males successfully compete with untreated or wild males for mating with untreated or wild females. Protocols for the handling, transfer and release of sterile mosquitoes to the target sites are also being developed. Currently, releases for small pilot studies are done from the ground, which will not be effective and cost-efficient for larger-scale programmes that will require releases by air. In that respect, IPCL and collaborators participated in February 2016 in the Drones for Good 2016 international competition, where the ROMEO (Remotely Operated Mosquito Emission Operation) system for aerial release of sterile male mosquitoes finished fourth place among over 1000 entries (<http://www.naweb.iaea.org/nafa/ipc/drones-romeo-mosquitoes.html>).

A critical step for mosquito SIT is the separation of males from females (for male-only releases) since elimination of female mosquitoes prior to male releases is essential because females transmit the diseases. In the absence of 100% efficient sex separation methods (or genetic sexing strains), SIT was integrated with IIT which is based on the symbiont *Wolbachia* that is known to (i) induce cytoplasmic incompatibility (it is expressed as embryonic mortality in crosses between infected males with females which lack the *Wolbachia* strain present in males) and (ii) to provide protection against some major human pathogens, including arboviruses that cause dengue, chikungunya, Zika virus disease and yellow fever.

The combined SIT/IIT approach was originally conceived by Professor Chris Curtis in the early 1980s. The strategy is based on the premise that in the absence of perfect sex separation methods, all suppression approaches have the risk of releasing some females which can potentially transmit disease. However, by application of IIT, females released will be *Wolbachia*-infected, and unable to transmit disease. Also, for most insect species including *Ae. aegypti* and *Ae. albopictus*, females can be completely sterilized with doses of irradiation that are much lower than those required for the complete sterilization of males. By combining the two approaches in a *Wolbachia*-infected *Aedes* mosquito line, any released females would have limited abilities to transmit pathogens such as dengue, chikungunya and Zika viruses due

to the presence of *Wolbachia*, and would also be completely sterile due to the low irradiation doses applied.

In conclusion, the combined SIT/IIT approach has potential to eliminate the risk of releasing fertile and pathogen-transmitting females, and to provide a biologically safe approach for controlling mosquito populations.

Intervention will be considered efficacious compared with the following alternatives

The combined SIT/IIT approach is proposed as a component of integrated vector management where intervention is applied against low-density *Aedes* spp. populations, following vector control measures such as reduction of breeding sites, larviciding and adulticide spraying. Areas with no combined SIT/IIT intervention can be used for comparison. Current best conventional practices should be used to reduce the density of vector populations in both the intervention and the control areas.

Significant expected outcomes of the intervention including potential benefits and harms

The major benefit of the combined SIT/IIT intervention is the significant reduction of the target mosquito population (or its elimination under certain conditions) which may significantly reduce or prevent disease transmission. In addition, the intervention eliminates a number of risks and potential harms that are associated with other suppression interventions, such as:

- (a) The risk of releasing fertile mosquito females. Unlike other interventions, the combined SIT/IIT approach does not leave any genetic or ecological footprint in the environment since it does not establish new (sub) species, strains or (trans) genes in nature.
- (b) The risk of releasing potentially pathogen transmitting females. The few females that might be released are *Wolbachia*-infected and hence they do not (or have drastically reduced potential to) transmit pathogens such as dengue, chikungunya, Zika and other viruses.
- (c) The risk of resistance developing. The combined SIT/IIT approach has low risk for resistance development. Irradiation induces dominant lethal mutations randomly in the reproductive cells and hence, there is little chance for resistance developing to radiation-induced sterility. The co-evolution of mosquito host and *Wolbachia* may result in low *Wolbachia* densities over time, which could reduce the pathogen blocking effect of *Wolbachia*. Similarly, the virus could evolve resistance against *Wolbachia*. However, since only sterile male mosquitoes are released the risk of resistance developing to the *Wolbachia* approach is predicted to be low.

The combined SIT/IIT approach proposes to eliminate the risk of releasing fertile females and reduce the potential for pathogen-transmitting females. It claims low risk for resistance development, and proposes a safe, secure and sustainable approach for *Aedes* mosquito population control.

4.1.3 DESCRIPTION OF THE PROTOTYPE PRODUCT

Ae. aegypti and *Ae. albopictus* strains infected with *Wolbachia* strains. Key insecticidal and vector control components: irradiation and *Wolbachia* strains

Low irradiation doses confer complete sterility of mass-reared female mosquitoes. Sterility of mass-reared male mosquitoes comes from *Wolbachia*-induced cytoplasmic incompatibility (CI) and irradiation. *Wolbachia* infections also provide protection against human pathogens (dengue, chikungunya, Zika and potentially other arboviruses).

To date, the strains developed by Professor Zhiyong Xi (*Aedes albopictus* HC line and *Aedes aegypti* WB2 line) and Prof. Pattamaporn Kittayapong (*Aedes aegypti* TH-AB line) and currently proposed are:

- 1) *Aedes albopictus* (HC, triple infected strain: wAlbA, wAlbB, wPip). *Ae. albopictus* is naturally infected with wAlbA and wAlbB *Wolbachia* strains. The HC line was developed with the transfer of the wPip strain from the mosquito *Culex pipiens quinquefasciatus* through embryonic cytoplasmic microinjections. The strain originates from the Guangzhou region of China.
- 2) *Aedes aegypti* (WB2, single infected strain: wAlbB). *Ae. aegypti* is naturally uninfected. The WB2 line was developed with the transfer of the wAlbB strain from mosquito *Ae. albopictus* through embryonic cytoplasmic microinjections.
- 3) *Aedes aegypti* (TH-AB, double-infected strain: wAlbA and wAlbB). The TH-AB line was developed with the transfer of the wAlbA and wAlbB strains from the *Ae. albopictus* TH-ALB strain through *Wolbachia* injections in adults as described previously (Ruang-areerate and Kittayapong, 2006). Using the combined SIT/IIT approach, the strain is fully sterile under laboratory conditions.

4.1.4 PRODUCT CLAIMS

The combined SIT/IIT approach can suppress target *Aedes* mosquito populations safely, securely and sustainably, and potentially below the density required for disease transmission.

4.1.5 JUSTIFICATION FOR THE CLAIMS

Data produced in the laboratory and in the field demonstrate that the combined SIT/IIT approach as part of an integrated vector management approach can suppress *Aedes* mosquito populations, potentially below the densities required for disease transmission, in a safe, secure and sustainable manner. The claim for population suppression is based on the fact that the systematic and continuous release of large numbers of sterile male mosquitoes will overwhelm a target population of females resulting in few, if any, fertilized females, and eventually resulting in the sustained suppression of the target population as shown in semi-field or laboratory and field pilot trials. The claim for safe, secure and sustainable suppression is based on that the combined SIT/IIT approach: (a) does not release fertile females and the few females that might accidentally be released being fully sterile and infected with *Wolbachia* thus eliminating or at least drastically reducing the

chance of pathogen transmission; (b) does not depend on antibiotics or human blood; and (c) has a low risk of resistance development.

4.1.6 EVIDENCE REVIEWED FROM KEY STUDIES IN SUPPORT OF CLAIMS

Entomological studies

The concept of the combined SIT/IIT approach and the advantages of other interventions have been discussed in two review articles (see list of relevant publications): Lees et al. (2015); Bourtzis et al. (2016). Results of three laboratory studies (Zhang et al. 2015a; Zhang et al. 2015b; Zhang et al. 2016) and one small-scale pilot trial run by Prof. Zhiyong Xi in China were presented for review.

Epidemiological studies

No epidemiological studies have been performed so far. Studies are planned in collaboration with the Pan American Health Organization and selected WHO collaborating centres.

Safety, health and environmental risk assessments

The International Plant Protection Convention (IPPC) recognizes sterile insects produced for SIT as beneficial organisms under the International Standards for Phytosanitary Measures (ISPMs).¹ For this reason, all SIT applications against fruit flies, moths, tsetse flies or screwworms have not raised any safety, health or environmental concern and have not required any special regulation.

All small-scale feasibility studies, pilot trials or future larger operational programmes for this intervention will be managed and owned by Member States. FAO/IAEA counterparts in Member States will communicate with their respective national regulatory and policy bodies to obtain the necessary permits for the combined SIT/IIT approach. For the pilot trial run by Prof. Zhiyong Xi in China, the permit was provided by the Ministry of Agriculture of the People's Republic of China. For the pilot trial run by Prof. Pattamaporn Kittayapong in Thailand, it was provided by Mahidol University's IRB (the institutional body for ethics approval).

Other information

The importance of managing the quality of sterile mosquito males to ensure their adequate performance and competitiveness after release is evident from examples in other species (Calkins and Parker, 2005). The estimation and quantification of the impact of mass rearing, radiation and handling on male mating competitiveness of sterile males has attracted a lot of research. Semi-field and field experiments have demonstrated that a radiation dose can be selected that gives sufficient sterility without significantly impacting competitiveness (Bellini et al., 2013; Madakacherry et al., 2014).

¹ Guidelines for the export, shipment, import and release of biological control agents and other beneficial organisms (https://www.evira.fi/files/attachments/fi/kasvit/torjuntaeliot/1146657660135_ispm3.pdf).

The following additional points should be noted:

- (a) The quality control of the produced sterile mosquito is performed during the entire cycle with very well-defined criteria for both immature and adult stages (development duration, survival, size, longevity, fecundity, fertility) as described in Zhang et al. (2015a).
- (b) The quality control and impact of sterilization on male longevity and sterility induced but also the required dose to completely sterilize females that would be accidentally released is performed as described in Zhang et al. (2015b) and Yamada et al. (2014).
- (c) The quality control of the final product is assessed by performing competitiveness assays in semi-field settings following standard operating procedures developed at the IPCL (Zhang et al., 2016; Zhang et al., unpublished and confidential data (see Figures 1–3); Madakacherry et al. 2014).

Standard operating procedures have been developed for diet preparation for larvae and adults, manipulation in the rack or tray system and for adult cages, egg collection, egg drying, egg quantification and egg storage (Zheng et al., 2015a,b).

There are also standard protocols available for assessing the efficiency of *Wolbachia* maternal transmission, cytoplasmic incompatibility, density levels and vector competence (selected reviews and original manuscripts: Bourtzis et al., 2014 and references therein; Moreira et al., 2009; Moreira et al., 2016).

4.1.7 LIST OF PUBLICATIONS CITED IN THE SUBMISSION

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4.2 CONCLUSIONS AND RECOMMENDATIONS

Summary

The Joint FAO/IAEA Division's Insect Pest Control Subprogramme "Combined SIT/IIT Approach" is being developed and validated in response to requests from, and resolutions endorsed by, Member States of FAO and IAEA. This approach aims to reduce populations of *Aedes* mosquitoes to levels below the density for transmission of dengue, Zika and chikungunya viruses. The SIT approach – a well-established technology with a proven record against agricultural and veterinary pests – relies on mass rearing of the target species, sex separation, sterilization by means of ionizing irradiation, and release of sterile males in target areas where they compete with wild males to mate with wild females. Over time, the systematic and continuous release of sterile males is designed to suppress the targeted population. Current mosquito sex separation technologies are imperfect, and therefore any approach that releases sterile male mosquitoes such as the SIT approach risks inadvertently releasing a small proportion of females, which could potentially contribute to transmitting viruses. The combined approach mitigates the risk of transmission by including a *Wolbachia*-based IIT with radiation-induced sterility. The IIT is based on the symbiont *Wolbachia* that (i) induces cytoplasmic incompatibility and (ii) protects against transmission by mosquitoes of dengue, Zika, chikungunya and yellow fever viruses. Use of this technology aims to sterilize any unintentionally released female mosquitoes due to radiation exposure and prevents them from transmitting viruses due to *Wolbachia* infection. Males become sterile from both radiation and the presence of *Wolbachia*. It also limits exposure to ionising radiation to a level that maximizes biosafety. The technology is available free of charge to FAO/IAEA Member States and, in response to official government requests, FAO/IAEA provide technical support and guidance in integrated SIT technology and help to build capacity for its deployment.

Conclusions and recommendations on the proposed intervention

The evidence presented suggests the combined SIT/IIT approach confers high levels of sterility to *Aedes* mosquitoes (as high as 100%) with low risk for developing resistance to this approach. Quality control in the rearing of released insects and resistance monitoring (e.g. assortative mating such that wild females avoid mating with released males) in the field should be conducted to ensure low risk of operational failure. The technology has considerable potential for long-term control of *Aedes*-borne disease. VCAG strongly recommends detailed review of results from entomological field trials before initiating epidemiological field trials on this intervention. Community engagement (i.e. sensitization and awareness campaigns in communities where releases are envisaged), and regulatory and ethical approvals will also need to be planned before any semi-field research or open field trial is initiated. Appropriate expertise will need to be recruited for the design of epidemiological trials.

Overall, the evidence reviewed indicates this submission is at Step 2.

The following specific comments were provided:

- The transmission blocking effects of different *Wolbachia* strains in the mosquito strains proposed will need to be demonstrated for different dengue virus strains and serotypes and other alpha- and/or flaviviruses.

- Baseline data collection will be critical to statistical power calculations for future entomological and epidemiological trial methodologies.
- The potential for development of behavioural resistance (e.g. assortative mating) and underlying population changes in mating preference over time should continue to be assessed as part of efficacy trials and monitoring. This should be emphasized as part of operational plans.
- Validation of entomological outcomes should be demonstrated in different settings before carrying out large-scale epidemiological trials.
- Trials with epidemiological outcomes should be conducted in partnership with institutions maintaining a credible track record in the design, running and analysis of cluster randomized controlled trials. Standard clinical trial governance structures should be adopted to ensure independent monitoring. Plans for epidemiological trials should be reviewed by VCAG before such trials are initiated.
- Preliminary approximate cost data should be generated using available information. A full costing and cost-effectiveness component should be included in the epidemiological trials and a qualified health economist should undertake this assessment. Optimization of factors in the production and implementation of the intervention should be sought to reduce costs.
- A community engagement strategy (sensitization and awareness campaigns) should be developed and community acceptability documented. Regulatory and ethical approvals will also need to be planned before any semi-field research or open field trial is initiated.
- The strategy for deployment should include assessing how to maximize the efficacy of SIT/IIT releases integrated with existing interventions and on developing strategies for deployment to remote areas.
- Risk assessment with WHO will be needed for a full policy recommendation.

Concluding statement on SIT/IIT combined approach for population reduction or extinction

VCAG concluded that the combined SIT/IIT technology has potential for long-term control of *Ae. aegypti* and *Ae. albopictus* mosquitoes. It strongly recommends further entomological and epidemiological field trials to validate the use of this intervention and its claims of efficacy against disease.

Summary of conclusions and recommendations on the combined sterile insect technique and incompatible insect technique technology

- The combined SIT/IIT technology has potential for long-term control of *Ae. aegypti* and *Ae. albopictus* mosquitoes.
- VCAG strongly recommends further entomological and epidemiological field trials be conducted to validate the use of this intervention and its claims of efficacy against disease.
- Overall, the evidence reviewed indicates this submission is at Step 2.

5. REDUCING VECTOR POPULATIONS THROUGH GENETIC MANIPULATION

5.1 OVERVIEW OF THE INTERVENTION CONCEPT¹

5.1.1 BACKGROUND SUMMARY

Over half of the world's population is at risk of contracting malaria, with hundreds of thousands of deaths annually, the majority being African children. The disease is transmitted through the bite of female *Anopheles* species mosquitoes infected with *Plasmodium* protozoa. Current interventions include the use of chemical vector control methods such as LLINs and IRS, and diligent application of these has substantially decreased malaria mortality. However, continued success is expected to require two to four times the current level of annual spending over, roughly, the next 15 years, and even then, the WHO Global Malaria Programme predicts there will still be malaria in over 60 countries. Moreover, the emergence of insecticide-resistant mosquitoes threatens to roll back progress to date. New malaria control interventions are desperately needed to solidify and extend recent gains. The goal of this application is to provide a novel, cost-effective biological intervention that will contribute to the elimination of malaria in Africa.

Target Malaria's vector control technology utilizes gene drive to reduce mosquito populations, allowing extremely selective vector control, specific to the species of malaria-transmitting *Anopheles* mosquitoes. Gene drive is a process of preferential inheritance that allows a gene to rapidly increase in frequency in a population even if it causes some harm to the organisms carrying it. Once established, the intervention should be self-sustaining and spread through the target *Anopheles* population on its own, requiring little maintenance. The product aims to be inexpensive to deploy and to substantially reduce transmission within 12–24 months of deployment. Also, this vector control technology will aim to require no significant changes in human behaviours to achieve disease reduction and work synergistically with other malarial interventions.

5.1.2 DESCRIPTION OF THE INTERVENTION CONCEPT

Target vector and human population

Since Africa is unmistakably the most affected area on the planet, Target Malaria has chosen to focus on reducing malaria transmission on this continent, where mosquitoes in the *An. gambiae* and *An. funestus* complexes are responsible for most malaria transmission.

¹ Information in this section was provided by the applicant.

It is well recognized that vector control reduces transmission of malaria, with much of the decrease in global malaria burden being achieved through the expansion of vector control interventions, including the use of measures for treatment of adults and larvae (WHO 2015; WHO, 2013; Tusting et al., 2013). Two transmission settings are envisaged: a moderate transmission setting and a high transmission setting.

Detailed description of the intervention proposed

The proposed intervention intends to use *Anopheles* mosquitoes expressing gene-drive constructs to significantly reduce mosquito population densities and thereby reduce vectorial capacity for malaria. The vector's density is a factor in determining vectorial capacity, and thus reducing the mosquito population is expected to reduce the vectorial capacity (Deredec et al., 2011).

Two product candidates are proposed for differential rates of disease prevalence (high and moderate). Neither of these product candidates is currently available but gene-drive is a robust and flexible technology.

There are two basic gene-drive approaches that can meet the product performance targets: genetic constructs to produce a male-biased sex ratio (Y-drive), and gene knockouts to inactivate genes required for female fertility. The product in this application will be a mix of mosquito lines, each carrying a single endonuclease construct configured to spread by mating into the local population of mosquitoes within the same species complex. It is also intended that these interventions will complement existing interventions and antimalarial technologies such as insecticide-treated bednets, mass drug administration and vaccines to create large zones of widespread elimination of the disease. Target Malaria is currently focused on interventions against the *An. gambiae* species complex; the most important group of vectors in sub-Saharan Africa.

This intervention will be considered efficacious compared with the following alternatives

The combined GM approach proposed will be compared with current best-practice interventions for malaria control in the target countries of Burkina Faso, Mali and Uganda.

Significant expected outcomes of the intervention including potential benefits and harms

The goal is to provide a novel, cost-effective biological intervention that will contribute to the elimination of malaria in Africa.

Target Malaria's vector control technology utilizes gene drive to reduce mosquito populations, allowing extremely selective vector control, specific to the species of malaria transmitting *Anopheles* mosquitoes. Gene drive is a process of preferential inheritance that allows a gene to rapidly increase in frequency in a population even if it causes some harm to the organisms carrying it. Once established, the intervention should be self-sustaining and spread through the target *Anopheles* population on its own, requiring little maintenance.

The product aims to be inexpensive to deploy, with substantially reduced transmission appearing within 12–24 months of deployment. Further, this vector control technology

will require little change in human behaviour to achieve disease reduction and will work synergistically with other antimalarial interventions.

Target Malaria is taking a step-wise approach to working with genetically modified mosquitoes in Africa, starting with a male-sterile strain with fluorescent markers that is not intended for use in malaria control, but rather to build capacity and transfer knowledge about working with genetically modified mosquitoes. This will be followed by work with a self-limiting male-fertile line, and then by a self-sustaining gene drive line. Only the self-sustaining gene drive line will be a product for malaria control. This approach aims to build a full understanding of how the product works in the environment, enable regulators to identify issues and risks, and build comfort and confidence among stakeholders regarding risks and benefits.

5.1.3 DESCRIPTION OF THE PROTOTYPE PRODUCT

The product prototype will consist of a self-sustaining vector control intervention, using gene-drive technology to selectively reduce the numbers of *An. gambiae* species complex in the target release areas. The product prototype will consist of adult male mosquitoes carrying one or more genes that encode sequence-specific DNA-cutting enzymes (endonucleases), each of which will target a specific sequence involved in mosquito reproduction or survival. Ultimately, two potential products with different TPPs are envisaged (one that could be used in areas with very high disease prevalence, the other for moderate disease prevalence). Endonuclease genetic components and associated regulatory sequences and (potentially) fluorescent marker genes are incorporated in the genetic construct.

5.1.4 PRODUCT CLAIMS

- Male *An. gambiae* expressing a gene-drive endonuclease genetic construct mate with local *An. gambiae* and transfer the genetic construct to the progeny.
- Release of a small number of male *An. gambiae* mosquitoes that express a gene-drive endonuclease construct will mate with mosquitoes in local *An. gambiae* complex populations.
- The nuclease genes will spread through the wild populations, reducing the density of mosquitoes in that species complex.
- Sustained reductions in mosquito vector populations will decrease malaria transmission and/or disease in target populations.

5.1.5 JUSTIFICATION FOR THE CLAIMS

Target Malaria is using gene-drive technology to reduce mosquito reproduction. It is designed to be extremely selective, affecting only the specific species of *Anopheles* mosquitoes that transmit malaria, with no anticipated off-target effects for humans or the environment.

The product prototype will consist of adult male mosquitoes carrying one or more genes that encode sequence-specific DNA-cutting enzymes (endonucleases), each of which will target a specific sequence involved in mosquito reproduction or survival. Two potential products with different TPPs are envisaged: one that could be used in areas with very high disease prevalence, the other for moderate disease prevalence.

It is the intention to release a small number of male mosquitoes at multiple sites where they will mate with mosquitoes in local *An. gambiae* complex populations. The nuclease genes spread through the wild population, reducing mosquito numbers significantly over several generations and requiring little maintenance, and thus will be inexpensive to deploy.

It is well recognized that vector control reduces transmission of malaria, with much of the decrease in global malaria burden being achieved through the expansion of vector control interventions, including the use of measures for treatment of adults and larvae (WHO 2015). Gene drive aims to deliver a significant reduction in disease prevalence very cost-effectively and without sustained human intervention.

5.1.6 EVIDENCE REVIEWED FROM KEY STUDIES IN SUPPORT OF CLAIMS

Entomological studies

Two basic gene-drive approaches are being pursued by the applicant: genetic constructs to produce male-biased sex ratios (Y-drive), and gene knockouts to inactivate genes required for female fertility.

Male-biased sex ratios (Y-drive)

Target Malaria has demonstrated that X-chromosome shredding at male meiosis can produce ~95% male progeny without significantly impairing male fertility (Galizi et al., 2014).

The expression of wild-type I-PpoI during spermatogenesis in transgenic mosquitoes causes cleavage of the paternal X chromosome but also results in complete male sterility because the protein's stability and persistence in mature sperm cells lead to subsequent cleavage of the maternal X chromosome in the zygote. There is systematic destabilization of the I-PpoI endonuclease with the objective to reduce its in vivo half-life and thereby restrict its activity to male meiosis, which occurs earlier than the formation of the zygote after female fertilization. The objective is population suppression via the development of transgenic male mosquitoes that are not sterile and produce mainly Y chromosome-bearing sperm (and hence will produce only male progeny when mated with wild-type female mosquitoes). Male transgenic progeny fathered by these transgenic male mosquitoes also produce Y-biased sperm so that the effect can be self-sustaining.

A series of I-PpoI variants were generated that display a range of thermal unfolding temperatures spanning 20°C, resulting in a range of enzyme half-life which in turn resulted in reductions in the expression and recovery of the recombinant protein, presumable due

to disrupted folding. The results show that significant male-biased sex ratios ranging from 70.2% to 97.4% were observed in the progeny of male mosquitoes carrying the chosen I-Ppol variants and that the sex distortion phenotype was stably inherited from male mosquitoes to their transgenic sons. Further population cage studies reported by Galizi et al. (2014) demonstrated that distorter male mosquitoes can efficiently suppress caged wild-type mosquito populations.

Female fertility targets

Target Malaria has demonstrated homing rates of ~95% at confirmed female fertility targets (Hammond et al., 2016). Three genes have been identified that confer a recessive female-sterility phenotype upon disruption and inserted into each locus by CRISPR-Cas9 gene-drive constructs designed to target and edit each gene. For each targeted locus a strong gene drive at the molecular level was found, with transmission rates to progeny of 91.4% to 99.6%. Population modelling (after the model of Deredec et al., 2011) and cage experiments indicate that a CRISPR-Cas9 construct targeting one of these loci, *AGAP007280*, meets the minimum requirement for a gene drive targeting female reproduction in an insect population.

The Deredec et al. (2011) paper constructed and analysed a model of mosquito population genetics and malaria epidemiology to determine the functionality of homing endonuclease genes (HEGs). The model, combined with existing data, indicates that populations of *An. gambiae* could be eliminated by releases 2–3 HEGs targeting female fertility genes, or by a driving chromosome that is transmitted to 75–96% of progeny. However, HEGs are not likely to be deployed in a vacuum, and other insect control methodologies will continue to be used, such as bednets and indoor residual sprays. Models of spatial structure of mosquito populations in different landscapes have also been developed and the conditions for spread, fixation and loss of HEGs in these landscapes explored (North et al., 2013).

Additionally, male sterile lines have been made that will be used for initial preparatory steps towards eventual field releases of the gene-drive strains. These male sterile lines have been described in Klein et al. (2012) and Windbichler et al. (2008).

Epidemiological studies

No epidemiological studies have been performed so far.

Safety, health and environmental risk assessments

Approvals have been given by the governments of the United Kingdom of Great Britain and Northern Ireland, Italy and the United States of America for the contained use and import of male sterile precursor strains to the prototypes under development. The Commonwealth Scientific and Industrial Research Organisation has conducted an independent quantitative risk assessment for the contained use activities of male sterile strains in Africa, which is publically available.¹ This is a standalone risk assessment independently commissioned by Target Malaria and not for regulatory purposes.

¹ Risk assessment for controlling mosquito vectors with engineered nucleases: sterile male construct. Record of expert elicitation. Hobart (Tasmania): CSIRO Biosecurity Flagship; 2015 (<https://publications.csiro.au/rpr/download?pid=csiro:EP153254&dsid=DS1>, accessed May 2017).

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5.2 CONCLUSIONS AND RECOMMENDATIONS OF THE GROUP

Summary

The proposed technology utilizes genetic modification (GM) with CRISPR-Cas9 constructs to drive a trait that induces sterility in wild female mosquitoes that mate with GM males. CRISPR-Cas9, a bacterially derived gene editing technique used to insert, delete or replace specific genes in a chromosome, is the basis for both gene drive systems proposed. The population reduction strategy is designed to offer selective vector control targeted to a particular species of malaria-transmitting *Anopheles* mosquito. Unlike previously reviewed genetic technologies, this approach relies on the use of gene drive, a process of preferential inheritance that allows a gene to rapidly increase in frequency in a population so that the intervention spreads quickly through the target population and once established is self-sustaining. This intervention is being developed with the aim of substantially reducing transmission of malaria parasites after deployment, to be inexpensive to deploy, to work synergistically with other interventions and to have the advantage of requiring no changes in human behaviour to achieve disease reduction.

Conclusions and recommendations on the proposed intervention

The committee noted that the initial laboratory-based evidence for proof of concept is encouraging and appropriate for this early stage of product development.

Greater elaboration of the planned development pathway as well as regulatory and ethical issues are needed. Operational aspects such as how the technology will be deployed, the predicted number of releases and the spatial scale should be detailed. This type of information will be critical to determining feasibility and costs, as well as for designing large-scale trials.

Overall, the evidence reviewed indicates this submission is at Step 1.

The following modifications to the product claims are suggested: (i) construct can be inserted in the targeted location; (ii) construct spreads from small (~10%) to large (> 90%) proportion of the target population; (iii) progeny bearing the construct stably express the desired sterility phenotype; (iv) spread of construct reduces the wild-type population density; and (v) population reduction cause reduction in human malaria parasite infection and/or disease.

It is recommended that the innovators produce one prototype mosquito strain in which multiple genes inducing sterility are targeted in the selected species of malaria vector, with focus on the long-term goal of reducing malaria transmission by that species.

The following specific comments were provided:

- A vector system should be selected and all evidence for the efficacy of this approach (entomological and epidemiological) should be generated in the selected system.
- Further studies are needed in the laboratory before considering semi-field or open-field experiments, including studies to improve understanding of how the genetic structure, demography and behaviour of target populations will affect spread and stability of the sterility phenotype.
- Theoretical work on modelling potential epidemiological impact and costs will be important.
- The investigators are encouraged to continue engaging with regulatory authorities and fostering community engagement.
- The product development plan for the intervention requires clarification and further development, including process, timelines and issues relating to measurable end-points and regulation; ethics require clarification and further development.
- Appropriate product development expertise will need to be recruited for the design of entomological and epidemiological trials as well as provisional costing estimates for the intervention.
- The potential for mosquitoes to develop resistance against CRISPR/Cas9 based mechanisms of gene cleavage should be carefully assessed, and risk mitigation strategies developed.

Concluding statement on genetically modified mosquitoes for population reduction or extinction

VCAG encourages further development of tools utilizing gene-drive based technologies while recognizing that these strategies are still in the early phases of development, and that important challenges lie ahead for their development and deployment. More evidence from laboratory-based studies is needed before semi-field or open field-testing should be undertaken.

General statement on gene-drive based technologies

While the committee recognized the potential of new gene-drive based technologies to suppress vector-borne diseases, it cautioned that transgenic vector strains possessing forms of the gene drive currently in development may be difficult to recall if they are released intentionally or unintentionally. This characteristic of such genetic modification strategies calls for extremely thorough cage trials in the laboratory accompanied by ecological and epidemiological assessments of relevance to target countries before conducting field trials where escape of strains into the environment is possible. Despite the need for more information on how to responsibly release gene-drive containing vector strains, VCAG supports continued efforts to develop this technology. The ultimate use of gene-drive based technology will require thorough assessment of the potential benefits and risks, including examination of ethical, legal and regulatory considerations as well as governance frameworks.

Summary of conclusions and recommendations on gene-drive technology

- While recognizing the many challenges that lie ahead, VCAG encourages further development of tools utilizing gene-drive based technologies; in this case, gene drive for reducing malaria vector populations.
- This submission requires more evidence from laboratory-based studies before field testing should be undertaken.
- Overall, the evidence reviewed indicates this submission is at Step 1.

6. ALTERING VECTOR POPULATIONS THROUGH GENETIC MANIPULATION

6.1 OVERVIEW OF THE INTERVENTION CONCEPT¹

6.1.1 BACKGROUND SUMMARY²

Malaria is a disease caused by protozoan parasites of the genus *Plasmodium* that are transmitted to humans by the bites of infected *Anopheles* mosquitoes. The call for malaria eradication was renewed in 2007 (Gates, 2007), and many researchers, public health workers and funding agencies worldwide accepted the challenges of this goal (malERA, 2011). Sequential steps to eradication with specific criteria for certification include control, elimination and prevention of reintroduction (WHO, 2014a).

No effective vaccines exist yet for any of the causative parasites of malaria, and WHO has raised an alarm that current disease-control capabilities are threatened by the potential failure of insecticide-based vector control due to mosquito resistance to common insecticides, and the rising frequency of antimalarial drug resistance (WHO, 2015). These circumstances support the need to develop new strategies against malaria based on novel technologies that can supplement current control practices. Among the more promising are genetic strategies that control vector mosquitoes and prevent parasite transmission (Adelman, 2015).

Two alternative genetic strategies seek either: (i) to eliminate mosquito vectors or reduce their densities below thresholds needed for stable parasite transmission (population suppression); or (ii) to make them incapable of transmitting parasites (population alteration/modification/replacement) (Adelman, 2015). However, long-term, cost-effective and sustainable regional malaria control and elimination require the development of genetic strategies that are resilient to the dispersal of parasite-infected mosquitoes and people, and the lack of such tools represents a significant unmet need in the malaria eradication agenda. Mosquito population alteration strains carrying genes conferring parasite resistance have the appropriate design features for this purpose (Macias and James, 2015). Wild, parasite-susceptible mosquitoes invading a region populated by an altered strain of the same species acquire the parasite-resistance genes by mating with the local insects; and persons harbouring parasites and moving into that region cannot infect the resident vectors, and therefore do not serve as a source of parasites for infecting other people.

Population alteration shares with other genetic control strategies the exploitation of the ability of male mosquitoes to locate females, and this is expected to offer access to vector populations that would be unreachable using conventional, locally-acting tools. Release of a population alteration strain in conjunction with other vector control measures should make it possible to reduce or eliminate pathogen-carrying mosquitoes in carefully selected endemic areas. As elimination efforts progress,

¹ Information in this section was provided by the applicant.

² Taken directly from the applicant's statements.

mosquito population alteration takes on a larger role and ultimately can serve as a mainstay of the prevention of reintroduction phase. As elimination is achieved, the stably-altered released mosquitoes facilitate consolidation of this success by allowing resources to be moved to another region with the confidence that the area just cleared will remain disease-free. Thus, population alteration offers a real chance to achieve sustainable elimination and therefore contribute significantly to the malaria eradication agenda.

6.1.2 DESCRIPTION OF THE INTERVENTION CONCEPT

Target vector and human population

The approach can be applied to many vectors of human disease. The current submission targets *Anopheles* vectors of human malaria contributing to local transmission of malaria in at-risk human populations.

Description of the intervention proposed

A gene-drive system used to spread anti-*Plasmodium* antibody genes into populations of wild mosquitoes, making them refractory to malaria parasite infection, which will reduce human infection and disease.

Intervention will be considered efficacious compared with the following alternatives

The GM approach proposed will be compared with current best-practice interventions for control of human malaria in the target countries.

Expected outcomes of the intervention including potential benefits and harms

If successful, this intervention would contribute to a reduction in human malaria transmission and potentially malaria eradication. It also aims to sustainably contribute to the prevention of reintroduction of malaria.

6.1.3 DESCRIPTION OF THE PROTOTYPE PRODUCT

The generic description is an autonomous gene-drive system for conferring malaria parasite resistance to *Anopheles* spp. mosquitoes.

The current design has dual antimalarial parasite effector genes based on single-chain antibodies driven by endogenous promoters derived from blood-meal responsive mosquito genes. These genes are linked to an autonomous gene-drive system based on CRISPR-Cas9 biology that includes the Cas9 nuclease recoded with mosquito codon biases and guided RNAs that target a gene that produces a visible phenotype (white eyes). Expression of the Cas9 nuclease is controlled by the promoter sequences of an endogenous mosquito gene expressed specifically in the germline. The construct also carries a dominant marker gene encoding a red fluorescent protein.

6.1.4 PRODUCT CLAIMS

The claims are that transgenic *An. stephensi* refractory to infection with *P. falciparum* will assist the malaria eradication effort by providing low-cost, effective and sustainable regional malaria elimination. Implicit in these claims are that molecular genetic and transgenesis technologies can be developed to generate population alteration strains of mosquitoes that will achieve the principal public health claims.

6.1.5 JUSTIFICATION FOR THE CLAIMS

Engineering efficacious anti-parasite genes based on single chain antibodies

Anti-parasite effector genes were constructed based on the findings that a number of mouse monoclonal antibodies (mAbs) that recognize surface-bound or secreted parasite molecules can inhibit pathogen development (Isaacs et al., 2011). Two mAbs, 4B7 and 1C3, target parasites early in their development within mosquitoes. 4B7 binds *P. falciparum* surface protein Pfs25, a molecule expressed on the surface of ookinetes, and inhibits parasite development completely when fed to mosquitoes in a gametocytemic bloodmeal (Barr et al., 1991). Conversely, 1C3 binds a parasite-secreted enzyme, *P. falciparum* chitinase 1, and inhibits oocyst formation when added to infectious bloodmeals (Li et al., 2004). A third mAb, 2A10, binds *P. falciparum* circumsporozoite protein, and when pre-incubated with sporozoites, the parasite stage infective to humans, greatly decreases their ability to infect cultured hepatocytes (Hollingdale et al., 1984; Burkot et al., 1991). Here, the engineered scFvs is referred to as "modified" 1C3, 4B7 or 2A10 (m1C3, m4B7, m2A10) to distinguish them from their parental forms, the *An. gambiae* Cecropin A gene was joined to the m4B7 and m2A10 coding sequences to form a single open reading frame. Cecropin A is an antimicrobial peptide that has microbiocidal activity against multiple *Plasmodium* species due to its ability to form large pores in cell membranes (Boman et al., 1987; Gwadz et al., 1989; Christensen et al., 1988). Thus, the m4B7 and m2A10 scFvs possess both parasite-binding and antimicrobial activity. The cecropin A peptide was not joined to m1C3 as the target of this scFv is a secreted enzyme (Li et al., 2005). Bloodmeal-inducible *An. gambiae* carboxypeptidase A (Edwards et al., 1997; Ito et al., 2002) gene regulatory sequences were included in the m4B7 and m1C3 transgenes to coordinate their expression with the development of ookinetes in the mosquito midgut. *An. stephensi* vitellogenin 1 (Nirmala et al., 2006) regulatory elements were joined to the m2A10 scFv to direct expression in the female fat body. These sequences also are regulated by a bloodmeal and m2A10 secreted from the fat body into the haemolymph was expected to interact with sporozoites migrating to the salivary gland. The effect of m4B7 and m1C3 on parasite development was measured by comparing the number of oocysts in transgenic and control mosquito midguts: m4B7 reduced by 29–81% and m1C3 by 47–73% the mean intensities of oocyst infection when compared with controls in challenge experiments; m2A10 reduced by 96–97% the mean intensity of sporozoite infection in transgenic mosquitoes fed every five days. These experiments confirmed that it was possible to build transgenes that could confer anti-parasite phenotypes for human malaria.

Generation of mosquitoes with “zero parasite” phenotypes

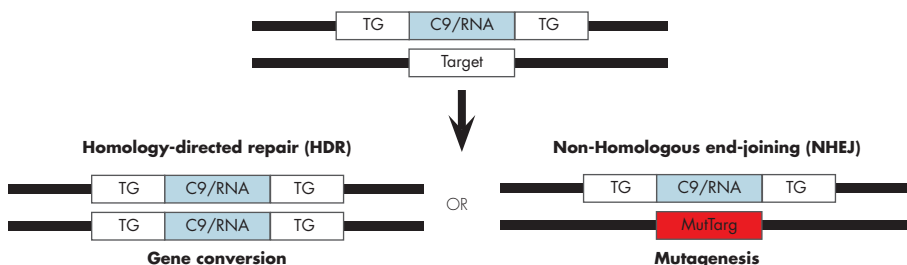
Building on the successes of the previous experiments, the applicants engineered transgene cassettes comprising m2A10 in combination with either m1C3 or m4B7 (“dual transgene”) (Isaacs et al., 2012). m4B7/m2A10 mosquitoes challenged with *P. falciparum* had few or no sporozoites in three of four experiments. The researchers observed that high infection levels could overcome the zero parasite phenotype; however, no sporozoites were detected in m1C3/m2A10 mosquitoes in challenge experiments when both genes were induced at developmentally-relevant times and parasite infections mimicked those observed in the wild. These studies support the conclusion that expression of a single copy of a dual scFv transgene can completely inhibit parasite development at parasite burdens relevant to natural disease transmission, and that m1C3/m2A10 was the preferred candidate transgene for further development.

Gene-drive of anti-parasite vector genes into mosquitoes

A highly effective autonomous Cas9-mediated gene-drive system was developed by the applicants to introgress the m1C3/m2A10 transgenes into *An. stephensi* (Gantz et al., 2015). The Cas9-encoded endonuclease is a component of the Type II CRISPR/Cas system that functions in prokaryotes as an adaptive restriction response that protects against introduction of exogenous nucleic acids (Horvath and Barrangou, 2010; Bhaya et al., 2011). Target nucleic acid sequence-specificity is mediated by “single-guide” RNAs that are short, single-stranded molecules ~85 nucleotides (nt) in length that combine a scaffolding domain that interacts with a nuclease and a 17–20 nt guide domain (Fu et al., 2014). The guide domain can be engineered to direct nuclease-mediated, double-strand DNA cuts in a specific gene sequence of interest. Cleavage mediated by a genomically-encoded wild-type endonuclease and sgRNAs can produce small deletion or insertion mutations (indels) resulting from non-homologous end-joining (NHEJ), or can result in homology-directed repair (HDR) under circumstances that include the availability of a homologous chromosome or exogenous DNA sequence that serves as a template for repair (Figure 1).

Figure 1. Schematic representation of genomically-encoded (autonomous) Cas9-mediated gene drive.

Top: Cas9 nuclease and sgRNAs (C9/RNA; green box) are inserted into a target gene (Target; TG, white boxes) in a chromosome (thick black line). A transient heterozygote (C9/RNA : Target) results when this chromosome is introduced by crossing into a diploid wild-type organism. Subsequent Cas9 nuclease activity directed by the sgRNA can result in homology-directed repair (left), which produces gene conversion and homozygosity of the Cas9/sgRNA genes. This is the genetic definition and functional basis for gene drive. Alternately, the cleavage can result in mutations in the target gene (MutTarg; red box), which produces a bi-allelic heterozygote (right). Note that the target gene is mutated in both copies.



HDR can be elicited in a wide range of organisms and served as the basis for developing autonomous gene-drive systems in the fruit fly *Drosophila melanogaster* and the malaria vector mosquito *An. stephensi* (Gantz and Bier, 2015; Gantz et al., 2015). The specific system developed results in progeny of males and females derived from transgenic males exhibiting a high frequency of germline gene conversion consistent with HDR. This system copies a ~17 kilobase construct from its insertion site to its sister chromosome in a faithful, site-specific manner. The dual m1C3/m2A10 anti-*P. falciparum* effector genes, a marker gene and the autonomous gene-drive components are propagated to 99.5% of the progeny following outcrosses of transgenic males to wild-type mosquitoes. The effector genes remain transcriptionally inducible upon blood feeding. In contrast, males and females derived from transgenic females, which have drive component molecules in the egg, produce progeny with a high frequency of mutations in the targeted genome

sequence resulting in inheritance of the transgene at ratios just above those expected by random Mendelian segregation. These data support the design of this system to be active strictly within the male germline. Recent studies confirm the male germline-specific expression of an *An. gambiae* *~2-tubulin* gene (Catteruccia et al., 2005), which can serve as a functional sequence to drive transgene expression exclusively in male mosquitoes. These combined results support further work to develop this technology for sustainable control and elimination as part of the malaria eradication agenda.

6.1.6 EVIDENCE REVIEWED FROM KEY STUDIES IN SUPPORT OF CLAIMS

Entomological studies

The investigators have demonstrated that three genes – one producing monoclonal antibody against *P. falciparum* oocysts, one producing a monoclonal antibody against *P. falciparum* sporozoites and an antimicrobial peptide (called Cecropin A) can be inserted into the genome of the malaria vector *An. stephensi*.

These genes can be transferred to future generations at higher than expected frequencies using a gene-drive mechanism. The resulting constructs express antibodies and peptides that are effective at reducing the intensity of parasite infection and can result in mosquitoes that are refractory to infection.

Specific descriptions of studies and references can be found in section 4.1.5, above.

Epidemiological studies

No epidemiological studies have been performed so far.

Safety, health and environmental risk assessments

No risk assessment studies have been performed so far.

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6.2 CONCLUSIONS AND RECOMMENDATIONS OF THE GROUP

Summary

Mosquito population alteration is a genetic control strategy whereby mosquito strains are engineered to carry genes that when introduced into *Anopheles* populations reduce the mosquitoes' ability to transmit malaria parasites to humans. The current autonomous gene-drive system design is based on CRISPR-Cas9 and linked with an antimalarial parasite effector gene construct, which causes mosquitoes to produce single-chain antibodies targeting parasites in response to a mosquito blood-meal. The gene construct causes a reduction in the number of transmission-stage sporozoites, with the aim of complete blockage of parasite development. Altered mosquitoes are deployed alone or in conjunction with other vector control measures to reduce or eliminate pathogen-carrying mosquitoes in endemic areas. The intervention claims to be a low-cost, effective and sustainable regional malaria elimination tool. Evidence to support these claims will be reviewed as part of policy development.

Conclusions and recommendations on the proposed intervention

The committee noted that the initial laboratory-based evidence for proof of concept is encouraging for this early stage of product development. The investigators have demonstrated that genes can be introduced into mosquitoes that reduce the development of malaria parasites, resulting in greatly reduced numbers of transmission-stage parasites in the mosquito vector.

Because this technology is in the very early stages of product development, further studies are needed in the laboratory to assess the stability and spread of the parasite-resistant phenotype before considering semi-field or open field experiments. A concern for this approach is the evolution of resistant parasites that avoid interference from single-chain antibodies in modified mosquitoes. The investigators are encouraged to prepare a TPP and a product development plan outlining the product testing pathway, including field testing and epidemiological trials with measurable outputs. Regulatory, legal and ethical issues will also need to be thoroughly addressed. The investigators should also consider providing a provisional costing for the intervention.

Overall, the evidence reviewed indicates this submission is at Step 1.

The following specific comments were provided:

- At present, the product claims are broad and would benefit from being made more specific. For example, current laboratory findings primarily refer to *P. falciparum* infections in *An. stephensi*. Because this is an early stage submission, the applicants' claims can be refined as their research progresses.
- The investigators are encouraged to demonstrate in the laboratory:
 1. That the gene construct is stable in laboratory populations of mosquitoes over multiple generations.
 2. That the fitness of the GMM (survival, fecundity and fertility) is similar to laboratory strains of mosquito in large cage experiments.

3. That the mating success of the GMM is comparable between laboratory strains in large-cage experiments in the laboratory.
4. That the GMMs produce no sporozoites following blood-feeding on a wide range of *P. falciparum* strains.
 - The investigators should produce a simple plan outlining the product testing pathway including field testing and epidemiological trials.
 - VCAG suggests that a face-to-face meeting with investigators and VCAG would benefit both parties in order to streamline and expedite generation of data for policy setting.
 - Regulatory and ethical issues will also need to be thoroughly addressed. The investigators should also consider providing provisional costing for the intervention.

Concluding statement on GMM for population reduction or extinction

VCAG encourages further development of tools utilizing gene-drive based technologies while recognizing that these strategies are still in the early phases of development, and that important challenges lie ahead for their development and deployment. More evidence from laboratory-based studies is needed before semi-field or open field-testing should be undertaken.

General statement on gene-drive based technologies

While the committee recognized the potential of new gene-drive based technologies to suppress vector-borne diseases, it cautioned that transgenic vector strains possessing forms of the gene drive currently in development may be difficult to recall if they are released intentionally or unintentionally. This characteristic of such genetic modification strategies calls for extremely thorough cage trials in the laboratory accompanied by ecological and epidemiological assessments of relevance to target countries before conducting field trials where escape of strains into the environment is possible. Despite the lack of sufficient information on responsible release of vector strains with gene drive, VCAG supports continued efforts to develop this technology. The ultimate use of gene-drive based technology will require thorough assessment of the potential benefits and risks, including examination of ethical and legal considerations as well as governance frameworks.

Summary of conclusions and recommendations on gene-drive based technologies

- While recognizing the many challenges that lie ahead, VCAG encourages further development of tools utilizing gene-drive based technologies. In this case, gene-drive for spread of malaria-refractory genes
- This submission requires more evidence from laboratory-based studies before field testing should be undertaken.
- Overall, the evidence reviewed indicates this submission is at Step 1.

7. STATUS UPDATES ON PREVIOUS SUBMISSIONS

The committee received updates on the status of four new products that it had reviewed in previous meetings: Spatial repellents, Oxitec OX513A, Eave tubes and Interceptor G2.

7.1 SPATIAL REPELLENTS

The innovator provided an update concerning accomplishments and modifications to the trial design. The original multi-centred trial planned for five countries was reduced to two countries. Studies have been discontinued in Kenya, Zambia and the United Republic of Tanzania. Trial activities are retained in Indonesia and Peru. Epidemiological and entomological study parameters in these sites remain unchanged. Updates were given on general management of the trials, programme monitoring and oversight, and preliminary outcomes from the spatial repellent product validation studies and from baseline surveys in the two retained study sites.

Conclusions

VCAG noted the changes to trial design, and requested protocols and a statistical analysis plan in addition to some preliminary data on product efficacy. The innovator is advised to consult with VCAG further on changes to trial design.

7.2 OXITEC OX513A

The innovator gave an update on plans to assess the epidemiological impact of OX513A in reducing transmission of dengue viruses, including plans for trials run independently of Oxitec in two locations (Brazil and Grenada). Concerns were raised regarding adequate community engagement for the trials planned for Brazil and Florida given the evidence of rejection by the community and protests against field release of OX513A mosquitoes in some trial areas. Adequate documentation of community support should be provided. For current and future trials, consistency in the entomological and epidemiological measurements should be a high priority. The composition and relative roles of the study steering committee and the study design team should be clarified. VCAG members provided recommendations for OX513A trial designs, but will not serve on the Oxitec study steering committee or the study design team.

Conclusions

VCAG support for the pilot deployment of this product in the context of the Zika virus disease public health emergency was presented at the emergency meeting (Geneva, March 2016). All large-scale pilot deployments should include rigorous monitoring and evaluation and a well-developed community engagement programme that respects the wishes of communities to participate. Field trials with measureable epidemiological outputs will need to be carried out in addition to pilot deployments.

7.3 INTERCEPTOR G2

The innovator of Interceptor G2 (a long-lasting insecticidal net treated with alpha-cypermethrin and chlorfenapyr) presented a revised claim that the LLIN product proposed performs better than a standard pyrethroid-only LLIN against insecticide-resistant mosquitoes. Preliminary reports were reviewed from experimental hut trials; the results showed evidence of increased mortality with no evidence of feeding inhibition. The efficacy data will be considered by WHO in 2017.

Conclusions

The data derived from Stage II experimental hut studies are promising and the manufacturers are encouraged to provide completed Phase I and Phase II data sets that meet the criteria described in the VCAG Guideline for testing claims of efficacy against resistant mosquitoes. Product claims should be clearly stated before further evaluations are undertaken. VCAG has not yet reviewed plans for community trials. Required epidemiological trials¹ on disease impact, which will be used for decision-making, can be run in parallel with the LLIN durability studies ("Phase III")² that are currently part of WHO product evaluation (WHO Prequalification of medicines³). That would reduce the time taken to generate the evidence needed for comprehensive policy-level decisions on a new product claim by WHO.

7.4 EAVE TUBES

The innovator described progress on the randomized control trial of this innovation, with the aim of epidemiologically validating the technology. Parameters to be investigated in the trial, including timeline and activities, were discussed. Two phases are planned. The first phase, years 1–3, will be a cluster randomized controlled trial with epidemiological outcomes. The second phase, years 3–5, will be smaller studies to inform implementation strategies. Baseline survey data and trial randomization were described. Trials were due to begin in January 2017.

Conclusions

Two active ingredients were being considered for use in the trial beginning in January 2017. VCAG recommended that the insecticide selected be well-justified based on relevant data. Provided initial studies demonstrate that both active ingredients meet the selection criteria (at least 50% mortality after 3 months), investigators should consider using a non-pyrethroid active ingredient in their trials. That recommendation is in line with current knowledge on the additive benefit of such ingredients in the presence of pyrethroid-based LLINs for insecticide resistance management, and would provide a secondary product in instances where first-choice products fail. Modification of the study protocol to include additional entomological monitoring should be considered.

¹ At least two complementary epidemiological trials conducted over two transmission seasons (see Section 3 of this document).

² Guidelines for laboratory and field-testing of long-lasting insecticidal nets. Geneva: World Health Organization; 2013.

³ WHO Essential Medicines and Health Products: Prequalification of medicines (<http://apps.who.int/prequal/vcp.htm>, accessed May 2017).

ANNEXES

Annex 1. Agenda

Wednesday 2 November 2016	
<ul style="list-style-type: none"> Open meeting: Until PM coffee includes VCAG + temporary advisers + selected observers Closed meeting: AM (pre-lunch) and PM (post coffee). VCAG only. 	
09:00–09:15	Opening of meeting
09:15–10:00	Overview of VCAG <ul style="list-style-type: none"> Purpose, functions and role in WHO policy setting Terms of reference, priorities and decision-making, confidentiality and declaration of interests Review of previous meetings, decisions and portfolio
10:00–10:30	Updates/briefings on any relevant meetings or policy issues from WHO
11:00–12:00	VCAG pathways <ul style="list-style-type: none"> Review concept note and discuss outcomes of meeting.
12:00–12:30	VCAG pathways – CLOSED SESSION <ul style="list-style-type: none"> Develop/finalize recommendations
13:30–14:00	Brief introduction to gene drive for vector control and discussion – remote presentation
14:00–15:30	Intro to different approaches <ul style="list-style-type: none"> Combined SIT/IIT approach Gene drive (population suppression)
16:00–16:30	(Intro cont'd) <ul style="list-style-type: none"> Gene drive (population alteration) – remote presentation
16:30–18:00	Closed discussion with innovators and VCAG in plenary (<i>relevant applicant and VCAG only</i>) <ul style="list-style-type: none"> Gene drive systems 1 (remote) and 2 (in person)
Thursday 3 November 2016	
<ul style="list-style-type: none"> Open meeting: Until PM coffee includes VCAG + temporary advisers + selected observers Closed meeting: PM (after coffee) VCAG only 	
09:00–10:00	Closed discussion with innovators and VCAG in plenary (<i>relevant applicant and VCAG only</i>) <ul style="list-style-type: none"> Combined SIT/IIT approach
10:00–10:30	Closed general discussion (<i>VCAG experts only</i>)
11:00–12:00	Open discussion on Combined SIT/IIT and gene-drive technologies – testing and data requirements
12:00–12:30	Overview of progress on guidelines <ul style="list-style-type: none"> Vector control evaluation methodology Efficacy testing for vector traps
13:30–14:30	Paradigm updates and discussion
14:30–15:30	Presentation and discussion on eave tubes trial
16:00–18:00	Closed session: Report finalization including summary and recommendation on SIT and both gene-drive technologies
Friday 4 November 2016	
<ul style="list-style-type: none"> Open meeting: Until PM coffee includes VCAG + temporary advisers + selected observers Closed meeting: PM (after lunch) VCAG only 	
09:00–09:30	General discussion, recap
09:30–12:30	Presentation to plenary on major points from group discussion (30 min per group) General discussion
13:30–15:30	Closed session: Finalization of the report and recommendations
16:00–17:30	General discussion, Closure of the meeting

Annex 2. List of participants

EXPERT PANEL MEMBERS

Immo Kleinschmidt, London School of Hygiene & Tropical Medicine (LSHTM), United Kingdom

Ashwani Kumar, National Institute of Malaria Research (ICMR), India

Steven Lindsay, Durham University, United Kingdom

Thomas Scott, University of California, USA

Hassan Vatandoost, Tehran University of Medical Sciences, Islamic Republic of Iran

TEMPORARY ADVISERS

Daniel Adjei Boakye, Noguchi Memorial for Medical Research, Ghana

Christophe Boëte, IRD – Aix-Marseille University – EHESP – INSERM, France

Heather Ferguson, University of Glasgow, Scotland, United Kingdom

Sarah Moore, Ifakara Health Institute (IHI), United Republic of Tanzania

Yasmin Rubio-Palis, Universidad de Carabobo Nucleo Aragua, Bolivarian Republic of Venezuela

Marc Schetelig, University of Giessen, Germany

Thomas Smith, Swiss Tropical Institute, Switzerland

Yeya Toure, Université des Sciences, Techniques et Technologies de Bamako (USTTB), Mali

TECHNICAL RESOURCE

Fred Gould (*via Skype*), North Carolina State University, USA

STAKEHOLDERS

Camilla Beech, Cambea Consulting, United Kingdom

Konstantinos (Kostas) Bourtzis, Joint FAO/IAEA Division of Nuclear Techniques in Food and Agriculture, Department of Nuclear Applications, International Atomic Energy Agency, Austria

Austin Burt, Imperial College London, United Kingdom

Anthony James (*via Skype*), University of California, Irvine, USA

Stephanie James, Foundation for the National Institutes of Health (FNIH), USA

Karen E. Logan, Imperial College London, United Kingdom

Eleanore Sternberg, Pennsylvania State University, USA

Matthew Thomas, Pennsylvania State University, USA

OBSERVERS

Lilia Gerberg, President's Malaria Initiative, USA

Fil Randazzo, Bill & Melinda Gates Foundation, USA

Michael R. Reddy, Bill & Melinda Gates Foundation, USA

Dan Strickman, Bill & Melinda Gates Foundation, USA

WHO SECRETARIAT

Department of Control of Neglected Tropical Diseases

Dirk Engels, Director

Raman Velayudhan, Vector Ecology and Management

Rajpal Yadav, Vector Ecology and Management

Anna Drexler, Vector Ecology and Management

Global Malaria Programme

Pedro Alonso, Director

Martha Quinones Pinzon, Entomology and Vector Control

Emmanuel Temu, Entomology and Vector Control

Health Statistics and Information Systems

Andreas Reis, Research, Ethics and Knowledge Management

Regulation of Medicines and other Health Technologies

Deusdedit Mubangizi, Prequalification Team

Dominic Schuler, Prequalification Team

Special Programme for Research and Training in Tropical Diseases

Florence Fouque, Vectors, Environment and Society

Annex 3. Terms of reference of the Vector Control Advisory Group

Rationale

The VCAG website should be consulted for the most recent versions of all VCAG documents. WHO develops global policies and strategies for the prevention, control and elimination of major vector-borne diseases. Vector control is a key strategy to target malaria and vector-borne neglected tropical diseases including *Aedes*-borne viral diseases (dengue, chikungunya, Zika virus disease and yellow fever). Developing policies, strategies and technical guidance for vector control is a cross-cutting area of work between the Global Malaria Programme and the Department of Control of Neglected Tropical Diseases. WHO has therefore established a Vector Control Advisory Group – a standing expert group – to advise WHO on the public health value of new intervention concepts in vector control.

Functions

The VCAG has the following functions:

1. to conduct an initial review of concept and determine data required to a) validate the product class, claim or variation and to b) support formulation of a WHO policy recommendation.
2. to advise on the process to generate the required data
3. to assess the evidence for new vector control tools / approaches (periodically as required)
4. to develop or refine the Target Product Profiles;
5. to establish public health value and provide recommendations to guide policy development.

Membership

The Group will have up to a maximum of 15 members comprising:

- a core group of seven members, including chair, all with a term of 3 years and eligible for a single re-appointment term of 3 years; and
- a flexible group of experts invited on an ad hoc basis to provide specific needed expertise to assess new tools (maximum of eight individuals).

All members of the Group are invited in their personal capacities to represent the broad range of expertise relevant to practical vector control, including vector biology, ecology, genetics and population biology, insecticides and insecticide resistance, epidemiology of vector-borne diseases, study design, statistics, product development and management of vector control programmes. In the selection of the members, consideration will be given to attaining an adequate distribution of technical expertise, geographical representation and gender balance.

Members of the Group, including the Chairperson, will be selected and appointed by the WHO Assistant Director-General, HIV/AIDS, Tuberculosis, Malaria and Neglected Tropical Diseases, upon the advice of the Director of the Global Malaria Programme and the Director of the Department of Control of Neglected Tropical Diseases.

The list of members and related biographical information will be made publicly available on the WHO website.¹

Prior to being appointed or renewed as a member, nominees shall be subject to a conflict of interest assessment by WHO based on the completed *Declaration of interests for WHO experts*² and in accordance with WHO procedures. Members shall be required also to submit forms every year of their term. In addition, before confirmation by WHO of their appointment as VCAG members, nominees shall be required to sign a WHO *Confidentiality undertaking*.

Members of the Group including the Chairperson must respect the impartiality and independence required of WHO. In performing their work, members:

- must not seek or accept instructions from any government or authority external to the Organization;
- must be free of real, potential, apparent or perceived conflicts of interest; and
- shall have an ongoing obligation throughout their tenure to inform WHO of any changes to their affiliations or the information that they would have disclosed on the Declaration of interests' form.

Real or apparent conflicts of interest may exclude a member from participating in some or all of a given meeting. Summaries of declared interests will be read out at the start of meetings and disclosed in reports of the Group.

The Chairperson and members of the Group will not be remunerated for their participation in meetings. However, WHO will cover their travel costs and per diem in accordance with the applicable WHO rules and policies.

Membership of the Group may be terminated by WHO for any of the following reasons:

- failure to attend two consecutive meetings;
- a conflict of interest incompatible with serving on the Group; and
- a lack of professionalism involving, for example, a breach of confidentiality.

Roles and responsibilities

Members of the Group have a responsibility to provide WHO with high-quality, well-considered, evidence-informed advice and recommendations on matters described in these terms of reference. Members play a critical role in ensuring the reputation of the Group as an internationally recognized expert advisory committee on innovation in vector control.

The Group has no executive or regulatory function; its role is solely to provide advice and recommendations to the WHO Director-General, including advice and recommendations

¹ WHO Neglected Tropical Diseases: Vector Control Advisory Group (http://www.who.int/neglected_diseases/vector_ecology/VCAG/en/, accessed May 2017).

² Declaration of interests for WHO experts – forms for submission (<http://www.who.int/about/declaration-of-interests/en/>, accessed May 2017).

on urgent public health issues related to the efficacy of new intervention concepts in vector control as needed.

All information presented as well as the deliberations of the Group must be treated as confidential and cannot be publicly disclosed by members. Members, experts and observers shall not speak on behalf of, or otherwise represent, WHO to any third party, and shall refer any such enquiries to WHO.

The Chairperson is elected by the core group of members, with responsibilities for:

- chairing meetings, liaison with the WHO Secretariat during and between meetings, assisting the Secretariat to finalize the reports of meetings of the Group; and
- participating in meetings of the WHO Malaria Policy Advisory Committee and the WHO Strategic and Technical Advisory Group for Neglected Tropical Diseases as an observer, as and when invited by the Organization.

The responsibilities of members of the Group include:

- reviewing dossiers on new tools, including target product profiles and claims, to determine whether the evidence provided supports the product or label claim;
- providing guidance on information and data requirements needed to pass each step of assessments of the Group including for evaluation of efficacy and safety of candidate products to formulate WHO policy recommendation;
- advising and supporting preparation for developing guidelines for evaluation of efficacy, effectiveness and safety of new tools and approaches for public health vector control; and
- advising the WHO Secretariat on any specific requirements to be met by the applicants or manufacturers of candidate tools proposed for evaluation.
- Members are expected to attend meetings as and when convened by WHO, to review documentation in advance of meetings and to provide their views for consideration by the Group.

Meetings and meeting participants

The Group will normally meet at least once each year or based on the need to evaluate new types of promising tools. WHO may convene additional meetings, including through teleconferences and videoconferences, on an ad hoc basis. WHO may furthermore request members to carry out activities between meetings, i.e. in preparation for or as follow-up to such meetings.

Each meeting will constitute two types of working sessions:

- **open sessions** at which general topics may be discussed and selected observers may be invited to attend;¹ and

¹ Observers may attend meetings on invitation and will be screened prior to attendance. They shall not speak unless requested to do so by the Chairperson and will not attend closed sessions of the Group or participate in the formulation of recommendations by the Group to WHO.

- **closed sessions** during which recommendations and/or advice to WHO will be formulated and shall be restricted to VCAG members and the WHO Secretariat.

The minimum quorum for meetings of the Group shall be seven experts including the core members and the advisers invited on an ad hoc basis.

Meetings will be conducted in English. Translation into other languages may be possible in some cases with advance requests to the WHO Secretariat.

The Group will make decisions and recommendations by consensus.

Meeting reports and dissemination

Reports of meetings will be submitted to WHO after being finalized by the Group and cleared by the Chairperson. All recommendations to WHO are advisory, and the Organization retains unfettered control over any subsequent decisions made or actions taken on any proposals, policy issues or other matters considered by the Group. WHO also retains full control over the use and publication of VCAG reports, including whether to use and/or publish them and/or to provide such reports to other WHO advisory groups including the Malaria Policy Advisory Committee and/or the Strategic and Technical Advisory Group for Neglected Tropical Diseases, subject to the protection of confidential information including confidential business information.

Role of the Secretariat

WHO shall provide the secretariat for the Group, including the provision of any necessary scientific, technical and other support. The WHO Secretariat shall provide members with the agenda, working documents and discussion papers in advance of each meeting, and be responsible also for editing, publishing and disseminating meeting reports.

Information and documentation

The information and documentation, to which members and advisers will have access during or in relation to meetings, may include confidential and proprietary information. To protect such information, all members and expert advisers will be required to sign a confidentiality undertaking and a declaration of interest form declaring any real or perceived conflicts in the objectivity or independence of the members in their performance of roles for the Group. Distribution of the meeting documents to observers is subject to the protection of confidential information, including confidential business information, as determined by the WHO Secretariat.

Members, advisers and observers shall refrain quotation from, and circulation and use of, documents of the Group for any purpose other than in a manner consistent with their responsibilities under these terms of reference.

Annex 4. Overview of existing and new product classes and claims

VARIATIONS OF CLAIMS FOR AN EXISTING PRODUCT CLASS				
	Insecticide treated bed nets against insecticide resistant vector populations	Insecticide treated walls against insecticide resistant vector populations	Perrifocal residual spraying (PRS) extension of IRS to target outdoor resting Aedes vector mosquitoes	Insecticide-treated curtain, within the impregnated bednet product class
Generic Exemplars	ITNs controlling IR populations for defined IR mechanism	IRS / wall linings controlling IR populations for defined IR mechanism	Residual Spray product for outdoor application	Fully Screened Houses (FSH) blocks household entry of mosquitoes to eliminate indoor transmission
Prototype	PermaNet 3 Interceptor G2	So far no prototype with claim for IR has been reviewed	Perifocal Residual Spray formulation (Bayer)	FSH using netting material with pyrethroid insecticide
Indoors against adults	✓	✓	✓	✓
Outdoors against adults			✓	✓
Outdoors against immatures				
CLAIM: Personal protection	YES/NO	NO	NO	YES
CLAIM: Community protection	YES	YES	YES	YES
Pipeline: VCAG / PQVC	WHOPES for long-lasting effect VCAG for IR claims	WHOPES for long-lasting effect VCAG for IR claims	WHOPES – PQ for entomological efficacy Disease technical group for operational utility	WHOPES – PQ for entomological efficacy Disease technical group for operational utility
VCAG epidemiological endpoint:	PP, and/or CP	CP	CP	PP, and/or CP
Progress	Under WHO / GMP review for operational guidance	No current submission	Complete, but new application needs review by technical group	Complete, but new application needs review by technical group

NEW PRODUCT CLASSES – CHEMICAL BASED						
Parameter	Attract and kill baits	Spatial repellents interrupting human-vector contact	Insecticide treated materials for specific risk groups	Vector traps for disease management	Lethal house lures	Systemic insecticide products for the control of human arthropod borne pathogens
Generic Exemplars	Attractive Toxic Sugar Bait	Passive emanator	Insecticide treated material	Adulticidal Oviposition traps	Eave tubes	Rodent bait for control of vectors of cutaneous leishmaniasis
Prototype	Bait station	metofluthrin or transfluthrin emanators	Blanket Clothes	ALOT, INZTRAP, AGO, TNK	Eave tubes	Imidicloprid based bait
Indoors against adults	✓	✓	✓	✓	✓	✓
Outdoors against adults	✓	✓	✓	✓	✓	✓
Outdoors against Immatures						
CLAIM: Personal protection	NO	YES	YES for specific risk groups	NO	NO	NO
CLAIM: Community protection	YES	YES	NO	YES	YES	YES
Pipeline: VCAG / PGVC	VCAG	VCAG	VCAG	VCAG	VCAG	VCAG
VCAG epidemiological endpoint:	CP	PP & CP	PP	CP	CP	CP
Progress (VCAG Step)	2	3	1	3	3	2

NEW PRODUCT CLASSES – BIOLOGICAL				
Parameter	Microbial control of human pathogens in adult vectors	Reducing vector populations through genetic manipulation	Population alteration of malaria vector mosquitoes	Combined sterile insect technique (SIT) and incompatible insect technique (IIT) for mosquito population control
Generic Description	Bacterial infection	Self-limiting genetic modification	Gene-drive system	Radiation based sterility and bacterial infection
Goal	Population alteration	Population suppression	Population alteration	Population suppression
Disease target	Dengue, Zika, Chikungunya	Dengue, Zika, Chikungunya	Malaria	Dengue, Zika, Chikungunya
Product	wMel strain <i>Wolbachia</i> in <i>Ae. aegypti</i>	OX513A, <i>Ae. aegypti</i> (RIDL)	CRISPR/Cas9 linked suppression construct in <i>An gambiae</i>	Sterilized male <i>Ae. aegypti</i> and <i>Ae. albopictus</i> infected with <i>Wolbachia</i> spp.
Mode of Action – Spread	Bacterial spread via reproduction and transovarially	No spread	GM spread via inheritance	No spread – released mosquitoes are sterile.
Mode of Action – Killing	Does not kill mosquitoes	Kills offspring at larval and pupal stages	Does not kill mosquitoes	Released mosquitoes are sterile – no offspring

Mode of Action – Disease transmission	Mosquitoes refractory to infection	N/A – suppress populations	N/A – suppress populations	Mosquitoes refractory to infection	Mosquitoes refractory to infection AND suppress populations
Use: against indoor adults	✓	✓	✓	✓	✓
Use: against outdoor adults	✓	✓	✓	✓	✓
Use: against outdoor immatures		✓	✓		✓
CLAIM: Personal protection	NO	NO	NO	NO	NO
CLAIM: Community protection	YES	YES	YES	YES	YES
Pipeline: VCAG / PQVC	VCAG	VCAG	VCAG	VCAG	VCAG
VCAG epidemiological endpoint:	CP	CP	CP	CP	CP
Progress (VCAG Step)	3	3	1	1	3

GMP, WHO Global Malaria Programme; IRS, indoor residual spraying; LLIN, long-lasting insecticidal net; VCAG, Vector Control Advisory Group; WHOPES-PQ, WHO Pesticide Evaluation Scheme-WHO prequalification programme CP, community protection; PP, personal protection; VCAG, Vector Control Advisory Group; N/A, not applicable; PQVC, WHO prequalification programme vector control

Annex 5. Evaluation pathways for vector control tools interventions (tools, technologies and approaches)

Summary

The Vector Control Advisory Group (VCAG) was formed by the World Health Organization (WHO) to advise on the efficacy of new tools, technologies and approaches for public health vector control. VCAG issues advice to WHO to inform policy recommendations as well as guidance to innovators on data generation for WHO policy purposes. To date, VCAG has assessed a number of new product classes¹ for vector control with diverse entomological modes of action, which aim to reduce the transmission and burden of vector-borne diseases in humans. Full information is contained in VCAG meeting reports available on the WHO website (http://www.who.int/neglected_diseases/vector_ecology/VCAG_resources/).

As part of a broad reform in the WHO process for evaluating vector control interventions WHO convened a special expert meeting in Geneva on 19 September 2016 to advise on the optimal pathway for evaluation and discuss expected evaluation methods, data requirements and efficacy indicators. The conclusions of this meeting were subsequently reviewed and revised at the VCAG meeting held in Geneva on 2–4 November 2016.

The following conclusions by WHO are based on the outcomes of the two expert meetings on pathways for new vector control tools under VCAG.

1. A product class in vector control is a category of intervention that shares a **common entomological mechanism of action** to reduce infection and/or disease. A WHO policy recommendation of a product class is based on the **evidence of epidemiological efficacy** that substantiates public health value, e.g. proven impact on infection and/or disease in humans. Each product class shall be defined through a target product profile (TPP).
2. In a given product class there could be products with one or several specific claims. WHO recognition of each claim, which constitutes a WHO recommendation, requires evidence of epidemiological efficacy that substantiates public health value, e.g. proven impact on infection and/or disease in humans.
3. For each new product class or claim² not yet recognized by WHO and for which there is no WHO policy recommendation, validation of the claims will require sufficient evidence from across different settings to demonstrate the efficacy of the new product in reducing infection and/or disease in human populations and to support evidence-based guidance for deployment.

¹ Product class replaces the word “paradigm” in this annex.

² Summary of new product classes: http://www.who.int/neglected_diseases/vector_ecology/Product-Categories-VCAG.pdf

4. Pathways Steps for New Tools, Technologies and Approaches

Concept Review and Data Definition. For each new product class or claim not yet recognized by WHO and for which there is no WHO policy recommendation, VCAG will provide a recommendation to WHO on the evidence required to substantiate the product claim(s) and will advise on the evaluation methods needed to generate these data.

Manufacturer-led data generation. Following the interaction with VCAG, manufacturers will produce a completed product data package containing the full evidence requested and submit this to WHO for review.

Assessment and recommendation. Once the completed product data package containing the full evidence requested is submitted to WHO for review, VCAG will assess whether the evidence provided validates the product claim(s), and will make recommendation to WHO on the public health value of the new product class. WHO will then consider the advice given by VCAG in order to recognize the product claim and formulate policy recommendations on new products.

5. VCAG advice on new interventions will include:

- early interaction with investigators on the submission to clarify if it constitutes a new product class and/or product claim;
- VCAG initial concept review and determination of data generation required in order to determine the public health value of a new product class or product claim; VCAG periodic review as requested by WHO or by investigators; and
- VCAG final review of evidence to determine public health value including completion of the TPP and validation of the product claims.

6. Once VCAG validates a new product class or claim, the following policy steps are anticipated.

- After a policy recommendation is issued by the WHO disease-specific programme for a new product class or claim, responsibility for further assessment of that product and subsequent products within that class or claim will thereafter be assumed by WHO's prequalification programme for vector control products.¹
- The relevant WHO disease-specific programmes (e.g. Global Malaria Programme or Department of Control of Neglected Tropical Diseases) will assess the situations and conditions appropriate for programmatic use of the intervention with the support of relevant expert groups (e.g. Malaria Policy Advisory Committee, Malaria Vector Control Technical Expert Group,

¹ <http://www.who.int/pq-vector-control/en/>

Strategic and Technical Advisory Group for Neglected Tropical Diseases), and may issue policy recommendations or other guidance for deployment.

- Specific variations within a product class (e.g. nets having combinations of insecticides at different dosages and with varying patterns of distribution) will be reviewed by WHO to clarify whether the product claim(s) are already recognized by WHO or if they constitute new claims for which no current WHO policy recommendation applies.

1. Background

The World Health Organization's (WHO's) Vector Control Advisory Group (VCAG) is an expert advisory body that reviews the efficacy of new tools and approaches and advises WHO on their value to public health vector control. This WHO-convened committee also provides guidance for innovators on evidence for efficacy and safety of new tools and approaches in order to support the translation of innovative concepts in vector control to public health impact. VCAG functions to enable the formulation of policy recommendations on the use of new classes of vector control products as well as products with a new claim within a given class. VCAG is managed jointly by WHO's Global Malaria Programme and the Department for Control of Neglected Tropical Diseases, with close involvement of the programme responsible for prequalification of vector control products in the Department of Essential Medicines and Health Products.

Currently, WHO recommends two core interventions for malaria vector control: pyrethroid incorporated long-lasting insecticidal nets and indoor residual spraying. Larval source management and personal protection are considered supplementary measures to be used under specific conditions. For the control of neglected tropical diseases, recommended strategies include indoor residual spraying, space spraying, larvicides, molluscicides and rodenticides. A summary of recommended interventions may be found in **Table 2** and are further detailed on the website of the WHO Global Malaria Programme.

Since 2013, VCAG has assessed a number of new product classes for vector control, representing a diverse range of technologies with different entomological modes of action and outcomes aimed at reducing the burden of vector-borne diseases. For most of these new product classes, no policy recommendations were available or the existing policies did not sufficiently cover new product claims or new product variations within a given class. To develop WHO policy recommendations for the public health use of products based on new concepts and/or approaches, evidence is needed to support claims of efficacy against disease. Investigators are encouraged to communicate early so that they can be advised on the type of evidence required by WHO to support policies for the use of such new technologies (tools/approaches/product claims) and to map out the pathway for product development and evaluation.

The VCAG process to assess a vector control invention of a new product class or claim has three key steps:

- (1) proof of principle in the laboratory;
- (2) small-scale field trials (or semi-field trials) with entomological outcomes; and
- (3) larger-scale field trials with epidemiological outcomes.

Engagement of innovators with VCAG during the early stages of development will provide an opportunity for VCAG to issue advice and guidance on critical aspects of the process, with the aim of generating appropriate epidemiological evidence to clearly demonstrate the public health benefit of the new product. This will enable the timely development of WHO policy recommendations for appropriate use in public health. Ultimately, WHO develops the policy and relevant guidance considering the expert advice and the public health need.

VCAG consultations involve product development experts and stakeholders and aim to reach consensus on the policy development of new vector control products based on new concept or novel approaches. This document lays out the agreed key steps needed to support policy development for new tools and approaches in vector control.

2. Definitions of key terms

A product class in vector control is a category of interventions that share a common entomological mechanism of action to reduce infection and/or disease in humans. It requires epidemiological evidence of efficacy as a proof of principle to confirm the product claim for reducing infection and/or disease.

A new product class in vector control is a new category of intervention that has a different entomological mechanism of action compared with established tools or approaches, and requires changes and/or additions to the evaluation process and the way the intervention is used.

A new product class has no existing WHO policy recommendation. Validation of the public health importance of a new product class will involve entomological and epidemiological evaluation of the first product representing a product class or product variation with a new claim within a class. A new product within a given class could have several claims, each of which may need specific evaluation methods and assessment of impact, before specific policy recommendations can be issued.

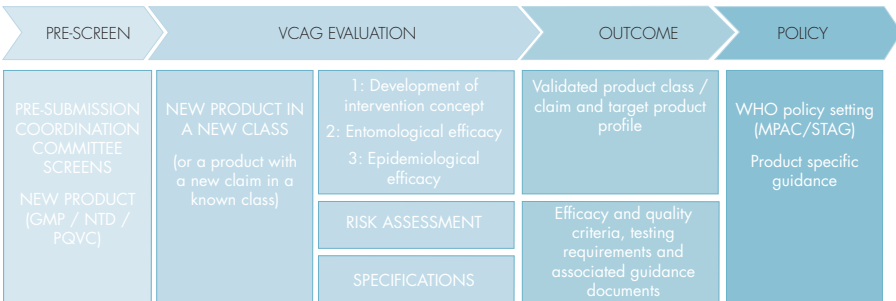
A glossary of key terms is provided in **Appendix 1**.

3. Policy pathways for vector control products

WHO develops policy recommendations on the use of new vector control tools and approaches to guide Member States and their partners on which intervention/s may be appropriate for public health use in a given setting. Policies are based on robust scientific evidence of entomological and epidemiological efficacy, supported by assessments of safety. A schematic of the current policy development pathways for new classes of vector control products is given below (Figure A5.1).

All new products will be submitted to a single entry portal jointly managed by the Global Malaria Programme, the Department of Control of Neglected Tropical Diseases and the Prequalification Programme, through which guidance will be given as to which evaluation pathway the product will need to follow. This will be defined through a pre-submission screening considering the submitted product claim and supporting information to determine whether (i) the new product is covered by existing policy recommendation/s (Appendix 2), in which case the product claim can directly be assessed by the Prequalification Programme on the basis of established evaluation methods; or (ii) the new product is not covered by existing policy recommendations, and either constitutes a first-in-line product of a new class or represents a variation within an existing class (e.g. a new claim within established product class) that requires different evaluation methods (Appendix 3). New products without policy recommendations will be directed to VCAG to either support the further development of the product or guide prompt generation of evidence required for policy recommendations. **Early interaction with WHO during the initial stages of development of new tools is essential to successfully guide development of new products.**

Figure A5.1. Schematic of WHO policy development pathways for new vector control products



MPAC/STAG, WHO Malaria Policy Advisory Committee/WHO Strategic and Technical Advisory Group for Neglected Tropical Diseases.

Once it has been determined that given new product is not covered by an existing policy recommendation, the new product enters the Policy Pathway under VCAG. VCAG works with innovators to guide the development of the intervention concept representing a new product class and reviews entomological and epidemiological proof of principle. A risk assessment is required and, where needed, the development of product specifications either via the FAO/WHO Joint Meeting on Pesticide Specifications or a WHO-convened expert group. The outcome of the VCAG process will be either a validated product class (and associated target product profile) or a validated product claim.¹

VCAG outcomes will feed into the WHO policy and guidance setting process. After VCAG endorses the efficacy claim of a new product or product class, WHO will then assess the potential use of the product within the appropriate vector-borne disease control strategy. This may require additional specific information to guide for operational use and deployment to be generated during the development process and assessed by WHO NTD and GMP.

VCAG outcomes are presented to the Malaria Policy Advisory Committee, which meets twice per year, and the Strategic and Technical Advisory Group for Neglected Tropical Diseases, which meets annually and may review items out of session as needed. Both committees are high-level policy advisory committees that assist WHO to develop policy. After a policy recommendation is issued, the dossier/data assessed by VCAG will directly feed into the final assessment process of the PQVC. Further details on assessment under PQVC may be found on the website at pqvectorcontrol@who.int.

4. VCAG evaluation procedures and data requirements for new product classes or claims

Data requirements for each stage of the VCAG assessment process are detailed in the 2013 VCAG Operational Procedures and summarized in **Appendix 4**. Of particular importance, before products can be recommended for operational implementation, are field trials with epidemiological endpoints, safety assessments and, in the case of a new product class, development of specification criteria. **At least two well conducted and randomized epidemiological trials in different and complementary entomological settings, ideally covering two transmission seasons, are required as proof of principle for a new product class or product variation with a new claim within an existing class.** Sample evaluation pathways under VCAG are shown in **Figures A5.3 and A5.4**.

¹ Further details on the WHO evaluation process for vector control products may be found at: <http://www.who.int/malaria/publications/atoz/evaluation-process-vector-control-products/en/>

Figure A5.3. Evaluation steps of new product as prototype in a new product class

VCAG evaluation of a new product class – biological. Example <i>Wolbachia</i> -infected <i>Aedes aegypti</i>	
1	Early interaction / pre-submission meeting <i>Review letter of intent, claims and determine whether there is need for new policy</i>
2	VCAG initial concept review (first review in VCAG meeting) <i>Provide advice on data needed for disease programme policy-making, including safety, efficacy (entomological, epidemiological) and quality control</i>
3	Data generation step <i>VCAG tracks progress, interacts regularly with innovators and convenes expert groups as needed (for example, to assess risk, develop quality criteria and guide efficacy trials)</i> Data requirements: <ul style="list-style-type: none"> - entomological and epidemiological efficacy data generated (at least two epidemiological trials as proof of principle) - other defined product criteria reviewed (eg. feasibility, manufacturing sustainability, etc) - specifications/quality control criteria developed - risk assessment
4	VCAG data review for prototype of new concept/product class (final review in VCAG meeting) <i>Is the intervention efficacious against vectors and/or disease?</i> Decision point: VCAG (<u>DOES</u> or <u>DOES NOT</u>) recommend that WHO endorse the new product class efficacy claims.

Figure A5.4. Evaluation steps of new product claim within an established product class

VCAG evaluation of a new product claim (VARIATION) within an established product class. Example: extending claims to different vector target population such as long-lasting insecticidal nets (LLINs) targeting insecticide resistant vectors	
Steps	VCAG assessment
1	Pre-submission meeting <i>Review letter of intent, claims and determine whether there is need for new policy</i>
2	VCAG initial concept review (first review in VCAG meeting) <i>Provide advice on any needed data for disease programme policy-making, including safety, efficacy (entomological, epidemiological) and quality control</i>
3	Data generation step : LLIN efficacy against insecticide-resistant vector populations Data requirements: <ul style="list-style-type: none"> - laboratory and small-scale field trials testing <u>insecticide resistance</u> claims according to VCAG guidelines; - other defined product criteria reviewed (e.g. feasibility, manufacturing sustainability, etc.) - 2 cluster RCTs with epidemiological endpoints comparing a standard LLIN versus a new LLIN (non-pyrethroid active ingredient or pyrethroid plus new active ingredient pyrethroid), with entomological endpoints to include one season baseline and two seasons of follow up after the intervention
4	VCAG data review for insecticide resistance efficacy (final review in VCAG meeting) <i>Is the intervention efficacious against disease or infection in areas of vector insecticide resistance?</i> Decision point: VCAG (<u>DOES</u> or <u>DOES NOT</u>) recommend that WHO endorse claims of efficacy in areas of insecticide resistance.

Epidemiological outcomes must be assessed for several key reasons.

1. Only epidemiological outcomes provide sufficient evidence relevant to the actual public health benefit, which is of relevance to programmes and funders. A minimum of two epidemiological trials, conducted in settings with different ecological and vector diversity, covering two transmission seasons, are required to give a good degree of representation of seasonal and epidemiological variability to support generalization of findings. Vector control tools should be assessed according to the same criteria required for other public health products, such as medicines and vaccines.
2. Entomological measurements highlight the usefulness of the intervention in reducing mosquitoes. However, there is great variation in its measurements, which are often compounded by biased and insensitive entomological sampling tools and techniques.
3. Entomological proxies such as vectorial capacity and entomological inoculation rate are difficult to measure. There is no validated surrogate entomological marker or entomological correlate that accurately reflects the impact on disease.
4. Entomological indicators are not linearly associated with disease outcomes and, therefore, cannot be reliably used in many situations to predict epidemiological effect.
5. Epidemiological outcomes can be linked with economic data to allow estimation of cost–benefit or cost–effectiveness (e.g., cost per case of disease averted). However, this is not a primary assessment measure for VCAG since cost will differ between a trial prototype, a country situation and an established product for large-scale use.

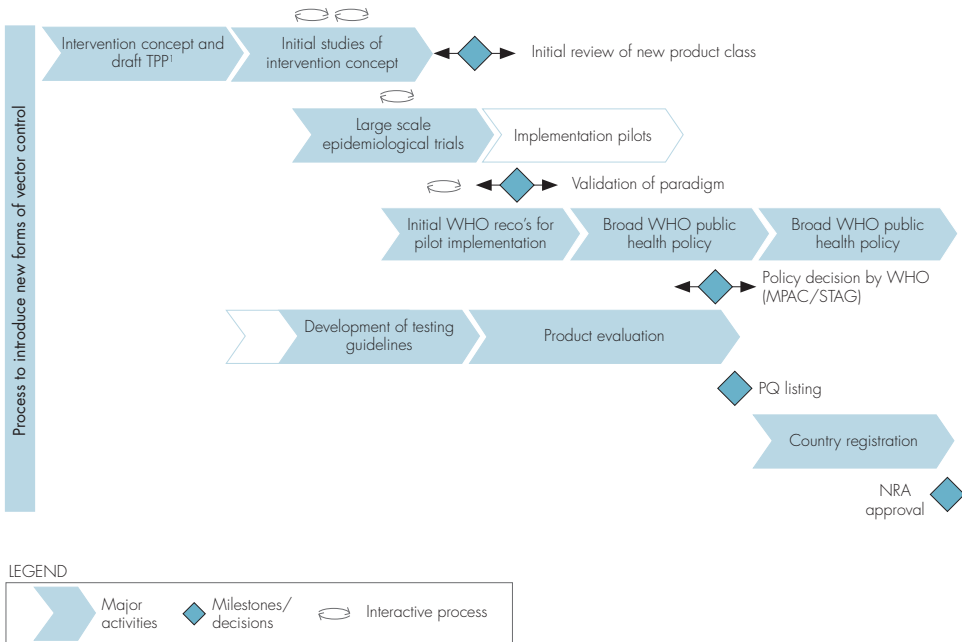
There are several examples of studies where entomological endpoints do not correspond to protection against clinical disease. For example, while studies of topical repellents show personal protection against biting by anopheline and other vectors, a meta-analysis of field trials (1) and a cluster randomized trial with epidemiological outcomes did not show any protection against clinical malaria due to issues of user compliance with the repellent (2). Similarly, a trial of long-lasting insecticidal nets (LLINs) deployed for use against visceral leishmaniasis reported a reduction in sandfly density in homes, but did not show any effect on infection in study participants, attributed to transmission occurring outside the home and/or poor compliance with the intervention (3,4).

For epidemiological evidence, a cluster randomized controlled trial (cluster RCT) is considered the gold standard to evaluate the efficacy of public health interventions because that study design provides the least biased, most robust estimate of intervention efficacy. For vector control tools, randomization is usually by cluster (village or community). RCTs should be adequately powered.

5. Additional anticipated policy steps

As described above, VCAG outcomes on the product claim assessment will feed into WHO policy-making processes at regular intervals. After VCAG endorses the efficacy claim, WHO disease-specific programmes with the support of expert advisory bodies will assess the potential of the intervention for deployment in vector-borne disease control programmes (Figure A5.5). Key milestones include: initial review of the new product class, validation of the product class, the policy decision by WHO, and product listing by WHO PQ. In most cases, NRA approval is needed before broad scale programmatic use of a new type of vector control tool. Global Policy Development (as shown in Figure A5) is undertaken by NTD/GMP, assisted by Technical Expert Groups or Advisory Groups (e.g. VCTEG) to assesses where and how interventions should be deployed and provide operational guidance. This feeds into the Policy Decision by WHO, advised by MPAC/STAG) where a policy statement is issued on the use of the new product claim to target vector-borne diseases.

Figure A5.5. General schematic for WHO policy and guidance setting for new forms of vector control



6. Conclusion

VCAG encourages the development of new and effective vector control tools and approaches in order to reduce the global burden of vector-borne diseases. Data requirements, therefore, must reconcile the urgent need for new tools to reduce disease burden and address biological threats (e.g. insecticide resistance and spread of *Aedes*-borne diseases) with the requirement for robust data to ensure safety, low environmental impact and appropriate use for maximum public health impact.

Review by VCAG will feed directly into the final assessment by the WHO Prequalification Programme process of any new product because the same data assessed by VCAG will be transferred and used for listing by the Programme. Considerable time and data generation efforts will be saved in the process if all steps are followed and requirements are adequately fulfilled.

Appendix 1. Glossary of terms

Chemical mode of action	The way a chemical acts on the target insect species; e.g. including biochemical pathway, binding site, etc.
Entomological mode of action	The mechanism by which the entomological effects of the intervention lead to impact on human disease or infection; i.e. killing of target vectors, repellency, reproductive inhibition, etc.
Epidemiological mode of action	The way in which a vector control intervention is proposed to achieve a health impact on the basis of its chemical and entomological mode of action; e.g. personal protection versus community protection.
First-in-line product	The first product or prototype representing a new product class.
Product class	In vector control, a category of intervention that shares a common entomological mechanism of action to reduce human infection or disease. It requires epidemiological evidence of efficacy as a proof of principle to confirm the product claim of reducing infection or disease.
Target product profile (TPP)	Every new product claim in an established product class should indicate under what condition(s) it is meant to be deployed and mention its benefits and risks, if any.
	A document that guides the product development process by outlining the target features and performance of the intended novel vector control tool. This will guide the portfolio of data that needs to be generated in order to review the product efficacy.
MPAC	Malaria Policy Advisory Committee; high-level policy advisory committees that assist WHO to develop policy for Malaria.
STAG	Strategic and Technical Advisory Group for Neglected Tropical Diseases; high-level policy advisory committees that assist WHO to develop policy for NTDs.

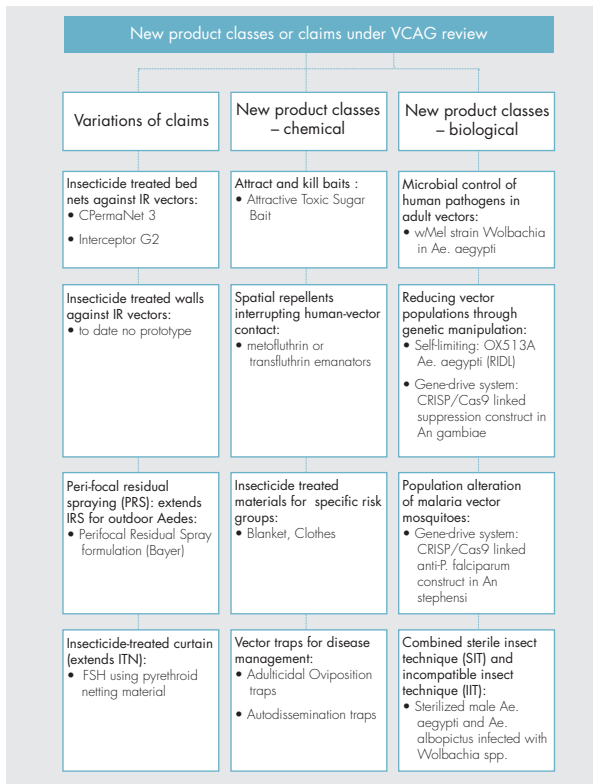
Appendix 2. Overview of vector control intervention types and product classes for vector control products (5–10)

Malaria vector control products assessed through revised evaluation process								
Intervention types	Insecticide-treated nets	Indoor residual spray products	Mosquito larvicides	Products providing personal protection	Space spray products	Aircraft disinsection products	Molluscicides	Rodenticide
Class	<p>Pyrethroid-only nets including LUNs:</p> <ul style="list-style-type: none"> • Covered by existing policy • Eligible for PQT assessment 	<p>OP, organochlorine, carbamate or pyrethroid formulations:</p> <ul style="list-style-type: none"> • Covered by existing policy • Eligible for PQT assessment 	<p>OP, benzoylurea, spinosyn, juvenile hormone analogs or with Btph1 gene or with Btph1:</p> <ul style="list-style-type: none"> • Covered by existing policy • Eligible for PQT assessment 	<p>Topical repellents for personal protection: Icaridin, DEET, IR3535:</p> <ul style="list-style-type: none"> • Covered by existing policy • Eligible for PQT assessment 	<p>Indoor space spray pyrethroid formulations, outdoor space spray with OP and pyrethroid formulations:</p> <ul style="list-style-type: none"> • Covered by existing policy • Eligible for PQT assessment 	<p>Pyrethroid-based AIs and products (e.g. cyphenothrin, IR permethrin):</p> <ul style="list-style-type: none"> • Covered by existing policy • Eligible for PQT assessment 	<p>Recommended single fast-acting compound (inclosamid), New similar products:</p> <ul style="list-style-type: none"> • Covered by existing policy • Eligible for PQT assessment 	<p>Anticoagulants and fast-acting products applied with or just after insecticides (or flea control) in outbreaks:</p> <ul style="list-style-type: none"> • Covered by existing policy • Eligible for PQT assessment
	<p>Pyrethroid plus synergist (PBO) nets:</p> <ul style="list-style-type: none"> • Covered by existing policy limiting deployment to pilot exploratory implementation • To be reviewed by ERG in June 2017 	<p>Fast-acting insecticide formulations:</p> <ul style="list-style-type: none"> • Covered by existing policy • Eligible for PQT assessment if comparative entomological effectiveness compared to the approved product classes can be demonstrated 	<p>Larvicide not meeting above classification:</p> <ul style="list-style-type: none"> • Not covered by existing policy • To be assessed by VCAG 	<p>Products designed for personal protection not meeting above classification:</p> <ul style="list-style-type: none"> • Not covered by existing policy • To be assessed by VCAG 	<p>Space spray products not meeting above classification:</p> <ul style="list-style-type: none"> • Not covered by existing policy • To be assessed by VCAG 	<p>Aircraft disinsection products not meeting above classification:</p> <ul style="list-style-type: none"> • Not covered by existing policy • To be assessed by VCAG 	<p>New molluscicide products not meeting above classification:</p> <ul style="list-style-type: none"> • Not covered by existing policy • To be assessed by VCAG 	<p>New rodenticide strategies (e.g. endectocides):</p> <ul style="list-style-type: none"> • Not covered by existing policy • To be assessed by VCAG
	<p>Non-pyrethroid insecticide nets:</p> <ul style="list-style-type: none"> • Not covered by existing policy • To be assessed by VCAG 	<p>Slowing insecticide formulations:</p> <ul style="list-style-type: none"> • Not covered by existing policy • To be assessed by VCAG 						
	<p>Nets containing IGR or sterilizing agent/s:</p> <ul style="list-style-type: none"> • Not covered by existing policy • To be assessed by VCAG 	<p>Formulations containing an IGR or sterilizing agent/s:</p> <ul style="list-style-type: none"> • Not covered by existing policy • To be assessed by VCAG 						

Abbreviations

ERG: Evidence Review Group
 IGR: Insect Growth Regulator
 OP: Organophosphate
 PQT: Prequalification Team
 VCAG: Vector Control Advisory Group

Appendix 3. New product classes or claims with no WHO policy recommendations currently under VCAG review



Appendix 4. Data requirements for VCAG submission on new product class

Parameter	Step 1 : Concept	Step 2 : Entomological Efficacy	Step 3: Epidemiological Efficacy
Entomology	Define the key measurements to indicate entomological impact according to mode of action. Consider any product failure risk analysis.	Laboratory, semi-field and small-scale field trials with proxy and progressively refined prototype products to show the basic parameters of the TPP can be achieved and will have the anticipated (entomological) impact.	No further demonstration for Step 3.
Epidemiology	Creation of a credible case for added impact in disease control by supplementing or replacing existing interventions. This may include simulation modelling based on expected entomological impact.	Plans for randomized controlled field trials to demonstrate the efficacy of a new approach with pathogen-specific outcomes. Consider the additional value of models for entomological correlates (if appropriate) as a proxy for epidemiological endpoints.	Randomized controlled field trials to demonstrate the efficacy of the product with pathogen specific outcomes. Consider level of compliance and coverage issues in relation to efficacy testing.
Economics	Estimate the expected cost of protection per person (at scale). Potential demand: is the impact worth the cost and effort?	Initial cost analysis of prototype or approach and comparison with sustainability model. Explore financing mechanism with key donors and purchasers.	Projection of cost per person protected and cost-efficacy of prototype in new category.
Technology development	Review technical feasibility of making a prototype. How will the prototype be applied?	Manufacturers and developers supply proxy or early prototype products. Manufacturers develop prototype products, ending in final product stage. Technical issues of feasibility are challenged at this stage.	Product is essentially mature, but may require minor changes to improve the method in response to trial outcomes.
Manufacturability sustainability	Initiate discussion with potential manufacturers to explore issues and opportunities. Solve, in principle, any intellectual property (IP) issues.	Business case for manufacturing. Advance on addressing IP issues.	Confirmation of commercial sustainability by manufacturer or producer. Early manufacturing or production runs at volume. IP issues resolved and commercial production possible.
User compliance and acceptability	Define target user groups and expected mode of application. Assess initial reactions to the product concept.	User reactions to the proxy or prototype products tested in detail; e.g. focus group studies.	Completion of studies of user acceptability and compliance.
Delivery and feasibility of implementation	Identify distribution routes, potential distributors, and issues to be resolved.	Identify, test and resolve issues for product delivery. Confirm distribution routes and distributors for the trial.	Demonstrate feasibility of implementation of intervention.
Regulatory, safety, ethical and environmental impact	Identify safety and environmental issues to be tested. Identification of new risk assessment models that may be required.	Identification of safety, environmental and ethical issues for testing. Risk assessment model developed, supporting data generated, and products assessed against model. Institutional review boards and process for review of protocols using human subjects.	Experimental registration of the product to allow trials. Check for adverse events during the trials. Plan product stewardship.
Target product profile (TPP)	A first draft of the TPP is created highlighting gaps and unknowns.	TPP evolves from draft to refined status.	TPP confirmed by trials noted above.
Policy or strategy	No requirements for Step 1.	Innovator should initiate VCAG communication and dialogue.	Engagement of national control programmes or institutes in the trials process. VCAG reviews trials outcomes and reports to MPAC and STAG. If applicable, WHOPEP starts work on category draft.

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The WHO Vector Control Advisory Group (VCAG) supports national and global efforts to control and eliminate vector-borne diseases worldwide by strengthening WHO's capacity to assess the public health efficacy of new vector control innovations and to develop appropriate technical recommendations. This report details the proceedings and outcomes of its fifth meeting, held in November 2016.

Vector Control Advisory Group (VCAG)
Vector Ecology and Management (VEM)
Department of Control of Neglected Tropical Diseases (NTD)
and
Vector Control Unit (VCU)
Global Malaria Programme (GMP)
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland