Ninth meeting of the WHO Vector Control Advisory Group
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BACKGROUND

The WHO Vector Control Advisory Group (VCAG) serves as an advisory body to WHO on new tools, technologies and approaches – collectively referred to as “interventions” – for the control of vectors of malaria, dengue and other vector-borne diseases. VCAG is managed by the WHO Global Malaria Programme (GMP), the WHO Department of Control of Neglected Tropical Diseases (NTD), and the WHO Prequalification Team (PQT) for vector control products. To assist WHO in developing public health policy, VCAG assesses new interventions and provides guidance on developing the evidence needed for public health value assessment and policy. VCAG assesses this evidence once it is generated and provides recommendations to WHO on the public health value of new tools.

As of November 2018, VCAG is reviewing 18 new interventions, spanning a range of innovative technologies from new insecticide combinations for insecticide-treated nets (ITNs) to modified, transgenic or sterile mosquitoes to suppress or replace wild populations. Highlights include:

- six new intervention classes for malaria comprised of 11 tools1 including five new ITNs; and
- seven new intervention classes for NTDs comprised of six tools for Aedes-borne diseases and two for leishmaniasis control;
- For 12 tools, innovators have moved to the stage of either planning or already conducting epidemiological trials to generate evidence to assess their public health value.2

VCAG experts, innovators and other stakeholders convened in Geneva on 12–14 November 2018 for the 9th VCAG meeting. Eight VCAG members were joined by six ad hoc experts, five of whom attended in person and one by phone. The open session was attended by members of VCAG, applicants and product developers, WHO staff from GMP, NTD and PQT, and other stakeholders, including representatives of donor and procurement agencies. A WebEx link was provided so participants could also join the open session remotely. The closed meeting was attended by VCAG members and ad hoc experts, the WHO Secretariat and the relevant parties only. The participants are listed in Annex 1.

VCAG functions

VCAG has the following specific functions:

1. To provide guidance to product developers, through WHO, on data requirements and study designs to enable assessment of the public health value of new vector control tools, technologies and approaches.

2. To assess the public health value of new vector control tools, technologies and approaches submitted to WHO.

3. To provide advice to WHO, for submission to the Malaria Policy Advisory Committee (MPAC) and the Strategic and Technical Advisory Group for neglected tropical diseases (STAG), on the public health value of new tools, technologies and approaches.
Dr Mwelecele Malecela, NTD Director, Dr Pedro Alonso, GMP Director and Dr Suzanne Hill, Director, WHO Essential Medicines and Health Products, welcomed VCAG members to Geneva and wished them successful deliberations.

Dr Alonso noted the importance of VCAG’s role in assisting with policy development for new malaria vector control options and highlighted the outcomes of the GMP policy review process supported by the Boston Consulting Group. The review of GMP policy development processes had identified that the pathway for vector control products, which VCAG is part of, should serve as a model for overall policy development for malaria interventions within GMP. Speaking on the ongoing transition in VCAG membership, Dr Alonso announced the appointments of Professor Heather Ferguson as the Vice-Chair of VCAG, commencing immediately, and Dr Salim Abdulla as the new incoming Chair of VCAG, to be formalized following the 9th VCAG meeting in accordance with the revised Terms of Reference. Dr Alonso noted the hard work, time and valuable contributions of Dr Thomas Scott in chairing the VCAG for the past three years and thanked him as the outgoing chair on behalf of WHO.

Dr Alonso updated the participants on the process to recruit new VCAG members. Members will be selected and appointed by the WHO Assistant Director-General for Communicable Diseases, upon the advice of the Director GMP and the Director NTD. In selecting members, consideration will be given to attaining an adequate distribution of technical expertise, geographical representation and gender balance.

Dr Malecela discussed the importance of vector control in overcoming NTDs, nearly half of which are vector borne, resulting in 600 million cases annually. Existing vector control tools must be used to their full potential and new vector control options are urgently needed in the context of growing insecticide resistance, expanding urbanization, globalization and climate change. Many new tools on the horizon include NTDs as a target disease, including sterile and Wolbachia-infected Aedes mosquitoes, vector traps, spatial repellents, genetically modified mosquitoes and systemic cattle treatments for leishmaniasis control. The work of this advisory body is crucial for guiding new approaches in vector control. VCAG outcomes play a key role in setting WHO policy, thereby supporting NTD and GMP in determining whether specific new interventions should be added to the range of interventions available to vector-borne disease control programmes.

Dr Hill noted the importance of vector control in public health and the value that WHO places on this issue, as reflected in the joint dedication of the three departments – GMP, NTD and PQT – to this work. WHO is undertaking a process of transformation, including product evaluation, which has involved reviewing processes and procedures for policy-making with the aim of identifying best product evaluation practices to support access to safe, efficacious and high-quality public health interventions.

All the invited experts were required to declare any conflicts of interest before the meeting started. The assessed declarations of interest were read out to the meeting by Alma Alic, Ethics Officer, WHO Compliance, Risk Management and Ethics. The declarations of interest are stated in Annex 2.
Progress updates

Summary of discussions

The Chair, Dr Thomas Scott, provided an update on the work of VCAG, including its role and placement within the WHO evaluation pathway for vector control products. He described the newly established process of “off-cycle reviews” whereby VCAG applicants submit requests for review and relevant supporting materials outside of the regular meeting schedule. Requests are then addressed by VCAG members electronically, through teleconferences and/or email. When an applicant requests an urgent review and the next face-to-face VCAG meeting is scheduled more than three months from the request, WHO will facilitate such a review by VCAG members in due course. In addition, an overview of product classes and prototypes/products under VCAG review for assessment of public health value, and Standard Operating Procedures for VCAG Applicants have been published on the VCAG website.

Dr Raman Velayudhan, NTD Vector Ecology and Management (VEM) Coordinator, briefed the open session on the outcomes of the STAG meeting (Geneva, 26–27 April 2018). In the past, insecticides recommended for use in malaria interventions have been recommended for use also against vector-borne NTDs. STAG encouraged the generation of evidence to support claims of efficacy against vector-borne NTDs, including demonstrating the impact on reducing vectors and showing non-inferiority to current best practice measures for vector control in comparative studies.

Dr Jan Kolaczinski, GMP Entomology and Vector Control (EVC) Coordinator, summarized the main developments from the EVC team:

- The Guidelines on malaria vector control are scheduled for publication in the near future.

- A meeting of the Evidence Review Group (ERG) on determining non-inferiority of ITNs and indoor residual spraying products within an established class was held on 5–6 July 2018. The meeting report and a study protocol for non-inferiority trial designs will be published online for public consultation, and input from mosquito net manufacturers actively solicited. A subsequent ERG will be planned to determine whether the proposed non-inferiority approach can be used to extend policy recommendations to second in class products once further data are available.

- An ERG to assess malariogenic potential was held on 3–5 September 2018. This group focused on metrics of malariogenic potential to inform elimination strategies and prevent re-establishment of transmission.

- A District Health Information System (DHIS) 2 module for collection and visualization of malaria vector insecticide resistance data has been developed in 2018 and will be piloted in 2019, with a view to expanding the module to support data collection on other key malaria vector control indicators.

Dominic Schuler, Technical Officer, PQT Vector Control (PQT-VC), summarized the activities of PQT-VC to support assessment of safe, efficacious and high-quality products. Major achievements include:

- Products recommended by the WHO Pesticide Evaluation Scheme (WHOPES) have been included on the WHO List of Prequalified Vector Control Products managed by PQT-VC. Associated guidance on prequalification is published at http://www.who.int/pq-vector-control/en/.
• The PQT-VC team has now recruited necessary staff to support its functions.

• The Vector Control Product Assessment Group met from 28 May to 1 June 2018 to evaluate seven new submissions.

• Plans to re-evaluate priority active ingredients for which new information on safety, efficacy or quality indicates there is the need; one re-evaluation has been initiated.

• The product review of piperonyl butoxide (PBO) pyrethroid nets has been initiated.

• Manufacturing facility inspections in India, Pakistan and the United Republic of Tanzania; 16 inspections have been conducted to date.

• As of June 2018, PQT-VC is the designated WHO secretariat for the FAO/WHO Joint Meeting on Pesticide Specifications (JMPS).

Update on PBO net study in the United Republic of Tanzania

Summary of discussions
Dr Natacha Protopopoff led the update to VCAG on the third-year results from a cluster-randomized trial testing the efficacy of the pyrethroid-PBO net Olyset Plus for control of malaria transmitted by pyrethroid-resistant mosquitoes in north-western Tanzania. The trial is designed as a four-arm cluster-randomized factorial design with 12 clusters per arm. It aims to answer the following questions: (i) Does the combined use of indoor residual spraying (IRS) with pirimiphos-methyl and standard pyrethroid only long-lasting insecticidal nets (LLINs) provide more transmission control than nets alone when net usage is high? (ii) Are pyrethroid-PBO nets more protective than pyrethroid-only LLINs against insecticide-resistant vectors? (iii) Is the combined use of pyrethroid-PBO nets and pirimiphos-methyl IRS more protective than pyrethroid-PBO nets alone, given the potential for PBO to inhibit the metabolic activation of pirimiphos-methyl? Preliminary results were presented from year three on malaria prevalence, anaemia and Anopheles density. Further steps include: (i) assessing net durability and active ingredient persistence for pyrethroid-PBO nets using cone and tunnel bioassays on wild, resistant Anopheles mosquitoes and standard laboratory strains of resistant and susceptible mosquitoes; (ii) finalizing the analyses of data on durability, bioefficacy and cost effectiveness; and (iii) comparing outputs from the current trials with transmission models in development.

Recommendation
• The term ITN rather than LLIN should be used in connection with pyrethroid-PBO nets to align with current WHO terminology, since a long-lasting effect for these nets in line with WHO-set thresholds has not yet been demonstrated.

• To better understand why the study net usage declined over time and whether this is related to the acceptability of the intervention, investigators should assess where deployment of new pyrethroid-only nets occurred in relation to where trial nets were distributed in the study sites. For future trials, strengthening the social/behavioural components may help improve adherence to the intervention being tested during the study.

• VCAG supports the research team in its plans to conduct further testing of net samples using resistant anopheline mosquito strains to maximize the information gained on the residual activity of PBO-pyrethroid in ageing nets as they start to deteriorate with time and continued use.
Update on PBO net study in Uganda

Summary of discussions
Dr Samuel Gonahasa, Infectious Diseases Research Collaboration (IDRC), and Professor Janet Hemingway, Liverpool School of Tropical Medicine (LSTM), presented a cluster-randomized trial being conducted to measure the impact of ITNs with and without PBO on malaria indicators in Uganda. The aim of the study is to determine whether parasite prevalence is lower in intervention clusters (health sub-districts [HSDs] randomized to receive PBO nets) than in control clusters (HSDs randomized to conventional nets) in eastern and western Uganda. The study is expected to run from January 2017 to December 2019.

The study is being carried out in collaboration with the Ministry of Health (MOH) of Uganda. The MOH, working through the Ugandan National Malaria Control Programme and other stakeholders, delivered the intervention through a routine ITN distribution campaign in 2017–2018. The research team designed the study, including randomization, and will conduct the evaluation.

Conclusion
• VCAG noted the innovative study design, which integrates estimating the impact of the nets with routine distribution by the National Malaria Control Programme. Close partnership with the MOH facilitated implementation of this trial.

Recommendations
• The investigators are encouraged to publish the trial design including lessons learnt from its implementation.
• The investigators are strongly encouraged to conduct bioassays, including synergist bioassays. If resources are available, collections of host-seeking mosquitoes in addition to resting collections would be valuable to estimate direct entomological indicators of transmission including vector density, infection rates, outdoor vs indoor biting rates and the entomological inoculation rate.
• The duration of epidemiological assessment, excluding the baseline period, should cover at least two years, to account for inter-annual variation in transmission.9
• VCAG requests to review the analytical protocol and the statistical analysis plan.

Completed and planned systematic reviews for vector control products

Summary of discussions
Professor Paul Garner, LSTM, explained the value of systematic reviews, synthesis of the evidence and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system for assessing the certainty of evidence in reviews, and for formulating evidence-based recommendations. This approach is used by WHO to develop recommendations and guidelines. Professor Garner shared a summary of systematic reviews for malaria that have been carried out, are planned or ongoing (see Table 1), and discussed the lessons learnt. These systematic reviews have informed the development of the Guidelines for Malaria Vector Control and have helped to identify gaps in research.
TABLE 1.
Summary of systematic reviews for malaria conducted, planned or ongoing

<table>
<thead>
<tr>
<th>STATUS</th>
<th>REVIEW</th>
<th>PUBLISHED</th>
<th>TRIALS INCLUDED</th>
</tr>
</thead>
<tbody>
<tr>
<td>Update</td>
<td>Larvivorous fish to prevent malaria transmission</td>
<td>December 2017</td>
<td>No studies in main analysis; 15 studies examining fish and larvae/pupae</td>
</tr>
<tr>
<td>New</td>
<td>Mosquito repellents to prevent malaria</td>
<td>February 2018</td>
<td>10 RCTs; topical repellents, insecticide-treated clothing, spatial repellents</td>
</tr>
<tr>
<td>New</td>
<td>Insecticide space spraying to prevent malaria</td>
<td>November 2018</td>
<td>Two interrupted time series from India</td>
</tr>
<tr>
<td>Update</td>
<td>ITNs to prevent malaria</td>
<td>November 2018</td>
<td>23 trials</td>
</tr>
<tr>
<td>New</td>
<td>PBO + pyrethroid vs pyrethroid to prevent malaria</td>
<td>November 2018</td>
<td>15 trials including 5 cluster-RCT field trials</td>
</tr>
<tr>
<td>New</td>
<td>Combined IRS and ITNs vs ITNs alone to prevent malaria</td>
<td>March 2019 (intended)</td>
<td>Six cluster-RCTs</td>
</tr>
<tr>
<td>New</td>
<td>Larviciding to control malaria</td>
<td>March 2019 (estimate)</td>
<td>One cluster-RCT, two controlled before and after studies, one crossover trial</td>
</tr>
<tr>
<td>New</td>
<td>IRS to control malaria</td>
<td>Protocol being finalized</td>
<td>Quasi-experimental designs will be included in update</td>
</tr>
<tr>
<td>New</td>
<td>Housing improvements to prevent malaria</td>
<td>Protocol being written</td>
<td>Quasi-experimental designs will be included</td>
</tr>
</tbody>
</table>

IRS, indoor residual spraying; ITN, insecticide-treated net; PBO, piperonyl butoxide; RCT, randomized control trial

Conclusion

- VCAG noted that researchers embarking on conducting epidemiological trials for products under review by WHO should seek confirmation that the trial design is sufficiently robust to generate reliable data as required to meet the inclusion criteria for rigorous and reliable systematic reviews. Such requirements are also necessary to contribute to the development/revision of WHO guidelines. Early engagement with WHO for feedback on planned trials is encouraged to seek such clarification.

Update on the policy review process in GMP

Summary of discussions

Dr Alonso presented the findings from the GMP Policy Making and Dissemination Process Review. The review findings are based on interviews with more than 80 people, including academics, donors, innovators, manufacturers, regulatory authorities, procurers, country programme managers and WHO national programme officers, among others.

The GMP review found that:

- policy-making and policy dissemination in GMP have dramatically improved since the introduction of MPAC;
• GMP brings unique value to countries;

• there are three main areas for change: (i) the process for developing guidance is perceived as lengthy; (ii) recommendations are perceived as inconsistent; and (iii) suboptimal use of GMP outputs at country level;

• seven areas were identified for actions to improve the policy-making process, as described in the GMP Policy Review update.\textsuperscript{10}

In addition to the interviews, a survey of WHO Member States was conducted that had 96 respondents. The aim of the survey was to confirm the diagnosis of the key strengths and challenges of GMP policy-making and dissemination processes, and to inform options on how to improve policy uptake at country level. Three ways to improve dissemination emerged from the survey: (i) improve structure of documents, (ii) improve GMP website, and (iii) develop new opportunities to exchange information and best practices within the network. Dr Alonso added that the review process also found that the evaluation process for vector control products was viewed as a good model to inform the development of policy for other malaria control interventions.

**VCAG DELIBERATIONS – CLOSED SESSION**

**Policy updates**

**Summary of discussions**

Dr Anna Drexler, VEM Technical Officer, reviewed the full VCAG portfolio and discussed supporting normative and policy activities in departments related to VCAG work. Activities include the development of guidance and standard operating procedures for non-inferiority of ITNs, publication of a guidance document on efficacy testing of vector traps,\textsuperscript{11} the development of impact assessment frameworks for sterile insect and genetically modified technologies, and operational guidance frameworks for *Wolbachia*-based population alteration and sterile insect technique for *Aedes*.

The current policy development process is a balance between WHO’s responsibilities to its Member States to provide evidence-based recommendations and facilitates quick access to needed products that are safe, effective and of high quality. VCAG emphasized that evidence-based guidance is needed, and that countries regularly deploy WHO-recommended products based on this guidance. The group recognized the challenges faced by stakeholders in conducting epidemiological trials for all products, particularly considering increases in the number of ITN products in the pipeline for malaria control and the complexity of trials against diseases such as dengue, which are highly unpredictable in space and time. However, until correlation of entomological and epidemiological end-points has been validated or refuted, epidemiological data remain an essential requirement to inform a policy recommendation for a new product class.

**Conclusions**

The definitions of “product classes” and “prototype/products” under VCAG review will be updated to ensure they are simple and clear, and that they fully capture the spectrum of products within the class. VCAG recognized the need for active horizon scanning to enable early discussion of the evidence required for assessment of new interventions.
VCAG operations, processes and feedback

Summary of discussions

Anna Bowman, VCAG Project Manager, presented recent improvements to the running of VCAG, such as the publication of standard operating procedures for applicants and initiation of a formal off-cycle review process. Plans for revisions to the VCAG application form and the development of data requirements for applicants submitting the findings of epidemiological studies were also discussed.

To increase awareness of VCAG and the tools, technologies and approaches under its review, WHO is developing information sheets for the products under review, in layman’s language.

It was agreed that the VCAG meetings for 2019 will take place on 13–15 May and 11–13 November.

PRODUCTS AND PRODUCT CLASSES: CONCLUSIONS AND RECOMMENDATIONS

Auto-dissemination devices – update

Background

The In2Care® Mosquito Trap targets ovipositing Aedes vectors, exposing them to both a slow-kill adulticide and a juvenile hormone analogue for dissemination. The intention is to reduce mosquito populations and prevent transmission of Aedes-borne diseases. In2Care® Mosquito Traps are currently intended to be deployed by pest management professionals (PMPs) as a component of integrated vector management approaches to Aedes control.

The applicants propose a device that includes the fungus Beauveria bassiana, which infects and kills adult mosquitoes, and pyriproxyfen, which is a highly effective insect growth regulator and pupacide. The “auto-dissemination” component of the trap refers to the distribution of pyriproxyfen dust to surrounding aquatic habitats by exposed mosquitoes exiting the trap. The contamination of mosquitoes by fungal spores and pyriproxyfen is mediated by applying these to electrostatic netting within the device. The netting retains large quantities of adulticidal fungus and pyriproxyfen particles and facilitates their transfer to mosquitoes entering the trap. The presence of pyriproxyfen in the trap also ensures that any eggs laid within the trap will not develop to the adult stage.

Update

The applicants provided updates on entomological and epidemiological trials in progress and at the planning stage. In trials, a general deployment rate of 10 traps per acre (approximately one trap every 400 m²) is recommended by the applicants, but it could be as low as six traps per acre (approximately one trap every 674 m²) depending on habitat suitability. Preliminary data from one of the first entomological field trials (Florida, USA) showed a reduction in the number of Ae. aegypti/albopictus captured between treatment (with traps) and control (without traps) sites, as measured using BG Sentinel Traps (Biogents AG) and human landing catches. The pyriproxyfen within the
In2Care traps continued to kill 100% of larvae that developed from oviposited eggs for more than 10 weeks. During this period, the viability (germination) of fungal spores in traps decreased to 30%.

In2Care gave an overview of trials in progress and in preparation that are being led by several institutions; In2Care is providing mosquito traps and technical advice on their use. Trials are planned in a diverse range of settings throughout Asia and the Americas. In Cambodia, one trial is examining the combined impacts of trap deployment, larval source reduction, larviciding and community participation on dengue vectors and disease. Entomological outcomes in the Cambodia trial include measuring reductions in adult density (using CDC light traps) and in the proportion of *Aedes*-positive aquatic habitats. Human exposure to dengue will also be measured on the basis of serology. In the Lao People’s Democratic Republic, traps are being deployed across control and treatment sites, and local partners are monitoring the impact of traps on larval and adult mosquito indices. Data on disease incidence in the Lao trial are being provided through routine passive surveillance by the public health system. In the Philippines, the entomological impact of deployed In2Care traps is being monitored using Gravid *Aedes* Traps (GATs). These trials will also simultaneously monitor seroconversion for dengue in humans. In Malaysia, In2Care traps are being deployed in high-rise buildings, in combination with space spraying, outdoor residual spraying and community-led approaches. The Malaysia trials will monitor entomological impacts and passive disease surveillance data will be provided by the public health system.

Previously, VCAG had asked In2Care to provide information on effective distances of auto-dissemination and on the impact of the fungus trap component on vectorial capacity. Given the challenge of conducting such studies under resource-limited field-trial conditions, In2Care has decided to remove product claims related to the impacts of *Beauveria* on exposed mosquitoes. To address VCAG’s request for information on the length of the replacement cycle for trap components (In2Mix refill sachet), the investigators presented data suggesting a replacement cycle of 6–8 weeks is appropriate. To address VCAG’s request for data to support the original deployment recommendation that traps be used at 10 traps per acre, or one trap per 400 m², the investigators presented data from field studies to indicate the deployment range can be as low as six traps per acre, or one trap every 674 m², depending on the suitability of the area to *Aedes* oviposition (i.e. fewer traps may be needed in areas such as open fields where there are fewer aquatic habitats in competition).

In2Care requested guidance on trials with epidemiological end-points described and whether these would be sufficient for VCAG approval if the results were positive. Applicants also asked for an update on the status of the new WHO guidelines for efficacy testing of traps.

**Summary of discussion**

The consensus from the discussion was that more detail about the trial designs being used in epidemiological investigations is needed before VCAG can provide guidance. VCAG cannot advise on whether these epidemiological trials are likely to generate data of sufficient quality to support a policy recommendation until the detailed protocols are provided for review. Similarly, concern was raised that trials involving an evaluation of In2Care traps in combination with a suite of other interventions will not allow an assessment of the specific impact of the In2Care trap alone.

VCAG also discussed the previous recommendation that data be provided to confirm the slow–killing impact of the *Beauveria* fungus in the trap and field dissemination of pyriproxyfen. For any active ingredients in products, evidence should be provided to demonstrate the benefit of adding them in terms of how they contribute to the efficacy, and hence public health value, of the product.
In2Care was informed that the guidance on procedures for efficacy testing of traps for control of Aedes spp. mosquito vectors have been published and can be referred to for guidance on testing.

With respect to the large-cage study data reviewed, VCAG discussed whether further semi-field or field studies would allow the investigators to quantify the entomological effect of the fungus on adult Ae. aegypti mortality and how to interpret this in terms of the purpose of this trap component. For example: are a large proportion of exposed females contaminated with the fungus, and, if so, are their lives shortened to the extent that they represent a reduced public health risk?

Based on this, the following note for the record is made to PQT-VC for consideration:

- With respect to the impact of the fungus on adult Ae. aegypti mortality, the current data provided to and reviewed by VCAG was not sufficient to show a pronounced impact on mortality of Ae. Aegypti, and further data would be needed to clearly demonstrate the killing effect of the fungus on adult Ae. aegypti. Any additional studies should be conducted according to the WHO guidance on efficacy testing of traps and, ultimately, be designed to substantiate the entomological efficacy of the product as indicated on the label.

Conclusions

In2Care® mosquito traps are being tested in a wide range of geographical and epidemiological contexts. The scope and variety of studies described will be important to understand the settings in which these devices perform best. VCAG would like to review the protocols for any planned trials to provide feedback regarding their design and the quality of the data likely to be generated. It was noted that no additional data were provided related to dissemination of pyriproxyfen and the slow-killing fungus components of In2Care® mosquito traps; further evidence on these components would be of value to better understand the trap function and design.

Recommendations

- The applicant is strongly encouraged to share protocols for the trials with entomological and epidemiological end-points with VCAG before the trials are initiated, so that VCAG can provide constructive feedback. It would be helpful if the applicant invited experts carrying out the trials to participate in VCAG meetings.
- To the extent possible, trial designs should be standardized to be able to compare results across trials. For guidance, the investigators can refer to resources such as the WHO Guidance on phase III vector control field trial design and Efficacy testing of traps for control of Aedes spp. Vectors.
- In trials that deploy the traps within an integrated vector management framework that includes additional interventions, care should be taken to ensure that the added value of the trap above and beyond other interventions can be assessed.
- Further evidence should be provided on the field autodissemination of pyriproxyfen.


Genetically modified mosquitoes (GMMs, or “genetically engineered” or “living modified organisms”) are mosquitoes in which the strain, line or colony has been altered using
recombinant DNA technology. This technology was first reviewed by VCAG in November 2014 in the form of a prototype GMM for population suppression (OX513A) submitted by Oxitec, Ltd. This GMM prototype targets Ae. aegypti mosquitoes and therefore Aedes-borne diseases including those caused by dengue, chikungunya, and Zika viruses.

**Update**

Oxitec has developed a new genetically modified Ae. aegypti strain, hereafter referred to as the “2nd generation strain”. Both strains proposed by Oxitec are engineered to be self-limiting, maintaining a tTAV (tetracycline repressible Trans Activating Variant) effector gene and a DsRed2 fluorescent marker gene for identification of transgenic mosquitoes. For both strains the expression of this tTAV protein kills immature mosquitoes, likely by interfering with the transcriptional and translational machinery, resulting in essential housekeeping genes not being expressed and leading to cell death. The major difference between them is that the 2nd generation strain only results in death of immature females, whereas the first strain proposed (OX513A) kills immature male and female progeny.

Until now, OX513A was under evaluation by VCAG as a “first-in-class” vector control product under the product class “Genetic manipulation of vectors for disease control – Population reduction – self-limiting approach.” At the November 2018 VCAG meeting, Oxitec enquired about the concept of a bridging strategy between the earlier strain and its 2nd generation strain. Bridging between strains would allow Oxitec to continue the VCAG evaluation process with the new strain as the new first-in-class vector control product under the same product class. The applicants propose that the active and inert ingredients in both strains do not differ significantly, and that the 2nd generation strain has several features when compared to OX513A that could increase the population suppression impact of each release, namely the genetic male-selecting feature to allow for male-only rearing and multi-generational suppression. In addition, the applicants propose that the new technology may lower the frequency of insecticide resistance genes in the target pest mosquito populations, although the applicant shared that further studies are being conducted to more fully understand this potential feature.

**Summary of discussions**

Discussions revolved around the extent to which the 2nd generation strain is different from the 1st generation strain and is self-limiting. Based on laboratory studies, the built-in genetic-sexing mechanism in the 2nd generation strain enables the transgene to persist in the population for multiple but still a limited number of generations. The released 2nd generation strain males mate with wild females and produce viable male progeny, potentially causing introgression of the 2nd generation strain genome into the wild mosquito population, including transmission of the transgene to subsequent generations, where only males carrying the transgene will survive but females carrying the transgene will die.

The technical mode of action remains essentially unchanged between the two strains (i.e. introducing a lethal gene to reduce population size). The group discussed whether ecological and human health risks had been considered for the new strain, including potential horizontal gene transfer of the male-selecting genetic construct. Oxitec informed the group that a range of studies were being carried out presently, and that risk assessments were being developed for national regulatory authorities.

**Conclusions**

Oxitec sought to discuss with VCAG the new strain and to discuss how it might switch its current product to the new strain of transgenic mosquitoes, which differs from its earlier strain (OX513A) that VCAG has previously reviewed.
The applicant refers to this as a self-limiting strain, but this will depend on the self-limiting nature of the transgene in the target population. The assumption that the released transgene will disappear from the target population will need to be substantiated with further experiments, as Oxitec is doing currently.

Because of the persistence of the transgene in generations following the initial release, the 2nd generation strain is quite different from OX513A. VCAG therefore considers the 2nd generation strain distinct from the first (OX513A). Oxitec is currently performing laboratory work on the 2nd generation strain and is working under field permits in Brazil to gather data on field efficacy, which will be helpful to VCAG as it further evaluates the technology, should Oxitec pursue VCAG’s feedback.

The applicant proposed that the 2nd generation strain may be used to manage insecticide resistance by introducing insecticide susceptible genes into target populations, and Oxitec is currently conducting studies to this end.

Recommendations

- The applicants should note that VCAG assesses evidence on products that are intended for public health use; therefore, to allow VCAG’s assessment of this product the applicants should provide a case for public health impact to this committee, in addition to their case for entomological efficacy.

- A more detailed strain-bridging plan describing analyses of existing data and/or the design of future studies is needed for the transition from OX513A to a 2nd generation strain. Specifically, as Oxitec knows, the plan should address the fate of the transgene in the environment and in Aedes populations over time. This should include the likelihood of horizontal gene transfer with the 2nd generation strain as compared to OX513A. After review of this information, the applicant may need to carry out tiered human health and ecological risk assessments for the 2nd generation strain; the applicants should consult with PQT-VC on these assessment requirements.

- Depending on the new bridging plan, VCAG may recommend that additional laboratory, semi-field and small-scale field data should be gathered to show that the product will have the anticipated entomological impact. The completion of these steps will allow VCAG to recommend epidemiological trials with the 2nd generation strain.

- If the insecticide resistance management claim for the 2nd generation strain is to be retained, the applicants should provide laboratory and field data to substantiate this claim.

Pyrethroid plus insect growth regulator net (Royal Guard) and pyrethroid plus non-pyrethroid insecticide net (Interceptor G2) – review of protocols

Background

Royal Guard is an ITN containing a combination of a pyrethroid (alpha-cypermethrin) and an insect growth regulator (pyriproxyfen). Pyriproxyfen has been added to sterilize mosquitoes that may survive exposure to a pyrethroid alone (likely due to resistance). Theoretically, this sterilizing effect should lead to an overall reduction in the next generation of vectors and ultimately reduce the vector population. Royal Guard first came to VCAG in October 2017. The assessment by WHO was initiated in 2015 under WHOPES, and the full dossier, including data from phase I and phase II studies, is currently under review by PQT-VC.
Interceptor G2 is an ITN containing alpha-cypermethrin and chlorfenapyr. This ITN uses a novel insecticide (chlorfenapyr), with a new chemical mode of action targeting mitochondrial energy production (i.e. oxidative phosphorylation), in combination with a pyrethroid to control insecticide-resistant mosquitoes. Interceptor G2 was first reviewed by VCAG in November 2016. It had previously been evaluated by WHOPES. Based on the WHOPES evaluation it received an interim WHOPES recommendation in March 2017 and was subsequently converted and listed by PQT-VC. To date this category of net is not covered by a WHO recommendation; Interceptor G2 is thus considered to be covered under the WHO policy recommendation for pyrethroid-only nets until epidemiological data to allow a comprehensive assessment by VCAG are available.

VCAG has recommended that for both Interceptor G2 and Royal Guard, at least two epidemiological trials should be carried out to generate data allowing assessment of public health value of these first-in-class ITN products.

BASF and Disease Control Technologies (DCT), the parent companies of Interceptor G2 and Royal Guard, respectively, are collaborating with LSHTM to develop two epidemiological trials that will be carried out in Benin and the United Republic of Tanzania.

VCAG has reviewed the Tanzanian protocol twice at the request of BASF and DCT. The first review, requested by BASF, was carried out in October 2017 at the seventh VCAG meeting and focused on Interceptor G2 only. The second review, requested by DCT, was an “off-cycle” review (i.e. conducted outside of VCAG meetings) in August–September 2018 to assess the proposed evaluation of Royal Guard, and is incorporated into this meeting report below. The review of the randomized control trial (RCT) in Benin, requested by LSHTM and supported by the two companies, was carried out at this meeting of VCAG, and is also detailed in this meeting report.

1. Protocol review of trial in the United Republic of Tanzania: off-cycle review requested by Disease Control Technologies

Background

VCAG was requested by Disease Control Technologies to comment on the suitability of the trial protocol by Protopopoff et al, LSHTM, for evaluating the Royal Guard net in an RCT in the United Republic of Tanzania.

It is noted that this protocol describes a four-arm trial. A very similar protocol for a five-arm trial has previously been reviewed by VCAG when considering its suitability for the evaluation of Interceptor G2. The authors of the trial protocol have provided a response to earlier VCAG comments on the evaluation of Interceptor G2. The current review looks at the evaluation of the Royal Guard net within the updated protocol.

The trial is a multi-arm, single-blinded, cluster-randomized trial with a village hamlet as the unit of randomization. It is a superiority trial that will compare the Royal Guard net against a standard pyrethroid-only LLIN in an area of high pyrethroid resistance in Misungwi District of northern Tanzania. The trial is powered to detect a minimum 28% reduction in prevalence and 23.6% reduction in incidence of malaria infection.

VCAG noted that the study protocol was approved by the relevant institutional review committees and that baseline data collection was under way. The VCAG review group has provided some comments specifically on the suitability of the protocol to evaluate the dual active ingredient Royal Guard net.
Conclusions

The clusters in the trial will consist of a core area, including a minimum of 200 households, and a buffer area of a minimum of 300 m where householders will receive the intervention but not be included in the cross-sectional surveys and entomological monitoring. VCAG is concerned that this buffer zone may be inadequate to avoid spillover effects, particularly for a product that is designed to reduce the overall vector population size in addition to killing mosquitoes.

The current protocol will follow the same cohort of children for two years. The applicants propose to use a design in which a new cohort of children is selected for the second year and monitored for one year of follow up. This design would reduce the potential problem of selection bias due to attrition and, importantly, the effect of changed disease profile for the closely followed single cohort of children. While the sample sizes proposed in the current protocol seem sufficient, changing the cohort in year two would increase the power of detection in the study.

The study intends to measure the impact of the different net products on insecticide resistance to assess their potential role in resistance management. However, the entomological work planned as part of this trial will not be sufficient to evaluate the role of these nets as part of a resistance management strategy (the stated claim). Currently, a single round of bioassays is planned for each study arm in each site, which may not be able to capture heterogeneity in resistance due to season, species composition, breeding site and other factors. It is also important that resistance to all active ingredients in the trial is measured to fully describe the mosquito population in the study. Furthermore, the protocol mentions resistance as a covariate in the primary objective section. The protocol should clarify that the inclusion of any covariate associated with resistance levels will be secondary to the main objective. The aim of the study should thus be amended, or the study design needs to be enhanced to generate the data required to assess the utility of these products in resistance management.

It was noted that the applicant requested to be considered by WHO under the policy recommendation and assessment criteria used for pyrethroid-only LLINs. This does not accurately reflect the composition of the product nor its intended mode of action. The claim should be reworded to be aligned with the product characteristics and its intended purpose, which VCAG assumes is superior performance when compared to that of a pyrethroid-only net when deployed in an area of pyrethroid resistance.

Applicants should note that WHO no longer provides interim recommendations for public health use of vector control products, as was common practice under the WHOPES process.

Recommendations

- Applicants should consider whether the buffer zone is sufficiently large to control for likely spillover effects from a product that is designed to reduce the population size. In particular, they should ensure that the entomological monitoring in the core and buffer zones is sufficient to measure any such effect.

- Applicants should review whether they have sufficient power with the current single cohort design and consider enrolling a new cohort of children in year two if warranted.

- The applicants should carefully consider what they claim the product can do, ensuring they refrain from assigning attributes to the product (such as resistance management) that are not possible to evaluate within the given study design. The product attributes should describe the intended mode of action of the product.
2. Protocol review of trial in Benin – reviewed in VCAG meeting

Background

The trial is a three-arm, single blinded, cluster-randomized trial with the village as the unit of randomization. The following three arms are proposed: (i) Royal Guard LN, (ii) Interceptor G2 and (iii) the control arm, a standard pyrethroid-only LLIN. The trial will take place over two years in an area where malaria vectors are resistant to pyrethroids in Benin, West Africa.

Summary of discussions

VCAG discussed the following points with the applicants:

- Incidence: It was noted that the incidence of malaria in study participants is likely to change over the age range of study participants, aged 6 months to 10 years. An age-stratified analysis would be of interest, although not necessarily required for the analysis of primary outcomes.

- Insecticide resistance detection: concerns were raised about the frequency and breadth of the sampling to detect insecticide resistance.

- Non-inferiority: The experimental hut trial is not powered sufficiently to detect non-inferiority. The applicant is aware of this and stated that their objective with this component of the study is to provide data to parameterize models.

- Modelling: It was noted that models are not a replacement for empirical information; however, the effort of the applicants to collect data vital to inform modelling was noted.

- Removal of nets from clusters for durability analyses: VCAG discussed sampling from outside the trial area or sampling evenly across trial clusters.

- Entomological outcomes: It was pointed out that current WHO guidance for large-scale (phase III) testing of LLINs specifies entomological follow-up until 36 months after net distribution and the current study only includes 30 months of follow up (6 months baseline + 24 months post-intervention).

The following specific points were discussed about Royal Guard:

- Product class: The applicants proposed that their product be covered by the policy recommendation for pyrethroid-only nets until they are able to provide data to allow review of this product as a new ITN class. According to the procedures of the revised WHO evaluation process, new generation ITNs such as Royal Guard should not be considered as being covered by a policy recommendation for pyrethroid-only nets, given that their product design and intended impact go beyond pyrethroid-only nets. Evidence of epidemiological impact obtained by adding pyriproxyfen will thus be required to formulate an appropriate policy recommendation justifying the roll out of such a new generation net.

- Safety, quality and efficacy review: It was confirmed by PQT-VC that the dossier submitted for safety, quality and efficacy was accepted for review and assessment.

- Timelines for review: The net manufacturers raised the challenge of production timelines, highlighting that delays in the evaluation of the products may delay product introduction into the market. VCAG has optimized its review processes, hence keeping timelines to an absolute minimum, meaning that once data are
available an assessment can be conducted rapidly. Generation of the required data to allow for a comprehensive assessment does, however, require a certain amount of time. VCAG does not consider this as a delay but as an essential foundation to justify the introduction of new, often more expensive, interventions. As for other health technologies, the time needed for evaluation should be factored into overall product development timelines and any plans for market introduction.

Conclusions

The study protocol was well prepared and provides a reasonably complete description of the trial design. VCAG concurred with the investigators that incidence, rather than prevalence, is the preferred primary end-point. VCAG noted some minor points for clarification in the protocol. First, while the protocol indicates the trial will be single blinded, it is not explained how this will be achieved; for example, whether the textiles are indistinguishable. Second, the statistical analysis section of the protocol does not make clear whether the primary analysis will be adjusted or unadjusted.

The protocol assumes a 30% reduction in malaria cases will be associated with use of the dual active ingredient nets and the study design has 80% power to detect this level of decline, assuming all the households are exposed to resistant mosquitoes. However, a 30% effect may be optimistic, based on publications cited by the investigators (Tiono et al., 2018), which show a 12% reduction. The VCAG guidance on phase III vector control field trial design says that while in general at least a 30% reduction in epidemiological outcomes is desirable, this will depend on the intervention and the setting in which it will be used. Trials should be powered with generous allowance for wastage and/or loss to follow-up, making it possible to have a statistically significant result with a smaller effect size than the one used in the power calculation.

The research team indicated that resistance will not be systematically assessed in all clusters and will not be a stratification variable for the randomization. VCAG noted that the proportion of susceptible and resistant mosquitoes will likely vary over time and across the locations in the study. If the variability of susceptible and resistant mosquitoes is inconsistent across the clusters during the study and/or if a high(er) proportion of mosquitoes are susceptible, the power to detect a 30% decline in malarial incidence may be reduced. The study design could therefore be improved with further details on how the randomization will be implemented, how – if at all – clusters will be stratified by presence of resistant and susceptible mosquitoes and how – if at all – baseline levels of resistance would be included in the statistical analysis.

To determine the sample size required to assess the second end-point, prevalence, the applicants indicated that they will conduct age-stratified surveys of parasite prevalence in human participants during baseline data collection. VCAG noted that age-specific prevalence rates would be extremely useful before setting the age strata.

Recommendations

- Cohorts: The applicants may choose to either follow the same cohort over two years or recruit a new cohort after one year; both are acceptable options.

- Resistance levels in clusters: Further details should be provided on how the restricted randomization will be implemented, and how – if at all – baseline levels of resistance would be included in the statistical analysis to deal with unmeasured variables that could be unbalanced at the time of cluster assignment.
• Insecticide resistance: The applicant is encouraged to conduct further insecticide resistance testing of the local vector population in the area where the hut trials will take place, potentially with more frequent testing and using resistance bioassays in addition to the proposed molecular markers.

• As the mode of action of active ingredients (AIs) on the nets is not solely “fast acting”, standard cone bioassay requirements would be inadequate to assess the residual efficacy of the non-pyrethroid AIs on the nets. Bioassays to assess the insecticidal activity of secondary AIs (e.g. delayed mortality or impacts on fecundity/fertility) may need more investigation and should be further discussed with PQT-VC.

• Net sampling: The current study design envisages intensive net sampling from a small number of clusters for durability assessment. To address concerns that the removal of nets for durability assessment does not influence the outcomes of the epidemiological study by distorting the age (and hence efficacy) of the study nets, the investigators should consider: (i) conducting durability studies and net sampling in areas adjacent to – but not part of – any active clusters included in the cluster-randomized trial; or (ii) changing the design so that a small number of nets from all clusters are used, thus spreading the potential impact on the age of nets under investigation so that there is no disproportionate effect on any particular clusters.

• Incidence: Applicants are asked to provide further details on how the incidence of multiple malaria infections per child per year will be recorded, and whether multiple events per person will be included in the analysis.

• The applicants plan to update their protocol per VCAG feedback prior to submission to UNITAID. VCAG recommends that, if possible, the revised protocol is shared with VCAG at the earliest convenience and, ideally, before final ethical approval and field implementation.

Spatial repellents – update

Background

Spatial repellents are designed to interrupt human–vector contact through vector behaviour modification induced by airborne chemicals, potentially offering protection from bites from vectors and nuisance pests. The spatial repellent intervention proposed is a transfluthrin-based passive emanator produced by SC Johnson, designed to release a volatile chemical into the air and prevent human–vector contact within the treated space. The intervention targets *Anopheles*, *Aedes* and *Culex* spp., and is intended to protect all age groups and populations in countries endemic for mosquito-borne diseases from daytime, early-evening or late-night biting from mosquitoes in enclosed and semi-enclosed structures. The product claims are that deployment of the spatial repellent product in enclosed and semi-enclosed spaces will reduce human pathogen transmission. Epidemiological trials are currently under way in Sumba Island, Indonesia, and Iquitos, Peru, to generate data to allow assessment of the product’s public health value against infection with malaria or *Aedes*-borne viruses, respectively.

Update

The applicant provided an update on two trials: the Sumba Island trial in Indonesia on malaria and the trial in Iquitos, Peru, on *Aedes*-borne viruses.

The RCT in Indonesia investigating the intervention on malaria infection outcomes ended in April 2018 and the study team is reviewing the results of the trial. The applicant provided an update on analysis of efficacy and acceptability, including a framework for
monitoring adverse events, and on malaria diagnosis results from both microscopy and polymerase chain reaction (PCR) testing of blood spots from the study sites.

The RCT in Peru is ongoing, with a planned end date of January 2019. Follow-up surveys on efficacy and acceptability of the intervention are under way and will be completed within the study timeline. Systems are in place to identify and report adverse events and severe adverse events. Assessment of these data by the study’s Data and Safety Monitoring Board (DSMB) have so far not indicated concerns about the continued use of the product. Longitudinal seroconversion surveys and febrile surveillance continue in the designated study clusters according to the protocol.

VCAG reviewed new protocols and statistical analysis plans for two more trials. The first study is proposed for Kenya and its primary objective is to demonstrate and quantify the protective efficacy of spatial repellents in reducing malaria infection in human cohorts in a second study site, in accordance with VCAG recommendations on the number of trials needed to assess the public health value of new vector control tools. The second study is proposed for Sri Lanka and its primary objective is to demonstrate and quantify the protective efficacy of spatial repellents in reducing dengue infection in human cohorts, again adding the second study required by VCAG.

**Summary of discussions**

VCAG noted the progress of the ongoing trials. Both studies are on course to finish according to the anticipated schedule. The applicants have also addressed many of the recommendations and feedback provided at the last VCAG meeting. VCAG would appreciate receiving the final report related to the resolution of discrepancies in the PCR results from the Eijkman Institute for Molecular Biology and the University of Notre Dame.

With respect to the proposed study designs for Kenya and Sri Lanka, VCAG asked for further information on the actual cluster size and population to be included, and how participants in cohorts will be selected. If only members of the cohort receive the intervention (or placebo), the overall impact will be lower than if everyone in the cluster were to receive it. Cohorts must be representative of the overall study population, as this will be critical for estimation of the overall community effect.

For the entomological sampling in the proposed trials, VCAG noted that the proposed entomological sampling design does not appear to be based on preliminary data on vectors from the sites or on power analysis.

VCAG discussed the potential for spatial repellents to divert vectors to neighbouring areas where the intervention has not been deployed. This “diversion effect” is not currently being measured in any ongoing trial. For the new trials, the trial planned for Kenya includes measuring community effect in those living in neighbouring intervention areas, but the trial planned for Sri Lanka does not. This raises the issue that none of the trials for Aedes (e.g. ongoing in Peru, planned for Sri Lanka) are planning to measure diversion. VCAG noted that it would be of great value if the Sri Lanka trial could incorporate assessment of diversion to generate information on potential diversionary impacts on Aedes as well as on Anopheles vectors.

**Recommendations**

- Planned trial in Kenya: The applicant should provide confirmation on the source of the epidemiological values used to update sample size calculations.

- Proposed duration of trials in Kenya and Sri Lanka: VCAG recommends a 24-month period of follow-up, exclusive of baseline in both sites.
For both study designs (Kenya and Sri Lanka), further description of how the intervention will be allocated within the clusters should be provided. VCAG recommends adding text in the protocol that describes: (a) how clusters will be defined, including approximate population and spatial dimensions; (b) how clusters will be randomized to trial arms (i.e., is there any matching; is there a public draw, etc.) and the extent to which allocation is blinded (if at all); (c) what proportion of the households receive the intervention/placebo in each cluster; (d) how the cohort households (e.g., cohort I and II) are selected.

Entomological sampling in proposed trials: Applicants should review information on baseline entomological characteristics at each study site and use these to justify the proposed entomological sampling plan.

Measuring diversion effect in Aedes trials: The potential diversionary effect of spatial repellents on Aedes vectors should be assessed. There are no plans to measure this potential effect in the Sri Lanka study and it is also not being assessed in the ongoing trial in Iquitos, Peru. VCAG encourages the applicants to consider incorporating assessment of diversion into the Sri Lanka trial; understanding that such a study design may be costly and/or logistically challenging given the scale that may be required as a result of virus transmission heterogeneity.

Insecticide resistance: The applicants should clarify the number of sites and the frequency of insecticide resistance testing for all studies. VCAG considers it as very important to assess pyrethroid resistance throughout the study site due to the unknown impact of potential differences in heterogeneity and spatial patterns of resistance. Recognizing the challenges of working with volatile pyrethroids, the investigators should consider performing bioassays measuring resistance intensity in at least one standard non-volatile pyrethroid in addition to transfluthrin bioassays.

**VCAG responses to specific questions from the applicants**

1. Feedback on the Indonesian trial statistical analysis plan: VCAG is pleased to see a well-written statistical analysis plan for the Indonesian trial. In addition to the primary analyses with covariate adjustment, VCAG would also expect to see a supplementary analysis without covariate adjustment.

2. Requirement of independent data analysis: VCAG does not normally carry out independent verification of the study data. However, in some instances VCAG may recommend that the applicants conduct a re-analysis or that the secretariat facilitates a specific re-analysis with the support of the applicant. For guidance on reporting trial results, applicants should consult the CONSORT Statement and the WHO Guidance on phase III vector control field trial design.

3. Public health value assessment: The full assessment will take into consideration the primary, secondary and tertiary end-point analyses for the two trials per disease once these have been completed. While the demonstration of public health impact is critical for the formulation of a policy recommendation, other end-points may influence the content and wording of the recommendation issued.

4. VCAG provides public statements on the outcomes of VCAG reviews in the form of published meeting reports; the secretariat can facilitate “off-cycle” review of documentation and additional feedback, if justified.

5. VCAG endorses the protocols for Kenya and Sri Lanka subject to the suggested revisions described above.
Repel and lure strategy for malaria control (push–pull strategy) – off-cycle advice

Background
The intervention, termed push–pull, is designed to repel host-seeking mosquitoes from houses and their immediate surroundings (the “push”), and to lure them towards odour-baited mosquito traps which are placed outside the home (the “pull”). The system is comprised of two components: a cotton fabric treated with a spatial repellent product, which is placed on eaves of houses, and an odour-baited trap powered by solar energy outside houses.

At the Eighth VCAG meeting in May 2018, the applicants presented plans to conduct an RCT in Malawi. VCAG clarified to the applicant that at least two well-conducted and randomized epidemiological trials in different geographical settings, ideally covering two years, are required to generate data to assess the potential public health value for a new product class. After the meeting, the applicant sought VCAG’s advice on a potential site for a second proposed RCT. The applicant proposed to conduct the second RCT in Kenya. The sites/countries were proposed based on diversity of climate, mosquito composition and malaria seasonality, as well as prior experience working in the area and established collaborations.

Recommendation

- VCAG acknowledges that the two proposed sites (Kenya and Malawi) incorporate sufficient ecological and epidemiological variations to satisfy current requirements for site diversity. On this basis, VCAG supports the selection of Kenya for a second RCT of this intervention.

- If entomological inoculation rates and/or vector density are likely to be included as secondary outcomes in the trial, VCAG recommends collecting baseline data on these variables at trial sites to inform power analysis. VCAG recommends that information on baseline entomological characteristics of study sites and proposed sampling design be reviewed at a future meeting as plans for the study progress.

Endnotes

1. Note that some interventions are for both malaria and NTDs so appear twice. The total number of product classes under VCAG review is 18.


4. Following this meeting, the terminology for VCAG leadership will change from Chair/Vice-Chair to Co-Chairs. Professor Heather Ferguson and Dr Salim Abdulla will consequently be considered Co-Chairs of VCAG.


14. Please refer to How to design vector control efficacy trials: guidance on phase III vector control field trial design provided by the Vector Control Advisory Group (http://www.who.int/neglected_diseases/vector_ecology/resources/WHO_HTM_NTD_VEVM_2017.03/en/).


## ANNEX 1. AGENDA

### MONDAY, 12 NOVEMBER 2018

**Session 1: Introductory session**

**09:00–09:30 Opening of meeting**
- Organizational matters
- Opening remarks
- Declarations of interest
- Appointment of chair and vice chair
- Update on process to appoint VCAG members

**09:30–09:45 Introductory remarks for VCAG members**

**09:45–10:15 VCAG discussion on upcoming topics**

**Session 2: Open session**

**10:45–11:30 Progress updates**
- General progress and update on VCAG
- NTD update, relevant outcomes from STAG
- GMP update, relevant outcomes from MPAC
- PQT-VC

**11:30–12:30 Update on PBO net study in the United Republic of Tanzania**

**13:30–14:30 Update on PBO net study in Uganda**

**14:30–15:00 Open discussion**

**15:30–16:30 Completed and planned systematic reviews for vector control products**

**16:30–17:30 Update on the policy review process in GMP**

### TUESDAY, 13 NOVEMBER 2018

**Session 3: Review of dossiers**

**9:00–10:30 Auto-dissemination devices (In2Care® Mosquito Trap) and EaveTubes (for information only) – update**
- Chair of session: Audrey Lenhart
- Applicant presentation (09:00–09.30)
- Closed discussion (09:30–10:00)
- Recommendation to applicants (10:00–10:30)

**10:45–12:30 Pyrethroid plus nonpyrethroid insecticide net (Interceptor G2) and pyrethroid plus insect growth regulator net (Royal Guard) – review of protocol**
- Chair of session: Hilary Ranson
- Applicant presentation (10:45–11:30)
- Closed discussion (11:30–12:00)
- Recommendation to applicants (12:00–12:30)

**13:30–15:00 Population reduction – self-limiting approach (Oxitec OX5034) – update**
- Chair of session: Thomas Scott
- Applicant presentation (13:30–14:00)
- Closed discussion (14:00–14:30)
- Recommendation to applicants (14:30–15:00)

**15:15–17:00 Group discussion – VCAG policy**
- Discussion on policy review process in GMP
- Overview of product classes and prototype/products under VCAG review
- Preferred product characteristics (PCC)
- Off-cycle reviews – summary of feedback provided by Dossier Review Groups

**17:00–18:00 Summary of Day 3 and working sessions to draft recommendations**
**WEDNESDAY, 14 NOVEMBER 2018**

### Session 3: Review of dossiers (cont’d)

09:00–10:30  **Spatial repellents (transfluthrin passive emanator) – review of data**

- Chair of session: Salim Abdulla
- Applicant presentation (09:00–09:30)
- Closed discussion (09:30–10:00)
- Recommendation to applicants (10:00–10:30)

### Session 4: Discussion and finalization of recommendations (closed)

10:45–11:45  **Group discussion – VCAG operations, processes, feedback**

1. Standard operating procedures for VCAG applicants
2. Off-cycle review process
3. VCAG information sheets on new technologies
4. VCAG application form
5. Template for submission of final data package
6. Proposed VCAG meetings in 2019

11:45–12:30  Finalization of the wording of recommendations

13:30–15:00  Finalization of the wording of recommendations (cont’d)

15:15–17:00  Plenary sessions to finalize report

17:00–17:30  Close of meeting

** VCAG members with conflicts of interest will be asked to leave the room.
VCAG experts

Chairperson
Thomast SCOTT
University of California Davis
United States of America

Salim ABDULLA
Ifakara Health Institute
Ifakara, United Republic of Tanzania

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ANNEX 2. LIST OF PARTICIPANTS

Participants

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Achim REDDIG
Susanne STUTZ

Disease Control Technologies
Rod FLINN

Clariant
Francis BAUD

In2Care
Marit FARENHORST
Anne OSINGA

Infectious Diseases Research Collaboration (IDRC)
Samuel GONAHASA

London School of Hygiene & Tropical Medicine (LSHTM)
Natacha PROTOPOPOFF
Mark ROWLAND
Jackie COOK

Liverpool School of Tropical Medicine (LSTM)
Janet HEMINGWAY

Oxitec
Meredith FENSOM, Intrexon (by phone)
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Hudu MOGTARI

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Target Malaria
Karen LOGAN

Remote participation

Bayer
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Target Malaria
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Anna DREXLER
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Regulation of Medicines and other Health Technologies
Suzanne HILL
Director, Essential Medicines and Health Products

Dominic SCHULER
Technical Officer, Prequalification Team, Vector Control Group
ANNEX 3. DECLARATIONS OF INTEREST

All VCAG members and invited experts completed the Declaration of interests form for WHO experts prior to the meeting. The VCAG secretariat in consultation with the WHO Office of Compliance, Risk Management and Ethics assessed the interests declared by the experts and, with the exception of those described below, the declared interests were not found to be directly related to the topics under discussion at the meeting. It was therefore decided that those experts could participate in the meeting, subject to the disclosure of their interests at the meeting.

The following interests were declared and assessed to be related to topics under discussion at the meeting. The disclosed interests listed below did not warrant full exclusion, rather partial participation. The conclusions and mitigating actions are described below.

Dr Hilary Ranson (Liverpool School of Tropical Medicine) informed the WHO VCAG Secretariat of a potential conflict of interest regarding Royal Guard LN and Interceptor G2.

Conclusion: Dr Ranson did not participate in any discussions or in the drafting and finalization of the recommendations regarding Royal Guard and Interceptor G2 at the meeting.

Dr Robert Reiner (Institute for Health Metrics and Evaluation) declared a conflict of interest with regard to spatial repellents.

Conclusion: Dr Reiner did not participate in any discussions or in the drafting and finalization of the recommendations on spatial repellents.

Dr Thomas Scott (University of California, Davis) declared a conflict of interest with regard to spatial repellents.

Conclusion: Dr Scott did not participate in any discussions or in the drafting and finalization of the recommendations on spatial repellents.

Dr Thomas Smith (Swiss Tropical Institute) declared a conflict of interest with regard to the push–pull strategy and Royal Guard LN.

Conclusion: Dr Smith did not participate in any discussions or in the drafting and finalization of the recommendations regarding the push–pull application of Royal Guard LN.

Dr Neal Alexander (Centro Internacional de Entrenamiento et Investigaciones Médicas (CIDEIM) and LSHTM) declared a conflict of interest with regard to auto-dissemination devices. He also declared that he is on the Data & Safety Monitoring Board for Spatial Repellents.

Conclusion: Dr Alexander did not participate in any discussions or in the drafting and finalization of the recommendations regarding auto-dissemination devices. Dr Alexander did not participate in the VCAG working group for spatial repellents; however, he did participate in the discussion of the topic with the entire group.
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