



**Vector Control
Advisory Group**

MEETING REPORT
11-13 May 2018

Eighth meeting of the WHO Vector Control Advisory Group



**World Health
Organization**



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BACKGROUND

The Vector Control Advisory Group (VCAG) serves as an advisory body to the World Health Organization (WHO) on new tools, technologies and approaches for the control of vector-borne diseases. VCAG is jointly managed by the WHO Global Malaria Programme (GMP), the WHO Department of Control of Neglected Tropical Diseases (NTD) and the WHO Prequalification Team (PQT) for vector control products. VCAG assesses new interventions that are not yet covered by WHO policy recommendations and provides innovators with guidance on how to develop the required evidence to assess the public health value of these interventions. Once generated, VCAG assesses the evidence and provides recommendations to WHO to underpin the development of public health policy.

VCAG experts and stakeholders convened in Geneva on 14–16 May 2018 for the eighth VCAG meeting. The open session was attended by members of VCAG, applicants and product developers, the WHO Secretariat, and other stakeholders including representatives of donor and procurement agencies.¹ The closed meeting was attended by VCAG members, the WHO Secretariat, VCAG applicants and relevant parties only. During the meeting, nine applications were reviewed, two of which were new submissions.

GENERAL VCAG OBJECTIVES

1. To assess the public health value of new vector control tools, technologies and approaches submitted to WHO for evaluation.
2. To provide guidance to product developers on data requirements and study designs to generate the evidence required for a VCAG assessment.
3. To advise WHO and its policy advisory groups, the GMP Malaria Policy Advisory Committee (MPAC) and the NTD Strategic and Technical Advisory Group (STAG) on the public health value of new tools, technologies and approaches, including updates on evidence gaps that preclude such assessment.

OPEN SESSION

Of the 13 members of VCAG, 12 were present. One ad hoc expert was invited by WHO to join the Group for this meeting. The participants are listed in Annex 1.

Dr Gautam Biswas, NTD Director ad interim, and Deusdedit Mubangizi, PQT Coordinator, welcomed VCAG and stakeholders. Dr Biswas discussed the importance of vector control to neglected tropical diseases, most of which have a vector component and require vector control interventions to achieve the goals for control and elimination. VCAG is important to bring forward new tools for use against these diseases and in allowing such tools to move towards operational use for target diseases. WHO leadership is moving towards universal health coverage, and vector control forms an important component of this.

Dr Pedro Alonso, GMP Director, joined the meeting on the last day. He thanked Dr Steven Lindsay and Dr Immo Kleinschmidt for their contributions to VCAG over the past 6 years, and the outgoing chair Dr Thomas Scott for having served 6 years with VCAG and for agreeing to extend his participation until the end of 2018.

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 of interest are stated in Annex 2.

Progress updates

Summary of discussions

The Chair, Dr Thomas Scott, provided an update on the work of VCAG. Some 18 tools or interventions are under review, 12 of which are at the planning stage or undergoing epidemiological trials.

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

Dr Jan Kolaczinski, GMP Entomology and Vector Control (EVC) Coordinator, provided a high-level update on policy activities as recently presented to MPAC (<http://www.who.int/malaria/mpac/en/>). Malaria vector control guidelines are under development and are planned for submission to the WHO Guidelines Review Committee on 30 May 2018. Two evidence review groups have met to: (i) determine non-inferiority of insecticide-treated nets (ITNs) and indoor residual spray (IRS) products within an established class (Geneva, 5–6 July 2018); and (ii) assess malariogenic potential, namely receptivity, vulnerability and vector infectivity, to inform elimination strategies and plans to prevent re-establishment of transmission (3–5 Sept 2018). The WHO *Global report on insecticide resistance in malaria vectors 2010–2016* has been published.²

Marion Law, PQT Vector Control (PQT-VC) Group Leader, summarized the activities of PQT-VC to support assessment of safe, efficacious and good-quality products. PQT-VC manages the WHO point of entry for assessment of vector control products.³ Major achievements include completion of the conversion of products recommended by the WHO Pesticide Evaluation Scheme (WHOPES) to listing by PQT and making publicly available a website containing guidance on the prequalification process. PQT-VC will hold a meeting of the Vector Control Product Assessment Group to evaluate new products covered by WHO policy and to initiate manufacturing facility inspections (28 May to 1 June 2018). The team will focus on post-market activities, such as a label improvement initiative, procedures to trigger product re-evaluation and development of post-marketing feedback process into WHO prequalification.

Dominic Schuler, PQT-VC Case Manager, provided an update on the conversion process. In summary, 89 product applications for conversion, were received in PQT and of which 71 were prequalified. Critical findings and follow-up actions were identified as follows:

- **Labels.** The quality of labels was variable. PQT-VC plan to define requirements for a PQT-VC label and initiate plans to improve labels.
- **Age of evaluations.** Some products rely on safety, quality and efficacy data evaluated before 1997. PQT-VC plans to initiate prioritized re-evaluations of active ingredients for which recent regulatory actions have been taken.
- **Conversion to PQT listing of equivalent products.** Products claiming equivalence will not be prequalified until the reference (generator and owner of the data)

has been prequalified. The data requirement and guidelines for determination of equivalency will be reviewed, and a policy developed for prequalification of equivalent products.

- **Partial evaluations.** Pyrethroid-piperonyl butoxide (PBO) long-lasting insecticidal nets (LLINs) are supported by partial reviews.⁴ On a per product basis, the physicochemical properties of the PBO component and the entomological efficacy against well characterized resistant strains of mosquitoes have not been fully assessed. PQT-VC will implement a plan for prioritized product reviews.
- **Follow-up from conversion.** PQT-VC plan to meet with procurers to determine if important tools have not been prequalified and to contact manufacturers of products identified in the Gap Analysis, as well as encourage manufacturers to submit products for evaluation.

Framework for resource use data collection during efficacy studies

Summary of discussions

Dr Edith Patouillard, GMP Health Economist, and Christopher Fitzpatrick, NTD Health Economist, presented ongoing work to develop a framework for resource use data collection during efficacy studies. A draft document was presented to VCAG for input, which will be developed into a section to supplement the guidance on design of phase III vector control field trials.⁵

In the draft document presented to VCAG, resource data refer to all the inputs used at any point in the supply and use of a vector control product. As the quantity and value of these resources (e.g. their costs) will likely vary within and across countries, as well as over time, the draft focuses on resource items expressed in natural units (e.g. type and number of full-time equivalent staff required to distribute a product). Of further interest are resource items that differ between the products being evaluated during an efficacy trial and that are potentially important to decision-makers (e.g. additional human resource capacity required to deliver a new product, needs of equipment and/or transport).

Although VCAG will not draw on these data to assess the public health value of a product, WHO encourages trial investigators to identify and report on those items of resource use that may differ between alternative products. Reporting on the range and quantity of resources required to deliver and use a product compared with alternative(s) will contribute to development of an evidence base and formulation of programmatic guidance.⁶

Conclusions

- VCAG recognized the value of guidance on data collection of resource use during efficacy trials, but highlighted that costs measured under trial conditions may differ significantly from phase III efficacy trials, phase IV effectiveness trials or from operational use. If such data are to be collected, applicants should consult with a health economist during the development of the trial design.
- VCAG members asked WHO to further clarify the rationale for collecting such data and how these data will be used.
- VCAG asked WHO to share the document with health economists outside WHO to seek feedback prior to its finalization.

Plans for VCAG sustainability and improvement

Summary of discussions

Anna Bowman, VCAG Project Manager, EVC-GMP, provided an update on the development of a VCAG sustainability plan and the VCAG improvement plan. In 2018, the Boston Consulting Group with financial support from the Bill & Melinda Gates Foundation supported WHO to develop a VCAG sustainability plan. The cost recovery model proposed by the consultants was shared during the open session. In developing the funding model, 21 stakeholders with potential to contribute funds to VCAG were interviewed, including applicants (10), procurement agencies (3), countries (3), donors (2) and others (3). The consultants concluded that while most stakeholders acknowledge the value of VCAG function and recent progress, VCAG did not meet their expectations in terms of scope and operating model. More detail on the feedback received can be found in the slides.⁷

In follow-up to this feedback and its own observations, the VCAG Secretariat has developed an improvement plan that was shared with participants during the Open Session. The Secretariat acknowledged that feedback on VCAG was provided only by those stakeholders with the potential to contribute financially to VCAG, and focuses on the end users of VCAG policy recommendations, i.e. WHO Member States. To seek additional feedback, the VCAG Secretariat plans to survey a broader range of stakeholders to elicit feedback on VCAG and to further elaborate the Improvement Plan. Stakeholders participating in the Open Session were invited to email the VCAG Secretariat (vcag@who.int) with any feedback or suggestions they have to improve VCAG.

An updated draft of the diagram outlining the WHO Evaluation Process for Vector Control products was shared with participants in the Open Session. An information note outlining the Evaluation Process was published in July 2017 and is being revised based on implementation experience.

Recommendations

- VCAG recommends that a survey be undertaken to gather views from Member States and other stakeholders on the functioning of VCAG and the results used to refine the VCAG Improvement Plan.
- VCAG commends the Secretariat for its work to clarify the Evaluation Pathway for Vector Control Products and the roles and responsibilities within WHO, and offered its support in reviewing the draft as it evolves. VCAG was particularly interested in helping to update the overview of intervention types and classes to accurately reflect all tools, technologies and approaches under VCAG review.

i2i perspectives on vector control product listing and policy guidance at WHO

Summary of discussions

Angus Spiers, Director of Innovation to Impact (i2i), presented some different perspectives on product evaluation based on consultations with the various stakeholders, including stringent regulatory authorities or SRAs (e.g. United States Environmental Protection Agency (EPA), Pesticides and Pest Management (PMRA) Canada, and Australian Pesticides and Veterinary Medicines Authority (APVMA)), manufacturers of LLINs, procurers (PMI, Global Fund), donors (BMGF, UNITAID), one Member country (Zambia) and individual experts. Stakeholders were asked three questions:

- How could use of preferred product characteristics strengthen the evaluation process?
- How might doing so make product classification clearer, simpler and more consistent?
- How might WHO roles and responsibilities evolve with this type of approach?

i2i's aim was to share suggestions for how to simplify the definitions and processes underlying WHO evaluation of new vector control products and product classes. For example, it was suggested that preferred product characteristics (PPCs) may be a more relevant mechanism to help clarify product classes than target product profiles (TPPs). Under the proposed plan, PCCs would be developed early in the product development timeline, and comprise a core set of attributes including indication, target populations, implementation strategies and desired data related to safety and efficacy. It was proposed that the primary variables used to define a product class should be delivery mechanism and entomological effect. It was noted that there is a need for epidemiological data for new product classes; however, concerns were raised about how the product classes are being defined, particularly extensions of the LLIN class. To address the need for new products, initial policy guidance could be based on "strength of predictability"⁸, with unanswered questions about how a product actually works (e.g. sub-lethal effects or lack of ento-epi correlation) addressed by entomological effect and delivery mechanism.⁹ This approach is broadly in line with how SRAs define product classes. The post-market aspects (outside of the PQT-led life-cycle management) would answer questions around cost-effectiveness and build up field data on efficacy in various epidemiological, climatic and resistance settings. That may well include sub-lethal effects or ento-epi correlation. If a product can demonstrate efficacy that is non-inferior to another product in its class, then it should be considered as part of that class. Several examples were explored for public health vector control products for malaria.

Conclusions

- VCAG was concerned that the proposed approach would have the unintended consequence of complicating the assessment process because evidence of public health value¹⁰ is necessary to develop public health policy and the proposed system would not be applicable across the diversity of interventions being submitted to WHO.
- On the use of entomological effect¹¹ to define product class, VCAG noted that entomological effect is currently one of the defining criteria. However, because entomological data are often confounded by variability in vector populations and in trial quality, and because a clear correlation of entomological and epidemiological end-points has not been demonstrated to date, entomological effect alone cannot be used to generalize across diseases and across all use settings. Hence, entomological data must be linked to strong evidence of epidemiological impact in reducing human infection and/or disease in order to support WHO Member countries; i.e. so they can make informed decisions on allocation of limited resources for disease control.

Pathway to deployment of gene drive mosquitoes as a potential biocontrol tool for elimination of malaria in sub-Saharan Africa

Summary of discussions

Professor Steven Lindsay gave a presentation on recommendations for field testing and implementation of gene drive-modified mosquitoes to control malaria transmission in Africa. The recommendations were developed by a multidisciplinary working group convened by the Foundation for the National Institutes of Health (FNIH). Professor Lindsay was a member of the working group.

During 2016–2017, FNIH led a broad consultative effort to develop field testing considerations for low threshold gene drives, building on the WHO/TDR 2014 Guidance Framework for testing genetically modified mosquitoes. As described in the WHO Guidance Framework, testing of new investigational gene drive products will follow an incremental pathway that begins with small-scale laboratory studies for efficacy and safety testing under appropriate containment conditions and operating procedures. Such studies can proceed through testing in larger population cages within the laboratory setting, including large environmentally controlled indoor spaces that aim to simulate a field setting. The group discussed safety considerations for moving investigational gene drive products from physical confinement to field testing, including the need for well-reasoned and supported justification that the products will do no more harm to human health than wild-type mosquitoes of the same genetic background and no more harm to the ecosystem than other conventional vector control interventions. Specific recommendations for physically confined studies, small-scale isolated and open releases and large-scale open releases were shared with VCAG and have been published by FNIH.¹²

VCAG DELIBERATIONS – CLOSED SESSION

Pesticides in national regulatory authorities

Summary of discussions

Marion Law, PQT-VC Group Leader, summarized the regulation of pesticides in national regulatory authorities, including information intent of pesticide registration/authorization by national authorities, pesticide review processes, data requirements, types of registration applications, pesticide labelling and post-market activities.

Public health value of house screening for vector-borne disease prevention and control

Summary of discussions

Professor Steven Lindsay, VCAG member, led a discussion on how VCAG should assess environmental management interventions, such as house improvements. Some 80–100% of malaria transmission in sub-Saharan Africa occurs indoors (Huho et al. *Int J Epidemiol* 2013;43:235–47). The *Global Vector Control Response 2017–2030* recommends house improvements, such as installing window screens, but the evidence base has not been reviewed independently for inclusion in WHO guidelines. WHO has recently published *Keeping the vector out: housing improvements for vector control and sustainable development*.¹³ Professor Lindsay presented the findings of a systematic review on malaria, housing and household randomized controlled studies, which he was involved in.

Conclusions

- VCAG has considered new interventions for vector control that are housing modifications, e.g. the product class *Lethal house lures – Eave tubes*. These are intervention packages that can be tested through randomized controlled trials in order to generate evidence for their use.
- WHO has issued best practice statements supporting housing improvements and environmental management, but has not made policy recommendations in this area. In many cases interventions improve standards of living, but the direct impact on disease of a single improvement (e.g. piped water) is difficult to measure. Guidance on housing improvements is included in guidance for dengue control. GMP will incorporate a section on housing in the Malaria Vector

Control Guidelines after an independent systematic review has been conducted and examined by its guidelines development group.

Recommendation

- Intervention types and classes in the evaluation process for vector control products¹⁴ should be updated to include housing improvements, and the different classes of tools, technologies and approaches that are available under this category.

A short introduction to a novel RCT design

Summary of discussions

Dr Immo Kleinschmidt, VCAG member, presented a novel randomized controlled trial (RCT) design, the cluster randomized test-negative design (CR-TND) proposed by Anders et al (2018)¹⁵ and by Jewel et al (2018). The method is proposed to assess the efficacy of an intervention that is randomly allocated to study clusters using conventional cluster randomized trial procedures. However, trial participants are recruited by sampling patients presenting at health facilities with symptoms consistent with the disease of interest, who are subsequently classified as test-positive cases or test-negative controls on the basis of diagnostic testing. This design has the advantage of efficiency, lower cost and may be logistically simpler, since investigators do not need to follow cohorts, which, in cases of viral seasonal diseases, may need to be very large. An odds ratio-based effect estimate can be derived from the clustered data. A number of assumptions must be met for a test-negative approach to be valid, including that test-negative illness must not be associated with the intervention, healthcare seeking behaviour must be similar between test-positives and negatives, and it must be possible to generalize from the test group to the overall population, i.e. the efficacy of the intervention should not be confined to a particular subgroup. The diagnostic test should be highly specific and highly sensitive. Further work is required to extend regression-based methods to the CR-TND to adjust for individual-level covariates while simultaneously allowing for the clustered intervention allocation. Power calculations for the CR-TND currently require simulation studies to be performed using baseline data, since presently available sample size formulae are inadequate.

Recommendation

- If the test-negative trial designs can generate the required epidemiological impact data, it could be considered for inclusion in a trial design document after expert review by VCAG.

Conditions for early terminations of trials

Dr Immo Kleinschmidt, VCAG member, introduced a discussion on conditions under which investigators might consider early termination of epidemiological trials. The introduction to the topic was based on Pocock (2005), among others. Early stopping may be considered for a number of reasons including early demonstration of benefit, unacceptable adverse events indicating evidence of harm, low accrual, poor data quality and poor adherence. Early stopping for benefit should only be considered if provision for this was explicitly stated in the trial protocol and the Data and Safety Monitoring Board (DSMC) charter, describing a statistical stopping approach. It should be based on interim analysis carried out by the DSMC, centred on a predefined statistical stopping boundary for the primary outcome. The stopping boundary should be sufficiently stringent, i.e. demonstrating very strong evidence of a treatment difference with a very small P value “to match the ethical and public health implications of a decision to stop the trial” (Pocock, 2005). The interim analysis should show proof beyond reasonable doubt that a treatment difference is sufficient to affect future health policy.

Trials that are stopped early for benefit may overestimate the beneficial impact of the intervention, since it may have been stopped on a “random high” (Pocock, 2005). Quoting from Pocock, “If a trial is for regulatory approval, the sponsor and trialists should be encouraged not to stop early, since the regulators require substantial evidence of both efficacy and safety, often in at least 2 trials reaching their intended full size and patient follow-up” (Pocock, 2005).

Recommendation

- As recommended in previous VCAG reports, investigators are encouraged to establish an independent DSMB to provide trial oversight to assess the progress, the safety data and the efficacy end-points and to recommend whether to continue, modify or stop a trial. Interim analysis should only be carried out if this is clearly described in the protocol and the DSMC charter. This should include a description of who will have access to the interim results. The final decision to stop should always rest with the DSMC, not the investigators, or the funder. Since trials that are submitted to VCAG are intended to demonstrate public health value, the committee strongly recommends that trials are not stopped early for benefit, and that early stopping should only be considered under the conditions outlined above.

Push–pull strategy for malaria control – new submission

Background

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

Summary of discussions

The applicants provided background information to support the proof of concept of the push–pull strategy, including results from a pilot field study of push–pull in a malaria-endemic region of Kenya and studies of the pull component with entomological and epidemiological outcomes in Kenya. VCAG thanked the applicant for the quality of the background documents and presentation of the concept, as well as preliminary elements of a planned large-scale trial with epidemiological and entomological outcomes. Some questions remain on the combined effects of the push and pull components with regard to entomological outcomes, which will be further investigated during a large-scale trial.

Most of the discussion with the applicant concerned epidemiological outcomes of the field trial that is currently being developed. The applicant indicated that it is envisaged to use malaria prevalence as the primary indicator of epidemiological efficacy. During the earlier studies of the pull strategy in Kenya, the incidence of clinical malaria was unexpectedly low and did not demonstrate an impact, whereas malaria prevalence significantly reduced (by 30%) between treatment arms (supported by a 69% reduction of population density of the main malaria vector, *Anopheles funestus*). Because similar or lower levels of malaria prevalence are expected for the proposed phase III trial in Malawi, malaria prevalence was used in the proposed study design based on an effect size of 30%. VCAG suggested that incidence of infection could be an alternative primary outcome indicator for this evaluation and that broadening the age group under study should be considered.

Concerns were raised by the applicant on the safety dossier of the repellent delta-undecalactone and the lack of data on the long-term exposure by inhalation of humans

to the long-lasting formulation. Because review of safety data is not within VCAG's mandate it was suggested that the applicant should contact PQT-VC for assistance with compiling the safety dossier. VCAG also suggested that the study design should consider the safety of the indoor environment in houses with treated eaves and the possible inappropriate usage of the treated netting applied to eaves.

Other points of discussion dealt with the need to develop entomological indicators (indoors and outdoors) that will ensure comparability of results between trial arms. The trial protocol for the proposed study states that the density of outdoor biting will be measured by the number of mosquitoes caught in the outdoor trap. The need to measure human exposure to bites using a method that is independent of the intervention itself was emphasized.

Conclusion

VCAG appreciates the effort made by the applicant to support the proof of concept of the push-pull strategy and the planned epidemiological large-scale trial. The applicant was encouraged to further develop the design of a phase III trial and submit the trial protocol, including detailed power calculations, to the VCAG Secretariat to facilitate review by the group before starting the trial.

Recommendations

- At least two well-conducted and randomized epidemiological trials in different geographical settings, ideally covering 2 years, are required as proof of public health value for a new product class.
- To evaluate the epidemiological impact of the push-pull strategy, it is recommended to use incidence of infection as the primary indicator, possibly in the age group 6 months to 14 years. Cohorts of children aged under 15 years should be recruited from each cluster, parasite infections should be cleared with effective treatment at enrolment, and testing for new infections should be conducted at regular intervals (every 2 weeks during the malaria season) after implementation of the intervention. Incidence of clinical malaria and malaria prevalence should be monitored as secondary indicators.
- To develop a protocol through which human exposure to mosquitoes can be estimated, both indoors and outside, using methods that are independent of the intervention itself (i.e. the SUNA trap) such as human landing catches. Alternative methods (e.g. CDC light traps) may be appropriate for use inside houses. This will be necessary to assess whether human exposure inside houses is reduced by the intervention, and does not increase outdoors due to mosquitoes being repelled from houses.
- To provide solar panels and lights to households in the control arm, and the "push" only arm, so that the effect of the interventions can be clearly distinguished from that of providing households with light.
- To contact PQT-VC for discussion and guidance on how to develop the safety dossier for the use of delta-undecalactone as a spatial repellent formulation of the push component.
- To develop a system of quality control for the interventions, including a participant communication plan, in order to ensure that each component of the push-pull system will be properly used (e.g. SUNA trap working every night), and to avoid use for other purposes (e.g. treated material used for filtering water or food preparation).

- To develop specific protocols to support the product claim and determine efficacy under field conditions, including measurement of the residual efficacy of the odour-baited formulation and the long-lasting eave treatment.
- To develop a specific protocol to support the product claim on the radius of efficacy of the pull system around protected houses (5 m around household).
- To consider measuring temperature/humidity in houses protected by repellent-treated eaves, and ensure that these are not modified by the closing the eaves in a way that could induce respiratory discomfort or the willingness to use mosquito nets.
- To develop a specific protocol to monitor potential adverse events of the different strategies.

Peridomestic residual spraying for visceral leishmaniasis control – new submission

Background

This is the first formal submission of a proposal to evaluate insecticide spraying of exterior walls and boundary fences of dwellings to reduce visceral leishmaniasis (VL) incidence in humans and to reduce the abundance and human biting rates of the VL vector, *Phlebotomus orientalis*, in Sudan. Current integrated vector control protocols, such as IRS and ITNs to combat VL in East Africa, target indoor resting and biting vectors. However, *P. orientalis* does not rest or bite indoors. Communities in endemic areas use ITNs primarily against mosquitoes, but not during the season when sandflies transmit *Leishmania* parasites.

The submission included a comprehensive description of a cluster randomized trial to be carried out in Gedarif state, Sudan, comparing outdoor residual spraying (ODRS) plus current integrated vector management (IVM) practice with IVM alone. The current IVM practice consists of conducting IRS with pyrethroids twice a year plus household provision of LLINs (currently Permanet 2.0). ODRS consists of spraying the exterior walls of homes and both sides of perimeter fencing with insecticide. Pirimiphos-methyl CS is proposed as the insecticide used in the trial. Clusters will consist of individual villages or parts of villages with 20 contiguous houses per cluster, and separation distance of 300 m from each other. Candidate villages will be selected on the basis of historically high VL case incidence. The primary outcome will be the *Leishmania* infection rate measured by Leishmanin skin test (LST) conversion in 50 initially LST-negative adults aged < 30 years in each cluster. Some 20 clusters per arm will be recruited for 80% power to show a 50% difference in LST between study arms over 2 years, assuming a pre-intervention LST incidence of 0.071 per annum. The secondary outcome will be exposure to sandfly bites, measured by seroconversion to anti-saliva IgG antibody response using rK39 rapid diagnostic tests in the same cohorts.

Summary of discussions

VCAG made recommendations to the investigators on the comprehensive proposal that has been developed for carrying out a cluster randomized trial to assess the efficacy of outdoor residual spraying for the prevention of VL.

Conclusion

Given the envisaged cluster randomized trial design, the applicants seek to generate evidence that is in accordance with VCAG requirements for demonstrating public health impact. VCAG therefore welcomes the overall approach that is being proposed. The recommendations below are intended as suggestions for consideration to improve the trial.

Recommendations

- At least two well-conducted and randomized epidemiological trials in different geographical settings, ideally covering 2 years, are required as proof of principle for a new product class.
- Generalizability of the trial results: Please indicate in the protocol in which additional areas and countries ODRS will be indicated as an effective protection against VL if the trial shows evidence of significant effect. This will be important for future policy recommendations.
- In the proposal, justified concern is expressed about the potential degradation of bioavailability of active ingredient due to UV exposure on outdoor surfaces. It is important that this is monitored during the trial, but it would be better to investigate this before the start of the trial as a preparatory activity during the baseline year. Actellic CS residual activity has been reported to vary between types of surfaces, even indoors.
- Entomological evaluations: Trapping locations must be randomly selected in clusters if they are to have value as outcome indicators. There is no mention of how locations will be selected. Three trapping locations per cluster (inside houses, outside houses, outside boundary fence) are insufficient because there will be variation between positions within clusters. Ideally, there should be replication within each cluster for each biohabitat.
- Interventions that are common to both study arms should be specified more clearly. There is mention of IRS and universal coverage of LLINs as an IVM strategy. This needs to be implemented in both study arms to ensure valid comparison, and active efforts must be made to verify that the coverage of these interventions does not differ significantly between study arms.
- Size of clusters and potential spill-over effects: With clusters of 20 contiguous houses there may be human movement between intervention and control clusters, which could result in spill-over effects even if migration of the vector between intervention and control areas is minimal. Consider collecting some information during the baseline period to assess whether this is likely to be a problem or not.
- The design of the cluster randomized trial has now been clarified. VCAG supports the decision to abandon the matched pair design. The precise method of ensuring balance between study arms should be stated in the protocol.
- The integrated vector control section of the Federal Ministry of Health and Social Welfare in Khartoum should provide a rationale for how the choice of insecticide fits into an integrated resistance management scheme, taking into account selection pressure on both VL and malaria vectors. Susceptibility of the local vector population to pirimiphos-methyl CS (Actellic 300CS) should be assessed. To truly reflect the IVM approach, susceptibility testing should be conducted for both the anopheline and the sandfly vector populations in the area.
- The protocol should mention whether householders and others will be blinded to the study arm they are in, for example by spraying placebo “insecticide” on outside walls and perimeter fences (ODRS) in the reference (control) arm of the study.
- Because the intervention may impact malaria vectors, investigators could consider recording density of *An. arabiensis* concurrently with sandfly measurements.
- Monitoring impact on non-target species, such as pollinators, in the study arms should be considered if feasible, noting that that this may be too large an undertaking to add to the trial.

Sterile Insect Technique / Incompatible Insect Technique - update

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 first reported to VCAG in November 2016. This approach aims to reduce populations of *Aedes* mosquitoes to levels below the density for transmission of dengue, Zika and chikungunya viruses. The SIT approach relies on mass rearing of the target species, sex separation and sterilization through ionizing irradiation. The combined approach additionally includes the symbiont *Wolbachia* that (i) induces cytoplasmic incompatibility and (ii) 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.

Update

Updates were provided on the following topics: (a) strain development (genetic sexing strains); (b) mass rearing; (c) irradiation; (d) packing, transport, release; (e) quality control; (f) mass-rearing facility design; (g) public awareness and (h) trials.

Summary of discussions

As reported previously, VCAG noted that the combined SIT/IIT technology has potential for long-term control of *Aedes aegypti* and *Ae. albopictus* mosquitoes. This combined approach confers complete sterility to mosquitoes, with low to no possibility for development of resistance to the mechanisms of radiation-induced sterility. The possibility of resistance to *Wolbachia*-related mechanisms due to mosquito or viral adaptation to the bacteria is considered a low risk since *Wolbachia*-infected females are sterile and the potential duration of contact between virus and *Wolbachia*-infected female mosquitoes is very short.

Conclusions

VCAG appreciated the effort by the SIT-IIT group to improve the processes by which they produced their product. They highlighted the improved sexing of mosquitoes, improved mass rearing techniques and facility design, improved product transport and quality control and developments of communication tools for public awareness. VCAG noted that the role of *Wolbachia* in the SIT/IIT product is a second-line protection against incomplete sterilization or sexing, by providing cytoplasmic incompatibility in fertile males and potential virus infection blocking in released females. Effects of the *Wolbachia* component, however, are challenging to standardize across diverse local genetic backgrounds and environmental conditions. Reported technical improvements in sexing are significant advances, and tend to diminish the relative importance of the *Wolbachia* component in the product, which should promote product standardization. Continued product development, for example the generation of multiple new inversion-linked strains, is a trade-off that requires new cycles of testing, and may delay standardization. Reported field trials with collaborators appear to deploy different SIT/IIT products, which decrease comparability. Thus, development of a reliable and scalable key product before the initiation of large-scale field trials with primary entomological end-points will be important for success. Engagement with Member States, other stakeholders and especially the communities where the intervention will occur will be crucial for the success of this intervention.

Recommendations

VCAG reiterates its recommendation from the last submission by the SIT/IIT group,¹⁶ namely that field trials with epidemiological end-points are needed to validate a promising vector control intervention.

Many of the recommendations listed below are consistent with the recommendations arising from the previous submission, because the current submission focused largely on selected components of the intervention (i.e. optimizing product development and deployment) and not epidemiological trials.

- A standardized defined product and TPP need to be developed.
- Robust trial designs should be used for both entomological and epidemiological trials. Trial designs should use well-established trial methodology, and numbers of units should be based on statistical power calculations from assumptions derived from baseline data collection.
- The transmission blocking effect of *Wolbachia* in the mosquito strains proposed needs to be demonstrated for different dengue serotypes and other alpha- and/or flaviviruses, i.e. chikungunya and Zika viruses. Data supporting the blocking effect for each mosquito species or pathogen (serotype) pair should be provided with the next submission for this intervention.
- Trials with epidemiological outcomes should be conducted in partnership with institutions maintaining a credible track record in the design, running and analysis of cluster randomized controlled trials.
- Preliminary approximate cost data should be generated using available information. A full costing and cost-effectiveness component should be included in the epidemiological trials. A qualified health economist should undertake this assessment.
- Risk assessment with WHO will need to be undertaken prior to carrying out epidemiological trials.

Gene drive – population reduction - 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 is release of male *Anopheles* mosquitoes bearing a gene drive construct that either triggers infertility in the females they mate with and/or causes a distortion in the offspring 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 that target the X-chromosome (producing a male-biased sex ratio) or female fertility genes (producing sterile females), or both. While still in very early stages of development, these interventions will aim to substantially reduce malaria infection and/or disease compared with current vector control interventions for malaria. This is a new technology, and Target Malaria envisages developing a series of constructs (at least two) of increasing efficacy. The first product ("Product 1") will aim to achieve 67% proportionate reduction in vectorial capacity over 3 years in moderate transmission settings in sub-Saharan Africa. The second product ("Product 2") will aim to achieve 99% reduction in vectorial capacity for a duration of 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.

The applicants made the following claims:

- construct can act in the targeted manner;
- construct spreads from a small ($\approx 1\%$) to large ($> 90\%$) proportion of the target mosquito population;
- progeny bearing the construct stably express the desired phenotype;
- spread of the construct reduces the wild-type population density; and
- vector population reduction causes a reduction in malaria infection and/or disease in humans.

Update

Target Malaria's vector control technology was initially reviewed by the fifth VCAG meeting (2–4 November 2016).¹⁷ In this meeting, VCAG encouraged further development of tools using gene drive based technologies, while recognizing that these are still in early phases of development, and recommended that more evidence from laboratory-based studies be generated before field testing was undertaken.

In the current meeting, Target Malaria provided updated information on the development of the TPP for the two proposed strategies for genetic control of *An. gambiae* mosquitoes through population suppression. The applicants presented ongoing work to refine these strategies in terms of overall efficacy and duration of efficacy, and initial proof of concept investigations to develop self-limiting constructs (i.e. no drive strain that will persist for a while but die out) as part of a proposed step-wise developmental pathway for gene-drive products.¹⁸ The applicant described investigations into construct failure in terms of development of resistance to gene drives and options to retard the development of resistance. Regulatory progress in target countries, advances in stakeholder engagement best practice and key publications on containment, quality of genetically modified arthropods and safety of gene drives were presented. Considerable efforts have been made to develop risk assessment processes internally to the project and externally with other risk assessment groups.

Summary of discussions

Although two products are described in the application, VCAG clarified with the applicant that Product 1 (leading to a 67% reduction in vectorial capacity over 3 years in moderate transmission settings) is expected to be the first to be ready for deployment and, therefore, will become the focus of the VCAG assessment process.

In response to previous issues raised during VCAG review about the possibility of resistance emergence, the applicants provided useful data from laboratory studies documenting the potential emergence of resistance to Cas9 gene drive constructs. This openness from the investigators is much appreciated. These data show that under laboratory conditions, if nothing is done to prevent resistance from evolving, then it can emerge within a few generations and significantly reverse the effect of the gene drive with population rebound. These studies provided a deeper understanding of how resistance can evolve, and suggested several strategies for retarding it. Continued research on the impact of resistance and efforts to retard its effect are merited to improve estimates of durability of efficacy and the product development timeline.

The applicants presented a general step-wise strategy for their work in Africa, using a series of genetically modified lines, starting with (i) a sterile male strain with a fluorescent marker, (ii) a self-limiting male fertile line (no gene drive), and (iii) the self-sustaining gene-drive line. Moving in a logical series of well-conceived steps is a reasonable way to develop ethically and safely a controversial yet potentially beneficial

tool for prevention of mosquito-borne disease. The proposed approach constitutes a process by which the applicants could address critical issues, incorporate adjustments in a timely manner and reduce the risk of unanticipated environmental or epidemiological consequences.

The applicants described ongoing work to develop a generic risk assessment framework aligned with existing global guidance on the use of genetically modified insects and to incorporate elements of emerging guidance in quantitative ecological risk assessment and socioeconomic impact assessment. Ecological risk assessments are needed as is understanding on how quantitative estimates of probability, mathematical modelling and other quantitative tools could be best utilized to augment the typically qualitative risk assessments required by the country regulatory frameworks. This understanding builds on approaches taken by CSIRO, for example, who are working with the project in undertaking independent ecological risk assessments for various stages of the project. This approach is reasonable, and must be done in concert with collection of empirical data in the laboratory and/or under contained or semi-field studies to specifically investigate potential areas of ecological risk. Such studies should follow WHO and other relevant guidance documents for laboratory activities, semi-field studies and open field release of genetically modified mosquitoes (GMM).

Conclusions

VCAG notes that its conclusions and recommendations developed in 2016 for gene-drive based approaches, remain in place.¹⁹ For ease of reference these are provided below.

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

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

Summary of conclusions and recommendations on gene-drive technology

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

Recommendations from the present meeting

1. VCAG recommends that the applicants continue to focus on target mosquito population density and entomological inoculation rate as their primary entomological outcomes, as described in their TPP. Vectorial capacity is a valuable concept for understanding broad patterns in transmission of mosquito-borne pathogens. It is not possible to measure it in field settings and, thus, it would be best to limit the application of vectorial capacity to activities such as modelling exercises that predict broad-scale epidemiological impact following different release scenarios of different gene-drive systems. Model predictions will need to be validated with empirical data.
2. VCAG support of semi-field or field release studies will require review of all protocols. Documentation submitted should include a detailed description of proposed activities, what will be measured and what monitoring will take place.
3. In addition to the comprehensive stakeholder engagement plan described, the applicants need to follow WHO and other relevant guidance documents for laboratory activities, semi-field studies and field release of genetically modified mosquitoes, including engagement with social, ethical and regulatory bodies as well as local and regional communities in locations where research with genetically modifies mosquitoes is being done or will be done.

Gene drive – Population alteration - update

Background

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

Population alteration of malaria vector mosquitoes was presented originally to the fifth VCAG meeting (2–4 November 2016). This report is an update on progress made since then and May 2018. The theory behind this class of intervention is that resistance to parasites can be spread through wild mosquito populations using a genetic drive mechanism that has potential to spread across vector populations over large regions and remain functional in wild populations for several years. Making populations of vectors resistant to malaria parasites is highly innovative and represents state-of-the-art technology. If spread of effective resistance genes can be achieved safely it would be a major advance for malaria control and elimination.

The current design has antimalarial parasite effector genes based on single-chain antibodies driven by endogenous promoters derived from blood-meal responsive mosquito genes. Genes are linked to an autonomous gene-drive system based on CRISPR-Cas9 biology. Constructs are being developed to target *An. gambiae* s.l. in sub-Saharan Africa and *An. stephensi* in urban India. The goal of this intervention is reduction of the entomological inoculation rate, compared with current best practice LLIN interventions.

The applicants make the case that the need to develop new tools to assist malaria elimination is a priority, since present available tools may be insufficient to achieve this goal alone. This technology is designed to reduce malaria transmission through engineered resistance of the malaria vector and should be considered a supplementary intervention to be used in combination with other malaria control tools. It should, however, be recognized that gene-drive technologies are still at very early stages of development.

Update

There have been multiple developments since the investigators' last report to VCAG.

- At the behest of VCAG the investigators have produced a TPP for population alteration. The TPP was broad in its aspirations, which is entirely appropriate for a new vector control class in early stages of development. Over time the TPP will become more refined and detailed as more information is obtained.
- Gene-drive efficacy protocols for the first prototype line from the last submission, AsMCRkh2 10.1, were tested using small cage experiments with *An. stephensi*.
- Fitness cost to females caused by loss of function of the insertion target site gene, *kynurenine hydroxylase-white* (kh^w), was repaired by construction of a second prototype line, SWAP, which complements kh^w inactivation with a separate wild-type kh^w gene. The promoter, AsVasaP, driving the Cas9 nuclease is unchanged.
- Identification of genes in *An. gambiae* that are expressed specifically in the male germline to mitigate the female-specific generation of non-homologous end joining alleles, which is expected to lead to third prototype with a new Cas9 promoter replacing AsVasaP.
- Identification of new parasite target molecules and corresponding single-chain target antibodies to prevent the selection of malaria pathogens that are not killed by the antibodies is in progress.

Summary of discussions

The investigators view this technology as being a "sustainable" technology, resulting in long-term changes in the vector population that prevents the carriage of malaria parasites. If this is the case, it may well be a cost-effective intervention.

That said, at these early stages of product development we do not yet have a clearly defined product and we do not know how quickly effector genes will spread through malaria vector populations, nor if they do, how long they will remain established in the population. If multiple effector genes are driven into vector populations it may be that these are unstable in nature or could compromise survival of vectors carrying these genes. Given the extraordinary diversity of *Plasmodium* populations, an important concern is the strong selection pressure for development of parasites that are resistant to the genetically-modified mosquitoes. It is also the case that we lack information on the cost of such interventions, so it is not possible at this stage to claim that the technology is cost effective.

VCAG recommends that the claim be refined to "population alteration has the potential to reduce the level of malaria infection in populations of *An. gambiae* s.l. and *An. Stephensi*". In future iterations of the TPP this should be further refined to describing one specific product for one vector species.

Conclusions

VCAG notes that its conclusions and recommendations developed in 2016 for gene-drive based approaches remain in place.²⁰ For ease of reference these are provided below.

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

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

Summary of conclusions and recommendations on gene-drive technology:

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

Recommendations

The product claims are broad, and can be made more specific if the intention is that these will be supported by laboratory findings that refer to *P. falciparum* infections in *An. gambiae* s.l. and *An. stephensi*. Because this is an early stage submission (Step 1), claims may be refined as the research progresses. Eventually, a TPP specific to one product selected for maximal effectiveness and acceptability for malaria control will need to be developed.

VCAG have previously recommended that the investigators demonstrate in the laboratory:

1. That the gene construct is stable in laboratory populations of mosquitoes over multiple generations. This proof-of-concept study has been done in the laboratory.
2. That the fitness of the GMM (survival, fecundity and fertility) is similar to laboratory strains of mosquito in large cage experiments. This has not been done.
3. That the mating success of the GMM is comparable between laboratory strains in large-cage experiments in the laboratory. This has not been done.

4. That the GMM produces no sporozoites following blood-feeding on a wide range of *P. falciparum* strains. This has not been done.
5. VCAG recommends that the applicant continues moving forward with implementing recommendations listed above (2–4).

The investigators should produce a simple plan outlining their product testing pathway, including field testing and epidemiological trials. Provisional costings of the intervention should also be considered. For guidance, the investigators can refer to resources such as the WHO Guidance Framework for testing genetically modified mosquitoes²¹ and the National Academy of Sciences report on gene drive technologies.²² The investigators are responsible for developing plans for a pathway to develop their product and can submit their plan to VCAG for comment.

VCAG suggests that periodic face-to-face meetings with investigators will continue to benefit both parties in order to streamline and expedite generation of data for policy setting.

wMel *Wolbachia* - update

Background

This strategy involves the introduction of *Wolbachia* intracellular bacterium, which is naturally found in many insects, into the mosquito *Aedes aegypti*. *Wolbachia* has been shown in laboratory and field studies to reduce the ability of *Ae. aegypti* to transmit dengue, Zika and chikungunya viruses. The intervention involves a series of controlled releases of *Wolbachia*-infected *Ae. aegypti*, to establish *Wolbachia* in local mosquito populations. The intervention aims to be community led, sustainable and cost effective.

Update

The applicant was congratulated on the progress that has been made since they last presented to VCAG. Significant progress has been made, including:

- long-term monitoring in existing field sites;
- Initiation of a cluster randomized trial in Yogyakarta, Indonesia; and
- commencement of large-scale pilot implementations in Brazil and Colombia and planning for pilot deployments in several other countries.

Summary of discussions

A trial with epidemiological outcomes using a test-negative study design is under way in Yogyakarta, Indonesia, with an anticipated completion date of December 2019. Pilot implementations are ongoing or planned in several other sites, which will rely on observational data to detect epidemiological impact.

VCAG recommends that the frequency of *Wolbachia* in mosquito populations continue to be monitored after introduction so that its presence at expected frequencies can be verified.

On 1 February 2016, WHO declared the clusters of microcephaly and Guillain-Barré Syndrome having a temporal association with transmission of Zika virus as a Public Health Emergency of International Concern. Under this emergency mandate, WHO recommended the pilot deployment under operational conditions of two tools (*Wolbachia*-based biocontrol and OX513A transgenic mosquitoes). The Public Health

Emergency of International Concern for Zika virus infection officially ended in November 2016. Therefore, while WHO encourages completion of the work initiated under the emergency mandate, further exploratory pilot implementation is no longer endorsed by WHO.

Conclusions

- VCAG commends the significant community engagement undertaking by the applicants, which provide examples of best practice engagement strategies for vector control trials.
- VCAG commends the thorough studies using field-derived mosquitoes and blood from naturally infected humans to demonstrate the reduced ability to *Ae. aegypti* to transmit arboviruses.

Recommendations

- VCAG recommends that longitudinal monitoring of *Wolbachia* infections in mosquito populations over space and time be incorporated into plans for operational deployment. While this is not a requirement, heterogeneities in *Wolbachia* establishment merit development of plans for long-term, routine monitoring. This will be particularly important for resource-constrained settings in which dengue, Zika and chikungunya virus are endemic.
- Given that the pathogen-blocking is incomplete, the applicants should consider the differential pathogenicity and/or transmissibility of the viruses that are not blocked.
- VCAG recommends that a second trial with epidemiological end-points be carried out, so that the public health value of this intervention can be assessed.

Attractive targeted sugar baits - update

Background

Attractive targeted sugar baits (ATSBs) are designed to attract and kill sugar-seeking mosquitoes. The concept was initially reviewed by VCAG at its third meeting in 2014. In 2015, a two-year proof-of-concept study was initiated in Mali in collaboration with the Innovative Vector Control Consortium (IVCC) using seven treated and seven untreated villages.

Update

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 in three sites (Kenya, Mali and Zambia). The applicants confirmed that the epidemiological protocol submitted to VCAG is the designated protocol for which feedback and guidance are sought; earlier communication had indicated that a revised protocol may be under development.

Summary of discussions

A comprehensive epidemiological trial protocol was presented. This protocol will be used for the epidemiological trials. Discussion among the collaborators is ongoing with regards to the data analysis plan.

Initial data on ATSBs were generated using a neonicotinoid active ingredient, and the trial implementation will continue with this product. Extensive data were provided on

how non-target effects had been investigated in a previous study in Mali, indicating minimal potential for non-target impacts on other invertebrates. Additional studies will be performed in 2018 during the entomological proofing studies in Kenya and Zambia before the start of the epidemiological studies. Product development is still under way, as is work on manufacturing capabilities to support the trial needs.

Results show that ATSBs may be effective at changing the age structure of the vector population via continuous exposure of mosquito populations. Durability studies will be conducted throughout the trial to monitor attraction and susceptibility of local vectors to the ATSBs that have been deployed in the field. The goal is to identify potential development of physiological or behavioural resistance.

Conclusions

The applicants have made substantial progress in collecting data on entomological impact, non-target impacts and community acceptability with an extensive pilot study in Mali. This effort and results represent promising proof-of-concept. VCAG noted that ATSBs will soon go forward to evaluation in an epidemiological trial. The applicant was encouraged to share a detailed and site-specific protocol for the trials for VCAG review. With regard to specific questions raised by the applicant, VCAG responded as follows:

- On estimating “public health value” in the epidemiological trials, VCAG clarified the primary end-point should be clinical disease (i.e. fever plus a positive RDT).
- On age groups in cohorts, VCAG recommends the epidemiology study focus on children, with the specific age range being defined on the basis of age-infection relationships at a specific study site, and any other age-specific interventions that may be on going; e.g. seasonal malaria prophylaxis.
- On the range of information considered necessary for a public health recommendation. For a malaria intervention, VCAG makes a recommendation to GMP about the public health value of the product. This is then presented by GMP to MPAC. Based on the advice of MPAC, GMP will then formulate a policy recommendation.

Recommendations

- The applicants should continue to develop and refine the protocol for the studies planned in Kenya, Mali and Zambia based on the advice provide by VCAG. Specifically, this will require work in the following areas:
 - The study design should be guided by power analysis performed for each site, based on the specific local entomological and epidemiological characteristics, rather than mean assumed values as presented in the previously submitted protocol.
 - Power analysis for the entomological study should be based on the trapping method that will be used to assess primary impact on mosquito density, with the rationale for this choice given in the protocol. Note if the applicant wishes to make a specific claim about this product being effective against outdoor biting, the study should be powered on the basis of the trapping method used to assess that claim.
 - Due to the choice of insecticide, a neonicotinoid, VCAG emphasized that assessment of non-target impacts be specifically incorporated into the protocol for all trials in Kenya and Zambia.
 - Plans for resistance monitoring and disposal of ATSBs should also be included for all sites.
 - The applicants will need to work with PQT to develop a safety dossier for WHO assessment.

- Evaluation of the intervention over 2 years is recommended to assess impact across multiple fluctuations in transmission dynamics.
- VCAG understands there are issues with the quality of the current ATSB product, which needs further development before it is ready for deployment in a trial. VCAG does not recommend proceeding with epidemiological trials until the applicants have a final product that they are confident will meet the necessary quality and durability standards for the duration of the trial.
- Before proceeding with trials in Zambia and Kenya, VCAG recommends a thorough analysis and review of baseline entomological data from each site.
- A buffer zone of 2 km was suggested between clusters to limit mosquitoes flying between treated and untreated areas.
- VCAG can provide further review and detailed feedback on the study design of the epidemiological trial once the above modifications to the protocol have been addressed. Communication between VCAG and the applicant will be through the VCAG Secretariat. VCAG would like to review the protocols for baseline entomological studies that will be conducted in the two new sites (Kenya and Zambia).

Lethal house lures and eave tubes - update

Background

Eave tubes target indoor biting mosquitoes, specifically anophelines that enter houses via the eaves (open areas between the roof and walls) and that transmit human malaria parasites. Eave tubes aim to reduce mosquito entry into houses by killing host-seeking mosquitoes, and thereby lowering the risk of malaria transmission, if deployed at sufficient coverage. Additional benefits could include lowering the population of nuisance mosquitoes and improving airflow inside houses with sealed eaves.

The intervention is a combination of housing improvements, including screening windows, closure of eaves and other mosquito entry points, and installation of eave tubes, which contain an insecticide-treated mesh. The efficacy of eave tubes against clinical episodes of malaria is being evaluated in a randomized controlled trial in Côte d'Ivoire in West Africa. This is a 2-year study that commenced in April 2017. During the seventh VCAG meeting, it was recommended that a second RCT should be conducted in a different eco-epidemiological setting to assess the public health value of eave tubes.

Summary of discussions

The applicants came to VCAG to discuss trial design options for a second RCT. Two options for VCAG's consideration were presented, and a number of specific questions were raised, as outlined below.

Conclusion

VCAG noted the progress that has been made on the Côte d'Ivoire trial, that the team has constructively addressed previous input, and that design(s) for a second trial are being investigated.

Recommendations

In response to the specific questions posed by the applicant, VCAG provided the following recommendations:

On the intervention (“eave tubes” or “eave tubes with a specific insecticide”) under VCAG review. The active ingredient used for the eaves-tubes insert as well as the formulation of the netting can be changed for future trials. It is recommended that the new inserts are formulated from active ingredients currently used in WHO-recommended (i.e. prequalified) vector control products to ensure the intrinsic insecticidal activities are known, and that technical materials are sourced from WHO-recommended manufacturers with specifications for these materials. Further data supporting the entomological efficacy end-points of any second-generation products should be collected during the proposed trials. WHO guidance to support such data generation is under development.

On the number and site(s) of trials. The general requirement is for at least two epidemiological trials in different settings remain applicable. The addition of eaves tubes to the control arm at the end of the present trial would not provide important additional information, because the two groups would not be comparable at that stage. The second trial should be cluster-randomized and sufficiently powered to show an epidemiological effect in a different setting to support generalization of the results. It is recommended that a second trial is conducted in East Africa; i.e. with a different vector system and 10–40% prevalence of *Plasmodium falciparum*. No WHO recommendation will be made prior to the results of the second epidemiological trial. WHO no longer provides interim recommendations for public health use of vector control products.

On what should be measured. Ideally, the same primary outcome should be used for both trials, but the greater expense and complexity of the incidence trial outlined in the applicant’s presentation provides a strong argument for the trial with a primary outcome of prevalence. If prevalence is used as the primary trial outcome, data should also be collected on incidence of disease by trial arm, and on rates of care-seeking, in order to check if the intervention induces behavioural change.

On trial duration. Entomological data will be important to explain results and to allow extrapolation to additional use-settings. The requirement for a 2-year trial duration, excluding baseline data collection, applies irrespective of the size of the trial. This duration is required to generate data on the consistent entomological and epidemiological outcomes across consecutive high and low transmission seasons.

On data requirements. Data on insecticide resistance in the study setting(s) should be collected using WHO protocols for resistance monitoring. These data are needed to contribute towards generating an understanding of the efficacy of eave tubes in the local context against resistant mosquitoes, but alone will not demonstrate that this tool can reduce levels of pyrethroid resistance in the vector population.

On what interventions should be compared. While two completed trials should be sufficient for VCAG to assess public health value and make a recommendation to WHO, the design of the second trial will likely affect the wording of such a recommendation. For instance, if the investigators choose to conduct a two-arm trial that compares eave-tubes plus screening with a control arm, this would likely mean that eave tubes would be recommended by WHO only as part of a package with screening. VCAG therefore reiterates the importance of obtaining evidence on whether the impact of eave tubes depends on whether or not houses are screened. The factorial designs described in the presentation to VCAG or a three-arm trial that includes an eave tube only arm would make the effects of eave tubes and screening separately identifiable. These effects cannot be separated on the basis of smaller studies. An important aspect should be that there is sufficient power to test the effect of the combination of eave tubes with screening vs neither (control).

VCAG will review the detailed study protocol after it is submitted to the VCAG secretariat.

Spatial repellents - update

Background

Spatial repellents are designed to interrupt human–vector contact through vector behaviour modification induced by airborne chemicals, potentially offering protection from bites from vectors and nuisance pests. The spatial repellent intervention proposed is a transfluthrin-based passive emanator produced by SC Johnson, designed to release a volatile chemical into the air and prevent human–vector contact within the treated space. The intervention targets *Anopheles*, *Aedes* and *Culex* spp., and is intended to protect all age groups and populations in countries endemic for vector-borne disease from daytime, early-evening or late-night biting from mosquitoes in enclosed and semi-enclosed structures. Epidemiological trials are currently under way in Sumba Island, Indonesia, and Iquitos, Peru, to generate evidence of public health effect against malaria and *Aedes*-borne viruses, respectively. No field data on efficacy against *Culex* have been provided to date, hence preventing VCAG assessment of the claimed effect against this genus.

Update

In Indonesia, the epidemiological and entomological follow-up to confirm the number of malaria cases and sporozoite-positive mosquitoes was completed in April 2018. Mosquito sample processing from human landing catches in 12 clusters and subsequent confirmation by polymerase chain reaction (PCR) for sporozoite detection is ongoing. PCR confirmation of human blood sample infections, and resolution to PCR discrepancies is ongoing. Insecticide susceptibility tests against primary malaria vectors in study clusters were completed in January 2017 and September 2017, and indicated susceptibility to permethrin, deltamethrin and transfluthrin using CDC bottle bioassays and WHO filter paper tests. Insecticide susceptibility monitoring is planned for up to 6 months post-intervention (ending in October 2018).

In Peru, epidemiological and entomological follow-up is ongoing. A total of 43 rounds of mosquito surveys have been carried out in each cluster to include indoor adult aspiration and immature sampling. Mosquito sample processing and confirmation are ongoing. Other ongoing studies include insecticide susceptibility testing and blinded surveys to gather information on perceptions of efficacy and acceptability of the product in enrolled households in Iquitos, Peru. Trial follow-up in Peru is expected to be completed in December 2018.

Summary of discussions

Power analysis in Indonesia indicates that, as expected by the applicants, the trial is underpowered, and would have needed additional clusters to meet the standard threshold of 80% power. The power for detecting the protective efficacy threshold of 30% with the current design of 12 clusters per treatment arm was discussed.

Plans for development of protocols for two additional trials, one for malaria and another for *Aedes*-borne infections, to meet VCAG data assessment requirements of new product categories were outlined. The utility of PCR versus microscopy for the primary end-point of infection in malaria trials was discussed.

Information from laboratory assays was provided comparing the transfluthrin content over time, predicted emanation rate, and bioefficacy in terms of knockdown between the first generation product and a second-generation product. VCAG discussed appropriate testing following the published WHO guidelines on spatial repellents.

Conclusions

Significant progress has been made in the implementation of epidemiological trials in both Indonesia and Peru. For the malaria trial in Indonesia, the investigators have addressed issues raised previously by VCAG regarding the expected power to confirm the initially assumed protective effect. Based on the recalculation of the sample size, the trial in Indonesia is not sufficiently powered to conclusively show a modest efficacy of the intervention. This is attributed to large variability of events in clusters and hence the previous suggestions from VCAG to extend the follow up period would not resolve this, and therefore was not undertaken by the investigators. Data analysis is ongoing for the trial, and once completed, VCAG will review the final trial results and provide comments and recommendations. It should be noted, however, that in the case of inconclusive trial results it may be difficult for VCAG to make concrete recommendations on the public health value of the intervention based on this trial.

VCAG will provide feedback on the protocol for the second trial against *Aedes*-borne viruses after the site has been decided and a protocol submitted. VCAG encourages the investigators to review the performance of procedures and results of the ongoing trial to guide the design and implementation of the second trial.

The data submitted indicate the first-generation product and a second-generation product have equivalent predicted emanation rates. The two products both induce knockdown throughout the products stated lifespan.

Recommendations

On data requirements for the proposed second-generation product. The applicants can consider using the second-generation product in future trials as a replacement product for the first-generation product based on performance in inducing mosquito knockdown and transfluthrin content over time. Further data supporting the entomological efficacy end-points should be collected during the proposed trials.

On the reviewed study protocol and statistical analysis plan for the Kenya trial. The study design and statistical analysis plan is appropriate for this evaluation. More recent data on case incidence should be used as a basis for the sample size calculations to ensure that the trial is sufficiently powered. The follow up proposed for the trial is 18 months; however, 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. Applicants should note that a standardized PCR analysis may be a core methodology for detection of primary end-points in the trial, although blood slides and or rapid diagnostic tests can also be done. VCAG will provide further comments and recommendations on the full protocol once it has been submitted to this committee for review.

On the topic of the second *Aedes*-borne virus clinical trial necessary to meet VCAG phase III data requirements. The applicants should consider another epidemiological area with different vector ecology, and potentially a site in Asia with high transmission of dengue virus. While the general design of the Iquitos trial protocol presented is appropriate, the assumptions will need to be updated once a site has been selected. VCAG will provide concrete comments and recommendations once a site has been identified and a full protocol is submitted to the committee.

On adverse events. A summary of the adverse events including those judged by the investigators to be related to the product and any events of withdrawal of consent to have the product in homes should be included in reporting of all field trials with the second-generation product to address any concerns associated with more adverse events and/or refusals.

On PCR sample processing. Ongoing work on the data from the Indonesia trial to resolve discrepancies in malaria detection using PCR, of total processed samples to date, should be prioritized. PCR is the primary end-point for this trial, and interpretation of trial results will be significantly compromised without these data.

Endnotes

1. Presentations from the open session are available from the VCAG webpage: <http://www.who.int/vector-control/vcag/may2018/en/>
2. Global report on insecticide resistance in malaria vectors: 2010–2016. Geneva: World Health Organization; 2018 (<http://www.who.int/malaria/publications/atoz/9789241514057/en/>).
3. WHO Prequalification Vector Control: resources (<http://www.who.int/pq-vector-control/resources/en/>).
4. Conditions for deployment of mosquito nets treated with a pyrethroid and piperonyl butoxide: recommendations. Geneva: World Health Organization; 2017 (<http://www.who.int/malaria/publications/atoz/use-of-pbo-treated-llins/en/>).
5. How to design vector control efficacy trials: guidance on phase III vector control field trial design. Geneva: World Health Organization; 2017 (http://www.who.int/neglected_diseases/vector_ecology/resources/WHO_HTM_NTD_VEM_2017.03/en/).
6. Report of the seventh meeting of the Vector Control Advisory Group, Geneva, 24–26 April 2017 (<http://apps.who.int/iris/bitstream/handle/10665/259743/WHO-HTM-NTD-VEM-2017.11-eng.pdf>).
7. See <http://www.who.int/vector-control/vcag/may2018/en/>
8. i2i defines as “The notion that, based on a product’s performance against defined thresholds (that have been shown to have epidemiological impact), one can assume a product to be non-inferior to others in the same class. E.g. IRS insecticides are considered to be in the same class, irrespective of AI, if they meet the standard mortality thresholds in phase 1 & 2 testing.”
9. i2i defines as “The means by which the chemical/active ingredient comes into contact with the vector. E.g. LLIN, IRS, space spray, larvicide etc.”
10. Public health value: A product has public health value if it has proven protective efficacy to reduce or prevent infection and/or disease in humans. (WHO 2017. The evaluation process for vector control products).
11. Entomological effect refers to a product’s effect on a disease vector in terms of killing, deterring, and reducing fertility or susceptibility to infection. Products with different biochemical modes of action may have similar entomological effects on target insects. (WHO 2017. The evaluation process for vector control products).
12. 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 (http://www.ajtmh.org/content/journals/14761645/98/6_Suppl).
13. Keeping the vector out: housing improvements for vector control and sustainable development [policy brief]. Geneva: World Health Organization; 2017 (http://www.who.int/social_determinants/publications/keeping-the-vector-out/en/).
14. The evaluation process for vector control products [information note]. Geneva: World Health Organization; 2017 (<http://apps.who.int/iris/bitstream/handle/10665/255644/WHO-HTM-GMP-2017.13-eng.pdf>).
15. Anders KL, Cutcher Z, Kleinschmidt I, Donnelly CA, Ferguson NM, Indriani C, et al. Cluster randomized test-negative design (CR-TND) trials: a novel and efficient method to assess the efficacy of community level dengue interventions [accepted manuscript]. *Am J Epidemiol.* 2018 (<https://academic.oup.com/aje/advance-article/doi/10.1093/aje/kwy099/4993480>).
16. The full text of these conclusions and recommendations should be consulted. These may be found at <http://apps.who.int/iris/bitstream/handle/10665/255824/WHO-HTM-NTD-VEM-2017.02-eng.pdf>
17. Report of the fifth meeting of the Vector Control Advisory Group, Geneva, 2–4 November 2016. Geneva: World Health Organization; 2017 (<http://apps.who.int/iris/bitstream/handle/10665/255824/WHO-HTM-NTD-VEM-2017.02-eng.pdf>).

18. Guidance Framework for testing genetically modified mosquitoes. Geneva: World Health Organization on behalf of the Special Programme for Research and Training in Tropical Diseases; 2014 (<http://www.who.int/tdr/publications/year/2014/guide-fmrk-gm-mosquit/en/>).
19. The full text of these conclusions and recommendations should be consulted. These may be found at <http://apps.who.int/iris/bitstream/handle/10665/255824/WHO-HTM-NTD-VEM-2017.02-eng.pdf>
20. The full text of these conclusions and recommendations should be consulted. These may be found at <http://apps.who.int/iris/bitstream/handle/10665/255824/WHO-HTM-NTD-VEM-2017.02-eng.pdf>
21. Guidance Framework for testing genetically modified mosquitoes. Geneva: World Health Organization on behalf of the Special Programme for Research and Training in Tropical Diseases; 2014 (http://www.who.int/tdr/publications/year/2014/Guidance_framework_mosquitoes.pdf).
22. Gene drives on the horizon: advancing science, navigating uncertainty, and aligning resources with public values. Washington (DC): The National Academy Press (<https://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and>).

ANNEX 1. AGENDA

MONDAY, 14 MAY 2018

Session 1: Introductory session and policy updates

09:00–09:15	Opening of meeting <ul style="list-style-type: none">• Opening remarks• Organizational matters• Declarations of interest
09:15–10:15	Progress updates <ul style="list-style-type: none">• General progress and update on VCAG• NTD update, relevant outcomes from STAG• GMP update, relevant outcomes from MPAC• PQ Vector Control: updates and analysis of the findings from the WHO conversion process for pesticide evaluation

Session 2: Updates on VCAG work in progress

10:45–11:15	Framework for resource use data collection during efficacy studies; to be added to trial design manual
11:15–11:45	Plans for VCAG sustainability and improvement

Session 3: Scoping and feedback

12:45–13:30	An introduction to the use of target product profiles and their potential advantages in the evaluation of new vector control products
13:30–14:15	Pathway to deployment of gene drive mosquitoes as a potential biocontrol tool for elimination of malaria in sub-Saharan Africa
14:15–15:00	Open Discussion

Session 4: Closed Session

15:30–16:00	Introductory remarks for VCAG members Appointment of rapporteurs
16:00–16:30	Scoping discussion on integrating national regulatory authority reviews into VCAG processes
16:30–17:30	Public health value of house screening for vector borne disease prevention and control

TUESDAY, 15 MAY 2018

Session 5

09:00–09:45	<ul style="list-style-type: none">• A short introduction to a novel RCT design• Conditions for early terminations of trials
09:45–10:30	Push–pull strategy for malaria control – new submission <ul style="list-style-type: none">• Chair of session: Fabrice Chandre• Applicant presentation (09:45–10:00)• Closed discussion (10:00–10:15)• Recommendation to applicants (10:15–10:30)
10:45–11:45	Peridomestic residual spraying for visceral leishmaniasis control – new submission <ul style="list-style-type: none">• Chair of session: Immo Kleinschmidt• Applicant presentation (10:45–11:15)• Closed discussion (11:15–11:35)• Recommendation to applicants (11:35–11:45)

Session 6

11:45–12:45	Sterile insect technique/Incompatible insect technique – update <ul style="list-style-type: none">• Chair of session: Robert Reiner• Applicant presentation (11:45–12:15)• Closed discussion (12:15–12:35)• Recommendation to applicants (12:35–12:45)
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Session 7	
13:30–14:30	Gene drive population reduction – update <ul style="list-style-type: none"> • Chair of session: Tom Scott • Applicant presentation (13:30–14:00) • Closed discussion (14:00–14:20) • Recommendation to applicants (14:20–14:30)
14:30–15:30	wMel Wolbachia – update <ul style="list-style-type: none"> • Chair of session: Audrey Lenhart • Applicant presentation (14:30 – 15:00) • Closed discussion (15:00–15:20) • Recommendation to applicants (15:20–15:30)
Session 8	
15:50–16:50	Gene drive population alteration – update <ul style="list-style-type: none"> • Chair of session: Steven Lindsay • Applicant presentation (15:50–16:20) • Closed discussion (16:20–16:40) • Recommendation to applicants (16:40–16:50)
16:50–17:00	Plenary discussion, feedback, orientation for next day
17:00–18:00	Working groups – discussion and finalization of recommendations
WEDNESDAY, 16 MAY 2018	
Session 9	
08:30–09:00	Group discussion – VCAG operations, process, feedback
09:00–10:00	Attractive targeted sugar baits – update <ul style="list-style-type: none"> • Chair of session: Heather Ferguson • Applicant presentation (09:00–09:30) • Closed discussion (09:30–09:50) • Recommendation to applicants (09:50–10:00)
10:00–11:00	Lethal house lures and eave tubes – update <ul style="list-style-type: none"> • Chair of session: Thomas Smith • Applicant presentation (10:00–10:30) • Closed discussion (10:30–10:50) • Recommendation to applicants (10:50–11:00)
11:00–12:00	Spatial repellents – update Chair of session: Salim Abdulla Applicant presentation (11:00–11:30) Closed discussion (11:30–11:50) Recommendation to applicants (11:50–12:00)
12:00–13:00	Working groups – discussion and finalization of recommendations
Session 10	
14:00–17:00	Plenary sessions to finalize report
17:00–17:30	Close of meeting

ANNEX 2. LIST OF PARTICIPANTS

VCAG experts

Chairperson

Thomas SCOTT

University of California Davis
United States of America

Salim ABDULLA

Ifakara Health Institute
Ifakara, United Republic of Tanzania

Fabrice CHANDRE

Institut de recherche pour le développement
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Heather FERGUSON

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Glasgow, United Kingdom

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Liverpool, United Kingdom

Robert REINER

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

Thomas SMITH

Swiss Tropical Institute
Basel, Switzerland

Ad hoc expert

Ken VERNICK

Institut Pasteur
Paris, France

Participants

Attractive Targeted Sugar Bait (ATSB): Amir Galili,
Westham; Günter Müller, University of Bamako;
Megan Littrell, PATH, Mathias Mondy, IVCC

Gene Drive – Population Reduction: Austin Burt,
Karen E. Logan, Imperial College London and
Camilla Beech, Consultant

Gene Drive – Population Alteration: Rebecca
Carballar and Anthony James (by phone), University
of California

Lethal House Lures / Eaves tubes: Eleanore
Sternberg, Penn State University; Marit Farenhorst
and Anne Osinga, In2Care

Peridomestic Residual Spraying for visceral
leishmaniasis control: Dia Elnaiem University of
University of Maryland and Orin Courtenay (by
phone), University of Warwick

Push–pull strategy for malaria control: Willem
Takken, Wageningen University

Sterile Insect Technique / Incompatible Insect
Technique : Konstantinos Bourtzis, Joint FAO/IAEA

Spatial Repellents: Nicole L. Achee, University of
Notre Dame

wMel Wolbachia: Peter Ryan, Monash University

Observers

Adey Business Development GmbH
Richard ADEY

Armed Forces Pest Management Board (AFPMB)
Gabriela Zollner ROMERO

Bill & Melinda Gates Foundation
Dan STRICKMAN

Global Speciality Solutions
Robin SLATTER

Global Fund
Kate KOLACZINSKI

Innovation to Impact (i2i)
Angus SPIERS

Mainpol GmbH
Raphael Perez Del Castillo

NEPAD
Hudu MOGTARI

UNITAID
Alexandra CAMERON
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Participation via WebEx

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ANNEX 3. DECLARATIONS OF INTEREST

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

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

Dr Immo Kleinschmidt (London School of Hygiene & Tropical Medicine) declared a conflict of interest with the eaves tubes project on attractive targeted sugar baits at the Secretariat the meeting.

Conclusion: Dr Kleinschmidt did not participate in any discussions, or participate in the drafting and finalization of the recommendations regarding the eaves tubes project.

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

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

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

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

Dr Thomas Smith (Swiss Tropical Institute) declared a conflict of interest with regard to the push-pull strategy to the Secretariat at the meeting.

Conclusion: Dr Smith did not participate in any discussions, or participate in the drafting and finalization of the recommendations regarding the push-pull application.

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**FOR FURTHER INFORMATION
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