Sixteenth meeting of the WHO Vector Control Advisory Group
Sixteenth meeting of the WHO Vector Control Advisory Group
## CONTENTS

1. Background  
2. Welcome and opening remarks  
3. VCAG members’ discussion  
   3.1. Modification of intervention class name  
4. Submissions  
   4.1. Intervention class: reduction of pathogen transmission induced by gene drive  
      4.1.1. Intervention: Cas9/gRNA strategies to modify *Anopheles* species  
   4.2. Intervention class: bait stations  
      4.2.1. Intervention: ATSBs  
   4.3. Intervention type: housing modifications  
      4.3.1. Intervention classes: eave tubes and house screening  
5. Stakeholder open session  
6. Concluding remarks  
7. References  
Annex 1. Declarations of interest  
Annex 2. Agenda  
Annex 3. List of participants
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. These interventions include novel tools, technologies and approaches. VCAG is jointly coordinated by the Vector Control and Insecticide Resistance Unit of the Global Malaria Programme (GMP/VCR), the Veterinary Public Health, Vector Control and the Environment Unit of the Department of Control of Neglected Tropical Diseases (NTD/VVE) and the WHO Prequalification Unit Vector Control Product Assessment Team within the Department of Regulation and Prequalification (RQP/PQT-VCP). The specific functions of the advisory group 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 16th VCAG meeting was convened on 28–30 March 2022 virtually due to the ongoing COVID-19 pandemic. This report details the proceedings and outcomes of the meeting. VCAG provided feedback and recommendations to applicants who had made submissions for the following interventions:

• eave tubes;
• house screening;
• gene drive strategies (Cas9/gRNA approaches to modify Anopheles populations); and
• attractive targeted sugar baits (ATSBs).

The meeting was co-chaired by Dr Heather Ferguson and Dr Audrey Lenhart. Twelve of the 14 VCAG members were in attendance, along with two temporary advisors, the applicants (being product developers, innovators and researchers), and the WHO Secretariat.

Before the meeting, all VCAG members and invited experts completed “Declaration of interests for WHO experts” forms. The declared interests and how they were managed by the WHO VCAG Secretariat are summarized in Annex 1.

The agenda is reproduced in Annex 2, and the participants are listed in Annex 3.

2. WELCOME AND OPENING REMARKS

VCAG members and temporary advisors were officially welcomed by Dr Pedro Alonso, Director of WHO’s Global Malaria Programme. Dr Alonso offered his continued thanks and appreciation for the contributions of VCAG members and temporary advisors in what is a critical endeavour to bring new vector control tools to the field. Dr Alonso noted three major points in his opening remarks.
In line with VCAG’s rotation of co-chairs, Dr Alonso welcomed Dr Audrey Lenhart to the role of VCAG co-chair starting this 16th VCAG meeting. Dr Lenhart will take on the role for the next three years. She will serve alongside Dr Heather Ferguson, who will stay on as co-chair of VCAG until the end of her term as member. Dr Alonso also thanked Dr Salim Abdulla, who stepped down from the role of co-chair after the 15th VCAG meeting, for his service as co-chair and contributions to VCAG over the last three years.

Dr Alonso shared the news of his retirement with VCAG, and acknowledged the friendship, partnership and support he has received at WHO over the last eight years. He commented on the flattened progress in the eradication of malaria, irrespective of the recent challenges associated with the COVID-19 pandemic; many millions of malaria cases are still recorded every year. He noted the need to find new methods to tackle malaria in the next decade, and the important role that VCAG plays in this space in providing both scientific advice and leadership in the broader vector control community. Dr Heather Ferguson offered her thanks, both personally and on behalf of VCAG, to Dr Alonso for the inspiration, support and enthusiasm he has given to VCAG over the last years. Dr Alonso highlighted the collaborative efforts of Ms Marion Law (RPQ/PQT), Dr Raman Velayudhan (NTD/VVE) and Dr Jan Kolaczinski (GMP/VCR) in the coordination of VCAG, and thanked them for their efforts and successes.

Finally, a minute’s silence was held in memory of the late Dr Mwelecele Ntuli Malecela, who served as the Director of WHO’s Department of Control of Neglected Tropical Diseases. Dr Alonso shared his sadness over the loss of Dr Malecela both as a friend and as a colleague, and acknowledged the loss to the field of neglected tropical diseases. Dr Ferguson also spoke of the sadness and grief felt by the neglected tropical diseases and vector control community at Dr Malecela’s passing, and highlighted her efforts to demand attention and action in the fight against neglected tropical diseases. Dr Malecela’s commitment to global health has been, and will continue to be, an inspiration to all.

3. VCAG MEMBERS’ DISCUSSION

The Secretariat provided an update on several operational changes intended to improve the communication with broader stakeholders within the vector control community and provide them with updates as both the evaluation process and the guidelines process evolve.

The VCAG Terms of Reference (TOR) and the Standard Operating Procedures (SOPs) are being updated in line with a coordinated effort to align the TORs of scientific advisory groups throughout the Organization.

The Secretariat updated VCAG on the forthcoming publication of the interactive online report on intervention classes within the WHO vector control evaluation process. This platform is anticipated to better articulate the linkages between intervention classes, the trials in progress within these intervention classes, and the associated recommendations for established classes. The report, which will replace the static table “Overview of intervention classes and prototype/products under Vector Control Advisory Group review for assessment of public health value” on the VCAG website, will also reflect the recent changes to and additions of intervention classes within the evaluation framework (see 3.1 Modification of intervention class name).

3.1. Modification of intervention class name

At this meeting, the name change for one intervention class was communicated.

The intervention class of “lethal house lures” was developed following the original intended deployment of eave tubes as part of an integrated deployment strategy, in combination with full house screening (1). A first trial conducted in Côte d’Ivoire
demonstrated epidemiological impact against malaria when the two interventions were co-deployed. However, it was not possible to calculate the individual or incremental effects of either component of the “lethal house lures” in the analyses. VCAG advised the applicants that if they sought a recommendation for eave tubes as a standalone intervention, then public health value⁠¹ would need to be demonstrated for that intervention, without co-deployment with screening (2). In line with how the company intends to market the intervention, the applicants are now pursuing the required minimum two trials to generate evidence of epidemiological impact for eave tubes, independent of house screening.

To accommodate this change in the intended deployment strategy for the intervention, the tentative “lethal house lures” intervention class is therefore being renamed as “eave tubes”. The evidence generated in the Côte d’Ivoire trial will be considered supplementary support for eave tubes during any deliberations of the Guideline Development Group, following demonstration of public health value.

House screening, the other component of the former “lethal house lures” intervention class, is already associated with a WHO recommendation, and therefore is itself an established intervention class (3). House screening holds a conditional recommendation for deployment, based on low-certainty evidence. In an ongoing trial in Uganda (see Section 4.3.1 below), full house screening is being further assessed as a standalone intervention alongside eave tubes in a three-arm trial. Despite the existing recommendation for the deployment of house screening, any additional data generated in support (or otherwise) of the intervention can be included in an updated systematic review of the evidence upon which the WHO recommendation is based. Any necessary revisions to the recommendation will be incorporated into future revisions of the Guidelines.

The table below summarizes the two relevant intervention classes, each falling under the intervention type of “housing modifications”, and the status of evaluation for each.

<table>
<thead>
<tr>
<th>INTERVENTION CLASS</th>
<th>INTERVENTION</th>
<th>STATUS</th>
</tr>
</thead>
</table>
| Eave tubes (previously lethal house lures) | Eave tubes | Tentative intervention class  
• No WHO recommendation is in place.  
• One trial in Côte d’Ivoire on the combined use of eave tubes + screening was completed, but was unable to assess evidence of the individual impact of eave tubes.  
• At minimum, two trials are needed on the standalone intervention to assess public health value and trigger the guideline development process (if warranted) to formally establish the intervention class. |
| House screening | Untreated house screening | Established intervention class  
• WHO recommendation is in place (3).  
• Any additional evidence generated can be reviewed and incorporated into future revisions of the Guidelines. |

Further details about these intervention classes and additional amendments to the naming of particular intervention classes will be available with the forthcoming publication of the online interactive report on VCAG intervention classes.

---

¹ Public health value is deemed to be demonstrated for an intervention following completion of a minimum of two trials with epidemiological end-points, with the results conclusively demonstrating a reduction in the clinical burden and/or infection rate of the target disease.
4. SUBMISSIONS

In total, VCAG reviewed four interventions from three applicants. One of the applicants who participated in this 16th meeting also requested an off-cycle review following the th meeting. This off-cycle review is also captured in the present meeting report.

4.1. 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. These technologies are thought to 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, which has resulted in the resurgence of disease in the past.

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

4.1.1. Intervention: Cas9/gRNA strategies to modify Anopheles species

Applicant: University of California Malaria Initiative (UCMI)

The UCMI is developing gene drives and effector genes that aim to reduce or eliminate the potential of Anopheles gambiae and An. coluzzii to transmit Plasmodium falciparum parasites.²

The applicant had previously participated in the fifth, eighth and 14th VCAG meetings, describing their present strategy, which is to engineer mosquito strains 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 (P. falciparum) effector genes based on two single-chain antibodies (scFv) regulated by promoters derived from blood-meal responsive mosquito genes expressed in gut and fatbody cells, respectively. The effector genes are incorporated into an autonomous gene drive system based on CRISPR-Cas9 biology. Constructs are being developed to target An. gambiae s.s. and An. coluzzii.

At the 14th meeting, the applicant updated VCAG on progress relating to the product’s target product profile (TPP); creation and laboratory testing of a homing-type gene drive system based on the RNA-guided DNA endonuclease Cas9; laboratory testing and development of a prototype gene drive brake and reversal system in Drosophila melanogaster; and 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. Evidence was presented indicating that the drive system functioned in multiple strains of An. gambiae, and tests in other members of the species complex are in progress. The applicant indicated that preliminary talks about collaboration

² More information on the initiative can be found at: https://stopmalaria.org/
were under way with two oceanic nations, with a view to conducting field trials in the future.

**Updates**

At the 16th VCAG meeting, the applicant presented progress on the development of *An. gambiae* (AgTP13, AgTP24 and AgTP43) and *An. coluzzii* (AcTP13 and AcTP24) strains containing gene drives with anti-parasite effector genes. This included demonstrating the efficacy of gene drive in three geographically distinct *An. gambiae* strains.

New data were presented on the successful introgression of the basic drive plus effector construct (TP13 and TP24) gene drive systems into *An. coluzzii*. The applicant observed results in laboratory-based cage experiments measuring the efficacy of the drive system that were comparable to those obtained in *An. gambiae* s.s. The applicant is planning to do the same experiments in *An. arabiensis* and *An. merus*. The applicant also reported life-table evaluations of strains for transgene insertion effects and analyses of Cas9 off-target and non-target effects. Data were presented on the efficacy of the two scFvs’ combined effect on *P. falciparum* development in *An. gambiae* and *An. coluzzii*. Reduced numbers of sporozoites were found in salivary glands and the applicants suggested that, based on recent data, it may not be necessary to eliminate all sporozoites from the salivary glands to eliminate infectivity.

The applicant summarized the next steps as:

- completing life-table analyses of *An. gambiae* and *An. coluzzii* effector strains;
- evaluating the long-term stability of gene drive systems;
- conducting parasite challenge assays with diverse geographical and genetic strains of *P. falciparum*;
- evaluating the relationship between sporozoite loads in salivary glands and mosquito infectiousness;
- testing genetic mitigation strategies.

**Summary of discussions**

The applicant requested comments/inputs from VCAG regarding: i) the introgression range of species, ii) parasite threshold level parameters, and iii) parasite diversity to be incorporated into efficacy trials.

**Introgression screen:** The applicant introgressed TP13 into *An. coluzzii* for > 5 generations (estimated replacement of approximately 90% of the genome with that of the target) and performed parasite challenges. The applicant indicated that they are also undertaking whole genome sequencing to quantify introgression efficacy. VCAG considered that these introgression studies are likely to provide useful data to the applicant and others regarding the drive system’s robustness to varying genetic backgrounds, including the interspecific transfer of the system through the somewhat porous species boundaries within the *An. gambiae* species complex.

**Parasite diversity:** A major question associated with this population modification strategy concerned the performance of any collection of *Plasmodium* effector genes in the context of parasite diversity. There was discussion about the diversity of parasite lines being used in challenge experiments compared to the known natural parasite genetic diversity, with the applicant suggesting that geographical representation should bring a high degree of genetic diversity to the studies. The applicant is also preparing to perform challenge assays using different *P. falciparum* isolates. The variance in the performance of the set of effectors between genetically distinct parasites will begin to reveal their robustness. VCAG agreed with the applicant that data addressing the robustness of any parasite neutralization system will be informative for decision-makers.
Stability, durability and the TPP: The applicant reported data showing that the two single-chain antibody effectors used in combination do not completely block sporozoite infection of the salivary glands. However, the applicant suggested that it may not be necessary to achieve genetically modified mosquitoes that are completely refractory (zero sporozoites in the salivary glands) in order to be effective, referring to some recent estimates of the minimum number of infectious sporozoites required to initiate an infection. As management of parasite resistance to the effector genes will likely be important, VCAG was interested to see how incomplete refractoriness to parasite infection impacts the estimated risks of resistance evolution. The applicant also presented new constructs with additional effector genes, although these have not been tested. The applicant confirmed that they are very interested in the FREP1 locus, discovered through genome-wide association studies, that has been shown to be an important mediator of *Plasmodium* infection.

The applicant plans to evaluate the genetic stability of three constructs (TP13, TP24, TP43) in *An. gambiae* and *An. coluzzii* through a series of multigenerational small population studies in the laboratory. VCAG agreed that estimating the stability of the gene drive constructs will be useful when considering the intervention’s ability to deliver a positive public health outcome. The modelling studies referred to by the applicants, which suggest construct stability over the minimum period required by the TPP (two transmission seasons), are also of interest to VCAG, as these will help when considering future testing and implementation scenarios for this intervention.

4.2. Intervention class: bait stations

Bait stations are interventions that are designed to attract and kill target vectors. 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 attracting the mosquitoes to a source that also contains a lethal toxicant.

To date, there is one intervention assigned to this intervention class. The applicant for this intervention is planning three field trials to evaluate the epidemiological impact of ATSBs on malaria transmission in Africa.

4.2.1. Intervention: ATSBs

**Applicant: Westham**

The ATSB concept was first reviewed by VCAG at its third meeting in November 2014 (4). Over subsequent years, further product development has taken place and the applicant has regularly engaged with VCAG. The intervention has been shown to reduce mosquito vector populations and the survivorship of individual mosquitoes, as well as to decrease the proportion of mosquitoes with malaria parasites (5). The applicant assessed the risk posed to non-target organisms to be negligible with the current product prototype. The applicant has planned three parallel epidemiological trials in Kenya, Mali and Zambia.

The applicant engaged with VCAG during revisions of their protocols for the epidemiological trials and associated statistical analysis plans (SAPs). These revisions incorporated flexibility for interim analyses after one year (with appropriate adjustments to sample sizes).

**Off-cycle review**

The applicant requested an off-cycle review in October 2021, just after the 8th VCAG meeting. In accordance with VCAG’s Standard Operating Procedures,³ the Secretariat assessed the justifications provided by the applicant and agreed that there was significant grounds to grant the off-cycle assessment.

³ The SOPs can be consulted at the following link: https://apps.who.int/iris/bitstream/handle/10665/274450/WHO-CDS-VCAG-2018.02-eng.pdf
Updates

At a recent stage-gate review meeting with the Bill & Melinda Gates Foundation, the applicant was given the green light to proceed with the epidemiological studies in Zambia in 2021. In preparation for commencement, the applicant performed a full costing of the planned trials, based on the most recent protocol endorsed by VCAG and other stakeholders. This exercise indicated that costs would considerably exceed the available trial budget. Consequently, the existing protocols for the trials planned in Kenya and Zambia were revisited, with the aim of streamlining trials to reduce costs while still meeting the objective of demonstrating epidemiological impact.

For this off-cycle review, the applicant submitted a detailed summary of all proposed protocol modifications and the rationale behind them. Major proposed amendments included fewer epidemiological and entomological end-points; a switch from year-round to seasonal deployment and sampling of the intervention (Zambia); a reduction in entomological sampling in Kenya; and a reduction in the frequency of ATSB monitoring and the range of additional information collected on use, coverage and non-target organism impacts. The applicant sought VCAG’s feedback and advice on these amendments.

Summary of discussions

The applicant’s presentation was followed by a question-and-answer session, during which VCAG asked for clarification and further information, as summarized below.

The applicant proposed to reduce the statistical power to detect a difference in outcomes from 90% to 80%. The applicant confirmed to VCAG that 80% power would be maintained over the whole trial, while allowing for stoppage at interim analysis if strong evidence for a benefit has been obtained.

The applicant indicated that baseline studies suggested that loss to follow-up (LTFU) in the cohort would likely be higher than originally estimated (from 20% to 30%+). The applicant has amended the power calculations to reflect this increase. VCAG queried the feasibility of assessing the intervention with LTFU rates considerably greater than 30%. The applicant indicated that high LTFU rates in the baseline studies were mainly due to low parasite clearance rates after the first treatment, which they believe can be improved through more rigorous engagement of community health workers to reinforce treatment adherence.

One of the major changes in the Zambia trial will be to deploy the intervention only during the rainy season. VCAG queried whether this might miss an important component of the intervention mechanism, for example, if its impact is greatest in the dry season due to low competition from other plant sugar sources. The applicant responded that, based on preliminary work, they do not anticipate ATSB efficacy to vary seasonally, but acknowledged that feeding rates on ATSBs may be higher in the dry season. The applicant also expressed their thought that the deployment of this intervention by control programmes would most likely be seasonal rather than year-round.

VCAG expressed concern about the proposal to drop all entomological sampling in the second year of the Kenyan trial. The applicant proposed to do monthly sampling in Year 1 and none in Year 2. VCAG enquired as to why they did not want to split the 12 months of entomological sampling time over both years instead (i.e., six months per year). The applicants responded that this was due to simpler logistics and costs of restricting entomological surveillance to one year. Given that the entomological end-point in the Kenya trial has now been shifted to parity (whether mosquitoes have laid eggs), VCAG questioned the value of sampling during the dry season when sample sizes may be too small to yield much information on mosquito parity. The applicant responded that their initial power analysis indicated that sample sizes over the whole 12 months should be sufficient for this end-point.

VCAG sought clarity on the plan to drop wider monitoring of ATSB impacts, including potential non-target impacts. The applicant responded that extensive data on non-target organism presence on bait stations have now been collected from all three trial sites and
that this work continues. The data will be reviewed by a specialist environmental consultant to determine whether they are sufficient or what further observations would be required to assess whether there are off-target impacts. The applicant mentioned that such data are also being collected in their other ASB trials, but these have yet to be shared with VCAG.

A question was raised about the rationale for dropping some of the insecticide classes from the originally proposed resistance bioassays in the Kenya and Zambia trials. The applicant clarified that these decisions were made by the local trial teams and the insecticides were dropped as they had not been used for vector control in those locations in recent years.

There was discussion on the risks associated with reduced ATSB monitoring frequency, and the potential loss of information and ability to act quickly to address problems with coverage. The applicant indicated their proposal to switch to a system of community-based surveillance, with formal monitoring by the research team conducted only once every two months (rather than monthly); a more limited range of data would be collected. The applicant clarified that they are confident that this modified approach will still be sufficient to react quickly to address problems with ATSBs in the field, based on their experience using a similar approach in other ASB studies.

Conclusions

While the proposed modifications will reduce the amount of information from the Kenya and Zambia trials, VCAG concluded that the revised protocols seem generally appropriate to generate the intended data and should still allow for the assessment of the public health value of ATSBs. However, VCAG concluded that a small number of the proposed revisions could impair the interpretation of trial results. These are summarized in the below recommendations.

VCAG highlighted that a number of the proposed changes will increase the risk of the trial producing inconclusive results. For example, the reduction of power, the reliance on only one epidemiological end-point, and considerable cut-back on the collection of entomological and coverage data mean that outcomes will be restricted to the bare minimum to show an effect. If all aspects of the trial go as expected, the data should still be sufficient to demonstrate public health value, if such value exists. However, it means that the trials will be less robust to small deviations from the starting assumptions about efficacy and impact. Therefore, VCAG fully supports the applicants’ plan to search for additional funding in order to return some of the previously planned aspects of the studies.

Recommendations

1. VCAG recommended that the applicant aims to sample mosquitoes from the Kenya trial site as representatively as possible in terms of both space and time, and collect at least some entomological efficacy data each year, rather than only in Year 1.

2. The applicant proposed that community health teams will monitor ATSB condition every two months. While recognizing funding constraints, VCAG recommended that the applicant assesses the extent to which the proposed monitoring approach will meet the study’s data quality objectives. It would be useful to determine whether the proposed monitoring approach adequately detects poor ATSB condition, and whether it does so in a timely manner to ensure replacements or repairs in the field to minimize loss of ATSB coverage. If the proposed monitoring approach indicates a loss of coverage greater than what was anticipated in the original study design, the applicant will have information to help characterize epidemiological results.

3. VCAG recommended that the applicant provides a brief summary of the rationale for the choice of insecticide classes for resistance monitoring in Kenya and Zambia, and clarify whether assays will be based on exposure just to the discriminating dose or will include measurement of resistance intensity for insecticides for which resistance is detected.
4. VCAG requested clarification on the parameters of the interim analysis, including the significance level, the power to detect a stated effect size, and the theoretical framework (e.g. alpha spending (6)).

5. The applicant indicated that infection via PCR will be dropped as an end-point, but that they still intend to collect samples and will analyse these if funds become available. VCAG asked the applicant to confirm with the relevant committees the ethical acceptability of this approach. The applicant was also asked to clarify whether they are still considering clearance of parasites as an end-point, given that this was linked to the PCR analysis.

6. VCAG recommended that the applicant presents a full summary of the available baseline entomological data, including data on efficacy and non-target organisms.

**On-cycle review**

**Updates**

For this 16th VCAG meeting, the applicant provided an updated presentation and supplied the latest versions of their SAP and Master Protocol (previously reviewed) as supplementary information. During the meeting, the applicant presented a summary of some baseline entomological results from the three trial sites in Kenya, Mali and Zambia; a summary of modelling results used to support aspects of trial design and deployment; and studies of non-target impacts. The applicant additionally responded to some of the recommendations made by VCAG during the off-cycle review (although said responses were not formally reviewed). Finally, the applicant provided the status of current epidemiological trials. The Zambia trial is under way, and the trials in Kenya and Mali are being launched in March and May 2022, respectively. The presentation was followed by a question-and-answer session, as summarized below.

The applicant did not request a formal review at the present meeting; the presentation was provided for VCAG’s information only. Given the nature of this interaction, VCAG did not provide recommendations arising from this meeting.

**Summary of discussions**

VCAG commented on the relatively high rate of ATSB removal by community members observed in the Zambia trial, especially near the start of the trial, and asked for the applicant’s opinion on why this happened.

The applicant believed that this was due to community perceptions that mosquitoes could be attracted to the devices and could then proceed to feed on people in greater numbers, possibly passing on toxic substances from the devices to people. Device barcoding also raised concerns, as did the red colour of the liquid contents, which evoked associations with blood. Increased community engagement and sensitization subsequently addressed these concerns.

VCAG asked whether investigation of non-target organism impacts was conducted only for honeybees, as described in the presentation.

The applicant clarified that their primary focus was on honeybees. Analyses of non-target organism impacts were based on timed observations and photographic images that revealed no occurrence of honeybee feeding on ATSBs in Kenya, Mali or Zambia. Further observations revealed that two wild colonies of *Apis mellifera* within 120 m of the field station at the Zambia study site remained active, despite the presence of ATSBs in the area. The applicant commented that some other insects, including houseflies, beetles and spiders, were observed on ATSBs, but the numbers were low.
VCAG asked about the extent to which effectiveness measurements based on a 48-hour exposure to the bait station reflect field conditions.

The applicant mentioned that both 24-hour and 48-hour assessments were performed and that the results were reproducible. The applicant also pointed out that measuring an effect on mortality requires extended exposure. The applicant acknowledged that these measurements do not provide a complete picture of efficacy and confirmed that they are also performing attractiveness and feeding studies in the field.

VCAG enquired about the details of the approach taken to investigate seasonal changes in ATSB feeding rates as a function of changes in the availability of vegetation.

The applicant explained that the estimates of sugar resource per unit area were obtained from botanical surveys to identify the most abundant plants/nectar sources, followed by trait analysis of those species and a modelling process to extrapolate beyond the surveyed areas. Mango was identified as one major source of sugar.

VCAG commented on the applicant’s observation that the replacement rate of ATSBs in the Zambia trial was higher than expected.

The applicant said that these data are still being collected. The applicant is trying to establish how much mould can accumulate on the devices while still maintaining their efficacy.

VCAG asked whether the recent finding that ATSBs should optimally be deployed in a protected location (shaded and away from rain) has considerably reduced the number of structures where they can be deployed at trial sites.

The applicant clarified that ATSBs are being deployed on all eligible structures, regardless of whether or not they can be installed in a protected location. The applicant mentioned that protected locations, which normally means placement of bait stations under house eaves, are less commonly available in Mali because of smaller eaves. The estimated percentage of devices in protected locations in Mali is therefore roughly 50%. Baseline entomological data presented at this meeting suggested that ATSBs’ residual efficacy is lower in unprotected than in protected sites.

VCAG asked what level of coverage was assumed in the modelling work that predicted a minimum of 2.5% feeding rate would be required by the vector population at each site to achieve the target epidemiological impact.

The applicant responded that ATSB coverage was not explicitly considered in these models.

4.3. Intervention type: housing modifications

Housing modifications involve physical or structural changes to a house or domicile in order to reduce the capacity for vectors to enter the living space of the target population. Depending on the style of architecture, such modifications may include structural changes to the housing itself that inhibit vector entry, or installation of removable or semipermanent fittings that may or may not be additionally treated with an insecticide.
4.3.1. Intervention classes: eave tubes and house screening

Applicant: U.S. Centers for Disease Control and Prevention and Infectious Diseases Research Collaboration, Uganda

The applicants from the Uganda Housing Modification Study attended VCAG for the second time; their first participation was in the 12th meeting (June 2020) when they presented the plans for a two-phase trial. The first phase of the trial, undertaken in Uganda, is intended to provide preliminary information on the feasibility, acceptability, costing and entomological effectiveness of four different interventions in small-scale deployment. These interventions are eave tubes, eave ribbons, full house screening and partial house screening.

VCAG previously recommended that the applicants provide a detailed trial design protocol and SAP for Phase 2 of the trial. VCAG also asked the applicants to consider local insecticide resistance profiles and the influence these would have on intervention choices. More detail was requested on how the applicants planned to account for variation in housing type in Phase 2 of the trial.

Updates

Following preliminary assessment of the four treatment interventions, the two most promising interventions (full house screening and eave tubes) are being evaluated in a large-scale randomized controlled trial (RCT). During the present interaction with VCAG, the applicants provided an update on Phase 1 and presented the RCT protocol and plans for Phase 2.

The documents submitted to VCAG included version 3.0 of the study protocol (2 September 2021), a pilot report on the applicants’ Phase 1 study, a qualitative assessment report, and a costing report based on the pilot study.

Summary of discussions

VCAG congratulated the applicants on completion of the pilot study and the informative data collected. VCAG asked the applicants whether the initial intra-cluster correlation coefficient (ICC) estimation might be updated based on their experience during the pilot study, which could enable a more refined power calculation. The applicants replied that epidemiological data were not collected during the pilot study and the ICC estimation was based on previous data from the study area.

There was some discussion on the use of self-reporting and passive surveillance and whether this might compromise the robustness of the epidemiological data obtained. The applicants indicated that the study teams are scheduling multiple check-ins with enrolled subjects and are actively working with community health volunteers to encourage participation.

VCAG remained eager to review the SAP when ready. The applicants reported that they would be finalizing the SAP once the protocol was finalized.

The applicants’ insecticide resistance monitoring plan was discussed, and there was general consensus within VCAG that it would be more valuable to conduct more frequent monitoring for resistance to the most relevant insecticides used in the area compared to what is laid out in the proposed monitoring scheme (e.g. less frequent monitoring of a wider range of insecticides, including ones not used locally). The applicants were open to VCAG’s recommendation and suggestions regarding the proposed frequency and specific insecticide targets.

The applicants expressed interest in collecting data over two years instead of the currently planned one-year trial duration. Although a two-year trial is not a requirement for demonstration of public health value of interventions other than insecticide-treated nets (7), VCAG agreed that a longer data collection period would considerably

Sixteenth meeting of the WHO Vector Control Advisory Group 11
strengthen the evidence base for these interventions. The duration of a trial should be determined based on the estimated sample size required to demonstrate public health value and based on the characteristics of the specific intervention, such as its likely duration of efficacy and associated need for its replacement. Extending the trial duration in Uganda would not only strengthen the evidence base related to the efficacy of the interventions, but could also provide additional insights into practical aspects of deploying these interventions, such as methods for routine deployment and durability under field conditions. Moreover, as there will be different housing types across arms of the trial (traditional and modern), a longer trial could provide an opportunity to estimate more nuanced effect sizes across these housing types. This, in turn, could allow for greater generalizability of the impact of this intervention.

**Conclusions**

The applicants generated valuable data in a pilot study to inform their decisions regarding the interventions to deploy in an epidemiological trial.

**Recommendations**

1. VCAG recommended that the applicants share the SAP with the group when it becomes available.
2. VCAG recommended that the applicants evaluate the balance across the arms of the trial as early as possible.
3. VCAG recommended that the applicants modify the insecticide resistance monitoring plan to reduce the number of insecticides being tested (i.e. to maintain a focus on insecticides that are primarily used in the area), and instead increase the frequency of testing, especially if the trial is extended to two years.
4. VCAG supports the extension of the trial to a second year, as this will allow for more precise estimates of the public health impact of the interventions across various housing structures.

**5. STAKEHOLDER OPEN SESSION**

Dr Raman Velayudhan introduced the new Global Arbovirus Initiative. The Initiative, officially launched on 31 March 2022, is co-managed by the WHO Health Emergencies Programme, the Department of Control of Neglected Tropical Diseases and the Immunization, Vaccines and Biologicals Department.

The Initiative has been developed in response to the continuing threat of arthropod-borne virus outbreaks, largely as a result of Aedes-borne virus transmission, including dengue, chikungunya, yellow fever and Zika viruses. As evidenced by the global COVID-19 pandemic, much of the world is insufficiently prepared to manage an epidemic/pandemic. While not all arboviruses cause mortality, they often cause severe morbidity. The overarching goals of the Initiative are to strengthen integration in terms of detection, response and control; advance innovation in diagnostics and medical interventions; and improve supportive care for those infected, while empowering communities to support surveillance, prevention and sustained vector control efforts.

The six pillars of the Global Arbovirus Initiative are as follows:

1. Monitor risk and anticipate.
2. Reduce epidemic risk.

---

4 More information on the initiative can be found at: https://www.who.int/news-room/events/detail/2022/03/31/default-calendar/global-arbovirus-initiative.
3. Strengthen vector control.
4. Prevent and prepare for pandemics.
5. Enhance innovation and new approaches.
6. Build a coalition of partners.

The Global Arbovirus Initiative will be supported by a Technical Advisory Group and the WHO Global Arbovirus Initiative Working Group until 2025.

6. CONCLUDING REMARKS

VCAG co-chair Dr Audrey Lenhart thanked the VCAG members and temporary advisors for their commitment, time and effort in supporting VCAG activities, and for their participation. The VCAG Secretariat echoed the thanks of the co-chair, acknowledging the dedication of the advisory group members.

The 17th VCAG meeting is scheduled for the first week of October 2022. Depending on the COVID-19 epidemiological situation leading up to the meeting, WHO will consider convening the meeting in person in Geneva, Switzerland.

7. REFERENCES

ANNEX 1. DECLARATIONS OF INTEREST

The 16th Vector Control Advisory Group (VCAG) meeting was convened to review and evaluate three applicant submissions on novel vector control interventions.

Before the meeting, all VCAG members and temporary advisors completed their “Declaration of interests for WHO experts” forms. The VCAG Secretariat assessed the interests declared by the experts and, except for the points described below, found that the interests 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 mitigating actions taken in relation to the disclosed interests are described.

The reading of these interests constitutes public disclosure to participants at this meeting. These interests will also be recorded and disclosed in the report of the meeting and/or relevant publications or work products.

**Dr Camilla Beech** has been involved in consultancies relating to regulatory aspects of genetically modified insects. 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.

Dr Beech’s involvement in work on regulatory aspects of gene drive was not deemed to pose a conflict in the review of the submission also using genetic modification technology. Dr Beech’s participation in the meeting and development of advice within the report was not restricted.

**Dr Heather Ferguson** works in the same department as a researcher who consults on the ATSB research programme (a few hours per month). Dr Ferguson has no involvement in the programme or related studies.

In reviewing this declaration, the secretariat considered factors not limited to the ATSB submission in question, and the role and contribution of Dr. Ferguson’s colleague to the ASTB research programme. All considered, the participation of Dr Ferguson in the review was not deemed to pose a conflict of interest in this instance. Dr Ferguson’s participation in the meeting and development of advice within the report was not restricted.

**Dr Mamadou Coulibaly** 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 it targets a different species.

Dr Coulibaly’s work on gene drive was not deemed to pose a conflict of interest in the review of the submission also using genetic modification technology. As such, Dr Coulibaly’s participation in the meeting and development of advice within the report was not restricted.

**Dr David O’Brochta** is involved with the GeneConvene Collaboration.

No conflict of interest was identified, and Dr O’Brochta’s participation in the meeting and development of advice within the report was not restricted.

**Dr Audrey Lenhart** has staff under her supervision who are working on the Housing Modification project, and her department is a collaborator on the project. Dr Lenhart herself is not an investigator or otherwise involved.

Dr Lenhart was not permitted to partake in the development of recommendations or guidance as part of the working group for this submission. However, her participation during question time and VCAG member discussions on the topic was not restricted.
### ANNEX 2. AGENDA

**MONDAY, 28 MARCH 2022**

<table>
<thead>
<tr>
<th>Session 1: Welcome and updates</th>
<th>Presenters</th>
<th>Closed session</th>
</tr>
</thead>
<tbody>
<tr>
<td>11:45 – 12:00 Preliminary welcome</td>
<td>WHO VCAG Secretariat</td>
<td>For information</td>
</tr>
<tr>
<td>Overview of running of meeting</td>
<td>Pedro Alonso</td>
<td>For information</td>
</tr>
<tr>
<td>Reading of advisors’ Declarations of Interest</td>
<td>Heather Ferguson</td>
<td></td>
</tr>
<tr>
<td>Audrey Lenhart</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session 2: VCAG discussion</th>
<th>Presenter</th>
<th>Closed session</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:00 – 12:30 Official opening of VCAG meeting</td>
<td>WHO VCAG Secretariat</td>
<td>For information</td>
</tr>
<tr>
<td>Chair of session: VCAG co-chairs</td>
<td>Pedro Alonso</td>
<td></td>
</tr>
<tr>
<td>Opening remarks: Director, Global Malaria Programme</td>
<td>Heather Ferguson</td>
<td></td>
</tr>
<tr>
<td>Opening remarks: VCAG co-chairs</td>
<td>Audrey Lenhart</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session 3: Applicant presentation</th>
<th>Applicants</th>
<th>Closed session</th>
</tr>
</thead>
<tbody>
<tr>
<td>12:30 – 13:15 Discussion amongst VCAG</td>
<td>WHO VCAG Secretariat</td>
<td>For discussion</td>
</tr>
<tr>
<td>Chair of session: VCAG co-chairs</td>
<td>Pedro Alonso</td>
<td></td>
</tr>
<tr>
<td>Discussion session</td>
<td>Heather Ferguson</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Audrey Lenhart</td>
<td></td>
</tr>
</tbody>
</table>

**TUESDAY, 29 MARCH 2022**

<table>
<thead>
<tr>
<th>Session 4: Applicant feedback</th>
<th>Applicants</th>
<th>Closed session</th>
</tr>
</thead>
<tbody>
<tr>
<td>14:00 – 15:00 Feedback – Housing modifications</td>
<td>U.S. Centers for Disease Control and Prevention (CDC)</td>
<td>For guidance</td>
</tr>
<tr>
<td>Chair of session: Robert Reiner</td>
<td>Infectious Disease Research Collaboration (IDRC)</td>
<td></td>
</tr>
<tr>
<td>Closed discussion</td>
<td>Pedro Alonso</td>
<td></td>
</tr>
<tr>
<td>Applicants join the call</td>
<td>Heather Ferguson</td>
<td></td>
</tr>
<tr>
<td>Feedback to applicants</td>
<td>Audrey Lenhart</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session 5: Applicant updates</th>
<th>Applicants</th>
<th>Closed session</th>
</tr>
</thead>
<tbody>
<tr>
<td>15:15 – 16:05 Presentation – ATSBs</td>
<td>Westham</td>
<td>For information &amp; discussion</td>
</tr>
<tr>
<td>Chair of session: Heather Ferguson</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Applicant presentation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q&amp;As</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| 16:15 – 17:05 Presentation – Gene drive | University of California Malaria Initiative (UCMI) | For information & discussion |
| Chair of session: David O’Brochta | | |
| Applicant presentation | | |
| Q&As | | |

**WEDNESDAY, 30 MARCH 2022**

<table>
<thead>
<tr>
<th>Session 6: Stakeholder engagement</th>
<th>Presenters</th>
<th>OPEN session</th>
</tr>
</thead>
<tbody>
<tr>
<td>14:00 – 15:00 Open session</td>
<td>Raman Velayudhan</td>
<td>For information</td>
</tr>
<tr>
<td>Chair of session: Heather Ferguson</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Topic: WHO Global Arbovirus Initiative</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Session 7: VCAG discussion and wrap-up</th>
<th>Presenters</th>
<th>Closed session</th>
</tr>
</thead>
<tbody>
<tr>
<td>15:00 – 15:30 Wrap-up</td>
<td>VCAG co-chairs + Secretariat</td>
<td>For information</td>
</tr>
<tr>
<td>Chair of session: Audrey Lenhart</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
## ANNEX 3. LIST OF PARTICIPANTS

### VCAG MEMBERS

**Co-Chairs**

- **Heather Ferguson**
  University of Glasgow
  Glasgow, United Kingdom of Great Britain and Northern Ireland

- **Audrey Lenhart**
  United States Centers for Disease Control and Prevention
  Atlanta, United States of America

**Members**

- **Neal Alexander**
  Centro Internacional de Entrenamiento et Investigaciones Médicas (CIDEIM)
  Bogotá, Colombia

- **Camilla Beech**
  Cambea Consulting Limited
  Berkshire, United Kingdom of Great Britain and Northern Ireland

- **Steven Bradbury**
  Iowa State University
  Ames, United States of America

- **Mamadou Coulibaly**
  Université des Sciences, des Techniques et des Technologies de Bamako
  Bamako, Mali

- **David O’Brochta**
  The Foundation for the National Institutes of Health
  North Bethesda, United States of America

- **Hilary Ranson**
  Liverpool School of Tropical Medicine
  Liverpool, United Kingdom of Great Britain and Northern Ireland

- **Robert Reiner**
  University of Washington
  Seattle, United States of America

- **Leanne Robinson**
  Burnet Institute
  Melbourne, Australia

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

- **Alfred Tiono**
  Centre National de Recherche et de Formation sur le Paludisme (CNRFP)
  Ouagadougou, Burkina Faso

### PARTICIPANTS – VCAG APPLICANTS

**Bait stations (attractive targeted sugar baits; ATSBs)**

- **Julian Entwistle**
  Innovative Vector Control Consortium (consultant)

- **Amir Galili**
  Westham Inc.

- **Angela Harris**
  Innovative Vector Control Consortium (consultant)

- **Megan Littrell**
  PATH

**Housing modifications (eave tubes and house screening)**

- **John Gimnig**
  United States Centers for Disease Control and Prevention

- **Samuel Gonahasa**
  Infectious Diseases Research Collaboration

- **Moses Kamya**
  Infectious Diseases Research Collaboration

- **Catherine Maiteki-Sebuguzi**
  Uganda Ministry of Health

- **Henry Maweje**
  Infectious Diseases Research Collaboration

- **Joaniter Nankabirwa**
  Infectious Diseases Research Collaboration

- **Nelli Westercamp**
  United States Centers for Disease Control and Prevention

**Gene drive (Cas9/gRNA strategies for population modification)**

- **Anthony A. James**
  University of California Irvine

### WHO HEADQUARTERS, GENEVA

**Global Malaria Programme**

- **Pedro Alonso**
  Director

- **Jan Kalacinski**
  Unit Head, Vector Control & Insecticide Resistance

- **Isabelle Abello**
  Assistant to Team, Vector Control & Insecticide Resistance

- **Lauren Carrington**
  Technical Officer, Vector Control & Insecticide Resistance

### TEMPORARY ADVISORS

- **Olubukola Tolulope Adenubi**
  Federal University of Agriculture
  Abeokuta, Nigeria

- **Mutizwa Odwell Muzari**
  Cairns Queensland Health
  Cairns, Australia