



**Vector Control
Advisory Group**

MEETING REPORT
13–15 May 2019

Tenth meeting of the WHO Vector Control Advisory Group



**World Health
Organization**



**Vector Control
Advisory Group**

MEETING REPORT
13–15 May 2019

Tenth meeting of the WHO Vector Control Advisory Group



**World Health
Organization**

WHO/CDS/VCAG/2019.02

© World Health Organization 2019

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. Tenth meeting of the WHO Vector Control Advisory Group. Geneva: World Health Organization; 2018 (WHO/CDS/VCAG/2019.02). 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.



CONTENTS

Background	1
Open session	1
Updates: summary of discussions	2
Roles and responsibilities in the WHO process for the evaluation of vector control products	4
WHO guidelines for malaria vector control	4
Closed session	5
Human health assessment of Chlorpyrifos	5
Interventions and intervention classes: conclusions and recommendations	5
Off-cycle reviews	5
Sterile insect technique / incompatible insect technique	5
Auto-dissemination devices	7
Interventions reviewed during the meeting	9
Adulticidal oviposition and larvicidal traps – new product	9
Endectocides – new product	10
Spatial repellents – review of data	14
Population reduction – gene drive approach – update	19
Attractive targeted sugar bait – update	21

Product intent to impact – terminology and definitions	23
Evaluation standards and procedures for assessing new vector control interventions	24
Group discussion – VCAG operations, processes and feedback	25
Endnotes	26
Annex 1. Agenda	28
Annex 2. List of participants	30
Annex 3. Declarations of interest	32

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 for vector control products (PQT-VC).

The specific functions of VCAG are:

1. to provide guidance to product developers, innovators and researchers on the generation of epidemiological data and study designs to enable assessment of the public health value of new vector control interventions;
2. to assess the public health value of new vector interventions 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 interventions..

VCAG experts, innovators (referred to as “applicants”) and other stakeholders met in Geneva on 13–15 May 2019 for the tenth VCAG meeting. The agenda is reproduced in Annex 1. Ten VCAG members were joined by four other experts (three in person and one by phone) and a prequalification assessor. The open session was attended by the VCAG (including ad hoc experts), applicants and product developers, WHO staff from GMP, NTD and PQT-VC and other stakeholders, including representatives of donor and procurement agencies. A WebEx link was provided for participants who participated in the open session remotely. The closed meeting was attended only by VCAG members and ad hoc experts, the WHO Secretariat and relevant parties. The participants are listed in Annex 2.

OPEN SESSION

Dr Mwelecele Malecela, Director, NTD, and Ms Emer Cooke, Director, Regulation of Medicines and Other Health Technologies, welcomed VCAG members to Geneva and wished them successful deliberations. Ms Cooke noted that for the first time the meeting included an assessor from the prequalification team to provide technical advice. This and the definition of the roles and responsibilities of the various departments involved in evaluating vector control products – PQT-VC, the Global Malaria Programme (GMP) and the department of Neglected Tropical Diseases (NTD) – are signs of a functioning integrated approach to the evaluation of new interventions. Dr Malecela commented that NTDs affect more than one billion people and cost billions of US dollars every year to developing economies. Nine of the 20 NTDs are vector-borne and result in an estimated 600 million cases annually. Vector control is thus an important part of the NTD department’s strategy for tackling these diseases.

Dr Pedro Alonso, Director, GMP, joined the meeting on the last day. He thanked VCAG members for their expert advice to WHO and welcomed the two new co-chairs.

All the invited experts were asked to declare any conflicts of interest before the meeting. The declarations of interest were reviewed by an ethics officer from the WHO Office of Compliance, Risk Management and Ethics, and relevant interests were disclosed. The declarations are presented in Annex 3.

Updates: summary of discussions

Anna Bowman, VCAG Project Manager, provided an update on the work of VCAG, including presenting the list of interventions under VCAG review (1). She explained that the terms of reference of the Group (2) have been updated to clarify VCAG's role in reviewing entomological data. In summary, PQT-VC is responsible for assessment of entomological data, in the context of meeting data requirements for prequalification, and development of associated guidance on test procedures. VCAG is responsible for providing guidance to applicants, through WHO, on generation of epidemiological data on new vector control interventions to allow VCAG assessment of public health value. The provision of this advice by VCAG may require a review of entomological data generated for the prequalification assessment, as these data may inform the epidemiological study design and supporting studies. In cases where entomological evaluations are conducted alongside epidemiological trials to generate supporting/explanatory evidence, VCAG is expected to review and guide the study design.

In terms of next steps for the evolution of VCAG, there are plans to look at the harmonization of current documents on the evaluation of vector control interventions ("The evaluation process for vector control products" (32) and "How to design of vector control efficacy trials" (3)) and to better align them with the revised GMP policy making process (4). The aim of this consolidation is to provide one single document on the evaluation process and standards used to assess new vector control interventions. WHO also plans to further diversify VCAG membership with a view of expanding expertise in epidemiology and product development/evaluation procedures used by national regulatory agencies.

Dr Raman Velayudhan, Coordinator, NTD Vector Ecology and Management, briefed the open session on the work of the unit. Within the context of strategy for control, elimination and eradication of NTDs, the team is updating normative guidance and supporting implementation of the *Global vector control response 2017–2030* (GVCR); preventing and controlling dengue, chikungunya and other *Aedes*-borne diseases; and investigating new tools for the prevention and control of vector-borne diseases.

Dr Velayudhan noted that a significant reduction was reported in the number of dengue cases in the Americas in 2017. However challenges remain, with 128 endemic countries and 50–100 million cases per year (5). The NTD Vector Ecology and Management team is working on the revision and update of the *Dengue Guidelines and the Global Strategy for Dengue Prevention and Control*.

Dr Velayudhan described the outcomes of the meeting of the Strategic and Technical Advisory Group for NTDs on 29–30 April 2019, including the development of a new NTD Roadmap, 2021–2030 (6), which is planned to be launched in October 2020. The following recommendations were made during the meeting with regard to vector-borne diseases.

- Urban environments (especially informal settlements) facilitate the spread of *Ae. aegypti* and associated arboviral infections. It was recommended that the NTD department should facilitate cross-sectoral action, working with appropriate actors to tackle issues related to the spread of arboviral infections in urban environments.

- The NTD department should work closely with appropriate actors to address the issues of medicines for NTDs and insecticide resistance.
- Existing Technical Working Groups that report to the Director NTDs should include dengue and arbovirus control.

Dr Jan Kolaczinski, Coordinator, GMP Entomology and Vector Control (EVC), summarized the main developments in malaria vector control. Including the following:

- Guidelines on malaria vector control were published in February 2019 (7).
- A District Health Information System 2 (DHIS 2) module for collecting and visualizing data on resistance of malaria vectors to insecticides was developed in 2018 and is being rolled out in the WHO African Region as part of broader surveillance strengthening work and creation of national data repositories. Other DHIS 2 modules are under development to facilitate data reporting on malaria entomology and vector control interventions.
- The EVC team continues to support implementation of the GVCR through financial and technical assistance on development and implementation of regional GVCR strategies and national vector control needs assessments.
- In accordance with a recommendation of the Malaria Policy Advisory Committee, WHO has developed a study protocol for non-inferiority studies focused on insecticide-treated nets and indoor residual spraying. Interested parties were asked to provide comments on the non-inferiority study protocol and/or the notice of intent by 31 December 2018. GMP revised the protocol on the basis of the feedback and have also prepared a document with consolidated responses to questions and comments received (8). Non-inferiority trials on pyrethroid-piperonyl butoxide nets are anticipated to start towards the end of 2019.
- A technical consultation was scheduled for June 2019 to assess the potential threat of *An. stephensi* spreading to new areas.
- The handbook on practical entomology in malaria is being updated in collaboration with the National Institute for Communicable Diseases, South Africa. A technical consultation on the handbook is planned for late 2019.

Dr Kolaczinski also updated meeting participants on the evolution of the GMP policy-making process, sharing with them the draft overview of this process (4). In addition, he updated participants on the GMP initiative: High Burden to High Impact (9).

Marion Law, Team Lead, PQT-VC, summarized the activities of PQT-VC to support assessment of safe, efficacious and high-quality products. Major achievements include:

- The team has completed all the necessary recruitment, meeting its 2018 staffing priorities, with two case managers/policy analysts, a product/analytical chemist and an entomologist.
- Inspections have been conducted at 16 manufacturing sites for vector control products.
- Six vector control products have been prequalified since 2018, and nine are being assessed (10).

- Policies have been developed during “assessors’ sessions” on product labelling, acceptance of publicly available information to support applications and re-evaluation of active ingredients.
- The following activities have also been included in the Assessors Sessions:
 - risk assessment model assessment;
 - label improvement plan;
 - comprehensive review of chlorpyrifos;
 - product review of combination of active ingredients;
 - advance discussion on periodic re-evaluation program and label improvement program for PQ listed products; and
 - regulation framework – data requirements for a gene drive mosquito product.

PQT-VC team has the following priorities for 2019:

- continued assessment of new applications (new products, protocols, changes);
- assessors’ sessions;
- post market activities;
- implementation of label improvement plan;
- continued implementation of the process for complaint handling, targeted oversight-surveillance & monitoring;
- post-market product review;
- JMPS & CIPAC procedures;
- specification submission review;
- capacity building in countries- fact finding; and
- guideline review.

Roles and responsibilities in the WHO process for the evaluation of vector control products

Dr Kolaczinski, on behalf of the VCAG Secretariat presented an overview of the roles and responsibilities in the WHO process for the evaluation of vector control products (11), which was jointly developed by GMP, NTD and PQT-VC. The document was developed to clarify the respective responsibilities of the different WHO departments during evaluation of vector control interventions. The “responsible, accountable, consulted and informed” chart is used to indicate the level of involvement of each stakeholder.

WHO guidelines for malaria vector control

Dr Kolaczinski presented the WHO guidelines on malaria vector control (7), published in February 2019, which represent a compilation of more than 20 guidance documents. The guidelines are a web-based document and will be updated as new evidence is reviewed.

CLOSED SESSION

Human health assessment of Chlorpyrifos

Marion Law explained that PQT-VC has conducted a comprehensive review of available information on chlorpyrifos and from this developed a hazard assessment, an exposure assessment associated with the proposed long lasting insecticidal net formulation and has characterized the risk to human health. A PQ assessor presented the process and outcome of the human health risk assessment to VCAG, for their information.

Interventions and intervention classes: conclusions and recommendations

Off-cycle reviews

If an applicant requests an urgent review and the next VCAG meeting is to take place more than three months later, an “off-cycle review” can be conducted, facilitated by the Secretariat, in which the VCAG working group reviews the dossier and associated materials electronically, through teleconferences or email, and provides provisional advice to the applicant. In accordance with the VCAG terms of reference (2), the official report of the off-cycle review is incorporated into the report of the next meeting of VCAG once it has been reviewed by all members.

Three off-cycle reviews were conducted after the VCAG meeting in November 2018, on: sterile insect technique /incompatible insect technique (SIT/IIT); auto-dissemination devices; and spatial repellents. The first two are summarized below, while the off-cycle review of spatial repellents is summarized on page 14, including VCAG interactions with the applicant during the meeting.

Sterile insect technique / incompatible insect technique

Background

The Joint FAO/IAEA Division’s Insect Pest Control Subprogramme “Combined SIT/IIT Approach” was conceived in response to requests by Member States of FAO and IAEA and was first reported to VCAG in March 2016 (12). The aim of the approach is to reduce the population density of *Aedes* mosquitoes below the threshold for transmission of dengue, Zika and chikungunya viruses. The SIT approach is based on mass rearing of the target species, separation by sex and sterilization of males with ionizing irradiation. The combined approach also includes the symbiont *Wolbachia*, which induces cytoplasmic incompatibility and protects, under certain conditions, against mosquito transmission of dengue, Zika, chikungunya and yellow fever viruses. Over time, the systematic and continuous release of sterile males is designed to suppress the targeted population.

A randomized controlled trial on the impact of SIT/IIT on dengue in Bangkok, Thailand, is being supported by the Special Programme for Research and Training in Tropical Diseases.

Conclusions

VCAG agrees there is a pressing need for proven arbovirus interventions and continue to believe the SIT/IIT approach is ready for epidemiological trials. Nevertheless, VCAG had a number of concerns about the current protocol, which are listed below in order of appearance, not priority.

Site selection

The group had significant concerns about the site selected for the trial. The SIT/IIT team identified one of the main goals of site selection as "...the size of the selected study sites should be manageable and partly isolated geographically". The current description of the site selection in Bangkok does not seem to meet these criteria. Given the day biting nature of *Ae. aegypti*, individuals residing within clusters are very likely to spend time at risk of exposure outside of their respective cluster. Beyond concerns of contamination, the effect size can only be applied to the fraction of time the individuals in the treatment arm are actually in their cluster. For example, if 50% of an individual's time at risk is spent in their cluster, and the effect size is 50%, one would only expect an observed effect size of 25%. Given these clusters are being selected from some of the highest-risk areas of Bangkok, it seems quite likely that once an individual leaves the treatment area, they will be at significant risk of infection. Human movement is discussed briefly in the data collection sections of the protocol, but it is unclear if it has been adequately considered for site selection.

A related concern is on cluster size and identification, more detail is needed to understand how cluster boundaries will be set.

End-points:

- **Epidemiological.** Further clarity needs to be provided on the primary epidemiological end-points/outcome of the study. The protocol indicates that incidence data will be passively collected from clinics and hospitals, however, it is not clear what these data will consist of e.g. the number of dengue cases, serological prevalence or rate of morbidity. The investigators should also clarify their plans for case confirmation, i.e. whether confirmation of suspected dengue cases by polymerase chain reaction is critical or whether other methods are to be used, and how they will link this information to the cited morbidity rates. While not explicitly said, once a case has been "confirmed", the cluster and arm of the trial containing the individual's home would be recorded. Also, the primary epidemiological end-point must be clearly defined in order to assess the related power calculations.
- **Entomological.** If there is an entomological end-point, it should be more clearly defined as well as the associated baseline values.

Power calculation:

- VCAG provided detailed advice on the power calculations and sample size calculations which was conveyed directly to the applicant.

Data collection:

- VCAG suggested that more detail be provided about the frequency and level of collection of ethnographic and disease incidence data, e.g. all individuals or a subset. VCAG also suggested that more details be provided of how movement of individuals at the study site will be assessed.
- The protocol should also describe how the entomological traps will be placed and maintained in houses or sentinel sites.

Other issues:

- VCAG recommends that duration of epidemiological assessment, excluding the baseline period, should cover at least two years, to account for inter-annual

variation in transmission. Implementing the intervention at the end of the trial is reasonable (assuming efficacy is shown), but this aspect of the trial does not count as a “second year”.

- More detail is needed in the protocol on what vector control interventions are currently used in Bangkok to manage dengue.

Recommendations

VCAG appreciated the opportunity to comment on the trial protocol before commencement of the trial. VCAG identified several concerns, some of which are related to a lack of clarity and others are more fundamental for the trial design. VCAG recommends that the applicant revise the draft protocol on the basis of the feedback, and specifically the following:

- Consideration is needed to assess the optimal cluster site configuration given the highly urban site selected.
- Clearly define the primary end-points of the trial.
- Recalculate the sample size calculations and provide citations for value estimates.
- Provide more detail about data collection (e.g. frequency, percentage of all houses sampled).
- Consider human movement both within the trial design and analysis.

VCAG would welcome the opportunity to review and comment on subsequent versions of the protocol.

Auto-dissemination devices

Background

The In2Care[®] Mosquito Trap targets ovipositing *Aedes* vectors, exposing them to both a slow-kill adulticide and to 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 as a component of integrated vector management approaches for *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 leaving the trap. Mosquitoes are contaminated by fungal spores and pyriproxyfen applied to electrostatic netting in the device, which is transferred to mosquitoes entering the trap. The presence of pyriproxyfen in the trap also ensures that any eggs laid in the trap will not develop to the adult stage.

Update

In line with the recommendation from the VCAG at its ninth meeting, the applicant shared the protocol for an epidemiological trial in the Philippines, in the form of a manuscript submitted to the journal *Trials*.

Conclusions

The investigators are planning a cluster randomized trial with 20 clusters, using seroconversion to measure dengue epidemiological outcomes. It was noted that it would be useful if the investigators provided more quantitative information about the numbers of people to be enrolled and expected disease rates, as well as the geographical size of clusters in the protocol.

VCAG referred the investigators to “How to design vector control efficacy trials” (32) and the CONSORT guidelines for cluster randomized trials (13) for advice on important design aspects.

VCAG notes, it is important to allow for within cluster correlation in the primary outcome when assessing the power of the trial. The protocol does not do this and consequently suggests that a smaller number of children need to be recruited than is likely to be the case. The investigators do envisage allowing for clustering using random effects models in the statistical analysis, so if they implement this protocol they would be likely to find effects of the anticipated size to be non-significant.

The clusters are rather small but exclusion of buffer zones should minimize spill-over due to mosquito movement among clusters. This does not, however, address the issue of human movement among clusters. It is not clear how much exposure may occur when children are outside the cluster to which they are assigned, which is implicitly (but not explicit) that they will be assigned to the cluster of their residence. VCAG asked how the investigators proposed to account for exposure at school. For example, if half of a student’s time at risk is away from home, an overall efficacy of 50% of an intervention that works only at home would have to be perfectly efficacious in the home.

More clarity needs to be provided in the protocol on the seroconversion in the process to enrol candidates in the study. As there are only four serotypes, it is unclear whether people who have already been exposed to one or more serotypes will be enrolled. Identification of tertiary and quaternary infections with immunoglobulin G is difficult, and those who have been exposed to all four serotypes cannot be re-infected. These children would by definition not be counted in the power calculations. Furthermore, the Group asked, for the saliva-based assay, are there data available on cross-reactivity with Zika. Concerning the disease rates, the authors appear to confuse “incidence rate” with “force of infection” causing a flaw in the sample size calculations.

When reconsidering the age-dependent percentage of the population whose next infection could be detected by measuring immunoglobulin G, the authors should carefully consider how many children would have to be recruited to obtain the 2,054 children they indicate are needed. It is frequently not an option to assess serological history at enrolment, but that is either necessary or recruitment must include more children to account for those who will not count towards the end-point.

Currently, the only measure of entomological impact will be the density of adult mosquitoes measured in gravid *Aedes* traps. As such, it will therefore be difficult to distinguish entomological impact attributed to autodissemination from the entomopathogenic fungus. In addition, monitoring of the development of insecticide resistance to both pyriproxyfen and *B. bassiana* should be considered. The investigators might consider measuring other entomological end-points, such as whether the traps have any sterilizing effect or how the dengue infection rates in vectors change. In this context, the investigators could refer to “Efficacy-testing of traps for control of *Aedes* spp. mosquito vectors” (14), which includes guidance on procedures for estimation of impacts in the field and other relevant protocols, such as assessment of optimal trap density.

The protocol would benefit from a more detailed description of the placement of the intervention traps (In2Care®) in time and space in relation to the gravid *Aedes* traps.

An important element of a well-conducted randomized trial is blinding of both the participants and the investigators. This is often difficult with vector control interventions but should be feasible to some extent with the In2Care® Trap. It would be beneficial to address this aspect in the protocol.

Recommendations

The investigators should carry out an analysis of the power of their trial design, reviewing the assumed incidence, and allowing for the clustering of dengue infections in their study area. They should share this with VCAG as soon as possible, and recruit more children/clusters if this is indicated. They should also address the issues of human movement and blinding.

Interventions reviewed during the meeting

Adulticidal oviposition and larvicidal traps – new product

Background

The ALO trap is a larvicidal trap designed to attract *Aedes* mosquitoes to deposit their eggs into the provided artificial water bodies (180 x 180 mm), where they will be destroyed by physical means before they can develop into adult mosquitoes. The current version of ALO is fully autonomous and communicates with human operators via the Internet. Human operators are required only to correct malfunction. The product is currently being used to reduce nuisance mosquito-biting in two holiday resorts in Indonesia and in a private home in Singapore. During its development, ALO was used in several industrial settings, including construction sites and a dormitory housing some 5000 workers. The applicants presented their product to VCAG for the first time, seeking preliminary guidance on the steps required for assessment of its public health value.

Summary of discussions

- VCAG noted that, in the context of the WHO process to evaluate of vector control products, investigators need to first provide quantitative evidence of the entomological impact of their intervention and consider how they would measure public health impact.
- Concerns were raised around the need for both electricity and Internet for the product to perform, and that this might limit the scope of its use in some disease endemic settings.
- It was unclear exactly how the product disposed of eggs and larvae. While the term “destroyed” was used, it was unclear if the eggs and larvae were flushed out onto the ground or buried underground. The former could present a problem as *Aedes* eggs can survive desiccation.

Conclusion

This product is at an early stage of product development, and is currently being used to reduce nuisance biting by mosquitoes in resort settings. If the applicants wish to continue progressing their product in the WHO process, they should begin to build an evidence base for their product’s use in vector control for public health.

Recommendations

Given the early stage of the product development, the applicants are encouraged to review the Efficacy-testing of traps for control of *Aedes* spp. mosquito vectors (14). This should assist in orienting them to identify the types of evidence they should seek to generate in their subsequent studies of the trap as a public health vector control intervention. They are encouraged to meet with the PQT-VC to discuss the requirements for prequalification.

The applicants should seek collaborators to assist in the design and implementation of the recommended studies to collect the quantitative entomological evidence necessary to move to the next stage of the process.

Endectocides – new product

Background

The objective of the “broad one health endectocide-based malaria intervention in Africa” (BOHEMIA) project is to determine the efficacy of ivermectin given by mass drug administration to humans and to humans and livestock to reduce residual transmission of malaria. The rationale is that mosquito blood meals containing a sufficiently high concentration of ivermectin increase mosquito mortality. The project comprises two epidemiological trials, one in Mozambique and one in the United Republic of Tanzania, designed to evaluate the impact of ivermectin in preventing malaria infection. The target livestock species is pigs in Mozambique and cattle in the United Republic of Tanzania.

Each trial has three arms, the interventions or albendazole + placebo changing in each arm between the first and the second year. In arm A, ivermectin is given to humans (with some exclusions; e.g. children less than 5 years of age and females of child-bearing age) in three monthly doses at the start of the rainy season in year 1 (humans in this group also receive placebo + albendazole) and to humans and livestock (three treatment rounds, one month apart, in parallel with human dosing) in year 2. In arm B, albendazole + placebo–ivermectin (1 albendazole tablet and weight-adjusted placebo–ivermectin tablets over the three months) are given to humans in year 1 and ivermectin to humans in year 2. In arm C, there are no interventions in year 1, while albendazole + placebo is given to humans in year 2. Hence, arm B receives the same intervention in year 2 as arm A did in year 1, and arm C receives the same intervention in year 2 as arm B did in year 1. This is illustrated in the following table, adapted from the material provided by the applicants:

Year	Arm A	Arm B	Arm C
1	Ivermectin given to humans	Control (albendazole plus placebo)	
2	Ivermectin given to humans and livestock	Ivermectin given to humans	Control (albendazole plus placebo)

The trial is double-blinded. The intervention group will receive weight-adjusted ivermectin plus placebo–albendazole. The control group will receive albendazole + weight-adjusted placebo–ivermectin.

The applicants reported that both sites have high coverage with long-lasting insecticide-treated nets (LLINs), and they will therefore not distribute LLINs themselves.

The primary outcome is the incidence of malaria infection in children under 5 years, as measured monthly with two rapid diagnostic tests (RDTs). The children will not

receive ivermectin but should benefit from any reduction in malaria transmission at the community level. This is the primary study end-point.

The applicant sought feedback from VCAG on the study description and justification document, after which they will develop a full protocol for VCAG review.

Summary of discussions

In response to a question concerning the lack of pharmacokinetic analyses in pigs in the background material, the applicants indicated that a review of such studies in pigs had been completed, with one parameter being the area under the curve (AUC) of ivermectin blood concentration over time. The applicants indicated that ivermectin treatment may be more efficacious against mosquitoes in pigs than in cattle, given the higher AUC in the former.

The applicants said that the trials would be conducted according to “good clinical practice” and that the participants would be under active surveillance for adverse events for six days after receipt of each of the three monthly doses of 400 µg/kg body weight ivermectin. They would remain under passive surveillance for the remainder of the month by monitoring at local health facilities in the study areas.

The documentation provided to VCAG specified a 10-day LC₅₀ (i.e. the concentration that causes 50% mortality in a population of tested mosquitoes within 10 days) of 2 ng/mL blood for *Anopheles arabiensis*. The value was not supported by literature cited in the documents submitted by the applicant. The applicants said that they had reviewed the literature – which they subsequently indicated included work by Chaccour et al. (15) and Smit et al. (16) – and their synthesis of the toxicology data, concluded that a concentration of 2 ng/mL could reasonably be expected to achieve the target mosquito mortality rate.

The applicants confirmed that the study would be conducted with the oversight of a Data and Safety Monitoring Board and would be subject to ethical approval at the institutional and national levels.

The applicants refer to the end-point measurement process as active case detection (ACD), even though not all infections so detected will be symptomatic (page 17 of the study description says that ACD will consist of measuring infection incidence, and that all children will be tested monthly). In other words, the use of the word “case” may be misleading.

The applicants indicated that the main end-point will be based on all malaria infections in children under five years of age within each group (arm), rather than the time to first infection. It may be worth including time to first infection, at least as a secondary end-point, due to the unknown but probably relatively short duration of the effect of ivermectin.

The applicants said that they would monitor *Anopheles* throughout the trial to address the concern of possible development of resistance to ivermectin.

The applicants indicated that the impact of the drugs on human intestinal parasites and the development of drug resistance in human helminth parasites were outside the scope of the study and would not be addressed. The applicants mentioned related studies (performed by other investigators) they considered adequate to address those issues. The applicants do plan to monitor faecal egg counts in a subset of treated livestock to measure of possible tolerance to ivermectin in veterinary helminth parasites. The

applicants indicated that untreated livestock could serve as refugia to reduce selection pressure on veterinary parasites. While management of resistance to veterinary parasites is outside the scope of a VCAG review, regulatory authorities may wish to consider this issue.

The applicants were asked about the choice of albendazole (a nematode control drug) to be used with placebo in the control regimen. Specifically, they were asked whether they had confirmed that this drug is unlikely to kill mosquitoes at the selected dose. They replied that, although they did not expect such an effect, they had planned a study to evaluate the issue.

The target coverage of people treated with ivermectin was stated to be 64%. No corresponding figure for livestock was mentioned.

The applicants reported that they have a plan for stakeholder engagement, led by a social scientist.

Conclusions

Topics of primary concern, based on the supporting documentation and discussions with the applicants, are summarized below.

Ivermectin toxicity to mosquitoes and livestock pharmacokinetics. The mosquito mortality rate is related to ivermectin blood concentration in a dose-dependent manner (17). The two key factors that influence the efficacy of ivermectin in reducing malaria transmission are: 1) human and livestock ivermectin plasma levels after administration of the specified dose and 2) the duration the plasma concentration is sustained above the mosquito plasma LC_{50} . The materials provided to VCAG and the references cited therein do not provide a clear presentation as to how the LC_{50} was derived and selected, nor is it clear how pharmacokinetic studies in cattle and pigs were evaluated to ensure ivermectin plasma concentrations in these livestock would be sustained above a lethal level for mosquitoes. The applicants referenced an ivermectin pharmacokinetic study in Zebu Gobra (*Bos indicus*) (18), a West African cattle breed, as being a representative study but did not provide an analysis documenting that cattle breeds in eastern and southern Africa would exhibit similar kinetics. Ndong et al. (18) reported that physiological differences among breeds may influence the pharmacokinetics of ivermectin. The applicants also did not provide a summary of pharmacokinetics studies of ivermectin in pigs.

While VCAG assumed that the applicants had performed a robust synthesis and interpretation of the literature on mosquito toxicity and livestock pharmacokinetic the strength of the submitted study design would be enhanced with the inclusion of these analyses in the final protocols. These summaries would provide insights on the strengths and limitations of the supporting information and the extent to which uncertainty in mosquito toxicity and/or pharmacokinetics data influences the study design. The summaries will also be useful for assessing the epidemiological results.

Length of the study. Currently, "VCAG recommends that duration of epidemiological assessment, excluding the baseline period, should cover at least 2 years, to account for inter-annual variation in transmission." (19)¹. The proposed trials do have two years of follow-up, although no arm receives the same intervention for both years. The comparison of most interest to the applicants seems to be between i) ivermectin in

¹This duration is not a WHO requirement for assessment of epidemiological impact.

humans and ii) control (albendazole + placebo in humans). This comparison can be made between arms A and B in year 1 and between arms B and C in year 2. Hence the trials comply with the cited guidance, although in an atypical way (by using three arms to make a binary comparison). Switching interventions after one year will restrict the available information on the durability of the interventions and on sociocultural issues related to sustained implementation, including coverage.

Generalizability. The differences between the study sites in terms of malaria transmission enhance the generalizability. The applicants noted there is already some evidence on the use of ivermectin as an endectocide in West Africa (e.g. Foy et al. (20)) and that at least one further trial is planned in that region. The applicants also noted the risks of people infected with *Loa loa* for encephalopathy after treatment with ivermectin (21) but confirmed that Mozambique and the United Republic of Tanzania are not endemic for this infection. Nevertheless, should the intervention prove effective, the extent of *Loa loa* infection would constrain its applicability geographically.

Stakeholder engagement plan. VCAG noted the importance of the stakeholder engagement plan in refining the study design and assessing the likelihood of participation of people within the clusters. VCAG need not review this plan before finalizing the study design and protocols; however, access to the plan will likely assist interpretation of the study results.

Recommendations

The applicants indicated that they would write a detailed protocol on receipt of feedback from VCAG. The protocol should take into account general guidelines such as SPIRIT (22) and CONSORT (13) and WHO guidance (3). More specifically, VCAG recommends that the applicants provide:

- the rationale for the choice of design, bearing in mind effects resulting from delayed acquisition of immunity in the child population. In particular, the experimental interventions, the control intervention and the changes over time within arms should be justified. The protocol should make clear why the proposed design is preferable to a more standard one (in which each arm would stay on the same interventions). Bearing in mind the evidence for an effect of oral albendazole on head lice (23), caution is warranted in the use of albendazole as part of the control set of interventions, as long as a non-negligible effect on mosquito mortality cannot be ruled out.
- the rationale for the choice of end-point (infection as opposed to disease) and the choice of the monthly frequency for measuring this.
- the rationale for why the stated effect size of 20% is realistic.
- the rationale for the cited value of 25% for the between-cluster coefficient of variation, preferably referring to existing data from the trial sites.
- a detailed explanation of the sample size method. If matching is to be used, then the matching criteria should be explained and justified.
- a statement of the exact expected power (under a base scenario, and possibly others).
- a description of how the statistical analysis will make the comparisons of main interest (and in due course a separate statistical analysis plan).
- a summary of evidence (peer-reviewed or not) on the potential impact of ivermectin on resistance in human parasites.

- a description and justification of the target coverage of livestock.
- an addendum describing determination of the ivermectin LC₅₀ value, including
 - summary of available toxicity studies and associated references, and
 - analysis supporting a 10-day, 2 ng/mL LC₅₀ and the associated uncertainties.
- an addendum addressing cattle and swine ivermectin pharmacokinetics, including
 - a summary of pharmacokinetic studies, data quality and associated references.
 - analysis of data, including interpretation of interspecies differences, that establishes time course of plasma levels reached in cattle and pigs after a given dose and the duration for which plasma concentrations are sustained above the lethal plasma mosquito LC₅₀.
- an addendum including stakeholder engagement plan.

VCAG noted that the applicants will provide information to WHO to support their estimates of the potential environmental impact of the intervention. It would be helpful to provide VCAG a more complete list of environmental variables that are being considered for monitoring environmental impact; these variables may also be helpful for interpreting the epidemiology study results.

Spatial repellents – review of data

Background

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

At the ninth VCAG meeting the applicant provided an update on the two trials: the Sumba Island trial in Indonesia on malaria and the Iquitos trial in Peru on *Aedes*-borne viruses. Subsequently, the applicant submitted a revised protocol and a statistical analysis plan for a trial of spatial repellents in Kenya for off-cycle review. At the tenth VCAG meeting, the applicant presented the findings from the double-blinded epidemiological trial in Indonesia and received further feedback on the protocol for the trial in Kenya, which had been updated after the off-cycle review. The trial conducted in Indonesia was a double-blind placebo-controlled cluster randomized trial comparing spatial repellent implemented in 12 clusters and the control devices in 12 other clusters. The primary end-point was the incidence of malaria infection as tested in a randomly selected cohort of children aged 5–59 months. The study team monitored subjects for 24 months during the intervention, during which one time a month blood samples were taken from all subjects, regardless of symptoms (active detection), and every two weeks blood samples were taken from only those subjects reporting fever in the previous 48 hours (passive detection).

Review of the protocol and the statistical analysis plan for a trial in Kenya: off-cycle review

Background

The applicants requested VCAG to carry out an off-cycle review of a trial protocol to demonstrate the protective efficacy of spatial repellents in reducing malaria infection in human cohorts in Kenya. The protocol under review is a 'split cohort' study design as opposed to the single cohort study design reviewed by VCAG in November 2018. The applicants also asked VCAG to review the related draft statistical analysis plan for the Kenya trial.

Conclusions

At the time of the off-cycle review, VCAG could not provide final recommendations on the protocol as some inconsistencies in the documentation were observed and clarifications were required to resolve key aspects of the experimental design and statistical analysis plan for the proposed spatial repellents trial in Kenya. VCAG provided feedback on the areas where further information and clarity were needed, and requested the applicants to resubmit the final documents for review at the tenth VCAG meeting. Based on the documents submitted for the off-cycle review, VCAG provided the following preliminary feedback:

Two-cohort design: VCAG approved of the applicants proposal to switch to recruiting two separate cohorts for measurement of disease incidence, each with 12-month follow up over two consecutive years, from the previous plan of following one cohort over 24 months.

Selection of clusters: VCAG requested the protocol incorporate description of how clusters will be defined, including approximate population and spatial dimensions as required for assessment of study design.

Baseline: It was not clear whether the protocol would include a baseline monitoring period. VCAG does not recommend excluding a baseline monitoring period, unless the applicants can demonstrate that there is good, recent and site-specific epidemiological and entomological data available that could be used to stratify the clusters. These data should be sufficient for sample size calculation for epidemiological and entomological outcomes.

Power analysis for diversion cohort: The explanation of the power analysis for estimating the diversion/community effect was difficult to interpret. VCAG asked for clarification of the magnitude of the decrease/increase in "near-zone" incidence that the study is powered to detect.

Boundary zone for diversion: The applicant proposes a 500-m buffer zone around each cluster for the study of diversion. Justification for this should be given.

Entomological monitoring: Entomological monitoring was proposed for only three clusters of each treatment (10% of total), to be based in four households per cluster, with the same households sampled throughout the study. Given the often large heterogeneity in mosquito densities among households and clusters, this seems insufficient and unlikely to represent the study area or impacts of different interventions. The applicants were encouraged to specify the effect size they wish to detect for entomological outcomes, and carry out sample size calculations for the number of households that would need to be sampled to measure this. Additionally, VCAG encouraged the applicant to consider wider-scale and representative entomological sampling within the constraints of the study design.

The applicants proposed different entomological monitoring approaches for the primary and diversion cohort (human landing catch vs CDC light traps). To avoid potential bias due to differential sampling efficiency, researchers should consider collecting data to confirm the association between indoor human landing catch and CDC light traps in the study area.

Insecticide resistance: The applicants proposed to measure insecticide resistance in only four clusters per arm. This would allow the applicants to confirm if the local vector populations are insecticide resistant, but not more fine-scale investigation of whether the impact of the intervention is modified by the degree of insecticide resistance in the vector population (e.g. at cluster level). If the applicants aim to investigate this, resistance monitoring should be conducted throughout the study area. VCAG recommended that the applicants perform additional bioassays (e.g. the use of 5 x and 10 x intensity assays) in addition to the standard discriminatory dose approach.

Interim analysis: VCAG emphasized the value of continuous assessments through the Data and Safety Monitoring Board (DSMB) in terms of providing information to evaluate whether the trial should be stopped for unacceptable adverse events indicating evidence of harm, low accrual, poor data quality or poor adherence. As stated previously, VCAG does not intend to make recommendations to WHO on the basis of an interim analysis and therefore did not recommend that a formal interim analysis of efficacy be made. If the applicants are planning an interim analysis, VCAG recommended that it be carried out by the DSMB with the investigators blinded, if possible. Further guidance and recommendations can be found under “Conditions for early termination of trials” on pp. 7 and 8 of the eighth VCAG meeting report (19).

Statistical analysis plan: VCAG requested that the applicants address some inconsistencies in the description of the statistical analysis methods proposed in the trial protocol and the accompanying statistical analysis plan.

VCAG expects that the analysis will follow the CONSORT guidelines for cluster randomized trials (CRTs).

In addition to the adjusted analysis that is described in the statistical analysis plan VCAG encouraged the statistician(s) to report an analysis without covariates included. It is hoped that the design will ensure that there is reasonable balance for these covariates and so their inclusion in the analysis is not expected to make a substantial difference to the efficacy estimates. To avoid potential accusations of data dredging, it is essential that the investigators clearly state their primary analysis plan. The applicants were asked to provide clarification on nature of some of the covariates in the models.

Proposed analysis of entomological indicators: In its current state the proposed analysis for potential entomological indicators of epidemiological effect in the statistical analysis plan is limited. The applicants were provided with feedback and suggestions for further development of the analysis, including clarification of the epidemiological outcome of interest, consideration of testing for time-lagged associations, incorporation of relevant covariates and which entomological indicators may be most appropriate.

Review of findings from the trial in Indonesia and review of the protocol for the trial planned in Kenya – reviewed during tenth VCAG meeting

Update

The applicants reported the preliminary results from the recently completed trial of spatial repellents in Indonesia. They also presented an update on the progress of the

spatial repellents trial on *Aedes*-borne viruses in Peru. Surveillance of febrile illness and longitudinal sampling of viral incidence in this trial was completed in March 2019, however sample processing was ongoing and anticipated to be completed by August 2019. The applicants also sought VCAG feedback on a statistical analysis plan for the trial in Peru and on the revised protocol and statistical analysis plan for the planned trial in Kenya.

In relation to the above mentioned updates the applicants posed the following questions for VCAG which are answered in the conclusion and recommendations sections.

- i. Does VCAG consider Indonesia trial to have a positive outcome?
- ii. Does VCAG require additional statistical analysis for Indonesia database?
- iii. Does Indonesia trial satisfy one of the two required for trials for the spatial repellents public health value assessment?
- iv. Does Panel endorse Peru statistical analysis plan?
- v. Does Panel endorse Kenya study protocol and statistical analysis plan?
- vi. Any further comments following up from the response to off-cycle review?

Summary of discussions

Discussions largely focused on the preliminary results from the trial in Indonesia. The applicants highlighted that the primary outcome (incidence of first-time and all malaria infections) from the Indonesia trial showed some sign of protective efficacy; however this effect was not statistically significant at $p = 0.05$ level. Applicants indicated that the trial design had lower statistical power than originally anticipated based on the power analysis before the study started. The applicants highlighted that this was likely due to the unexpected large variability in baseline incidence and some clusters exhibiting zero baseline incidence, which precluded the ability to detect an effect as there was no malaria risk to subjects in the zero-baseline-incidence clusters. The applicant reported that there was also no statistically significant effect of the spatial repellent product on secondary entomological outcomes, anopheline human biting rate.

However, further analysis of some subgroups of clusters (e.g. those in which malaria infection was detected and entomological monitoring was conducted) did show a statistically significant effect of the intervention. The relevance of these sub-analyses and the potential contribution of these data for future consideration of WHO policy recommendation for spatial repellents was discussed. There was also discussion of the number of epidemiological trials needed before WHO would consider making a policy recommendation versus the relative strength of evidence from different trials. It was clarified that the minimum requirement for WHO to initiate the process of evidence review and policy formulation is two epidemiological trials. The minimum number of "two" is based on the need for at least some degree of replication of results from different studies as a precondition for any assurance that an intervention will be generalizable. More trials with epidemiological endpoints may, however, be required if the initial two studies generate contradictory results or suffer from design limitations that precluded comprehensive assessment of potential epidemiological impact.

There was also a discussion of the updated protocol and statistical analysis plan for the Kenya trial on impact of the spatial repellent product on anopheles mosquitoes, the statistical analysis plan for the trial in Peru and the outline of a future trial of spatial repellents against *Aedes* in Sri Lanka. Following review of the Sri Lanka study protocol in November 2018, VCAG recommended that the applicants incorporate measurement

of possible diversionary impacts of the spatial repellents in one of their *Aedes* trials. Evaluation of diversion was not part of the original aims of the *Aedes* trial in Peru. VCAG appreciates the applicant's additional consideration of a retrospective analysis of the Peru trial for signs of diversionary effects, while advocating for testing in a future trial. Applicants have responded they will do this by "post-hoc analysis" of differences in epidemiological end-points among households within intervention clusters that received the spatial repellents and those that decline them. VCAG observed that if the very high intervention adherence observed in Indonesia is repeated in Peru and Sri Lanka, then there will be hardly any non-users. Thus this type of opportunistic post hoc approach may not be informative.

Whilst the applicants were encouraged to explore whether any information could be obtained using this approach from data already collected in Peru, VCAG did not consider this approach to be robust or reliable to measure the potential diversion effect in future studies (e.g. the planned trial in Sri Lanka). The applicants responded that full epidemiological evaluation of potential diversionary effects for *Aedes* would require monitoring of an unfeasibly large number of clusters and enquired whether VCAG would view collection of data on entomological diversion in the Sri Lanka trial as a useful compromise. VCAG discussed this proposal and, in lieu of capacity for full epidemiological assessment, tentatively supported the concept of using this approach for this specific situation. It should, however, be recognized that VCAG does not consider this approach as yielding the same certainty of evidence as one using epidemiological end-points.

Conclusions

Indonesia trial results: VCAG concluded that the first trial (Indonesia) investigating the impact of the spatial repellent product on malaria shows promising results but was underpowered for demonstrating clear protective efficacy. The primary per-protocol analyses of the Indonesian trial provides an estimate of protective efficacy against malaria infection of 27%, which is close to the efficacy of 30% assumed in the power calculations. This effect, however, was not statistically significant and the confidence intervals are wide and include zero. There were 298 first time infections, in contrast to an expected number of at least 417 in the sample size calculations, which results in the trial being underpowered. Although further analysis of some subgroups of clusters (e.g. those where malaria infection was detected, and where entomological monitoring was carried out) did show a statistically significant effect of the intervention. Consequently, VCAG concludes that the trial was inconclusive with respect to the protective efficacy of the intervention and there is a pressing need for further evidence.

While more evidence will be required to determine whether or not a WHO recommendation for spatial repellents as a malaria control intervention is warranted, VCAG highlighted that this trial generated useful data that can contribute to a future assessment. The entomological results and sub-group analyses are promising and strongly support the continued evaluation of the potential epidemiological impact of this tool. VCAG does not require any further analyses of the Indonesia data, but requests the applicants share the full documentation for review after all analyses are completed.

Both the primary and secondary results of the Indonesia trial will contribute usefully to the overall weight of evidence on spatial repellents. Once data from at least one additional trial are available, WHO will be able to review the available evidence. Whether a future review will lead to a recommendation for or against the intervention and/or a request for additional data generation will depend on the effect observed and the certainty of the evidence available in at least two trials.

Trial protocol and statistical analysis plan of the trial in Kenya: VCAG endorsed the updated Kenya Trial Protocol and statistical analysis plan that now provides clarification

on sources of background data for power and sample size calculations, selection of clusters, allocation of spatial repellent intervention etc. This document could nevertheless benefit from some further clarification and minor revision, with details provided in the recommendations below.

Statistical analysis plan of the trial in Peru: VCAG endorsed the updated statistical analysis plan for the trial in Peru. The applicants indicate in the report that the Medical Monitor has reviewed AE reports for the Peru trial and suggested there is evidence for the product being associated with respiratory complaints. The safety report should be submitted to PQT-VC.

Assessment of diversion in the planned trial of spatial repellents against Aedes-borne vectors in Sri Lanka: VCAG accepted use of entomological indicators to measure diversion in the trial in Sri Lanka as a better alternative to the previously proposed post-hoc analysis based on disease rates in households who declined the spatial repellent product. VCAG would prefer that diversion be formally measured in an epidemiological trial design with disease outcomes; however, given this is not logistically practical or economically feasible in the current trial, collecting entomological data on diversion is preferable to not making any measurements.

Recommendations

Major

- VCAG strongly supported continuing evaluation of spatial repellents against both Aedes (Sri Lanka) and Anopheles transmitted diseases (Kenya).
- VCAG endorsed the statistical analysis plan for the trial in Peru.
- VCAG recommended that the applicants collect data to test for entomological diversion of the spatial repellent product in Sri Lanka if it is not possible to measure epidemiological impacts. VCAG will review a protocol for this additional component of the trial, including definition of specific entomological indicators that will be used to assess the diversionary effects.
- VCAG endorsed the revised protocol and statistical analysis plan submitted for the proposed trial of spatial repellents against malaria in Kenya but recommended minor revisions and updates to the documents as outlined below.

Minor

Proposed minor revisions to the protocol and statistical analysis plan of the trial in Kenya:

- VCAG asked for clarification of the length of the follow-up period, which is stated to be 10 months in Annex 6 of the statistical analysis plan and 12 months in the protocol.
- The Group also asked for clarification of whether covariate adjustments will be included in the primary analysis or when there is imbalance in the distribution of the covariates. The assumption is that randomization will result in balanced groups for comparison. The Group noted that the “imbalance” referred to in section 7.2, where 99% of households had the same type of wall, is a case of homogeneity not imbalance (the statistical analysis plan for the trial in Peru has a similar terminological issue).
- The Group noted that the statistical analysis plan states that the “distance of each household in the near zone to the centre of the core zone” will be used as a predictor of the diversion effects. VCAG suggest that this should instead be the distance to the nearest intervention house in the core zone.

- The applicants proposed to investigate the relationship between spatial repellents and insecticide resistance by “pairing insecticide resistance levels” (at baseline and in each study year) with the corresponding malaria incidence. VCAG found it unclear how this would allow evaluation of the impact of insecticide resistance on spatial repellents or vice versa. The applicants should clarify how this assessment will be done.
- The applicants should clarify the basis for the choice of transfluthrin doses selected as discriminating doses in each study (12 µg/mL in Indonesia, 7.5 µg/mL in Peru and 0.2 µg/bottle in Kenya).

Population reduction – gene drive approach – update

Background

Target Malaria’s vector control technology uses gene drive to reduce mosquito populations, with the aim of developing selective vector control, specific to the *Anopheles gambiae* s.l. vectors that transmit human malaria parasites in Africa. Gene drive for vector control is a process of preferential inheritance that allows a gene to rapidly increase in frequency in a targeted vector population. The proposed intervention will involve the release of male *Anopheles* mosquitoes bearing a gene drive construct that causes either infertility in females and/or a distortion in the sex ratio. Both interventions are designed to reduce malaria transmission by suppressing mosquito vector population density.

The proposed candidate gene drive products use sequence-specific nucleases to produce a male-biased sex ratio or sterile females, or both. While still in very early stages of development, these interventions will aim to substantially reduce malaria infection and/or disease. This is a new technology, and Target Malaria envisages developing a series of constructs (currently called products 1 and 2) of increasing efficacy. The aim of using the first product (“Product 1”) is to achieve at least a 67% proportionate reduction in vectorial capacity over three years in moderate transmission settings in sub-Saharan Africa. The aim of using the second product (“Product 2”) will be to achieve at least a 99% reduction in vectorial capacity for 10 years in all transmission settings in sub-Saharan Africa. The applicant defines the desired outcome of their tool as providing a novel, cost-effective biological intervention that will contribute to the elimination of malaria in Africa.

Updates

An update on the project’s progress was presented with notable accomplishments being highlighted, including:

- The identification of a highly conserved, resistance-mitigating homing site that results in a recessive phenotype in which genetic females develop as sterile, non-biting intersexes (24);
- Country-level modelling of a male-biased gene drive predicting the potential efficacy of spread of a Product 2-like gene drive construct when released from only 10% of settlements/villages in Burkina Faso (25);
- Theoretical work involving the development of a new method for estimating mosquito population size from estimates of the number of independent mutation events leading to a common *kdr* mutant phenotype using data from the *An. gambiae* 1000 genomes project (26), which is a global collaboration using whole-genome deep sequencing to provide a high-resolution view of genetic variation in natural populations of *An. gambiae*, the principal vector of *Plasmodium falciparum* malaria in Africa (27); and
- Continued progress in developing responsible stakeholder engagement practices.

The applicants also shared two new draft papers summarizing progress and practice in stakeholder engagement and knowledge exchange (28, 29).

Summary of discussions

VCAG acknowledged these updates represent significant progress and encouraged Target Malaria to continue its product development and stakeholder engagement efforts.

With respect to the phased testing pathway that was proposed for experimental release of Target Malaria's genetically modified (GM) mosquitoes, the group understood and supported the rationale for this step-wise approach involving initial release of self-limiting (non-driving) GM mosquitoes and eventually the release of gene-drive-containing GM mosquitoes. The group was somewhat unclear and discussed the rationale for conducting field releases of GM sterile male mosquitoes without gene drive in one country and GM mosquitoes of Target Malaria's "self-limiting" male-biased line without gene drive in other countries. Because site-specific baseline entomological data will be needed prior to any experimental release of GM mosquitoes with or without gene drive, VCAG thought that working in multiple sites was potentially complicating an already challenging project. The field site for the first field trial of Target Malaria's Product 1 has not been determined, although the applicants indicate that site characteristics may include geographically or otherwise isolated locations. VCAG and the applicants recognized that, once the trial site is identified, extensive ecological surveys should be carried out to identify optimal release sites for mosquitoes (e.g. potentially close to larval habitat sites where wild populations of mosquitoes mate).

The applicants were encouraged to liaise with PQT-VC to discuss possible regulatory issues, appropriate safety end-points and entomological outcomes. They were also encouraged to engage with VCAG to receive feedback on early stage-planning of epidemiological trials by submitting preliminary trial designs and protocols for review.

VCAG informed the applicants that with regard to any policy decisions on geographical scale for eventual deployment/policy decision, WHO cannot comment on what a potential policy decision will be before VCAG has had a chance to see trial results. VCAG does not have any *a priori* expectations regarding geographical scale of deployment as this will be dependent on the nature of the evidence-base supporting deployment.

The applicants had a query with regards to how forthcoming guidance from other United Nations organizations may impact the WHO evaluation process for vector control products. Given that this guidance is not yet available, WHO is not in a position to comment on how the guidance from other organizations may impact the process.

Conclusions

Target Malaria is making significant progress in both technical development of their products and in engagement activities with stakeholders.

Recommendations

- VCAG reiterated its previous recommendation: "VCAG encourages further development of tools utilizing gene drive based technologies while recognizing that these strategies are still in the early phases of development, and that important challenges lie ahead for their development and deployment. More evidence from laboratory-based studies is needed before semi-field or open field-testing should be undertaken." (19)

- Target Malaria was encouraged to continue using the phased approach in development and testing of GM mosquito products (30, 31).
- Target Malaria should begin discussions with PQT-VC on the requirements for prequalification of Product 1.
- Target Malaria should continue to explore options for designing a trial to assess the entomological impact of Product 1. The design should involve confining the early evaluation of interventions to a restricted geographical area and a concrete proof of concept is achieved with entomological outcomes before considering release of gene drive mosquitoes in other areas or countries.
- VCAG recommended that Target Malaria carry out baseline entomological studies at the proposed trial site of Product 1, when determined, and to not rely solely on entomological baseline data collected at different sites used for pilot releases of GM sterile mosquitoes.
- Target Malaria was encouraged to keep VCAG updated on its progress and plans as it moves closer to considering initial trials of its gene drive mosquitoes, so that VCAG can provide input on trial design.

Attractive targeted sugar bait – update

Background

Attractive targeted sugar baits (ATSBs) are designed to attract and kill sugar-seeking mosquitoes. The concept was first reviewed by VCAG at its third meeting in 2014. In 2015, a two-year proof-of-concept study was initiated in seven treated and seven untreated villages in Mali in collaboration with the Innovative Vector Control Consortium. In May 2018 the applicants presented a summary of updates related to the 14-village entomological study in Mali, a social science study conducted in parallel and a draft protocol for trials with epidemiological outcomes at three sites, in Kenya, Mali and Zambia.

Updates

The applicants provided detailed updates on their plans to conduct three cluster randomized control trials of the ATSB for malaria control in Kenya, Mali and Zambia. These included details of a master protocol for the three proposed trials, in addition to country-specific protocols tailored to specific settings. In each setting, the impact of ATSB on clinical malaria will be assessed over a two year period. In Kenya, the intervention will be evaluated over a continuous 24 month period, while in Mali and Zambia, where transmission is seasonal, the intervention will be assessed during the major transmission period in two successive years. Key updates to earlier versions of these protocols submitted to VCAG were highlighted, these included specification of the study area in each country, definition of the primary outcomes, power analyses performed for primary and secondary outcomes based on baseline data from each study, and estimated sample sizes for the number of clusters and participants in cohort studies. The applicants confirmed that their sample size estimates had been reviewed and validated independently by the trial services at Medicine Technology Evidence Knowledge Sciences (Vancouver, Canada) in February 2019. Information on qualitative studies designed to understand the factors that influence the acceptability and coverage of ATSB, and how their use may influence LLIN use were also summarized. A detailed overview of the status of the ATSB product was also given, including the current status of manufacturing, prototype optimization and targets for scaling-up. A brief overview of the baseline entomological studies initiated at the trial sites in Kenya and Zambia was given; detailed information on baseline studies in Mali were presented previously during the eighth VCAG meeting (19).

Summary of discussion

VCAG asked for further detail on the status and timeline of the baseline entomological investigations that are being carried out at all trial sites in advance of the intervention

study. The applicants confirmed that these are under way and that further details, including of specific protocols, could be shared on request. VCAG advised the applicants to liaise with the PQT-VC concerning submission of data on entomological efficacy from the trials.

The applicants clarified how the proposed primary outcome (incidence of clinical disease) would be assessed in the epidemiological trial, including exclusion criteria, monitoring of children in the cohort study, choice of diagnostics, and use of passive surveillance data on malaria cases from health clinics as a secondary outcome.

The applicants described challenges in developing a prototype product for the trials. Although many improvements have been made since the previous year, the product has not yet met all the applicants internal development stage-gates required before starting epidemiological trials. This has resulted in a delay of the expected start date until 2021.

VCAG discussed the importance of minimizing the risks of vector control products to non-target insects and the need to incorporate assessments of the potential risk to non-target insects in testing the product.

Conclusions

VCAG judged the proposed designs for the epidemiological trials in Kenya, Mali and Zambia to be robust and appropriate, while suggesting some minor revisions or changes, as indicated below under the recommendations. VCAG noted, however, that the final protocol might have to be further refined closer to the start date of the trials to take into account necessary in-country risk assessments and final product characteristics, and as such may need to be reviewed again by VCAG.

Recommendations

Major

- VCAG recommends development of a formal statistical analysis plan for the planned epidemiological trials, including thorough definition of exclusion criteria, whether children in the cohort study will continue to be followed after they get malaria then clear infection, and details of statistical models for analysis of each end-point. It would be helpful if a fuller definition of the environmental variables to be measured can be considered and provided as these may influence how the intervention works.
- VCAG recommends the applicants review and update the power analyses with additional baseline data that they will collect before the start of the epidemiological trials.
- VCAG requests that the applicants provide a more detailed overview of the nature and associated timeline of the baseline entomological studies being carried out. This information along with any preliminary results could be shared with VCAG for information at the time of the next review.
- Due to ongoing development of the product prototype, the versions of the prototype used at different stages of assessment may differ (e.g. baseline entomology and full epidemiological trials). To inform the assessment of the epidemiological trial results, the applicants should provide a full overview of what prototypes were used at each stage.

Minor

VCAG requests the applicants incorporate the following minor changes and revisions into their current protocols for the epidemiological trials:

- Include an explanation of the strategy to ensure an even balance of access to clinics for passive reporting of cases between the control and intervention clusters.
- Clarify whether children in the cohort will continue to be followed-up or excluded after they develop and are treated for malaria infection.
- Consider adding additional exclusion criteria for subject safety into the incidence cohort study: i. allergic reaction to study drugs ii. participants under antimalarial prophylaxis iii. previous participation in a malaria vaccine study.
- Consider standardization of entomological sampling methods across sites, such that common end-points are estimated using similar sampling methods. E.g. avoid estimating sporozoite and parity rates from host-seeking collections at some sites and from resting collections at others, as these methods sample different components of the vector population.
- Some minor areas of inconsistencies were noted in the descriptions of similar procedures in the master and the country-specific protocols. For example, the master protocol indicates a follow-up period of 12 months over two years in Kenya, while the Kenya-specific protocol states follow-up for either 6.5 or 12.5 months. The master protocol indicates that an interim analysis will be conducted only to assess entomological outcomes and data quality, while some of the country-specific protocols state that an interim analysis for fertility will be conducted.

Product intent to impact – terminology and definitions

Marion Law, presented on the link between the intended use of a product and product claims from a regulatory perspective. She provided information on how the intended use of the product and product claims influence and determine the regulatory approach for different products. She did this through providing examples of how this is applied to vector control products and other product types.

She explained that a “claim” is a statement that a product has a certain benefit, impact or effect and that claims are identified by assessing the “net impression” conveyed by all elements of a label, including text, product name and description. Reliable scientific evidence is required to substantiate all product claims. Assessments should be based on tests, analyses, research, studies or other evidence provided by professional experts, which were conducted and evaluated objectively by qualified people using procedures generally accepted in the profession to yield accurate, reliable results.

Evaluation standards and procedures for assessing new vector control interventions

Dr Kolaczinski explained that, in May 2018, GMP had extensively reviewed WHO’s processes for developing and disseminating policy on malaria. This initiative gathered input from a broad range of stakeholders in order to better understand needs and perceived bottlenecks. A number of areas requiring improvement were identified, such as a perceived lack of transparency, inconsistent review standards and lengthy timelines. With the support of the Malaria Policy Advisory Committee, a number of recommendations were developed to address these issues. The new policy development process has three high-level steps:

- **Better anticipate:** activities that build-up to and trigger the policy development process.
- **Develop policy:** develop policy recommendations.

- **Optimize uptake:** dissemination of policy guidance and monitoring of its use.

The new policy development process calls for the formalization and publication of review standards. For evaluation of vector control products, two documents are currently used: "Evaluation process for vector control products" (31) and "How to design vector control efficacy trials. Guidance on phase III vector control field trial design" (3). Both should be updated to address changes in the policy making process and lessons learnt since their publication in 2017.

Dr Kolaczinski proposed to bring these two documents together into a document which articulates the evaluation standards and procedures for the assessment of the public health value of new vector control interventions. The new document could:

- explain how the evaluation process works,
- articulate the WHO requirements for assessing the public health value of interventions, and
- provide advice on designing studies and incorporate the guidance for collecting data on resource use.

Dr Kolaczinski said that the Secretariat will develop a draft of the proposed document and then will carry out technical and/or partners consultations.

Conclusions

Within the context of advice being provided by VCAG to applicants, VCAG discussed moving toward use of more standardized recommendations.

VCAG also discussed trial duration, they noted that optimal trial duration will depend on key factors related to the mode of action. Ultimately, a trial should generate robust and consistent data, for which a trial period of at least two full transmission seasons would generally be recommended.

Group discussion – VCAG operations, processes and feedback

Summary of discussions

VCAG members provided the Secretariat with feedback on their experience of conducting off-cycle reviews, whereby VCAG carries out a review outside the regular meeting schedule (see page 5). VCAG asked the Secretariat to develop criteria for screening applicants for off-cycle reviews more stringently, including ensuring that documentation is complete before being sent to VCAG.

VCAG would benefit from receiving updates from WHO when new vector control products are prequalified; either at meetings or via email from the Secretariat, when listings are made between meetings.

Endnotes

1. Overview of intervention classes and prototype/products under VCAG review for assessment of public health value. Geneva: World Health Organization; 2019 (<https://apps.who.int/iris/bitstream/handle/10665/274451/WHO-CDS-VCAG-2018.03-eng.pdf>, accessed July 2019).
2. Vector Control Advisory Group (VCAG) on new tools, technologies and approaches – terms of reference (WHO/CDS/VCAG/2018.04.Rev.2). Geneva: World Health Organization; 2019 (<https://apps.who.int/iris/bitstream/handle/10665/276401/WHO-CDS-VCAG-2018.04-eng.pdf>, accessed July 2019).
3. How to design vector control efficacy trials. Guidance on phase III vector control field trial design. Provided by the Vector Control Advisory Group). Geneva: World Health Organization; 2017 (https://www.who.int/neglected_diseases/vector_ecology/resources/WHO_HTM_NTD_VEM_2017.03/en/, accessed July 2019).
4. Malaria Policy pathway Overview. Geneva: World Health Organization; 2019 (<https://www.who.int/malaria/policy/en/>, accessed July 2019).
5. Dengue and severe dengue. Geneva: World Health Organization; 2019 (<https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue>, accessed July 2019).
6. WHO launches global consultations for a new Roadmap on neglected tropical diseases. Geneva: World Health Organization; 2019 (https://www.who.int/neglected_diseases/news/WHO-launches-global-consultations-for-new-NTD-Roadmap/en/, accessed July 2019).
7. Guidelines for malaria vector control. Geneva: World Health Organization; 2019 (<https://www.who.int/malaria/publications/atoz/9789241550499/en/>, accessed July 2019).
8. Data requirements and protocol for determining non-inferiority of insecticide-treated net and indoor residual spraying products within an established WHO policy class. Geneva: World Health Organization; 2019 (<https://www.who.int/malaria/publications/atoz/non-inferiority-protocol/en/>, accessed July 2019).
9. WHO, RBM Partnership to End Malaria. High burden to high impact: a targeted malaria response. Geneva: World Health Organization; 2019 (<https://www.who.int/malaria/publications/atoz/high-impact-response/en/>, accessed July 2019).
10. Prequalified lists. Vector control products. Geneva: World Health Organization; 2019 (<https://www.who.int/pq-vector-control/prequalified-lists/en/>, accessed July 2019).
11. Roles and responsibilities in the WHO process for the evaluation of vector control products. Geneva: World Health Organization; 2019 (<https://www.who.int/vector-control/vcag/vcag-may2019-roles-and-resp.pdf>, accessed July 2019).
12. Mosquito (vector) control emergency response and preparedness for Zika virus. Geneva: World Health Organization; 2016 (https://www.who.int/neglected_diseases/news/mosquito_vector_control_response/en/, accessed July 2019).
13. Campbell MK, Piaggio G, Elbourne DR, Altman DG, Consort Group. Consort 2010 statement: extension to cluster randomised trials. *BMJ*. 2012;345:e5661.
14. Efficacy-testing of traps for control of *Aedes* spp. mosquito vectors. Geneva: World Health Organization; 2018 (<https://apps.who.int/iris/bitstream/handle/10665/275801/WHO-CDS-NTD-VEM-2018.06-eng.pdf>, accessed July 2019).
15. Chaccour CJ, Alonso S, Zulliger R, Wagman J, Saifodine A, Candrinho B, et al. Combination of indoor residual spraying with long-lasting insecticide-treated nets for malaria control in Zambezia, Mozambique: a cluster randomised trial and cost-effectiveness study protocol. *BMJ Global Health*. 2018;3:e000610.
16. Smit MR, Ochomo EO, Aljayyousi G, Kwambai TK, Abong'o BO, Chen T, et al. Safety and mosquitocidal efficacy of high-dose ivermectin when co-administered with dihydroartemisinin-piperaquine in Kenyan adults with uncomplicated malaria (IVERMAL): a randomised, double-blind, placebo-controlled trial. *Lancet Infect Dis*. 2018;18(6):615–26.
17. WHO preferred product characteristics: endectocide for malaria transmission control. Geneva: World Health Organization, Global Malaria Programme; 2017 (<https://www.who.int/malaria/publications/atoz/endectocide-transmission-control/en/>, accessed July 2019).
18. Ndong TB, Kane Y, Ba MA, Sane I, Sutra JF, Alvinerie M. Pharmacokinetics of ivermectin in zebu Gobra (*Bos indicus*). *Vet Parasitol*. 2005;128:169–73.
19. 8th VCAG meeting report. Geneva: World Health Organization; 2018 (<https://apps.who.int/iris/bitstream/handle/10665/273106/WHO-CDS-VCAG-2018.01-eng.pdf>, accessed July 2019).

20. Foy BD, Alout H, Seaman JA, Rao S, Magalhaes T, Wade M, et al. Efficacy and risk of harms of repeat ivermectin mass drug administrations for control of malaria (RIMDAMAL): a cluster-randomised trial. *Lancet*. 2019;393(10180):1517–26.
21. Twum-Danso NA. Serious adverse events following treatment with ivermectin for onchocerciasis control: a review of reported cases. *Filaria J*. 2003;2(Suppl 1):S3.
22. Chan AW, Tetzlaff JM, Altman DG, Laupacis A, Gotzsche PC, Krleza-Jeric K, et al. SPIRIT 2013 statement: defining standard protocol items for clinical trials. *Ann Intern Med*. 2013;158(3):200–7.
23. Akisu C, Delibas SB, Aksoy U. Albendazole: single or combination therapy with permethrin against pediculosis capitis. *Pediatr Dermatol*. 2006;23(2):179–82.
24. Kyrou K, Hammond AM, Galizi R, Kranjc N, Burt A, Beaghton AK, et al. A CRISPR–Cas9 gene drive targeting doublesex causes complete population suppression in caged *Anopheles gambiae* mosquitoes. *Nature Biotechnol*. 2018;36:1062–6.
25. North AR, Burt A, Godfray HCJ. Modelling the potential of genetic control of malaria mosquitoes at national scale. *BMC Biol*. 2019;17:26.
26. Ag1000g. London: Wellcome Sanger Institute, Genome Research Ltd; 2019 (<https://www.sanger.ac.uk/science/tools/ag1000g>, accessed July 2019).
27. Khatri BS, Burt A. Robust estimation of recent effective population size from number of independent origins in soft sweeps. *Molec Biol Evol*. 2019; pii: msz081. doi: 10.1093/molbev/msz081.
28. Hartley S, Thizy D, Ledingham K, Coulibaly M, Diabaté A, Dicko B, Diop S, et al. Knowledge engagement in gene drive research for malaria control. *PLoS Negl trop Dis*. 2019;doi.org/10.1371/journal.pntd.0007233.
29. Thizy D, Emerson C, Gibbs J, Hartley S, Kapiriri L, Lavery J, et al. Guidance on stakeholder engagement practices to inform the development of area wide vector control methods. *PLoS Negl Trop Dis*. 2019;doi.org/10.1371/journal.pntd.0007286.
30. Foundation for the National Institutes of Health, World Health Organization, Special Programme for Research and Training in Tropical Diseases. Guidance framework for testing of genetically modified mosquitoes. Geneva: World Health Organization; 2014 (https://apps.who.int/iris/bitstream/handle/10665/127889/9789241507486_eng.pdf, accessed July 2019).
31. James S, Collins FH, Welkhoff PA, Emerson C, Godfray HCJ, Gottlieb M, et al. Pathway to deployment of gene drive mosquitoes as a potential biocontrol tool for elimination of malaria in sub-Saharan Africa: recommendations of a scientific working group. *Am J Trop Med Hyg*. 2018;98:1–49.
32. The evaluation process for vector control products. Information note. Geneva: World Health Organization; 2014 (<https://apps.who.int/iris/bitstream/handle/10665/255644/WHO-HTM-GMP-2017.13-eng.pdf>, accessed July 2019).

ANNEX 1. AGENDA

MONDAY, 13 MAY 2019

Session 1: Introductory session

09:00–09:15	Opening of meeting <ul style="list-style-type: none">• Opening remarks• Introductions• Declarations of interest
09:15–9:45	Introductory remarks for VCAG members
9:45–10:15	Off-cycle reviews – summary of feedback provided by review groups

Session 2: Open session

10:45–11:30	Updates <ul style="list-style-type: none">• VCAG update• NTD update, relevant outcomes from the Strategic and Technical Advisory Group• GMP update, relevant outcomes from the Malaria Policy Advisory Committee• PQT Vector Control update
11:30–12:00	Roles and responsibilities in the WHO process for the evaluation of vector control products
12:00–12:15	WHO guidelines on malaria vector control
12:15–12:30	Open discussion: feedback on VCAG processes

Session 3: Discussion

13:30–14:00	Human health assessment of chlorpyrifos
-------------	---

Session 4: Interactions with applicants

14:00–15:30	Adulticidal oviposition and larvicidal traps – brief on new product Chair of session: Kalpana Baruah Applicant presentation (14.00–14:30) Closed discussion (14.30–15.00) Recommendations to applicant (15.00–15.30)
16:00–17:30	Endectocides – new product Chair of session: Neal Alexander Applicant presentation (16:00–16.30) Closed Discussion (16:30–17.00) Recommendations to applicant (17.00–17.30)
17:30–17:45	Summary of day 1

TUESDAY, 14 MAY 2019

Session 4: Interactions with applicants (continued)

9:00–10:30	Spatial repellents – review of data Chair of session: Salim Abdulla Applicant presentation (9:00–9.30) Closed discussion (9:30–10.00) Recommendations to applicant (10.00 – 10.30)
11:00–12:30	Population reduction – gene drive approach – update Chair of session: David O’Brochta Applicant presentation (10:45–11.15) Closed discussion (11:15–11.45) Recommendations to applicant (11.45–12:30)

13:30–15:00	Attractive targeted sugar bait – update Chair of session: Heather Ferguson Applicant presentation (13.30–14.00) Closed discussion (14.00–14.30) Recommendations to applicant (14.30–15.00)
15:30–17:00	Working sessions to draft recommendations
17:00–18:00	Summary of day 2

WEDNESDAY, 15 MAY 2019

Session 5: Discussion

9:00–9:45	Product intent to impact – terminology and definitions
9:45–10:30	Evaluation standards and procedures for the assessment of new vector control interventions
10:45–11:15	Group discussion – VCAG operations, processes, feedback

Session 6: Discussion and finalization of recommendations

11:15–12:30	Finalization of the wording of recommendations
13:30–15:00	Finalization of wording of recommendations (continued)
15:15–17:00	Plenary sessions to finalize report
17:00–17:30	Close of meeting

ANNEX 2. LIST OF PARTICIPANTS

Co-Chairs

Salim ABDULLA

Ifakara Health Institute,
Ifakara, United Republic of Tanzania

Heather FERGUSON

University of Glasgow,
Scotland, United Kingdom

VCAG experts

Neal ALEXANDER

Centro Internacional de Entrenamiento et
Investigaciones Médicas (CIDEIM),
Cali, Colombia

Kalpana BARUAH

National Vector Borne Disease Control Programme,
Ministry of Health and Family Welfare, New Delhi,
India

Steven BRADBURY

Iowa State University,
Ames, United States of America

Audrey LENHART

US Centers for Disease Control and Prevention,
Atlanta, United States of America

David O'BROCHTA

The Foundation for the National Institutes of Health,
North Bethesda, United States of America

Hilary RANSON

Liverpool School of Tropical Medicine,
Liverpool, England, United Kingdom

Robert REINER

Institute for Health Metrics and Evaluation,
Seattle, United States of America

Thomas SMITH

Swiss Tropical Institute,
Basel, Switzerland

Ad hoc experts

Mamadou Brahim COULIBALY (by phone)

Vector Genomics and Proteomics Laboratory,
Malaria Research and Training Centre, University of
Sciences, Techniques and Technologies, Bamako,
Mali

Philip COYNE

Prequalification Review Team, World Health
Organization, Geneva, Switzerland

Alfred B. TIONO

Centre National Centre for Research and Training in
Malaria, Ouagadougou, Burkina Faso

Alia ZAYED

Cairo University, Cairo, Egypt

Tongyan ZHAO

Laboratory of Vector Biology and Vector-borne
Disease, Department of Vector Biology and Control,
Institute of Microbiology and Epidemiology, Academy
of Military Medical Sciences, Beijing, China

Participants

Bamako University

Gunter MULLER (attractive targeted sugar bait)

ISGlobal Barcelona

Regina RABINOVICH
Carlos CHACCOUR
Marta MAIA
Felix HAMMANN (all working on systemic
insecticides)

Innovative Vector Control Consortium (IVCC)

Mathias MONDY (attractive targeted sugar bait)

London School of Hygiene and Tropical Medicine

Immo KLEINSCHMIDT (attractive targeted sugar bait)

Sumeritec

Sumarni
Erich DOLLANSKY (both working on a larvicidal trap)

PATH

Megan LITTREL (attractive targeted sugar bait)

SC Johnson

Thomas MASCARI
David ELAND (both working Spatial Repellents)

Target Malaria

Austin BURT
Karen LOGAN
Camilla BEECH
Geoff TURNER
Frederic TRIPET (all working on population reduction
– gene drive approach)

University of Notre Dame

Nicole ACHEE
John GRIECO (both working on spatial repellents)

Westham

Amir GALILI (attractive targeted sugar bait)

Observers

Bill and Melinda Gates Foundation

Helen JAMET

Swiss Centre for Applied Human Toxicology

Martin WILKS

UNITAID

Katerina GALLUZZO

VESTERGAARD

Melinda HADI
Aurelie DALBAERE

Remote participation

Armed Forces Pest Management Board, USA

Erica LINDROTH

BASF

Susanne STUTZ

Foundation for the National Institutes of Health

Stephanie JAMES
Karen TOUNTAS

Ifakara Health Institute

Brian TARIMO

Malaria and Other Vector Borne Diseases Department of Health, South Africa

Eunice MISIANI

Ministry of Health, Zambia

E.H KOOMA

Monash University, Australia

Seth REDMOND

Sumitomo Chemical

Dave MALONE

Syngenta

Clay SCHERER
Chantel BRISWALTER

Tianjin Yorkool International Trading Co

Fu HAILI

World Mosquito Program

Peter RYAN

WHO Secretariat, Geneva

Compliance, Risk Management and Ethics

Alma ALIC
Ethics Officer

Global Malaria Programme

Pedro ALONSO
Director, Global Malaria Programme

Jan KOLACZINSKI
Coordinator, Entomology and Vector Control

Anna BOWMAN
VCAG Project Manager, Entomology & Vector Control

Department of Control of Neglected Tropical Diseases

Mwelecele MALECELA
Director, Neglected Tropical Diseases

Raman VELAYUDHAN
Coordinator, Vector Ecology & Management

Rajpal YADAV
Scientist, Vector Ecology & Management

Anna DREXLER
Technical Officer, Vector Ecology & Management

Prequalification & Technology Assessment

Emer COOKE
Director, Regulation of Medicines and Other Health
Technologies

Deuseddit MUBANGIZI
Coordinator, Prequalification

Marion LAW
Team Lead, Prequalification Team, Vector Control
Group

Dominic SCHULER
Technical Officer, Prequalification Team, Vector
Control Group

Jeannette MARTINEZ
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 before the meeting. The VCAG secretariat, in consultation with the WHO Office of Compliance, Risk Management and Ethics, assessed the interests declared by experts and, with the exception of those described below, found that they were not directly related to the topics under discussion at the meeting. It was therefore decided that those experts could participate in the meeting, subject to disclosure of their interests at that time.

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

Dr Neal Alexander (Centro Internacional de Entrenamiento et Investigaciones Médicas and London School of Hygiene and Tropical Medicine) sits on the Data and Safety Monitoring Board for Spatial Repellents.

Conclusion: Dr Alexander did not participate in the VCAG review group for spatial repellents, however, he was able to participate in discussions on the topic with the whole group.

Dr Mamadou Coulibaly (University of Sciences, Techniques and Technologies, Bamako, Mali) has received a collaboration grant, through his institute, with Imperial College to carry out work related to genetically modified mosquitoes for malaria control.

Conclusion: Dr Coulibaly did not have access to related documentation or participate in discussions or in the drafting and finalization of the recommendations on population reduction – gene drive approach.

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

Conclusion: Dr Reiner did not have access to related documentation or participate in discussions or in the drafting and finalization of the recommendations on spatial repellents.

**FOR FURTHER INFORMATION
PLEASE CONTACT:**

Vector Control Advisory Group
World Health Organization
20 Avenue Appia
CH-1211 Geneva 27
Switzerland
vcag@who.int
www.who.int/vector-control/vcag

