Vector Control Advisory Group

MEETING REPORT
19–21 April 2021

Fourteenth meeting of the WHO Vector Control Advisory Group

World Health Organization

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1. BACKGROUND

The Vector Control Advisory Group (VCAG) of the World Health Organization (WHO) serves as an advisory body to WHO on new interventions for the control of vector-borne diseases, including tools, technologies and approaches. VCAG is jointly coordinated by the WHO Global Malaria Programme, the WHO Department of Control of Neglected Tropical Diseases and the WHO Prequalification Team for Vector Control Products. Its specific functions are:

- to provide guidance to product developers, innovators and researchers on the generation of epidemiological data and study designs to enable assessment of the public health value of new vector control interventions;
- to assess the public health value of new vector control interventions submitted to WHO; and
- to provide advice to WHO, for submission to the Malaria Policy Advisory Group and the Strategic and Technical Advisory Group for Neglected Tropical Diseases on the public health value of new interventions.

The 14th VCAG meeting was convened with all 15 VCAG members, as well as product developers, innovators and researchers (jointly referred to as "applicants") on 19-21 April 2021. The meeting was co-chaired by Heather Ferguson and Salim Abdulla. The agenda is reproduced in Annex 1, and the participants are listed in Annex 2.

This report details the proceedings and outcomes of the meeting, which was held virtually due to the ongoing COVID-19 pandemic. VCAG provided feedback and recommendations to applicants who had made submissions under the following intervention classes:

- bait stations,
- spatial repellents and
- insecticide-treated nets (ITNs) designed to kill host-seeking insecticide-resistant mosquitoes.

Two additional applicants presented updates to the VCAG committee on other intervention classes, namely:

- lethal house lures and
- reduction of pathogen transmission induced by gene drive.

Before the meeting, all VCAG members and invited experts completed declaration of interests forms for WHO experts. The declared interests and how they were managed by the WHO VCAG Secretariat are summarized in Annex 3.

2. WELCOME AND OPENING REMARKS

VCAG members were officially welcomed by Dr Rogerio Paulo Pinto De Sá Gaspar, Director, WHO Regulation and Prequalification, the department responsible for assessing and prequalifying vector control interventions, among other activities. He noted the importance of continued efforts to evaluate new vector control interventions despite the challenges of the COVID-19 crisis. Accessibility to new and innovative vector control tools remained a priority, especially as many of those impacted by vector-borne

diseases are often the most vulnerable and come from the poorest countries. The work of VCAG, supported by the three WHO departments, is therefore essential. WHO remains committed to encouraging the development and accessibility of innovative and effective new tools for the populations at risk.

3. OPEN SESSION

3.1. Introduction to the WHO guideline development process

Dr Elie Akl, American University of Beirut, described the processes involved in developing WHO guidelines and the data requirements that underpin the recommendations contained therein. Dr Akl, a seasoned guideline methodologist, has been closely involved in preparing numerous WHO guidelines, including the consolidation of the malaria vector control guidelines with those of other technical areas in malaria. His presentation gave a high-level overview of the process and introduced the characteristics of the data required to inform WHO recommendations. Importantly, WHO guidelines are developed in response to the needs of decision-makers in Member States. The presentation is available on the VCAG webpage *(1)*.

3.2. Guidelines for malaria vector control: development, updates and use of MAGICapp

Dr Jenny Stevenson, WHO Global Malaria Programme, presented the consolidated malaria guidelines published by WHO in February 2021, which merge the previously published WHO guidelines on malaria case management and malaria vector control into a single platform. They include recommendations and good practice statements, with associated evidence profiles, justifications, background information and references. The consolidated guidelines are hosted on the WHO website *(2)* and on MAGICapp *(3)* in a format that is easy to search and download specific topics. The website's structure was demonstrated to show examples of recommendations for vector control and how to access the results of underlying systematic reviews that underpin recommendations. The guidelines section on malaria vector control will evolve further in 2021–2022 to incorporate information from ongoing systematic reviews. The presentation material is available on the VCAG webpage *(1)*.

4. SUBMISSIONS

4.1. Intervention class: bait station

Bait stations are defined as interventions that are designed to attract and kill target vectors. Attractive targeted sugar baits (ATSBs), which fall within this class, are specifically designed to attract and kill sugar-seeking mosquitoes. As both male and female mosquitoes feed on plant-derived sugars to maintain energy for survival, ATSBs exploit the almost-daily need for sugar by baiting the mosquitoes to a source that also contains a lethal toxicant.

To date, no epidemiological trials have been initiated under this intervention class, although one applicant (Westham) is actively planning three field trials to evaluate the efficacy of ATSBs against malaria transmission in Africa.

4.1.1. Intervention: attractive targeted sugar baits

Applicant: Westham

The ATSB concept was first reviewed by VCAG at its third meeting in November 2014 *(4)*. In 2015, a two-year proof-of-concept entomological study was initiated in seven treated and seven untreated villages in Mali. The study was performed through a

collaboration between Westham and the Innovative Vector Control Consortium. At the eighth VCAG meeting in May 2018 *(5)* the applicant presented a summary of this study, which demonstrated that the product reduces mosquito vector populations and the survivorship of individual mosquitoes and decreases the frequency of mosquitoes with malaria parasites. Assessment indicates that the risk posed to non-target organisms is negligible with the current product prototype.

In parallel, the applicant presented a draft protocol for three planned epidemiological trials in Kenya, Mali and Zambia. The applicant provided updates on the draft protocols at the tenth VCAG meeting in May 2019 *(6)* for trials in the three countries along with an overview of the status of manufacturing for the product and related baseline entomological data for Kenya and Zambia.

At the most recent (13th) VCAG meeting in December 2020 *(7)* the applicant submitted a revised protocol for the epidemiological trials and associated statistical analysis plans (SAPs) to incorporate flexibility for interim analyses after one year (with appropriate adjustments to sample sizes) and early presentation of results to WHO, should overwhelming benefit be observed.

Updates

The applicant submitted an updated application form and presentation summarizing the material submitted for review at this meeting in response to previous recommendations from VCAG, namely updated versions of the Master Trial Protocol and SAP. The applicant sought VCAG's review at this meeting of both documents.

Summary of discussions

The applicant's presentation covered a general update on the status of product development and timeline for the proposed trials, and how the Master Protocol and SAP had been adjusted in response to VCAG's previous review. Most aspects of the presentation had been covered in documents submitted before the meeting; however, the applicant flagged a more recent update to the proposed adjustment of *P* values in interim and final statistical analysis. Initially, they had proposed to use the O'Brien-Fleming rule but are now exploring how it should be adapted or changed to accommodate the cluster-randomized design, more specifically the non-linearity in the rate at which information is accrued.

The applicant clarified that there is still no final product for use in trials, as it is unclear whether the previously identified problem with leaching has been addressed in the updated prototype. VCAG reiterated previous feedback on the necessity of finalizing the product before proceeding with trials. The applicant indicated that an independent stage gate evaluation will take place in October 2021. The applicant described a range of baseline data collection currently under way in all sites, including baseline entomology and epidemiology studies in Zambia; entomology and passive case detection in Mali; and a cohort study due to start in June in Kenya. The applicant confirmed that data from the baseline entomology studies will be shared with VCAG later in 2021 and presented during a symposium at the annual meeting of the American Society of Tropical Medicine & Hygiene (Maryland, USA, 17-21 November 2021).

There was discussion of how the RTS,S status of children in the Kenyan trial will be taken into account during cohort selection. For the Zambian trial, the applicant clarified that the background standard of care will be a mixture of long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS); most clusters will have one or the other but not both. Randomization will ensure that there are no systematic differences between the study arms in terms of the proportion of clusters with IRS or LLINs. The applicant clarified that all trials will have separate data and safety monitoring boards.

VCAG queried the applicant's proposal to include flexibility to exclude clusters of "atypically high transmission" from final selection, based on baseline data only, and expressed concern that excluding on this basis could impact the generalizability of results if not clearly justified.

VCAG questioned how the diagnostic dose for the proposed dinotefuran resistance assay will be determined. The applicant clarified this would likely be done via a topical rather than ingestion assay, as the latter is not feasible for large-scale monitoring. There was discussion about whether the switch from polymerase chain reaction to rapid diagnostic tests for determining infection prevalence in the survey could generate bias by misclassifying individuals in the two arms due to low specificity of rapid diagnostic testing (bias towards the null) and about if the frequency of HRP2 deletions within the study populations is known. VCAG highlighted the expertise of the WHO Global Malaria Programme in this area and offered to follow up with the applicant for discussion. Additionally, the applicant confirmed that the sensitivity and specificity of the rapid diagnostic test had been incorporated into the updated sample size calculations for the cross-sectional surveys. The applicant may wish to consider the ethics of not treating the asymptomatic infections detected during the cross-sectional surveys in the protocol, as this may be raised by ethics review committees.

Finally, there was discussion about the anticipated rate of ATSB replacement within the target 6-month window of duration. The applicant has anticipated that about 10% of units may need replacement within this period and plans to collect further data during current baseline studies to guide consideration of whether there is a threshold rate of replacement above which it may not be possible to clearly evaluate the impact over the intended 6-month period.

In the updated protocol, it was clarified that ATSBs will be installed only on household structures that fit prespecified eligibility criteria. VCAG queried whether data on the proportion of household structures considered to be eligible for installation will be collected during baseline, and whether a minimum target will need to be met to reach target coverage. The applicant intends to collect data on structure eligibility so that coverage can be calculated. A minimum target coverage has yet to be discussed but will be reflected in future protocol updates when set.

Conclusions

VCAG recognizes the applicant's continued progress, including plans for epidemiological trials in 2022 and the initiation of extensive baseline data collection. Additionally, VCAG appreciates the rigorous and thorough revisions to the Master Protocol and SAP in response to its previous recommendations. These revisions are appropriate and largely sufficient to address the Group's previous feedback. While there remain areas where VCAG has requested further clarification or explanation, as reflected in the recommendations below, the current protocol and SAP are robust and appropriate. These documents conditionally meet VCAG's requirement for data generation to allow assessment of public health value subject to remaining clarifications. In the presentation the applicant indicated that these documents are still working versions, with some details to be finalized only after baseline completion (final sample sizes, etc.) or before data lock (covariate choice for models). Should major changes to the study design be required as a result of baseline data collection or other circumstances, the applicant should liaise with VCAG via the WHO Secretariat to determine whether further review is needed.

VCAG would appreciate summary results from the entomology and other baseline studies to be shared when available.

In addition to the recommendations below, a list of minor textual revisions/corrections was provided to the applicant to make at their discretion (without the need for VCAG review).

Recommendations

VCAG recommends the following clarifications to the applicant's documentation.

ATSB revised master protocol

- The applicant should clarify how RTS,S vaccination status will be taken into account during cohort recruitment or restricted randomization in the Kenya trial, particularly data on vaccination status of cohort children (unvaccinated, 1, 2 or 3 doses).
- The exclusion criteria should include any contraindication to the drug to be used for the initial clearance.

- Details on how human safety will be monitored in the Master Protocol should be provided by expanding the section on human safety assessment to include regulatory definitions of the adverse and serious adverse events they wish to collect.
- The applicant should formalize a mechanism for communication between data safety monitoring boards on sharing important updates of common interests (e.g. decision to proceed with early presentation of results at one site; evidence of adverse and serious adverse events).
- The applicant should incorporate a description of the topical assay to be used for assessing resistance to dinotefuran, including a description of or reference to how the diagnostic dose will be determined, and the methodology, types of mosquitoes (e.g. wild or F1) and number of replicates.

Revised SAP

- Should the applicant wish to exclude clusters of "atypically high transmission" from final selection, please provide more specific detail on how these will be identified based on predefined criteria (quantitatively).
- The plan for statistical analysis of entomology outcomes should also be included.

4.2. Intervention class: ITNs designed to kill host-seeking insecticide resistant mosquitoes

Mosquito nets that are treated with both a pyrethroid and the synergist piperonyl butoxide (PBO) are intended for use in areas where there is resistance to pyrethroids. PBO acts by inhibiting certain metabolic enzymes within the mosquito that detoxify or sequester insecticides before they can have a toxic effect on the mosquito. Compared with a pyrethroid-only net, theoretically, a pyrethroid-PBO net will have an increased killing effect on malaria vectors that express this resistance mechanism phenotype. However, the entomological and epidemiological impact of pyrethroid-PBO nets may vary depending on the bioavailability and retention of PBO in the net, and on the design of the net (i.e. whether only some or all panels are treated with PBO).

Pyrethroid plus PBO nets have been conditionally recommended by WHO since 2017 for use in areas where there is resistance to pyrethroids. This exceptional recommendation was based on the results of one epidemiological trial in the United Republic of Tanzania after the transition of efficacy testing for vector control interventions from the WHO Pesticide Evaluation Scheme to the WHO Prequalification Team. This was a (one-off) exception to the standard procedure for developing WHO recommendations for new vector control interventions, which requires a minimum of two epidemiological trials with demonstrated public health value.

VCAG has been awaiting the final results from a second large epidemiological trial of PBO nets to formally advise WHO that public health value has been demonstrated. Such an evaluation would trigger an updated systematic review and convening of the Guideline Development Group, and could lead to the conversion of the existing conditional recommendation to an unconditional recommendation.

4.2.1. Intervention: pyrethroid-PBO nets

Applicant: Liverpool School of Tropical Medicine for the LLIN Evaluation in Uganda Project (LLINEUP)

The researchers last interacted with VCAG at its ninth meeting in 2018 *(8)* where they presented their plans for a cluster randomized trial to measure the impact of ITNs with and without PBO on malaria indicators in Uganda. The study was coordinated in collaboration with the Ministry of Health of Uganda, namely the Ugandan National Malaria Control Programme, and other stakeholders who delivered the intervention through a routine ITN distribution campaign in 2017–2018.

The primary objective of the study was to determine whether parasite prevalence is lower in intervention clusters (health subdistricts randomized to receive PBO nets) than in control clusters (health subdistricts randomized to receive conventional nets) in eastern and western Uganda.

Updates

At this 14th meeting, the applicants submitted the final results of a second randomized controlled trial on pyrethroid-PBO nets in Uganda. The first trial on these types of nets had been conducted in the United Republic of Tanzania (9). As this intervention class has already (and exceptionally) received a conditional recommendation from WHO, the submission of the results from the LLINEUP trial was intended to fulfil the WHO requirement of demonstrated public health value derived from two trials with epidemiological end-points.

The study in Uganda, where pyrethroid resistance in *Anopheles* mosquitoes is high, was designed to evaluate the impact of pyrethroid-PBO nets versus standard LLINs (without PBO). The epidemiological and entomological results at baseline and at 6, 12 and 18 months after LLIN distribution were published in 2020 *(10)*. An additional report was provided to present the results from the last survey, at 25 months.

The primary outcome was parasite prevalence in children aged 2-10 years detected by microscopy. In the as-treated analysis, the parasite prevalence was significantly lower in the PBO arm compared with the non PBO arm at months 6, 12, 18 and 25 after LLIN distribution. The prevalence rates (PBO arm/non-PBO arm) were significant and ranged from 0.73 to 0.84. The prevalence of anaemia (secondary outcome) was lower in the PBO group than in the non-PBO group at 6 months but not statistically different at months 12, 18 and 25. Indoor vector density was significantly lower in the PBO group than in the non-PBO group at all four time-points and density ratios (PBO arm/non-PBO arm) and ranged from 0.14 to 0.27.

Summary of discussions

VCAG sought clarity from the applicants on several points of their submission and enquired about ongoing analyses after completion of the study as follows.

The applicants first explained why they focused their presentation on the as-treated (per-protocol) analysis. They indicated that some clusters (n=14) were lost to follow up as a result of COVID-19 disruptions. A further two clusters were excluded due to inaccuracies in the original mapping of health subdistricts and the distribution of nets to the wrong clusters, leaving a final sample size of 88 clusters. Therefore, the as-treated analysis was presented as the primary outcome as it more accurately reflects the LLINs that were received in each cluster, as opposed to the treatment arms they were initially allocated to.

The applicants also explained the use of a negative binomial model in generalized estimating equations to calculate vector density ratio and associated confidence intervals. A large number of clusters had an estimate of zero for the vector density, and these data points are appropriately modelled with negative binomial distributions.

VCAG enquired about the composition of species and associated insecticide resistance during the course of the study. The applicants found that the overall abundance of *Anopheles gambiae* s.s. and *An. funestus* s.l. decreased during the study; *An. arabiensis* densities were more stable over time. These differential impacts meant that the relative proportion of *An. arabiensis* increased during the study, in line with observations of intervention-driven shifts in vector species composition in other East African settings. Although insecticide bioassays were not performed throughout the study, mosquitoes were genotyped for molecular markers of resistance. These data are being prepared for publication.

The applicants indicated that although there was no formal social science component of the trial to enable quantitative/qualitative analysis about the continued use of existing nets among study participants during the trial, there was a large observed increase in net

ownership and usage between baseline and the 6-month time-point. This suggests that where any existing nets remained in use beyond the start of the trial (as opposed to being replaced with a newly distributed net), the impact on the trial results would be small.

VCAG queried whether there were any differences in the performance of the two brands of PBO-pyrethroid nets used in the study. The applicants confirmed that the study was not powered to compare net types to begin with, and any comparisons of performance are further complicated by the imbalance in the number of clusters per arm, and the predominance of the lost-to-follow-up clusters being in the smaller arms. Baseline malaria prevalence also differed between clusters.

There are no plans for a 36-month time-point for this study. As outlined in *Norms, standards and processes underpinning development of WHO recommendations for vector control (11)*, there is a minimum requirement of 24 months for LLIN studies; this trial therefore fulfils the minimum requirements for study eligibility for this intervention class. The entomology data and durability study data are still being analysed. The WHO Prequalification Team mentioned that it would be valuable to share data on the durability of the nets with them before publication.

VCAG congratulated the applicants on completing such a large randomized controlled trial within the framework of operational roll out of ITNs and asked if they had any lessons to pass on to others considering a similar framework. The applicants noted that the omission of social science was a limitation in interpreting some of the findings but that they were satisfied that they had demonstrated the feasibility of this trial design approach.

Conclusions

In Uganda, PBO-pyrethroid nets conferred more effective protection against malaria than conventional non-PBO LLINs for up to 25 months. Considering the two independent epidemiological trials conducted with PBO-pyrethroid nets in Uganda and the United Republic of Tanzania, VCAG concludes that in areas where pyrethroid resistance of malaria vectors is high, PBO-pyrethroid nets are more effective than those without PBO.

VCAG confirms that public health value has been demonstrated for malaria protection over conventional non-PBO LLINs. VCAG recommends that specific guidelines for efficacy testing and evaluation of PBO nets (including criteria for PBO duration of efficacy) should be developed to provide the WHO Prequalification Team with data on efficacy and quality requirements adapted to this product class.

4.3. Intervention class: spatial repellents

Spatial repellents are designed to interrupt human–vector contact through vector behaviour modification induced by airborne chemicals, potentially offering protection from the bites of vectors and nuisance pests.

This intervention is being developed from control of both malaria and *Aedes*-borne viruses. Trials have been completed on Sumba Island, Indonesia and in Iquitos, Peru respectively.

While the Indonesian trial targeting malaria showed signs of protective efficacy, the results were not statistically significant. As such, at least two more trials targeting malaria are needed to demonstrate public health value of this intervention for malaria, and to trigger the development of a potential WHO recommendation. These trials are currently under way in Mali and Kenya.

For *Aedes*-borne viruses (dengue and Zika), the trial in Peru demonstrated that the spatial repellent significantly reduced arboviral infection. VCAG advised that this trial meets the criteria to be counted as one of the two trials needed to inform development of a WHO recommendation for deployment of this intervention to control arboviruses. The second trial is currently planned for Sri Lanka.

4.3.1. Intervention: transfluthrin passive emanators

Applicant: SC Johnson

The spatial repellent intervention proposed is a transfluthrin-based passive emanator produced by SC Johnson (Mosquito Shield™). It is designed to release the volatile pyrethroid into the air and prevent human–vector contact in the treated space. The intervention targets *Anopheles*, *Aedes* and *Culex* spp. mosquitoes, with claims to protect all age groups and populations in countries endemic for mosquito-borne diseases, from day-time, early-evening and/or late-night biting by mosquitoes in enclosed and semi-enclosed structures. Deployment of the spatial repellent product in enclosed and semi-enclosed spaces is intended to reduce human pathogen transmission.

Updates

Following the completion of their trial in Peru targeting dengue virus transmission, the applicants have submitted a manuscript describing the primary epidemiological outcomes for peer-reviewed publication. A preprint and supplemental information have also been posted in medRxiv *(12)*.

The applicants highlighted progress of the preparatory work for three trials that have either commenced with baseline follow up or are scheduled to begin baseline recruitment soon. These include trials targeting malaria in Kenya and in Mali, and another trial targeting dengue in Sri Lanka.

Kenya: malaria – commenced March 2021

The trial in Busia County in Kenya commenced baseline screening and enrolment on 1 March 2021, with all subject enrolment completed on 1 April 2021. Given the ongoing COVID-19 pandemic, a risk management plan has been developed and personal protective equipment (PPE) procured for study staff for the duration of the study. A "test" shipment of product from the SC Johnsonmanufacturing centre in Italy to the Kenya on-site storage facility has been successfully undertaken. Health officials in Busia County have agreed to adapt the county registry forms to assist with reporting adverse and serious adverse events. Baseline analyses for verification of study design assumptions on malaria incidence are planned for June 2021, with intervention (Mosquito Shield™) deployment planned for August 2021.

Mali: malaria – anticipated commencement August 2021

The trial in Mali is due to start on 1 August 2021. Regulatory approvals by the local Malaria Research and Training Center, the Institutional Review Board and the WHO Ethics Review Committee are complete. A COVID-19 risk management plan has been developed and PPE has been procured for the study period. Applications for an experimental use permit and an importation permit were submitted by the Malaria Research and Training Center of Mali in February 2021 and approved in April 2021. Product shipment will be coordinated by the manufacturer (SC Johnson), who is identifying optimal shipment routes and in-country brokers for customs clearance. Product storage facilities have been procured and will arrive on site in April 2021. Standard operating procedures have been established based on related documents from Kenya to ensure standardization of procedures, adapting as needed to the Mali context. Core field staffing and procurement for critical support materials such as computers, microscopes and malaria diagnostics is complete. A site evaluation visit by clinical study monitors was conducted in December 2020 for early determination of the University of Bamako's Malaria Research and Training Center infrastructure and capacity, as well as staff training. Census and household mapping of study clusters for baseline recruitment was completed in March 2021. A site initiation visit is planned for May 2021 to activate the site for baseline recruitment.

Sri Lanka: dengue – anticipated commencement August 2021

The trial in Sri Lanka will contribute a second dataset to evaluate the efficacy of the spatial repellent against dengue transmission. The study site has recently shifted from Colombo to Gampaha District as a result of overlapping deployment sites with the

World Mosquito Program's *Wolbachia* releases. Reassessment of sample size estimates is ongoing. Protocol submission to the local Institutional Review Board and to the WHO Ethics Review Committee regulatory authorities is anticipated in June 2021. Ramp-up activities are planned to support a January 2022 baseline recruitment start date. An early-stage Mosquito Shield™ manufacturing volume and shipping schedule has been outlined by SC Johnson. Refinement of these estimates will be conducted following household measurements during census of the new study site.

Summary of discussions

Kenya: malaria – commenced March 2021

The applicants sought recommendations on whether it would be necessary to submit baseline data to VCAG to review the study design. The baseline results are anticipated in July 2021. Given VCAG has previously reviewed the design, a re-evaluation is not necessary unless the applicant finds that the baseline data indicate the need to significantly revise the protocol and associated SAP. Based on the updates of the study documentation, the WHO Secretariat will provide guidance on whether a full review by VCAG is required or if a short update presentation to VCAG would suffice.

Mali: malaria – anticipated commencement August 2021

Similar to the situation in Kenya, the applicants sought feedback on whether VCAG would want to assess interim or final baseline results from the Mali data, to make recommendations on the study design. These results are anticipated in October–December 2021. Unless the applicant finds that the baseline data calls for a significant revision of the protocol and associated SAP, a re-evaluation by VCAG is not necessary. Based on the updates of the study documentation, the Secretariat will provide guidance on whether a full review by VCAG is required or if a short update presentation to VCAG would suffice.

Sri Lanka: dengue – anticipated commencement August 2021

Following discussion at the 13th VCAG meeting *(7)* it was recommended that if the applicants decide to employ a shorter duration primary analysis and adjust the effect size, a justification and required adjustments to the design would need to be made to the protocol and SAP for review by VCAG. At the present meeting the applicants indicated that they are exploring sample size requirements in relation to the incidence in Gampaha, and a diagnostic scheme for the primary end-point. Furthermore, the applicants had appropriately modified the protocol in response to VCAG's previous recommendation to indicate that both solicited and unsolicited adverse events are captured. Finally, given the change of study site within Sri Lanka (from Colombo to Gampaha District), the applicants asked whether VCAG would require assessment of the SAP following sample size finalization for the new Gampaha District, noting that statistical approaches will not change. VCAG agreed that review of the updated SAP would not be necessary unless significant changes are made in the protocol and SAP. In particular, this might be the case if the burden of disease and context of the study population are very different from Colombo. Based on the updates of the study documentation, the Secretariat will provide guidance on whether a full review by VCAG is required or if a short update presentation to VCAG would suffice.

Contingency plans in case of disruption

The applicants were questioned about whether there are contingency plans in case of disruption by unanticipated epidemics in Sri Lanka. They responded that dengue outbreaks do not affect the implementation of the protocol as routine Ministry of Health dengue control strategies will remain in place and reported across the study area during the trial. The applicants indicated that to limit exposure to coronavirus, household visits for the febrile surveillance cohort (secondary end-point of disease incidence) have been reduced and replaced by an enhanced surveillance system at health facilities. This does not apply to entomological surveys, which will continue to require household visits. The entomology technicians are staff who are/will be trained to reduce exposure to coronavirus and will receive and use PPE.

Conclusions

Overall, no significant concerns were raised for any of the studies. VCAG concludes the applicant is making good progress with the studies in Kenya, Mali and Sri Lanka, and planned designs are sound.

Recommendations

As noted previously, VCAG does not need to re-evaluate study designs or SAPs following baseline data collection in Kenya, Mali and Sri Lanka, unless the data necessitate a significant re-design of the studies. Where needed, proposed changes can be reviewed at a regularly scheduled VCAG meeting or through an off-cycle review, based on guidance from the Secretariat.

5. UPDATES

5.1. Intervention class: lethal house lures

The "lethal house lure" intervention class falls under the intervention type of housing modifications. It consists of a combination of blocking mosquito entry points (such as windows and doors) and installing insecticide-treated materials in the eaves. Mosquitoes that are attracted to the odour and heat produced by humans inside the house are drawn to the upper eaves of the housing structure, where they come into contact with the insecticide-treated netting or other material. These interventions aim to lower the risk of malaria transmission in the community by restricting mosquito entry into houses, and by killing host-seeking mosquitoes as a result of their exposure to insecticides.

One trial has been completed under this intervention class *(13)*; evidence supports that lethal house lures (eave tubes combined with screening of doors and windows) can reduce malaria transmission. Results from a second trial are needed to confirm public health value.

5.1.1. Intervention: eave tubes (with and without screening)

Applicant: In2Care

The In2Care team has been interacting with VCAG since 2014. In2Care® eave tubes are made of plastic and contain a removable mesh with a static coating that holds powder-formulated insecticides. The tubes are inserted in the eaves of houses during construction or are retrofitted by means of a large drill or installed behind ventilation space. The tubes funnel the indoor human-scented air outwards through a netting barrier treated with insecticide, making the house a lethal lure for host-seeking mosquitoes.

The major results supporting this intervention come from a cluster-randomized controlled trial conducted in Côte d'Ivoire during 2017-2019 to evaluate the efficacy of the lethal house lure intervention using clinical episodes of malaria as the end-point. Results presented to VCAG in November 2019 *(8)* demonstrated a substantial reduction on malaria incidence. However, it was not possible to quantify the relative contribution of the eave tubes versus house screening in this trial, because they were deployed and evaluated in combination. It is therefore unclear whether the deployment of eave tubes on their own, as envisaged by the manufacturer, provides public health value.

At the 12th VCAG meeting in June 2020 *(14)* the applicants presented plans for a second trial that would be used to generate evidence to meet the requirements that could trigger development of a potential WHO recommendation. Their second trial will be conducted in the United Republic of Tanzania. This cluster-randomized controlled trial will have a factorial design, to enable evaluation of eave tubes as a standalone intervention as well as in combination with house screening. At the 13th meeting in December 2020 *(7)* the applicants proposed to conduct follow-on studies in their previous trial site in Côte d'Ivoire, and to possibly undertake a trial of eave tubes alone (without screening) in Uganda.

Updates

At the present meeting, the applicants presented a general update intending to clarify the mode of action of eaves tubes and the plan for deployment of insecticides in future trials. No new data were presented to VCAG.

Summary of discussions

Initial discussion focused on the status of funding for the second trial in the United Republic of Tanzania. The applicants informed VCAG that funding was still unconfirmed. They were also asked why the second trial was still planning to deploy pyrethroids. The applicants explained that, as they were not the manufacturers of insecticides themselves, they remain dependent on the availability of powdered capsule suspension formulations of insecticides. If insecticides from other classes were available in the required form, they would consider using these instead of pyrethroids.

Pre-submission meetings have been initiated with the WHO Prequalification Team, with discussion focused on the safety component of the prequalification dossier including the approach to conducting the risk assessment.

5.2. Intervention class: reduction of pathogen transmission induced by gene drive

Genetic alteration of mosquito populations using gene drive technologies is an emerging vector control strategy whereby mosquitoes carrying an engineered gene drive and associated effector genes are released into a target population. Successive generations of mating between released transgenic individuals and conspecific individuals in the target population lead to an increase in frequency of the introduced transgenes – a strategy sometimes referred to as "population modification".

Autonomous, low threshold gene drive systems are potentially self-sustaining vector-borne disease interventions. Population modification is not intended or expected to alter the local ecology since the community structure and food webs in which modified mosquitoes are embedded will be unaffected. These technologies can be effective when insect population densities are low and are expected to be deployable in resource-constrained settings. The self-sustaining features of these technologies have the potential to be important in consolidating and maintaining malaria control gains when disease incidence becomes low and pressure to reallocate resources increases, as has resulted in resurgence of the disease in the past.

There are currently no active epidemiological trials under way for this intervention class. While there are applicants engaged with VCAG who plan to undertake trials with epidemiological end-points, progress has largely been in relation to optimizing drive efficiency, and mosquito fitness and competitiveness in laboratory and semi-field studies.

5.2.1. Intervention: CRISPR-Cas9 population alteration of Anopheles

Applicant: University of California Irvine Malaria Initiative

The UCI-Malaria Initiative is developing gene drives and effector genes that will reduce or eliminate the potential of *Anopheles gambiae* and *An. stephensi* to transmit *Plasmodium falciparum*.

The applicants participated in the fifth *(15)* and eighth *(5)* VCAG meetings, at which they described their present 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 design has antimalarial parasite effector genes based on single-chain antibodies (scFv) 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 to reduce the entomological inoculation rate, compared with current best practice LLIN interventions.

Updates

The applicants provided VCAG with a technical update concerning:

- the project's gene drive target product profile;
- the creation and laboratory testing of a homing-type gene drive system based on the RNA-guided DNA endonuclease Cas9;
- the creation and laboratory testing of transgene assembly consisting of genes encoding two scFvs, one targeting a *P. falciparum* secreted protein (chitinase) and the other a surface protein (circumsporozoite protein), which are expressed in two physiological compartments of an adult female *An. Gambiae* (the midgut and the haemolymph respectively);
- the planned adoption of a humanized mouse model system for investigating parasite evolution in response to selection pressures arising from the expression of anti-parasite scFvs; and
- the development and testing in the fruit fly, *Drosophila melanogaster*, of a prototype gene drive brake and reversal system that might be useful for interrupting the spread of a gene drive following its initial deployment.

The applicants described a homing-type gene drive based on Cas9 that is designed to insert/home into the *cardinal* gene that encodes a heme peroxidase in the ommochrome eye-pigment biosynthetic pathway and results in a loss of function phenotype – red eyes. Laboratory cage experiments lead to the rapid and efficient increase in the frequency of the drive. In response to concerns about standing and evolved resistance to homing-type drives, the gene drive insertion site was investigated and showed little natural variation in wild populations. In addition, the potential for off-target sites was evaluated; one of the five potential off-target sites in the genome was recognized by the drive system. Evidence was presented indicating that the drive system also functioned in other strains of *An. Gambiae* and tests in other members of the species complex are in progress. Overall, the drive system fit within the applicant's target product profile (TPP).

The project described TP13 which consisted of the gene drive described above with two anti-*Plasmodium* scFv-expressing transgenes. Laboratory cage experiments indicated that the drive characteristics of TP13 were similar to that of the gene drive alone.

P. falciparum challenge experiments showed significant reductions in parasite prevalence and mean intensity of sporozoite infections in TP13. Some sporozoites survived in the presence of the scFvs and successfully invaded the salivary glands. The applicants hypothesize that salivary gland sporozoite intensity need not be zero for the intervention to significantly reduce transmission (threshold dependent).

The applicants described their planned adoption of a humanized mouse model system that will enable them to investigate *P. falciparum* evolution in the laboratory.

A prototype system for reversing the effects of a homing-type gene drive was described and postulated as a potential biosafety tool that could provide some control over a gene drive following its release into a population.

Summary of discussions

Initial discussion focused on the TPP guiding the transition from discovery research to product development. Another TPP is being developed for the parasite effector component of the system. In response to questions, the applicant explained that the scFvs were effective in hetero- and homozygotes and that they intended to release homozygotes at field deployment. The significance of the observed off-target effects

was discussed and they were considered less as a safety risk because they occurred at low frequency in genes of unknown function and resulted in no visible phenotypes in the cage experiments. The applicants thought that at worst, these off-target effects might impact efficacy.

VCAG enquired about the project's community engagement activities that had been referenced in the presentation. The applicants briefly described their exploration of potential collaboration with partners in two oceanic nations – Sao Tome and Principe and the Comoros – with a view to future field trials. Both countries have mosquito populations that are very distinct when compared with the closest continental population; they reported having data supporting substantial genetic isolation. Entomological baseline data are being collected, although COVID-19 has disrupted these efforts. The applicants have begun interacting with authorities in both locations to establish engagement activities related to regulatory oversight.

In response to a question about the development timeline and time to first release, the applicants clarified that it is not possible to set a specific target date yet because the technology is not yet field ready. However, work on community engagement and risk/regulatory aspects of the project has been initiated, as these will likely be the rate limiters for field implementation rather than the technology development.

6. CONCLUDING REMARKS

The WHO VCAG Secretariat and the co-chairs thanked VCAG members for the time and effort in reviewing the applicant submissions and participating in yet another virtual meeting. For the second meeting in a row, VCAG has made positive recommendations on the public health value of a new tool, in this instance for malaria. Other submissions continue to make progress in generating evidence to inform assessment of their potential public health value.

Given the continued COVID-19 pandemic, the 15th VCAG meeting will be held virtually during the week of 4–8 October 2021.

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ANNEX 1. AGENDA

MONDAY, 19 APRIL 2021	
Session 1: Welcome and updates	
12:00–12:15	**Secretariat welcome** • Logistics and overview of meeting • Declarations of interest
12:20–12:40	**Official opening of the meeting** Chair of session: VCAG Co-chairs • Welcome from WHO Regulation and Prequalification Director (10 min) • Any other business (10 min)
Session 2: Information	
12:45–13:45	**Overview of WHO's guideline development process** Chair of session: VCAG Co-chairs • Presentation on data requirements and processes involved in developing WHO guidelines (30 min) • MAGICapp introduction (10 min) • Open floor for questions and answers (20 min)
Session 3: Update presentations from applicants	
14:15–15:00	**Presentation – Eave tubes** Chair of session: Tom Smith • Applicant presentation (30 min) • Questions and answers (15 min)
15:15–16:00	**Presentation – Gene drive** Chair of session: Dave O'Brochta • Applicant presentation (30 min) • Questions and answers (15 min)
TUESDAY, 20 APRIL 2021	
Session 4: Presentations from applicants	
12:00–13:00	**Presentation – ATSBs** Chair of session: Heather Ferguson • Applicant presentation (30 min) • Questions and answers (15 min) *Applicants leave the call* • Closed discussion (15 min)
13:15–14:15	**Presentation – Spatial repellents** Chair of session: Salim Abdulla • Applicant presentation (30 min) • Questions and answers (15 min) *Applicants leave the call* • Closed discussion (15 min)
14:45–16:00	**Presentation – Pyrethroid PBO nets** Chair of session: Fabrice Chandre • Applicant presentation (40 min) • Questions and answers (20 min) *Applicants leave the call* • Closed discussion (15 min)

WEDNESDAY, 21 APRIL 2021	
Session 5: Feedback to applicants	
12:00–12:45	**Feedback – ATSBs** Chair of session: Heather Ferguson • Closed discussion (25 min) *Applicants join the call* • Feedback to applicants (20 min)
13:00–13:45	**Feedback – Spatial repellents** Chair of session: Salim Abdulla • Closed discussion (25 min) *Applicants join the call* • Feedback to applicants (20 min)
14:15–15:15	**Feedback – PBO nets** Chair of session: Fabrice Chandre • Closed discussion (35 min) *Applicants join the call* • Feedback to applicants (25 min)
Session 6: VCAG wrap up	
15:15–15:45	**Wrap up** Chair of session: VCAG Co-chairs

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ANNEX 3. DECLARATIONS OF INTEREST

All VCAG members and invited experts completed the form for declaration of interests for WHO experts before the meeting. The VCAG Secretariat assessed the interests declared by the experts and, with the exception of those described below, found that they were not directly related to the topics under discussion at the present meeting.

The following declared interests were assessed as relevant (or potentially relevant) to the topics under review at the meeting. The disclosed interests did not warrant full exclusion from the meeting itself, but rather management or partial participation. The conclusions and mitigating actions taken in relation to the disclosed interests are described below.

Dr Camilla Beech (Cambea Consulting, UK)

Dr Beech has been involved in consultancies relating to regulatory aspects of genetically modified insects as part of the Target Malaria consortium. She was a subject matter expert for the Convention on Biological Diversity for synthetic biology and has provided evidence to the UK House of Lords enquiry on genetically modified insects.

- *Conclusion and action:* Dr Beech's involvement with Target Malaria was not deemed to pose a conflict with the review of the submission from other teams also using genetic modification technology. She was able to participate in discussions relating to genetically modified insects in the meeting and in developing recommendations and drafting the report for the respective applicant.

Dr Mamadou Coulibaly (University of Science and Technology of Bamako, Mali)

Dr Coulibaly has indicated that he is working on a gene drive project in mosquitoes. The intervention approach differs from that of the applicant at this meeting (population suppression/reduction vs population alteration), and targets a different species. Dr Coulibaly declared a conflict of interest with the spatial repellent submission.

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

Dr Heather Ferguson (University of Glasgow, UK)

Dr Ferguson has indicated a previous involvement in the risk assessment of genetically modified insects as part of the Target Malaria consortium.

- *Conclusion and action:* Dr Ferguson's involvement in risk assessments relating to a different applicant was not deemed to be a conflict of interest to the gene drive applicant participating in this meeting. As such, she was able to participate fully in respective session on genetically modified mosquitoes and in developing recommendations and drafting the report for the respective applicant.

Dr Audrey Lenhart (United States Centers for Disease Control and Prevention, USA)

Dr Lenhart is an external scientific advisory board member for the spatial repellents project.

- *Conclusion and action:* Dr Lenhart's involvement in the advisory board was acknowledged; however, it was not deemed to be a conflict. She was able to participate in the discussion on the applicant submission and in developing recommendations and drafting the report for the respective applicant.

Dr Dave O'Brochta (Foundations for the National Institutes of Health, USA)

Dr O'Brochta is involved with the GeneConvene Global Collaborative, a collaboration that provides a source of strategy neutral and scientifically credible information, advice, training and coordination on gene drive technologies.

- *Conclusion and action:* No conflict of interest was identified, and Dr O'Brochta was therefore able to participate fully in discussions relating to genetically modified insects in the meeting, and in developing recommendations and drafting the report for the respective applicant.

Dr Hilary Ranson (Liverpool School of Tropical Medicine, UK)

Dr Ranson has contributed to the Cochrane Reviews for the PBO net systematic review. She works in the same institute as one of the researchers on this programme but has not been involved in the research programme or in undertaking the studies of PBO nets or analysis or interpretation of data.

- *Conclusion and action:* It was acknowledged that Dr Ranson works in the same institute as one of the applicants, and that she has been involved in the independent review of the PBO net data as part of the Cochrane systematic review. Neither of these two points were deemed to be a conflict of interest. She was thus able to participate fully in discussions relating to PBO nets and in developing recommendations and drafting the report for the respective applicant.

Dr Robert Reiner (Institute for Health Metrics and Evaluation, USA)

Dr Reiner declared a conflict of interest with the spatial repellent submission, as he is a co-applicant.

- *Conclusion and action:* Dr Reiner was fully recused from all sessions on spatial repellents. He did not have access to submitted documentation, nor did he participate in closed discussions or in the drafting and finalization of the recommendations on spatial repellents submission.

Dr Leanne Robinson (Burnet Institute, Australia)

Dr Robinson declared a conflict of interest with the spatial repellent submission.

- *Conclusion and action:* Dr Robinson was fully recused from all sessions on spatial repellents. She did not have access to submitted documentation, nor did she participate in closed discussions or in the drafting and finalization of the recommendations on spatial repellents submission.

Dr Thomas Smith (Swiss Tropical Institute, Switzerland)

Dr Smith is involved in the modelling of numerous malaria interventions under different deployment scenarios, one of which is the PBO nets.

- *Conclusion and action:* Dr Smith's involvement in modelling deployment scenarios was not deemed to pose a conflict of interest in evaluation of the pyrethroid-PBO intervention itself. As such, he was able to participate fully in discussions on this topic and in developing recommendations and drafting the report for the respective applicant.

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