

# SIXTH MEETING OF THE VECTOR CONTROL ADVISORY GROUP

VCAAG



GENEVA, SWITZERLAND  
26–28 APRIL 2017



**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 Entomology and Vector Control of the Global Malaria Programme of the World Health Organization.

Design & Layout: Patrick Tissot WHO/HTM/NTD

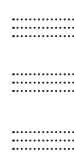
# SIXTH MEETING OF THE VECTOR CONTROL ADVISORY GROUP

VCAAG

GENEVA, SWITZERLAND  
26–28 APRIL 2017



**World Health  
Organization**



## © World Health Organization 2017

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; <https://creativecommons.org/licenses/by-nc-sa/3.0/igo>).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: "This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition".

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization.

**Suggested citation.** Sixth meeting of the Vector Control Advisory Group. Geneva, Switzerland, 26–28 April 2017. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO.

**Cataloguing-in-Publication (CIP) data.** CIP data are available at <http://apps.who.int/iris>.

**Sales, rights and licensing.** To purchase WHO publications, see <http://apps.who.int/bookorders>. To submit requests for commercial use and queries on rights and licensing, see <http://www.who.int/about/licensing>.

**Third-party materials.** If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

**General disclaimers.** The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

Please consult the WHO Neglected Tropical Diseases website for the most up-to-date version of all documents ([www.who.int/neglected\\_diseases/en](http://www.who.int/neglected_diseases/en))

Printed in France.

WHO/HTM/NTD/VEM/2017.05

## CONTENTS

|  |    |
|--|----|
| 1. SUMMARY -----   | 1  |
| 2. BACKGROUND -----  | 2  |
| 3. POLICY DEVELOPMENT FOR NEW PRODUCTS AND PRODUCT CLASSES<br>FOR CONTROL OF VECTOR-BORNE DISEASES ----- | 3  |
| 4. RECOMMENDATIONS FROM THE EXPERT ADVISORY GROUP<br>ON EPIDEMIOLOGICAL TRIAL DESIGNS -----              | 5  |
| 5. GUIDANCE FOR TESTING THE EFFICACY OF VECTOR CONTROL<br>PRODUCTS -----                                 | 7  |
| 5.1 Manual on epidemiological study design -----   | 7  |
| 5.2 Guidelines on efficacy testing of vector traps -----   | 7  |
| 6. CONCLUSIONS AND RECOMMENDATIONS ON NEW VECTOR<br>CONTROL PRODUCT CLASSES -----                        | 9  |
| 6.1 Yorkool LN G2.0 and G2.1 – initial assessment and guidance on<br>data generation -----               | 9  |
| 6.2 Interceptor G2 – update and guidance on data generation -----  | 9  |
| 6.3 wMel <i>Wolbachia</i> – update on randomized controlled trials<br>and pilot deployment -----         | 11 |
| 6.4 OX513A <i>Aedes aegypti</i> – update on randomized controlled trials<br>and pilot deployment -----   | 12 |
| 6.5 Spatial repellents – update on trial design and statistical<br>methodology -----                     | 12 |
| 7. DISCUSSION -----  | 15 |
| ANNEXES -----  | 16 |
| Annex 1. Agenda -----  | 16 |
| Annex 2. List of participants -----  | 18 |
| Annex 3. Declaration of interests -----  | 20 |



## 1. SUMMARY

The sixth meeting of the Vector Control Advisory Group (VCAG) was held at the headquarters of the World Health Organization (WHO) in Geneva, Switzerland on 26–28 April 2017. The objectives of the meeting were to review and provide guidance on potential new vector control tools for use in public health and to discuss the requirements for data and epidemiological study designs to demonstrate the epidemiological efficacy of new tools.

VCAG reviewed updates on progress in developing and assessing products in its portfolio (including Yorkool LN G2.0 and G2.1, Interceptor G2, Spatial Repellents, wMel *Wolbachia Aedes aegypti* and OX513A *Aedes aegypti*), two guidance documents (one on trial design, the other on vector traps) and the outcomes of a WHO Expert Advisory Group meeting on study design for vector control trials (Geneva, 24–25 April 2017).

### DECLARATIONS OF INTEREST

All the invited experts completed a declaration of interests form, which was submitted to and reviewed by the Secretariat before the meeting. A summary of any declared interests is given in *Annex 3*.

## 2. BACKGROUND

VCAG was established in 2012 as an independent advisory body to WHO to review and provide advice on the public health value of new tools and approaches for the prevention and control of vector-borne diseases. The role of VCAG is to:

- conduct an initial review of a new intervention concept and determine which data are required to (i) validate the product class, claim or variation, (ii) determine the public health value, (iii) support the formulation of a WHO policy recommendation;
- advise WHO and applicants on the process for generating the required data;
- assess the data for new vector control tools and approaches once it has been generated to determine whether the public health value of a new product has been demonstrated;
- develop or refine the target product profiles of new vector control classes; and
- provide recommendations to guide policy development.

The purpose of the meeting was to review and provide guidance to innovators on the data requirements for a number of technologies including new long-lasting insecticidal nets (LLINs) claiming efficacy against mosquitoes that are resistant to insecticides as well as several other well-advanced technologies in the VCAG portfolio. The group was briefed on: (i) an advanced draft of an information note on the revised process for evaluating vector control products; (ii) the conclusions of an expert advisory group meeting convened under VCAG on appropriate trial designs for epidemiological data generation (Geneva, 24–25 April 2017); and reviewed (iii) an advanced draft manual on epidemiological study design; and (iv) other guidance documents under development, including a draft manual on efficacy testing of vector traps for control of Aedes-borne diseases and guidance on the field testing of genetically modified mosquitoes with driving transgenes for malaria control.

The meeting was held in open and closed sessions. The open sessions were attended by stakeholders and observers. The closed sessions were restricted to VCAG experts and members of the WHO Secretariat. The meeting agenda is given in *Annex 1* and the list of participants in *Annex 2*.



### 3. POLICY DEVELOPMENT FOR NEW PRODUCTS AND PRODUCT CLASSES FOR CONTROL OF VECTOR-BORNE DISEASES

Vector control is a core public health intervention to reduce the global impact of vector-borne diseases. Countries need new and innovative vector control tools and strategies that address insecticide resistance, expanding vector-borne arboviral diseases, multiple disease settings and disease elimination contexts. Member States rely on WHO guidance for the best use and management of vector control tools, including which new products are safe and effective, and can meet specific needs of disease control programmes.

Recently, WHO has implemented several key reforms to improve guidance to Member countries on products for vector control, including streamlined processes for assessment and recommendation of vector control products under a new WHO Prequalification Team for Vector Control (PQT-VC), as well as a defined policy development pathway and expanded guidance for use and management of vector control tools under the disease technical units (VEM/NTD and EVC/GMP). Full details are available in the WHO Information Note published in 2017,<sup>1</sup> which outlines the key principles of the revised evaluation process for vector control products and current policy recommendations for malaria vector control interventions.

VCAG was briefed on recent policy documents including: (i) the revised process for evaluation of vector control products<sup>1</sup> and (ii) clarifications of existing WHO policy recommendations for vector control interventions.<sup>2</sup> These topics were broadly discussed in the plenary session.

The following topics were discussed during the open plenary sessions, and represent important points to clarify for applicants and other stakeholders.

- **The evidence required for indoor residual spraying (IRS) products and long-lasting insecticidal net (LLIN) products**

Although multiple insecticide classes with different chemical modes of action have been approved for use in IRS, LLINs for malaria control have only been approved for a single insecticide chemical class: pyrethroids. The effectiveness of LLINs is due to both personal protection from mosquito bites and community protection from killing mosquitoes that contact the nets. Additionally, insecticides on LLINs can have multiple impacts on vectors, including repellency, change of biting patterns or other behaviours, and effects on reproduction. How these multiple entomological effects contribute to epidemiological impact is as yet hard to quantify, and will likely differ between insecticide classes. Given the lack of a clearly established link between entomological effects and epidemiological impact for LLINs, the use of entomological correlates of protection to assess

<sup>1</sup> The evaluation process for vector control products. Geneva: World Health Organization; 2017 (WHO/HTM/GMP/2017.13, [www.who.int/malaria/publications/atoz/evaluation-process-vector-control-products/en/](http://www.who.int/malaria/publications/atoz/evaluation-process-vector-control-products/en/)).

<sup>2</sup> Malaria vector control policy recommendations and their applicability to product evaluation. Geneva: World Health Organization; 2017 (WHO/HTM/GMP/2017.12, [www.who.int/malaria/publications/atoz/vector-control-recommendations/en/](http://www.who.int/malaria/publications/atoz/vector-control-recommendations/en/)).

the “public health value” of new-generation LLNs is currently not accepted by WHO. Therefore, first-in-class LLN products are required to generate the epidemiological data needed for VCAG to assess their public health value. The WHO information note on malaria vector control policy recommendations should be consulted for further details.

- **The need for epidemiological evidence to demonstrate public health value of a new product class**

VCAG assesses the available evidence on products that are intended for public health use. New products with novel entomological effects may claim to kill mosquitoes, but when such products target disease vectors and are positioned for use in public health, there is an implied claim of their public health value, for example, in reducing human infection and/or disease. Entomological impact does not directly correlate with a reduction in transmission of pathogens, which determines public health value. Complex entomological parameters may impact disease in ways not captured through measuring vector mortality alone. New products with evidence of an entomological effect, therefore, will require epidemiological trials to assess the level of protection afforded against infection and/or disease and demonstrate the public health value of the tool, even if they are submitted for assessment under entomological claims alone.

**Box 1. Hierarchy of study designs used to evaluate the public health value of new vector control tools**

| Study designs recommended by WHO to assess the public health value of a new intervention or product   |                                     |
|---|-------------------------------------|
| Level 1. Randomized controlled trial: individual or cluster randomized  | Recommended                         |
| Level 2. Randomized controlled trial: step-wedge, cross-over, factorial design  | Recommended                         |
| Level 3. Non-randomized trial with control: before-and-after studies, cohort study, case-control study, cross-sectional study, time-series or interrupted time-series | Recommended on a case-by-case basis |
| Level 4. Trials without a control or using a historical control group: such as time series or interrupted time series without control group                           | Not recommended                     |

## 4. RECOMMENDATIONS FROM THE EXPERT ADVISORY GROUP ON EPIDEMIOLOGICAL TRIAL DESIGNS

Demonstrated evidence of protection against infection and/or disease, product safety and product quality is a prerequisite for WHO policy recommendations to Member countries for use of vector control products to control disease. The burden of evidence to support policy must, however, balance the requirement for robust data with the urgent need for new vector control tools. The WHO Global Malaria Programme (GMP) and Department of Control of Neglected Tropical Diseases (NTD) therefore convened an informal expert advisory group (EAG) on trial design (Geneva, 24–25 April, 2017) to consider trial designs that could be used to efficiently assess the epidemiological impact of new vector control tools, and to advise WHO on their relative value and appropriate use for policy-making.

Working from the draft manual on epidemiological trial design developed by VCAG and the draft framework to evaluate second generation LLINs prepared by the United States Centers for Disease Control and Prevention, the EAG experts discussed and made recommendations on acceptable trial designs (*Box 1*) and data end-points. They also considered relevant trial designs for specific categories of products, including non-pyrethroid LLINs that are currently under WHO evaluation and slow-acting IRS insecticides. The recommendations of the EAG on trial design are summarized below; full details are available from the meeting report.<sup>1</sup>

In brief, the following recommendations were made.

- **Consensus recommendations on the hierarchy of trial designs**  
Level 1 and level 2 study designs are the only designs that are acceptable to substantiate the public health value of new tools that do not fall within an already existing class and hence are not covered by a policy recommendation. Level 3 designs may be accepted in exceptional circumstances.
- **End-points for studies to demonstrate the public health value of new tools, strategies and approaches for vector control**  
Primary end-points for epidemiological efficacy (phase III) studies are, in order of priority, incidence of disease or infection, prevalence of infection, or a validated correlate (e.g. sero-conversion for viral infections).
- **Consensus statement on measurement of cost effectiveness**  
Collection of cost and cost-effectiveness data is encouraged during evaluation of vector control products, particularly through phase IV studies. Although VCAG will not draw on these data to assess the public health value of a product, costing data will be useful to inform formulation of policy recommendations and

---

<sup>1</sup> Design of epidemiological trials for vector control products: report of a WHO Expert Advisory Group. Geneva: World Health Organization; 2017 (WHO/HTM/NTD/VEM/2017.04, [http://www.who.int/neglected\\_diseases/vector\\_ecology/resources/WHO\\_HTM\\_NTD\\_VEM\\_2017.04/en/](http://www.who.int/neglected_diseases/vector_ecology/resources/WHO_HTM_NTD_VEM_2017.04/en/)).

programmatic guidance. It is also noted that initially costly interventions may benefit from economies of scale and become considerably more affordable once they are produced and deployed in large quantities.

- **Consensus recommendations on efficacy trials for non-pyrethroid LLINs**

For LLINs containing a non-pyrethroid active ingredient either alone or in combination with a pyrethroid, entomological data are not considered reliable predictors of epidemiological impact. Therefore, until a policy recommendation is made that covers these new types of products, epidemiological data will need to be generated for the “first in class” product for all new non-pyrethroid LLINs.<sup>1</sup> Claims of public health value for products designed to control insecticide-resistant vectors should be evaluated through the VCAG review process.

- **Consensus recommendations for IRS formulations with slow-acting insecticides and other tools that may require altered or new test approaches**

WHO policy can be expanded to cover a new IRS product for which entomological data are available to indicate effectiveness of the product when compared to a reference product covered by the existing WHO policy recommendation for IRS products.<sup>2</sup> Relevant data will be generated from proof of concept in the laboratory, experimental hut studies and large-scale field trials for the assessment of efficacy, residual activity and operational and community acceptance. A new IRS product for which data do not indicate similar entomological effect to IRS products currently covered by a WHO policy recommendation will be considered a new product class. Guidance on acceptable epidemiological study designs should be followed (*Box 1*).

VCAG reviewed and endorsed the conclusions of the expert advisory group summarized above, which will be reflected in the WHO manual on study design for vector control trials. The main intention of this manual is to inform decision-making on the design of epidemiological trials for assessment of public health value for new vector control tools.

---

<sup>1</sup> A generic risk assessment model for insecticide-treated nets (revised edition). Geneva: World Health Organization; 2012 (WHO/HTM/NTD/WHOPES/2012.3, Generic risk assessment model for LLINs [http://whqlibdoc.who.int/publications/2012/9789241503419\\_eng.pdf](http://whqlibdoc.who.int/publications/2012/9789241503419_eng.pdf)).

<sup>2</sup> Malaria vector control policy recommendations and their applicability to product evaluation. Geneva: World Health Organization; 2017 (WHO/HTM/GMP/2017.12, [www.who.int/malaria/publications/atoz/vector-control-recommendations/en/](http://www.who.int/malaria/publications/atoz/vector-control-recommendations/en/)).

## 5. GUIDANCE ON EFFICACY TESTING OF VECTOR CONTROL PRODUCTS

### 5.1 MANUAL ON EPIDEMIOLOGICAL STUDY DESIGN

WHO uses evidence from field efficacy studies to assess public health value and, if this can be validated, to make policy recommendations on vector control tools. Phase III epidemiological field trials measure the efficacy of vector control interventions against epidemiological outcomes and are critical in driving public health decision-making. If an intervention does not reduce infection, morbidity or mortality, it will not be recommended.

The purpose of this manual is to provide guidance on the design and conduct of phase III epidemiological field trials of new vector control interventions. First, the manual outlines general concepts on study design for efficacy trials, including different study design options. Secondly, it defines a framework of steps and considerations for designing and conducting a study including defining the research question, randomization and sample size calculations. The target audience for the manual is innovators and researchers from academic institutions and country programmes. It aims to promote rigorously designed vector control studies in order to generate the high-quality evidence required for decision-making on new interventions for vector control for use at a country level.

VCAG reviewed in detail the content of the draft manual in order to finalize the document. Additions and changes were noted by the drafting team (Anne Wilson and Steve Lindsay). Broadly, VCAG agreed with the content of the manual with minor additions and changes. The lack of an evidence base demonstrating efficacy of existing vector control interventions, especially for non-malaria tools, highlights the importance of bringing a culture of evidence-based decision-making to vector control.

The study design manual will be circulated for a final review and agreement by VCAG before publication.

### 5.2 GUIDELINES ON EFFICACY TESTING OF VECTOR TRAPS

The public health use of vector traps and accompanying baits and/or insecticides for disease management is under review by VCAG.<sup>1</sup> At present, traps and baits that are proposed for mosquito control are part of the VCAG portfolio, which are both proposed for mosquito control. These include adulticidal oviposition traps (AOT), which target gravid female *Aedes* spp. mosquitoes, and attractive toxic sugar baits (ATSB), which lure adult mosquitoes to a toxic bait. The aim of these traps is to reduce vector populations and correspondingly lower pathogen transmission. Several investigators have initiated trials to generate evidence of the community impact on infection and/or disease of vector traps and baits.

---

<sup>1</sup> Guidelines for testing new long-lasting insecticidal net products to substantiate efficacy claims in areas of high insecticide resistance. In: Third meeting of the Vector Control Advisory Group [Annex 3]. Geneva: World Health Organization; 2014 [WHO/HTM/NTD/VEM/2015.1, [http://apps.who.int/iris/bitstream/10665/162861/1/9789241508674\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/162861/1/9789241508674_eng.pdf)].

While the primary aim of current trap products is to protect humans from infection or disease, several existing and new vector traps are being developed and evaluated for the purpose of vector surveillance. The primary aim is either to detect and/or estimate the abundance of vectors in an area, but not to reduce their abundance. New vector trap designs, new baits for baited-traps and insecticidal products are being developed for both surveillance and control of disease vectors. Investigators and industry partners have requested that WHO develop guidelines on and describe methodologies for generating efficacy data in support of the use of existing and newly developed traps and baits for programmatic vector surveillance and control. The purpose of these guidelines is to provide specific, standardized procedures and criteria for efficacy testing and evaluation of vector traps, including testing procedures, outcome measures and impact indicators to generate evidence for vector trap efficacy.

VCAG reviewed the draft document for scope, target audience and structure of content, and discussed efficacy criteria, outcome measures and future steps in development. It was agreed that the primary scope of the first set of guidelines will be traps for control of *Aedes* spp. mosquitoes, based on traps currently in the VCAG portfolio. Because traps proposed in the future may target other vectors (e.g. *Anopheles*, *Culex*, *Phlebotomus* spp.), general guidance on expanding to other vectors should be included to capitalize on parallels in overall experimental design across different vector species. VCAG also agreed that while a guideline is needed for traps for surveillance, this should be developed as a separate document, because it will likely require different overall study designs.

It was agreed that a drafting committee should be formed to include members of VCAG and experts in the development of vector traps. This committee will constitute an expert advisory group as per the Operational Procedures of VCAG and include, at a minimum, two VCAG members (Sarah Moore and Heather Ferguson), experts on *Aedes* vectors and vector traps, and lead to the development of testing guidelines. Terms of reference will be developed for this advisory group by the VCAG secretariat, with the aim of finalizing guidance on efficacy testing at the next VCAG meeting (October 2017).

## 6. CONCLUSIONS AND RECOMMENDATIONS ON NEW VECTOR CONTROL PRODUCT CLASSES

### 6.1. YORKKOOOL LN G2.0 AND G2.1 – INITIAL ASSESSMENT AND GUIDANCE FOR DATA GENERATION

Representatives from Tianjin Yorkool International, China presented preliminary information on early stage products to VCAG. Products discussed represent first-in-class LLINs based on organophosphate insecticides, and are intended to be used for malaria control in areas of pyrethroid-resistant vectors. Because current WHO policy recommendations apply only to pyrethroid LLINs, this review was intended to clarify the data requirements for product evaluation, determination of public health value for this product and policy development.

#### 6.1.1 CONCLUSIONS

The innovators should clearly state any claims of efficacy for the first-in-class product. A full laboratory evaluation of the proposed products should be conducted by the manufacturers according to the WHO 2017 guidelines for laboratory and field-testing of long-lasting insecticidal nets.<sup>1</sup> This entails evaluation with well-characterized susceptible and pyrethroid-resistant strains of anopheline mosquitoes. The innovator was encouraged to share test protocols with VCAG before trials on this product commence in order to ensure that the trial will generate the data required by VCAG. The innovator was encouraged to proceed in a stepwise manner to generate efficacy data on this product, and to share full laboratory testing outcomes with VCAG before beginning experimental hut trials and epidemiological trials. Separate dossiers should be developed for each product submitted for review by VCAG.

Complete risk assessments, conducted according to the WHO risk assessment model for LLINs,<sup>2</sup> are required for each product, and should consider each active ingredient used in this net, alone and in combination. These risk assessments will be assessed by WHO and are a requirement for proceeding to larger scale testing of this product.

### 6.2. INTERCEPTOR G2 – UPDATE AND GUIDANCE ON DATA GENERATION

Interceptor® G2 is a LLIN containing alpha-cypermethrin and chlorfenapyr. Representatives from BASF SE, Germany provided additional sets of laboratory and field data to support the claim that Interceptor® G2 is effective in controlling insecticide-resistant mosquitoes. Laboratory results using tunnel tests showed that mortality and blood-feeding inhibition of Interceptor® G2 was higher than Interceptor LN against pyrethroid-resistant mosquitoes.

<sup>1</sup> New guidelines for LLINs are due for publication in 2017. Current guidelines on efficacy testing of LLINs can be found at: [www.who.int/iris/bitstream/10665/80270/1/9789241505277\\_eng.pdf](http://www.who.int/iris/bitstream/10665/80270/1/9789241505277_eng.pdf)

<sup>2</sup> A generic risk assessment model for insecticide-treated nets (revised edition). Geneva: World Health Organization; 2012 (WHO/HTM/NTD/WHOPES/2012.3, Generic risk assessment model for LLINs [http://whqlibdoc.who.int/publications/2012/9789241503419\\_eng.pdf](http://whqlibdoc.who.int/publications/2012/9789241503419_eng.pdf)).

Results from experimental hut studies showed that Interceptor® G2, in most settings, caused higher killing effect than Interceptor LN against pyrethroid-resistant mosquitoes but did not improve personal protection. The higher killing effect of Interceptor® G2 was maintained after 20 standard WHO washes. No evidence was provided supporting a higher impact of Interceptor® G2 against mosquitoes being resistant to other class of insecticides (e.g. carbamates, organophosphates, etc.).

## 6.2.1 CONCLUSIONS

VCAG considered that:

- Interceptor® G2 complies with the generic risk assessment model (WHO/JMPS) and is unlikely to pose undue hazards to human health when used as instructed.
- Interceptor® G2 is under assessment by WHO (WHOPES Phase II) as a pyrethroid-treated LLIN.
- Interceptor® G2 outperformed Interceptor LN (washed and unwashed) in terms of its killing effect against pyrethroid-resistant mosquitoes in laboratory and experimental hut studies.

The applicant should develop a concept note detailing plans for at least two epidemiological trials to generate data allowing assessment of public health value of this first-in-class product. The document should be shared with VCAG for review before its next meeting (October 2017), to allow provision of feedback prior to the development of a full proposal. The final dossier of results should be submitted for WHO assessment by 2023 at the latest. VCAG encourages the applicant to conduct longitudinal field testing to evaluate the efficacy and durability of Interceptor® G2 under user conditions following the 2017 WHOPES guidelines on efficacy testing of LLINs in parallel with epidemiological studies.

- Based on the data provided by the applicant showing the higher killing effect of Interceptor® G2 against pyrethroid-resistant mosquitoes, the applicant should either revise the claim that Interceptor® G2 controls “insecticide resistant mosquitoes” to “pyrethroid resistant mosquitoes” or provide more evidence to support the current claim of better efficacy against mosquitoes resistant to insecticide classes other than pyrethroids.
- The applicant should provide to VCAG a full dossier containing all laboratory and field study data specified in the VCAG guideline for testing efficacy of LLINs for use in areas of high insecticide resistance.<sup>1</sup> This should include information on vector species and including resistance ratios, number of replicates for bioassays and percentage improvements of efficacy.
- The applicant is encouraged to provide any other information relevant for deployment of Interceptor® G2, for example potential negative interactions occurring between chlorfenapyr and piperonyl butoxide.

---

<sup>1</sup> Guidelines for testing new long-lasting insecticidal net products to substantiate efficacy claims in areas of high insecticide resistance. In: Third meeting of the Vector Control Advisory Group [Annex 3]. Geneva: World Health Organization; 2014 (WHO/HTM/NTD/VEM/2015.1, [http://apps.who.int/iris/bitstream/10665/162861/1/9789241508674\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/162861/1/9789241508674_eng.pdf)).



## 6.3 wMEL WOLBACHIA – UPDATE ON RANDOMIZED CONTROLLED TRIALS AND PILOT DEPLOYMENT

Symbiotic wMel strain *Wolbachia* spp. bacteria introduced into *Ae. aegypti* populations have been shown in laboratory and field trials to induce a broad range of pathogen interference, including reducing the ability of infected mosquitoes to transmit dengue and Zika virus to humans. Results indicate that *Wolbachia* remains stable in mosquito populations (current monitoring > 6 years). The intervention aims to be community led, sustainable and cost effective.

Peter Ryan from the Eliminate Dengue Programme, Monash University, presented the current status of trials involving the large-scale release of wMel *Wolbachia* mosquitoes and their approaches for measuring the impact of wMel *Wolbachia* infected mosquito deployment on infection and disease. Large scale community trials and pilot implementations are under way in five countries, and plans are being made for pilot release in six additional countries during the next 12–18 months. The evidence generated should be considered as a global efficacy portfolio for this intervention.

Current field sites are located in Australia, Brazil, Colombia, Indonesia and Viet Nam; additional releases are planned in Mexico and the Pacific Islands. Epidemiological trials designs include assessing disease surveillance data before and after releases (all studies) and in release and non-release areas (all studies), enhanced case-finding and diagnosis (Brazil, Colombia, Indonesia), spatial-temporal clustering analysis (Australia, Brazil, Colombia), large-scale deployment with case-control study (Colombia) and a cluster randomized trial (Indonesia). A cluster randomized trial is under way in Yogyakarta, Indonesia to assess the effect of wMel *Wolbachia* mosquito release on dengue infection and/or disease; a second cluster randomized trial in Viet Nam is being considered and a step-wedge design is to be used for a pilot implementation in Colombia.

An Independent Evaluation Group (WHO and independent experts) will review the pilot deployment activities and results for the Brazil and Colombia trials when results are available. This was considered an important process for establishing policy for programmatic use of wMel *Wolbachia* infected *Ae. aegypti*. Good clinical practices are being followed for the randomized trial in Indonesia, including a governance structure to safeguard independent evaluation (Independent Data Monitoring Committee, Independent Monitoring Group, Data Analysis Working Group).

### 6.3.1 CONCLUSIONS

The committee noted the importance of the data and safety monitoring boards and independent trial evaluation measures, which give assurance that studies are being conducted in accordance with VCAG guidelines. Innovators are encouraged to publish trial protocols from Indonesia and Colombia, to share protocol documents with VCAG and to discuss how the group addressed some of the challenges faced in implementing its trials. In particular, information on the environmental variation (e.g. the impact of temperature on adult mosquito and egg mortality, *Wolbachia* and the virus-blocking phenotype); insights from integrating *Wolbachia* infected *Ae. aegypti* with other vector control interventions will be useful in making fully informed policy recommendations. Two points were noted for additional elaboration in the trials described. The primary consideration is the impact of human movement on the effect size and, secondarily, the density of *Ae. albopictus* in the study sites as a covariate in the analysis.

#### **6.4. OX513A Aedes Aegypti – UPDATE ON RANDOMIZED CONTROLLED TRIALS AND PILOT DEPLOYMENT)**

OX513A is a transgenic strain of *Ae. aegypti* engineered to carry a lethal repressible genetic system. Without antibiotic treatment, larvae carrying the OX513A gene construct develop normally, but die before they reach functional adulthood. The inclusion of a fluorescent marker gene into the genetic construct allows identification of transgenic mosquitoes (via fluorescent microscopy), including monitoring of released transgenic populations. This technology relies on the release of male mosquitoes only, which mate with wild *Ae. aegypti* females to suppress the population density of wild mosquitoes. The innovators described field trials in Brazil, Cayman Islands and Panama, which demonstrated the ability to reduce the *Ae. aegypti* populations in small-scale field trials, but there is currently no data on epidemiological impact of this approach. Regulatory risk assessments are under way for this product, and Oxitec has initiated a risk assessment with WHO. Updates were given on a new manufacturing facility in Brazil, and the current release strategies, which include development of an electronic platform to support adaptive decision-making for mosquito release and monitoring. Several epidemiological trials are in planning, and Oxitec is exploring funding options, trial designs and study partners for randomized controlled trials.

##### **6.4.1 CONCLUSIONS**

VCAG noted that the manufacturers are moving forward to plan randomized controlled trials with epidemiological outcomes to build evidence for routine programmatic use of OX513A *Aedes* against *Aedes*-borne diseases. Oxitec is encouraged to share their study design for review by VCAG, and is strongly encouraged to involve a specialist in trial design in the planning of their studies. Innovators are invited to publish trial protocols and share these with VCAG to address some of the challenges faced in implementing these trials. The VCAG noted that their mass production facility will be a benefit in manufacturing sustainability. Future transgenic lines described by the innovator are promising concepts, and data on these should be reviewed by VCAG when they are available.

#### **6.5. SPATIAL REPELLENTS – UPDATE ON TRIAL DESIGN AND STATISTICAL METHODOLOGY**

Spatial repellents interrupt human–vector contact through vector behaviour modification induced by airborne chemicals, potentially offering protection (personal and/or community) from bites from medically important vectors and nuisance pests. Proposed products include transfluthrin and metofluthrin passive emanators. This product class was initially reviewed by VCAG in November 2014. Epidemiological trials are currently under way in Indonesia and Peru to generate evidence of public health value against malaria and dengue, respectively. These trials represent a scale back from the original plan for epidemiological studies reviewed by WHO in 2014.

Key implications of the change in study design are that the protective efficacy for each disease can now be addressed in only one setting and the required product coverage can be addressed only in a limited fashion, resulting in unfortunate knowledge gaps. Further, the questions of whether a diversion effect will be shown, how efficacy varies with geography and vector bionomics, and how current pyrethroid repellents are affected by pyrethroid resistance in vector populations will not be answered by the current studies.

Guidance was sought from VCAG on the outcomes and further steps following completion of the trials in Indonesia and Peru.

### 6.5.1 CONCLUSIONS

#### **On demonstration of protective efficacy against malaria in a single trial**

Demonstrating protective efficacy in a single site is at present not considered to be sufficient for a VCAG recommendation on the public health value of any new product class. Therefore, if the Indonesia trial on spatial repellents demonstrates protective efficacy, this alone will not be sufficient for a full policy recommendation from VCAG to WHO. Recommendations for pilot implementation have only been endorsed in public health emergencies for selected vector control tools and therefore this would not cover spatial repellents currently.

If the investigators maintain a broad claim of protective efficacy of spatial repellents to reduce and prevent malaria infection and disease, at least one additional trial would be required with epidemiological outcomes in a different and complementary ecological setting outside of Asia, the priority being sub-Saharan Africa. The committee recognizes that this intervention is likely to be particularly sensitive to local vector behaviour and ecology; thus it is essential to test this intervention in a variety of settings.

However, if the first trial targeting malaria demonstrates protective efficacy, this committee would consider making a recommendation for a geographically restricted area, if (i) the claim was narrowed to reflect this and (ii) a further trial showing public health value in this setting was done. The narrowed claim could be specific to Indonesia, or a larger geographical area in South-East Asia with similar ecological and entomological characteristics. It should be noted that a single species complex was targeted within this trial that is not representative of all South-East Asian malaria vectors, and this should be reflected in any revised claim. A second trial could be an effectiveness trial in a programmatic context provided that the evaluation is robust, including randomization.

In both cases (broad or narrowed claim), the subsequent trial(s) should address the questions of diversion versus community-wide protection, and should entail replication in a different geographical area with different vector behaviour, ecology and insecticide resistance status. In either case in addition to public health, entomological outcomes should be assessed. Where possible, the choice of the second trial site should also allow the question of efficacy against insecticide resistant vectors to be addressed. Entomological studies in further settings are also likely to be needed to determine where the intervention is applicable before a general recommendation can be made.

### **New spatial repellents within the proposed new product class**

Data generated from ongoing trials on an existing product may be relevant to making a recommendation for a future product in the same product class. To support this, evidence of the new product's entomological equivalence or superiority in preventing human-vector contact for a relevant vector species would be required. Product information can include the nature of differences between the first-in-line and new product, including design, chemistry and any existing comparative efficacy data from laboratory and other entomological studies from the manufacturer. Entomological efficacy data can be generated according to published guidelines on the efficacy testing of spatial repellents.<sup>1</sup> Any epidemiological trials that use a new product would need to demonstrate equivalent or superior entomological efficacy compared with the previous product.

### **Dengue trial recommendations**

While the investigator did not specifically ask for feedback on the ongoing trials in Peru for dengue, VCAG would require a second trial with the new product to meet the VCAG requirements of two trials in different settings. The subsequent trial should entail replication in a different geographical area with different vector behaviour and ecology, and insecticide resistance status. The applicants are encouraged to share their study design with VCAG and to discuss how the group addressed some of the challenges faced in implementing these studies.

---

<sup>1</sup> Guidelines for efficacy testing of spatial repellents. Geneva: World Health Organization; 2013 ([http://apps.who.int/iris/bitstream/10665/78142/1/9789241505024\\_eng.pdf](http://apps.who.int/iris/bitstream/10665/78142/1/9789241505024_eng.pdf)).

## 7. DISCUSSION

The conclusions of VCAG are included in the summaries of the meeting sessions described above. The wording of recommendations was finalized during the closed sessions and, in some cases, following the meeting. Any conclusions of relevance to WHO policy-making will be presented to NTD and GMP, for further discussion with their policy advisory bodies, the Strategic and Technical Advisory Group (STAG) and Malaria Policy Advisory Committee (MPAC), respectively.

Moving forward, templates are needed to guide manufacturers on the purpose of discussions with VCAG and what information they will need to provide for review of their product. Manufacturers should provide information to VCAG one month in advance of meetings to allow preparation for thorough review at the meeting. Building and maintaining trust between applicants and members of the advisory group is critical. Stakeholders are encouraged to attend open sessions of VCAG meetings; however, sufficient time must be devoted to closed sessions in order to protect the independence of the expert group.

VCAG meetings will occur biannually, typically in March and October. Timing will be coordinated with MPAC and STAG meetings, to allow timely review of VCAG conclusions by higher level policy advisory bodies.

## ANNEXES

## ANNEX 1. AGENDA

| Wednesday 26 April 2017 – OPEN MEETING: Full day |  |
|--|--|
| 09:00–09:10                                      | Opening remarks and welcome (Dirk Engels and Pedro Alonso)   |
| 09:10–09:20                                      | Administrative remarks, Declarations of interest, Appointment of Chair/Rapporteurs (Tom Scott, Chair VCAG)   |
| 09:20–09:40                                      | Overview VCAG (VCAG Secretariat) <ul style="list-style-type: none"> <li>• purpose, functions and role in WHO policy-setting</li> <li>• terms of reference, priorities and decision-making, confidentiality</li> <li>• meeting objectives and expected outcomes</li> </ul>  |
| 09:40–10:30                                      | Updates/briefings on relevant policy issues (for information) <ul style="list-style-type: none"> <li>• Global vector control response: scope, content and status; briefing on relevant STAG outcomes (Raman Velayudhan)</li> <li>• MPAC/VCTEG meeting and outcomes relevant to malaria vector control (Jan Kolaczinski)</li> </ul> |
| 11:00–12:00                                      | Overview of (i) Pathway for evaluation of vector control products (Raman Velayudhan) and (ii) WHO policy recommendations for malaria vector control interventions (Jan Kolaczinski); followed by discussion  |
| 11:30–12:30                                      | Detailed review of study design manual and section-by-section comments (Steve Lindsay/Anne Wilson)   |
| 13:30–17:00                                      | Detailed review of study design manual and section-by-section comments (continued) (Steve Lindsay/Anne Wilson)<br>Discussion and decisions   |

| Thursday 27 November 2017 – OPEN MEETING 09:00–12:30; CLOSED MEETING 13:30–18:00 (relevant applicants and VCAG only) |   |
|--|---|
| 09:00–10:30  | Discussion on outcomes of trial designs' meeting (for input) (Thomas Scott)   |
| 11:00–11:45  | Upcoming guidelines 1: Vector traps (Anna Drexler) <ul style="list-style-type: none"> <li>• Agree on scope, target audience and structure of content</li> <li>• Discuss traps for surveillance</li> </ul>   |
| 11:45–12:30  | Upcoming guidelines 2: Initiating update to WHO handbook on GMMs (Karen Tountas) <ul style="list-style-type: none"> <li>• FNIH workshop outcomes on efficacy trial considerations for GMMs with driving transgenes and updating WHO handbook (Karen Tountas)</li> </ul>   |
| 13:30–18:00  | Applicant presentations and discussions in plenary with VCAG, including innovator updates on status of tools in portfolio (45 min discussion with each applicant) <ul style="list-style-type: none"> <li>• 14:15–15:30 Interceptor G2 – update and guidance on data generation (Susanne Stutz and Egon Weinmuller, BASF)</li> <li>• 16:00–16:45 wMel <i>Wolbachia</i> RCT and pilot deployment (Peter Ryan, Eliminate Dengue, Monash University)</li> <li>• 16:45–17:15 OX513A <i>Aedes aegypti</i> RCT and pilot deployment (Hadyn Perry and Simon Warner, Oxitec)</li> <li>• 17:15–18:00 Spatial repellent trial design update and statistical methodology (Nicole Achee, Eck Institute for Global Health)</li> </ul> |

| Friday 28 April 2017 – CLOSED MEETING: All day |  |
|--|--|
| 09:00–12:30                                    | Finalization of VCAG recommendations in working groups |
| 13:30–15:30                                    | Finalization of the report and recommendations         |
| 16:00–17:30                                    | General discussion. Closure of the meeting             |

## ANNEX 2. LIST OF PARTICIPANTS

### Members of the Expert Advisory Group

**Thomas Scott (Chair)**, University of California, United States of America

**Professor Immo Kleinschmidt**, London School of Hygiene and Tropical Medicine, London, United Kingdom

**Professor Steven Lindsay**, Durham University, Durham, United Kingdom

**Professor Hassan Vatandoost**, School of Public Health, Tehran, Islamic Republic of Iran

**Professor Heather Ferguson (nominee for new membership)**, University of Glasgow, United Kingdom

### Ad-hoc experts to the meeting

**Vincent Corbel**, Institut de Recherche pour le Développement (IRD), France

**Sarah Moore**, Ifakara Health Institute, United Republic of Tanzania

**Thomas Smith**, Swiss Tropical Institute, Switzerland

### Invited participants

**Anne Wilson** (rapporteur), Durham University, United Kingdom

**Karen Tountas**, Foundation for the National Institutes of Health, United States of America

### Manufacturer/product developer representatives

Eck Institute for Global Health, United States of America – Nicole Achee (via conference call)

Tianjin Yorkool International, China – Bill Li and Yi Qing

Oxitec LTD, United Kingdom – Hadyn Parry, Simon Warner, Geoff Turner

Eliminate Dengue, Monash University, Australia – Peter Ryan

BASF SE, Germany – Susanne Stutz, Egon Weinmüller

### Observers

Bill & Melinda Gates Foundation, United States of America – Dan Strickman

Innovative Vector Control Consortium, United Kingdom – Tom McLean



**WHO Secretariat**

Global Malaria Programme (GMP):

**Jan Kolaczinski**, Coordinator, Entomology & Vector Control

**Emmanuel Temu**, Entomology & Vector Control

Department of Control of Neglected Tropical Diseases (NTD):

**Raman Velayudhan**, Coordinator, Vector Ecology & Management

**Rajpal Yadav**, Scientist, Vector Ecology & Management

**Anna Drexler**, Technical Officer, Vector Ecology & Management

Regulation of Medicines and other Health Technologies

**Deusdedit Mubangizi**, Prequalification Team

**Dominic Schuler**, Prequalification Team

### ANNEX 3. DECLARATION OF INTERESTS

All VCAG and invited experts completed the Declaration of interests form for WHO experts prior to the Meeting for assessment by the WHO Secretariat. The following interests were declared:

Dr Thomas Scott receives / received institutional research support from major US national funding organizations and donors, which were assessed as insignificant or minimal for this meeting. However, due to his involvement in the evaluation Spatial Repellents, Dr Scott did not participate in the drafting and finalisation of the recommendations on this topic.

All other interests declared were assessed as insignificant or minimal for this meeting as they were unrelated or only tangentially related to the subject of the activity or work and its outcome.



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 sixth meeting, held in April 2017.

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