Vector Control Advisory Group

Seventeenth meeting of the WHO Vector Control Advisory Group

Meeting report, 3–6 October 2022

World Health Organization

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ABBREVIATIONS

BOHEMIA	Broad One Health Endectocide-based Malaria Intervention in Africa
CDC	United States Centers for Disease Control and Prevention
COPA	Communities Organized to Prevent Arboviruses
COVID-19	coronavirus disease
cRCT	cluster-randomized controlled trial
EHI	Environmental Health Institute
FAO	Food and Agriculture Organization of the United Nations
IAEA	International Atomic Energy Agency
IG2	Interceptor G2
IIT	incompatible insect technique
ITN	insecticide-treated net
MDA	mass drug administration
NEA	National Environment Agency
RG	Royal Guard
SAP	statistical analysis plan
SIT	sterile insect technique
VCAG	Vector Control Advisory Group
WHO	World Health Organization

1. BACKGROUND

The Vector Control Advisory Group (VCAG) of the World Health Organization (WHO) serves as an advisory body to WHO on new interventions 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;
- to advise WHO (i.e. the relevant technical departments) on whether public health value has been demonstrated for a new vector control intervention.

The 17th VCAG meeting was convened on 3–6 October 2022 at the Mandarin Oriental Hotel in Geneva, Switzerland. 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:

- sterilization of male mosquitoes;
- systemic endectocide treatment;
- spatial repellents;
- population reduction induced by gene drive;
- insecticide-treated nets (ITNs) designed to kill host-seeking insecticide-resistant mosquitoes; and
- ITNs designed to sterilize and/or reduce the fecundity of host-seeking insecticide-resistant mosquitoes.

The meeting was co-chaired by Dr Heather Ferguson and Dr Audrey Lenhart. All VCAG members joined the meeting – eight in person and six via remote connection. Members were joined by four temporary advisors, three observers, 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 Raman Velayudhan, Director ad interim of the Department of Control of Neglected Tropical Diseases, officially welcomed VCAG members, temporary advisors and the Secretariat. Dr Velayudhan offered his thanks and appreciation for the continued contributions of VCAG members, and welcomed the temporary advisors to this meeting.

Dr Velayudhan thanked Dr Mamadou Coulibaly for his contributions to the group over the last three years as a VCAG member, as Dr Coulibaly's term will be coming to an end following this meeting. Dr Heather Ferguson was also thanked for her commitment and dedication to the advisory group over the last six years, as she will be stepping down from the position of co-chair with the end of her tenure as a VCAG member following this meeting. Many applicants have benefited from her experience, and her leadership of multiple review groups and collaboration with the Secretariat are sincerely appreciated.

3. SUBMISSIONS

VCAG reviewed eight submissions across six intervention classes at its 17th meeting.

3.1 Intervention class: Sterilization of male mosquitoes

Interventions within this class share the common goal of suppressing mosquito populations by releasing sterile males into the population that will mate with the wild females and inhibit the oviposition of fertile eggs.

The sterility of the males can be induced by:

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

Irrespective of the mode of sterilization, all interventions in this class rely on the rearing of mosquitoes in the laboratory and the subsequent separation of males from females. The separated males are then released at regular intervals until the population is suppressed to eradication, or suppressed and maintained at a population density below the threshold required for sustained pathogen transmission; the level of suppression would depend on the goals of the control programme in operational terms.

3.1.1 Intervention: IIT

This intervention exploits male sterility induced by a phenomenon known as "cytoplasmic incompatibility" in released *Wolbachia*-infected males within a wild mosquito population. This technique is also known as the "*Wolbachia* suppression" approach. When the released *Wolbachia*-infected males mate with *Aedes aegypti* females in the target population that are not infected with *Wolbachia*, the females lay nonviable eggs due to cytoplasmic incompatibility. Systematic and repeated releases of *Wolbachia*-infected males can significantly reduce the target population size.

Applicant: United States Centers for Disease Control and Prevention (CDC) and Verily

The applicants first engaged with VCAG at the 11th meeting in 2019 *(1)*, where they presented their plans for a large-scale epidemiological trial in Puerto Rico to be conducted by Communities Organized to Prevent Arboviruses (COPA). COPA is a collaboration between the Ponce Health Sciences University, Puerto Rico Vector Control Unit, CDC and the citizens of Puerto Rico.

The trial was designed to test the hypothesis that the release of *Wolbachia* (*w*AlbB)-infected male *Ae. aegypti* would reduce the density of *Ae. aegypti* adults in target vector populations to a level at which the incidence of human infections and diseases caused by dengue, chikungunya and Zika viruses would be reduced. The target effect size

was a 50% reduction in the incidence of arboviral infections in residents of intervention clusters relative to those in control clusters. The production, transport and release of the *Wolbachia*-infected male *Ae. aegypti* in intervention clusters were overseen by the Debug Project of Verily Life Sciences Inc. Verily has developed mass-rearing and sex-sorting technologies for mosquitoes that enabled them to produce the *Wolbachia*-infected males at their facility in California at the scale and frequency required for the project.

Updates

The applicants presented to VCAG the results of their planned three-year trial, which was unfortunately suspended after 15 months due to a lack of expected entomological impact and lack of dengue transmission. Only a single dengue case was detected (by IgM) at the trial site in the first year, which was considerably lower than the anticipated 3% incidence per year (translating to 24 infections across all clusters).

The applicants informed VCAG that the first *Wolbachia*-infected male releases occurred in September 2020; however, in January 2021, the number of clusters in the trial was reduced from the originally planned 19 to four due to suboptimal suppression levels achieved in the intervention clusters during the initial months of the study. Mosquito release rates were commensurately increased in the remaining four clusters. Following releases in the intervention clusters, mosquito numbers were reduced by approximately 55%. This reduction was less than what was previously observed in other entomological trials using the same intervention approach (some of which the applicants had been involved with). Releases were stopped in December 2021, and the applicants re-focused their efforts on investigating the possible reasons for the lower than anticipated entomological effect.

Summary of discussions

VCAG discussed with the applicants the possible factors that may have influenced the observations of the trial. Following the applicants' first presentation of the study design to VCAG during the 11th VCAG meeting, they made some adjustments to the number of clusters and incorporated a mobility study, based on the recommendations received. At that meeting, VCAG had raised concerns about the potential fitness of the released mosquitoes following shipment. Unfortunately, those concerns held true, exacerbated by severe disruptions to the shipment of mosquitoes during the trial as a result of the coronavirus disease (COVID-19) pandemic.

There was substantial evidence of a loss of fitness of the adult male mosquitoes following shipment from California to the trial site, which in some instances took over 36 hours (considerably longer than the target of 24 hours or less). Transported males were less competitive in mating experiments and had shorter lifespans than males that were not transported. Verily is conducting extensive work on the packaging and shipment of mosquitoes to overcome these challenges, but logistical delays in shipment nevertheless remain possible, even outside of a global pandemic.

Variable and potentially suboptimal overflooding ratios also impacted the entomological outcome. These ratios were likely caused, in part, by the high initial mosquito population size at the trial site, and were potentially exacerbated by the substantial temporal and geographical variation in mosquito density and by difficulties in obtaining sufficient numbers of surviving males to release following shipment. In accounting for the drop in clusters from 19 to four, attempts were made to increase the ratio of released males by undertaking more frequent releases and targeting areas with the highest mosquito density. Moreover, some locations were identified as difficult to reach by vehicle and the team added manual releases.

While overflooding ratios were sometimes able to meet levels that had led to more successful suppression in other locations, local factors may have influenced the release dynamics in Ponce. In contrast to other independent studies where *Wolbachia*-mediated population suppression has been piloted, no additional interventions were implemented

to reduce the mosquito density at the trial site in Puerto Rico. It is likely that this intervention could be more effective if *Wolbachia*-infected mosquitoes were released at a time when the native mosquito population was already low, coinciding with normal seasonal population fluctuations, or otherwise suppressed using supplemental mosquito control interventions.

The possibility that accidental release of *Wolbachia*-infected females may have resulted in the establishment of *Wolbachia* in the local *Ae. aegypti* population was considered, but discounted after surveying larvae in each of the four intervention clusters over six time periods and finding no evidence of *w*AlbB infection in the mosquitoes.

The role of entomological surrogates of epidemiological outcomes was discussed. It was noted that while there is currently no link between entomological and epidemiological outcomes for arboviruses, there is value in collecting the entomological data to investigate whether such a correlation might exist.

Conclusions

VCAG appreciated the significant efforts of the COPA and Verily teams, and their openness about the challenges they had encountered. The trial in Puerto Rico faced a mixture of constraints that contributed to the early termination and inconclusive outcome. The COVID-19 pandemic undoubtedly impacted the logistics of long-distance transport of mosquitoes, and these issues impacted the fitness of the released male mosquitoes. A much lower than expected dengue incidence precluded any assessment of epidemiological impact. Despite this, the trial has generated important entomological data that will provide a valuable addition to the dossier of evidence on this intervention class. Important lessons learned include the need to have the necessary resources in place to ensure that regular and viable mosquito releases can be achieved.

VCAG noted that if sufficient overflooding ratios cannot be achieved, future trials should consider evaluating IIT under conditions in which mosquito population densities are already low or have been lowered through other mosquito suppression methods.

Recommendations

VCAG recommended analysis of the available data to learn more about the relationship between overflooding ratios and mosquito suppression, with a particular focus on spatio-temporal analyses. Finally, if future trials are going to employ similar long-distance transport, VCAG advised further consideration of how to improve adult mosquito transport or exploration of alternative approaches, such as transportation of eggs in concert with local infrastructure to rear and sort mosquitoes, prior to the initiation of the trial.

3.1.2 Intervention: Combined SIT/IIT

The combined SIT/IIT approach is designed to provide complementary benefits over either the SIT or IIT in isolation. In an SIT operation, high doses of irradiation ensure male sterility and also decrease male mating competitiveness. Low doses of irradiation reduce the negative effects on male mating fitness, but may also fail to induce complete sterility in males (females, however, are more sensitive and can still be rendered infertile with low doses). In terms of male releases, it is essential to find the optimal balance of irradiation in all exposed males in order to achieve effective population suppression. At the same time, an IIT operation relies solely on the induced cytoplasmic incompatibility between *Wolbachia*-infected males and wild females. The integrity of the approach depends on *Wolbachia* never becoming established in the population through the inadvertent release of a *Wolbachia*-infected female. As such, stringent and highly sensitive sex-sorting apparatus and procedures must be in place to separate and release only males.

Therefore, compared to SIT alone, the release of irradiated *Wolbachia*-infected males means that lower doses of irradiation can be used to induce complete sterility, while

retaining mating competitiveness against the wild males. Compared to IIT alone, the addition of low doses of irradiation applied to the mosquitoes before sex separation renders any inadvertently released females infertile, avoiding the potential establishment of *Wolbachia* in the population and allowing some leeway with the stringency of sex sorting.

Applicant: Food and Agriculture Organization of the United Nations (FAO)/ International Atomic Energy Agency (IAEA)

The combined SIT/IIT approach of the Joint FAO/IAEA Centre of Nuclear Techniques in Food and Agriculture's Insect Pest Control Section was conceived in response to requests by FAO and IAEA Member States. This approach was first reported to VCAG in March 2016 *(2)* and an update was provided in 2018 *(3)*. The approach aims at reducing the population density of *Aedes* mosquitoes below the threshold for transmission of dengue, Zika and chikungunya viruses. The SIT approach is based on mass rearing of the target species, separation by sex and sterilization of males with ionizing irradiation. The combined approach involves mosquito populations infected with one or more strains of *Wolbachia*, which induces cytoplasmic incompatibility in the target wild population. Over time, the systematic and continuous release of sterile males is designed to suppress the targeted population to a level that is unable to sustain arbovirus transmission.

Updates

FAO/IAEA provided an update on advances in mass rearing, sex separation, automatic mosquito release systems and the use of X-rays for inducing mosquito sterility. There are currently 42 trials being undertaken, all with epidemiological end-points. Some of the trials are using SIT only and others are employing the combined SIT/IIT approach. While most of these trials are at the stage of collecting baseline data, there are four large-scale, pre-operational SIT/IIT trials underway in China, Mexico, Singapore and Thailand. Multiple pilot studies of SIT alone to target *Ae. albopictus* are ongoing in several European countries and in Sri Lanka. SIT studies targeting *Ae. aegypti* have been conducted and others are underway in several sites in the Americas, including Brazil, Mexico and the United States of America.

Summary of discussions

Given that the applicants were presenting work on both SIT and SIT/IIT combined, VCAG asked about the benefit of using the combined approach versus using each approach individually. The applicants noted that, in the absence of SIT, there is a risk of *Wolbachia* establishment in the population due to the accidental release of females; conversely, using SIT alone requires higher irradiation doses to ensure that the males are sterilized.

The viability of irradiated male mosquitoes post-shipment was discussed. Improvements to shipping conditions have reduced the loss of fitness during transportation, and journeys of less than 24 hours do not appear to be detrimental to mosquitoes if the temperature can be maintained throughout transport.

While the remit of FAO/IAEA does not extend to epidemiological studies, VCAG encouraged the implementing partners to collect and analyse routine case data in areas where these interventions are being deployed in order to support the collation of evidence on the public health benefit of this intervention. The importance of long-term entomological monitoring was stressed i) to determine whether wild-type females remain receptive to the sterile males and ii) to assess the survival and fitness of the remaining wild mosquito population for any changes in vector competence.

VCAG appreciated the update from FAO/IAEA on process improvements and noted the wide range of international settings in which entomological studies are ongoing. VCAG recognized that FAO/IAEA are not responsible for assessing the public health impact of the SIT and SIT/IIT approaches, but hoped that opportunities would arise to permit implementing partners to conduct robust evaluations of the epidemiological impact of these interventions. With FAO/IAEA's engagement with implementing partners and

Member States, the potential data generated from these large-scale deployments could be of great value.

VCAG saw a benefit to longer term entomological surveillance at sites where SIT/IIT or SIT have been implemented for several years in order to assess sustainability and operational feasibility. In particular, this may include screening for any evidence of behavioural resistance (caused, for example, by a reduction in the receptivity of wild-type females to sterile males) and assessment of the remaining mosquito population for any changes in fitness (resulting from a reduction in the density of the overall population), such as changes in longevity or vector competence. VCAG would find it particularly valuable to have information from more robust trials that include multiple replicates.

Conclusions

Implementing partners and Member States should be encouraged to collate and analyse case data from intervention and non-intervention sites. VCAG would be pleased to review any related study protocols for trials that seek to assess the public health value of these tools.

3.1.3 Intervention: Combined SIT/IIT

Applicant: Singapore National Environment Agency (NEA), Environmental Health Institute (EHI)

Singapore's dengue control programme has historically been based on environmental management, including source reduction, and rapid case detection and intervention. In 2016, the first pilot releases of *Wolbachia* (*w*AlbB)-infected male *Ae. aegypti* commenced and subsequent success led to a rapid scale-up of the intervention combining SIT with IIT, mediated by the cytoplasmic incompatibility induced by *Wolbachia*-infected males. The operation is being led and conducted by the EHI, which is the public health research and risk assessment arm of the Singapore NEA.

The SIT/IIT operation in Singapore now covers approximately 31% of high-rise residential estates in the island nation. It has demonstrated up to 98% suppression of *Ae. aegypti* populations. Based on routine data collection as part of the national surveillance programme, a 30–88% reduction in dengue cases has been observed at study sites.

In the third quarter of 2022, the NEA began the first cluster-randomized controlled trial (cRCT) of this intervention in 15 clusters located in high-rise public buildings. The trial employs a test-negative design to help correct for differences in health-seeking behaviour. The primary end-point is dengue incidence, with cases being reported through hospitals and primary health care. Secondary end-points include prevalence of *Ae. aegypti* and *Ae. albopictus* mosquitoes, as monitored through Gravitraps, and public acceptance, attitudes and knowledge of relevant vector control interventions. The trial is being conducted in areas of the country with the highest risk of dengue. The *w*AlbB strain has been outcrossed into the local *Ae. aegypti* population for multiple generations and has a mating competitiveness and insecticide resistance profile very similar to that of the local strain.

This meeting is the first time the Singapore NEA has presented to VCAG. The applicants presented the protocol for their cRCT that has recently started.

Summary of discussions

Following the presentation on Singapore's recent epidemiological dengue situation and control efforts, the discussions focused on the difficulty of conducting a cRCT for an intervention that is already being used at scale in the country. The intervention is already considered very effective at suppressing populations of *Ae. aegypti* and anecdotal evidence indicates that it reduces the occurrence of dengue cases in treated areas. The ethical dimensions of this situation were discussed and used to justify the several rounds of interim analysis that are planned as part of the trial. The responses to alternative

outcomes from these analyses were discussed. A severe outbreak of dengue may lead to pressure to terminate the trial early. The pros and cons of a step-wedge design as an alternative to a standard cRCT were briefly discussed; this design had previously been considered and rejected by the applicants for reasons of statistical power and feasibility. The Singapore NEA Dengue Expert Advisory Panel will be responsible for any recommendations on early termination.

The trial design involves the core clusters (which encompass high-density high-rise apartments) and buffer zones around each cluster. The trial is releasing irradiated *Wolbachia*-infected males at three levels within each cluster (ground level, mid level and high level of each apartment block), as well as in the buffer zones between the clusters (albeit at a lower density than in the cluster itself and only at ground level). The applicants confirmed that they had sufficient capacity to sustain releases until the completion of the trial.

While the trial is powered to detect a 50% reduction in cases (based on the success of earlier implementation), there was discussion about how it might be challenging to detect such a large effect size in this trial. VCAG suggested that the applicants may want to consider adjusting the analytical plan to enable detection of smaller protective effects, as these could still have public health value. At present, the trial design does not account for the likely movement of people out of clusters. The small geographical size of the clusters increases the risk that dengue cases may be acquired while individuals are outside of their normal place of residence. Consequently, some modifications to the trial design were discussed, including capturing data on human movement, which may increase the likelihood of a positive outcome. Adapting the current binary classification of dengue based on primary site of residence to a more quantitative measure of time spent in each study arm was suggested for the applicants' consideration.

Following earlier releases, the applicants detected the presence of *Wolbachia* in wild female *Ae. aegypti* populations, restricted to a small area. The spread of *Wolbachia* through the female population would cause the sterility induced by cytoplasmic incompatibility to be lost. To mitigate this, the applicants have increased the irradiation dose for the mosquitoes used in releases in order to ensure that males and any inadvertently released females are sterile.

The role of the existing extensive data generated by the applicants in assessing the effectiveness of SIT/IIT in Singapore was discussed. While WHO is in the process of updating the systematic review of conventional vector control interventions for dengue prevention, population suppression of *Ae. aegypti* using SIT/IIT may be included once data from two trials with epidemiological end-points have been assessed.

Conclusions

VCAG acknowledged the applicants' extensive efforts to enhance the evidence base for SIT/IIT. It was noted that, locally, Singapore may have sufficient evidence to make informed decisions on the effectiveness of this strategy. VCAG therefore noted the value of this trial for its contributions to the global evidence base that may inform recommendations more broadly.

Recommendations

VCAG recommended that the applicants consider two modifications to their ongoing trial that could improve the power to detect an epidemiological impact. First, VCAG recommended that the applicants consider revising the study design to enable detection of smaller effect sizes. Specifically, VCAG advised the applicants to increase the threshold number of events required to terminate the trial early if warranted. Second, VCAG recommended the collection of further data on location of workplace (and place of education, if relevant) in test-positive cases in order to enable a secondary analysis of the impact of movement.

3.2 Intervention class: Population suppression induced by gene drive

Gene drive promotes preferential inheritance of target genetic elements, increasing frequencies in a population at a rate that is greater than normal inheritance patterns. Traits of interest tied to the genetic element thus have increased potential to be passed on to the next generation. While interventions in this class have the ultimate goal of population suppression, this can be achieved in different ways: by reducing fertility or fecundity, by inducing sterility or by biasing the sex ratio.

3.2.1 Intervention: Gene drive (population suppression)

Applicant: Target Malaria, Imperial College London

Target Malaria's vector control technology uses gene drive to reduce mosquito populations, with the aim of developing selective vector control, specific to the *Anopheles gambiae* s.l. vectors that transmit human malaria parasites in Africa. The proposed intervention is the release of male *Anopheles* mosquitoes bearing a gene drive construct that causes infertility in females and/or a distortion in the sex ratio in progeny. Both interventions are designed to reduce malaria transmission by suppressing mosquito vector population density in subsequent generations.

The candidate gene drive products proposed by the applicants use sequence-specific nucleases to produce a male-biased sex ratio, sterile females, or both. Target Malaria envisages developing a series of constructs of increasing efficacy. The first product ("Product 1") aims at achieving at least a 67% proportionate reduction in vectorial capacity over three years in moderate-transmission settings in sub-Saharan Africa. The aim of the second product ("Product 2") is to achieve at least a 99% reduction in vectorial capacity for 10 years in all transmission settings in sub-Saharan Africa.

Updates

Since the applicants' last engagement with VCAG *(4)*, they have made substantial progress in developing a lead candidate product and addressing identified challenges.

The applicants updated VCAG on their product development, which includes their current lead candidate strain for Product 1 (QFS2), based on the *doublesex* gene. This strain was developed to mitigate the effects of target site variation in populations of *An. gambiae* and contains two gRNA sequences (multiplexed). However, in mid-2021, during the course of routine product development assays, transgene mutations were observed in QFS2 that compromised the molecular stability of the strain. On account of this, the applicants are now developing alternative constructs based on the same gene as potential candidates for Product 1. The applicants have developed a protocol to facilitate early identification of similar instabilities based on polymerase chain reaction molecular stability assays and sequencing. These methods will be incorporated into ongoing routine molecular and phenotypic strain analyses.

Risk and regulatory specialists within Target Malaria published the first systematic analysis of plausible pathways to potential harm for a specific gene drive construct in a defined receiving environment *(5)*. A series of workshops with a broad cross-section of external stakeholders explored the technical aspects of risk assessment and the role of stakeholder participation for both project and regulatory risk-based decision-making. From the workshops, nine recommendations were identified and published to advance future environmental risk assessment of gene drive applications *(6)*. The proceedings of this workshop series will inform future stages of Target Malaria's work and establish a valuable precedent for others in the field.

Target Malaria has commissioned a strategic environmental assessment scoping study for the impact of population suppression gene drive use. This scoping exercise will serve to further inform topics for a future, more comprehensive strategic environmental assessment of environmental, social, economic and health impacts in order to support

policy development, plans and governmental programmes. The applicants provided VCAG with the results of a modelling exercise conducted as part of their preparations for the SEA scoping study. The modelling investigated the potential for gene drive releases to reduce the burden of malaria in 16 areas (12 000 km^2) of West Africa. The modelling investigation combines an entomological model, which simulates the spread of gene drives in malaria vector populations, with an epidemiological model, which simulates malaria infection dynamics in humans.

Summary of discussions

VCAG noted the speed at which the applicants had addressed the issues observed with the QFS2 variant of their candidate gene drive product. There was a discussion of the implications of the QFS2 instability for the efficacy of gene drive products in the long run. In particular, even if there is a small chance of instability in the newer QFS variants currently being evaluated, given the expected large scale of the intervention application, even rare events may impact gene drive efficacy. The applicants' technical approaches for assessing the stability of newly developed QFS variants were discussed.

The definition of the target organism for this gene drive product was considered at length, as were the consequences of this definition for the measurement of impact and for environmental risk assessment. Given the potential spread of gene drive between sibling species of the *An. gambiae* s.l. complex, the definition of target species may need to be expanded beyond the species initially released. Interspecific hybridization within the complex could be anticipated with greater frequency in sympatric species with closer phylogeny, and more rarely in species that are phylogenetically more distant and more isolated. Moreover, as the applicants have yet to refine their trial design or implementation scenarios to explicitly define how many species within the complex their product will encompass, questions remain as to the exact description of the product itself. While these discussions have far-reaching implications beyond public health impact (including risk assessment), such questions may also be premature, as the target organism (or organisms) will likely follow directly from a finalized product claim.

There was some discussion around the modelling efforts presented to VCAG, as well as potential future directions of research including such a modelling component. The applicants agreed that the results of their models are sensitive to mosquito dispersal. Accurately characterizing uncertainty in mosquito movement will be critical as the applicants move towards fine-scale analyses. In particular, it was noted that there will be complex questions regarding the design of any trials seeking to measure public health impact, due to the potential for contamination of control areas. The potential ease at which the intervention could spread spatially will have to be carefully considered to ensure that the control arm of any trial is as free from contamination as possible, or that contamination is explicitly accounted for in both design and analysis. The applicants indicated that they have begun to consider more spatially and temporally explicit entomological components in their model at finer resolutions and smaller scales in order to estimate more local and short-term effects relevant to the initial trials.

Conclusions

VCAG noted the applicants' thorough consideration of the complex issues surrounding gene drive and commended the applicants on the speed at which they had worked to solve the instability issues with their initial product. The applicants posed a number of questions to VCAG, the responses to which are provided below.

VCAG agreed that the applicants' questions relating to definitions of target species and target species complexes are somewhat premature until the applicants specify their product and associated claims. A clear product claim will inform the target and non-target organisms, as well as guide the design of epidemiological studies and problem formulation in risk assessments.

VCAG did not feel it was best positioned to comment on the adequacy of the molecular assays (polymerase chain reaction and amplicon sequencing assays), limits of detection

and repetition of analyses in the evaluation of QFS strains under development because such aspects are beyond the group's remit and specific area of specialization. VCAG encouraged the applicants to seek the highly specialized technical expertise in this area from within the wider research community.

In terms of useful temporal and spatial scales for modelling efforts, VCAG suggested that as the product moves closer to trials assessing the entomological or epidemiological impact, the scale of modelling should address finer spatial and temporal resolutions in order to support the planning of the initial phases of trials, and to account for the potential impact of contamination of the control arms from the intervention arms.

Finally, in response to the question about what other vector control interventions for malaria are on the horizon that may be considered as comparators in future trials, VCAG pointed the applicants to its website (https://www.who.int/groups/vector-control-advisory-group), which provides a summary of the interventions currently under evaluation. If a trial were to be conducted in the near term, the standards of care against which gene drive could be evaluated would likely be indoor residual spraying or ITNs, depending on the local setting and national vector control policies.

Recommendations

VCAG recommended that the applicants continue to develop their product and product claim, as this is a critical first step before issues surrounding the demonstration of public health value and environmental impact can be considered.

If the applicants seek further technical guidance on their proposed protocol for monitoring the molecular instability of their gene drive constructs, VCAG recommended eliciting additional expert opinion from specialists in the field.

VCAG recommended that the applicants begin to consider the design and analysis of trials that would assess either the entomological or epidemiological impact of their product. In particular, this intervention could present novel challenges due to the potential for contamination of control clusters. VCAG recognized the potential utility of models in aiding the design of trials and recommended that the applicants work to extend their models to operate at the spatial and temporal scales of a trial.

3.3 Intervention class: Spatial repellents

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.

3.3.1 Intervention: Transfluthrin passive emanator

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

The spatial repellent intervention proposed by SC Johnson is a transfluthrin-based passive emanator (Mosquito Shield™) that is designed to release 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.

SC Johnson is collaborating with the University of Notre Dame to evaluate their 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.

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 that seek to demonstrate the public health value of the intervention for malaria are underway: 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 being planned in Sri Lanka.

The applicants last provided an update to VCAG during the 14th meeting *(8)*, where the preparatory work for three planned trials was presented.

Updates

The applicants provided updates on the ongoing prospective double-blind cRCT in Kenya (*Anopheles*/malaria), Mali (*Anopheles*/malaria) and Sri Lanka (*Aedes*/arboviruses). The applicants also shared updates on associated study protocols and statistical analysis plans (SAPs).

Kenya: malaria

The baseline phase of the trial in Kenya started in March 2021 and was completed in July 2021. This trial originally included 60 clusters. Baseline incidence analyses led to two clusters being dropped, resulting in 58 clusters in total. The first cluster was excluded because of a zero incidence rate, and the second cluster was removed to maintain a balanced number of clusters per arm.

The trial in Kenya involves two sequential and independent cohorts. The intervention was first deployed in cohort one in October 2021, with study product deployment, efficacy, safety and entomological evaluations conducted as per the protocol. Cohort one follow-up will end in October 2022 with a formal, pre-planned interim analysis of the primary end-point anticipated in November 2022. Recruitment, consent and enrolment of cohort two will take place concurrently.

Mali: malaria

The trial includes 60 clusters and a single cohort. The baseline phase in Mali started in July 2021 and was completed in January 2022, followed by the cluster randomization and allocation in February 2022. The trial is ongoing with regular follow-up and is scheduled to finish in April 2024.

Sri Lanka: Aedes-borne viruses

This trial includes 30 clusters with a longitudinal cohort for follow-up on the primary end-point of seroconversion and a febrile surveillance cohort for monitoring clinical disease. The trial received ethical approvals in March 2022, and the study area census and mapping are underway. Site activation is anticipated to take place in October 2022 with participant enrolment to be completed in December 2022.

Summary of discussions

The main points of discussion during the meeting were related to the four specific questions the applicants posed to VCAG. The questions were:

1. What is the preferred mechanism for sharing the interim output report from the unblinded cRCT in Kenya?
2. Is VCAG willing to convene a meeting with Unitaid and/or the applicants to discuss the interim report from the cRCT in Kenya, given that the report is planned to be submitted for an off-cycle review? How would VCAG therefore communicate its recommendations?
3. When or would VCAG/Prequalification Unit Vector Control Product Assessment Team assist in organizing or sponsoring a workshop to review and modify the spatial repellent efficacy guidelines and outline the requirements for non-inferiority evaluations of spatial repellents?

4. If a positive signal of protective efficacy is indicated by the interim analyses of the cRCT in Kenya, does VCAG recommend conducting non-inferiority evaluation(s) of second in-class spatial repellent product(s) at the time of reporting the interim analyses (outside the current trial study area)? Or does VCAG recommend waiting until the time of reporting the final analyses (conducting studies within the trial clusters)?

In response to the questions raised by the applicants, VCAG re-emphasized its previous statement that stipulates it neither evaluates nor makes recommendations based on interim results *(9)*. When applicants declare that their submitted findings are final, a review is performed on an unblinded report. As indicated in the VCAG standard operating procedures, review of results should take place during a regularly scheduled VCAG meeting to ensure that all VCAG members are involved in active deliberations of the assessment. As is customary, applicants are welcome to invite their funders to their sessions to interact and actively take part in the discussions with VCAG members.

Non-inferiority evaluations are not a current WHO mandate or requirement for assessment of spatial repellent interventions; however, WHO is in the process of piloting non-inferiority assessments for dual active ingredient nets. VCAG appreciated the proactive planning of the applicants. However, the VCAG Secretariat indicated that, from a WHO perspective, it was still premature to discuss meetings on testing guidelines and non-inferiority assessments for spatial repellents. This perspective does not prevent the manufacturers and other stakeholders from meeting to discuss non-inferiority trials for spatial repellents or for other interventions not currently covered by the WHO study protocol for non-inferiority.

During the discussion, VCAG raised some questions about technical aspects of the ongoing/planned trials and analyses. A point was raised about the applicants' intention to base their primary analysis on a one-sided p-value, which is not considered the standard in randomized trials. The applicants provided a written rationale to VCAG regarding their primary analysis. VCAG expressed an interest in discussing this topic further in internal discussions. VCAG also asked whether any other *Aedes* control activities were taking place in the study area in Sri Lanka. A small-scale release of *Wolbachia*-infected mosquitoes was mentioned by the applicants, but this is occurring outside the spatial repellent cRCT study area. No additional activities beyond routine dengue control measures are anticipated to be implemented or are foreseen by the Ministry of Health where the trial is planned.

Conclusions

VCAG acknowledged and commended the applicants on the solid progress of the trials in Kenya and Mali, and is looking forward to reviewing the final results. In response to the applicants' questions, VCAG clarified it would not review any interim trial results and/or make any assessment based on those results unless the applicants deemed them to be the definitive results. The Secretariat clarified that the guideline development for efficacy evaluation and non-inferiority trials of spatial repellents is outside the remit of VCAG, but is being developed within WHO.

Recommendations

VCAG did not have any specific recommendations for the applicants other than encouraging them to pursue their activities as planned.

3.4 Intervention class: ITNs designed to kill host-seeking insecticide-resistant mosquitoes

As outlined in the Malaria Policy Advisory Committee meeting in May 2020 *(10)*, this intervention class has been defined as "ITNs designed to kill host-seeking insecticide-resistant mosquitoes and for which a first-in-class product has demonstrated public health value compared to the epidemiological impact of pyrethroid-only nets". This class was provisionally thought to include both insecticide treatments with active ingredients other than pyrethroid-based formulations and nets with synergists, such as pyrethroid-PBO nets. Pyrethroid-PBO nets were covered under an interim WHO policy recommendation pending the results of trials demonstrating public health value in at least two study sites. Demonstrated public health value of pyrethroid-PBO nets was confirmed following assessment of the second trial at the 14th VCAG meeting *(8)*. Associated recommendations have since been updated and published *(11)*.

The class is to be further expanded to include pyrethroid + chlorfenapyr nets once their public health value has been demonstrated by means of at least two geographically separate epidemiological trials. The class may also include other products with the same entomological effect but with different chemical modes of action to pyrethroid-only nets without the need for further epidemiological trials. At VCAG's 15th meeting *(12)*, it assessed the results of the first trial of pyrethroid + chlorfenapyr nets conducted in the United Republic of Tanzania. Results from the second trial, undertaken in Benin, were reported during the present VCAG meeting.

3.4.1 Intervention: Interceptor G2

Applicant: BASF

Interceptor G2 (IG2) nets, which are treated with a pyrethroid + chlorfenapyr, are the first-in-class dual active ingredient nets targeting host-seeking pyrethroid-resistant mosquitoes. Of its two active ingredients, the pyrethroid alpha-cypermethrin acts as a neurotoxicant in the mosquito, while the chlorfenapyr inhibits oxidative phosphorylation within the mosquito. The biochemical pathways involved in each of these effects are distinct, meaning that even a pyrethroid-resistant mosquito must overcome additional selective pressure to survive exposure to the nets.

BASF, the manufacturer of IG2, has been collaborating with researchers at the London School of Hygiene and Tropical Medicine to conduct the two required cRCTs with epidemiological end-points. A second intervention, Royal Guard (RG) nets, manufactured by Disease Control Technologies, has been independently evaluated in the same trials as IG2 (see Section 3.5.1 of this meeting report). The trials simultaneously evaluating IG2 and RG have been conducted in the United Republic of Tanzania (alongside pyrethroid-PBO nets) and in Benin. VCAG reviewed the Tanzanian protocol at its seventh and ninth meetings, and the Beninese protocol was reviewed at its ninth meeting *(3, 13)*.

The results of the trial in the United Republic of Tanzania were reviewed at the 15th VCAG meeting *(12)*, with conclusive evidence of protective efficacy of IG2 compared to a standard pyrethroid-only (alpha-cypermethrin-only) net. The trial in Benin also compared IG2 to the same standard pyrethroid-only net. The second year of follow-up for the trial in Benin was due to finish in the first half of 2022.

Updates

The applicants shared epidemiological and entomological results from their trial evaluating IG2 over 24 months in Benin. Additional updates provided to VCAG were the published trial protocol *(14)*, published manuscripts describing the baseline entomological and epidemiological characteristics of the trial site in Benin *(15, 16)*, and the updated SAP. Finally, the applicants summarized some key results from the third year of follow-up for the trial in the United Republic of Tanzania.

Summary of discussions

The applicants presented the summary of the results from the trial in Benin, with the primary epidemiological end-point of malaria incidence in children and additional end-points of malaria and anaemia prevalence. Multiple entomological indicators were also reported, with the primary entomological end-point of human biting rate. The primary analysis was based on the intention-to-treat population, but there were secondary per-protocol analyses conducted for other key outcomes. The results showed a strong protective effect of the intervention, with a 46% reduction in malaria incidence in the IG2 arm compared to pyrethroid-only nets over the two-year trial period. While the protective effect of the intervention was stronger during the first year (54%) than the second year (43%), a significant impact relative to the control arm was demonstrated over the two-year period. Although there was no significant difference detected for anaemia (at six months or 18 months), significant reductions in malaria prevalence were detected (at six months and 18 months). There were also significant reductions in the indoor and outdoor human biting rates and entomological inoculation rate throughout the two years. When the data were analysed based on per-protocol intervention status, impact was less pronounced but still significant, suggesting an important community protective effect of the intervention.

Additional discussion points included the apparent lack of balance between the study arms in terms of the entomological indicators at baseline. Since entomological indicators were not considered for the randomization, this did not constrain the data analysis. The relatively low coverage of the study nets compared to other types of ITNs in the study area was also discussed, as well as the perceptions of the local communities regarding net preferences. The notably higher frequency of adverse events reported in the pyrethroid-only net arm could have been due to the greater quantity of alpha-cypermethrin on those nets than on the IG2 nets. With respect to insecticide resistance, the bioassay data suggested that resistance to pyrethroids remained high over the study period, whereas mosquitoes remained fully susceptible to chlorfenapyr.

The applicants briefly presented some key results from the third year of follow-up for the study in the United Republic of Tanzania. An unexpected finding was that IG2 appeared to be associated with reduced malaria prevalence at the 30-month time point (in the per-protocol analysis), despite net coverage only being approximately 23%. Potential reasons for this finding were discussed, with the applicants hypothesizing that it may be due to a lagged effect of prevalence suppression from the previous two years of the trial.

One of the major questions from VCAG was why IG2 net usage fell markedly as the trial progressed in both Benin and the United Republic of Tanzania. Factors that potentially contributed to this were discussed, with the applicants feeling that it could be partially attributed to the preference of community members to continue using older nets and keep the newer IG2 nets in storage. Information on the durability and bioefficacy of nets is being collected over three years in both Benin and the United Republic of Tanzania.

Conclusions

VCAG congratulated the investigators for the successful completion of the trial of IG2 in Benin. Given the considerable difficulties experienced over the last two years as a result of the COVID-19 pandemic and associated disruptions, executing such a robust and rigorous trial is a noteworthy achievement and will make a very important contribution to the evidence base on this intervention. VCAG commended the manufacturer and funders for contributing the additional resources to ensure that activities could go forward.

VCAG concluded that IG2 has now demonstrated evidence of significant public health value, as demonstrated in two cRCTs in different eco-epidemiological settings. This clear protective effect has been shown in two settings where the vector populations are highly resistant to pyrethroids.

Recommendations

Given the convincing evidence of its public health value, VCAG recommended to WHO that IG2 be referred to the Guideline Development Group for malaria vector control to undergo systematic review and meta-analysis for the eventual drafting of a formal WHO recommendation.

Given this conclusion, no further submissions from the applicant to VCAG are needed to support demonstration of public health value. Nevertheless, VCAG remains available to review additional trial data, particularly the year-three efficacy data, for the benefit of improving its understanding of epidemiological impact over time and related entomological outcomes. As requested by the applicants, VCAG collated some suggestions for further data collection in these final months of the trial. VCAG also identified some areas of the SAP that would benefit from further minor clarification and explanation in subsequent dissemination efforts. These are summarized below:

- **Collection of additional data in year three of the trial in Benin:** Given the strong skew in the mosquito biting profile towards early morning hours at baseline, mosquito collection periods could be extended (e.g. until 10 am) at feasible sites to assess whether mosquitoes continue to bite during morning hours. In addition, it would be useful to capture further information on net usage in year three, including information on perceptions of the value of IG2 nets in the community and reasons for deciding to use other net types.
- **Clarification and update of SAP:** VCAG provided the applicants with a list of minor discrepancies between documents (e.g. protocol, SAP and analyses shared) and areas where further clarification would be beneficial in order to assist with further dissemination and forthcoming publications.
- **Sharing of year-three results and remaining secondary analyses:** A number of secondary and supplementary analyses from the trial in Benin are still ongoing, including additional analyses of primary epidemiological outcomes (year three), entomological data on efficacy and resistance, bioefficacy and durability. In response to previous recommendations from VCAG, the applicants have planned further supplementary analyses to assess the impact of the pandemic on the trial and to assess net equity. These results would be of great interest to VCAG and, in turn, may be informative in the context of WHO guideline development. VCAG would welcome an update from the applicants on these results at a future meeting. VCAG is available to provide additional feedback and suggestions if requested.

3.5 Intervention class: ITNs designed to sterilize and/or reduce the fecundity of host-seeking insecticide-resistant mosquitoes

The intervention class to which this submission relates was endorsed by the Malaria Policy Advisory Committee and defined as "ITNs designed to sterilize and/or reduce the fecundity of host-seeking insecticide-resistant mosquitoes for which a first-in-class product has demonstrated public health value compared to the epidemiological impact of pyrethroid-only nets" *(10)*. This class was provisionally thought to include pyrethroid + pyriproxyfen nets (pyriproxyfen being an insect growth regulator), but at least two geographically separate epidemiological trials would be needed before public health value could be assessed.

3.5.1 Intervention: Royal Guard

Applicant: Disease Control Technologies

The RG net is treated with alpha-cypermethrin, a pyrethroid that acts as a neurotoxicant, and pyriproxyfen, an insect growth regulator. Mosquito exposure to pyriproxyfen is intended to sterilize males and reduce oviposition in any females that survive pyrethroid exposure as a result of their resistance to this class of insecticides.

Disease Control Technologies, the manufacturer of RG, has worked in collaboration with the London School of Hygiene and Tropical Medicine to generate evidence from two trials with epidemiological end-points with the aim of demonstrating the public health value of this first-in-class intervention. VCAG first reviewed the protocol for the trial to be conducted in the United Republic of Tanzania in an off-cycle review prior to the ninth VCAG meeting and subsequently reviewed the protocol for the trial in Benin during the ninth meeting ***(3)***. Trial updates were provided to VCAG at the 12th meeting *(17)*, and the results of the first trial were presented for assessment of public health value at the 15th VCAG meeting *(12)*. The trial in the United Republic of Tanzania did not provide clear evidence of public health value for RG over the use of a pyrethroid-only net *(12)*, despite having sufficient statistical power to detect a protective effect.

Updates

The applicants shared epidemiological and entomological results generated over two years in Benin. These results are considered in the SAP, and by VCAG, as the main trial analysis, although a third year of follow-up is ongoing and will further add to the evidence base. Additional updates provided by the applicants were the published trial protocol *(14)*, the published manuscripts describing the baseline entomological and epidemiological characteristics of the trial site in Benin *(15, 16)*, and an updated SAP. Results of the third year of the trial in the United Republic of Tanzania were briefly presented, in addition to another related observational study not previously presented to VCAG that is being conducted in Mozambique.

Summary of discussions

The discussion focused on the results from the trial in Benin where RG was compared to pyrethroid-only (alpha-cypermethrin) ITNs. The study demonstrated no evidence of superior protective efficacy of RG relative to the comparator. The hazard ratio for malaria incidence in the RG arm was 0.86, relative to pyrethroid-only ITNs, with a 95% confidence interval of 0.65–1.14 (p=0.28). Although no epidemiological impact of the intervention over the comparator was detected in this trial, there was some indication of a moderate enhanced entomological impact. In particular, the indoor entomological inoculation rate was significantly lower in the RG arm at year one (58% reduction).

Potential reasons for the lack of impact were discussed. The RG nets' insecticide concentrations met pre-defined targets. Although there was high pyrethroid resistance in both arms at baseline, mosquitoes were susceptible to pyriproxyfen. The applicants presented results on insecticide resistance and human biting rates over the course of the trial. The *Anopheles* species composition was presented and was found to remain similar over time. The parameter values used for trial sample size calculation, in particular the between-cluster variation, were close to the values found in the actual trial data, so the choice of those values was unlikely to have impacted the study outcome.

The applicants reflected that low net usage may have been the main factor contributing to the lack of impact. RG coverage (uptake) was less than optimal (as low as 52% in year two). The applicants considered that achieving much higher coverage would have been particularly important for an insect growth regulator such as pyriproxyfen to have significant impact. Some characteristics of the nets were not aligned with the preferences of the study population, including the size of the nets distributed and the type of netting material (RG uses polyethylene, whereas other available net types are polyester-based).

There was also a discussion on whether the observed sterility effect of RG (~60–80%) would be sufficient to generate an epidemiological impact. Although the sterility effect appears to be relatively large, it may not be sufficient to impact transmission under field conditions. The applicants clarified that there are no pre-defined targets set for sterility that have been demonstrated to be sufficient to reduce mosquito population size. The applicants are considering carrying out mathematical modelling of the expected impact on malaria transmission in order to investigate this area in more detail.

Some follow-up measurements from the trial in Benin will continue for another year, including measurement of epidemiological and entomological end-points, ITN bioefficacy and durability, and insecticide resistance. Other secondary and supplementary analyses are still underway. These include supplementary assessment of the degree of equity in access to nets and the impact of the COVID-19 pandemic on the trial.

The applicants clarified that the covariates used in randomization were included in the secondary but not in the primary analysis. The inclusion of these covariates did not materially affect the results. Again, including baseline entomological parameters in the analysis gave similar results.

The applicants presented interim unadjusted results from an observational study in Mozambique and indicated that the analysis of the routinely collected data is expected to be completed in the first quarter of 2023. It should be noted that these results have not been considered in the present assessment of public health value.

Conclusions

VCAG congratulated the investigators on the successful completion of the trial in Benin. Given the considerable difficulties experienced over the last two years due to the pandemic and associated disruptions, executing such a robust and rigorous trial is an impressive achievement and will make an important contribution to the evidence base on this intervention.

As was the case with the previous trial in the United Republic of Tanzania, the trial in Benin did not demonstrate the public health value of RG nets compared to the control arm. Nevertheless, WHO has determined that the data from these trials will be included alongside other epidemiological data on pyriproxyfen-pyrethroid dual active ingredient nets in a systematic review to inform deliberations by the WHO Guideline Development Group for malaria vector control.

VCAG would appreciate presentation of the remaining data from the trial in Benin, including from the third year of follow-up, in order to contribute to its understanding of product performance over time.

Recommendations

As requested by the applicants, VCAG has collated some suggestions for further data collection in these final months of the Benin trial. VCAG has also identified some areas of the SAP that would benefit from further minor clarification and explanation, in subsequent dissemination efforts. These are summarised below:

- **Collection of additional data in year 3 of the Benin trial:** Given the strong skew in the mosquito biting profile towards early morning hours at baseline, we suggest extending the mosquito collection during sampling days to assess whether mosquitoes continue to bite during morning hours. Additionally, it would be useful to capture further information on net usage in the third year, including information on community perceptions of the value of RG nets, and preferences for specific net types.
- **Clarification and update of SAP:** VCAG provided the applicants with a list of minor discrepancies between documents (e.g. protocol, SAP and analyses shared) and areas where further clarification would be beneficial, to assist with further dissemination and forthcoming publications.
- **Sharing of year-three results and remaining secondary analyses:** A number of secondary and supplementary analyses from the trial in Benin are still ongoing, including additional analyses of primary epidemiological outcomes (year three), entomological data on efficacy and resistance, bioefficacy and durability. In response to previous recommendations from VCAG, the applicants plan to

conduct supplementary analyses to assess the impact of the pandemic on the trial and to assess net equity. These results would be of great interest to VCAG and, in turn, may be informative in the context of WHO guideline development. VCAG would welcome an update from the applicants on these results at a future meeting. VCAG could provide additional feedback and suggestions if requested.

3.6 Intervention class: Systemic endectocide treatment

3.6.1 Intervention: Ivermectin

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 these hosts. The premise of the intervention is that female mosquitoes will feed on ivermectin-treated hosts and consume blood meals containing lethal concentrations of the drug. The drug may also have additional sublethal effects that impact vector populations (e.g. reductions in mosquito fertility and fecundity). There are several ongoing trials with ivermectin evaluating its potential role in malaria vector control, although not all groups have engaged with VCAG.

Applicant: ISGlobal, BOHEMIA project

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 for reduction of malaria transmission. The BOHEMIA project consists of a combination of studies organized around two cRCTs: one in Mozambique and the other originally planned 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) were planned for both countries, and each has an independent protocol. ISGlobal last participated in the 13th VCAG meeting in December 2020 *(9)*.

Updates

The applicants' objective for the meeting was to provide an update on their progress with the trial in Mozambique. They had no specific questions for VCAG.

The applicants provided VCAG with an updated SAP (May 2022) for efficacy and safety, as well as updated protocols. These documents reflected the change in study design presented at the 13th VCAG meeting. The 12-month study now includes entomological assessments conducted throughout (with three months of baseline and nine months of impact assessments), and MDA administered from months 4–6 with concurrent epidemiological follow-up from months 4–9 inclusive. The control arm comprises humans treated with albendazole. Treatment arm one sees ivermectin administered to humans only, while treatment arm two consists of ivermectin administered to both humans and livestock *(9)*. The protocols also now address the collection of environmental and entomological data to help support the generalizability of results, including data on livestock biting rates and blood meals, as previously recommended by VCAG. The documents also include the entomology protocol for the second trial in Kwale, Kenya.

Change of study site

An important update was that the applicants were no longer able to conduct the second trial in the United Republic of Tanzania as planned, because the required authorities did not grant approval to work in the area. A potential alternative trial site in the Kisarawe district was determined to be unsuitable after taking into account the dominant suburban land use, separation of cattle from humans within the district, malaria burden and population density. The applicants subsequently selected the Kwale district in Kenya as the trial site based on several attributes, including malaria burden and cattle density. In addition, this site has existing infrastructure, where the applicants can leverage trained personnel.

Human pharmacokinetic study

The applicants summarized a pharmacokinetic study of ivermectin and albendazole to ascertain the cumulative mosquito mortality after being fed blood from four groups of volunteers: those treated with a single dose 400 mg of albendazole (the human control drug in the trial); a single dose 400 µg/kg of ivermectin; one dose 300 µg/kg of ivermectin per month over three months; and an untreated control group. The albendazole treatment demonstrated no significant effect on mosquito survival compared to controls. Blood sampled at day 0 + 4 hours from volunteers given a single dose of 400 µg/kg ivermectin caused significant cumulative mortality in mosquitoes compared to controls. Cumulative mortality in mosquitoes following consumption of blood from hosts at days 7, 10, 14 and 21 post-treatment with ivermectin was significantly greater than in controls; however, by day 28, that difference had waned to an undetectable level.

Mozambique trial

The trial in Mopeia, Mozambique was initiated in March 2022 and will finish in March 2023. The applicants determined that their original plan for the Mozambique trial of having 147 clusters with a central core of 35 children and a 1 km radius buffer zone with 200 adults in the core and buffer was not feasible. This was due to the practical limitations of treating up to 140 000 people that this design would require. The team ultimately determined that using a buffer with a 400 m radius would be sufficient to minimize contamination from neighbouring clusters and maintain the trial's power. For the Mozambique trial, this equated to 159 clusters with a buffer radius of 400 m, with approximately 42 000 potentially eligible adults to treat and 20 children per cluster in the core.

There were major challenges in the implementation of the trial due to five cyclones in one season, which resulted in significant flooding and mortality. A large number of workers supporting the effort also had malaria and/or cholera during the course of the trial. Consequently, only 100 of the originally targeted 159 clusters were included in the trial (20 children/cluster; approximately 21 000 adults receiving ivermectin). The 100 clusters were randomly assigned to three different study arms: i) ivermectin in humans and swine; ii) ivermectin in humans only; and iii) albendazole in humans only, as the control.

Each cluster comprised a core zone surrounded by a 400 m buffer zone, with no buffers between non-discordant clusters. The human ivermectin treatment was three monthly oral doses of 400 µg/kg and the livestock dose (1% solution) was injected monthly for three months. Albendazole was administered orally once monthly at a dose of 400 mg. Data were collected over six months. Six months of sampling for the efficacy outcome was undertaken following the last administered dose of ivermectin.

In addition, there was an asynchronous start to the trial, with approximately 30% of clusters starting one month later. Furthermore, instead of the intended dosing of humans and livestock over the course of a week, dosing occurred over the course of around 30 days, with approximately 5% of adults treated daily. The BOHEMIA team noted that some of the delays were due to the unanticipated time required to inform and seek consent from participating adults on the day designated for dosing.

The applicants summarized that the MDA was completed, and five of seven rounds of efficacy follow-up sampling had since been conducted. Preliminary entomological and safety data were provided; the applicants anticipated providing the overall findings of the trial at the next VCAG meeting.

Summary of discussions

Re-definition of cluster buffer zones

During discussions, VCAG noted that the coefficient of variation assumption may underestimate variability, as the number of children decreased from 35 to 20 in the core.

There was also a concern about changes in cluster contamination should mosquitoes have maximum flight distances greater than 660 m *(18)*.

Trial in Kwale, Kenya

After considering alternative trial sites in the United Republic of Tanzania, which were ultimately deemed unsuitable, the applicants selected the Kwale district in Kenya as the trial site based on several attributes, including malaria burden and cattle density. In addition, this site has existing infrastructure, where the applicants can leverage trained personnel.

While the attributes of the Kwale site support its use as the second trial site, VCAG noted that the human population density at the site was around four times higher than at the site in Mozambique and 10 times higher than at the site in the United Republic of Tanzania. In addition, the precipitation rate at the Kwale site was two times lower than at the site in Mozambique and 3.5 times lower than at the site in the United Republic of Tanzania. It was noted that some of the current protocols and SAPs do not reflect the recent change to the site in Kenya. The applicants indicated that they had undertaken a power analysis based on Kwale, Kenya and will provide the information to VCAG.

Trial in Mozambique

During discussions, VCAG suggested that the asynchronous human dosing may not have adversely impacted the community mosquito mortality rates. Further analyses addressing the reduced number of clusters and any impact of asynchronous dosing for detecting a 20% decline in malaria incidence would be helpful. Documentation of lessons learned regarding implementation logistics could be informative for planning and executing the trial in Kenya and more broadly. While data on human ivermectin treatment were presented, the coverage of the livestock treatment was not shared.

Conclusions

VCAG commended the BOHEMIA consortium, collaborators and field workers on their outstanding commitment and perseverance to undertake the trial in Mozambique. Through no fault of the team, the target sample size was not reached so the trial is likely underpowered. However, no conclusive assessment regarding the outcome of the trial should be made until the final data are available. It remains important to glean as much information from the trial as possible to help inform planning of the trial in Kenya.

Selection of Kwale, Kenya as the site for the second trial seems reasonable. However, in the submitted documents it was unclear how some attributes, such as population and livestock density and proportion of zoophagic vectors, were considered with respect to the design and power analysis.

VCAG considered the approach to re-define the cluster size to be acceptable; however, there were some concerns about study power related to the variability among children in the core and the extent to which greater mosquito dispersal distances could increase cluster contamination.

The concerns over lack of synchronicity in the treatments highlighted by the applicants warrant further investigation.

Recommendations

Given the importance of the trial in Kenya to demonstrate efficacy of the MDA, VCAG recommended that the applicants revisit assumptions in the power analysis and cluster design, as well as the influence of asynchronous dosing. In due course, the applicants are requested to provide VCAG with any updated protocols and SAPs. Especially with regard to the asynchronous dosing, the applicants are encouraged to work with their modelling collaborators to better understand the extent to which this may influence results.

Documenting and disseminating the lessons learned from the trial in Mozambique will not only help in the implementation of the second trial in Kenya, but will also provide useful insights for the broader research community.

4. CONCLUDING REMARKS

VCAG co-chairs Dr Audrey Lenhart and Dr Heather Ferguson thanked the VCAG members and temporary advisors for their commitment, time and effort in supporting VCAG activities, and for their participation. The return to in-person meetings was welcomed. The group was pleased to have been able to engage with so many applicants in a single meeting, and to assess the results of the second trial for both IG2 and RG. The VCAG Secretariat echoed the thanks of the co-chairs, acknowledging the dedication of the advisory group members.

The 18th VCAG meeting is intended to be held virtually, the week of 24 April 2023.

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15. Yovogan B, Sovi A, Padonou GG, Adoha C, Akinro B, Chitou S, et al. Pre-intervention characteristics of the mosquito species in Benin in preparation for a randomized controlled trial assessing the efficacy of dual active-ingredient long-lasting insecticidal nets for controlling insecticide-resistant malaria vectors. PLoS One. 2021;16:e0251742. doi:10.1371/journal.pone.0251742.

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18. Verdonschot PFM, Besse-Lotoskaya AA. Flight distance of mosquitoes (Culicidae): a metadata analysis to support the management of barrier zones around rewetted and newly constructed wetlands. Limnologica. 2014;45:67–79. doi:10.1016/j.limno.2013.11.002.

ANNEX 1. DECLARATIONS OF INTEREST

The 17th VCAG meeting was convened to review and evaluate eight applicant submissions on novel vector control interventions across six intervention classes.

This convening consisted of four categories of invitees, namely:

1. members (including the co-chairs)
2. observers
3. VCAG applicants, which in this case were the investigators and manufacturers presenting their research and plans for testing their interventions
4. WHO staff.

Respective applicants each participated in their own open sessions, alongside the members, WHO VCAG Secretariat, and observers, where appropriate. Observers were not permitted to join closed sessions in which VCAG deliberated upon and developed the recommendations for the meeting report.

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

Members

Dr Camilla Beech declared a conflict of interest relating to the Target Malaria submission. Dr Beech was recused from all sessions relating to the Target Malaria submission in the capacity of a VCAG member and was not permitted to contribute to the development of guidance for the Target Malaria submission.

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

Dr David O'Brochta is involved with the GeneConvene Collaboration. No conflict of interest was identified and Dr O'Brochta's participation in the meeting and development of advice within the report was not restricted.

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

Dr Lenhart works in the same institution (CDC) as investigators working on the IIT submission presented at this meeting. Due to the potential for a perceived conflict of interest, Dr Lenhart was permitted to observe the presentation of this session, but was not allowed to engage in any questions and was recused from all discussions and development of guidance for this submission.

Dr Hilary Ranson's research group has received research funding relating to the New Nets Project (which comprises the IG2 and RG nets). Dr Ranson's involvement in the research programme of the New Nets Project was deemed a conflict of interest. Dr Ranson was recused from all sessions relating to the IG2 and RG submissions in the capacity of a 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 a 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 a VCAG member and was not permitted to contribute to the development of guidance for the submission.

Dr Tom Smith sits on the Data and Safety Monitoring board for the New Nets Project (which comprises the IG2 and RG nets). Given a foreseeable perceived conflict of interest and the importance of maintaining independence and integrity of the two groups overseeing/evaluating the trial, Dr Smith did not participate in the presentation or discussion sessions or contribute to the development of guidance for either submission.

Observers

Ms R. D. Jeevanie Harishchandra has received indirect support for her previous studies on SIT from IAEA. Ms Harishchandra was permitted to be a silent observer during the FAO/IAEA session in the meeting. She was not permitted to engage in any questions or join the discussion session for the submission, but could freely listen.

Dr Corine Ngufor's research group receives funding to work on the trials evaluating the public health value of the IG2 and RG nets as part of the New Nets Project. To avoid perception of a conflict of interest, Dr Ngufor was recused from all sessions relating to these submissions in the capacity of a VCAG temporary advisor.

Dr Joshua Yukich works on a wider cost-effectiveness study on next-generation nets, which includes the nets evaluated within the New Nets Project (IG2 and RG), but is not directly working on the trials being evaluated for public health value. As an observer representing the Guideline Development Group, Dr Yukich was permitted to be a silent observer during the presentation, Q&A and feedback components of these sessions; however, he was recused from the discussion among VCAG members and observers for these two interventions.

ANNEX 2. AGENDA

MONDAY, 3 OCTOBER 2022			
Session 1: Welcome and updates		**Presenters**	**Closed session**
09:00 – 09:20	**Preliminary welcome** • Overview of running of meeting • Reading of declarations of interest statement	• VCAG members • Observers • WHO VCAG Secretariat	For information
09:20 – 10:00	**Official opening of VCAG meeting** Chair of session: VCAG co-chairs • Opening remarks from Director ad interim Department of Control of Neglected Tropical Diseases • Briefing from Prequalification Unit Vector Control Product Assessment Team: meeting with National Regulatory Authority representatives on exploring collaborative evaluation activities	• Raman Velayudhan (Director ad interim Department of Control of Neglected Tropical Diseases) • Marion Law (Prequalification Unit Vector Control Product Assessment Team) • VCAG members • Observers • WHO VCAG Secretariat	For information
Session 2: Applicant presentations and feedback		**Invitees**	**Open session**
10:30 – 12:15	**Presentation – Aedes SIT/IIT (Singapore)** Chair of session: Hilary Ranson • Applicant presentation • Q&As • VCAG + observer discussion	• **Singapore NEA/EHI** • VCAG members • Observers • WHO VCAG Secretariat	For information & discussion
13:45 – 15:30	**Presentation – Aedes IIT (Puerto Rico)** Chair of session: Robert Reiner • Applicant presentation • Q&As • VCAG + observer discussion	• **CDC / Verily** • VCAG members • Observers • WHO VCAG Secretariat	For information & discussion
16:00 – 16:30	**Feedback – Aedes SIT/IIT (Singapore)** Chair of session: Hilary Ranson • Feedback to applicants	• **Singapore NEA/EHI** • VCAG members • Observers • WHO VCAG Secretariat	For information & discussion
16:30 – 17:00	**Feedback – Aedes IIT (Puerto Rico)** Chair of session: Robert Reiner • Feedback to applicants	• **CDC/Verily** • VCAG members • Observers • WHO VCAG Secretariat	For information & discussion
Session 3: Formulation of VCAG advice		**Contributors**	**Closed session**
17:00 – 18:00	**Formulation of advice (from day 1)** • Development of recommendations • Draft technical guidance for report	• VCAG Working Groups	For guidance

TUESDAY, 4 OCTOBER 2022			
Session 4: Applicant feedback		**Applicants**	**Closed session**
09:00 – 10:30	**Presentation & feedback – Aedes SIT/IIT (field studies) – update only** Chair of session: Robert Reiner • Applicant presentation • Q&As • VCAG + observer discussion • Feedback to applicants	• **FAO/IAEA** • VCAG members • Observers • WHO VCAG Secretariat	For information & discussion
11:00 – 12:15	**Presentation – Endectocides (BOHEMIA)** Chair of session: Audrey Lenhart Applicant presentation Q&As	• **ISGlobal/BOHEMIA** • VCAG members • Observers • WHO VCAG Secretariat	For information & discussion
14:00 – 15:00	**Feedback – Endectocides (BOHEMIA)** Chair of session: Audrey Lenhart • VCAG + observer discussion • Feedback to applicants	• **ISGlobal/BOHEMIA** • VCAG members • Observers • WHO VCAG Secretariat	For information & discussion
15:30 – 17:00	**Presentation & feedback – Spatial repellents (AEGIS)** Chair of session: Salim Abdulla • Applicant presentation • Q&As • VCAG + observer discussion • Feedback to applicants	• **University of Notre Dame** • VCAG members • Observers • WHO VCAG Secretariat	For information & discussion
Session 5: Formulation of VCAG advice		**Contributors**	**Closed session**
17:00 – 18:00	**Formulation of advice (from day 2)** • Development of recommendations • Draft technical guidance for report	• VCAG Working Groups	For guidance

WEDNESDAY, 5 OCTOBER 2022			
Session 6: Applicant presentations and feedback		**Invitees**	**Open session**
09:00 - 10:30	**Presentation – Interceptor G2** Chair of session: Heather Ferguson • Applicant presentation • Q&As	• **BASF and affiliated applicants** • VCAG members • Observers • WHO VCAG Secretariat	
11:00 – 12:30	**Presentation – Royal Guard** Chair of session: Neal Alexander • Applicant presentation • Q&As	• **Disease Control Technologies and affiliated applicants** • VCAG members • Observers • WHO VCAG Secretariat	
14:00 – 15:00	**Feedback – Interceptor G2** Chair of session: Heather Ferguson • VCAG + observer discussion • Feedback to applicants	• **BASF and affiliated applicants** • VCAG members • Observers • WHO VCAG Secretariat	

15:30 – 16:30	**Feedback – Royal Guard** Chair of session: Neal Alexander • VCAG + observer discussion • Feedback to applicants	• **Disease Control Technologies and affiliated applicants** • VCAG members • Observers • WHO VCAG Secretariat	
Session 7: Formulation of VCAG advice		**Contributors**	**Closed session**
16:30 – 18:00	**Formulation of advice (from day 3)** Development of recommendations Draft technical guidance for report	• VCAG Working Groups	For guidance

THURSDAY, 6 OCTOBER 2022			
Session 8: Applicant presentations and feedback		**Ivitees**	**Open session**
09:00 – 10:15	**Presentation – Gene drive (population suppression)** Chair of session: David O'Brochta • Applicant presentation • Q&As	• **Target Malaria** • VCAG members • Observers (as necessary) • WHO VCAG Secretariat	For information & discussion
10:45 – 11:45	**Feedback – Gene drive (population suppression)** Chair of session: David O'Brochta • VCAG + observer discussion • Feedback to applicants	• **Target Malaria** • VCAG members • Observers (as necessary) • WHO VCAG Secretariat	For information & discussion
Session 9: Report writing and VCAG meeting wrap-up		**Contributors**	**Closed sessions**
11:45 – 12:30	**Formulation of advice (from day 4)** • Development of recommendations • Draft technical guidance for report	• VCAG Working Groups	For guidance
14:00 – 15:30	**Report writing** • Review report status • Finalize technical guidance to be developed	• VCAG Working Groups	For guidance
16:00 – 16:30	**Report writing** • Review report status • Finalize technical guidance to be developed	• VCAG Working Groups	For guidance
16:30 – 17:00	**Wrap-up of VCAG meeting** • VCAG discussion	• VCAG members • WHO VCAG Secretariat	For information

ANNEX 3. LIST OF PARTICIPANTS

VECTOR CONTROL ADVISORY GROUP MEMBERS

Co-Chairs

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

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

Members

Salim Abdulla (remote participation)
Ifakara Health Institute
Ifakara, United Republic of Tanzania

Neal Alexander (remote participation)
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 (remote participation)
Iowa State University
Iowa, United States of America

Fabrice Chandre (remote participation)
Institut de Recherche pour le Développement
Montpellier, France

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

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

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

Robert Reiner
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Leanne Robinson (remote participation)
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(remote participation, unless noted)

Interceptor G2 (BASF)

Manfred Accrombessi
Martin Akogbeto
James Austin
Kelsey Barrett
Matthew Black
Mailys Bobin
Jackie Cook
Christen Fornadel
Kate Kolaczinski
Nancy Matowo
Jacklin Mosha
Corine Ngufor
Natacha Protopopoff
Achim Reddig (in-person)
Arthur Sovi
Susanne Stutz

Royal Guard (Disease Control Technologies)

Manfred Accrombessi
Martin Akogbeto
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Francis Baud
Matthew Black
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Andy Butenhoff
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Spatial repellents (University of Notre Dame/SC Johnson)

Nicole Achee
Kelsey Barrett
John Greico
Tom Mascari
Ashley Scott

Endectocides (ISGlobal)

Carlos Chaccour
Regina Rabinovich

Gene drive population reduction (Target Malaria)

John Connolly (in-person)
Karen Logan
John Mumford
Geoff Turner (in-person)

Sterile male suppression: Combined SIT/IIT (FAO/IAEA)

Kostas Bourtzis (in-person)

Sterile male suppression: Combined SIT/IIT (Singapore NEA)

Petrina Bey
Chee Seng Chong
Alex Cook
Jue-Tao Lim
Lee Ching Ng (in-person)
Shuzhen Sim
Wilson Tan
Kathryn Vasquez
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Sterile male suppression: IIT (Verily/CDC)

Laura Adams (in-person)
Roberto Barrera
Jacob Crawford
Evdoxia Kakani (in-person)
Gabriela Paz-Bailey
Liliana Sanchez-Gonzalez
Bradley White

WHO SECRETARIAT (in-person participation)

Global Malaria Programme

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