Vector Control Advisory Group

Eighteenth meeting of the WHO Vector Control Advisory Group

Meeting report, 24–26 April 2023

World Health Organization

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ISBN 978-92-4-007730-0 (electronic version)
ISBN 978-92-4-007731-7 (print version)

Suggested citation. Eighteenth meeting of the WHO Vector Control Advisory Group: meeting report, 24-26 April 2023. Geneva: World Health Organization; 2023. Licence: CC BY-NC-SA 3.0 IGO.

Cataloguing-in-Publication (CIP) data. CIP data are available at http://apps.who.int/iris.

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Abbreviations

ATSB	attractive targeted sugar bait
BOHEMIA	Broad One Health Endectocide-based Malaria Intervention in Africa
COVID-19	coronavirus disease
cRCT	cluster-randomized controlled trial
ITN	insecticide-treated net
MDA	mass drug administration
RCT	randomized controlled trial
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 new interventions for the control of vector-borne diseases. These interventions include novel tools, technologies and approaches. VCAG is jointly coordinated by the Vector Control and Insecticide Resistance Unit of the Global Malaria Programme, the Veterinary Public Health, Vector Control and the Environment Unit of the Department of Control of Neglected Tropical Diseases, and the WHO Prequalification Unit 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 18th VCAG meeting was convened virtually from 24 to 26 April 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:

- systemic endectocide treatment;
- spatial repellents;
- attractive targeted sugar baits (ATSBs); and
- *Wolbachia w*Mel.

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

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

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

2. Welcome and opening remarks

Dr Daniel Ngamije M., the newly appointed Director of the Global Malaria Programme, officially opened the 18th VCAG meeting. The occasion also represented 10 years since the inception of the advisory group. Dr Ngamije noted that, during that time, more than 30 unique interventions targeting malaria, dengue and other arboviruses, leishmaniasis and rodent-borne diseases had been submitted to VCAG. Dr Ngamije highlighted that, in the course of fulfilling its function, VCAG had assessed the results of 10 trials, while 10 more in its portfolio were either ongoing or in active planning. The outcomes of these activities included five interventions that had completed assessment by VCAG, leading to the development of WHO recommendations for three types of insecticide-treated nets

(ITNs) targeting malaria and a recommendation in development for *Wolbachia w*Mel targeting *Aedes*-borne diseases.

Dr Ngamije welcomed Dr Leanne Robinson to the role of co-chair for the next three years. She will serve alongside Dr Audrey Lenhart for the next two years. Other new members (Dr Francesca Frentiu and Dr John Bradley) were also welcomed to the group, along with the temporary advisors who were invited to support the work of VCAG at this meeting.

It was recognized that VCAG and its members are an integral link in the chain of WHO advisory groups that are convened to ensure that WHO recommendations and guidance to Member States are transparent and evidence-based. The Director thanked the five outgoing members of VCAG, who have each served two consecutive terms, for volunteering their time and expertise to the work of the group. Outgoing members are Dr Robert Reiner Jr., Dr Thomas Smith, Dr Fabrice Chandre, Dr Hilary Ranson and Dr Salim Abdulla, who also served as VCAG co-chair for three years.

Dr Ngamije appreciated that VCAG had taken on a global role in the international vector control community over the past 10 years. He noted that continued evolution of the group and its role was necessary to serve the malaria and neglected tropical diseases communities, and that the group maintains relevance within the fast-paced field of vector control. The three managing departments of the group (Regulation and Prequalification, Neglected Tropical Diseases and the Global Malaria Programme) remained committed to supporting the activities and efforts of VCAG.

3. General stakeholder information session

Professor Tom Churcher from Imperial College London gave a presentation on inferring the epidemiological benefit of vector control tools from entomological data, with a focus on dual active ingredient ITNs. This presentation built on discussions during the seventh VCAG meeting *(1)*, following which VCAG recommended reviewing the utility of modelling based on entomological surrogates to support the formulation of specific WHO recommendations.

Professor Churcher explained that finding reliable entomological correlates for epidemiological data was of interest to vector control evaluation, as this could reduce the time and expense required to bring new tools to market if there was sufficient validation of entomological bioassays to ensure correlation with epidemiological end-points. Randomized controlled trials (RCTs) using epidemiological end-points are considered to be the gold standard for clinical trials, as these trials provide data that directly measure disease impact. It was acknowledged, however, that even results generated in RCTs may be subject to contextual variability, as observed in meta-analyses. Such inter-trial variability can be attributed to numerous factors. The epidemiological profile of the population influences the force of infection of the pathogen, as does the baseline standard of care. This means that the true effect of the intervention can only be inferred by calculation, because it is necessarily layered upon the existing standard of care. Finally, mosquito insecticide resistance profiles and differences in intervention use at the various test sites create heterogeneity in the estimated impact.

It is therefore interesting to investigate alternatives to epidemiological end-points, as these can more directly measure factors that impact the vectors. The drawbacks of pilot implementation programmes using entomological end-points were discussed. Biological assays may be used to assess entomological–epidemiological correlates, but they need to be appropriately adapted to the intervention in question and focused on the key modes of action of the intervention. For example, for ITNs, the entomological end-points of interest may be increased mosquito mortality, reduced blood feeding

and reduced fecundity. For ATSBs, the entomological end-point might be restricted to increased mortality. It is important to determine the extent to which these end-points are correlated with impact on the target disease(s) for each intervention class. Therefore, all entomological assays should initially be evaluated in parallel with epidemiological end-points in the same trial in order to validate the assays and more directly interpret the relationships between the entomological and epidemiological results.

Professor Churcher presented results from modelling data obtained from experimental hut studies and cluster randomized controlled trials (cRCTs) for pyrethroid-pyrrole nets and pyrethroid-pyriproxyfen nets, with the goal of determining whether entomological data can be used to infer epidemiological end-points. The entomological end-points considered included mortality, fertility, fecundity and blood feeding. Conclusions drawn were that the experimental hut trials captured the key entomological impact of the diverse ITNs and, when combined with models, were broadly able to predict cRCT results. It was noted that there are no simple entomological correlates of protection for vector control at this time and that different interventions will require different assays; some will be easier than others to evaluate. For example, for indoor residual spraying and ITNs, experimental hut trials would be appropriate; however, for other interventions, entomological correlates would need to be tested using alternative methods. One possibility would be to assess entomological data derived from pilot implementation trials and routine surveillance that collects epidemiological data. Modelling of experimental hut trial data from the New Nets Project suggests that modelling malaria prevalence in areas undergoing pilot implementation can capture the dynamics.

The discussion following the presentation considered the implications of modelling research for policy development, the variability of net composition and the differentiation of individual products. Whether other interventions, such as spatial repellents, could be assessed using experimental hut studies is unclear, given that much of the transmission is likely to occur just outside the structure. Finally, there was a general discussion stressing the need to ensure that modelling results are more accessible so that they can inform and support decision-making.

Entomological surrogates for epidemiological trial data remain a significant point of interest for WHO in the context of non-inferiority assessment of second-in-class interventions.

4. VCAG discussion on hypothesis testing

A discussion was led by Dr John Bradley on the merits of one- and two-sided hypothesis testing, following on from the discussion during the 17th VCAG meeting *(2)*, when the subject was raised in relation to an applicant submission. VCAG therefore dedicated time to reviewing the positive and negative aspects of both approaches and the potential implications of using one approach over the other in light of VCAG's remit to assess vector control interventions. Dr Bobby Reiner and Dr Tom Smith presented various perspectives from statistical thinking; the points below summarize the key issues raised by the presenters.

- Study design is important for determining the type of hypothesis; non-inferiority tests, for example, call for a one-sided hypothesis and therefore employ a one-sided test. Unless necessitated by the study design, numerous journals (*New England Journal of Medicine* was provided as an example) require all other reported *P* values to be two-sided.
- Some statisticians believe that when deploying an intervention against a placebo, the claim (the hypothesis) is normally already directional (i.e. the intervention is superior than the standard of care, which is normally the control). In other words, one is testing whether the intervention has a benefit; if it does, the tool should be considered for deployment, but if it is not superior, then the

standard of care should remain in use. While a directional claim should therefore have a directional hypothesis, it was conceded that if the trial was testing two competing interventions, using a two-sided test would be more appropriate.

- Further to this point, one can still determine the effect size of an intervention, irrespective of any directional claim. Numerous statistical associations are moving away from an emphasis on *P* values, preferring to emphasize the reporting of effect size estimates and their distributions, alongside test statistics. This approach enables readers to arrive at their own interpretation of whether these effect sizes are meaningful. The *P* value itself provides no information about testing multiple hypotheses or about the size of the effect.
- The choice of test and choice of significance level are distinct questions. VCAG has never required or requested the use of a specific test or value for the type I error. VCAG notes that if there ever was a need, it would be straightforward to convert one-sided to two-sided *P* values and vice versa (i.e. by doubling the one-sided *P* values or halving the two-sided *P* values).
- Two-sided tests are the norm in medical research and tie in naturally with two-sided 95% confidence intervals, which researchers are used to interpreting. Furthermore, systematic reviews normally provide summary figures with two-sided confidence intervals. If researchers present their results with one-sided tests, it may cause confusion if systematic reviews use different statistical inference to fit the study into the review. Because of the general use of two-sided *P* values, most readers of scientific reports may assume by default that tests are two-sided; reports of one-sided tests may therefore be misinterpreted or considered to be a post hoc decision to manipulate significance when the results failed to demonstrate significance with a two-sided test; this could lead to skepticism towards the trial results.
- Some researchers may use a one-sided test because product developers think it is not possible for their product to cause a detrimental effect. This is a cognitive bias, since negative effects can occur with any intervention, for example, through risk compensation, a phenomenon whereby subjects may think that a supplemental intervention works and so they stop using an intervention that is already in place, resulting in an overall decline in efficacy.
- Motivation for using a one-sided test may be driven by the fact that one-sided tests are less stringent and it is easier to achieve significance. Therefore, researchers who are restricted by funding might be incentivized to conduct smaller trials (because less power is needed to reach the level of significance). As above, the choice of one-sided or two-sided *P* values should be dictated by the study design, and choosing one-sided *P* values to reduce the amount of evidence required is not a legitimate use of one-sided *P* values. To counterbalance this desire for a smaller *P* value, it was contended that adjusting the number and sizes of clusters is likely to be a better approach to maintain statistical power without compromising the rigour of statistical testing.

The session concluded with questions from other VCAG members. Following on from a point raised in the general stakeholder presentation by Professor Churcher, members discussed the practical implications of using one- and two-sided tests in terms of being able to detect the impact against disease. In most vector control intervention trials, the standard of care is used as the control, and as the standard of care continues to improve, it will become more challenging to detect the effect of an intervention. Therefore, a one-sided test could facilitate the introduction of new tools to the market sooner, but this should not be to the detriment of the quality of evidence.

Importantly, it is the responsibility of the applicants to justify their choice of test. Nevertheless, VCAG recognized the prerequisite for researchers to make the decision to use a one- or two-sided test prior to commencing a trial, and the rationale must be

articulated in the a priori statistical analysis plan (SAP). VCAG concluded that it is not the group's role to accept one method over the other, but VCAG must critically review the totality of the evidence presented, in view of the statistical approach taken.

5. Submissions

VCAG reviewed four submissions across four intervention classes at its 18th meeting.

5.1 Intervention class: bait stations

Bait stations are interventions that are designed to attract and kill target vectors. ATSBs, which fall within this class, are specifically designed to attract and kill sugar-seeking mosquitoes. As both male and female mosquitoes feed on plant-derived sugars to maintain energy for survival, ATSBs exploit the almost daily need for sugar by attracting the mosquitoes to a source that also contains an insecticide.

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

Intervention: ATSBs

Applicant: Westham, in collaboration with the Innovative Vector Control Consortium

Following its first submission to VCAG in November 2014 *(3)*, the ATSB concept has been further developed, with the applicants having engaged regularly with VCAG at its meetings. The intervention aims at reducing mosquito vector populations and, in doing so, decreasing the proportion of mosquitoes with malaria parasites *(5)*. The risk of the product to non-target organisms with the current prototype is considered to be negligible, based on results from preliminary studies *(4)*. The applicants are working on three parallel epidemiological trials in Kenya, Mali and Zambia.

The applicants last engaged with VCAG at the 16th meeting *(6)*, when they summarized baseline entomological results from the three trials and presented modelling results supporting aspects of the trial design and deployment.

Updates

The applicants presented an update on an interim analysis conducted for two trials, which investigated whether the trials should continue as planned for a second year, be stopped due to harm or be reported to VCAG due to statistically significant results. The Mali and Zambia trials have passed this interim analysis stage, and the trials are set to continue. Interim analysis and a Data and Safety Monitoring Board meeting for the Kenya trial were scheduled for the day after the applicants' presentation at the VCAG meeting.[1]

Summary of discussions

VCAG appreciated the update on the ongoing ATSB trials in Kenya, Mali and Zambia, and acknowledged the progress that had been made. VCAG is looking forward to seeing the results in due course.

VCAG asked about the higher number of damaged ATSBs in Zambia than in the other two countries and whether differences in environmental conditions, placement and/or use conditions were responsible for the discrepancy in the number of missing or damaged devices. The applicants explained that there are likely to be several reasons for the observed differences in the replacement rate of baits across locations. The

1 Following the meeting, the applicants informed VCAG that the Data and Safety Monitoring Board had recommended that the trial continue for a second year, as planned.

monitoring schedule and approach in each country are not the same, leading to differences in frequency of replacement. Different housing structures across countries also influence the likelihood of replacement; for example, different lengths of the eaves on houses cause baits to be more or less exposed to rain, which could promote leakage and mould growth on the bait surface. Finally, rodents were responsible for a proportion of bait damage in Zambia, but caused little to no damage in Kenya and Mali. Based on the information provided in the applicants' presentation, VCAG noted that devices being completely absent was not among the reasons for replacement. However, it is not straightforward for the applicants to calculate the precise number of devices that need replacing because some baits were missing altogether (e.g. lost or intentionally removed). Site-specific information can be estimated, however.

VCAG reviewed the standard operating procedure provided by the applicants for testing the attractiveness and efficacy of mouldy versus non-mouldy bait stations. VCAG inquired whether the applicants had data on the impact of holes and leaks on the efficacy of ATSBs, as these were also major reasons for the ATSBs being damaged and in need of replacement. The applicants replied that they had conducted some durability and bioefficacy studies before initiating the epidemiology trials. The applicants tested the stations irrespective of their condition, so if the stations had shown signs of leakage, they would still have been included.

VCAG also noted that different starvation time had been used when testing male mosquitoes during the bioefficacy monitoring. Males were starved for 12 hours in Zambia, but 24 hours in other countries. The applicants explained that, in Zambia, the colony males were used in the assay (as opposed to wild mosquitoes in Kenya and Mali). Excessive control mortality was observed in the colony after 24 hours of starvation, and so the procedure was adapted for this one country.

VCAG commented on the efficacy of ATSBs, which decreased in Mali when tested at the six-month mark. The applicants explained that, based on previous studies, this was an unanticipated result; the very dry and hot conditions in Mali during the period of the bioefficacy evaluation likely contributed to the dry and depleted bait stations.

VCAG inquired whether the applicants had information on the thermostability and photostability of the product, to which they responded that testing was under way.

Conclusions

VCAG thanked the applicants for their update and continued work on these important trials. Even though no specific feedback was requested by the applicants on this occasion, VCAG provided the following general advice to the applicants based on the update and discussion.

Recommendations

VCAG made the following suggestions/recommendations:

- Based on the different approaches being undertaken to monitor and replace damaged ATSBs between trials, VCAG encourages the applicants to consider in more detail how these different approaches may impact the rate of replacement, and the related implications for the efficacy and cost-effectiveness of the intervention.
- VCAG suggests that the applicants use their current experience to draft guidance on standardized approaches to monitoring and replacing ATSBs in future studies or implementation.
- VCAG considers it important for the applicants to collect data on lost, removed or intentionally damaged ATSBs, and would like to hear more about this when the applicants next engage with VCAG. Equally, VCAG is interested to hear an update on product design changes and thermostability and photostability testing.

5.2 Intervention class: spatial repellents

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

Intervention: transfluthrin passive emanator

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

The spatial repellent intervention proposed by SC Johnson is a transfluthrin-based passive emanator (Mosquito Shield™) that is designed to release the volatile pyrethroid insecticide into the air and prevent human–vector contact in the treated space. The intervention targets *Anopheles*, *Aedes* and *Culex* spp. mosquitoes, with claims to protect all age groups and populations in countries endemic for mosquito-borne diseases from 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 pathogen transmission.

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 two cRCTs and the plans for three more trials. One epidemiological trial for malaria has been completed on Sumba island, Indonesia. This trial demonstrated statistically inconclusive results in terms of protective efficacy against malaria infection. Two additional trials seeking to demonstrate the public health value of the intervention for malaria are under way: one in Kenya and the other in Mali. 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 Sri Lanka. The applicants last provided an update to VCAG during the 17th meeting *(2)* in October 2022, when they provided an update on their three ongoing trials and sought advice from VCAG on several topics.

Updates

For the current meeting, applicants submitted to VCAG:

- the blinded outcome report (sent by the investigator team) and unblinded outcome report (sent directly to VCAG from the funder, Unitaid) from the pre-planned and powered interim analysis of the Kenya trial, along with the study protocol and SAP for reference; and
- the Sri Lanka trial protocol, standard operating procedure and final cluster maps, for reference.

The applicants provided updates on the following points:

- Kenya trial: interim trial results (primary end-point of protective efficacy only), with an access code for working group members to access the unblinded file;
- Mali trial: activities and anticipated date for submission of final analyses; and
- Sri Lanka trial: subject enrolment, site visits to Sri Lanka, test shipments, field activities, social science studies and timelines for trial follow-up duration.

Summary of discussions

The applicants asked VCAG for its assessment of the interim results of the Kenya trial, in view of the fact that they consider the outcome of the primary end-point reported to be the definitive outcome for protective efficacy (primary end-point on incidence) for the Kenya trial. In view of this, VCAG was requested by the applicants to provide a clear statement that the Kenya trial would contribute to the data requirements

for demonstrating public health value for VCAG's assessment of public health value provided by spatial repellents. VCAG reiterated that the broader evidence review process can only be initiated once the results of two sufficiently powered, well conducted trials are available, including the secondary and safety outcomes.

The applicants confirmed that the outcome presented to VCAG during the meeting represented the definitive primary analysis for the Kenya trial *(8)*, as opposed to an interim analysis (which would mean that the primary end-point would be re-analysed at the end of the trial). As the trial and SAP were designed and adequately powered to detect this effect prior to the planned end of the trial, VCAG agreed that the summary results presented demonstrate the protective efficacy of the transfluthrin-based spatial repellent against malaria. VCAG indicated that this finding provisionally satisfies the key requirement for evidence of epidemiological impact from one trial. Nevertheless, to enable a comprehensive assessment of the impact of spatial repellents in this trial, VCAG would like to review the full complement of results *(9)*, including secondary epidemiological end-points, explanatory/supporting entomological data and any information relating to relevant adverse events (as defined in the applicants' a priori SAP). At this stage, VCAG did not see any reason to request additional analyses beyond those already planned by the applicants and articulated in their SAP.

The applicants informed VCAG that follow-up for the Kenya trial will continue through completion of the planned 24-month duration for purposes of secondary and tertiary end-point analyses. The funders (Unitaid) and the VCAG working group members concurred with the applicants' continued implementation of the study accordingly.

Finally, the applicants sought comment on the justification they provided to VCAG at the 17th meeting on the use of one- versus two-sided hypothesis testing in their trials, asking VCAG whether it had further discussed the issue of using a one-sided *P* value, as raised during the 17th VCAG meeting *(2)*. VCAG noted that the one-sided *P* value for the primary efficacy measure in the Kenya trial was so low that the interpretation would not change if a two-sided test were to be used. VCAG had discussed the issue of applicability of one- or two-sided tests for analysing vector control trials; a summary of this discussion is reported in Section 4 of this report. While there are varying opinions on the subject among members of the group, the applicants remain responsible for making an informed decision on the type of test used, as it is necessary to justify that decision. VCAG does not prescribe any specific statistical approach.

Conclusions

VCAG congratulated the applicants for their continued progress and especially for the positive results on the efficacy of spatial repellents from the analysis of time to first infection in the Kenya trial. VCAG concurred that the summary provided by the applicants demonstrated the protective efficacy of the spatial repellent against malaria, and that this efficacy finding provisionally satisfied the key requirement for evidence of epidemiological impact from one trial. In this context, VCAG will be pleased to see, in due course, the associated outcomes in a full analysis report that conforms with the SAP.

Recommendations

VCAG recommended that the applicants continue their adherence to the study protocols and looked forward to further updates. VCAG requested to see the associated analyses of all epidemiological and entomological end-points, as well as relevant safety data, to enable comprehensive assessment of the effect of spatial repellents in the Kenya trial.

5.3 Intervention class: systemic endectocide treatment

Intervention: ivermectin

This intervention involves mass drug administration (MDA) of a systemic endectocide (ivermectin) to humans and/or the livestock around the communities in order to kill the insects that feed on these hosts. It is proposed that with sufficient dosing of the hosts, female mosquitoes taking blood meals can, in turn, receive lethal or sublethal doses that sufficiently suppress vector populations (e.g. reducing mosquito survival, fertility and fecundity) and malaria infection incidence.

Several ongoing malaria trials with ivermectin are being conducted by groups that have not yet engaged with VCAG. Following the submission of two adequately powered, well conducted trials and VCAG's review, WHO will be in a position to commission a systematic review to inform deliberations on the development of a WHO recommendation for ivermectin as an endectocide against malaria.

Applicant: ISGlobal, Broad One Health Endectocide-based Malaria Intervention in Africa (BOHEMIA) project)

The objective of the BOHEMIA project is to determine the efficacy of ivermectin delivered by MDA either to humans alone or to humans and livestock in reducing malaria transmission. The BOHEMIA project consists of a combination of studies organized around two cRCTs: one in Mozambique and another that was originally planned to take place in the United Republic of Tanzania but was subsequently moved to Kenya.

The target livestock species are pigs (Mozambique) and cattle (Kenya). Four substudies (social science, entomology, health economics and animal health, and environmental impact) were planned for both countries, and each has an independent protocol. The 12-month trial in Mozambique began in March 2022 and was completed on 31 March 2023. The trial in Kenya is scheduled to start in June 2023.

The applicants last participated in the 17th VCAG meeting *(2)*. At that time, VCAG recommended that the applicants revisit assumptions in the power analysis and cluster design, as well as the influence of asynchronous dosing. VCAG requested that the applicants provide updated protocols and an SAP in due course. With regard to asynchronous dosing, the applicants were encouraged to work with their modelling collaborators to better understand the extent to which such dosing may influence the results. VCAG also noted that documenting the lessons learned from the trial in Mozambique would help in the implementation of the second trial in Kenya.

Updates

The applicants provided a progress report on the trial preparations in Kenya, which is due to start in June 2023 with two arms: human-only ivermectin dosing and human albendazole (control) dosing. The human plus cattle arm has been dropped due to logistical constraints, cost, the need for specialized personnel and uncertainty over the extent to which local cattle management practices include cattle migration. Even though preliminary data from the social science team did not suggest extensive cattle migration, the applicants determined that the risk of implementing the human plus cattle arm without definitive information on cattle management practices was too great.

The efficacy component in the Mozambique trial ended in November 2022, while the entomology, social science and economic substudies were completed in October 2022. The safety substudy will be completed in April 2023. The applicants provided, for information only, a preliminary interpretation of the semi-blinded data from the Mozambique trial, including the balance of baseline data, evaluation of power, trends in malaria incidence and an evaluation of treatment coverage with different asynchronous dosing patterns. Preliminary safety results were also provided. The applicants asked VCAG for guidance on how administration of ivermectin to pregnant women might be

managed in a programmatic setting and how labelling for ivermectin could be adapted within the list of essential medicines, in the event that the trials demonstrate efficacy against malaria. The applicants also raised the possibility of additional non-randomized studies once the current trials have finished

Summary of discussions

In the report of the 17th VCAG meeting *(2)*, it was recommended that the applicants take advantage of the lessons learned from the Mozambique trial in planning and executing the Kenya trial. In this regard, the applicants indicated that, for the Kenya trial, they will complete the informed consent process 30 days prior to the first dosing. This approach will help to increase the rate of cluster dosing per day and result in a more synchronized coverage of the arms over the three-dose administrations. In addition, the tracking of malaria incidence will cease after the first month post administration of the last dose. Finally, the social science study will include the collection of information on cattle management and migration, which may be helpful for interpreting the trial results and guiding potential future trial designs. More detailed aspects are described below.

Unbalanced baseline data – The applicants raised the concern that the incidence rate, based on passive case detection, may not be sufficiently balanced, despite random assignment of participants to the arms. The applicants noted that from January through December 2021, approximately five months before dosing, one of the arms typically had elevated incidence rates compared to the other two arms.

Coefficient of variation (k) – The observed between-cluster coefficient of variation in Mozambique was close to, but slightly higher than, the value used in the sample size calculations (0.39 versus 0.35). It varied from 0.21 to 0.52 between the arms.

Crude malaria incidence – Semi-blinded results were presented to VCAG, i.e. with treatment arms distinguished by letter codes (X, Y and Z). The applicants noted the limited utility of tracking the incidence rate beyond one month following the last dose, considering that blood concentrations of ivermectin will be much lower thereafter. The SAP specified tracking incident rates for four months after the last dose. A post hoc/ secondary analysis one month after the last dose will be undertaken.

Effect of the speed of MDA distribution – Delays in dosing because of multiple cyclones and flooding, combined with logistical bottlenecks in attempting to complete informed consent agreements and administer the first dose on the same day, meant that dosing was less than 5% of each arm per day. To make up for the initial slow rate of dosing across arms in some clusters, dosing for the second and third rounds was accelerated such that doses administered on any given day were approximately 18 to 20 days after the previous dose.

Consistent with the findings presented by the applicants at previous VCAG meetings, the applicants observed that the mosquitocidal effect of ivermectin waned quickly, with efficacy declining to approximately 30% after 10 days and with no protection remaining 30 days after administration. Combined with the prolonged administration of ivermectin in the population, the applicants calculated that the maximum expected effect of ivermectin was rarely more than 25%.

Collection of safety data – Major effort has been invested, considering population displacement due to cyclones and other factors, in attempting to trace women who received ivermectin and were subsequently found to be pregnant. This follow-up process is expected to be finished by the end of April 2023.

Conclusions

VCAG commended the applicants' progress with the trial in Mozambique in the face of exceptional challenges and encouraged the applicants to continue with the trial in Kenya.

With regard to reporting the results of the Mozambique trial, VCAG suggested following the CONSORT guidelines for cluster randomized trials *(10)*. The applicants may find it useful to bear this structure in mind when making future presentations of the results.

The applicants indicated that the SAP for the Kenya trial is being prepared, taking into account changes in the trial design, and should be completed by August 2023. The applicants anticipated that the selection of participants and completion of informed consent would be finished in May 2023. Dosing would occur in June, July and August 2023, and collection of incidence data would occur one month following the administration of the August dose.

As the questions posed to VCAG about product labelling and administration of the drug to population subgroups were outside of the scope of the advisory group, which is mandated to focus on the assessment of public health value, WHO will follow up with the applicants via means external to the VCAG meeting report.

Finally, VCAG concurred that dropping the human plus cattle arm in the Kenya trial was appropriate given the costs and logistical challenges in implementing cattle dosing and the uncertainty over cattle migration within and outside the clusters.

Recommendations

In terms of the unbalanced baseline data observed, VCAG recommended that the applicants consider descriptive measures, such as means and standard deviations, to quantify the magnitude of between-arm differences in the baseline data. Inferential methods, including confidence intervals, are not generally thought to be applicable to baseline data in clinical trials *(11)*. If concerns about imbalance remain, an analysis that adjusts for baseline values of malaria occurrence could be worthwhile, even though it would be post hoc (i.e. not mentioned in the SAP).

Responding to the applicants' question of whether additional resources for non-randomized studies should be sought, VCAG stated that it would be advisable to first complete the RCTs in Mozambique and Kenya to determine the public health value of ivermectin as an endectocide before embarking on additional data generation.

VCAG looked forward to reviewing the updated protocol and associated SAP for the Kenya trial in due course. VCAG encouraged the applicants to be specific in terms of the covariates to be adjusted for in the main analysis, and to refer to existing guidance, such as that from the European Medicines Agency *(12)*.

5.4 Intervention class: reduction of pathogen transmission induced by *Wolbachia*

Intervention: *Wolbachia w*Mel in *Aedes aegypti*

This intervention class involves the introgression of *Wolbachia*, a naturally occurring obligate intracellular bacteria, into a population of *Ae. aegypti* mosquitoes. *Ae. aegypti* that carry the *Wolbachia* strain *w*Mel are significantly less capable of transmitting arboviruses following their infection. This applies not only to dengue virus, but also to Zika and chikungunya viruses. As a result, stable *Wolbachia* introgression renders *Ae. aegypti* populations largely incapable of sustaining arbovirus transmission. Following introgression of *Wolbachia* into *Ae. aegypti* populations, the intervention is sustainable over time without the need for subsequent releases. The intervention is modelled to be cost-effective at large scales *(9)*. *Wolbachia w*Mel has been successfully introduced into *Ae. aegypti* populations in at least a dozen countries on several continents, where community support for the release of *Wolbachia*-carrying mosquitoes has generally been positive.

In December 2020, at its 13th meeting *(8)*, VCAG assessed the evidence of public health value for *Wolbachia w*Mel-infected *Ae. aegypti* against dengue submitted by the World Mosquito Program and advised WHO to initiate the guideline development process for this intervention. At that same meeting, the team from Emory University independently submitted their plans for a cRCT in Brazil using the same *Wolbachia w*Mel intervention. Given the prospect of refining WHO recommendations when additional evidence becomes available, the applicants were encouraged to continue their trial because, as a cRCT, it is likely to provide high-certainty evidence.

Applicant: Emory University

Updates

The applicants submitted their latest protocol (February 2023) and SAP for VCAG's review, in addition to six published papers (including the trial protocol) for reference. The applicants provided updates on the progress of the trial, which will soon be entering its fourth year, including enrolment status, *Wolbachia* deployment and infection rates:

- The study is fully enrolled and preparing for year 4 of participant follow-up starting in June 2023.
- Through year 3, 1709 participants dropped out for various reasons and these were replaced by 1636 new participants.
- Mosquito deployments ended in May 2022 and there is ongoing monitoring of levels of introgression in all clusters.
- There has been a low incidence of dengue in the previous two years in the study site.
- The applicants are planning to conduct follow-up for an additional year, making the study five years in total (four years of which are follow-up time).

The applicants indicated that the first interim analysis had yet to be conducted, as the serology data to enable the analysis were not yet available.

Summary of discussions

VCAG appreciated the update on the trial and the ability of the team to deal with the challenges arising from the coronavirus disease (COVID-19) pandemic at the start of the trial.

VCAG looked forward to the results of the initial serosurvey data, which will provide the serostatus of participants at baseline. The applicants indicated that they were expecting baseline flavivirus seroprevalence to be 50%, with most being monotypic for dengue virus serotype 1–4 antibodies. The baseline serology estimate will be based on serological data from 199 children who were enrolled but later excluded from the trial.

The applicants indicated that the target for cluster inclusion in the analysis was based on 60% *Wolbachia* prevalence, as they consider this to be the threshold above which *Wolbachia* normally spreads to fixation within a mosquito population.

The applicants explained that there had been low dengue virus transmission in the study site over the course of the trial, and therefore they planned to extend the trial to five years. They further noted that they will likely conduct an interim analysis from the paired samples from years 1 and 2, but it is unlikely that this will yield significant seroconversion rates due to a low dengue transmission season and incomplete deployment in all clusters.

With regard to the applicants' question about the SAP, VCAG would be interested in receiving more details about how the expected transmission rates and expected number of susceptible participants at baseline were estimated.

The applicants explained that the COVID-19 pandemic had contributed to the higher-than-expected dropout rate observed during years 1 and 2. VCAG had no concerns about the applicants' approach to replenish the participants, since the applicants are using a quasi-Poisson analysis with its assumptions of independence. However, VCAG thought it would be valuable to quantify the number of paired samples in each set of consecutive years, since this will impact the power calculations.

The applicants were optimistic that extending the trial by another year would enable them to reach a 13% event rate.

VCAG was interested in receiving further clarification on how participant time-use data will be included in the analysis. The applicants mentioned that they would be looking at time-use data and developing an SAP for this during the summer of 2023.

Conclusion

VCAG thanked the applicants for their update and appreciated the significant effort involved in the continued work on this trial, despite the challenges of COVID-19 and lower than expected dengue incidence. VCAG supported the applicants' proposal to extend the duration of follow-up to five years and their strategy of replacing participants. VCAG made several specific recommendations relating to the SAP and would appreciate further clarification on several aspects in due course. VCAG is looking forward to hearing the results of the initial serosurvey data in order to gain an understanding of the serostatus of participants at baseline and how the time-use analysis will be evaluated.

Recommendations

As requested by the applicants, VCAG identified some areas of the SAP that would benefit from further clarification and explanation in subsequent dissemination efforts. These are summarized below:

- Include strata in the primary analysis.
- Perform the intention-to-treat analysis as planned.
- Update the per protocol analysis:
    - to clarify criteria for inclusion of clusters or cluster-years;
    - to clarify how clusters that drop below the 60% *Wolbachia* infection prevalence will be treated in the analysis; and
    - to reflect exclusion of clusters that were untreated at the time of the second serosurvey.
- Provide information on how time-use data will be used in the analyses.
- While not all participants had received the intervention by the time of the second serosurvey, the low transmission during that time should help to minimize the impact of having untreated participants in treatment clusters. However, the per protocol analysis should not include the first year because of the incomplete administration of the intervention. The SAP should include clear criteria for inclusion of clusters or cluster-years.
- Provide information on how the expected transmission rates and expected number of susceptible participants at baseline were estimated.
- In addition, given the high rate of dropout and replacement, it would be helpful to know how the age distribution of the baseline population compares to that of the new recruits.

6. 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 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 19th VCAG meeting is planned for 27–29 September 2023; it is intended for this to be an in-person meeting.

References

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11. Altman DG, Doré CJ. Randomisation and baseline comparisons in clinical trials. Lancet. 1990;335(8682):149–53. doi:10.1016/0140-6736(90)90014-v.

12. Guideline on adjustment for baseline covariates in clinical trials. London: European Medicines Agency; 2015 (https://www.ema.europa.eu/documents/scientific-guideline/guideline-adjustment-baseline-covariates-clinical-trials_en.pdf, accessed 22 June 2023.

Annex 1. Declarations of interest

The 18th VCAG meeting was convened to review and evaluate four applicant submissions on novel vector control interventions across four intervention classes.

This convening consisted of three categories of invitees, namely:

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

Respective applicants each participated in their own open sessions, alongside the members, temporary advisors and the WHO VCAG Secretariat.

Before the meeting, all VCAG members and temporary advisors joining 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, found that the interests were not directly related to the topics under discussion at the present meeting.

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

Members

Dr Audrey Lenhart has staff under her professional supervision who are working on the spatial repellents AEGIS project and on the ATSB work programme, although she herself is not an investigator on either project, nor is she otherwise involved. Due to this potential conflict of interest, Dr Lenhart was recused from all sessions relating to the ATSB and spatial repellent submissions in the capacity of VCAG member and was not permitted to contribute to the development of guidance for either submission.

Dr Robert Reiner declared a conflict of interest relating to the spatial repellent submission. Dr Reiner was recused from all sessions relating to the spatial repellent submission in the capacity of VCAG member and was not permitted to contribute to the development of guidance for the submission.

Dr Leanne Robinson declared a conflict of interest with the spatial repellent submission. Dr Robinson was recused from all sessions relating to the spatial repellent submission in the capacity of VCAG member and was not permitted to contribute to the development of guidance for the submission.

Dr John Bradley declared a conflict of interest relating to the ATSB submission. Dr Bradley was recused from all sessions relating to the ATSB submission in the capacity of VCAG member and was not permitted to contribute to the development of guidance for the submission.

The reading of these interests constituted 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

Monday, 24 April 2023			
Session 1: Welcome and updates		**Presenters**	**Closed session**
13:00–13:10	**Preliminary welcome** • Overview of running of meeting • Reading of declarations of interest statement	• VCAG members • Temporary advisors • WHO VCAG Secretariat	For information
13:10–13:20	**Official opening of VCAG meeting** Chair of session: VCAG co-chairs • Opening remarks from Director Global Malaria Programme	• Director Global Malaria Programme • VCAG members • Temporary advisors • WHO VCAG Secretariat	For information
13:20–13:40	**Introduction** Chair of session: VCAG co-chairs • Brief introduction of VCAG members and temporary advisors	• VCAG members • WHO VCAG Secretariat	For information
Session 2: General stakeholder information		**Invitees**	**Open session**
13:40–14:45	**Inferring the epidemiological benefit from entomological data for dual active ingredient ITNs** Chair of session: VCAG co-chairs • Open presentation • Q&A / discussion	• **Speaker: Tom Churcher** Imperial College London • All interested stakeholders	For information
Session 3: Applicant presentations and feedback		**Invitees**	**Closed session**
15:00–16:25	**Presentation – ATSBs** Chair of session: Alfred Tiono • Applicant presentation • Q&A • VCAG discussion • Feedback to applicants	• **Westham / Innovative Vector Control Consortium team** • VCAG members • Temporary advisors • WHO VCAG Secretariat	For information & discussion
Session 4: VCAG discussion		**Contributors**	**Closed session**
16:25–17:00	**Discussion** Chair of session: John Bradley • One- vs. two-sided *P* values for end-point analyses • Future applications and interventions	• VCAG members • Temporary advisors • WHO VCAG Secretariat	For information
Tuesday, 25 April 2023			
Session 5: Formulation of VCAG advice		**Contributors**	**Closed session**
13:00–13:20	**Formulation of advice (from day 1)** • Development of advice for applicants Draft technical guidance for report	• VCAG working groups	For guidance
Session 6: Applicant presentations and feedback		**Invitees**	**Closed session**
13:20–14:45	**Presentation – spatial repellent** Chair of session: Salim Abdulla • Applicant presentation • Q&A • VCAG discussion • Feedback to applicants	• **SC Johnson / University of Notre Dame** • VCAG members • Temporary advisors • WHO VCAG Secretariat	For information & discussion

15:05–16:30	**Presentation – *Wolbachia* *w*Mel** Chair of session: Bobby Reiner • Applicant presentation • Q&A • VCAG discussion • Feedback to applicants	• **Emory / EVITA team** • VCAG members • Temporary advisors • WHO VCAG Secretariat	For information & discussion
Session 7: Formulation of VCAG advice		**Contributors**	**Closed session**
16:30–17:00	**Formulation of advice (from day 2)** • Development of advice for applicants • Draft technical guidance for report	• VCAG working groups	For guidance

Wednesday, 26 April 2023			
Session 8: Applicant presentations and feedback		**Invitees**	**Closed session**
13:00–14:25	**Presentation – ivermectin endectocide** Chair of session: Neal Alexander • Applicant presentation • Q&A • VCAG discussion • Feedback to applicants	• **ISGlobal / BOHEMIA team** • VCAG members • Temporary advisors • WHO VCAG Secretariat	For information & discussion
Session 9: Formulation of VCAG advice		**Contributors**	**Closed session**
14:25–15:00	**Formulation of advice (from day 3)** • Development of advice for applicants • Draft technical guidance for report	• VCAG working groups	For guidance
Session 10: VCAG meeting outcomes and wrap-up		**Contributors**	**Closed sessions**
15:15–16:15	**Report writing** • Review report status • Finalize technical guidance to be developed	• VCAG working groups	For guidance
16:15–17:00	**VCAG operations and wrap-up** Chair of session: VCAG co-chairs • Discussion on VCAG operations • Wrap-up of meeting	• VCAG members • Temporary advisors • WHO VCAG Secretariat	For discussion

Annex 3. List of participants

Vector Control Advisory Group members

Co-Chairs

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

Leanne Robinson
Burnet Institute
Melbourne, Australia

Members

Salim Abdulla
Ifakara Health Institute
Ifakara, United Republic of Tanzania

Neal Alexander
Centro Internacional de Entrenamiento e Investigaciones Médicas
Cali, Colombia

Camilla Beech
Cambea Consulting Ltd
Berkshire, United Kingdom of Great Britain and Northern Ireland

Steven Bradbury
Iowa State University
Iowa, United States of America

John Bradley
London School of Hygiene and Tropical Medicine
London, United Kingdom of Great Britain and Northern Ireland

Fabrice Chandre
Institut de Recherche pour le Développement
Montpellier, France

Francesca Frentiu
Queensland University of Technology
Brisbane, Australia

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

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

Robert Reiner
University of Washington
Seattle, United States of America

Thomas Smith
Swiss Tropical Institute
Basel, Switzerland

Alfred Tiono
Centre National de Recherche et de Formation sur le Paludisme
Ouagadougou, Burkina Faso

Temporary advisors

Sheila Ogoma Barasa
PMI VectorLink Abt Associates
Nairobi, Kenya

R.D. Jeevanie Harishchandra
Anti Malaria Campaign
Colombo, Sri Lanka

Sawdetuo Aristide Hien
Institut de recherche en sciences de la santé
Ouagadougou, Burkina Faso

Corine Ngufor
CREC/LSHTM Collaborative Research Programme
Cotonou, Benin

Gabriel Parra-Henao
Centro de Investigación en Salud para el Trópico
Santa Marta, Colombia

Thomas Churcher
Imperial College London
London, United Kingdom of Great Britain and Northern Ireland

Applicants

Attractive targeted sugar baits

Julian Entwistle
Christen Fornadel
Amir Galili
Megan Littrell
Mathias Mondy
Fred Yeomans

Spatial repellents

Nicole L. Achee
Kelsey Barrett
Matthew Black
Rachel Evans
John P. Grieco
Tom Mascari

Wolbachia *w*Mel

Ellie Butler
Matthew Collins
Derek Cummings
Greg Deye
Srilatha Edupuganti
Jamie Fraser
Matt Hitchings
Walt Jones
Albert Ko
Jordan Lundeen
Luciano Moreira

Mauricio Nogueira
Gail Potter
Nadine Rouphael
Mauro Teixeira
Michelle Wiles

Endectocides

Kelsey Barrett
Carlos Chaccour
Regina Rabinovich

WHO SECRETARIAT

Global Malaria Programme

Daniel Ngamije M.
Director

Jan Kolaczinski
Unit Head
Vector Control & Insecticide Resistance

Isabelle Abello
Assistant to Team
Vector Control & Insecticide Resistance

Lauren Carrington
Technical Officer
Vector Control & Insecticide Resistance

Jennifer Stevenson
Technical Officer
Vector Control & Insecticide Resistance

Department of Control of Neglected Tropical Diseases

Raman Velayudhan
Unit Head
Veterinary Public Health, Vector Control and Environment

Rajpal Yadav
Scientist
Veterinary Public Health, Vector Control and Environment

Qingxia Zhong
Technical Officer
Veterinary Public Health, Vector Control and Environment

Regulation and Prequalification

Dominic Schuler
Technical Officer
Prequalification, Vector Control Products

FOR FURTHER INFORMATION PLEASE CONTACT:

Vector Control Advisory Group
World Health Organization
20 Avenue Appia
1211 Geneva 27
Switzerland
vcag@who.int
www.who.int/groups/vector-control-advisory-group

9789240077300