Vector Control Advisory Group

Twentieth meeting of the WHO Vector Control Advisory Group

Meeting report, 25–28 March 2024

World Health Organization

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Abbreviations

COVID-19	coronavirus disease
cRCT	cluster randomized controlled trial
LLIN	long-lasting insecticidal net
NVC	natural vector control
PBO	piperonyl butoxide
SAP	statistical analysis plan
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 the evaluation of the public health value of 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 Regulation and Prequalification department. 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 20th VCAG meeting was convened virtually from 25 to 28 March 2024. 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:

- spatial repellents;
- topical repellents; and
- sterile insect technique in *Aedes aegypti*.

The meeting was co-chaired by Dr Audrey Lenhart and Dr Leanne Robinson. Eleven VCAG members were able to participate in the meeting. They were joined by six 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 Ibrahima Socé Fall, Director of the Global Neglected Tropical Diseases Programme, officially opened the 20th VCAG meeting, welcoming the members and temporary advisors. Dr Fall noted the continued progress being made in the trials presented to VCAG and emphasized the need for a comprehensive research and development blueprint for accelerating the control, elimination and eradication of neglected tropical diseases. Such a blueprint is being developed and will align with the goals of the road map for neglected tropical diseases 2021–2030 *(1)*. The blueprint aims to: i) increase shared awareness of research and development priorities among stakeholders; ii) increase the impact of research and development in the area of neglected tropical diseases through increased investment; iii) strengthen coordination and capacity-building; iv) reduce research waste; v) improve agility in response to emerging

challenges; and vi) accelerate the translation of innovation into widespread real-world application. Dr Fall noted the need for resources for such a task and highlighted the crucial role that VCAG plays in evaluating the public health value of new tools. Dr Fall extended his thanks to the participants of the meeting for their contributions to this critical cause, and to colleagues in the Global Malaria Programme and the Prequalification Team for Vector Control Product Assessment for their collaboration.

3. Submissions

At its 20th meeting, VCAG reviewed three submissions from three different intervention classes.

3.1 Intervention class: spatial repellents

Spatial repellents are designed to interrupt human–vector contact through vector behaviour modification induced by volatile chemicals. Such modification can include chemosensory disruption, sensitization and/or nervous system intoxication. The substance may be passively or actively aerosolized and dispersed. Interruption or inhibition of vector feeding offers protection from bites.

3.1.1 Intervention: transfluthrin passive emanators

The spatial repellent product proposed by SC Johnson is a transfluthrin-impregnated plastic sheet aided by a volatile substance that provides long-term controlled release of the transfluthrin indoors for up to 28 days (Mosquito Shield™). The exposure to a low dose of transfluthrin has been reported to incapacitate the vector and reduce host-seeking and biting behaviour *(2,3)*, while exposure to a higher dose leads to mosquito knockdown and mortality *(4)*. The intervention targets *Anopheles*, *Aedes* and *Culex* spp. mosquitoes, with claims that all age groups and populations in countries endemic for mosquito-borne diseases will be protected from daytime, early-evening and/or late-night biting by mosquitoes in enclosed and semi-enclosed structures. Deployment of the spatial repellent product in enclosed and semi-enclosed spaces is intended to reduce human–mosquito contact, which in turn is anticipated to minimize mosquito-borne pathogen transmission.

Applicant: SC Johnson and University of Notre Dame (Unitaid AEGIS project)

SC Johnson is collaborating with the University of Notre Dame to evaluate the intervention. The applicants have been engaging with VCAG since 2014, during which time they have presented to VCAG the results of three cluster randomized controlled trials (cRCTs; in Indonesia, Kenya and Peru) and acquired endorsement of their study protocols for two more trials (in Mali and Sri Lanka). The results of the epidemiological trial targeting malaria in Sumba Island, Indonesia were submitted to VCAG *(5)*, with the trial suggesting protective efficacy against malaria infection. However, the results were statistically inconclusive, as the trial was underpowered. Two additional trials to demonstrate the public health value of the intervention for malaria have been completed: one in Busia County, Kenya (preliminary results presented to VCAG at its 18th meeting *(6)*) and the other in Kolondieba District, Mali (which was completed in March 2024). For *Aedes*-borne viruses, one successful trial has been completed in Iquitos, Peru, with results demonstrating conclusive protective efficacy *(7)*. A second trial is under way in Gampaha District, Sri Lanka.

The applicants provided updates to VCAG during its 17th meeting *(8)*, summarizing their efforts in ongoing trials, and sought advice on several topics. As noted above, during its 18th meeting *(6)*, VCAG reviewed and noted the positive efficacy results of the spatial repellent intervention in the Kenya trial, based on an analysis of first-time malaria infection (primary end-point). VCAG also agreed that the summary provided by the applicants demonstrated the protective efficacy of the spatial repellent against malaria,

and concluded that this finding provisionally satisfied the key requirement for evidence of epidemiological impact from one trial. VCAG recommended that the applicants continue their adherence to the study protocols. VCAG requested to see the associated analyses of all epidemiological and entomological end-points, as well as relevant safety data, to enable a comprehensive assessment of the effect of the spatial repellent in the Kenya trial. In this context, VCAG encouraged the applicants to provide a comprehensive evaluation of the outcomes in a full analysis report conforming to the statistical analysis plan (SAP).

Updates

For the 20th VCAG meeting, the applicants submitted several documents related to the trial completed in Kenya, which included assessments of epidemiological impact, entomological efficacy, and safety. The submissions included analyses at two time points. The first set of analyses for the Kenya study were updates to those presented at the previous VCAG meeting *(9)*; these analyses were conducted prior to the end of the study (interim time point), at a pre-planned point in time when sufficient statistical power (80%) had been achieved to represent a definitive assessment of epidemiological impact. A second set of analyses were conducted using data on primary and secondary end-points from the entire trial duration. Based on these analyses, the applicants concluded the following:

- The epidemiological covariates were balanced between the spatial repellent and placebo arms.
- A statistically significant and conclusive protective effect of the spatial repellent against first-time malaria infection (primary end-point) and overall new infections (secondary end-point) at the interim time point and through the end of the intervention phase was demonstrated, reflecting extra protection above that provided by the placebo group of long-lasting insecticidal nets (LLINs) alone (LLINs treated with a pyrethroid insecticide + piperonyl butoxide (PBO)).
- The protective effect of the spatial repellent against first-time infection (primary end-point) was similar for younger (13 months up to 59 months old) and older (59 months to 10 years old) age groups.
- The hazard rate of first-time malaria infection (primary end-point) in the buffer zone of the intervention clusters was significantly smaller than that of the placebo clusters, demonstrating benefit beyond the area of spatial repellent use (lack of negative diversionary effect).
- The pre-planned entomological analyses did not suggest statistically significant effects of the spatial repellent compared to placebo treatment.
- There were no unexpected, implausible or extreme adverse events or serious adverse events reported during the trial.

The applicants also provided brief updates to VCAG on the now completed trial in Mali (for malaria) and the ongoing trial in Sri Lanka (for dengue).

Summary of discussions

VCAG acknowledged the considerable efforts of the applicants to successfully undertake the Kenya study and noted that the applicants had fulfilled VCAG's previous request *(6)* to review the associated analyses of all epidemiological and entomological end-points, as well as relevant safety data, to enable a comprehensive assessment of the effect of the spatial repellent on malaria infection in this study.

The applicants' primary question for VCAG at the 20th meeting concerned whether the reported outputs from the Kenya trial demonstrated positive results in terms of the protective efficacy of the spatial repellent, above that provided by LLINs (treated with pyrethroid + PBO) alone, based on first-time malaria infection. Based on the information

provided by the applicants and evaluation of the evidence submitted, VCAG determined that the public health benefit of the spatial repellent for the prevention of malaria had been demonstrated in one trial, specifically for malaria. VCAG was also pleased to see that the protective efficacy of the intervention was on top of that provided by LLINs.

In their submission, the applicants anticipated several subquestions that were likely to be asked by VCAG. The applicants' responses to these questions and VCAG's feedback are highlighted below.

a. Why was there no demonstrative spatial repellent effect on entomological end-points given there was a significant positive health impact?

The working group concluded that the applicants' interpretation of no observed effect on entomological end-points was reasonable, i.e. due to the low number of mosquitoes collected because of drought, a campaign that deployed LLINs combined with high variability in the data, and the fact that entomological data were only collected from a subset of clusters at a limited number of time points (quarterly for human landing catches and light traps). The applicants noted that to sufficiently power the trial to detect entomological effects (30% reduction by spatial repellent), 49 to 85 clusters per treatment arm would have been required, depending on the baseline value and number of households per treatment cluster, the cost of which would have greatly exceeded the available budget. VCAG appreciated that this power analysis had been conducted. The findings of the trial underscore the complexities in understanding the relationship between entomological and epidemiological end-points. VCAG suggested that the applicants continue to work with the WHO Prequalification Vector Control Product Assessment Team on the assessment of entomological data.

b. How could there be a spatial repellent community effect (reduction in malaria infection in buffer zones) in the absence of an entomological effect of the spatial repellent?

VCAG agreed that the applicants demonstrated a reduced malaria infection rate in the buffers around the spatial repellent clusters, compared to the placebo clusters. This observation indicates that mosquitoes were not being diverted from the intervention clusters and did not increase malaria transmission in the surrounding buffer areas; on the contrary, malaria transmission was reduced in these areas where no spatial repellent was deployed. VCAG agreed that this reduced infection could be due to reduced mosquito fitness following transfluthrin exposure and/or reduced transmission due to the movement of residents from intervention clusters to the buffer zones. VCAG concluded that, at this point, the trial does not support a community-level benefit claim (see discussions of community effects in the *WHO guidelines for malaria (10)* and Lines et al. *(11)*). While the current findings suggest that benefits outside a household are possible, future research and/or analyses of existing data would help to support a community benefit claim. For example, future efforts would need to demonstrate reduced mosquito fitness in the intervention cluster buffers. A study with mixed spatial repellent and placebo household use within an area, which is likely with deployment of the intervention, could also help to elucidate the extent to which benefits at the household level extend to other unprotected households within and outside a cluster.

c. Why was the observed effect of the spatial repellent for older children (59 months to 10 years) greater than the equivalent effect observed among younger children (13 months up to 59 around months)?

The applicants noted that the sample of older children was larger than that of younger children, which may have affected the precision the estimated protective efficacy more than the protective efficacy value itself. It was also suggested that the older children may have had different behavioural practices than younger children in relation to malaria risk (e.g. LLIN use). VCAG noted that the point estimate of the

effect in older children was larger than that in younger children, but recommended that the applicants undertake a post hoc statistical analysis of the potential interaction of age by treatment to determine the strength of evidence for a greater effect in older children. The applicants provided this analysis following the meeting, with the indication that this would be submitted for reference as part of their next formal submission.

In addition to these topics, the discussion explored the extent to which exposure to sublethal doses of transfluthrin in the buffer zone could contribute to increased pyrethroid resistance (metabolic detoxification and knockdown resistance) in the treatment area, as well as the potential for pyrethroid-resistant *Anopheles* spp. mosquitoes in the study area to undermine the efficacy of the spatial repellent intervention. The applicants' data from the Kenya trial indicate that even with resistant mosquitoes in the study area, the intervention demonstrated efficacy. Further studies by the broader scientific and public health communities could support deployment of this and other interventions through monitoring and evaluation programmes designed to assess background resistance and changes in resistance levels of the vector population with the deployment of interventions over time.

Finally, the applicants provided an update on the remaining statistical analyses, which included one secondary and four supplemental analyses. The applicants noted that the supplemental analysis on human behaviour adjusted protective efficacy had been refocused to examine the issue in the context of social science. Given the findings to date, the applicants proposed that there was no longer a need for the last secondary end-point analysis, since infections were dominated by a single pathogen. In addition, the applicants concluded that the remaining supplemental analyses (per protocol, temporality of protective efficacy effects, and adjusted human biting rate analyses) were no longer relevant. VCAG agreed that this was appropriate.

Conclusions

VCAG congratulated the applicants on completing their trial in Kenya, which demonstrated the public health value of the spatial repellent for the prevention of malaria, above that provided by LLINs alone (nets treated with a pyrethroid + PBO), based on the analysis of time to first infection (primary end-point). VCAG concluded that the summary and supporting documents provided by the applicants demonstrated conclusive protective efficacy of the spatial repellent against malaria in a transmission setting characterized by high malaria transmission, efficient vectors, insecticide resistance and universal coverage of LLINs – a milestone for the spatial repellent intervention class. Furthermore, these findings contribute to the evidence of epidemiological impact against malaria for one of the two required trials. In addition, VCAG noted that the trial findings demonstrate how continuous deployment of spatial repellents can complement the use of LLINs.

With regard to the Mali and Sri Lanka trials, the working group acknowledged the solid progress made with both studies, consistent with the previously reviewed protocols, SAPs and associated timelines *(7,12)*. VCAG looks forward to updates on both trials at its future meetings.

Advice to applicants

VCAG advised the applicants to undertake a post hoc statistical analysis of protective efficacy responses in older and younger children to assess the potential interaction of age by treatment. VCAG also suggested that the applicants monitor the ongoing social science study addressing human behaviour in association with spatial repellent use, which may provide insights into LLIN use across age groups. The results of this analysis may inform discussions on contextual factors during the systematic review process and any recommendation developed by WHO's guideline development group.

VCAG also advised the applicants to continue to work with the WHO Prequalification Vector Control Product Assessment Team on the assessment of entomological data.

3.2 Intervention class: topical repellents

Topical repellents are applied to the skin of individuals to protect them from the bites of host-seeking mosquitoes. Despite numerous studies having investigated the efficacy of topical repellents in preventing mosquito bites, it has been challenging to demonstrate epidemiological impact, often because studies have faced issues with adherence and regular application of the repellent products by the study participants.

Currently, there is a WHO conditional recommendation against the use of topical repellents for the purpose of providing community-level protection from vector-borne diseases, with low certainty of evidence supporting this recommendation *(10)*. The guidelines currently suggest that to achieve community-level impact, it is likely that a high level of individual compliance would be needed. More studies are needed to assess whether topical repellents confer individual protection against malaria, where outcomes are linked to adequate application of topical repellents (i.e. regular application in sufficient amounts to exposed skin) and, ultimately, what their public health value may be. While WHO is unable to prequalify topical repellents in the absence of an adequate assessment of public health value and associated WHO recommendation, topical repellents themselves are assessed by regulatory agencies and are therefore already available for purchase in many countries.

To evolve the WHO recommendation(s) on topical repellents, empirical evidence of efficacy against the target disease(s) will need to be generated and reviewed. This evidence would then be incorporated into an update of the available Cochrane systematic review and discussed by the guideline development group. In view of the challenges faced in other trials assessing topical repellents, the applicants are engaging with VCAG to help define the questions to be answered and ensure optimal study design to answer them.

3.2.1 Intervention: NOMO insect repellent

Applicant: NOMO Foundation

NOMO Foundation is a first-time applicant to VCAG. Their intervention is a topical repellent that is claimed to provide protection for 8–10 hours against disease-transmitting mosquitoes. It is also claimed to be a non-toxic lotion, containing a combination of p-menthan-3,8-diol and lemongrass oil, which affords a high-efficacy, low-cost repellent, with the inclusion of vanillin to promote high user acceptance while adding repellent benefits.

Having undertaken several studies in the laboratory and field to demonstrate efficacy against mosquito bites, the applicants are now seeking to undertake epidemiological trials to demonstrate impact against malaria. The applicants included in their application a protocol outline for a study intended to evaluate the effect of the NOMO insect repellent on malaria incidence in eastern Ghana. They sought feedback and guidance regarding their past and planned efforts to assess the NOMO insect repellent's ability to reduce the burden of malaria.

Summary of discussions

The applicants presented to VCAG a summary of the development of the NOMO repellent product beginning in 2006, as well as the outcomes of two studies evaluating the NOMO repellent. These included a published study *(13)* conducted in northern Ghana, which reported a reduction in malaria prevalence in a village where the NOMO repellent was used, compared to an untreated control village, and a field test of repellent efficacy conducted under two environmental conditions. Finally, the applicants presented their initial plans for a trial to be conducted in eastern Ghana.

Following the presentation, there was a discussion around the data from the applicants' two earlier studies (Dadzie et al. *(13)* and Coleman et al. (unpublished manuscript, 2024)) and whether those data would satisfy WHO's requirement of high-quality data from at least two trials in independent epidemiological/geographical settings *(14)*.

VCAG noted that the trial reported in Dadzie et al. *(13)* included a single replicate site for the control and treatment arms, meaning that the results are limited by a lack of replicates at the site. Furthermore, the two villages were not described as being randomly assigned. This observation was also made in a recent systematic review of topical repellents for malaria prevention *(15)*; the study was excluded from the review, as it did not meet the inclusion criteria for controlled before-and-after studies. In addition, it appears that an SAP was not developed a priori, and the report does not provide sufficient detail to understand whether representative samples for the cross-sectional surveys were collected at baseline and at the end. The data analysis section of the study report says that "malaria incidence" was compared using Fisher's exact test; however, i) a cross-sectional survey method was used to measure prevalence rather than incidence, and ii) a difference-in-differences approach should have been used rather than what appears to be a comparison of individual pre-post tests for each community. VCAG concluded that this study design carries a high risk of bias due to the lack of randomization and insufficient numbers of clusters per arm. With an inadequate description of study implementation to permit evaluation of additional potential biases, and an inappropriate statistical approach applied to the data collected, VCAG was not able to consider this trial as contributing to the evidence of efficacy of the topical repellent against malaria.

Coleman et al. (unpublished manuscript, 2024) also provided supporting evidence of the NOMO repellent's protection and potential to reduce malaria prevalence. However, multiple aspects of the study appeared to lack rigour and/or clarity, including the following:

- Communities (study sites) were not allocated randomly to treatment, with some of the "communities purposively assigned repellent intervention or control", which suggests an increased risk of bias.
- It was unclear whether the baseline cross-sectional survey was conducted after the communities were assigned to treatment, which is considered best practice *(16)*.
- There was insufficient detail in the methods to ascertain if and how individuals were randomly selected from households for the prevalence surveys. Information on how households were mapped and the population enumerated is important for understanding whether appropriate and unbiased sampling methods were used.
- The sample size calculation appears to have been performed incorrectly. The authors cited Hayes and Moulton *(17)* for their sample size methodology, but the formulae in that publication require specific parameters to characterize the between-cluster variation (either the coefficient of variation or the intra-cluster correlation coefficient). The calculation performed, however, did not include such parameters and assumed that each observation on an individual was independent, meaning that the study was most likely underpowered.
- The analysis methods were not clearly described and were likely not appropriate. The statistical analysis part of the methods section states that chi-square and Fisher's exact tests and multivariate logistic regression were used for parasitological indices. These are all inappropriate, as they do not account for intra-cluster correlation. Generalized estimating equation models are mentioned in the results section. Such models can be an appropriate method for analysing cluster-randomized trials, but they are not appropriate if there are fewer than 15 clusters per arm *(17)*.

Based on the studies submitted for review at the present meeting, VCAG concluded that there is insufficient data, clarity and study rigour to be able to comprehensively evaluate the public health value of the intervention based on the respective outcomes of these trials.

VCAG also identified similar issues with the study design for the proposed third trial in Ghana that was submitted by the applicants. The sample size calculation does not seem to include a parameter to characterize the level of variation between clusters, so the proposed sample size of five clusters will almost certainly be too small.

In further discussion relating to the planned trial, VCAG and the applicants discussed the unit of randomization for evaluating their repellent. While community-level and individual-level randomization was considered, the applicants also put forward the idea of randomization at the household level, given the potential for the intervention to be shared among family members. The applicants sought advice on how to proceed, and VCAG discussed the implications of cluster vs individually randomized trials and the reasons the applicants might wish to pursue one over the other.

The applicants discussed their intention to incorporate the use of a sham lotion (placebo) into their trial design to enable double blinding. VCAG raised concerns about the likely challenges of being able to develop an adequate placebo with the same texture and odour as the intervention, and whether a placebo is needed.

Finally, the applicants also sought advice on the incorporation of wearable devices to capture trial participants' body temperature as a proxy for fever and malaria infection. VCAG discussed some of the limitations of this approach, including the absence of validation data. As required for other trials, there is a need to have an epidemiological end-point tied to the target disease, rather than correlates or surrogates. Similarly, there was discussion about the use of self-reported fever and the daily use of the repellent or placebo lotion, which would need some form of active measurement, rather than passive reporting.

Conclusions

The NOMO repellent team presented an insect repellent that seems to effectively prevent mosquito bites, with product characteristics that could facilitate and encourage its use and impact against malaria. WHO has recognized gaps in the evidence underpinning its recommendation on topical repellents. The most recent systematic review on topical repellents *(15)*, which was the foundation for the current WHO recommendation *(10)*, concluded that there was insufficient evidence to support the use of repellents at the community level in areas of ongoing malaria transmission to prevent and control malaria. The NOMO applicants were strongly encouraged to pursue their plans to undertake epidemiological trials of their product in order to address important evidence gaps for this intervention class. Bolstering the NOMO team with additional expertise will enable them to meet the substantial challenges associated with generating high-quality data to conclusively address the question of the public health impact of a vector control intervention, particularly in challenging settings. VCAG expressed its willingness to support the applicants moving forward and is looking forward to engaging with them again as their plans develop.

VCAG advice to applicants

VCAG offered the following advice to the applicants:

1. Develop a comprehensive written protocol (as per the international guidance on clinical trials) as early in the trial design process as feasible and submit it to VCAG for targeted feedback and support on study design.

2. Prepare and submit an SAP in advance of the trial, with a clear indication of the a priori hypothesis, target effect sizes and levels of significance, justified by appropriate power calculations. As with any clinical trial, any and all deviations from the approved SAP and post hoc analyses should be documented and accompanied by adequate justification.

3. Continue the team's familiarization with the complexities of cRCTs with epidemiological end-points intended to contribute evidence for the assessment of public health impact of vector control interventions. VCAG encourages the applicants to consider published international guidance and the valuable resources outlined in Box 1, in development of their future study design and associated trial protocol.

4. Ensure that the NOMO investigation team has access to expertise in biostatistics, malaria epidemiology, and the design and analysis of cRCTs for vector control interventions with epidemiological outcomes. Academia is a potential source of partners and partnerships that could also expand the opportunities for funding.

5. Reconsider the inclusion of the sham lotion as an essential component of trials of the NOMO repellent. The anticipated challenges of creating a mosquito-behaviour-neutral mixture of volatiles that can be used as a sham control in a double-blinded study of the NOMO repellent and the confounding effects the sham might have on the study might justify designing a study that does not incorporate a placebo.

6. Reconsider the appropriateness of the diagnostics for measuring the end-point(s) of interest. Validated epidemiological end-points, such as fever followed by diagnostic tests, should be used to infer malaria infection. The use of wearable medical devices for collecting participants' body temperature data as the sole method for inferring malaria infection is discouraged, especially in the absence of data to validate the devices' sensitivity and specificity in the target population for this purpose. Instead, prioritizing established, validated methods of active case detection for collecting end-point data (incidence of malaria, prevalence of malaria infection) should be considered.

3.3 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 with the intention that these will mate with wild female mosquitoes, resulting in the reduction or elimination of viable offspring. To date, interventions submitted for evaluation to VCAG have focused on inducing male sterility using traditional irradiation techniques, exploitation of the reproductive phenotypes induced by intracellular bacteria such as *Wolbachia*, and a combination of the two techniques, intended to provide an additional layer of improved efficacy.

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. The principle of the intervention is that sterile males are then released in large numbers and at regular intervals until the population is eradicated from a geographical area or suppressed and maintained – by means of regular re-releases – at a population density below the threshold required for sustained pathogen transmission.

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 population suppression. Various technological advances in the areas of mass-rearing and male–female separation have supported the increasing feasibility of this insect control method for suppressing mosquito populations.

3.3.1 Intervention: sterile male *Aedes*: natural vector control (NVC)

Applicant: Forrest Innovations

Forrest Innovations is a first-time applicant to VCAG. Their intervention uses an approach that had yet to be reviewed by VCAG at the time of the application; it consists of the release of sterile *Ae. aegypti* males rendered infertile by treatment of the mosquitoes with a double-stranded RNA and thiotepa. By repeated releases of sterile males, the applicants aim to reduce dengue incidence.

The applicant presented to VCAG a series of results from entomological studies (some of which included correlated epidemiological data from routinely collected health surveillance systems), ranging from semi-field to field releases, all conducted in Brazil. The main studies in which there was associated epidemiological data were studies using a crossover study design (in Jacarezinho city, Paraná state) and a before-and-after design (in Ortiguera city, also Paraná state). The applicants requested VCAG's review and assessment of these studies, with a view to validating the public health impact of the intervention.

Summary of discussions

VCAG thanked the applicants for a detailed and interesting presentation, noting the impressive results observed in terms of the impact of the releases on *Ae. aegypti* populations in the intervention areas. The discussion centred on several key areas, including the epidemiological end-points measured, case detection, study design and potential biases.

VCAG sought clarification on whether dengue cases were defined on the basis of PCR, serological or clinical assessment as part of the trials. Applicants confirmed that blood samples were not actively collected as part of the studies, but that data on case numbers were received from the public health surveillance system, which included both PCR and serological confirmation of symptomatic cases, as is routine in Brazil. The applicants subsequently supplied surveillance data, which showed that the majority of dengue cases were defined as such on clinical grounds, with only 18–47% of diagnoses confirmed by laboratory means.

As outlined in Benchimol et al. *(18)*, there are biases inherent in routinely collected health data that need to be taken into consideration when using such data to answer research questions. It was not apparent to VCAG whether such potential sources of bias had been considered and included in the analysis.

The potential impact of different dengue serotypes on study results was also discussed. Clarification was sought on whether the applicants had considered the impact of pre-existing immunity to recent outbreaks with a particular serotype/genotype on estimates. VCAG noted that the applicants had not presented in their submission any data on serotype prevalence in the study areas, which could alter interpretations of the reductions in transmission dynamics. The applicants summarized their knowledge of serotype circulation, but did not address the potential impact on results. After the meeting, the applicants shared more detailed data, indicating that the dominant serotype in Paraná state was DENV-2 in 2020 and then DENV-1 from 2021 to date. However, there were very few serotyped samples from the study area.

Another potential source of bias was the impact of coronavirus disease (COVID-19) on testing and diagnostic capacity during the trial, and on health-seeking behaviour within the community. VCAG discussed the interpretation of outcomes based on the diversion of resources away from routine dengue testing to COVID-19 activities. The applicants indicated that the peak of COVID-19 cases in Brazil occurred towards the end of 2020 and at the start of 2021, which was the same time sterile insect deployments started. In 2021, they also observed a large reduction in the number of dengue cases across the entire state. The applicants therefore maintain that it was more likely that COVID-19 affected the whole state similarly, rather than affecting the intervention and control

cities differentially. Although no analyses were presented to rule out this confounder, the applicants do not believe that COVID-19 confounded the results.

VCAG enquired about the possible role of *Ae. albopictus* in dengue transmission in Brazil. The risk that *Ae. albopictus* could replace *Ae. aegypti* as the predominant species and continue to transmit dengue was also discussed, given that the former is also a competent vector. The applicants confirmed that *Ae. albopictus* is present in the study areas and that they monitored for both *Ae. aegypti* and *Ae. albopictus*; during the course of the study, they did not observe any changes in the relative density of the *Ae. albopictus* population. The applicants indicated that they are developing an NVC intervention targeting *Ae. albopictus*.

Finally, VCAG noted that while there are very promising trends arising from the studies presented, conclusions from the studies were based on indirect evidence of an association between the use of NVC and a reduction in dengue; VCAG was concerned that active case detection was not a feature of either trial conducted. It was further noted that the studies lacked randomization and replication of the intervention arms, and the short duration of the study in Jacarezinho did not appear to reflect the intended deployment approach of the intervention under operational conditions, which is advised *(14)*. Both trials were also undertaken in a single state in Brazil, whereas WHO requires evidence from trials conducted in different geographical and epidemiological settings. According to the *Norms, standards and processes underpinning development of WHO recommendations on vector control (14)*, the term "geography" in this sense is not restricted to physical geography, but encompasses other epidemiologically relevant factors, including local ecologies of co-circulating (and potentially interacting) pathogens, differences in vector ecology, and climatic factors. As such, applicants are encouraged to consider testing their intervention across different geographical settings and to engage with VCAG at a subsequent meeting.

The applicants were asked about their plans to conduct similar trials elsewhere and the next steps in their programme of work, specifically around study sites and study designs with active follow-up for epidemiological end-points and randomization. The applicants responded that they believed that their crossover study design was robust and superior to randomization, already reducing the risk of bias, and highlighted their intention to implement NVC on a larger scale with the Ministry of Health in Brazil.

The applicants requested WHO to validate that the intervention has public health value, given the body of evidence in support of *Ae. aegypti* population reduction and the associated passive dengue data, considering the global burden of dengue.

Conclusions

VCAG commended the applicants on the large body of work they had undertaken, noting that the data presented from the two studies were promising and could contribute to the body of evidence that may eventually be reviewed by a guideline development group. At present, however, the data do not meet WHO's requirements for assessment of public health value, as per the published *Norms, standards and processes underpinning development of WHO recommendations on vector control (14)*.

The study design has some notable limitations, including a lack of randomization, replication and reliance on passively collected data on dengue incidence (as opposed to prospectively and intentionally collected epidemiological end-points). Several other issues were identified, including the likelihood of multiple circulating serotypes that could influence prevalence during the study period, a lack of ability to account for the influence of population movement during the study, and the short duration of the intervention deployment in Jacarezinho, which may not reflect the way this intervention could be deployed in the future. Without a formal, comprehensive protocol outlining participant demographics for either study or an a priori SAP with power calculations, it is unclear to VCAG whether the studies were purposefully designed and powered to measure an impact on predefined epidemiological end-points.

Based on this submission, VCAG was unable to consider either of these trials as contributing to the requirement of two independent trials for assessing public health value. As outlined in WHO's guidance *(14)*, the strength of a WHO recommendation is influenced by the weight and strength of the available evidence. To this end, VCAG advised the applicants to consider conducting prospectively designed trials that conform to international guidance on clinical trials, and to reflect on the location of their epidemiological trials to ensure that they meet the requirement of trials in two geographical settings. The choice of geographical setting should be carefully considered so as to maximize evidence that this intervention can be deployed in different epidemiological settings.

WHO and VCAG acknowledge that the often-epidemic nature of dengue transmission means that it is particularly challenging to time a trial to coincide with an outbreak. WHO nevertheless requires rigorous adherence to systematic data and stringent standards for assessment of public health value to inform its recommendations, as outlined in its guidance *(14)*.

VCAG advice to applicants

VCAG strongly encouraged the applicants to continue their programme of work and to closely consider the guidance published in the *Norms, standards and processes underpinning development of WHO recommendations on vector control (14)* publication, and international guidance on clinical trial design.

Specifically, VCAG provided the following advice to applicants:

1. Develop a comprehensive written protocol (as per the international guidance on clinical trials) as early in the trial design process as feasible and submit it to VCAG for targeted feedback and support on design.

2. Prepare and submit an SAP in advance of the trial, clearly indicating the a priori hypothesis, target effect sizes and levels of significance, justified by appropriate power calculations.

3. Continue the team's familiarization with the complexities of cRCTs with epidemiological end-points intended to contribute evidence for the assessment of public health impact of vector control interventions. VCAG encourages the applicants to consider published international guidance and the valuable resources outlined in Box 1, in development of their future study design and associated trial protocol.

4. Review WHO's requirements for the development of recommendations for vector control interventions *(14)*. Of note, WHO requires a minimum of two well conducted and adequately powered trials with epidemiological end-points in different geographical settings to initiate the guideline development process, with trial durations commensurate with a realistic and intended deployment approach. The applicants are encouraged to consider such factors in future trial development plans.

Box 1. Suggested reading for applicants planning to develop clinical trial protocols for evaluating vector control interventions for assessment by WHO

- *Norms, standards and processes underpinning WHO vector control policy recommendations (14)*
- *WHO handbook for guideline development (19)*
- *WHO guidelines for malaria (10)*
- *CONSORT 2010 statement: extension to cluster randomised trials (20)*
- *Cluster randomised trials (17)*
- Chapter 8 of the *Cochrane handbook for systematic reviews of interventions (16)*
- SPIRIT statement and associated publications *(21,22)*
- *ICH guidelines E8 (R1) on general considerations for clinical studies (23)*
- *What study designs can be considered for inclusion in an EPOC review and what should they be called? (24)*
- Examples of published trial protocols from applicants having undergone VCAG review *(25–27)*

4. Concluding remarks

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 21st VCAG meeting is planned for the week of 21 October 2024, to be held in person at WHO headquarters in Geneva, Switzerland.

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Annex 1. Declarations of interest

The 20th VCAG meeting was convened to review and evaluate three applicant submissions on novel vector control interventions.

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 meeting.

The following declared interests were assessed as relevant (or potentially relevant) to topics under review at the 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 spatial repellent program, 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 *closed* discussion sessions on the spatial repellent submission and was not permitted to contribute to the development of a VCAG response to this submission. Questions were permitted to be posed in advance and delivered via the working group lead.
- **Dr Neal Alexander** is a member of the Data Safety Monitoring Board for the spatial repellent trials under review at this meeting.
  Given a foreseeable perceived conflict of interest and the importance of maintaining the independence and integrity of the two groups overseeing and evaluating the trials, Dr Alexander was recused from *closed* discussion sessions on the spatial repellent submission and was not permitted to contribute to the development of a VCAG response to this submission. Questions were permitted to be posed in advance and delivered via the working group lead.
- **Dr Leanne Robinson** indicated that she is working on a spatial repellent product related to the one under review at this meeting, although her work is unrelated to the assessment of public health value.
  Due to this potential conflict of interest, Dr Robinson was recused from *closed* discussion sessions on the spatial repellent submission and was not permitted to contribute to the development of a VCAG response to this submission. Questions were permitted to be posed in advance and delivered via the working group lead.

- **Dr Corine Ngufor** indicated that she is working on a spatial repellent product related to the one under review at this meeting, although her work is unrelated to the assessment of public health value.
  Due to this potential conflict of interest, Dr Ngufor was recused from *closed* discussion sessions on the spatial repellent submission and was not permitted to contribute to the development of a VCAG response to this submission. Questions were permitted to be posed in advance and delivered via the working group lead.
- **Dr John Bradley** is consulting on a trial for an unrelated spatial repellent product using a different technology.
  While this work was acknowledged, no conflict of interest was identified with assessment of the public health value of the product at the present meeting, and Dr Bradley's participation in the meeting and development of advice within the report was not restricted.

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.

Annex 2. Agenda

DAY 1: Monday, 25 March 2024			
Session 1: Welcome and updates		**Invitees**	**Closed session**
12:00–12:15	**Preliminary welcome** • Overview of running of meeting • Reading of declarations of interest statement	• VCAG members • VCAG temporary advisors • WHO VCAG Secretariat	For information
12:15–12:45	**Official opening of VCAG meeting** Chair of session: VCAG Co-chairs • Opening remarks from Director of the Global Neglected Tropical Diseases Programme • Round of introductions for members and temporary advisors	• Director of the Global Neglected Tropical Diseases Programme • VCAG members • VCAG temporary advisors • WHO VCAG Secretariat	For information
Session 2: Applicant submissions		**Invitees**	**Open session**
13:00–14:15	**Presentation – *Aedes* sterile insect technique** Chair of session: Francesca Frentiu • Applicant presentation (60 mins) • Q&A (15 mins)	• **Forrest Innovations** • VCAG members • VCAG temporary advisors • WHO VCAG Secretariat	For information
14:30–15:00	**Formulation of advice** • VCAG discussion (15 mins) • Development and drafting of technical guidance (30 mins)	• VCAG members • VCAG temporary advisors • WHO VCAG Secretariat	For information
DAY 2: Tuesday, 26 March 2024			
Session 3: Applicant submissions		**Invitees**	**Open sessions**
13:00–14:15	**Presentation – spatial repellents** Chair of session: Camilla Beech • Applicant presentation (60 mins) • Q&A (15 mins)	• **University of Notre Dame + SC Johnson** • VCAG members • VCAG temporary advisors • WHO VCAG Secretariat	For information
14:30–15:15	**Formulation of advice** • VCAG discussion (15 mins) • Development and drafting of technical guidance (30 mins)	• VCAG members • VCAG temporary advisors • WHO VCAG Secretariat	For guidance

DAY 3: Wednesday, 27 March 2024			
Session 4: Applicant submissions		**Invitees**	**Open sessions**
13:00–14:15	**Presentation – topical repellents** Chair of session: Corine Ngufor • Applicant presentation (60 mins) • Q&A (15 mins)	• **NOMO Foundation** • VCAG members • VCAG temporary advisors • WHO VCAG Secretariat	For information
14:30–15:15	**Formulation of advice** • VCAG discussion (15 mins) • Development and drafting of technical guidance (30 mins)	• VCAG members • VCAG temporary advisors • WHO VCAG Secretariat	For guidance
DAY 4: Thursday, 28 March 2024			
Session 5: Applicant submissions		**Invitees**	**Open sessions**
13:00–14:00	**Feedback to applicants** • *Aedes* sterile insect technique (20 mins) • Spatial repellents (20 mins) • Topical repellents (20 mins)	• **Forrest Innovations** • **University of Notre Dame + SC Johnson** • **NOMO Foundation** • VCAG members • VCAG temporary advisors • WHO VCAG Secretariat	
Session 6: VCAG discussions and meeting wrap-up		**Contributors**	**Closed sessions**
14:15–15:25	**Report writing** • Draft technical guidance for report • Review report status • Finalize technical guidance to be developed	• VCAG working groups (break-out rooms)	For guidance
15:20–15:40	**VCAG operations** • Discussion of operations and updates from WHO	• WHO VCAG Secretariat • VCAG members • VCAG temporary advisors	For information
15:40–16:00	**Meeting wrap-up** • Next steps and timelines	• WHO VCAG Secretariat • VCAG members • VCAG temporary advisors	For information

Annex 3. List of participants

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