



**Vector Control
Advisory Group**

MEETING REPORT
Virtual meeting, 7–10 December 2020

Thirteenth meeting of the WHO Vector Control Advisory Group



**World Health
Organization**



**Vector Control
Advisory Group**

MEETING REPORT
Virtual meeting, 7–10 December 2020

Thirteenth meeting of the WHO Vector Control Advisory Group



**World Health
Organization**

Thirteenth meeting of the WHO Vector Control Advisory Group

ISBN 978-92-4-002179-2 (electronic version)

ISBN 978-92-4-002180-8 (print version)

© World Health Organization 2021

Some rights reserved. This work is available under the Creative Commons Attribution-NonCommercial-ShareAlike 3.0 IGO licence (CC BY-NC-SA 3.0 IGO; <https://creativecommons.org/licenses/by-nc-sa/3.0/igo>).

Under the terms of this licence, you may copy, redistribute and adapt the work for non-commercial purposes, provided the work is appropriately cited, as indicated below. In any use of this work, there should be no suggestion that WHO endorses any specific organization, products or services. The use of the WHO logo is not permitted. If you adapt the work, then you must license your work under the same or equivalent Creative Commons licence. If you create a translation of this work, you should add the following disclaimer along with the suggested citation: "This translation was not created by the World Health Organization (WHO). WHO is not responsible for the content or accuracy of this translation. The original English edition shall be the binding and authentic edition".

Any mediation relating to disputes arising under the licence shall be conducted in accordance with the mediation rules of the World Intellectual Property Organization.

Suggested citation. Thirteenth meeting of the WHO Vector Control Advisory Group. Geneva: World Health Organization; 2021. Licence: CC BY-NC-SA 3.0 IGO.

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

Sales, rights and licensing. To purchase WHO publications, see <http://apps.who.int/bookorders>. To submit requests for commercial use and queries on rights and licensing, see <http://www.who.int/about/licensing>.

Third-party materials. If you wish to reuse material from this work that is attributed to a third party, such as tables, figures or images, it is your responsibility to determine whether permission is needed for that reuse and to obtain permission from the copyright holder. The risk of claims resulting from infringement of any third-party-owned component in the work rests solely with the user.

General disclaimers. The designations employed and the presentation of the material in this publication do not imply the expression of any opinion whatsoever on the part of WHO concerning the legal status of any country, territory, city or area or of its authorities, or concerning the delimitation of its frontiers or boundaries. Dotted and dashed lines on maps represent approximate border lines for which there may not yet be full agreement.

The mention of specific companies or of certain manufacturers' products does not imply that they are endorsed or recommended by WHO in preference to others of a similar nature that are not mentioned. Errors and omissions excepted, the names of proprietary products are distinguished by initial capital letters.

All reasonable precautions have been taken by WHO to verify the information contained in this publication. However, the published material is being distributed without warranty of any kind, either expressed or implied. The responsibility for the interpretation and use of the material lies with the reader. In no event shall WHO be liable for damages arising from its use.

This publication contains the report of the WHO Vector Control Advisory Group and does not necessarily represent the decisions or policies of WHO.



CONTENTS

Background	1
Closed session	1
Welcome	1
Updates from the WHO departments	2
Discussion topics	3
Trial analyses at different intervals	3
Guideline development process overview	3
VCAG reviews of applicant submissions	4
Intervention class: Bait stations	4
Intervention: Attractive targeted sugar baits (ATSBs)	4
Applicant: Westham / Innovative Vector Control Consortium (IVCC)	4
Background	4
Updates	4
Summary of discussions	4
Conclusions	5
Recommendations	5
Intervention class: Lethal house lures	7
Intervention: Eave tubes (with and without screening)	7
Applicant: In2Care	7
Background	7
Updates	7
Summary of discussions	8
Conclusion	9
Recommendations	9

Intervention class: Reduced pathogen transmission induced by <i>Wolbachia</i>	10
Intervention: <i>Wolbachia</i> (wMel)-infected <i>Aedes aegypti</i>	10
Background	10
Applicant: World Mosquito Program (WMP)	10
Updates	10
Summary of discussions	10
Conclusion	11
Recommendations	11
Applicant: EVITA (led by Emory University)	12
Initial submission	12
Summary of discussions	12
Conclusion	13
Recommendations	13
Intervention class: Spatial repellents	13
Intervention: Spatial repellents	13
Applicant: SC Johnson / University of Notre Dame	13
Background	13
Updates	14
Summary of discussions	14
Conclusion	15
Recommendations	16
Intervention class: Treatment of humans and/or livestock with systemic endectocides	16
Intervention: Endectocides (Ivermectin)	16
Applicant: BOHEMIA, ISGlobal	16
Background	16
Updates	17
Summary of discussions	17
Conclusion	17
Recommendations	18
Concluding remarks of the meeting	19
References	20
Annex 1. Declarations of interest	21
Annex 2. List of participants	23
Annex 3. Agenda of meeting	26

BACKGROUND

The World Health Organization (WHO) Vector Control Advisory Group (VCAG) serves as an advisory body to WHO on new tools, technologies and approaches – collectively referred to as “interventions” – for the control of vectors of malaria, dengue and other vector-borne diseases. VCAG is jointly coordinated by the WHO Global Malaria Programme (GMP), the WHO Department of Control of Neglected Tropical Diseases (NTD) and the WHO Prequalification Team for Vector Control Products (PQT/VCP). The specific functions of VCAG are:

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

VCAG experts met virtually with product developers, innovators and researchers (jointly referred to as “applicants”) from 7 to 10 December 2020 for the 13th VCAG meeting. The experts consisted of 14 VCAG members and three temporary advisors. The meeting was co-chaired by Heather Ferguson and Salim Abdulla. The full list of participants who were involved in the meeting can be found in Annex 1. The agenda for the meeting is reproduced in Annex 2.

This report details the proceedings and outcomes of the meeting, including advice provided to applicants who had made submissions relating to the following intervention classes:

- Bait stations
- Lethal house lures
- Reduced pathogen transmission induced by *Wolbachia*
- Spatial repellents
- Treatment of humans and/or livestock with an endectocide.

CLOSED SESSION

The initial closed session was attended by all VCAG members, the WHO VCAG Secretariat and affiliated WHO staff. All declarations of interest disclosed by VCAG advisors were reviewed in advance of the meeting, and relevant interests were disclosed, along with how they were being managed. The statement of declarations of interest is available in Annex 3.

Welcome

VCAG members were officially welcomed by Mr Deusdedit Mubangizi, Coordinator of RPQ/PQT (on behalf of Dr Mariângela Simão, Assistant Director General of MHP), Dr Pedro Alonso, Director of GMP and Dr Mwele Malecela, Director of NTD. The evolution of VCAG over the last number of years was noted. All three highlighted the

importance of the three departments' collaboration in navigating the evaluation of novel interventions in the vector control space and the importance of speaking with one voice. Dr Alonso noted that it is in the vector control space that some of the greatest progress is being made in the development of new and effective tools to combat malaria, and such advances need to continue. Dr Malecela informed VCAG that the NTD Roadmap 2021–2030 was approved by the World Health Assembly in its special session in November 2020. The Roadmap promotes a fundamental shift in the focus of delivery from disease-specific programmes to integrated approaches based on common delivery platforms. Integrated vector management, research and innovation are considered essential factors for the success of the Roadmap.

The effect of COVID-19 on the implementation of control programmes targeting both malaria and NTDs has clearly been felt over the past year, and the need to come together to support delivery efforts was echoed by all teams. All three speakers expressed their gratitude to the VCAG members for their dedication and commitment to the work of the group and the goal of bringing new and effective vector control interventions to the table.

Updates from the WHO departments

Since the 12th VCAG meeting (8–10 June 2020), WHO has published the latest evaluation standards for vector control interventions, called *Norms, standards and processes underpinning WHO vector control policy development (1)*. This publication was developed through the joint effort of the three departments (GMP/VCR, NTD/VVE, RPQ/PQT) as part of WHO's effort to improve communication around the linkage between the generation of data to inform the development of guidelines and how those guidelines are developed. This document provides both VCAG members and applicants alike with descriptions of WHO's revised evaluation standards for vector control interventions, replacing the document entitled *The evaluation process for vector control products*, which was published in June 2017. This revised guidance represents a move away from a one-size-fits-all approach and places greater emphasis on the proposal of trial designs that are suitable for specific epidemiological contexts and for the intended deployment and use patterns of the interventions. The generation of the highest quality evidence to demonstrate public health value remains paramount for each intervention that goes through the evaluation process.

Dr Jan Kolaczinski (GMP/VCR) informed VCAG of the position statement on genetically modified mosquitoes that was recently published by WHO, and the fact that WHO is supportive of further research assessing the potential epidemiological impact of this new technology. Dr Kolaczinski also informed VCAG that WHO's malaria guidelines are being collated into a single guideline (no longer separated by treatment, prevention and control). This guideline will be available on an online application called MAGICapp (as of early 2021), facilitating access to individual components of the guideline.

Dr Raman Velayudhan (NTD/VVE) provided further information on the new NTD roadmap (2), highlighting some of the key targets set by the roadmap and the mechanisms that are being put in place to ensure these targets are achievable. Progress on the Global Vector Control Response was also summarized, including details of the regional uptake of the response, progress over the first three years, development of normative guidance, infrastructure support provided, and development of an online hub to support coordination and monitoring of the progress and activities.

Ms Marion Law (PQT/VCP) presented an overview of the numbers and types of applications submitted to PQT/VCP in 2020. This included outcomes with respect to products prequalified, chemistry and manufacturing specifications established, and the number of requests for determination of pathway. In addition, an update on key projects of interest to VCAG was provided, such as work on reviewing and revising the data requirements for insecticide-treated nets (ITNs), the data call for specific non-pyrethroid-only ITNs, and the label improvement plan. Ms Law informed the group that the PQT/VCP overview document, which provides information such as the mandate, evaluation approach, process and operational policy underpinning the programme, is now complete. The team is also in the process of updating and developing new content for the PQT website.

Discussion topics

Trial analyses at different intervals

Drs Tom Smith and Neal Alexander led a short discussion on the topic of interim analyses, stopping rules for studies, and adaptive trial designs. This discussion was motivated by recent proposals from applicants responding to challenges arising from the COVID-19 pandemic, which have forced numerous trials to stop, pause or adjust their activities due to restrictions.

The last guidance from VCAG on pre-final trial analyses was in the report from the eighth VCAG meeting (May 2018) (3), following a discussion led by Dr Immo Kleinschmidt. Other published guidance, for example by CONSORT (4) and the FDA (5), does not differ in principle from VCAG's previous recommendations, outlining the conditions under which interim analyses and early stopping may be acceptable.

VCAG members concluded that their guidance on interim analyses remains the same as previously stated in the eighth meeting report. Specifically, the incorporation of interim analysis into trial design may be acceptable if sufficiently justified, pre-planned, and clearly defined in scope. VCAG also agreed that the established Data and Safety Monitoring Board (DSMB)¹ should recommend whether the results of an interim analysis warrant the stopping or continuation of a trial. VCAG should have no role in a trial's governance in this regard. It was also deemed important to pre-define any actions that might be taken should a given outcome be observed following any analysis at a pre-defined time point.

The discussion also considered the necessity of using the correct terminology for analyses. For example, the term "interim analysis" usually refers to an analysis that has been pre-planned and should not be used to describe ad hoc analyses conducted prior to trial completion. Further to this point, if the intent is to conduct a shorter, albeit adequately powered trial with the option of continuing beyond this potential stopping point, then such an analysis would not be considered interim either.

VCAG reiterates the guidance in its eighth report and recommends that all future trials with plans for interim analyses (or the potential for early stopping) articulate within the statistical analysis plan (SAP) and study protocol the role of the DSMB; the rules and trigger points for stopping the trial; and appropriate considerations for the consequences of multiple testing and impacts on p-value cut-offs in the final analyses.

Guideline development process overview

Dr Elie Akl gave a presentation to the VCAG members, introducing the processes involved in the development of WHO guidelines and policy recommendations. Dr Akl, from the Department of Medicine at the American University of Beirut in Lebanon, is a seasoned guideline methodologist and has been involved in the development of numerous WHO guidelines, including work on the revision and expansion of GMP's vector control guidelines and their consolidation with other technical areas into one malaria guideline document. His presentation aimed to provide a better understanding of the types of data needed in the guideline development process and how they inform policy recommendations. The presentation gave a high-level overview of the guideline development process and emphasized the fact that WHO guidelines are developed in response to the needs of decision-makers in Member States. Further information can be found in the *WHO Handbook for guideline development* (6).

¹ Data and Safety Monitoring Board may also be known as a Data Monitoring Committee (DMC).

VCAG reviews of applicant submissions

Intervention class: Bait stations

Intervention: Attractive targeted sugar baits (ATSBs)

Applicant: Westham / Innovative Vector Control Consortium (IVCC)

Background

Attractive targeted sugar baits (ATSBs) are designed to attract and kill sugar-seeking mosquitoes. As both male and female mosquitoes feed on plant-derived sugars to maintain energy for survival, the ATSB exploits the almost daily need for sugar by baiting the mosquitoes to a source that also contains a toxicant that kills them.

The ATSB concept was first reviewed by VCAG in late 2014. In 2015, a two-year proof-of-concept entomological study was initiated in seven treated and seven untreated villages in Mali. The study was performed through a collaboration between Westham and the IVCC. In the eighth VCAG meeting (May 2018), the applicants presented a summary of their study in Mali, which demonstrated that the product reduces mosquito populations and the survivorship of individual mosquitoes and decreases the frequency of mosquitoes with malaria parasites, while posing no significant risk to non-target organisms.

In parallel, the applicants presented a draft protocol for three epidemiological trials planned for Kenya, Mali and Zambia. In the 10th VCAG meeting (May 2019), the applicants provided detailed updates on their draft protocols for trials in the three countries. The team provided an overview of the status of manufacturing for the product and related baseline entomological data for Kenya and Zambia.

Updates

At this meeting, the applicants submitted a revision of their epidemiological trial design and the associated SAP for trials. The main modification was the incorporation of a planned analysis after one year (with adjusted sample size calculations) into the trial design. This aims to facilitate the detection of any unanticipated and large effect size consistent with 'overwhelming benefit' before the end of the two-year trial.

The team continues to refine the prototype of their product that is intended for use in the final trial and is conducting product optimization to ensure product durability under field conditions.

Summary of discussions

Initial discussion of the submission focused on the draft SAP and the implications of the proposed interim analysis for the duration of epidemiological trials. The applicants clarified that even if interim analysis revealed 'overwhelming benefit' after one year, their aim would be to continue data collection until the original end date in order to provide further information on safety and efficacy. Therefore, the applicants are not seeking permission to end the trial early if 'overwhelming benefit' is found, but to present these results to VCAG early if warranted and thus initiate the WHO process of developing a recommendation for this intervention earlier than would otherwise be the case. The applicants acknowledged that observing 'overwhelming benefit' may be unlikely, but they still see value in exploring this potential opportunity to shorten the time to a WHO recommendation.

Several changes would need to be made to the Master Trial Protocol to accommodate the proposed interim analysis and other updates mentioned in the presentation. The applicants clarified that they plan to revise the protocol to match the SAP after feedback from VCAG regarding the possibility of interim analysis. The applicants also mentioned that other interventions (RTS,S vaccine, seasonal malaria chemoprevention) may be implemented in their study sites.

Given the potential sensitivity of the ATSB to competition from natural sugar sources, there was discussion about incorporating a proxy for vegetation density in study clusters, either during stratification or as a covariate in analysis. The applicants are proposing to use human population density within clusters as an indirect proxy and to include this in the restricted randomization. They also mentioned that their collaborators are planning to carry out botanical surveys in the trial sites. VCAG also highlighted some additional satellite-derived data on vegetation that could be of use to the applicants for cluster-level characterization.²

There was discussion of the current status of the ATSB prototype. At the last VCAG review, the applicants explained that further work was ongoing to optimize and finalize the ATSB product for use in epidemiological trials. Since then, progress has been made with the prototype; the applicants have identified a remaining technical issue concerning the product stability in conditions of heavy rainfall and are in the process of validating the solution. Consequently, the start date of the trials has been pushed back from 2020 to the end of 2021. The applicants have set a final deadline of the third quarter of 2021 for product resolution. Epidemiological trials will not be initiated if the applicants are not satisfied that the product has met the required standard by this time.

Conclusions

VCAG was pleased to see the ongoing development and progress of this intervention, including the initiation of small-scale entomological trials in the proposed Zambian and Kenyan trial sites, drafting of the SAP, and further work on product optimization. The efforts made by applicants to address VCAG's recommendations from previous reviews were also noted. Most of these recommendations have been addressed, while others remain pending, as they relate to plans for the start of the trials.

Similar to the applicants, VCAG recognizes the ongoing delays with the finalization of the product prototype as the major barrier to progress. VCAG reiterates the need for the applicants to prioritize resolving this issue. If the final product for use in the trials differs considerably from the earlier prototypes used to obtain baseline entomological data, it may be necessary to provide bridging data to aid interpretation of the results from different stages. Ideally, data provided to WHO to inform its vector control evaluation process are generated using a product ready for mass production, rather than one or more prototypes and a final product.

VCAG considers the plan for the proposed analysis at one year to be generally sound in terms of having a clear a priori definition of procedures and trigger points, and appropriate adjustments to the study design to mitigate against any loss of statistical power should the study be stopped early. However, given the applicants' desire to continue data collection over two years, they should obtain confirmation that their DSMB will not require trials be stopped early in the event of 'overwhelming benefit'.

The Master Trial Protocol previously endorsed by VCAG (3) is now out-of-date with respect to the changes introduced in the draft SAP and others described in the presentation. VCAG will need to review an updated version of the protocol that is consistent with the SAP before formal endorsement.

Recommendations

Statistical analysis plan. VCAG views the general principles of the plan to be appropriate, but requests some further detail and clarification before expressing its full support for the planned trials. Requested revisions are listed below. Additionally, applicants will be provided with a separate annotated version of the SAP where further requests for minor edits and clarification are indicated.

² Examples of other satellite-derived data are MODIS satellite, which estimates vegetation indices with pixels of 250m size every 16 days (<https://modis.gsfc.nasa.gov/data/dataproduct/mod13.php>), and the European Space Agency's Land Cover for Africa, with 20m resolution (<http://2016africalandcover20m.esrin.esa.int/>).

- i. VCAG recommends that applicants provide a full list of all pre-planned primary and secondary statistical analyses, including specification of covariates and other details of the model structure. VCAG would not recommend adjustment for covariates within the primary analysis. When pre-specifying covariates, VCAG suggests that the applicants bear in mind guidance such as that from the European Medicines Agency (7).
- ii. The SAP and associated revised protocol should provide a clearer explanation of how temporary absences of participants from their homes will be taken into consideration when computing person-time.
- iii. During the presentation, the applicants mentioned a plan to select more clusters than needed in order to provide a buffer that would allow some clusters to be dropped in the event of difficulties with accessibility or zero cases. The SAP and associated documents should provide a description of this plan, including whether clusters will be excluded from the analysis and/or the study follow-up, and the pre-defined rules for dropping clusters.
- iv. The SAP states “Randomization will be conducted independently for each study site by the designated lead trial statistician”. It is recommended that an independent statistician carry this out.

Interim analysis. VCAG supports the applicants’ plan to incorporate interim analysis after one year to test for ‘overwhelming benefit’. VCAG suggests that applicants seek clarity from their DSMB on whether, in the event of overwhelming benefit being demonstrated, continued data collection would be permitted, and whether such continuation would fall under modified trial procedures.

Protocol. Applicants are requested to update their Master Trial Protocol to match the revised SAP and to submit both documents for VCAG to review the modifications. Applicants should consider whether further changes to sample sizes are needed to account for the potential impact of any other interventions planned in the vicinity of the study sites (e.g., RTS,S vaccine, seasonal malaria chemoprevention).

Entomological data. VCAG recommends that key results from entomological stage gate studies that are being conducted to understand the likely impact of the intervention be shared with VCAG when ready. These data will help VCAG to better understand the entomological impact that may be achieved by ATSBs and will be useful to inform its assessment of the epidemiological trial design and, ultimately, the results of these studies.

Product. VCAG recommends that the applicants ensure the product intended for deployment in the epidemiological trials meets all required entomological stage gate targets. To inform VCAG’s assessment of epidemiological trial results, applicants are requested to ensure that the product prototype deployed in these trials is clearly indicated (e.g., this could be done through the addition of a column in the summary table on entomological studies that was presented at the meeting, indicating which prototype version was used at each stage). Such an overview may also be valuable for the WHO prequalification assessment of the intervention.

Intervention class: Lethal house lures

Intervention: Eave tubes (with and without screening)

Applicant: In2Care

Background

The “lethal house lure” intervention type consists of a combination of screening mosquito entry points (such as eaves, windows and doors) and installing eave tubes. In2Care® eave tubes are made of plastic and contain a removable mesh with a static coating that holds powder-formulated insecticides; the tubes are inserted in the eaves of houses during construction or are retrofitted by means of a large drill. The tubes funnel the indoor human-scented air outwards, making the house a lethal lure for host-seeking mosquitoes, provided that other openings are screened with mesh. Lethal house lures aim to reduce mosquito entry by restricting access into houses and by killing host-seeking mosquitoes, thereby lowering the risk of malaria transmission.

The efficacy of the lethal house lure intervention against clinical episodes of malaria was evaluated in a cluster-randomized controlled trial (cRCT) in Côte d’Ivoire. The two-year trial started in April 2017, and the results were presented to VCAG in November 2019. The trial showed a substantial impact on malaria incidence. At present, however, the relative contribution of the tubes and the screening to this impact is unclear, as is the question of whether the deployment of eave tubes on their own, as envisaged by the manufacturer, provides public health value.

To meet the evidence requirements to trigger development of a potential WHO recommendation, it was previously indicated that a second trial should be conducted in a different geographical setting. At the 12th VCAG meeting (June 2020), the applicants presented an initial proposal for this second trial – a factorial cRCT to evaluate eave tubes as a standalone intervention and in combination with screening – in the United Republic of Tanzania. VCAG expressed its support for the draft design of the four-arm trial and its capacity to generate valuable data to enable assessment of the potential public health value of each of the two components of the lethal house lure intervention, as well as their combined impact. Additional epidemiological evidence would be required to build an adequate evidence base to evaluate the public health value of eave tubes in the absence of house screening.

Updates

For this meeting, the applicants submitted updates on further data arising from the Côte d’Ivoire cRCT with respect to insecticide resistance. The final epidemiological results from this trial are included in a manuscript that is currently under review. The applicants indicated that this manuscript will be shared with VCAG when it is ready.

The applicants also submitted requests to VCAG for more clarity on what degree of epidemiological impact would need to be shown for the eave tubes in the planned cRCT in the United Republic of Tanzania, and to which comparator this would apply for evaluating the epidemiological impact of eave tubes alone.

The applicants are proposing to conduct follow-on studies in their previous cRCT trial site in Côte d’Ivoire and asked for VCAG’s guidance on how to design this trial in order to obtain data that would be considered acceptable for demonstrating a standalone impact of eave tubes. They also asked whether it would be possible to submit interim data after one year, with a view to fast-tracking the process of developing a WHO recommendation for this intervention.

Funding has been received from the Bill & Melinda Gates Foundation for a pilot implementation of eave tubes (with screening) at an agricultural estate in the United Republic of Tanzania (October 2019), which aims to protect staff living on site. Finally, the applicants also mentioned the possibility of a trial of eave tubes alone (without screening) in Uganda.

Summary of discussions

In most respects, the information submitted to VCAG was clear. VCAG responded to several questions from the applicants.

In response to the applicants' question about the desired effect size for the Tanzanian trial, VCAG indicated that this is clarified in the recently published WHO document outlining the norms, standards and processes for evaluating novel vector control interventions (1). The document articulates that WHO does not pre-define target effect sizes for establishing public health value. It is for the applicants to propose an anticipated effect size based on current understanding of the intervention, and to design trials that are powered to show a statistically significant impact of the intervention over the current standard of care. VCAG evaluates the protocols and trial results to determine whether this has been achieved. During the process of developing a WHO recommendation, a Guideline Development Group will take into consideration the effect size achieved, the confidence in the estimates, and other factors such as cost-effectiveness and logistics in formulating a recommendation for the intervention.

As indicated in the VCAG-approved cRCT design for the United Republic of Tanzania, the main treatment comparison in the Tanzanian trial will be between eave tubes plus screening and a control arm. The approved design includes an assumed effect size of 38% for the combined intervention, in line with the results from the first trial, and an assumed mean incidence of 0.3 malaria cases per child per year with a coefficient of variance of 0.3. The proposed 12 clusters per arm with 50 children per cluster for 18 months is anticipated to obtain 80% power at the 5% significance level. If the criteria specified in the power analysis are met, this factorial design will enable detection of a 28% or greater difference in incidence between eave tubes and no eave tubes (aggregating across the screening groups). VCAG noted that the Tanzanian trial design is not powered to detect any specific effect size for the interaction between the individual arms of eave tubes and screening.

The applicants propose a follow-on trial at the existing Côte d'Ivoire site with the aim of identifying the impact of 'eave tubes alone' by monitoring incidence when the eave tubes are maintained but window-screening is allowed to naturally deteriorate. VCAG agreed that further studies and follow-up could potentially add to the evidence base on the sustainability of combined eave tubes/house-screening interventions, and possibly provide evidence on the impact of eave tubes alone. However, the evidence of public health impact generated from such a follow-on trial would carry less weight than from a cRCT because (i) the allocation of deterioration of window-screening is non-randomized; and (ii) there is uncertainty in how fast the screening will deteriorate or reach the point at which it can be guaranteed it is no longer part of the intervention. An approach to address these limitations should be provided in the protocol. In addition to the specific recommendations (see below), VCAG requested the applicants to consider the following issues in the design of this follow-on study:

- It may be more practicable to base longer follow-up on cross-sectional surveys, rather than on further analysis of the original cohort, owing to the gap in follow-up and decreases in event rates as the cohort ages. Cross-sectional surveys might also include younger participants.
- The existing control arm is not appropriate as a control group for a trial enrolling more clusters. However, a randomized stepped wedge roll-out of eave tubes alone across the existing control arm might be possible. There was originally a commitment to roll out to the control arm in the event that the intervention was successful and VCAG records its regret that this was not funded.

In response to the applicants' question about the need for entomological data collection within further epidemiological studies in Côte d'Ivoire, VCAG emphasized that it is crucial to characterize the entomological context in order to understand how the intervention works and what limits its effectiveness. Therefore, it is in the applicants' interest to collect these data whenever possible.

The issue of interim analysis of the Côte d'Ivoire trial was raised with short notice when the applicants received the new document outlining WHO's norms and standards for vector control evaluation (1). In general, VCAG is open to the inclusion of interim analysis in trial design where this is well justified. Therefore, VCAG is open to the applicants' proposal to conduct an interim analysis in the Côte d'Ivoire eave tubes-only trial. However, the applicants should refer to the guidance in the report of the eighth VCAG meeting (3) (especially regarding the role of the DSMB in any interim analysis) and WHO's latest norms and standards document (1). The process of developing a potential WHO recommendation for eave tubes as a standalone intervention will depend not only on the results of the interim analysis, but also on the rest of the available evidence, and will only commence once data on epidemiological impact are available from two separate trials. The applicants should be aware that evidence arising from interim analysis may carry less weight than that generated over a longer trial period. Applicants are thus referred to the recently published WHO document *Norms, standards and processes underlining WHO vector control policy recommendations (1)*, which addresses factors, including study duration, that may impact the strength of the evidence used to inform the formulation of WHO recommendations. Although not a WHO requirement (and provided it is consistent with the protocol and ethical considerations), VCAG sees value in continued follow-up of a shorter trial in order to address questions of consistency (to avoid short-term positive impact bias), durability of the impact with varied transmission dynamics (inter-annual variability), and biological (immunity) and socio-behavioural effects that are not easily observed in a shorter duration follow-up.

Conclusion

VCAG congratulates the applicants on the substantial progress made and on the informative submission. The plans outlined for the cRCT trial in the United Republic of Tanzania should be sufficient to estimate the impact of eave tubes on their own (which would count as the first demonstration of such effect) and in combination with window-screening (which, with the data from the Côte d'Ivoire trial, would count as the second demonstration of such effect for the lethal house lures intervention). The process for developing a potential WHO recommendation for lethal house lures could therefore commence once data from the Tanzanian trial are provided to WHO.

Recommendations

VCAG recommends that:

- *Côte d'Ivoire follow-on study*: In advance of further follow-up of the Côte d'Ivoire site, the applicants are requested to share with VCAG a clear protocol and analysis plan.
 - *Window-screening*: Given that there is some evidence that window-screening provides protection from malaria transmission (8), active removal of window-screening should not be carried out as part of these studies.
 - *Entomological data*: The collection of data on insecticide resistance is crucial for the interpretation of findings from these studies, given that a different insecticide class is proposed from that used in the previous trial. Other information on vector biting rates and behaviour could also be informative if data collection is feasible.
- *Interim analysis*: If the applicants intend to include an interim analysis or shorten the trial duration, both the revised protocol and SAP should be shared with VCAG for review. The purpose and procedures for interim analysis should be documented in the protocol, including any consequences for provision of the intervention to control groups, stopping rules and the required statistical adjustments. If the applicants were to propose a shortened trial duration, the statistical adjustments made to ensure sufficient power would be of particular interest.

Intervention class: Reduced pathogen transmission induced by *Wolbachia*

Intervention: *Wolbachia* (wMel)-infected *Aedes aegypti*

Background

This strategy involves the introduction of *Wolbachia*, a naturally occurring obligate intracellular bacteria, into a population of *Aedes aegypti* mosquitoes. *Ae. aegypti* that carry the *Wolbachia* strain wMel are significantly less capable of transmitting arboviruses that they imbibe from an infected human host. This applies not only to dengue virus, but also to Zika and chikungunya viruses. As a result, stable *Wolbachia* introgression largely renders *Ae. aegypti* populations incapable of sustaining pathogen transmission. Following establishment of *Wolbachia* in the *Ae. aegypti* population, 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* (wMel) has been successfully introduced into *Ae. aegypti* populations in numerous countries and continents, where community support for the release of *Wolbachia*-carrying mosquitoes has generally been positive.

Applicant: World Mosquito Program (WMP)

The WMP group has been engaging with VCAG since 2014. At the height of the Zika virus crisis in 2016, the former WHO Director-General convened an emergency meeting of VCAG to potentially fast-track some of the tools for *Aedes* control, including emergency deployment of *Wolbachia* to reduce arbovirus transmission (10). WMP's most recent interaction with VCAG was in May 2018, when they presented the Applying *Wolbachia* to Eliminate Dengue (AWED) trial planned for Yogyakarta, Indonesia, and the novel test-negative study design employed in this trial (reviewed in the eighth VCAG meeting report (3)). At that time, VCAG recommended that the applicants continue longitudinal monitoring of *Wolbachia* in release sites and undertake plans for a second trial with epidemiological endpoints (alongside the AWED trial) in order to generate evidence of public health value against dengue.

Updates

The applicants shared with VCAG a comprehensive data package consisting of results from the AWED cRCT conducted in Yogyakarta, Indonesia, along with four other non-randomized but controlled studies that have been conducted in countries both endemic for dengue (Indonesia, Brazil, Viet Nam) and non-endemic but outbreak-prone (Australia). The latter studies had not previously been shared with or reviewed by VCAG.

The data resulting from their recently completed cRCT in Yogyakarta, Indonesia demonstrated 77% protective efficacy against virologically confirmed dengue. The intervention further provided 86% efficacy against dengue hospitalization. The supporting data from the non-randomized trials showed similar trends, consistent with the magnitude of intervention effect observed in the cRCT in Yogyakarta.

Summary of discussions

In presenting the submission to VCAG, the applicants highlighted that no intervention against *Ae. aegypti* has yet received a positive assessment of public health value by the advisory committee. Data were presented from the recently completed AWED cRCT in Indonesia, which demonstrated a large (77%) and statistically significant reduction in virologically confirmed dengue cases in areas where wMel-infected *Ae. aegypti* had been released and wMel had introgressed into the local mosquito population, compared to areas without wMel releases. These findings were presented together with findings from four non-randomized trials that also demonstrated a similar level of epidemiological impact. In doing so, they fulfilled the requirement for evidence from at least two trials with epidemiological outcomes for assessment of public health value (1).

During the discussion, the applicants addressed questions raised by VCAG. With respect to the minimum levels of *Wolbachia* prevalence/establishment for the intervention to be effective, the applicants stated that empirical evidence is not yet available to inform an understanding of the minimum wMel prevalence needed for epidemiological impact. Future exploratory analyses of the AWED trial and Latin-American releases are planned in order to address this question.

In response to queries about the characteristics of sites where wMel might not become so readily established in the local mosquito population, the applicants acknowledged that there may be some ecological environments where wMel is unstable in the local mosquito population; however, based on global results, wMel is expected to introgress into most dengue-endemic locations.

VCAG asked about potential dilution of effect observed in the AWED trial due to human movement and/or spillover of wMel into untreated control clusters. The applicants indicated that accounting for wMel contamination and human movement between clusters in classifying an individual's wMel exposure did not increase the observed intervention effect size compared to the intention-to-treat result.

When asked why efficacy against hospitalization was greater than efficacy against virologically confirmed dengue, the applicants expressed caution because of the small numbers involved. However, they speculated that if breakthrough virus infections occur in wMel-infected mosquitoes, it might result in a smaller virus inoculum being injected into susceptible hosts.

In relation to the non-randomized trial sites, the applicants also confirmed that monitoring of disease outcomes through the public health surveillance system was planned for five years following the completion of releases.

A question was also raised relating to the cost of the intervention, to which the applicants responded that independent modelling estimates suggest it is already a cost-saving intervention in Indonesia (11) and that the cost of manufacture and deployment are likely to be significantly reduced with scale-up and over longer periods.

During the discussion, a point was raised that if VCAG concludes that the wMel intervention has public health value, it might cause difficulties with ethical committees for other (ongoing) trials using wMel, as it would mean that untreated control groups were not receiving an intervention with known public health benefit. The applicants acknowledged this point, but noted that these decisions would be subject to the individual decisions of the ethics committees. Furthermore, given the timing of the current review and the time taken to develop a WHO recommendation, a VCAG acknowledgement of public health value now may have little impact on the trials currently underway. Even in light of a WHO recommendation being developed, both VCAG and the applicants agreed on the added benefit for national policy-makers and programmes to continue the trials that are currently underway. These will generate additional high-quality, high-certainty evidence in different geographic locations to further inform a WHO recommendation and associated deployment guidance in the coming years.

Conclusion

VCAG concludes that the evidence presented by the applicants on wMel introgression into populations of *Ae. aegypti* demonstrates public health value against dengue.

Recommendations

Based on VCAG's assessment that public health value has been demonstrated, VCAG considers that there are sufficient data for WHO to initiate the guideline development process to formulate a recommendation on the deployment of the wMel intervention for dengue control (1).

Of the non-randomized studies submitted to VCAG, all but one are currently unpublished and hence not yet peer-reviewed. Therefore, VCAG recommends that WHO seek further detail and clarification on several methodological aspects of these studies. For any other studies not reported to VCAG that have shown impact of a smaller magnitude, it will also be important to understand the conditions of such studies in order to better assess the quality and strength of the evidence generated by these trials. Specifically, VCAG recommends that WHO consider the following issues to guide such evidence collation as part of a systematic review that will provide the foundation for deliberations by a WHO Guideline Development Group:

1. For comparing data between areas that did and did not receive the wMel intervention, it is important to know how comparable the areas were and how these areas were selected for comparison.
2. To understand whether observed reductions in incidence are limited in duration, and to provide an estimate of the time it takes for wMel to establish and reduce dengue incidence following introduction, data from longer term studies (several years before introduction [where available] and more than one year after) will be required.
3. There is a need to review any limiting factors (biotic or abiotic) for the deployment of the intervention based on the studies so far.

Applicant: EVITA (led by Emory University)

This is the first VCAG meeting in which the EVITA applicants have interacted with VCAG. The team intends to implement a cluster-randomized trial in Brazil that aims to evaluate the efficacy of *Wolbachia* wMel-infected *Ae. aegypti* mosquitoes in reducing the incidence of arboviral infection (EVITA). While the EVITA trial is being conducted independently of WMP's trials (see above), the teams are collaborating to maximize knowledge transfer and the potential for success of the trial. It is intended to be the second cRCT to generate additional high-certainty evidence in support of *Wolbachia* being used to reduce pathogen transmission by mosquitoes. These data may be used to refine a WHO recommendation for this intervention class and associated deployment guidance.

Initial submission

In their first interaction with VCAG, the EVITA team shared the protocol for the trial they recently began in Belo Horizonte, Brazil. This trial enrolls school-based clusters and focuses on the primary endpoint of seroconversion in children. The primary analysis endpoint will be conducted using a quasi-Poisson regression. A secondary endpoint using modelled estimates of infection timing is proposed, based on a model-based reconstruction of antibody dynamics. The applicants did not provide a detailed SAP, as it is still under development. They did, however, include details on an interim analysis procedure they will follow if there is a large outbreak in any year of their planned three-year trial.

Summary of discussions

The applicants presented their trial protocol and informed VCAG that identification of clusters, enrolment of participants, and allocation of clusters to treatment or control arms has already been completed. There was some discussion about diagnostic checks for constrained randomization. Upon further inspection, the applicants found that there was no cause for concern. There was a discussion around the justification for the planned interim analysis; the applicants re-emphasized that this would only occur in the case of a large outbreak. The large number of seroconversions associated with a large outbreak should provide ample signal to detect an effect of the intervention (90% power to detect an effect size as low as 30%). Moreover, large outbreaks in Belo Horizonte are typically followed by several years of low dengue transmission, so it would be unlikely that continuing the trial would result in a definitive result if one was not found in the interim

analysis. One of the concerns around short trials has been the temporal heterogeneity in transmission of arboviral diseases and the chance that the few years selected for the trial may “miss” an outbreak. This approach partially ameliorates these concerns about trial duration, as the trial may adaptively last longer if there is lower transmission in the early years. This will ensure that statistical power can be reached despite changes in transmission intensity from year to year. VCAG commends the applicants on this approach and agreed that this could be an appropriate approach for other trials in the future.

There was some discussion about an ongoing dengue virus vaccine trial within Belo Horizonte, but the applicants indicated that the vaccine trial is being conducted in a different section of the city and is unlikely to influence the outcome of this trial.

During the discussion, VCAG members noted that the trial protocol had insufficient detail on some aspects of the design, including who would monitor the event rate for the interim analysis, how the trial would monitor factors such as mosquito density and infection rates, and details associated with the power calculations (such as estimated seroconversion rates by age, or details on the sensitivity and specificity of the planned diagnostic tools). It may also be of interest to inspect the movement patterns of the trial participants, as the applicants indicated they enrolled more 11-year-old children than originally planned and these children may leave their respective cluster more frequently than 6- to 8-year-old children (thus introducing more opportunity for a loss of protection/contamination). Furthermore, due to the proposed method/timing of identifying seroconversions, there was some concern that many infections could be missed. Finally, it was noted that a complete and detailed SAP would be useful to understand the planned analyses.

Conclusion

The applicants were congratulated on the commencement of their trial. As the EVITA trial has already begun, any concerns about power calculations or participant identification are academic. However, understanding the nuances around planned analyses may influence the stopping criteria for the interim analysis. VCAG would, therefore, still appreciate seeing a detailed SAP when it is ready. As mentioned during the discussion, the applicants are commended for their adaptive trial duration, as this may avoid some issues associated with the unpredictable nature of arbovirus transmission and the implications this could otherwise have for the power of the study.

Recommendations

The applicants are recommended to provide VCAG with a detailed SAP, as well as more detail on the planned mosquito surveillance. The applicants are encouraged to continue their interactions with VCAG as the trial progresses and to inform WHO in advance of data becoming available to inform its guideline development process.

Intervention class: Spatial repellents

Intervention: Spatial repellents

Applicant: SC Johnson / University of Notre Dame

Background

Spatial repellents are designed to interrupt human–vector contact through vector behaviour modification induced by airborne chemicals, potentially offering protection from the bites of vectors and nuisance pests. The spatial repellent intervention proposed is a transfluthrin-based passive emanator produced by SC Johnson. It is designed to release the volatile pyrethroid into the air and prevent human–vector contact in the treated space. The intervention targets *Anopheles*, *Aedes* and *Culex spp.* mosquitoes, with claims to protect all age groups and populations in countries endemic for mosquito-borne diseases from day-time, early evening and/or late-night biting by

mosquitoes in enclosed and semi-enclosed structures. Deployment of the spatial repellent product in enclosed and semi-enclosed spaces is intended to reduce human pathogen transmission.

Epidemiological trials have been completed on Sumba Island, Indonesia, against malaria, and in Iquitos, Peru against *Aedes*-borne viruses (dengue and Zika). While the Indonesian trial targeting malaria showed protective efficacy, the results were not statistically significant. As such, at least two more trials targeting malaria are needed to demonstrate public health value of this intervention for malaria, and to trigger the development of a potential WHO recommendation for this intervention. These trials are currently planned for Mali and Kenya. For *Aedes*-borne viruses (dengue and Zika), the trial in Peru demonstrated that the spatial repellents significantly reduced arboviral infection. VCAG advised that the successful completion of the trial counted as one of the two trials needed to inform the development of a potential WHO recommendation for deployment of this intervention to control arboviruses. The second trial is currently planned for Sri Lanka.

Updates

The applicants provided updates on the completed trials in Indonesia (*Anopheles*/malaria) and Peru (*Aedes*/arboviruses), as well as plans for three new trials in Kenya (*Anopheles*/malaria), Mali (*Anopheles*/malaria) and Sri Lanka (*Aedes*/arboviruses).

Results of the Indonesian trial were published in *The American Journal of Tropical Medicine and Hygiene* in July 2020 (12). The applicants reported adjusted protective efficacy analyses for subject bed net usage, travel outside clusters, and product application rate. Analyses were completed for multiple primary and secondary outcomes, which are all outlined in the manuscript.

With regard to the trial in Peru, additional analyses indicated a statistically significant 12.5% reduction in the frequency at which female *Ae. aegypti* blood-fed mosquitoes were collected inside houses in the spatial repellent arm compared to baseline. In addition, the baseline characteristics were balanced between spatial repellent and placebo arms, and there was no statistically significant difference in blood-fed collection rates between treatment arms at baseline. Finally, the applicants reported that due to COVID-19, insecticide resistance testing post-intervention was cancelled and cannot be performed.

The applicants presented updates and protocol changes to the three proposed trials previously reviewed by VCAG as follows:

- In the Kenyan trial, the WHO Ethics Review Committee review led to the removal of pregnancy testing, which was part of the protocol, because of the need to avoid clearing parasites with artemether-lumefantrine in pregnant teenagers. The maximum age of the participants has now been reduced to less than 10 years of age to exclude those who might be pregnant.
- It is not yet clear if the same consideration may apply to the Malian trial.
- In the Kenyan trial, the COVID-19 pandemic has led to changes in procedures to reduce contact between KEMRI staff and participants. In particular, human landing collections will be carried out by local villagers, instead of by KEMRI staff.
- In the Malian trial, there is so far no indication that the trial will be affected by the COVID-19 pandemic.
- In Sri Lanka, there has been a change in study location to avoid co-location with the potential *Wolbachia* roll-out by WMP in Colombo.
- Active fever surveillance is not advised in Sri Lanka owing to COVID-19. Febrile individuals will be instructed to attend health facilities for testing for arboviruses.

Summary of discussions

VCAG confirmed that the updates on the additional analyses provided for the trials in Indonesia and Peru responded to the June 2020 VCAG request and thanked the applicants for the updated results. VCAG also appreciated the applicants' inability to undertake post-intervention insecticide resistance testing for the Peruvian trial, given the shut-down of study team field activities due to COVID-19 that extended into the close-out of programme period of performance.

During the discussion of the three new trials in Kenya, Mali and Sri Lanka, VCAG requested clarification on the implications of the COVID-19 pandemic for the respective plans. The applicants responded that the COVID-19 pandemic has had varied implications for the operations and procedures of the different trials (see "Updates" above); however, implementation of the trials remains as originally proposed.

In terms of the Sri Lankan study, it was confirmed that both solicited (of interest) and unsolicited adverse events will be documented in addition to those classified as "events of interest", and that this point will be clarified in the protocol. VCAG also requested clarification as to whether the number of sentinel houses (used to measure diversionary effects) recruited for each study cluster will be based on the structural features of houses in the cluster, or whether a fixed proportion of total houses in a cluster will be used. The applicant responded that the number and nature of the sentinel houses used to study diversionary effects in the Sri Lankan trial will be determined following the mapping and census activities at the time of trial implementation. This is because pre-defining an arbitrary proportion of additional homes (e.g., 5% to 10%) for diversionary effects may exceed resources if clusters have a high number of homes; if this is the case, then a fixed number of houses will be set, taking into account different structural/physical features of homes.

In light of WHO's new document outlining the norms, standards and processes for evaluating vector control interventions (1), the applicants raised additional questions for VCAG to consider:

1. The possibility of exploring varying effect sizes for the Sri Lankan RCT (i.e., > 30%) and impact on sample size.
2. The possibility of exploring varied follow-up for the Sri Lankan RCT (< 2yr) and impact on sample size/probability of seroconversion for primary analysis.
3. VCAG's position on an interim analysis of the Kenyan trial that would potentially shorten the duration to one year.

Responses to these questions are provided in the below conclusions.

Conclusion

VCAG congratulates the applicants on the two completed trials in Indonesia and Peru, which provide considerable information that contributes to the evidence base for the intervention, against both *Anopheles* and *Aedes*. VCAG also confirms that there are no additional requests for further analyses from the Indonesian database, nor requests for further updates on the Peruvian analyses.

With regard to the new trials, VCAG concludes that the planning to date is suitable for generating the required evidence base to enable assessment of the public health value of this intervention. VCAG supports the proposed approach to study diversionary effects in the Sri Lankan trial. It also notes that the Malian trial plan may need to be adjusted, as was done for the Kenyan study, under the assumption that the WHO Ethics Review Committee may also request the maximum age of the participants be reduced to exclude those who might be pregnant.

With regard to the applicants' questions concerning potential adjustments to the Sri Lankan and Kenyan trial protocols, given the recent publication updating information

on WHO's evaluation process for vector control interventions (1), VCAG is open to the applicants' suggestions to vary the effect size and follow-up duration and make the associated changes to the Sri Lankan protocol. Under the assumption that trials have yet to be initiated, VCAG is open to the applicants' suggestion to amend the SAP and include an interim analysis, or more appropriately stated, a primary analysis review for the Kenyan trial. Where reduced trial duration is counterbalanced by increased sample sizes and the trial remains adequately powered to detect an effect, trial results could be presented to VCAG earlier than anticipated. Applicants are referred to the recently published WHO document *Norms, standards and processes underlining WHO vector control policy recommendations (1)*, which addresses factors, including study duration, that influence WHO recommendations.

Recommendations

If the applicants decide to adjust the effect size and/or the follow-up duration in the Sri Lankan trial, VCAG recommends that the justification and the required adjustments be made to the protocol and SAP, and that these documents be shared with VCAG for review.

Although not a WHO requirement, VCAG sees value in continued follow-up of a shorter trial in order to address questions of consistency (to avoid short-term positive impact bias), durability of the impact with varied transmission dynamics (inter-annual variability), and biological (immunity) and socio-behavioural effects that are not easily observed in a shorter duration follow-up.

Minor recommendations

- In the Sri Lankan trial, clarify the protocol that both solicited (of interest) and unsolicited adverse events and severe adverse events will be captured.
- Review the feasibility of recruitment for the required numbers of subjects within the narrow age range for the Kenyan trial and update the power calculations; do so for the Malian trial as well if needed.

Intervention class: Treatment of humans and/or livestock with systemic endectocides

Intervention: Endectocides (Ivermectin)

Applicant: BOHEMIA, ISGlobal

Background

This intervention involves mass drug administration (MDA) of a systemic endectocide (ivermectin) to humans and/or the livestock that surround the communities in order to kill the insects that feed on them. The rationale is that female mosquitoes will feed on ivermectin-treated hosts, taking up blood meals containing a sufficiently high concentration of the drug to kill them. The drug may also have additional sublethal effects that impact vector populations (e.g., reductions in mosquito fertility and fecundity).

The objective of the Broad One Health Endectocide-based Malaria Intervention in Africa (BOHEMIA) project is to determine the efficacy of ivermectin delivered by MDA either to humans alone or to humans and livestock in order to reduce transmission of malaria. The BOHEMIA project consists of a combination of studies organized around two cluster randomized trials: one in Mozambique and the other in the United Republic of Tanzania. The target livestock species are pigs and cattle, respectively. Four sub-studies (social science, entomology, health economics and animal health, and environmental impact) will be carried out in both countries, and each has an independent protocol.

Several ongoing malaria trials with ivermectin are being conducted by groups not engaging with VCAG; the results emerging from such trials will be included in a systematic review once data from the BOHEMIA trials are available in order to inform the development of a potential WHO recommendation for ivermectin as an endectocide.

Updates

As well as responding to VCAG's suggestions from the previous review, the applicants made several changes to their protocol in response to the COVID-19 pandemic. Most significantly, the applicants propose evaluating the main efficacy and safety endpoints in a single season, with an efficacy read-out during the six months following the first drug dose. Additional evaluations of efficacy will also take place four months following the third dose, allowing for monitoring of the efficacy curve after the drug half-life has depleted.

In parallel, the study design was altered to address some of the challenges of the COVID-19 pandemic. The trial is still cluster randomized and controlled with three arms (ivermectin in humans vs. ivermectin in humans and livestock vs. control-albendazole), but it is now open label; this was necessary due to the challenges associated with obtaining, manufacturing and shipping a placebo at this time. There has been a minor increase in cluster size to optimize this analysis, and the trials remain robustly powered. The applicants anticipate that the net effect of these changes on a clear efficacy read-out will not change the 2022 timeline. The timeline applies equally to the human ivermectin and human–veterinary ivermectin arms, compared to control.

Summary of discussions

VCAG appreciated the need to change the study design due to the pandemic. Notwithstanding the protocol change, VCAG noted that the applicants had, overall, reasonably addressed previous suggestions.

In particular, the primary objective no longer implies an assessment of livestock safety; the statistical method for the primary objective will be a mixed effects Poisson regression model; clarification was made that the dosimetry is based on whole blood; a revised method for assessing bed bug infestations is outlined; and the entomology protocol was provided. In terms of the adjustment for multiple comparisons, the applicants had specified the Bonferroni method, although this is being reviewed with the DSMB statistician. Finally, a procedure was described for selecting variables for the final statistical analysis model.

VCAG asked whether the applicants had considered clearing infections before the start of follow-up in order to better measure incident infections. The applicants mentioned that this is not envisaged since infections detected by rapid diagnostic test (RDT) at enrolment would be treated. However, VCAG noted that, since ivermectin has no direct impact on malaria parasites in humans, pre-existing infections that are detected only after the start of the trial may bias the estimation of the intervention effect towards the null. In low-transmission settings, RDTs may only detect a third of asymptomatic infections (13) and asymptomatic *P. falciparum* infections may go undetected for some time (14).

Conclusion

A summary of conclusions drawn from the revised protocol is presented below.

Duration of arms. The applicants have reduced the duration to one year for three arms (human ivermectin dosing, human and livestock dosing, and albendazole control). There have also been some adjustments to the cluster sizes to address power considerations.

Blindness. The trial is now controlled (ivermectin vs. albendazole) but open label to address difficulties of obtaining, manufacturing and shipping a true placebo given the

pandemic. Both the intervention and control groups will experience a deworming effect. However, the protocol refers to unblinding in the case of serious adverse event (SAE), which presumably is an editorial error.

Human–livestock ratio. Cattle are the dominant livestock in the United Republic of Tanzania, while pigs are the dominant species in Mozambique. Livestock census should be completed by the third quarter of 2021 to enable clusters to be stratified at least six months prior to the trial. The United Republic of Tanzania prohibits the movement of cattle between districts; movement of cattle within districts will be assessed in the census. There are some feral pigs in Mozambique, but likely not enough to shift the human–livestock ratio appreciably. Blood meal analyses to identify host species will be undertaken as part of the entomological surveillance in advance of the trial interventions. Findings from these analyses should be available by the end of 2021.

Entomology protocol. The core entomological methods are suitable. However, the protocol still refers to the previous two-year study duration. It also refers to statistical analysis of mosquito counts as yielding incidence rate ratios, which may be confusing given that incidence of malaria will be addressed in other analyses.

Statistical analysis. The protocol envisages that several variables could be included in the final model, depending on the results of the selection procedure. VCAG suggests that the applicants consider existing guidance; e.g., European Medicines Agency (7).

Adequacy of revised study design. The trial is powered for one year, but the degree of evidence will be reduced given the short trial period, especially with respect to inter-annual variation of environmental and entomological factors, as well as household and community behaviour and livestock husbandry. The applicants are referred to the recently published WHO document *Norms, standards and processes underlining WHO vector control policy recommendations (1)*, which addresses factors, including study duration, that influence policy formulation.

Recommendations

VCAG supports proceeding with the new study design with recommendations on the following points:

1. The main trial and entomological protocols need to be edited and revised to consistently reflect the new study design, in particular in terms of duration and blinding.
2. To partially address VCAG's concerns about the generalizability of the results obtained in one year, it would be useful to collect data on environmental and entomological parameters during the study and compare these data to historical records to the extent they are available. Such parameters may overlap with the "planning factors" of WHO's recent publication on the norms and standards for evaluating vector control interventions (1).
3. Given that cattle and pigs are the dominant livestock in the United Republic of Tanzania and Mozambique, respectively, it is possible that the generalizability of the results could be limited if the human–livestock intervention is effective in only one country. Collection of livestock biting rates and blood meal data should be considered as a means to help interpret the trial results.

The following is a minor point of clarification for the protocol:

4. Any remaining references to unblinding, e.g., for SAE, should be removed from the efficacy and safety protocol.

CONCLUDING REMARKS OF THE MEETING

The meeting was concluded with the WHO VCAG Secretariat and Chairs thanking VCAG members for their contributions leading up to and during the meeting. The submissions made by VCAG applicants were of high quality, and numerous interventions are making considerable and rapid progress in generating evidence to inform assessment of their potential public health value. The meeting marked the first time that VCAG has provided a positive assessment of the public health value of a novel vector control intervention class (reduced pathogen transmission induced by *Wolbachia*), establishing the basis for WHO to initiate the guideline development process with a view to providing a recommendation for this intervention.

In light of the continuing COVID-19 pandemic, it is intended that the next meeting will again be held virtually. It is planned for the week of 19 to 23 April 2020.

REFERENCES

1. Norms, standards and processes underpinning WHO vector control policy development. Geneva: World Health Organization; 2020 (<https://www.who.int/publications/i/item/9789240017382>, accessed 3 January 2021).
2. Ending the neglect to attain the Sustainable Development Goals: a road map for neglected tropical diseases 2021–2030. Geneva: World Health Organization; 2020 (<https://www.who.int/publications/i/item/9789240010352>, accessed 3 January 2021).
3. Eighth meeting of the Vector Control Advisory Group. Geneva: World Health Organization; 2018 (<https://www.who.int/vector-control/publications/eighth-vcag-meeting-report/en/>, accessed 3 January 2021).
4. Campbell MK, Piaggio G, Elbourne DR, Altman DG, CONSORT Group. CONSORT 2010 statement: extension to cluster randomised trials. *BMJ*. 2012;345:e5661. doi:10.1136/bmj.e5661
5. Adaptive designs for clinical trials of drugs and biologics: guidance for industry. Silver Spring, MD: U.S. Department of Health and Human Services, Food and Drug Administration; 2019 (<https://www.fda.gov/media/78495/download>, accessed 3 January 2021).
6. WHO handbook for guideline development, 2nd edition. Geneva: World Health Organization; 2014 (<https://apps.who.int/iris/handle/10665/145714>, accessed 3 January 2021).
7. Guideline on adjustment for baseline covariates in clinical trials. Amsterdam: European Medicines Agency; 2015 (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-adjustment-baseline-covariates-clinical-trials_en.pdf, accessed 3 January 2021).
8. Tusting LS, Ippolito MM, Willey BA, Kleinschmidt I, Dorsey G, Gosling RD, Lindsay SW. The evidence for improving housing to reduce malaria: a systematic review and meta-analysis. *Malar J*. 2015;14:209. doi:10.1186/s12936-015-0724-1
9. Brady OJ, Kharisma DD, Wilastonegoro NN, O'Reilly KM, Hendrickx E, Bastos LS, et al. The cost-effectiveness of controlling dengue in Indonesia using wMel Wolbachia released at scale: a modelling study. *BMC Med*. 2020;18:186. doi:10.1186/s12916-020-01638-2
10. Mosquito (vector) control emergency response and preparedness for Zika virus, 18 March 2016. Geneva: World Health Organization; 2016 (https://www.who.int/neglected_diseases/news/mosquito_vector_control_response/en/, accessed 3 January 2021).
11. O'Reilly KM, Hendrickx E, Kharisma DD, Wilastonegoro NN, Carrington LB, Elyazar IRF, et al. Estimating the burden of dengue and the impact of release of wMel Wolbachia-infected mosquitoes in Indonesia: a modelling study. *BMC Med*. 2019;17:172. doi:10.1186/s12916-019-1396-4
12. Syafruddin D, Asih PBS, Rozi IE, Permana DH, Hidayati APN, Syahrani L, et al. Efficacy of a spatial repellent for control of malaria in Indonesia: a cluster-randomized controlled trial. *Am J Trop Med Hyg*. 2020;103:344–358. doi:10.4269/ajtmh.19-0554
13. Sumari D, Mugasa J, Selemani M, Shekalaghe S, Mugittu K, Gwakisa P. Prevalence of submicroscopic *Plasmodium falciparum* infections in asymptomatic children in low transmission settings in Bagamoyo, Tanzania. *MalariaWorld J*. 2016;7. <https://core.ac.uk/display/77102233>
14. Nguyen TN, von Seidlein L, Nguyen TV, Truong PN, Hung SD, Pham HT, et al. The persistence and oscillations of submicroscopic *Plasmodium falciparum* and *Plasmodium vivax* infections over time in Vietnam: an open cohort study. *Lancet Infect Dis*. 2018;18(5):565–572. doi:10.1016/S1473-3099(18)30046-X

ANNEX 1. DECLARATIONS OF INTEREST

Before the meeting, all VCAG members and invited experts completed forms for declarations of interests for WHO experts. The VCAG Secretariat assessed the interests declared by the experts and, except for those described below, found that the interests were not directly related to the topics under discussion at the present meeting.

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

Dr Camilla Beech (Cambea Consulting, UK) participated in consultancy work reviewing a regulatory dossier for the World Mosquito Program in early 2020. Regulatory dossiers do not fall under the remit of VCAG.

- *Conclusion and action:* Dr Beech's completion of this consultancy is acknowledged. She was not part of the working group for the *Wolbachia* wMel WMP submission and, as such, did not have access to the submitted documents. Dr Beech was able to participate in the discussion on the applicant submission with the whole group.

Dr Mamadou Coulibaly (University of Science and Technology of Bamako, Mali) declared a conflict of interest with the spatial repellents submission.

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

Prof Immo Kleinschmidt (London School of Hygiene and Tropical Medicine, UK) is participating in this VCAG meeting as an ad hoc expert for the review of the two *Wolbachia* submissions. Prof Kleinschmidt chaired the independent Data and Safety Monitoring Board for the AWED trial that is being reviewed by VCAG at this meeting.

- *Conclusion and action:* Prof Kleinschmidt is no longer performing this role on the DSMB as the trial is completed, but his previous participation on the board is acknowledged. Prof Kleinschmidt is on the working group for the applicant group presenting the AWED trial, and helped develop and draft the recommendations in the report.

Dr Audrey Lenhart (United States Centers for Disease Control and Prevention, USA) is an external scientific advisory board member for the spatial repellents project.

- *Conclusion and action:* Dr Lenhart's involvement in the advisory board is acknowledged. She was not part of the VCAG review group for the spatial repellents submission and, as such, did not have access to the submitted documents. Dr Lenhart was able to participate in the discussion on the applicant submission with the whole group.

Prof Phil McCall (Liverpool School of Tropical Medicine, UK) is participating in this VCAG meeting as an ad hoc expert for the review of the two *Wolbachia* submissions. Prof McCall participated in a research meeting in 2019 on *Wolbachia* research direction in Brazil as an independent advisor. His attendance at the meeting was supported by the World Mosquito Program.

- *Conclusion and action:* Prof McCall is not involved with the research program of the World Mosquito Program, but his previous participation in a research

meeting is acknowledged. Prof McCall is on the working group for the EVITA trial, which is based in Brazil, and helped to develop and draft the recommendations in the report.

Dr Hilary Ranson (Liverpool School of Tropical Medicine, UK) had a consultancy in 2018 with the World Mosquito Program, with fees received by her employer.

- *Conclusion and action:* Dr Ranson's completion of this consultancy is acknowledged. She was not part of the VCAG review group for the WMP submission and, as such, did not have access to the submitted documents. Dr Ranson was able to participate in the discussion on the topic with the whole group.

Dr Robert Reiner (Institute for Health Metrics and Evaluation, USA) is involved with the spatial repellents submission, as a co-applicant.

- *Conclusion and action:* Dr Reiner did not have access to related documentation as a VCAG advisor, nor did he participate in the closed discussions or in the drafting and finalization of the recommendations on the spatial repellents submission.

Dr Leanne Robinson (Burnet Institute, Australia) declared a conflict of interest with the spatial repellents submission.

- *Conclusion and action:* Dr Robinson did not have access to related documentation, nor did she participate in the closed discussions or in the drafting and finalization of the recommendations on the spatial repellents submission.

ANNEX 2. LIST OF PARTICIPANTS

VCAG MEMBERS

Co-Chairs

Salim ABDULLA

Ifakara Health Institute
Ifakara, United Republic of Tanzania

Heather FERGUSON

University of Glasgow
Glasgow, United Kingdom

Members¹

Neal ALEXANDER

Centro Internacional de Entrenamiento et
Investigaciones Médicas (CIDEIM)
Cali, Colombia

Camilla BEECH

Cambea Consulting Ltd
Berkshire, United Kingdom

Steven BRADBURY

Iowa State University
Iowa, United States of America

Fabrice CHANDRE

Institut de recherche pour le développement
Montpellier, France

Mamadou COULIBALY

University of Science and Technology of Bamako
Bamako, Mali

Audrey LENHART

US Centers for Disease Control and Prevention
Atlanta, GA United States of America

David O'BROCHTA

The Foundation for the National Institutes of Health
North Bethesda, United States of America

Robert REINER

University of Washington
Seattle, United States of America

Hilary RANSON

Liverpool School of Tropical Medicine
Liverpool, United Kingdom

Leanne ROBINSON

Burnet Institute
Melbourne, Australia

Thomas SMITH

Swiss Tropical Institute
Basel, Switzerland

Alfred TIONO

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

TEMPORARY ADVISORS

Immo KLEINSCHMIDT

London School of Hygiene and Tropical Medicine
London, United Kingdom

Philip MCCALL

Liverpool School of Tropical Medicine
Liverpool, United Kingdom

Stephen WATERMAN

Centers for Disease Control and Prevention
San Juan, Puerto Rico

Elie AKL

American University of Beirut
Beirut, Lebanon

PARTICIPANTS

Attractive targeted sugar baits (ATSBs)**Julian ENTWISTLE**

Innovative Vector Control Consortium

Amir GALILI

Westham

Helen JAMET

B&M Gates Foundation

Immo KLEINSCHMIDT

London School of Hygiene and Tropical Medicine

Megan LITTRELL

PATH

David MALONE

B&M Gates Foundation

Mathias MONDY

Innovative Vector Control Consortium

Endectocides**Kelsey BARRETT**

Unitaid

Carlos CHACCOUR

ISGlobal

Regina RABINOVICH

ISGlobal

¹ Kalpana BARUAH, National Vector Borne Disease Control Programme, Ministry of Health & Family Welfare, New Delhi, India was unable to participate in the 13th VCAG meeting.

Mary Ann RICHARDSON

ISGlobal

Lethal house lures (Eave tubes)

Marit FARENHORST

In2Care

Anne OSINGA

In2Care

Spatial repellents

Nicole ACHEE

University of Notre Dame

Kelsey BARRETT

Unitaid

John GREICO

University of Notre Dame

Jackson HUNGU

Unitaid

David MALONE

B&M Gates Foundation

Tom MASCARI

SC Johnson

Kara McCARTHY

SC Johnson

Bobby REINER

Univ. of Washington

Wolbachia wMel (EVITA)

Ellie BUTLER

Emory University

Matthew COLLINS

Emory University

Derek CUMMINGS

University of Florida

Gregory DEYE

National Institute of Health

Sri EDUPUGANTI

Emory University

Matt HITCHINGS

University of Florida

Walt JONES

National Institute of Health

Albert KO

Yale School of Medicine

Luciano MOREIRA

World Mosquito Program / FioCruz

Sofia PINTO

World Mosquito Program

Gail POTTER

EMMES

Nadine ROUPHAEL

Emory University

Mauro TEIXEIRA

Universidade Federal de Minas Gerais

Michelle WILES

Emory University

Wolbachia wMel (WMP method)

Katie ANDERS

World Mosquito Program

Stephen DONOHUE

Queensland Health Department

Suzanne DUFAULT

UC Berkley

Nick JEWELL

UC Berkley / LSTMH

Luciano MOREIRO

World Mosquito Program / FioCruz

Scott O'NEILL

World Mosquito Program

Peter RYAN

World Mosquito Program

Cameron SIMMONS

World Mosquito Program

Stephanie TANAMAS

World Mosquito Program

Adi UTARINI

University of Gadjah Mada

WHO HEADQUARTERS, GENEVA

Global Malaria Programme

Pedro ALONSO

Director

Jan KOLACZINSKI

Unit Head

Vector Control & Insecticide Resistance

Jennifer STEVENSON

Technical Officer

Vector Control & Insecticide Resistance

Chunzhe ZHANG

Junior Professional Officer

Vector Control & Insecticide Resistance

Isabelle ABELLO

Administrative assistant

Vector Control & Insecticide Resistance



Department of Control of Neglected Tropical Diseases

Mwelecele MALECELA

Director

Raman VELAYUDHAN

Unit Head

Veterinary Public Health, Vector Control and Environment

Rajpal YADAV

Scientist

Veterinary Public Health, Vector Control and Environment

Lauren CARRINGTON

Consultant

Veterinary Public Health, Vector Control and Environment

Regulation and Prequalification

Deusdedit MUBANGIZI

Unit Head

Prequalification Team

Marion LAW

Technical Officer

Prequalification - Vector Control Products

Dominic SCHULER

Technical Officer

Prequalification - Vector Control Products

Jeannette MARTINEZ

Entomologist

Prequalification - Vector Control Products

ANNEX 3. AGENDA OF MEETING

Listed times represent UTC +1 (CET, Geneva)

MONDAY, 7 DECEMBER 2020	
12:45 – 13:00	Small welcome and overview of running of meeting, declaration of interests, etc
Session 1: Presentations and discussion with applicants	
13:00–14:00	Presentation – Eave Tubes Chair of session: Tom SMITH <ul style="list-style-type: none">• Applicant presentation (30 mins)• Q&As (15 mins) <i>Applicants leave the call</i> <ul style="list-style-type: none">• Closed discussion (15 mins)
14:15–15:15	Presentation – ATSBs Chair of session: Heather FERGUSON <ul style="list-style-type: none">• Applicant presentation (30 mins)• Q&As (15 mins) <i>Applicants leave the call</i> <ul style="list-style-type: none">• Closed discussion (15 mins)
15:30–16:30	Presentation – Endectocides Chair of session: Neal ALEXANDER <ul style="list-style-type: none">• Applicant presentation (30 mins)• Q&As (15 mins) <i>Applicants leave the call</i> <ul style="list-style-type: none">• Closed discussion (15 mins)
TUESDAY, 8 DECEMBER 2020	
Session 2: Welcome and updates	
12:45–13:45	Official opening of VCAG meeting Chair of session: VCAG Co-chairs Welcome from: <ul style="list-style-type: none">• MHP Assistant Director-General• GMP Director• NTD Director• Updates from GMP• Updates from NTD• Updates from PQT• Any other business
Session 3: Feedback to applicants from Day 1	
14:00–14:45	Feedback – Eave tubes Chair of session: Tom SMITH <ul style="list-style-type: none">• Closed Discussion (20 min) <i>Applicants join the call</i> <ul style="list-style-type: none">• Feedback to applicants (25 min)
15:00–15:45	Feedback – ATSBs Chair of session: Heather FERGUSON <ul style="list-style-type: none">• Closed Discussion (20 min) <i>Applicants join the call</i> <ul style="list-style-type: none">• Feedback to applicants (25 min)

16:00–16:45	<p>Feedback – Endectocides</p> <p>Chair of session: Neal ALEXANDER</p> <ul style="list-style-type: none"> • Closed Discussion (20 min) • Feedback to applicants (25 min) <p><i>Applicants join the call</i></p>
-------------	--

WEDNESDAY, 9 DECEMBER 2020

Session 4: Presentations from applicants

12:30–13:45	<p>Presentation – Wolbachia wMel (WMP method)</p> <p>Chair of session: Audrey LENHART</p> <ul style="list-style-type: none"> • Applicant presentation (40 mins) • Q&As (20 mins) • Closed discussion (15 mins) <p><i>Applicants leave the call</i></p>
14:00–15:00	<p>Presentation – Wolbachia wMel (EVITA)</p> <p>Chair of session: Bobby REINER</p> <ul style="list-style-type: none"> • Applicant presentation (30 mins) • Q&As (15 mins) • Closed discussion (15 mins) <p><i>Applicants leave the call</i></p>
15:15–16:15	<p>Presentation – Spatial repellents</p> <p>Chair of session: Salim ABDULLA</p> <ul style="list-style-type: none"> • Applicant presentation (30 mins) • Q&As (15 mins) • Closed discussion (15 mins) <p><i>Applicants leave the call</i></p>

THURSDAY, 10 DECEMBER 2020

Session 5: Feedback to applicants from Day 3

12:30–13:15	<p>Feedback – Wolbachia wMel (WMP method)</p> <p>Chair of session: Audrey LENHART</p> <ul style="list-style-type: none"> • Closed Discussion (20 min) • Feedback to applicants (25 min) <p><i>Applicants join the call</i></p>
13:30–14:15	<p>Feedback – Wolbachia wMel (EVITA)</p> <p>Chair of session: Bobby REINER</p> <ul style="list-style-type: none"> • Closed Discussion (20 min) • Feedback to applicants (25 min) <p><i>Applicants join the call</i></p>

Session 6: Information

14:30–15:15	<p>Introduction to WHO’s Guideline Development Process</p> <p>Chair of session: VCAG Co–chairs</p> <ul style="list-style-type: none"> • Presentation on data requirements and processes involved in developing WHO Guidelines (35 mins) • Q&A (10 mins)
-------------	--

Session 5 (continued): Feedback to applicants from Day 3

15:30–16:15	<p>Feedback – Spatial repellents</p> <p>Chair of session: Salim ABDULLA</p> <ul style="list-style-type: none"> • Closed Discussion (20 min) • Feedback to applicants (25 min) <p><i>Applicants join the call</i></p>
16:15–16:30	<p>Wrap up</p> <p>Chair of session: VCAG Co–chairs</p>

**FOR FURTHER INFORMATION
PLEASE CONTACT:**

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

