

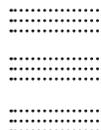
SEVENTH MEETING OF THE VECTOR CONTROL ADVISORY GROUP



GENEVA, SWITZERLAND
24–26 OCTOBER 2017



**World Health
Organization**



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Report of the 7th meeting of the WHO Vector Control Advisory Group

Geneva, 24–26 October 2017

Background

The WHO's Vector Control Advisory Group (VCAG) serves as an advisory body to WHO on new tools, technologies and approaches for the control of vectors of malaria and of other vector-borne diseases. VCAG is jointly managed by the WHO Global Malaria Programme (GMP) and the Department of Control of Neglected Tropical Diseases (NTD), and fully involves the WHO Prequalification Team (PQT) for vector control products. To assist WHO in developing public health policy on new tools, VCAG assesses new interventions and provides guidance on developing evidence. VCAG assesses this evidence once it is generated and provides recommendations to WHO on the public health value of new tools. To date, VCAG has reviewed 17 new tools, comprising 14 new potential product classes. For most of these new tools, technologies and approaches, developers are planning or conducting epidemiological trials to generate evidence to assess their public health value.

VCAG experts and stakeholders convened in Geneva on 24–26 October 2017 for the 7th VCAG meeting. The open session was attended by members of VCAG, applicants and product developers, WHO staff from GMP, NTD and PQT, and other stakeholders, including representatives of donor and procurement agencies. The closed meeting was attended by VCAG members, the WHO Secretariat and the relevant parties only.

General VCAG objectives

1. To assess the public health value of new vector control tools, technologies and approaches submitted to WHO for evaluation.
2. To provide guidance to product developers on data requirements and study designs to generate the evidence required for a VCAG assessment.
3. To provide guidance to WHO and its policy advisory groups, the Malaria Policy Advisory Committee (MPAC) and the Strategic Technical Advisory Committee (STAG) for GMP and NTD, respectively, on the public health value of new tools, technologies and approaches, including updates on evidence gaps that preclude such assessment.

Introductory orientation closed session with VCAG – for information

Five new members were appointed to VCAG in September 2017: Salim Abdulla, Fabrice Chandre, Audrey Lenhart, Hilary Ranson and Robert Reiner. The chair of VCAG, Thomas Scott, introduced the new members present at the meeting and described the functions of the group. He then reviewed the WHO evaluation and policy development pathways for vector control tools, technologies and approaches in the VCAG portfolio.

Conclusions and recommendations – general topics from open session

Updates from WHO

Raman Velayudhan, Coordinator of the NTD's Vector Ecology and Management (VEM), briefed the open session on the functions and activities of VCAG and on WHO's leadership role in policy development for new tools, technologies and approaches for vector control.

Marion Law, Group Lead, Prequalification Team – Vector Control Group (PQT-VC), summarized the activities of PQT-VC to support assessment of safe, efficacious and good-quality products. PQT-VC will initiate manufacturing site inspections and has undertaken co-leadership in the Joint Meeting on Pesticide Specifications (JMPS) of the Food and Agriculture Organization of the United Nations (FAO) and WHO, integrated prequalification of vector control products into the meeting on prequalification (Copenhagen, 17–22 September 2017), and recruited experts for vector control product assessment. The PQT-VC team includes a team leader, a programme manager, an inspection focal point and consultants.

Jan Kolaczinski, Coordinator of the GMP's, Entomology and Vector Control (EVC), reported on two evidence review groups (ERGs): one on comparative effectiveness that reviewed data requirements for new product classes, and another on pyrethroid-PBO (piperonyl butoxide) nets that reviewed new data from one epidemiological study. Detailed outcomes of these ERGs are available on the WHO website.¹ He also provided an update on the topics discussed at MPAC, including malaria threat maps,² guidelines on universal coverage of long-lasting insecticidal net (LLINs)³ and the VCAG update to MPAC. Critical feedback relevant to VCAG concerned the need to review definitions for new product classes and clarify the criteria for assigning the pathway for evaluation of new vector control product submissions. Detailed recommendations are captured in the MPAC meeting report.⁴

Conclusion

- **As per MPAC's request, WHO will work with VCAG to review definitions of new tools and product classes, and update documentation on the product evaluation process.**

Modelling entomological surrogates for epidemiological outcomes

Steve Lindsay and Thomas Scott summarized VCAG's work and recommendations related to entomological surrogates for epidemiological outcomes. A "surrogate" here refers to a biomarker intended to substitute for a clinical end-point. Tom Smith reviewed the possible uses and limitations of entomological surrogates in evaluating vector control interventions. Tom Churcher reported the preliminary results of a meta-analysis based on data generated from experimental hut trials and randomized control trials (RCTs) investigating the impact of indoor adulticidal mosquito control interventions against malaria. The analysis tested the ability of transmission dynamic models, parameterized with entomological data from experimental hut trials, to predict RCT outcomes in different epidemiological settings.

¹ <http://www.who.int/malaria/mpac/policyrecommendations/en>

² <http://apps.who.int/malaria/maps/threats/>

² <http://apps.who.int/malaria/maps/threats/>

³ <http://apps.who.int/iris/bitstream/10665/259478/1/WHO-HTM-GMP-2017.20-eng.pdf>

⁴ <http://www.who.int/malaria/publications/atoz/mpac-report-october-2017/en/>

Conclusions

- An extensive review of the data was not conducted by this committee. Rather, the two presentations explored the use of entomological surrogates and transmission dynamic models for predicting public health outcomes for specific purposes.
- One presentation highlighted that, for some vector-borne diseases (e.g. dengue and other *Aedes*-borne viral diseases), few epidemiologically relevant entomological surrogates have been identified and, for other diseases, surrogates that may be informative require considerable effort to collect (e.g. the entomological inoculation rate for malaria vectors).
- For interventions that target malaria vectors inside houses, a modelling study indicated that there is a positive correlation between model predictions based on data generated from experimental hut trials (i.e. WHO Pesticide Evaluation Scheme [WHOPES] Phase II for LLINs) and the observed epidemiological impact measured in an RCT. More data are needed to better understand the relationship between entomological data and epidemiological outcomes, and to use that information to predict the effectiveness of vector interventions.
- Modelling can help in trial design and in predicting how a new intervention will function; however, modelling based on entomological surrogates is not currently recommended as a replacement for epidemiological RCT data, and should not be used as the primary evidence supporting decisions on the efficacy to public health of new product classes.

Recommendation

- When further evidence is available, VCAG should review the utility of modelling based on entomological surrogates in supporting the formulation of specific WHO recommendations. At present, it is recognized that epidemiological data are key for policy development associated with new product classes.

Integrating entomological and epidemiological trial designs for LLINs

Some new LLINs under development will contain non-pyrethroid active ingredients, alone or in combination with pyrethroids. For pyrethroid-only nets or for nets where the active ingredient is fast acting, current entomological testing guidelines¹ can be used to generate entomological evidence to demonstrate efficacy, although an update of these guidelines is required to ensure that data requirements associated with the revised evaluation process for vector control tools are being met. For new LLINs that include a novel insecticide or a novel claim, VCAG requires both epidemiological and entomological data to assess the net's potential public health value. Studies on LLIN durability (i.e. WHOPES Phase III) will still need to be conducted. To investigate how to collect these data alongside RCTs, VCAG is developing guidance for an RCT protocol design that includes entomological data requirements relevant to LLIN durability. A sample protocol will be finalized in early 2018 (Q1/Q2) and will be made available for reference. VCAG will review and provide feedback on the protocol for integrating WHOPES Phase III evaluation into epidemiological trials as it is developed.

¹ Guidelines for laboratory and field testing of long-lasting insecticidal nets. Geneva: World Health Organization; 2013 (WHO/HTM/NTD/WHOPES/2013.1, <http://www.who.int/whopes/resources/9789241505277/en/>).

Open discussion on VCAG processes and policy development for new vector control tools

The following topics were raised for discussion with stakeholders during the open session: improved communication with stakeholders; clarity in WHO pathways for assessment and policy development for new vector control tools; addressing the cost and disadvantages of first-in-class products; funding for epidemiological trials; and encouraging the development of effective new products which may cost more than current tools.

Conclusions

- WHO policy recommendations need to be evidence based. VCAG is charged with reviewing evidence, but is sometimes criticized for causing delays in the deployment of innovations due to rigorous data requirements. VCAG's role to support WHO recommendations on public health policy for new products is critical for countries where vector-borne diseases are endemic and where lack of capacity and financial support in public sectors makes it more difficult to generate necessary evidence and to evaluate new products.
- Policy recommendations for all public health interventions, including vector control, require a well-developed evidence base and should not be based on minimal datasets. For all new public health products, including medicines and vaccines, the cost and time needed to generate evidence to support public health use is a challenge. For medicines and vaccines, however, evidence reviews are undertaken by national regulatory authorities that are highly advanced in many countries. Such reviews are generally not undertaken for vector control products.
- The absence of a comparable rigorous assessment process of efficacy, safety and quality of vector control tools caused Member States to request that WHO provides these independent assessments to provide an evidence base for policy development. Currently, Member States endemic for vector-borne diseases rely heavily on the evaluation of efficacy, safety and quality conducted by WHO (VCAG and PQT-VC).
- Manufacturers should justify to their leadership the cost and timelines for development of new vector control tools, and ensure that they have the capacity – just as manufacturers of drugs and vaccines do – to support the development of protocols and oversee evaluations in line with VCAG guidance. Manufacturers need to have adequate technical expertise or collaborate with partners that have the appropriate expertise to carry out independent RCTs under the new evaluation process.
- Clear evaluation criteria for new first-in-class products will assist manufacturers to plan for the costs and time associated with cluster randomized trials. Although to date the trials themselves have typically not been funded by manufacturers, VCAG acknowledges that manufacturers may experience significant difficulties in manufacturing a limited number of test products required for trials, followed by a period of no production while waiting for trial outcomes. Regulatory harmonization is being explored to help shorten timelines for first-in-class products.

Duration of trials

The current VCAG guidelines recommend two transmission seasons for epidemiological trials, which are envisioned to occur over 2 years. The ERG on pyrethroid-PBO nets, however, recommended an additional year of data collection for an ongoing trial in the United Republic of Tanzania to assess current expectations of an effective LLIN lifespan of 3 years, and epidemiological impact over this

duration. In this context, VCAG discussed amendments to the current recommendations on trial duration.

Conclusions

- VCAG recommends that at least two well-implemented RCTs with epidemiological outcomes be conducted for first-in-class products. The duration of epidemiological assessment, excluding the baseline period, should cover at least 2 years, to account for inter-annual variation in transmission.
- For LLINs, planning for a 3-year trial duration is recommended to allow assessment of whether the product meets current expectations of an effective LLIN lifespan of 3 years and the interval used to plan LLIN replacement campaigns. For other products that claim an effect longer than 2 years there may similarly be a longer trial period required to assess product claims.

Vector traps test guidelines

An update was given on the VCAG guidelines for efficacy testing of vector traps for disease control. VCAG has reviewed several prototype vector traps targeting *Aedes* mosquitoes. Manufacturers are working to generate the evidence to support proof of concept on the entomological and epidemiological efficacy of traps, and have requested guidance from WHO on the efficacy criteria and testing methodology to generate evidence that will support policy decisions on these new tools. A drafting committee was formed following the 6th VCAG meeting to develop these guidelines. Between September and November 2017 the committee conducted a review of commonly used methods for testing traps, and is consolidating evidence on this topic. A new draft will be prepared and circulated for peer review and public comment before the final guideline is published. A meeting to develop the final guideline should be planned to take place after the peer review and public comment.

Conclusions and recommendations: products and product classes

Sylando 240SC – new submission

Sylando 240SC, a chlorfenapyr-based indoor residual spraying (IRS) product, claims to induce mortality in malaria vectors when used in IRS applications, similar to other IRS products currently covered by WHO policy such as bendiocarb or alpha-cypermethrin. Chlorfenapyr, a broad-spectrum pyrrole-class insecticide used in agriculture and pest control, acts on contact with the mosquito to uncouple mitochondrial oxidative phosphorylation, causing mortality of the insect. The application dossier for Sylando 240SC included information from field efficacy studies showing that chlorfenapyr induces mortality in malaria vectors; however, it showed much lower mortality rates than other products, when evaluated using currently recommended cone bioassays. Chlorfenapyr's mode of action, disrupting oxidative phosphorylation in the mitochondria, differs from other public health insecticides, which act mainly as neurotoxins to cause rapid knock-down and mortality in exposed mosquitoes.

The product was reviewed twice by WHOPES – in 2013 and 2016.¹ Chlorfenapyr 240SC (Sylando 240SC) applied at a target dosage of 250 mg active ingredient (AI)/m² induced overall mortality rates between 22% and 69% (72-hour holding period) during the first 4 months after spraying, which fall below the minimum WHO criteria of ≥80% mortality in the cone bioassay. Cross resistance studies were done on pyrethroid susceptible and resistant mosquito strains as follows: kdr (*An gambiae*), oxidase (*An arabiensis* - Tanzania, *An gambiae* West and East Africa, *An funestus* – S africa), as well as AChE (*An gambiae*) OP/carb resistant strains. To date, no cross-resistance has been detected to chlorfenapyr.^{2,3,4} Currently, cross-resistance studies are being done using Centers for Disease Control and Prevention, Atlanta, Georgia (CDC) bottle assays to identify the diagnostic concentrations. Traditional WHO susceptibility assay protocols are under revision for this product due to product-specific difficulties impregnating the test papers with the active ingredient for WHO bioassays to monitor insecticide resistance.

Conclusions

- **Sylando 240SC has a different entomological effect from a pyrethroid IRS product, because it induces delayed mosquito mortality. Due to this novel mode of action, Sylando 240SC represents a first-in-class chlorfenapyr-based IRS product. There is a great need for non-pyrethroid IRS products to be evaluated as alternatives for malaria vector control. The product was therefore submitted to VCAG for further review and advice on the data requirements to demonstrate its public health value.**
- **This product does not meet the current thresholds as specified in the WHO testing guidelines of ≥80% mortality after a 30-minute exposure and 24-hour holding period.⁵ A revised bioassay methodology of a 2-hour exposure followed by a 72-hour holding period would be useful in evaluating the efficacy of Sylando 240SC.**
- **Whether the observed mortality in free-flying mosquitoes is sufficient to induce an epidemiological impact will need to be evaluated in field RCTs with epidemiological end-points. VCAG will work with the innovator to advise on trial design.**

Recommendations

- **Due to the delayed mortality effect, Sylando 240SC cannot be assessed against currently recommended evaluation criteria, and is not covered by current WHO policy for IRS products. It is therefore necessary to generate epidemiological evidence to assess its public health value.**
- **The product should be evaluated in at least two cluster randomized trials with epidemiological end-points in areas of high pyrethroid resistance. The study arms should be universal access to standard LLINs versus universal access to standard LLINs plus Sylando 240SC IRS.**

¹ Report of the twentieth WHOPES Working Group meeting. Geneva: World Health Organization; 2017 (<http://apps.who.int/iris/bitstream/10665/258921/1/WHO-HTM-NTD-WHOPES-2017.04-eng.pdf?ua=1>).

² Oxborough RM et al. Evaluation of indoor residual spraying with the pyrrole insecticide chlorfenapyr against pyrethroid-susceptible *Anopheles arabiensis* and pyrethroid-resistant *Culex quinquefasciatus* mosquitoes. *Trans R Soc Trop Med Hyg.* 2010;104:639–645.

³ N'Guessan R et al. Chlorfenapyr: a pyrrole insecticide for the control of pyrethroid or DDT resistant *Anopheles gambiae* (Diptera: Culicidae) mosquitoes. *Acta Tropica.* 2007;102:69–78.

⁴ Oliver SV et al. Evaluation of the pyrrole insecticide chlorfenapyr against pyrethroid resistant and susceptible *Anopheles funestus* (Diptera: Culicidae). *Trop Med Int Health.* 2010;15:127–131.

⁵ Guidelines for testing mosquito adulticides for indoor residual spraying and treatment of mosquito nets. Geneva: World Health Organization; 2006 (http://apps.who.int/iris/bitstream/10665/69296/1/WHO_CDS_NTD_WHOPES_GCDPP_2006.3_eng.pdf).

- **VCAG recommends that for all products in new product classes undertaking epidemiological trials, the duration of epidemiological assessment, excluding the baseline period, should cover at least 2 years, to account for inter-annual variation in malaria transmission.**

Interceptor® G2 - update

Interceptor® G2, an LLIN containing alpha-cypermethrin and chlorfenapyr, was reviewed by the 20th WHOPE Working Group¹ and the 6th VCAG.² This product received an interim recommendation as a pyrethroid-only net at the 20th WHOPE Working Group meeting. To allow assessment of the product against its full product characteristics, the manufacturer was advised to engage with VCAG for advice on data generation to determine the public health value of this potential first-in-class product of a new class of insecticide-treated mosquito nets (ITNs). At the 6th VCAG meeting, the applicant was requested to develop a concept note detailing plans for at least two epidemiological trials. Representatives from BASF SE, Germany, provided information on potential plans for cluster randomized trials, outlining two options (Burkina Faso and Malawi) in addition to an independent cluster randomized trial in the United Republic of Tanzania that is already planned by researchers at the London School of Hygiene & Tropical Medicine (LSHTM) and funded by the United Kingdom of Great Britain and Northern Ireland (United Kingdom) Medical Research Council.

A detailed protocol for the trial in the United Republic of Tanzania was presented by researchers from the LSHTM. The proposed trial is a multi-arm, single-blinded, cluster randomized trial with a village hamlet as the unit of randomization. The trial will compare Interceptor® G2 against the standard Interceptor net in an area of high pyrethroid resistance, using a superiority design with standard LLIN as the control arm. With the number of clusters available per arm, the trial can be powered for a 30% reduction or more (superiority) in incidence of the new products relative to control. The proposed trial design addresses a series of important questions about the use of LLINs in the context of growing concern about the impact of insecticide resistance.

VCAG cautioned that if the new method by Hooper and Bourke³ is used to calculate sample size, the study design should be based on more conservative assumptions than those currently applied, because there is no evidence presented to support the assumptions of temporal autocorrelation with this method in designing cluster randomized trials for vector control interventions. VCAG encourages the use of innovative methodology, but because this carries some risk, assumptions for sample size calculation should err on the side of caution. There was also concern that the trial may currently be designed to try to answer too many questions, and that the applicants should consider a simpler design with fewer study arms.

Conclusions

- **The concept note provided by BASF describes several trials to potentially evaluate Interceptor® G2, but was insufficiently detailed to gain a clear understanding of future research plans. The**

¹ Report of the twentieth WHOPE Working Group meeting. Geneva: World Health Organization; 2017 (<http://apps.who.int/iris/bitstream/10665/258921/1/WHO-HTM-NTD-WHOPES-2017.04-eng.pdf?ua=1>).

² Sixth meeting of the vector control advisory group. Geneva: World Health Organization; 2017 (<http://apps.who.int/iris/bitstream/10665/258682/1/WHO-HTM-NTD-VEM-2017.05-eng.pdf?ua=1>).

³ Hooper R and Bourke L. Cluster randomized trials with repeated cross sections: alternatives to parallel group designs. *BMJ*. 2015;350:h2925.

protocol presented by LSHTM for the trial in the United Republic of Tanzania was highly detailed and at an advanced stage of trial design.

- It was noted that no additional data have been provided to support the claim that the product can be used “to control insecticide resistance”; at present, evidence is limited to one trial conducted in an area of resistance to organophosphate and carbamate insecticides. No specific data on resistant mosquitoes were provided from that study location. To substantiate the current claim, further entomological studies should be conducted on a range of insecticide-resistant populations, and data provided on possible occurrence of cross-resistance and resistance allele frequencies to indicate resistance levels for mosquitoes that survive after exposure to the LLIN. Entomological evidence can be generated as standalone studies or embedded into an RCT.

Recommendations to BASF

- The company is strongly encouraged to partner or collaborate with organizations or investigators experienced in trial design for evaluation of vector control products and compliance with regulatory processes to support the development of a detailed study protocol.
- Once such a trial protocol is available, including specifics on the study location, it should be shared with VCAG for review and feedback. VCAG would be willing to undertake the required review remotely, if submission of the documentation does not coincide with one of the scheduled meeting dates.

Recommendations to researchers from LSHTM

- The primary outcome of epidemiological trials should be malaria case incidence rather than prevalence of malaria infection which could be a secondary outcome. Clinical malaria incidence is the most relevant end-point.¹
- The sample size calculation and the way in which the clusters are defined should be reconsidered to increase sample size per arm. This could be achieved by reducing the number of arms to allow for a larger sample size per arm.
- Applicants should consider the impact of the cross-sectional surveys on malaria transmission or infection incidence within the trial if the number of individuals in each cluster who are tested is a sizable proportion of the total population of the cluster.
- The applicants should consider a control arm of Interceptor LN (alpha-cypermethrin only LLIN) to demonstrate the benefit of the mixture chlorfenapyr plus alpha-cypermethrin over alpha-cypermethrin alone. This should be considered because metabolic resistance involving P450 genes was demonstrated in the targeted mosquito populations, and some P450 enzymes are specific to type I or type II pyrethroids. The trial should, therefore, maintain consistency in the type of pyrethroid used.
- Multiple resistance mechanisms involved in pyrethroid resistance should be monitored.
- VCAG recommends that the epidemiological assessment should cover at least 2 years, excluding the baseline period, in order to account for inter-annual variation in human malaria infection or disease.

¹ Hayes RJ and Moulton LH (2009). Cluster Randomised Trials. New York: Chapman and Hall/CRC.

Attractive targeted sugar baits – update

Attractive targeted sugar baits (ATSBs) are designed to attract and kill sugar-seeking anopheline mosquitoes. The concept was initially reviewed by VCAG in 2014. In 2015, a 2-year proof of concept study was initiated in Mali in collaboration with the Innovative Vector Control Consortium (IVCC) using seven treated and seven untreated villages. VCAG reviewed updates on the ongoing proof of concept assessments and development plan for ATSBs, including plans for RCTs to demonstrate epidemiological efficacy. The summarized data on the entomological trials in Mali indicated that ATSBs achieved targets of >30% daily feeding on bait stations and 84–95% reduction in the abundance of older female malaria vectors¹ relative to control villages.

The applicant provided summaries from current Phase II trials in Mali and pointed out negligible impact on non-target insects. These are interim data as the Phase II study is expected to be completed by January 2018. It is the applicant's intention to submit the final report to VCAG in 2018 for a full review. Information requested by VCAG includes a detailed proposal of cluster randomized trials and plans for large-scale production of the product.

With regard to choice of trial site, it would be beneficial to have one trial conducted in a low transmission setting because (1) it may prove more difficult to demonstrate epidemiological impact in a high transmission setting, when in fact a similar reduction in transmission may translate into a large reduction in clinical incidence or infection prevalence in a moderate to low transmission setting, and (2) the benefits of the technology may not translate from high to low endemicity settings or vice versa.

Trial governance should be outlined including the independent safety monitoring committee (data safety and monitoring board) appointed for each trial.

VCAG highlighted several points to consider during future protocol development, including consideration for double blinding the trials using placebo bait stations, the need for RCT protocol to address balancing the study arms and clarification on the upper age limit for cohort recruitment for active infection detection. Outcome measures such as clearance of parasites in cohort members at recruitment should be verified by microscopy. Cohort members should be asked about use of ITNs and status of ATSBs in the household at each visit to facilitate secondary per-protocol analysis. Strategy for sampling should be the same in each cluster; in particular, sampling in buffer areas of clusters should be avoided uniformly throughout, not just where adjoining clusters are of the opposite study arm, because it could cause bias due to individuals on peripheries of villages being different from those living in the “core” area. Overall the study research team composition should include experienced expertise from all relevant disciplines. Additionally, VCAG recommended the applicants collect baseline data on the vector species composition and feeding behaviour of vectors at prospective sites before initiating trials. Such baseline data are necessary to anticipate the degree of outdoor biting, location-specific rates of feeding on ATSB which may vary between sites depending on competition from alternative sugar sources, and potential for non-target effects. Trials should only go forward if this baseline indicates the product meets minimum thresholds for efficacy (e.g. 30% feeding rates) and safety at the site.

The applicant specifically asked for advice on methods of age determination of mosquitoes and approaches that can be used to ensure that the results are not biased by observer differences. Alternative options are to use proxies for mosquito age including near-infrared spectroscopy (NIRS), age grading by counting the number of ovarian dilations, parity rate (proportion of parous to non-parous mosquitoes) and sporozoite rates determination where possible. Observer bias in age grading can be reduced by

¹ That is, anopheline females with more than three gonotrophic cycles.

developing an age grading score to be used to compare the proportion of mosquitoes in a given age category recorded by different observers.

Conclusions

- The innovators have presented plans for well-designed trials to evaluate a first-in-class ATSB and addressed many of VCAG's earlier concerns. The applicant has clarified that the projected 30% reduction in incidence is independent of the relative contribution of outdoor biting at each site.
- VCAG noted that the original dossier mentions numerous alternatives for the toxin but justification for selecting a neonicotinoid active ingredient was not provided. Information on safety of the product and the full safety dossier should be reviewed by WHO.

Recommendations

- Innovators are encouraged to submit the full protocol for the RCT to VCAG for review, once it becomes available.
- Subsequent submissions to VCAG should also include a full report in addition to data summaries, so VCAG can make an informed opinion.
- Trials should be appropriately powered to also show differences by study arm for the entomological outcomes. The impact of vector ecology and behaviour at the study sites on the efficacy of the intervention should be investigated as part of the trials. For the trial design presented, VCAG recommends the investigators carefully consider the sampling of households for entomological collections, including clusters per arm. Power calculations are needed for at least one of the entomological outcomes in order to ensure that the sampling is sufficient to show differences by study arm. Preliminary entomological investigations should look at species composition, exophilic biting behaviour, and the potential for competing sugar sources to impact the attractiveness of ATSBs at the selected study sites.
- **An RCT should be considered in moderate to low transmission settings.** Investigators should consider the value of conducting one trial in moderate to low transmission settings, because reductions in transmission in these settings may translate into larger observed reductions in clinical incidence or infection prevalence. This would also help to demonstrate whether the technology can be used in both high and low endemicity settings.
- **All products in new product classes reviewed by VCAG will require a risk assessment and development of specifications before a full WHO recommendation is made.** In addition to a WHO risk assessment taking into account the safety of the product use in and around houses, specific investigations into the potential impact on non-target organisms should be conducted at all study sites. Justification should be provided for the choice of neonicotinoid active ingredient to address potential environmental concerns.
- **Trial governance should be outlined, and a clear statement made that a fully independent safety monitoring committee (data safety and monitoring board) will be appointed for each trial. The applicants should consider if it is appropriate to refine the product claims and the target product profile under development, because while the product is placed outside houses it also may impact indoor biting and transmission.** The target product profile should be broad enough to encompass

other similar products within the product class. Replacement criteria for the bait stations will also need to be defined and testing guidelines developed for ATSB products.

Lethal house lures and eave tubes – update

Eave tubes target indoor biting mosquitoes, specifically anophelines that enter houses via the eaves (open areas between the roof and walls) and that transmit human malaria parasites. Eave tubes aim to reduce mosquito entry into houses by killing host-seeking mosquitoes, and thereby lowering the risk of malaria transmission, if deployed at sufficient coverage. Additional benefits include lowering the population of nuisance mosquitoes and improving airflow inside the houses.

The intervention is a combination of housing improvements, including screening, and installation of eave tubes, which contain an insecticide-treated mesh. The eave tubes consist of a 6-inch polyvinyl chloride (PVC) tube that is built into the wall which is then closed off by an insert – a circular polyethylene casing embedded with gauze that has an electrostatically charged coating. This gauze can be treated with different bioactives in powder form. As part of the current installation for the intervention, the eaves, if present in houses, are closed and custom window screening is installed, limiting mosquito entry. Odours from the inhabitants released through the eave tubes lure host-seeking mosquitoes to the tubes, where they encounter a lethal dose of the insecticide.

The efficacy of eave tubes against clinical episodes of malaria is being evaluated in an RCT in Côte d'Ivoire in West Africa. This is a 2-year study that commenced in April 2017. Preliminary findings for the first 3 months of this trial were presented at the VCAG meeting.

In summary, the trial is a two-arm cluster randomized trial to determine the impact of the eave tubes and household screening in combination with the universal coverage of LLINs, compared to universal coverage of LLINs alone, on malaria incidence and malaria infection incidence in Côte d'Ivoire. The trial has treatment and control arms with village as the unit of randomization. Forty villages were selected and assigned to treatment and control arms using restricted randomization based on demographic, socioeconomic and parasite prevalence data. In the treatment arm, householders were offered the opportunity to have their houses screened and modified with eave tubes. Villages in both groups received LLINs. Fifty children, aged 6 months to 8 years, have been enrolled from randomly selected households in each of the 20 treatment villages and in each control village, and are being followed for malaria infection using active case detection to estimate malaria incidence following initial parasite clearance, which will be the primary end-point. Study cohort children are also being surveyed at the end of each transmission season to estimate the prevalence of anaemia and respiratory infections in addition to the primary malaria readouts. Exposure to malaria parasites is assessed using CDC light traps and human landing catches followed by molecular confirmation of *Anopheles gambiae* species and testing for sporozoite infection. Acceptability of the intervention is being captured using focus group discussions, questionnaires and ethnographic surveys, and by measuring the indoor climate. A cost-effectiveness analysis will be conducted to estimate disability-adjusted life years (DALYs) averted by the intervention.

The work for the cluster randomized trial began in January 2016 with the aim of completing all the installations and preparatory studies by January 2017. Monitoring and evaluation is due to run for 2 years following this preparatory phase. Preliminary trial results indicate reductions in malaria vector density and malaria incidence in the arm of the trial with eave tubes compared to the control arm; that is, 41% efficacy of the eave tubes against clinical malaria in children. Preliminary data presented are

encouraging, but results from the full 2-year study are required for an assessment of public health impact.

Conclusions

- VCAG notes that the initial findings from the cluster randomized trial in Côte d'Ivoire are encouraging, and show initial declines in clinical malaria incidence; however, the trial that commenced in April 2017 is still in an early stage and future results will show whether the initial reductions in vector density and malaria incidence will be maintained for the duration of the trial.
- This intervention is supplementary to the use of LLINs and consists of two components: insecticide-treated mesh in eave tubes and house screening.

Recommendations

- **A second RCT should be conducted in a different eco-epidemiological setting to assess the public health value of eave tubes.** Investigators should initiate planning for a second cluster randomized trial of eave tubes with epidemiological outcomes in another location with different ecology and transmission dynamics using the same insecticide or another fast-acting insecticide. In this trial it would be important to separate out the control achieved by eave tubes alone versus house screening alone. One method of demonstrating this would be a four-arm trial consisting of (1) eave tubes, house screening and LLINs, (2) eave tubes and LLINs, (3) house screening and LLINs and (4) LLINs alone. Such a trial would be best conducted in an area of low or moderate malaria transmission in order to maximize the observed protective efficacy of the interventions. The specific details of the trial (i.e. design and location) should be developed through further dialogue between the investigators and partners, and shared with VCAG for review and feedback.
- **Investigators should consider the impact of building material, house architecture, indoor climate and the number of people sleeping indoors on the entomological efficacy of the intervention.** The insecticidal efficiency of the eave tubes may vary according to the rate at which human odours pass out of the eave tubes, which is dependent on a number of factors including building material, house architecture, indoor climate and the number of people sleeping indoors. Investigators should consider running small-scale field studies to determine whether these sources of variation lead to significant changes in the entomological efficacy of the intervention, which will help to inform formulation of policy recommendations and programmatic guidance.
- **Investigators should conduct household studies of human behaviour related to use of the intervention during the trial.** Differences in behaviour between eave tube users and non-users in villages with eave tubes will impact the efficacy of the intervention, including behaviour such as nighttime door opening and closing during the trial. VCAG recommends that efforts are made to capture any social and behavioural information in the groups, which may include the social and economic positions of those enrolled in the study groups as well as information on the types of house structures. Follow-up studies on the intervention should also note the size of any holes or gaps around the doors, windows, eave tubes and walls at various intervals during the trial.

Spatial repellents – update

Spatial repellents interrupt human–vector contact through vector behaviour modification induced by airborne chemicals, potentially offering protection from bites from vectors and nuisance pests. The spatial repellent intervention proposed is a transfluthrin-based passive emanator produced by SC Johnson,

designed to release a volatile chemical into the air and prevent human–vector contact within the treated space. The intervention targets *Anopheles*, *Aedes* and *Culex* spp., and is intended to protect all age groups and populations in vector-borne disease endemic countries from daytime, early-evening or late-night biting from mosquitoes in enclosed and semi-enclosed structures. Epidemiological trials are currently under way in Sumba Island, Indonesia, and Iquitos, Peru, to generate evidence of public health effect against malaria and dengue, respectively.

In Indonesia, epidemiological and entomological follow-up is ongoing to confirm the number of malaria cases and sporozoite-positive mosquitoes. Insecticide susceptibility tests are under way for the primary malaria vectors in the study clusters, to determine whether there is evidence of resistance development. Trial follow-up in Indonesia is expected to be completed between December 2017 and March 2018.

In Peru, a protocol amendment was made in June 2016 due to evidence for Zika transmission in the area. The amendments were for (1) expanding the inclusion criteria for cases to include cases with rash, arthralgia, arthritis or non-purulent conjunctivitis without fever;; (2) permission to collect other bodily fluids (e.g. urine, saliva and nasal fluids); and (3) to include a questionnaire to assess household participants' perceptions of efficacy of the Shield spatial repellent product. Follow-up epidemiological measures in the study site include febrile surveillance and seroconversion for the longitudinal cohort study. Baseline pupal demographic surveys were conducted at least twice before product deployment, with adult aspirator collections conducted every 2 weeks thereafter. Other ongoing studies include insecticide susceptibility testing and blinded surveys to gather information of efficacy and acceptability in Iquitos, Peru. Trial follow-up in Peru is expected to be completed in December 2018.

The applicants provided a summary of specific questions they wanted feedback on from VCAG, which are addressed in the Conclusions.

Conclusions

- VCAG notes the significant progress made in the trials in Indonesia and Peru, and appreciates the efforts made by applicants to address previous recommendations, including acquisition of transfluthrin resistance data and quality assurance.
- On the question of endorsement for use in Indonesia if protective efficacy is shown in the current study, the committee advises a second epidemiological trial would still be needed if a policy recommendation based on public health value is to be made, and encourages the applicants to consider a second trial conducted in Africa for malaria. The committee regrets that support for the originally planned studies in Africa was withdrawn, and continues to see such a study as essential for the assessment of the public health value of the product.
- A major challenge identified at the last review was the issue of manufacturing sustainability for the current product, which may be replaced by a new version with longer activity in the field. VCAG concluded that if a subsequent trial was done with the new product, it could still be considered under the spatial repellents product class if the new product can be shown to have a similar entomological effect and, ideally, longer activity in the field. Further advice will be sought from PQT-VC on procedures that will be followed within the prequalification programme for product variations.
- Preliminary results from Indonesia and Peru indicate that prevalence (and entomological inoculation rate for malaria) may be lower than originally assumed when doing power calculations for the trial, and noted that it may be possible to extend the length of the study in order to detect differences between the study arms.

Recommendations

- VCAG strongly encourages the applicants to revisit the original power analyses with updated information to determine if the current studies are sufficiently powered. If needed, applicants should consider extending the length of studies to achieve minimal sample size requirements.
- A second RCT should be conducted in a different eco-epidemiological setting to assess the public health value of spatial repellents against malaria. VCAG recommends that a second trial for malaria prevention be carried out in Africa, and that this trial uses a design that addresses spillover between clusters and evaluates the diversion effect on vectors to unprotected people.
- For replacement of the current product with a next-in-line product for future RCTs, entomological data should be presented to demonstrate the similarity in entomological effect between the current and new proposed product.

Vector traps: adulticidal oviposition traps – update

Adulticidal oviposition traps (AOT) target gravid *Aedes aegypti* mosquitoes with the aim of reducing vector populations to control transmission of *Aedes*-borne arboviral diseases.

AOTs are proposed as simple, effective devices for control of *Aedes* mosquitoes that can be deployed and maintained at the community level. The devices are designed to be compatible with traditional *Aedes* vector control measures and also used as a standalone method to reduce vector populations. They are claimed to have limited impacts on non-target organisms and to selectively target older age classes of female mosquitoes, which are most likely to be the virus-infected stages of the vector. AOTs are also claimed to be simple and inexpensive, and suitable for use in vector surveillance as well as control.

The innovators submitted updates to the dossier, including results based on work with the adulticidal gravid ovitrap (AGO) in Puerto Rico related to entomology, an epidemiological study related to chikungunya, and statements about economics and costing, technology development, compliance, delivery and environmental impact of this product. Initial results from one study in one city in Puerto Rico compared chikungunya infection (via serology) at two sites with and two sites without AGOs (deployed at three per household). Publications were also provided to support the assessment including general reviews of a range of trap prototypes, and small ovitraps for surveillance.

Conclusions

- Entomological data summaries from field trials in Puerto Rico indicated significant reductions in *Aedes* mosquito densities. In order for VCAG to conclusively evaluate this study, the detailed study protocol, statistical analysis and results (i.e. dataset) are needed.
- The results from a preliminary epidemiological study in Puerto Rico are encouraging, but cannot substitute for properly designed and powered RCTs. Doing such a trial is the necessary next step to advance the evidence supporting this approach.
- Achieving and maintaining compliance will play a large role with this intervention. The monitoring and trap upkeep scheme proposed (i.e. routine monitoring and regular replacement of three traps per house, every 6 to 8 weeks, with 85% coverage) seems very demanding. The risks associated with failing to do this are also high, because unserviced traps could turn into larval development sites. More information should be provided on the feasibility of this programmatic delivery, as should data on the potential risk from leaving containers unserviced.

- **Vector traps should be considered as part of a multipronged integrated vector management approach rather than as a standalone intervention, because current evidence suggests that tools used in isolation are unlikely to reduce incidence of *Aedes*-borne diseases.**

Recommendations

- **Innovators are encouraged to submit the current trial protocol and any subsequent plans for detailed review by VCAG. Data related to the previous recommendations from this group should also be provided; for example, how the traps work on different vector species, and the impact of behavioural and ecological differences on trap efficacy.**
- **Investigators should provide data on the optimal density of application (number per house) and coverage of the trap, how compliance estimates were achieved and feasibility of the intervention.**
- **Information on the durability and attrition of traps under field settings would be needed for a policy recommendation.**
- **Two RCTs will be needed for VCAG assessment. RCTs conducted in different eco-epidemiological settings will be needed for full assessment of the public health value of vector traps.**

Vector traps: auto-dissemination devices – update

In2Trap, an auto-dissemination device, aims to attract gravid *Aedes* mosquitoes and expose them to both a slow-kill entomopathogenic fungus and the insect growth regulator larvicide, pyriproxyfen. Egg-laying females visiting the trap are contaminated with pyriproxyfen and adulticidal fungal spores. The pyriproxyfen kills late-stage larvae and pupae that develop in the trap and is disseminated by the contaminated females when they visit other egg-laying sites. The fungal spores induce a slow-killing effect (within 14 days) for infected adult mosquitoes. The slow-killing mode of action of the fungus enables active pyriproxyfen auto-dissemination by the contaminated or infected mosquitoes. Further studies are needed, however, to determine the impact on infection or disease. An improved prototype was developed and is being marketed by the manufacturers. The trap is now registered as a professional pest control product in more than 30 countries, with registration pending in a further 20 countries. A summary of findings to support the product claim was given based on studies conducted in Manatee County in Florida and Grand Cayman Island. Plans are being developed for epidemiological studies in four Asian countries. The manufacturer has submitted entomological data from semi-field studies and small-scale field studies, as well as information on costing and manufacturing sustainability. No epidemiological data have been provided to VCAG.

In2Care traps provide continuous vector control and need servicing with fresh water and refills every 4–6 weeks. The traps are placed outdoors at a recommended density of 1/400 m² (10 traps per acre) in areas where *Aedes* mosquitoes are abundant and where there is active transmission of *Aedes*-borne diseases or a risk thereof. They are especially suited for vector control in hotspot areas where small and cryptic (hard to find) breeding sites are abundant. The prototype has been adapted (the 2.0 model has an increased container size to improve evaporation time, possibility of fixation tools increasing trap stability, and fewer separate components). Production capacity is now 1.5 million traps per year, and the production capacity for refill sachets is now 10 000 per week. In2Care Mosquito Trap was registered as a professional pest control product in the United States of America by the US Environmental Protection Agency in July 2017.

Conclusions

- While the In2Trap is already largely commercialized for use as a professional pest control product, the available entomological evidence suggests this trap may also have potential to reduce diseases caused by *Aedes*-transmitted viruses. This justifies carrying out trials with epidemiological outcomes to assess its public health value. The In2Trap should not be considered as a standalone intervention, but as part of an integrated vector management approach.
- The In2Care Mosquito Trap fits within the product class of auto-dissemination traps for disease management. Further entomological evidence should be generated to advise the design of large-scale epidemiological trials.

Recommendations

- The innovator recommends a trap density of 1/400 m² (10 traps per acre). Data should be provided to estimate the contamination of breeding sites in relation to the distance from In2Trap, and to demonstrate the duration of efficacy that can be expected from the trap, specifically with respect to impact on mosquito populations from re-dissemination of pyriproxyfen.
- Semi-field experiments should be carried out to determine whether the killing effect on adult *Aedes aegypti* mosquitoes will be high enough to impact vectorial capacity.
- The residual activity after application of a refill sachet (In2Mix) is reported to be 4–6 weeks. Additional data should be provided to demonstrate this interval is appropriate under variable external factors, such as temperature.
- For optimal efficacy, the innovator recommends that natural larval development sites be removed as much as possible. This should be quantified; that is, determining what effort is required to accompany use of this product and what the estimated density is of natural container sites with which the product can effectively compete.
- Before undertaking epidemiological studies, larger entomological intervention trials with randomized clusters are needed to demonstrate entomological efficacy.
- The assessment of risk to humans of handling and application of the product and environmental risks (including non-target organisms) should be done based on the data provided by the innovator.

Genetically modified mosquitoes/Oxitec – update

OX513A is a transgenic strain of *Aedes aegypti* engineered to reduce targeted mosquito populations via a genetic system that causes larvae carrying the OX513A construct to develop normally but die before functional adulthood. VCAG has previously concluded that these transgenic mosquitoes have the potential to reduce and suppress *Aedes aegypti* populations significantly, which could lead to declines in the transmission of dengue and Zika viruses, and recommended the developers carry out trials to evaluate epidemiological effectiveness of this tool. The current update provided a high-level overview of plans for development of an RCT and additional information on field production facilities for OX513A mosquitoes.

Information provided in the update on a field production facility was consistent with and supported previous confidence in the production capacity of OX513A mosquitoes for a field trial. A preliminary comparison of dengue cases reported from a single treated and control area in Brazil adds support to the recommendation to assess this product in epidemiological field trials.

Conclusions

- Results from epidemiological trials remain the primary missing information for assessment of the public health value of this product. Epidemiological studies must be carried out to assess the public health value of reducing vector populations through the application of OX513A.
- Concerns were raised that the draft design presented at the meeting is underpowered, that primary and secondary outcomes merit additional consideration and more thorough explanation, and that proposed serological measurement of baseline data and trial outcomes will be complicated by pre-existing dengue and Zika virus immunity.

Recommendations

- VCAG requests that a detailed epidemiological study design be submitted for review before initiation of a trial.
- Empirical evidence should be provided regarding how quickly populations recover and how frequently (and at what volume) releases need to be maintained to sustain a long-term population reduction effect.
- Alternative models should be explored in the planning for RCTs, and the model proposed¹ does not adequately address the needs for this stage of project planning.
- As data from RCTs are developed, the innovators are encouraged to provide a detailed overall plan for costs of deploying this product, a refined target product profile, and further plans for scaling up delivery in an operational context for review. Although VCAG will not draw on these data to assess the public health value of a product, costing data will be useful to inform formulation of policy recommendations and programmatic guidance.
- A strong community engagement and acceptance strategy will be critical for this intervention.

Systemic insecticides – update

Systemic insecticides for control of vector-borne diseases were proposed to VCAG in 2015, through a prototype systemic insecticide that targets arthropods feeding on rodent reservoirs of cutaneous leishmaniasis and plague. The current proposal presents a cattle treatment product that works primarily as a systemic drug to control biting sandflies that transmit visceral leishmaniasis. This product claims to be safe for use in cattle and humans, and to be effective for a duration of 1 month. The current alternative control measure for leishmaniasis is IRS. In India, DDT remains the only chemical approved for sand fly control using IRS. A synthetic pyrethroid was tested over the past several years by CARE, however this was for experimental use only.

The manufacturer presented recent results from trials completed in India on the safety testing of a fipronil bolus for treatment of cattle for vector control, and reviewed the status of safety and regulatory approval processes under way. Data were presented from pilot studies using fipronil bolus implants in cattle to control leishmaniasis, which indicate that this intervention can reduce sandfly populations. A large-scale community trial has been planned, and the protocol will be shared with VCAG for review.

Conclusions

¹ Focks DA, Brenner RJ, Hayes J and Daniels E. Transmission thresholds for dengue in terms of *Aedes aegypti* pupae per person with discussion of their utility in source reduction efforts. Am J Trop Med Hyg. 2000;62:11–8.

- The use of systemic insecticides in animals for controlling vector populations is highly original and has the possibility of making an important contribution to disease control.
- Trials are still in very early stages. Future results will determine whether the initial reductions in vector density and disease will be maintained for the duration of the trial.

Recommendations

- The investigators should modify their product claim for VCAG evaluation, specifically focusing on using fipronil bolus implants in cattle to reduce sandfly populations and control leishmaniasis.
- VCAG recommends the investigators carry out two RCTs with epidemiological end-points to estimate the protective efficacy of this tool for leishmaniasis control in different ecological and epidemiological settings. This can also be done in a setting where both visceral leishmaniasis and malaria are present (e.g. Sudan), with epidemiological outcomes on both leishmaniasis and malaria, if the manufacturer also wishes to generate evidence supporting present or future claims of efficacy against malaria.
- A multi-arm trial design that can assess the impact of fipronil on leishmaniasis when used in concert with an IRS intervention is recommended. Any RCTs should include some monitoring for the development of drug resistance in vectors and other pathogens in cattle, which are usually treated by similar veterinary drugs.
- Developers are strongly encouraged to build expertise within their own companies or collaborate with a group experienced in trial design and evaluation of vector control products, and to share trial protocols with VCAG for review and feedback as early as possible in the trial design process.

Combined intervention with treated clothing for malaria control in the Greater Mekong subregion – new submission

The Consortium for Health Action submitted an application to VCAG with a view to achieving WHO policy recommendations for two vector control products: (1) the “Red to Green, keep it Green” information system implementation as an intervention to achieve high vector control usage, and (2) permethrin-treated clothing as product for malaria prevention.

Conclusions

- The VCAG mandate to assess the public health value of new tools for vector control does not cover information systems, because these cannot be considered vector control products or interventions.
- VCAG notes that an application for permethrin-treated clothing is within the mandate of this group. Such an application should include specific product claims, review existing evidence for the public health impact of this tool, and detail plans (e.g. trial design proposals) to generate evidence that the product is effective at reducing infection or disease in the targeted population.

Introductory discussion with Disease Control Technologies LLC – Royal Guard®

An initial conversation with Disease Control Technologies LLC was held by teleconference on Royal Guard® LN, an innovative vector control LLIN product for review by VCAG. Royal Guard® LN is an LLIN with a combination of pyrethroid (alpha-cypermethrin) and insect growth regulator (pyriproxyfen)

active ingredients. The combined active ingredients are being proposed in order to sterilize mosquitoes that may survive exposure to a pyrethroid alone (likely due to resistance). In theory, this sterilizing effect should lead to an overall reduction in the next generation of vectors and ultimately reduce the vector population.

WHOPES Phase I testing and a human risk assessment were completed for Royal Guard® LN and Phase II testing is under way in Benin and the United Republic of Tanzania. The data from these studies will be reviewed in detail and discussed before the next VCAG meeting. The process of interim approvals (as previously issued under WHOPES) for pyrethroid-only LLINs is no longer supported by WHO after the transition of vector control product assessment to PQT-VC. Royal Guard® LN is a new type of LLIN with dual active ingredients. For WHO to assess the public health value of this first-in-class product in a new product class, evidence should be provided from at least two well-implemented RCTs with epidemiological outcomes. The duration of epidemiological assessment, excluding the baseline period, should cover at least 2 years, to account for inter-annual variation in transmission. The RCT design protocol should be submitted to VCAG for review before the commencement of the trial.

Conclusions

- The current policy issued by GMP for new LLINs with alternative active ingredients was published in a recent summary of malaria vector control policies¹ and the WHO evaluation pathway document,² and should be complied with for all new submissions.
- As per the WHO policy for new LLINs, Royal Guard® LN cannot be recommended as a pyrethroid-only net without evidence supporting the public health value of adding pyriproxyfen to the LLIN, potentially for use in settings of pyrethroid resistance.

Recommendations

- While trials for other mosquito net products with an insect growth regulator may be ongoing, no other products have been submitted for evaluation by WHO. VCAG therefore recommends that the manufacturers conduct two epidemiological trials, and begin to develop protocols drawing on relevant expertise in the field.
- The developer is strongly encouraged to share trial protocols with VCAG for review and feedback as early as possible.

Operational considerations and final recommendations

- Currently, vector control tools under VCAG review are assessed for public health value. In the case of LLINs, however, where new active ingredients may be added in addition to pyrethroids, the additional public health value of any added ingredients should be considered. This is in line with regulatory processes for medicines and vaccines, where justification is needed for all active ingredients in combination or mixture formulations. VCAG can discuss this topic in more depth at the next VCAG meeting or as a topic for a future expert advisory group on study design.

¹ Malaria vector control policy recommendations and their applicability to product evaluation. Geneva: World Health Organization; 2017 (WHO/HTM/GMP/2017.12, <http://www.who.int/malaria/publications/atoz/vector-control-recommendations/en/>).

² The evaluation process for vector control products [information note]. Geneva: World Health Organization; 2017 (<http://apps.who.int/iris/bitstream/10665/255644/1/WHO-HTM-GMP-2017.13-eng.pdf>).

- Opportunities should be explored to bring together manufacturers of medicines and vaccines with manufacturers of vector control products in order to share knowledge and experiences in product development.
- VCAG recommends that as part of the RCT study design, an independent data safety and monitoring board be established to make decisions about the need for interim analysis of data. Updates from any interim analyses can be presented to VCAG.
- VCAG has prepared updated guidance on what materials should be submitted by applicants. Applicants should submit all application and update information to the WHO Secretariat at least 1 month before each scheduled meeting, including all materials that will be presented at the VCAG meeting. While summary data are useful, VCAG cannot make a comprehensive evaluation without receiving detailed data and trial results. Applicants are asked to only send material directly relevant to the support of their product. After materials are submitted to the WHO Secretariat, VCAG members should have a minimum of 2 weeks to review documents that will be discussed at the meeting.
- As part of their presentation at a VCAG meeting, applicants are encouraged to prepare specific questions for which VCAG guidance is sought; for example, trial design, data analysis and interpretation of results.

Annex 1. Agenda

7th Vector Control Advisory Group (VCAG)

24–26 October 2017

UNAIDS building, 4th floor, Room D-46025

General objectives

- To assess the public health value of new vector control tools, technologies and approaches submitted for evaluation to WHO.
- To provide guidance to product developers on data requirements and study designs to generate the evidence required for a VCAG assessment.
- To provide guidance to WHO and its policy advisory groups (Malaria Policy Advisory Committee – MPAC, and Strategic Technical Advisory Committee – STAG) on the public health value of new tools, technologies and approaches, including updates on evidence gaps preventing such assessment.

Deliverable

- Recommendations to product developers and WHO in the form of a summary report.

Open sessions include VCAG (members + experts) + WHO + selected observers + stakeholders + other participants. Closed sessions are VCAG (members + experts) + WHO only. Observers should contact the WHO Secretariat for an invitation to the meeting at vcag@who.int.

Tuesday, 24 October 2017	
08:30 – 09:30 CLOSED SESSION	Introductory meeting for VCAG members
OPEN SESSION BEGINS: 09:30 – 15:30	
09:30 – 09:40	Opening of meeting – Raman Velayudhan, Coordinator VEM/NTD, and Jan Kolaczinski, Coordinator of EVC/GMP Organizational matters , appointment of rapporteurs – Tom Scott, Chair VCAG
09:40 – 10:00	Overview VCAG – Raman Velayudhan
10:00 – 10:40	Updates/briefings from WHO <ul style="list-style-type: none"> • Update from WHO PQT-VC – Marion Law • Outcomes of comparative effectiveness ERG – Jan Kolaczinski • PBO ERG briefing – Jan Kolaczinski • Relevant outcomes from MPAC – Jan Kolaczinski
10:40 – 11:00 break	
11:00 – 12:30	Entomological surrogates for epidemiological outcomes (1) Introduction by Steve Lindsay / Tom Scott (10 min)

	<p>(2) Modelling entomological surrogates for epidemiological outcomes to evaluate vector control tools – Presentations by Tom Smith and Tom Churcher (50 min)</p> <p>(3) Discussion (30 min)</p>
12:30 – 13:30 lunch break	
13:30 – 14:00	<p>(1) Introduction by Raman Velayudhan</p> <p>(2) Integrating epidemiological and entomological study designs for LLINs – presentation by Mark Rowland and Natacha Protopopoff (20 min)</p> <p>(3) Discussion (10 min)</p>
14:00 – 14:45	Open discussion: supporting innovation in vector control
14:45 – 15:20	Development of guidance on efficacy testing of vector traps – Heather Ferguson and Anna Drexler
15:20 – 15:50 break CLOSED SESSION BEGINS	
15:50 – 17:00	<p>Closed discussion with innovators and VCAG in plenary. (<i>Relevant applicant and VCAG only</i>)</p> <p>Note – session includes 15 minutes orientation (led by dossier leads – <u>VCAG ONLY</u>), 1 x 40-minute innovator presentation plus plenary discussion (<u>VCAG + relevant applicant</u>). Presentation start times are <u>underlined</u> below.</p> <p>Sylando 240SC – new submission – Susanne Stutz and Egon Weinmüller, BASF (<u>16:10 PM</u>)</p>
17:00 – 17:30	<p>Closed discussion: guidance on epidemiological trial duration for non-pyrethroid LLINs.</p> <p>(1) Introduction by Jan Kolaczinski: VCAGs current guidance on trial duration</p> <p>(2) Discussion: Is the current recommended trial duration sufficient to generate evidence for public health use?</p>
Last 15 min	Plenary review and discussion before close: feedback on session operations, orientation for next day
Wednesday 25 October 2017 – CLOSED SESSIONS	
08:30 – 12:30	<p>Closed discussion with innovators and VCAG in plenary. (<i>Relevant applicant and VCAG only</i>)</p> <p>Note – session includes 10 minutes orientation (led by dossier leads – <u>VCAG ONLY</u>), 2 x 40-minute innovator presentation plus plenary discussion (<u>VCAG + relevant applicant</u>). Presentation start times are <u>underlined</u> below.</p> <p>08:30 Interceptor® G2 – update</p> <ul style="list-style-type: none"> • Mark Rowland and Natacha Protopopoff (<u>8:40 AM</u>) • Susanne Stutz and Egon Weinmüller, BASF (<u>9:20 AM</u>) <p>10:20 Attractive toxic sugar baits (ATSB) – update</p> <ul style="list-style-type: none"> • Presentations by Amir Galili, Günter Müller and Mathias Mondy, IVCC (<u>10:30 AM</u>) <ul style="list-style-type: none"> ○ Introduction: The path for ATSB product development (Amir Galili) ○ Interim report of the proof of concept in Mali (Günter Müller) ○ Presentation of the Phase III plan (Mathias Mondy) ○ Conclusion (Amir Galili, Mathias Mondy) <p>11:50 Lethal house lures / eave tubes – update</p> <ul style="list-style-type: none"> • Marit Farenhorst, In2Care (<u>12:00 PM</u>) <p>Break at 10:00; lunch at 12:45</p>

13:30 – 18:00	<p>Closed discussion with innovators and VCAG in plenary. Session includes 10 minutes orientation (led by dossier leads – <u>VCAG ONLY</u>), 40-minute (<u>VCAG + relevant applicant</u>). Presentation start times are <u>underlined</u> below.</p> <p>13:30 Continued: Lethal house lures / eave tubes – update • Matt Thomas, Penn State (<u>13:30 PM</u>)</p> <p>14:10 Spatial repellents – update • Nicole Achee, Eck Institute for Global Health (<u>14:20 PM</u>)</p> <p>15:00 Vector traps: adulticidal oviposition traps – update • Mike Banfield, Springstar (<u>15:10 PM</u>)</p> <p>16:10 Vector traps: auto-dissemination traps: In2Trap • Marit Farenhorst, In2Care (<u>16:20 PM</u>)</p> <p>17:00 Genetically modified mosquitoes / Oxitec – update • Kevin Gorman, Oxitec (<u>17:10 PM</u>)</p> <p><i>Break at 15:50</i></p>
Thursday 26 October 2017 – CLOSED SESSION	
08:30 – 10:30	<p>08:30 Systemic insecticides – update • Treating cattle with systemic insecticides to control sandflies – Richard Poche, Genesis Laboratories (<u>8:40 AM</u>)</p> <p>09:20 Treated clothing for malaria control in the Greater Mekong – new submission • Colin Ohrt, Consortium for Health Action (<u>9:30 AM</u>)</p> <p>10:10 Introductory discussion on new LLIN submission to VCAG • Disease Control Technologies – Royal Guard®, Rod Flinn by teleconference (<u>10:10 AM</u>)</p> <p><i>Break at 10:40</i></p>
11:00 – 11:45	Update from Global Fund to Fight AIDS, Tuberculosis and Malaria on funding for LLIN efficacy trials
11:45 – 12:30	Closed discussions on outcomes and recommendations from MPAC – for input <i>Lunch at 12:30</i>
13:30 – 15:00	Working Groups to finalize the report <i>Break at 15:00</i>
15:30 – 17:00	Plenary discussion of the report and recommendations Final discussion and closing of meeting

Annex 2. List of Participants

VCAG experts

Salim Abdulla, Ifakara Health Institute, United Republic of Tanzania
Fabrice Chandre, Institut de Recherche pour le développement, France
Marc Coosemans, Institute of Tropical Medicine, Belgium
Heather Ferguson, University of Glasgow, United Kingdom of Great Britain and Northern Ireland (United Kingdom)
Immo Kleinschmidt, London School of Hygiene & Tropical Medicine, United Kingdom
Audrey Lenhart, US Centers for Disease Control and Prevention (CDC), United States of America (USA)
Steven Lindsay, Durham University, United Kingdom
Robert Reiner, Institute for Health Metrics and Evaluation, USA
Hilary Ranson, Liverpool School of Tropical Medicine, UK (*not in attendance*)
Thomas Scott, University of California, USA
Thomas Smith, Swiss Tropical Institute, Switzerland
Abdelbaset Zayed, Faculty of Science, Alazhar University, Egypt

Participants

Attractive toxic sugar bait (ATSB): Amir Galili, Westham; Günter Müller, University of Bamako; Megan Littrell, PATH
Consortium for Health Action: Colin Ohrt (*via teleconference*)
Eave tubes, Penn State University: Matthew Thomas, Eleanore Sternberg
Genesis Laboratories: Richard Poche, Larisa Polyakova
Imperial College, London: Thomas S Churcher
In2Care for eave tubes and In2Trap: Marit Farenhorst, Anne Osinga
Interceptor® G2 and Sylando, BASF SE: Egon Weinmüller, Susanne Stutz
Innovative Vector Control Consortium (IVCC) for ATSB: Mathias Mondy, Chris Helm
London School of Hygiene & Tropical Medicine: Mark Rowland, Natacha Protopopoff
Oxitec: Simon Warner, Kevin Gorman, Mauro Teixeira, Clara Ocampo
SC Johnson for spatial repellents: David Eland
Springstar Inc: Michael Banfield
University of Notre Dame for spatial repellents: Nicole L Achee, John P Grieco

Observers

Bill & Melinda Gates Foundation: Dan Strickman
Global Fund to Fight AIDS, Tuberculosis and Malaria: Kate Kolaczinski
Innovative Vector Control Consortium (IVCC): Sarah Rees
UNITAID: Alexandra Cameron, Yohannes Ambachew Medhin

WHO Secretariat

Global Malaria Programme

Pedro Alonso, Director

Jan Kolaczinski, Coordinator, Entomology and Vector Control

Emmanuel Temu, Technical Officer, Entomology and Vector Control

Regulation of Medicines and other Health Technologies

Marion Law, Technical Officer – Group Lead, Prequalification Team – Vector Control Group

Dominic Schuler, Technical Officer, Prequalification Team – Vector Control Group

Department of Control of Neglected Tropical Diseases

Gautam Biswas, Director (acting)

Raman Velayudhan, Coordinator, Vector Ecology and Management

Rajpal Yadav, Scientist, Vector Ecology and Management

Anna Drexler, Technical Officer, Vector Ecology and Management

Annex 3. Declarations of Interest

All VCAG and invited experts completed the Declaration of Interests form for WHO experts prior to the meeting. The WHO secretariat assessed the interests declared by the experts and with the exception of the interests described below, these were not found to be directly related to the topics under discussion at the meeting. It was therefore decided that these experts could participate in the meeting, subject to the disclosure of their interests in the meeting.

The following declared interests were assessed to be related to topics under discussion at the meeting: Dr Thomas Scott and Dr Robert Reiner received grants to their respective institutions from the Bill & Melinda Gates Foundation for evaluating the impact of Spatial Repellents on dengue in Peru, where Dr Scott serves as the project leader of the Iquitos Peru trial site. They were therefore excluded from the drafting groups that assessed these products. They were also asked to abstain from discussions or recommendations made on Spatial Repellents.