Vector Control Advisory Group

Nineteenth meeting of the WHO Vector Control Advisory Group

Meeting report, 27–28 September 2023

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Abbreviations

a.i.	active ingredient
CRT	cluster randomized trial
FDA	United States Food and Drug Administration
ITN	insecticide-treated net
LLIN	long-lasting insecticidal net
PBO	piperonyl butoxide
SAP	statistical analysis plan
SIT	sterile insect technique
VCAG	Vector Control Advisory Group
WHO	World Health Organization

1. Background

The Vector Control Advisory Group (VCAG) of the World Health Organization (WHO) serves as an advisory body to WHO on new interventions to control 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, the Veterinary Public Health, Vector Control and Environment Unit of the Global Neglected Tropical Diseases Programme, and the WHO Prequalification Vector Control Product Assessment Team within the Department of Regulation and Prequalification. The specific functions of the advisory group are:

- to support WHO in guiding applicants, via the WHO VCAG Secretariat, on study designs for the generation of epidemiological data intended to enable assessment of the public health value of new vector control interventions;
- to support WHO in evaluating the public health value of new vector control intervention classes, based on epidemiological studies submitted to WHO; and
- to advise WHO (i.e. the relevant technical departments) on whether public health value has been demonstrated for a new vector control intervention.

The 19th VCAG meeting was convened from 27 to 28 September 2023. This report details the proceedings and outcomes of the meeting. VCAG provided feedback and advice to applicants who had made submissions relating to the following interventions:

- eave tubes;
- sterile insect technique (SIT) in *Aedes aegypti*; and
- systemic endectocide treatment for Lyme disease.

The meeting was co-chaired by Dr Audrey Lenhart and Dr Leanne Robinson. Eleven VCAG members were able to join the meeting. They were joined by five temporary advisors, applicants (product developers, innovators and researchers) representing three intervention submissions, 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

Dr Rogerio Paulo Pinto de Sà Gaspar, Director of the Regulation and Prequalification department, officially opened the 19th VCAG meeting, welcoming the members and temporary advisors to Geneva. Dr Gaspar spoke about the work of WHO and the pivotal role of the Regulation and Prequalification department in supporting numerous divisions in the assessment of medicines, devices and products across many fields of health. Within WHO, a working group has been formed between the Medicines and Health Products and Science divisions in an organization-wide effort to streamline and expedite the evaluation and review of health products, as well as to simplify and bring consistency to complex decision-making between departments and across all product streams. This will better enable WHO to facilitate access to quality-assured, safe and effective interventions.

3. General stakeholder information session

Dr Jackie Cook and Dr Corine Ngufor provided an update to VCAG on the third year of a cluster randomized trial (CRT) in Benin, which formed part of the New Nets Project. Their presentation addressed the potential epidemiological benefit of dual active ingredient (a.i.) nets in the third year of the trial, with supporting entomological data. Next-generation insecticide-treated nets (ITNs) have been developed with different modes of action to counteract pyrethroid resistance. These include pyrethroid-piperonyl butoxide (PBO) nets, pyrethroid-pyriproxyfen nets and pyrethroid-chlorfenapyr nets. Each have been reviewed by WHO, and a recommendation has been developed accordingly. Interceptor G2 (pyrethroid-chlorfenapyr) and Royal Guard (pyrethroid-pyriproxyfen) were each assessed with CRTs conducted in Benin and the United Republic of Tanzania. Data from these trials supported a strong recommendation for the use of pyrethroid-chlorfenapyr nets and a conditional recommendation for pyrethroid-pyriproxyfen nets in areas where mosquito vectors are highly resistant to pyrethroids.

Dr Cook presented the results of the third year of the CRT in Benin, comparing standard pyrethroid-only nets with Interceptor G2 and Royal Guard nets. Although malaria incidence was still lower in areas with Interceptor G2 nets in the third year in Benin, unlike in years 1 and 2, the difference was not statistically significant. These epidemiological results were consistent with the indoor vector density data of the third year. It was noted that these findings differed from the results of the related trial in the United Republic of Tanzania *(1)*, which showed a significant epidemiological impact with Interceptor G2 in the third year. Consistent with the first two years of the trial, Royal Guard nets continued to demonstrate no additional effect compared to the pyrethroid-only nets on either epidemiological or entomological outcomes. Possible reasons for these observations include reduced net usage over time and lower quality of remaining nets due to physical and chemical degradation. With a lack of evidence that the dual a.i. nets provide additional benefit by the third year of use, there are implications for the increased costs associated with these nets and the potential need for more frequent deployment.

Within the same framework of the New Nets Project, studies were conducted on net durability, including attrition, fabric integrity, bioefficacy and chemical content. Dr Ngufor presented data on the rapid loss of bioefficacy for all nets tested in the third year of the RCT, with bioefficacy of chlorfenapyr and pyriproxyfen declining substantially in laboratory bioassays. The chemical content of chlorfenapyr in Interceptor G2 had also declined substantially at 24 months. Both dual a.i. nets performed similarly to pyrethroid-only nets in experimental hut efficacy studies at 36 months, which aligned with the epidemiological findings. Blood-feeding inhibition was also found to decline substantially for all three net types at 36 months, likely due to increased fabric damage.

Following the presentations, VCAG discussed in a closed session the implications of using dual a.i. nets and whether they provide a benefit over the cheaper pyrethroid-PBO nets and pyrethroid-only nets when used for longer than two years. Given that the increased efficacy is largely lost in the third year, cost-effectiveness considerations were discussed. WHO considers factors associated with resource use in the development of its guidelines and will draw on additional cost-effectiveness data on dual a.i. nets during future deliberations of the guideline development group, with a view to refining existing recommendations.

4. Submissions

VCAG reviewed three submissions across as many intervention classes at its 19th meeting.

4.1 Intervention class: eave tubes

Eave tubes are tubes installed within the eaves of traditional African style houses to funnel the indoor human-scented air outwards and attract host-seeking mosquitoes. This intervention class has a single intervention that is actively generating evidence of epidemiological impact: the In2Care® EaveTubes. Eave tubes were initially considered part of the lethal house lures intervention class, which combined deployment of the eave tubes with the screening of entry points (such as eaves, windows and doors) to the home. A first trial conducted in Côte d'Ivoire demonstrated epidemiological impact against malaria when the two interventions were co-deployed *(2)*. However, it was not possible to calculate the individual or incremental effects of either component of the "lethal house lures". Given the intention to deploy eave tubes without house screening, VCAG advised at its 16th meeting *(3)*, in coordination with the WHO Secretariat, that the intervention class be changed from "lethal house lures" to "eave tubes". The applicants are now pursuing the required minimum of two trials to generate evidence of epidemiological impact for eave tubes, independent of house screening.

4.1.1 Intervention: EaveTubes

Applicant: In2Care

In2Care® EaveTubes are made of plastic and contain a removable mesh with a static coating of a powder-formulated insecticide. The tubes are inserted into the eaves of houses during construction. Alternatively, they are installed behind ventilation openings or retrofitted into the wall by drilling, cutting or chiselling. The static-coated mesh transfers a sufficient dose of pyrethroid insecticide particles to be lethal to both pyrethroid-resistant and susceptible wild-type mosquitoes.

The In2Care team has interacted with VCAG since 2014 *(4)*, working towards generating evidence of disease impact against malaria for their EaveTubes product. The results of the first trial conducted in Côte d'Ivoire were presented to VCAG at its 11th meeting in November 2019 *(2)*. These results demonstrated a substantial impact on malaria incidence, albeit when deployed in combination with house screening as part of the lethal house lures intervention class. Supporting entomological studies were also presented to VCAG, which demonstrated efficacy against mosquitoes in the absence of screening.

At the 15th VCAG meeting (October 2021) *(5)*, the applicants presented plans for a new trial in Côte d'Ivoire, in an area close to where the previous trial had been conducted. This trial employs deltamethrin-treated EaveTubes without house screening and will enable comparison of the results with those of the previously published trial that tested house screening and EaveTubes *(6)*.

The applicants are also undertaking a trial in Uganda; this trial was originally reviewed at the 12th VCAG meeting in April 2020 *(7)*. This study includes three arms: deltamethrin-treated EaveTubes in the presence of pyrethroid-PBO long-lasting insecticidal nets (LLINs) or house screening in the presence of PBO LLINs as the two intervention arms, and PBO LLINs only in the control arm.

Together, the trials in Côte d'Ivoire and Uganda are intended to generate evidence for the assessment of the public health value of EaveTubes, independent of house screening, in two different settings.

Updates

The applicants informed VCAG that their trial in Uganda had recently been completed. While data analyses were still ongoing, the applicants provided initial results of the intervention implementation, interim cross-sectional results and some entomological results. The applicants expect that the full study results will be submitted to VCAG for review in the spring of 2024.

For the trial in Côte d'Ivoire, the applicants summarized baseline prevalence data and implementation progress, and provided an updated study protocol with amendments. The baseline prevalence survey was conducted from the end of May to mid-June 2023, while clinical follow-up with intervention will start in October 2023 and is planned to finish in October 2025.

Summary of discussions

The applicants asked VCAG whether they need to submit data on cost-effectiveness and user acceptance. VCAG replied that it would be interested in seeing these data; however, such data do not directly affect the assessment of public health value and hence are not a requirement for VCAG. It was noted that these data would contribute to the data considered by the guideline development group when it goes through the evidence-to-decision process as part of the guidelines development process. VCAG therefore strongly encouraged the applicants to collect and share such data with WHO in due course.

The applicants also asked VCAG whether they could pursue a prequalification listing and development of a recommendation if they demonstrated public health value in the Uganda and second Côte d'Ivoire trials. VCAG responded that applicants are free to engage with WHO Prequalification at any time they choose. Processes related to the development of recommendations will be initiated by WHO once VCAG has comprehensively assessed two adequately powered and well conducted trials. It should, however, be noted that WHO will not publish a recommendation in the absence of a positive prequalification assessment, nor will there be a prequalification listing in the absence of a WHO recommendation. To this end, WHO aligns its internal processes as much as possible to provide both a prequalification listing and a recommendation in a synchronized manner, provided they are supported by the data submitted.

There was a discussion of the planned analysis in the Côte d'Ivoire trial and the approach to conduct a single formal interim analysis to test the primary hypothesis. The investigators will apply the O'Brien-Fleming rule *(8)* after one year of the trial to assess protective efficacy on the primary end-point, i.e. the incidence of clinical malaria infections. It was established that the investigators were planning to use appropriate *P* value cutoffs consistent with the rule; therefore, if significance on the primary end-point is shown after one year, the data submitted on the primary end-point may be considered as the final trial result for efficacy. However, it is understood that the study will continue to complete data collection on secondary and safety end-points throughout the two-year follow-up without inflation of type I error. Such secondary data generated over the full two years of the trial will be informative for the guideline development group (and other stakeholders).

VCAG enquired about whether dust on the netting inserts may reduce the static charge and the efficacy of the intervention, considering the type of environment in which it would be deployed. The applicants noted that dust was indeed a potential problem, but that bioefficacy studies have shown that the deltamethrin powder-treated EaveTubes remain efficacious against resistant *Anopheles* mosquitoes for up to one year with dust on them. Therefore, while the durability of the a.i. on the EaveTubes can be up to three years, durability could be reduced with the presence of dust. To date, the impact of dust on durability has yet to be assessed in detail.

VCAG asked the applicants to clarify the criteria for replacing netting inserts and how this is being done in the two trials. The applicants indicated that, in both trials (in Uganda and Côte d'Ivoire), EaveTubes inserts are monitored bimonthly to inform the timing of

re-treatment. Inserts will be replaced based on efficacy bioassay results evaluating the mortality of wild-type *Anopheles* mosquitoes. If the cumulative mortality of sampled inserts from a single cluster is below 80%, then inserts from all trial clusters will be replaced. In the Uganda trial, there was no replacement needed, as the EaveTubes inserts retained their entomological efficacy for more than one year.

VCAG stressed the importance of monitoring ITN use in all trial arms throughout the duration of the study to ensure that any observed effects can be attributed to the EaveTubes and to support interpretation of the trial outcome. The applicants confirmed that new (WHO-prequalified) LLIN products had been distributed at the start of the trial to ensure universal coverage and that LLIN use is being monitored.

The applicants also confirmed that the cohort of children monitored for the primary end-point was selected randomly from the whole village, not just from houses with EaveTubes. This monitoring design is important because it will give an estimate of protection for the whole community, rather than just for those in the treated households.

The issues of possible changes in mosquito behaviour and resistance to pyrethroid insecticides were raised. Outdoor mosquito catches could be used to support monitoring of metabolic resistance (CYP450) if the trial budget permits.

Conclusions

VCAG thanked the applicants for their clear presentations and commended their work to date. The ongoing trials are well designed and likely to provide robust evidence on the efficacy of EaveTubes against malaria. VCAG looks forward to seeing the results at future meetings.

The applicants can engage with WHO Prequalification for assessment of their product at any time, although a listing may only be made once public health value (based on a minimum of two trials) has been confirmed by VCAG and WHO has developed and published a recommendation for the intervention class of eave tubes through the guidelines development process.

Recommendations

Following review of the submission, VCAG offered the following advice to the applicants:

- VCAG suggests that the investigators consider monitoring outdoor biting and metabolic resistance to insecticides over the two-year period. Although these data are not essential to demonstrate public health value, they will provide important additional information that can help to inform guidance on deployment of the intervention.

4.2 Intervention class: sterilization of male mosquitoes

Interventions within this class share the common goal of suppressing mosquito populations by releasing sterile males into the population that will mate with the wild females, resulting in the reduction or complete cessation of viable offspring. The sterility of the males can be induced by:

- irradiation (following the traditional SIT that has been used in agriculture for decades) using gamma rays, X-rays or electron beams;
- exploiting the reproductive manipulation of the intracellular bacteria *Wolbachia* to create incompatible crosses between *Wolbachia*-infected male mosquitoes and uninfected wild females, known as the incompatible insect technique; or
- combining the two techniques, which provides an additional layer of improved efficacy, as indicated in the respective sections below.

Irrespective of the mode of sterilization, all interventions in this class rely on the large-scale rearing of mosquitoes and the subsequent separation of males from females. Sterile males are then released at regular intervals until the population is suppressed or eradicated from a geographical area (for example, on an island, or in newly endemic area) or suppressed and maintained – by means of regular re-releases – at a population density below the threshold required for sustained pathogen transmission; the level of suppression will depend on the goals of the control programme in operational terms, and feasibility.

The efficacy of the method is well established against multiple agricultural pests and in the control of human African trypanosomiasis. There is also a growing body of entomological data indicating the potential successful use of this method for mosquito control. Various technological advances in the areas of mass-rearing and male–female separation have enabled this insect control method to become increasingly feasible for controlling mosquitoes.

4.2.1 Intervention: SIT in *Aedes*

Applicant: TDR with collaborators

The Pacific Islands Consortium for the Evaluation of *Aedes* SIT (PAC-SIT) are new applicants to the WHO process and were attending their first VCAG meeting. They are planning to investigate whether a SIT intervention to suppress *Ae. aegypti* populations will reduce arboviral disease at study sites on two islands of French Polynesia (France) – Tahiti and Tetiaroa – compared to control sites not receiving the intervention. TDR and its collaborators, which make up the consortium, are conducting studies to test the efficacy of classic SIT against dengue virus infection.

This submission to VCAG included the study protocol for epidemiological and entomological analyses. The applicants requested that VCAG review and consider the study design in view of their plans to assess the impact of SIT against dengue virus infection at these island sites.

Summary of discussions

The applicants introduced the principle behind SIT, its demonstrated utility in agriculture and their progress in mass-rearing and automating sterile male production in French Polynesia. They then presented their proposed SIT study for Paea (island of Tahiti), the first study site, which involves a bidirectional release front with a buffer zone of 1.5 km between the release and control areas *(9)*. The applicants plan to conduct weekly releases of sterile males over 12 months, at a ratio of 10:1 sterile to wild mosquitoes (adjustable over the course of the study depending on wild male numbers), supported by pre-release chemical fogging to reduce the mosquito population. Mosquito population monitoring will be undertaken using BG-Sentinel traps and ovitraps, complemented by genomic analysis of the population structure. The study will start in October 2023 and end in April 2025, and recruit 600 human participants, a sample size that represents 5% of the population of Paea. The population targeted is people between 18 and 75 years old who have lived on the island of Tahiti for at least two years, but will exclude pregnant women and those who are unable to give proper informed consent. Participants will be sampled at four different time points: at the start of the study and then at three follow-ups every six months. Blood will be collected from finger pricks and tested for dengue virus IgM and IgG, as well as for antibody response to mosquito salivary proteins. Socioeconomic data will be collected through interviews of participants. The applicants requested that VCAG review and comment on the proposal and protocols provided and provide advice/recommendations on the critical points in the methodology, as this will improve the study design for future releases at other island sites.

Following the presentation, VCAG enquired as to whether there was information on baseline serology to guide the determination of appropriate sample sizes. The applicants responded that dengue virus serology is not routinely monitored and that

previously published antibody prevalence information has been at the archipelago rather than island level. The applicants were confident that they could adequately detect seroconversion and IgM response in the six-month intervals proposed for sampling of participants. The applicants were encouraged to consider mining existing serological data to obtain estimates of baseline prevalence and conduct a power calculation.

As a detailed statistical analysis plan (SAP) had not yet been prepared, the working group offered suggestions for developing the future SAP. The applicants did not address the possible confounding effects of the movement of people into and out of the intervention areas, something that has been raised in submissions from other applicants in the past (see *(2,10)* for examples). The working group thought that more attention to human movement patterns, either through modelling their impact or conducting interviews/time-use surveys, would improve the study.

The exclusion of children from the study was discussed, as dengue-naïve children normally offer the best opportunity to detect seroconversion. The applicants responded that in addition to several ethical considerations taken into account when developing the protocol (including the challenges of obtaining approval to collect samples from children) and the fact that dengue virus similarly affects adults and children in French Polynesia, children would be excluded from the study.

There was also discussion between VCAG and the applicants regarding the specificity of their serology assay to distinguish between bites of *Ae. aegypti* and *Ae. polynesiensis*. Although the assay has not yet been validated to discriminate between the two species, the applicants felt confident that *Ae. aegypti* was the predominant species at the study sites. In future, they will consider using species-specific antigens for increased specificity.

The likelihood of a high dengue transmission season was discussed, which would impact the number of seroconversions observed during the study. The applicants stated that there had not been an outbreak since 2020; however, outbreaks/epidemics seem to occur every 2–3 years and there is an increased chance of one occurring in 2024.

The current dengue interventions (e.g. vector control) in the study sites are based on elimination of breeding sites only, and the working group thought that the applicants should have a plan if a major dengue outbreak were to occur during the study period and consider how that might impact their studies. The applicants were encouraged to consider how usual vector control methods (fogging) in response to any outbreak may impact the outcomes of their deployment and thus study results.

VCAG questioned the unbalanced nature of the site selection at the Tetiaroa site, which comprises two zones – one of which is a smaller, uninhabited island. The applicants clarified that the study site will not be used to measure epidemiological impact of the intervention, but would serve to optimize sterile male transportation and release methods in advance of expanding the project to other islands in the Pacific. A point was made that the release and control sites on the island of Tahiti were very close together, which may confound observations, especially on an island where the winds are strong and can carry mosquitoes greater distances.

Conclusions

The applicants presented a detailed programme of work, including evaluation of entomological and epidemiological end-points. VCAG recognized that major recommendations to modify the protocol may not be feasible given that the study protocol has been reviewed by the WHO Ethics Review Committee. VCAG appreciated that this is the first epidemiological protocol brought to VCAG that is intended to generate evidence of public health value of SIT for dengue. However, the applicants were reminded that since the studies are not randomized controlled trials and are relatively small in size, even under the best conditions, the data obtained may carry limited weight in providing sufficient evidence to inform deliberations of public health value and development of a WHO recommendation.

Recommendations

VCAG identified important gaps in the study design and was concerned that epidemiological impacts may be inconclusive, even under the best conditions, as there were several areas that may limit the certainty of evidence generated in the study. To this end, consultation of WHO's *Handbook for guideline development, second edition (11)* and the review paper by Wilson et al. *(12)* will be valuable for guiding the generation of high-quality evidence.

VCAG offered the following major and minor recommendations and suggestions to the applicants:

Major

- VCAG recommends that the applicants prepare a detailed SAP that includes power analyses for ability to detect an epidemiological impact, potentially using existing serological data from previous studies or data collected at study baseline. The SAP should, for example, clearly identify the primary end-point of the trial and describe corresponding statistical methods.
- VCAG recommends that applicants consider the impact of the movement of people between intervention and control areas on the ability to detect an effect of the intervention, and that any such impact be acknowledged. These measures could include questions posed to participants (or a subset of participants) regarding the time spent in release versus control areas. Alternatively, human movement could be modelled mathematically and potential impact assessed.
- VCAG recommends identifying the potential risks to the study outcomes, including possible epidemics that may require intervention from local authorities, and how these events will be reported in the context of the study.

Minor

- VCAG encourages the applicants to consider the potential for cross-reactivity with other flaviviruses.
- VCAG encourages using PCR, if possible, to detect very new infections that may not be captured by IgM serology immediately following the sampling.
- VCAG suggests that the applicants review routine clinical dengue incidence data before and after release of the sterile male mosquitoes, as a source of additional supporting evidence of impact.
- VCAG suggests submitting future protocols for VCAG review prior to submitting them to the WHO Ethics Review Committee in order to obtain advice and optimize the study design before final approvals are granted.
- VCAG suggests that the applicants consider conducting larval sampling as a supplementary measure to contribute to the assessment of the population suppression of mosquitoes.
- VCAG encourages the applicants to clarify in future submissions how epidemiological impact will be demonstrated at each of the study sites. It would be helpful if expected entomological and epidemiological end-points and impacts were clearly listed for each specific study site/ island.

4.3 Intervention class: systemic endectocide treatment for Lyme disease

Endectocides are drugs that are effective against endoparasites and ectoparasites. They are intended as population-level treatments and are lethal for the vectors that feed on them. Circulating systemically in the host, ingestion of the endectocide by the vector following a blood meal leads to reduced vector densities and interrupted transmission cycle of vector-borne pathogens. Endectocides may be insecticides or acaricides (intending to kill members of the Acari family, including mites and ticks).

Lyme disease, caused by *Borrelia* spp. of bacteria (primarily *B. burgdorferi*), has a two-year transmission cycle. The *Borrelia* pathogen is transmitted mainly by the blacklegged tick (*Ixodes scapularis*). This tick species has three life cycle stages: larva, nymph and adult. Larvae and nymphs feed mostly on small mammals, including white-footed mice, the main reservoir host of *B. burgdorferi*. White-tailed deer are the main reproductive host for adult female *I. scapularis* and are thus responsible for maintaining high tick densities in Lyme disease endemic areas. Oral bait treated with fipronil for systemic control of *I. scapularis* females during blood feeding on deer may therefore reduce tick densities and subsequently reduce the incidence of Lyme disease.

For Lyme disease, no WHO recommendations currently exist for control of *Borrelia* vectors; therefore, this is the first intervention assigned to this intervention class. The intervention class remains tentative until sufficient high-quality evidence has been generated and submitted to WHO to warrant the development of a WHO recommendation, thereby establishing the intervention class.

4.3.1 Intervention: fipronil pellet baits

The transmission cycle for Lyme disease involves multiple host species, e.g. white-footed mice (*Peromyscus leucopus*) and white-tailed deer (*Odocoileus virginianus*), and humans as accidental hosts. Therefore, the administration of a systemic insecticide fed to one or both wildlife host species has the potential to kill the vectors responsible for transmission before the cycle is complete. A fipronil-laced food pellet has been developed for introduction into the feed of the white-tailed deer, the reproductive host responsible for maintaining high tick densities in Lyme disease endemic areas. Following a blood meal on treated deer, ticks are killed within 24–48 hours. This intervention is designed to reduce tick populations below a density threshold to interrupt transmission of *B. burgdorferi* and potentially reduce the incidence of Lyme disease.

Applicant: Scimetrics Limited Corp.

This is the first submission to VCAG of an endectocide for treatment of Lyme disease. The submission included multiple proof-of-concept studies tested in the laboratory and under semi-field conditions, and preparations to conduct a field trial of a fipronil-laced oral bait for control of ticks infesting the white-tailed deer. Although the applicants are not yet at the stage of preparing for evaluation of epidemiological impact, they were interested in gaining feedback from VCAG on the concept of the work and guidance on what is needed to evaluate the public health value of the proposed intervention against Lyme disease.

Summary of discussions

The applicants provided background information on Genesis laboratories, including experience on disease vectors. They have worked on leishmaniasis in India using a fipronil bolus in cows to control *Phlebotomus argentipes* sand flies, and on malaria control in Kenya using systemic insecticides.

The applicants informed VCAG of their work developing fipronil for the purpose of vector control. Previous efforts include the development of a low-dose fipronil block targeting questing nymphs on white-footed mice, an important host within the transmission cycle.

The low-dose bait was demonstrated to be safe for non-target animals and highly efficacious, and is currently under review by the Center for Veterinary Medicine of the United States Food and Drug Administration (FDA). In addition, the applicants want to target adult ticks that feed on white-tailed deer, using a similar fipronil-based approach.

The applicants are working with the deer facility at Penn State University to refine their formulations and delivery system (block vs. pellet) for fipronil for the target host and working to optimize the fipronil concentration. In experiments with *Amblyomma* and *Ixodes* placed on deer, the applicants found that *Ixodes* were highly sensitive to fipronil, with ticks being killed part way through the blood meal. *Amblyomma* fed more slowly, but 80–90% of the ticks died within 10 days of feeding. Current results indicate that a concentration of 25 ppm causes maximum tick mortality, but the applicants are planning to repeat the studies at lower concentrations. Previous experiments showed that this dose level did not affect consumption of the pellets by the deer. The applicants have also measured non-target animal exposure of the pellets by monitoring bait stations with cameras.

In sum, the applicants showed that feed containing a low concentration of fipronil can have high efficacy in killing ticks. Field studies will begin in Maine, United States of America, in 2024.

The applicants are planning to provide a product development plan to the FDA by the end of the year. One of the regulatory requirements is to establish the fipronil maximum residue level in deer tissue that, if not exceeded, will ensure the safety of humans consuming deer that ingested the bait.

Although the applicants are not yet at the stage of submitting epidemiological trial protocols for review by VCAG, the group did discuss with the applicants several points they might wish to consider as they move forward in their project plans:

- There are potential study design limitations and challenges with the need for randomization, blinding, control placebos and experimental replication. Some of these design considerations may impact the power of study results. In this regard, euthanizing deer for fipronil and fipronil metabolite residue analyses could affect sample size and efficacy estimates. There were also questions regarding measurement of tick end-points, given that fipronil is fast-acting for *Ixodes* but slower acting for *Amblyomma*.
- VCAG pointed to considerations around the broader strategy, including the targeting of white-footed mice as a priority, since they are the reservoir host. It could thus be easier to detect an impact on Lyme disease if the intervention targeted mice rather than deer. Reduction of larval and nymphal ticks would involve treatment of mice feed, whereas reduction of adult ticks would require treatment of deer. The applicants proposed that treatment of deer in addition to mice could amplify the overall efficacy of the approach. In this regard, the applicants noted that they envisioned a deer intervention employed in concert with a white-footed mice intervention.
- Developing a study design with sufficient power to detect changes in Lyme disease incidence in a future trial will be challenging given that the relationship between tick density and human infection is nonlinear, and that both deer and human movement could affect estimates of impact on disease. In this regard, VCAG noted a recent review *(13)*, with references therein, that could be helpful for designing trials to ascertain the public health benefit of the intervention. Trials related to badger culling for bovine tuberculosis *(14)* or rabies control bait *(15,16)* could also serve as points of reference.
- VCAG suggested that over the long term, development of tick resistance to fipronil should be monitored to support selection of doses and delivery methods for implementing resistance management practices.

- VCAG and the applicants also discussed the potential impact of fipronil on non-target organisms, especially as most of the fipronil ingested by deer is not metabolized but is excreted in the feces. As fipronil enters the environment, it could be cause for concern.

VCAG and the applicants also discussed the different assessments performed by FDA and WHO in terms of their respective remits, in an effort to move through the evaluation processes efficiently.

Conclusions

VCAG commended the applicants for pursuing the development of a first-in-class intervention targeting Lyme disease. To support the development of a global recommendation for the intervention, WHO will require evidence of epidemiological impact against the target disease(s). As such, the applicants were advised that FDA approval alone would not suffice as a proxy for WHO to make a recommendation on this intervention, because the two agencies have different criteria for approvals and recommendations. VCAG nevertheless supported the applicants' early engagement with the group to start considering the designs of pilot and semi-field studies of fipronil's efficacy that can support and inform future trial designs, intended to measure disease impact within this complex transmission cycle. The applicants were encouraged to look for collaborations around epidemiological trial design and development, and the broader strategy as to whether such trials might focus on mice, deer or both species. The applicants could also consider how climate change and One Health approaches *(17)* may help to frame the trials.

Finally, VCAG noted the general importance of resistance management against fipronil and suggested that monitoring of the efficacy of this acaricide should be considered as work in this field continues. Resistance management strategies considered over the long term may include alternating endectocides or alternative dosing in the pellets in any deployment strategy.

The applicants were encouraged to review WHO guidance documents, especially on guideline development *(11)*, and how strength of evidence is determined to help inform trial design with epidemiological end-points. VCAG welcomes re-engaging with the applicants at a future meeting when they are ready for input and discussion around the design of such epidemiological trials.

Recommendations

VCAG provided the following suggestions and advice to the applicants:

- The applicants are encouraged to review the *WHO handbook for guideline development (11)* to become familiar with how WHO guidance for public health interventions, including new vector control tools, is developed.
- Although the deer bait product was the basis of the presentation, it is part of a larger body of work that includes bait products for white-footed mice. As the applicants progress towards epidemiological trials to assess public health impact, it will be important to carefully consider the appropriateness of assessing deer *vs.* mice *vs.* combined interventions in an integrated strategy. The applicants are welcome to bring a proposal to VCAG for a more detailed discussion on the merits of these approaches and are encouraged to present any protocols for review as experimental trials begin to take shape to ensure that the evidence generated will be appropriate to inform development of recommendations.
- The applicants are encouraged to consider collaboration with groups who have expertise in designing trials to evaluate the epidemiological impact of vector control interventions.

5. Concluding remarks

VCAG members participated in a discussion led by VCAG co-chair Dr Robinson on VCAG operations, which was followed by a briefing by the WHO VCAG Secretariat on upcoming member rotations. VCAG co-chairs Dr Lenhart and Dr Robinson thanked the VCAG members and temporary advisors for their commitment, time spent and effort in supporting VCAG activities, reviewing applicant submissions and participating during the meeting. The VCAG Secretariat echoed the thanks of the co-chairs, acknowledging the continued dedication of the advisory group members.

The 20th VCAG meeting is planned for the week of 25 March 2024, to be held virtually.

References

1. Mosha JF, Matowo NS, Kulkarni MA, Messenger LA, Lukole E, Mallya E, et al. Effectiveness of long-lasting insecticidal nets with pyriproxyfen–pyrethroid, chlorfenapyr–pyrethroid, or piperonyl butoxide–pyrethroid versus pyrethroid only against malaria in Tanzania: final-year results of a four-arm, single-blind, cluster-randomised trial. Lancet Infect Dis. 2023. doi:10.1016/S1473-3099(23)00420-6.

2. Eleventh meeting of the WHO Vector Control Advisory Group: meeting report, Geneva, 11–13 November 2019. Geneva: World Health Organization; 2020 (https://iris.who.int/handle/10665/330681, accessed 8 November 2023).

3. Sixteenth meeting of the WHO Vector Control Advisory Group: meeting report, 28–30 March 2022. Geneva: World Health Organization; 2022 (https://iris.who.int/handle/10665/356857, accessed 8 November 2023).

4. Report of the second meeting of the vector control advisory group, Geneva, Switzerland, 10–14 February 2014. Geneva: World Health Organization; 2014 (https://iris.who.int/handle/10665/137318, accessed 8 November 2023).

5. Fifteenth meeting of the WHO Vector Control Advisory Group: meeting report, 4–6 October 2021. Geneva: World Health Organization; 2021 (https://iris.who.int/handle/10665/350633, accessed 8 November 2023).

6. Sternberg ED, Cook J, Ahoua Alou LP, Assi SB, Koffi AA, Doudou DT, et al. Impact and cost-effectiveness of a lethal house lure against malaria transmission in central Côte d'Ivoire: a two-arm, cluster-randomised controlled trial. Lancet. 2021;397(10276):805–15. doi:10.1016/S0140-6736(21)00250-6.

7. Twelfth meeting of the WHO Vector Control Advisory Group: meeting report, 8–10 June 2020. Geneva: World Health Organization; 2020 (https://iris.who.int/handle/10665/334001, accessed 8 November 2023).

8. O'Brien PC, Fleming TR. A multiple testing procedure for clinical trials. Biometrics. 1979;35:549–56.

9. Hendrichs J, Vreysen M, Enkerlin WR, Cayol JP. Strategic options in using sterile insects for area-wide integrated pest management. In: Dyck VA, Hendrichs J, Robinson AS, editors. Sterile insect technique: principles and practice in area-wide integrated pest management, second edition. Boca Raton: CRC Press; 2021.

10. Thirteenth meeting of the WHO Vector Control Advisory Group: meeting report, virtual meeting, 7–10 December 2020. Geneva: World Health Organization; 2021 (https://iris.who.int/handle/10665/339989, accessed 8 November 2023).

11. WHO handbook for guideline development, second edition. Geneva: World Health Organization; 2014 (https://iris.who.int/handle/10665/145714, accessed 8 November 2023).

12. Wilson AL, Boelaert M, Kleinschmidt I, Pinder M, Scott TW, Tusting LS, et al. Evidence-based vector control? Improving the quality of vector control trials. Trends Parasitol. 2015;31:380–90. doi:10.1016/j.pt.2015.04.015.

13. Ostfeld RS, Keesing F. Does experimental reduction of blacklegged tick (*Ixodes scapularis*) abundance reduce Lyme disease incidence? Pathogens. 2023;12:714. doi:10.3390/pathogens12050714.

14. Donnelly CA, Woodroffe R, Cox DR, Bourne J, Gettinby G, Le Fevre AM, et al. Impact of localized badger culling on tuberculosis incidence in British cattle. Nature. 2003;426:834–7. doi:10.1038/nature02192.

15. Freuling CM, Busch F, Vos A, Ortmann S, Lohr F, Hedimbi N, et al. Oral rabies vaccination of dogs: experiences from a field trial in Namibia. PLoS Negl Trop Dis. 2022;16:e0010422. doi:10.1371/journal.pntd.0010422.

16. Gilbert A, Johnson S, Walker N, Wickham C, Beath A, VerCauteren K, et al. Efficacy of Ontario Rabies Vaccine Baits (ONRAB) against rabies infection in raccoons. Vaccine. 2018;36:4919–26. doi:10.1016/j.vaccine.2018.06.052.

17. Ending the neglect to attain the sustainable development goals: One health – approach for action against neglected tropical diseases 2021–2030. Geneva: World Health Organization; 2022 (https://iris.who.int/handle/10665/351193, accessed 8 November 2023).

Annex 1. Declarations of interest

The 19th VCAG meeting was convened to review and evaluate three applicant submissions on novel vector control interventions. The meeting also hosted a general stakeholder information session.

The meeting consisted of four categories of invitees, namely:

- temporary advisors, including members
- participants (including applicants, and invited presenters)
- observers
- WHO staff.

Respective applicants each participated in an open session addressing their submission, alongside VCAG members, temporary advisors, observers where appropriate, and the WHO VCAG Secretariat.

Before the meeting, all VCAG members and temporary advisors who participated in the meeting in their individual capacity completed a "Declarations of interests for WHO experts" form. The VCAG Secretariat assessed the interests declared by the experts and, except for the points described below, determined 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 topics under review at the 19th VCAG meeting. The disclosed interests did not warrant exclusion of individuals from the entire meeting, but limited participation of some individuals to sessions for which no conflict was identified. The mitigating actions taken by WHO are as follows:

- **Dr Audrey Lenhart** has staff under her professional supervision who are working on the EaveTubes™ trial, although she herself is not an investigator on the project, nor is she otherwise involved. Due to this potential conflict of interest, Dr Lenhart was recused from all sessions relating to the EaveTubes™ and was not permitted to contribute to the development of a VCAG response to this submission. Further, the SIT project being conducted in the Pacific Islands reviewed at the meeting, is funded by the United States Centers for Disease Control and Prevention, the same institution for which Dr Lenhart works, although the project is being funded by a different division. This is deemed a potential perceived conflict of interest. As such, Dr Lenhart was permitted to join the presentation and Q&A session, but was not able to engage in questions or participate in the closed discussions or development of a VCAG response to the submission.
- **Dr Corine Ngufor** presented at the meeting in a professional capacity during the general information stakeholder session, relating to the third- and final-year results from the ITN trial in Benin, as part of the New Nets Project. Due to VCAG's and WHO's continued interest in trial duration in relation to ITN evaluation, and the VCAG closed discussion following the stakeholder presentation, Dr Ngufor was recused from participating in this closed discussion and in the formulation of any VCAG response to it.
- **Dr Manju Rahi**, temporary advisor, indicated that she is a member of the WHO ad hoc scientific committee that has been established as part of the SIT in *Aedes* submission being presented at this meeting. Given a foreseeable perceived conflict of interest and the importance of maintaining independence and integrity of the two groups overseeing and evaluating the trial, Dr Rahi was not permitted to participate in the presentation or discussion sessions or contribute to the development of a VCAG response to the submission.

The reading of these interests at the start of the meeting constitutes public disclosure to participants of this meeting. These interests will additionally be published in any publications or work products related to this report.

Annex 2. Agenda

Wednesday, 27 September 2023			
Session 1: Welcome and updates		**Presenters**	**Closed session**
09:00–09:15	**Preliminary welcome** • Overview of running of meeting • Reading of declarations of interest statement	• VCAG members • Temporary advisors • WHO VCAG Secretariat	For information
09:15–09:30	**Official opening of VCAG meeting** Chair of session: VCAG co-chairs • Opening remarks from Director of the Regulation and Prequalification department	• Director of the Regulation and Prequalification department • VCAG members • Temporary advisors • WHO VCAG Secretariat	For information
09:30–10:00	**Introduction** Round of introduction of members and temporary advisors	• VCAG members • Temporary advisors • WHO VCAG Secretariat	For information
Session 2: General stakeholder information session		**Participants**	**Open session**
10:30–11:45	**General stakeholder session – Trial update Interceptor G2 / Royal Guard** Chair of session: VCAG co-chairs • Presentation (60 mins) • Q&A (30 mins)	• London School of Hygiene and Tropical Medicine Benin trial team • VCAG members • Temporary advisors • WHO VCAG Secretariat • General stakeholders	For information
Session 3: VCAG discussion		**Participants**	**Closed session**
11:45–12:15	**VCAG discussion** • Two vs three years of trial data for ITN assessments	• VCAG members • Temporary advisors • WHO VCAG Secretariat	For discussion
12:15–12:30	**Operational updates** • VCAG operations and news	• VCAG members • Temporary advisors • WHO VCAG Secretariat	For information
Session 4: Applicant submissions		**Participants**	**Closed session**
13:45–15:30	**Presentation – EaveTubes™** Chair of session: John Bradley • Applicant presentation (60 mins) • Q&A (15 mins) • VCAG discussion (15 mins) • Feedback to applicants (15 mins)	• In2Care • VCAG members • Temporary advisors • WHO VCAG Secretariat	For information & discussion
Session 5: Formulation of VCAG advice		**Participants**	**Closed session**
16:00–17:00	**Formulation of advice** • Report drafting	• VCAG members • Temporary advisors	For guidance

Thursday, 28 September 2023			
Session 6: Applicant submissions		**Participants**	**Closed session**
09:00–10:45	**Presentation – SIT** Chair of session: Francesca Frentiu • Applicant presentation (60 mins) • Q&A (15 mins) • VCAG discussion (15 mins) • Feedback to applicants (15 mins)	• TDR and collaborators • VCAG members • Temporary advisors • WHO VCAG Secretariat	For information & discussion
11:15–13:00	**Presentation – fipronil baits** Chair of session: Leanne Robinson • Applicant presentation (60 mins) • Q&A (15 mins) • VCAG discussion (15 mins) • Feedback to applicants (15 mins)	• Scimetrics Limited Corp. • VCAG members • Temporary advisors • WHO VCAG Secretariat	For information & discussion
Session 7: Formulation of VCAG advice		**Participants**	**Closed session**
14:30–15:30	**Formulation of advice** • Report drafting	• VCAG members • Temporary advisors	For guidance
16:00–17:00	**Formulation of advice** • Report drafting	• VCAG members • Temporary advisors	For guidance
Session 8: Closing discussions		**Participants**	**Closed session**
17:00–17:15	**Wrap-up of VCAG meeting** • VCAG discussion	• VCAG members • Temporary advisors • WHO VCAG Secretariat	For information

Annex 3. List of participants

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Marit Farenhorst
Anne Osinga
Nelli Westercamp

Fipronil pellets

Richard Poché

SIT for *Ae. aegypti*

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