THIRD MEETING
OF THE
VECTOR CONTROL ADVISORY GROUP

GENEVA, SWITZERLAND
12–14 NOVEMBER 2014

World Health Organization

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ABBREVIATIONS AND ACRONYMS

AI	active ingredient
ARS	Agricultural Research Service
ATSB	attractive toxic sugar bait
CI	confidence interval
GMO	genetically modified organism
GMP	WHO Global Malaria Programme
GTS	Global Technical Strategy
IRS	indoor residual spraying
IVCC	Innovative Vector Control Consortium
IVM	integrated vector management
LITE	Liverpool Insect Testing Establishment
LLIN	long-lasting insecticidal net
NTD	neglected tropical disease
PBO	piperonyl butoxide
RCT	randomized controlled trial
SIT	sterile insect technique
TPP	target product profile
USDA	United States Department of Agriculture
VCAG	Vector Control Advisory Group
WHO	World Health Organization
WHOPES	WHO Pesticide Evaluation Scheme

INTRODUCTION

The third meeting of the World Health Organization (WHO) Vector Control Advisory Group (VCAG), an advisory group to WHO on new forms of vector control for malaria and other vector-borne diseases, was convened from 12 to 14 November 2014 in Geneva, Switzerland. The objective of the meeting was to review the dossiers and target product profiles (TPPs) of nine potentially novel public health vector control paradigms. The meeting was divided into open and closed sessions (see *Annex I: Agendas*). On the first day an open session was held at the Hotel Manotel in Geneva, Switzerland, where innovators presented prototype products that they believed represented novel paradigms for broad discussion. The open meeting was attended by 11 of the 13 members of VCAG, partners from industry, observers and special invitees (see *Annex II: List of participants*). Professor Marc Coosemans was appointed as Chair of the meeting and Dr Ashwani Kumar, Dr Anna Drexler and Dr Emmanuel Temu as rapporteurs. Seven of the nine submitted products were discussed in the open session. Two paradigms were not discussed publically. The open session was followed by interactions between participants and VCAG members to discuss confidential information and provide individual feedback on the products.

The meeting was opened by Dr Dirk Engels, Director of the Department of Control of Neglected Tropical Diseases (NTDs). The topic of innovation brings together a broad array of stakeholders across the vector control community. Innovation in vector control is of critical importance and remains at the forefront of public health needs due to rising concerns over insecticide resistance, the need for effective tools for use in multi-disease settings and the challenges of rapidly expanding arboviral diseases, in particular dengue and chikungunya. The recently published third WHO report on NTDs[1] makes a case to the international community that investment is critical to controlling vector-borne diseases. A broad initiative for investment and innovation in vector control will be needed to combat NTDs and improve global public health.

Dr Pedro Alonso, Director of the WHO Global Malaria Programme (GMP), discussed the progress made in malaria control and the new Global Technical Strategy 2015–2030, discussed by the Executive Board in January 2015. He attributed many successes in malaria control to the scale up of core vector control interventions, long-lasting insecticidal nets (LLINs) and indoor residual spraying (IRS) in particular. Sustaining these achievements in the face of insecticide and drug resistance, residual malaria transmission and programmatic hurdles will be challenging. New goals and targets for 2015–2030 are laid out in the GMP's Global Technical Strategy (GTS), to be presented to the World Health Assembly in January 2015. GTS targets are achievable at the country level, and have been set in consultation with country malaria control and elimination programmes. Scaling up vector control is critical to reaching the GTS targets, and current estimates attribute 60% of GTS costs to vector control activities. Entomological monitoring and disease surveillance will be important components of the new GTS. New innovations in vector control and drugs are needed to sustain gains in malaria control and progress towards elimination. Many challenges remain, including insecticide resistance and residual transmission, which require new innovations, highlighting the importance of the work of VCAG.

[1] Investing to overcome the global impact of neglected tropical diseases: third WHO report on neglected tropical diseases. Geneva: World Health Organization; 2015 (WHO/HTM/NTD/2015.1).

Dr Raman Velayudhan, Coordinator of Vector Ecology and Management, WHO Department of Control of Neglected Tropical Diseases, welcomed the participants and discussed general administrative considerations. Following this, Dr Marc Coosemans called the open meeting to order, thanking participants for their presence and emphasizing the need for innovative vector control to combat malaria and vector-borne NTDs worldwide.

The closed session of the meeting (13–14 November) was attended by members of the VCAG and the WHO Secretariat. Nine product submissions were discussed (summarized in *Table 2*). VCAG also reviewed progress updates for the submissions discussed in February 2014 and finalized guidelines for the efficacy testing of LLINs with claims against resistant mosquito populations.

DECLARATIONS OF INTEREST

All the invited experts completed a form of declaration of interests for WHO experts, which was submitted to and assessed by the WHO Secretariat prior to the meeting. The following interests were declared:

Dr John Beier is part of the group developing attractive toxic sugar baits (ATSB) and has received support in the past. He therefore did not participate in the session on ATSB.

Professor Dr Marc Coosemans' institute has received grants for evaluating the impact of repellents on malaria in Cambodia from the Bill & Melinda Gates Foundation. The institute has also received repellents free of charge for use in the study from S C Johnson & Johnson Inc. USA.

Dr Tom Burkot was involved in assessing the durable wall linings donated by Vestergaard for an intervention trial in the Solomon Islands. He therefore did not participate in reviewing the Vestergaard submission to VCAG and was assigned another dossier for review.

Professor Steven Lindsay's university received research support to produce a Cochrane review on larval source management from Valent BioSciences. The institute also received a donation of bednets for a clinical trial in Burkina Faso and the Gambia.

The interests declared by the experts were assessed by the WHO Secretariat. The declared interests were not found to be directly related to the topics under discussion at the meeting. It was therefore decided that all of the above-mentioned experts could participate in all of the evaluations, subject to the public disclosure of their interests.

CLARIFICATIONS ON THE ROLE AND FUNCTIONS OF THE VCAG

The distinction between a "product" and a "paradigm" and the operational setting in which paradigms might be used needs to be clarified for innovators in particular and the vector control community in general.

According to its operational procedures, the VCAG has the following functions:

1. To review and assess the public health value of new tools, paradigms, approaches and technologies; and
2. To make recommendations on their use for vector control within the context of integrated vector management in a disease or multi-disease settings.

Products and paradigms

Several vector control paradigms are already recommended for use, including IRS, LLINs and larvicides. Within each of these paradigms are multiple products, each of which conforms to an overarching minimum target product profile (TPP).[1] For these established paradigms, proof of concept has already been demonstrated, so any subsequent products that meet the minimum TPP do not have to demonstrate public health efficacy. Rather, they are assumed to have equivalency and to function in a similar manner as a "first in class" product, unless there is a dramatic change in the underlying vector population (*Box 1*).

Box 1. Definitions	
Product	A specific intervention, e.g. Olyset nets
Prototype	A first candidate product example of a paradigm that complies with the minimum TPP for that paradigm
Paradigm	A group of products that conform to an overarching minimum TPP in a format that will allow public health (epidemiological) assessment of the prototype to be extrapolated to other products within the group.
Operational setting	The vector space where the product will be used
Target product profile (TPP)	A detailed technical description that defines the ideal end goals for a product and guides the development process. The TPP summarizes essential and desirable characteristics as well as the specific studies that will supply the evidence for each conclusion about that product

Operational settings

The operational setting in which a product works does not constitute a paradigm in itself. Broadly, there are three main operational settings in which paradigms might work: indoors against adult mosquitoes, outdoors against adult mosquitoes, or indoor/outdoor against immature mosquito stages (while not common, indoor control of immature stages can be done for *Aedes* and *Culex* spp. in certain scenarios). Some paradigms, such as attract-and-kill baits, could work in multiple operational settings (Table 1), while some paradigms

[1] For example, the TPP for IRS and LLINs can be found at: http://www.ivcc.com/download/file/fid/493

share the same operational setting but have distinct TPPs and thus require the evidence base supporting their public health utility. LLINs and IRS, for example, both target adult mosquitoes indoors (i.e. have the same operational setting) but their TPPs are separate and the epidemiological evidence that supports LLIN use does not justify IRS use, or vice versa. Additionally, products may be similar in form to an existing TPP but differ in operational use. For example, LLINs are in essence insecticide impregnated materials. Other insecticide impregnated materials could include curtains, wall hangings, material-based emanators, blankets, tents, hammocks and clothing, but these products would not comply with the overarching TPP for LLINs given the operational differences in their use. Any product that diverges sufficiently from the TPPs of an established paradigm and fails to meet the product equivalency test would need new randomized controlled trials (RCTs) to demonstrate epidemiological impact.

Generating evidence for new paradigms

For innovators targeting a public health route, VCAG will guide the data generation process to maximize efficiencies of both time and cost for the paradigm class. Demonstrating proof of concept for the public health value of new paradigms will require substantial evidence, and the time and money required for this task may vastly exceed the costs of introducing these same products to a consumer market. LLINs, for example, took roughly 20 years to generate epidemiological evidence supporting the paradigm and considerable funding. VCAG does not currently define a broader research agenda or provide funding or specific detailed product development advice to manufacturers.

If VCAG perceives value in a paradigm, its role is to provide feedback on which studies are needed to support this claim. Once these data have been generated, VCAG reviews the evidence, provides a technical evaluation and refines the TPP. Paradigms should be covered by a single overarching TPP under which multiple similar products can be grouped, so that all subsequent products can benefit from the proof of paradigm undertaken by the first in class prototype, thereby reducing the overall number of large-scale trials needed. VCAG will also recommend to policy-makers what, if any, public health benefits can be expected from the paradigm and subsequent products within the paradigm that conform to the minimum published TPP.

Epidemiological end-points

There are currently two types (levels) of epidemiological end-points applicable to public health vector control: personal protection and community protection. For personal protection, users that comply with the recommended use are protected against infection and/or disease. This impact can be demonstrated in a randomized trial with randomization at the level of the individual (e.g. treated blankets) or household (e.g. spatial repellent). The indicator would be, for example, malaria incidence (control versus treated arm). For community protection, all individuals in the community (including non-users) are expected to be protected due to the mass effect on the vector population and on transmission. Community protection can only be demonstrated in RCTs; the indicator would be, for example, malaria prevalence.

In most cases, VCAG will not consider paradigms claiming only personal protection as having public health value. However, if the claim includes protection for well-specified risk groups (mobile outdoor populations, disasters, etc.) that cannot be protected in another way, VCAG will consider such claims. This should exclude products aimed at nuisance-insect control and consumer products that may be used against vectors. A key differentiating factor will be whether a product needs a recommendation to sell via large-scale initiatives or national government procurement mechanisms. Products that can access markets without a recommendation (such as coils, repellents, candles and other household "consumables", and emergency supplies available through various nongovernmental organization routes) will not be evaluated by VCAG. Rather, any "household product" seeking a WHO recommendation will have a route through the WHO Pesticide Evaluation Scheme (WHOPES). At present, however, none has undergone WHOPES testing. It is unlikely that the mass market for specified risk groups reliant on WHO recommendations would ever justify the costs of generating the evidence for such a recommendation by the manufacturer or whether reliance on the more ad hoc publications undertaken by various groups in these settings is a better route.

Current and new paradigms for public health vector control

Table 1 summarizes the existing and new paradigms for public health vector control, including progress in their evaluation. IRS and LLINs are divided into two categories: for susceptible and for insecticide-resistant vector populations. For IRS, VCAG has not reviewed any prototype with specific claims of efficacy for areas of substantive pyrethroid resistance, although novel combination products (including non-pyrethroid mixture prototypes) are being developed that may fit within this category.

Table 1. Existing and new vector control paradigms

Parameter	Existing paradigms			New paradigms (supplementary)	
	Larval source management	Insecticide-treated bednets against susceptible vector populations	Insecticide-treated walls against susceptible vector populations	Insecticide-treated bednets against insecticide-resistant vector populations	Insecticide-treated walls against insecticide-resistant vector populations
Generic exemplars	Larvicides	LLINs	IRS/wall linings	LLINs controlling IR populations for defined IR mechanism	IRS/wall linings controlling IR populations for defined IR mechanism
Prototype				PermaNet 3.0, Interceptor G2	To date, no valid prototype with an explicit claim for IR populations has been reviewed
Operational setting					
Indoors against adult mosquitoes		√	√	√	√
Outdoors against adult mosquitoes					
Outdoors against immature mosquito stages	√				
CLAIM: personal protection	NO	YES	NO	YES/NO	NO
CLAIM: community protection	YES	YES	YES	YES	YES
WHOPES/VCAG	WHOPES	WHOPES	WHOPES	WHOPES for long-lasting effect VCAG for IR claims	WHOPES for long-lasting effect VCAG for IR claims
VCAG epidemiological end-point: • personal protection (PP) • community protection (CP)				PP and/or CP; see (1) and (2)	CP
Progress of paradigm	Complete	Complete	Complete	VCAG Step 3	TBD

CP, community protection; IR, insecticide-resistant; IRS, indoor residual spraying; LLIN, long-lasting insecticide-treated net; PP, personal protection; TBD, to be determined; VCAG, Vector Control Advisory Group; WHOPES, WHO Pesticide Evaluation Scheme

(1) As first-generation dual-treated nets are all likely to include pyrethroids as an active ingredient and some later nets with two non-pyrethroid actives may not have a personal protection (PP) function, then efficacy claims made for these nets will need to be carefully crafted and individually scrutinized rather than VCAG giving a blanket recommendation for this LLIN group against IR vectors paradigm.

(2) The burden of proof must be structured around the specific claims for each net. Claims should be stated simply, and not overstated. PP function may be retained through the presence of pyrethroid insecticide in some settings, but this will not be uniformly true and thus will require evaluation on a case-by-case basis.

Table 1. (cont'd) Existing and new vector control paradigms

Parameter	New paradigms						
	Attract-and-kill baits	Microbial control of human pathogens in adult vectors	Spatial repellents interrupting human–vector contact	Insecticide-treated materials for specific risk groups	Reducing vector populations through genetic manipulation	Vector traps for disease management	Lethal house lures
Generic exemplars	Attractive toxic sugar bait	*Wolbachia*-based bio control	Passive emanator	Insecticide-treated material	Self-limiting gene technology	Traps with lures	Eave tubes
Prototype	Bait station	*Wolbachia in Aedes aegypti*	metofluthrin or transfluthrin emanators	Blanket Clothes	OX513A *Aedes aegypti*	ALOT IN2TRAP	Eave tubes
Operational setting							
Indoors against adult mosquitoes	√	√	√	√	√	√	√
Outdoors against adult mosquitoes	√	√	√	√	√	√	√
Outdoors against immature mosquito stages					√	√	
CLAIM: personal protection	NO	NO	YES	YES for specific risk groups	NO	NO	NO
CLAIM: community protection	YES	YES	YES	NO	YES	YES	YES
WHOPES/VCAG	VCAG	VCAG	VCAG	VCAG	VCAG	VCAG	VCAG
VCAG epidemiological end-point: • personal protection (PP) • community protection (CP)	CP	CP	PP & CP	PP	CP	CP	CP
Progress of paradigm (VCAG step)	2	3	3	1	2	3	2

CP, community protection; IR, insecticide-resistant; IRS, indoor residual spraying; LLIN, long-lasting insecticide-treated net; PP, personal protection; TBD, to be determined; VCAG, Vector Control Advisory Group; WHOPES, WHO Pesticide Evaluation Scheme

VECTOR CONTROL PARADIGM SUBMISSIONS REVIEWED BY VCAG

1. REDUCING VECTOR POPULATIONS THROUGH GENETIC MANIPULATION

1.1 PARADIGM

The paradigm is **reducing vector populations through genetic manipulation**. This will allow for prototypes using genetically modified organism (GMO) approaches other than the "self-limiting gene technology (RIDL)" approach defined here to be evaluated against the same performance criteria despite variations in TPP.

Status of evidence for the paradigm

The most advanced prototype in this paradigm is in the process of completing data gathering to attain Step 2.

Data are provided describing the results of four open field releases of OX513A *Aedes aegypti* demonstrating reduction in ovitrap indices and egg numbers (from ovitraps) compared to untreated areas. These releases also demonstrate the development of production/release capabilities that have been scaled to small, community-sized operations. The portfolio provides safety assessments of risk to human, animal and environmental health of the release of the OX513A *Ae. aegypti* mosquito, concluding there is negligible risk in all categories.

1.2 PROTOTYPE: OX513A TRANSGENIC *AEDES AEGYPTI*

Description of the prototype

OX513A is a transgenic strain of *Ae. aegypti* engineered to carry a dominant lethal gene that suppresses *Ae. aegypti* mosquito populations in a manner similar to Sterile Insect Technique (SIT) or Sterile Male Release. Released transgenic males mate with Ae. aegypti females from wild populations causing offspring lethality, either "female-specific" (female offspring do not survive to adulthood) or "bisex" (neither sexes survive to adulthood). The lethal gene is dominant: larvae carrying one or more copies of the OX513A insertion will develop normally but die before functional adulthood. The lethal gene is repressible by tetracycline (or analogues), allowing the prototype to be reared in controlled conditions. A DsRed2 fluorescent marker gene allows tracking-introduced genetic material in mosquito larvae. The prototype also includes protocols for mass rearing, releasing and monitoring OX513A *Ae. aegypti* male:wild-type *Ae. aegypti* female mating ratios.

Prototype claims

- With sustained releases, the product reduces the target mosquito density to a level at which the ovitrap index is less than 15%. Sustained use of the product has the potential to eliminate local *Ae. aegypti* populations, provided immigration of *Ae. aegypti* is limited.

- In areas currently free of *Ae. aegypti* but at risk of infestation, the product can prevent a wild population from becoming established and hence provide protection from virus infection disease. Sustained releases will maintain/reduce target mosquito populations below the relevant local (measured or modelled) dengue transmission threshold.

Mode of action of the prototype

Entomological mode of action

OX513A is a transgenic strain of *Ae. aegypti* engineered to carry a dominant, repressible, non-sex-specific, late-acting lethal genetic system, together with a DsRed2 fluorescent marker. Without tetracycline or its analogues, larvae carrying one or more copies of the OX513A insertion develop normally but die before functional adulthood. In larvae reared in the absence of tetracycline, small amounts of tetracycline transcriptional activator protein (tTAV) generated by the effect of a promoter on the genetic construct engineered into the genome of OX513A *Ae. aegypti* bind to tetO binding sites on the insert, creating a positive feedback loop that enhances expression of tTAV. When the tTAV protein accumulates in sufficient quantities it affects cellular function, resulting in lethality, normally at the late stages of larval development (fourth-instar larvae). In the presence of sufficient (e.g. 30 µg/ml) tetracycline, tTAV is prevented from binding to the tetO sites and cannot, therefore, enhance the expression from the promoter. This prevents the build-up of tTAV, hence avoiding its over-expression, and the larva develops normally through to the functional adult stage.

In a field setting, released OX513A *Ae. aegypti* males homozygous for the genetic insert mate with wild-type *Ae. aegypti* females, producing heterozygous offspring. Developing in larval habitats lacking effective concentrations of tetracycline, 95% or greater of the heterozygous offspring will die before the adult stage

Epidemiological mode of action

Sustained release of OX513A *Ae. aegypti* males at densities relative to wild-type *Ae. aegypti* males sufficient to achieve a mating ratio of 50% (i.e. 50% of offspring carry the OX513A construct) results in a progressive reduction in *Ae. aegypti* population density over time. Epidemiological impact is achieved by driving or maintaining the vector population below the virus transmission threshold, which is the abundance of adult vectors required per person to sustain the transmission within the human population.

Paradigm development stage for the prototype

Based on the supporting information provided, this prototype is in late Step 2, development of the proof of concept. The applicant is requesting guidance on how best to build a scientifically rigorous evidence base for the epidemiological impact of OX513A *Ae. aegypti* in a pragmatic and cost–effective way.

Summary of key studies supporting the claim

The investigators have demonstrated:

i. Safety/health/environment risk assessments suggest no meaningful risks have been identified.

ii. Protocols have been developed to enable efficient mass rearing/sex separation/release of OX513A *Ae. aegypti* sufficient to achieve required mating ratios.

iii. Published and preliminary reports of field releases suggest that sustained release of OX513A *Ae. aegypti* males effectively reduces wild *Ae. aegypti* abundance, as reflected in ovitrap indices used to monitor the populations.

iv. Regulatory approvals have been received from relevant governmental agencies where releases are being conducted.

Safety (risks/hazards)

A generic risk assessment model should be developed for this technology and/or specific risk assessments for OX513A *Ae. aegypti* undertaken through WHO[1].

Supporting documentation (summary)

Supporting documentation includes two published papers describing (i) mating competitiveness of the OX513A *Ae. aegypti* males; (ii) suppression of a field population of *Ae. aegypti* following sustained release of OX513A *Ae. aegypti* males; (iii) two unpublished reports describing suppression of *Ae. aegypti* following sustained release of OX513A *Ae. aegypti* males in two communities in Brazil; (iv) an assessment of risk to human, animal and environmental health of the release of the OX513A *Ae. aegypti* describing a lack of risk in any of the areas considered; (v) a list of regulatory approvals received from several government agencies for importation and release of OX513A *Ae. aegypti* or for organisms with related genetic constructs; and (vi) a video describing the OX513A *Ae. aegypti* rearing/release process developed for use in Brazil.

1.3 CONCLUSIONS AND RECOMMENDATIONS: OX513A *AEDES AEGYPTI*

For paradigm

The applicants propose a paradigm "self-limiting gene technology for the suppression of pest arthropod populations", which is a derivation of the SIT or sterile male release using an introduced dominant lethal genetic construct to produce mortality in offspring of released males x wild-type female crosses rather than male sterility induced by radiological or chemical means. As such it involves an entomological mechanism not adequately described by the SIT paradigm, and warrants consideration as a new paradigm. The VCAG recommends that the paradigm should be more broadly defined as "Reducing vector populations through genetic manipulation", allowing additional prototypes using GMO approaches other than the "self-limiting gene technology (RIDL)" approach defined here to be evaluated against the same performance criteria despite variations in TPP.

While limited regulatory approval has been granted for using GMOs in this capacity, general reluctance to introducing genetically modified mosquitoes into communities for this purpose is likely to persist and additional community outreach to determine acceptability is essential.

It is a significant burden on the developers/implementers of this paradigm to demonstrate safety, probably beyond the high demand for safety placed upon traditional SIT (e.g. screwworm) or chemical insecticide-based interventions. While the OX513A *Ae. aegypti* prototype has undergone fairly comprehensive risk assessments, it is likely

[1] See http://apps.who.int/iris/bitstream/10665/127889/1/9789241507486_eng.pdf

that additional questions about risk will arise about this prototype (and any additional constructs) as new markets are developed.

For prototype

The OX513A prototype described fits within the broad paradigm of "Reducing vector populations through genetic manipulation". The following recommendations for the prototype were discussed by VCAG.

i. Entomological efficacy should be quantified using measures directly related to mosquito population abundance (adult density, pupa/person measures) in addition to the ovitrap indices that have been incorporated into the monitoring procedures.
ii. The effects of releasing homozygous OX513A *Ae. aegypti* females and of the less than 100% penetrance of lethality in heterozygous offspring on vectorial capacity and dengue virus transmission dynamics should be evaluated.
iii. This prototype is supported by sufficient information to warrant moving into Stage 3 development; i.e. cluster randomized trials to evaluate epidemiological effectiveness. Although studies of this type can be challenging to design and implement, they are absolutely essential. VCAG recommends recruiting the appropriate expertise to advise on epidemiological trial design.

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2. ATTRACT-AND-KILL BAITS

2.1 PARADIGM

The paradigm is **attract-and-kill baits**. These baits can be used as an effective way of suppressing vector insect populations sufficiently to have a beneficial impact on malaria and/or other insect-borne disease transmission.

Status of evidence for the paradigm

The most advanced prototype in this paradigm is in the process of generating data for Step 2, development of the proof of concept.

2.2 PROTOTYPE: ATTRACTIVE TOXIC SUGAR BAITS

Description of the prototype

Attractive toxic sugar baits (ATSBs) are a new strategy for controlling mosquitoes, sandflies and other biting flies. Female and male mosquitoes and sandflies need plant-derived sugars and carbohydrates to maintain energy for survival. This almost daily need for sugar presents an opportunity to leverage the sugar-feeding process with a bait containing a toxicant. The basic approach of ATSBs is to lure mosquitoes or sandflies to a toxic bait and kill them.

Prototype claims

The ATSB approach uses fruit or flower scents as an attractant, sugar solution as a feeding stimulant and oral toxin to kill the target insects. The ATSB solutions are either sprayed on vegetation or suspended in simple bait stations and the insects ingesting the toxic solutions are killed. Suppressing these vector insect populations has a beneficial impact on malaria and/or other insect-borne disease transmission.

Mode of action of the prototype

The intervention is based on three critical steps:

i. Female and male mosquitoes or sandflies that are searching for natural sugar sources are diverted and attracted to ATSB baits either sprayed on vegetation or suspended in bait stations.
ii. Mosquitoes and sandflies that feed on the ATSB bait ingest a toxin orally as they feed.
iii. Mosquitoes and sandflies are killed.

Paradigm development stage for the prototype

Early Step 2: generating data for proof of concept. A range of prototypes were presented by the innovator. VCAG recommends that the innovator select the prototype with most potential for public health use and continue continue work to develop the TPP.

Summary of key studies supporting the claim

1. Female and male mosquitoes and sandflies are attracted to local fruits/seedpods and flowering plants (*2–4*) and the availability of sugar sources affects mosquito populations (*5*).

2. Numerous field trials in Israel and Mali suggest that ATSBs can reduce mosquito densities, and thus vectorial capacity. This has been shown with various active ingredients (AIs), including spinosad, boric acid, dinotefuran and eugenol, and in different transmission settings, including Israel (*Anopheles claviger, Culex pipiens* and *An. sergentii*), Mali (*An. gambiae* s.l.), Morocco (*Cx. perexiguus*) and Florida, USA (*Ae. albopictus*) (*6–13*). Field studies of ATSB containing eugenol demonstrated significant control: > 70% reduction for *Ae. atlanticus*, *Ae. infirmatus* and *Cx. nigripalpus* and > 50% reduction for *An. crucians*, *Uranotaenia sapphirina*, *Culiseta melanura* and *Cx. erraticus* 3 weeks post-ATSB application (*14*).

3. Field trial of ATSB for controlling sandflies. Field trials spraying ATSB containing spinosad effectively controlled *Phlebotomus papatasi* sandflies in the Jordon Valley of Israel (*15*).

4. When ATSBs are applied to nonflowering vegetation or presented in bait stations, their effects on non-target organisms are low. Non-target feeding of seven insect orders (Hymenoptera, Lepidoptera, Coleoptera, Diptera, Hemiptera, Orthoptera and Neuroptera) occurred 0.9% of the time when the application was applied on green nonflowering vegetation and significantly impacted Culicidae (mosquitoes) and Chironomidae (non-biting midges) only, with no impact on pollinators or predatory non-targets. In Florida, 5.5% of the nontargets were stained in the flowering vegetation application site, but the impact on non-target insects was very low when ASTB was applied to nonflowering vegetation or in bait solutions. Non-target feeding for six insect orders (Hymenoptera, Lepidoptera, Coleoptera, Diptera, Hemiptera and Orthoptera) was low for all non-target groups (0.9%). However, application of the ATSB to flowering vegetation resulted in significant staining of the non-target insect orders, highlighting the need for application guidelines to reduce non-target effects (*1, 10, 14–15*).

5. Recent work conducted by the United States Department of Agriculture (USDA) shows that a variety of agricultural pesticides can be used for ATSB. Two insecticides (boric acid and spinosad) were initially field tested as oral toxicants and both were found suitable for the ATSB system. Additional work at the USDA/ARS (Agricultural Research Service) laboratories tested a series of chemicals in the laboratory from five classes of insecticides (pyrethroids, phenylpyroles, pyrroles, neonicotinoids and macrocyclic lactones) against three mosquitoes (*Cx. quinquefasciatus, Ae. taeniorhynchus* and *An. quadrimaculatus*). The results of this work showed that, in general, the three most effective AIs were fipronil, deltamethrin and imidacloprid. Other effective actives were, in order, spinosad, thiamethoxam, bifenthrin, permethrin and cyfluthrin. The least effective were chlorfenapyr and ivermectin. Some caveats to this work include that solutions

were not optimized for inclusion into an ATSB delivery system and efficacy was based on 24-h knockdown, which may negatively impact slower-acting products such as chlorfenapyr. Even after ingesting slow-action pesticides, mosquitoes were refraining from taking blood-meals. Two of the field-tested AIs (spinosad and boric acid) were further compared to determine their cost on a per station basis. In comparing rates for each chemical and average pricing, it is clear that both highly active/expensive chemicals and less active/less expensive chemicals would have a fit in the ATSB system. Neither chemical would appear to have a significant impact on the overall cost of a bait station.

6. Low-risk AIs (see above and publications), especially microencapsulated garlic, are used in the ATSB product presently marketed in the USA. This material is claimed to work as well as traditional pesticides (*1*). Several insecticides from different classes of chemistry have potential for use in the ATSB system. Just about any AI will work and the effectiveness of the concept is more about placement and positioning of the stations than what AI is used. Accordingly, this method will potentially solve resistance problems. Active ingredients can be rotated or a suitable cocktail of chemical classes can be used, similar to combination antibiotic treatment, to avoid the onset of resistance.

Safety (risk/hazard) information

A single ATSB prototype was not proposed at the time of VCAG review. Insecticides from different classes of chemistry have potential for use in this system and ATSBs using low-risk AIs (e.g. microencapsulated garlic) are being marketed in the USA at present. For each specific prototype, information must include a generic model for risk assessment and risk assessments of each AI must be completed.

Supporting documentation (summary)

Full dossier and supporting documents including publications, reports and unpublished results.

2.3 CONCLUSIONS AND RECOMMENDATIONS: ATTRACTIVE TOXIC SUGAR BAITS

Overall, this is a promising paradigm for malaria, dengue and leishmaniasis control. Its positive features include:

i. The potential for use in an integrated vector management (IVM) strategy.
ii. Reliance on ingestion rather than contact killing gives broad scope for AIs with the possibility for use towards resistance management.
iii. The potential of effect against outdoor biting vectors, and daytime biters such as *Ae. aegypti*.
iv. ATSB components are in the public domain and thus a competitive market is likely to develop, although quality control may be a challenge for subsequent products.

For paradigm

i. Evidence is needed from smaller field trials (semi-field, small-scale field) with adequate statistical power to show that the anticipated primary entomological impact is achieved. Comparing one intervention versus one control site is inadequate even for study with entomological outcomes.

ii. VCAG Step 3 requires randomized controlled field trials in an endemic setting to demonstrate epidemiological efficacy.

iii. Indoor and/or outdoor use needs further investigation to determine whether the product is intended as a household protection device, or whether it is an effective public health intervention.

iv. Community acceptability and compliance for the intervention must be assessed and the potential negative impact on compliance for LLIN use considered.

v. Cost analysis should include both cost set-up and maintenance/servicing of ATSB stations, including training for bait station maintenance and replacement fees. Costs will be in addition to existing vector control interventions. Durability should also be assessed before embarking on large field trials.

vi. Complete risk assessment studies will be needed.

For prototype

i. VCAG recommends that the innovator select the prototype with most potential for public health use and work to develop the TPP.

ii. Field efficacy studies should monitor the effect of the prototype on population age structure and parity. The effects of field settings for the trap, in particular high vegetation, need further assessment.

iii. Although the innovators claim this will not select for resistance, insects may develop behavioural resistance mechanisms based on trap avoidance.

iv. Adverse effects on non-target organisms need further examination.

v. The study design should be modified to assess effects on outdoor biting.

vi. The susceptibility of baits to rodent damage should be assessed and weather durability established.

vii. A full list of potential AIs for use in the traps should be identified, including toxicological profiles, safety and risk information.

viii. This prototype is not sufficiently advanced to warrant trials with epidemiological outcomes. Trials should be restricted to village-scale studies with entomological outcomes for the time being.

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3. INSECTICIDE-TREATED MATERIALS FOR SPECIFIC RISK GROUPS

3.1 PARADIGM

The paradigm is insecticide-impregnated materials with potential public health impact in protecting specific at-risk populations (nomads, displaced populations, disaster situations) in situations where use of an insecticide-treated net or indoor residual spraying are not feasible. It can be applied broadly to many product types (e.g. curtains, wall hangings, material-based emanators, blankets, tents, hammocks, clothing). These materials diverge sufficiently from LLINs in use that they would fail to meet a product equivalency test that would allow them to benefit from the RCTs done previously for LLINs. This paradigm protects against outdoor transmission but is not expected to provide a community effect.

Status of evidence for the paradigm

Step 1, early notification, due to the need for product development to support this paradigm.

3.2 PROTOTYPE: SKINTEX™ MR III

Description of the prototype

The Skintex™ MR III blanket is a lightweight, durable synthetic blanket treated with microencapsulated permethrin. The blanket is intended to provide personal protection from mosquito bites and malaria infection in situations where use of an insecticide-treated net or indoor residual spraying is not feasible. Blanket use disrupts permethrin microcapsules, releasing the insecticide, which repels and kills mosquitoes landing on the blanket.

Prototype claims

1. The blanket provides a physical barrier against mosquito bites.
2. Permethrin in the blanket deters mosquito landing and probing, and kills mosquitoes following exposure (100% knockdown, 100% mortality).
3. The encapsulation of the permethrin provides extended persistence of the permethrin as the capsules are gradually opened by movement and friction during blanket use.
4. By reducing mosquito bites, the prototype provides personal protection from malaria infection in situations where use of insecticide treated nets or indoor residual spraying are not feasible.

Mode of action of the prototype

The prototype acts by both providing a physical barrier to mosquito bites and by killing mosquitoes that land on the blanket. The AI has a long-lasting killing effect due to the encapsulation of the insecticide, which is released by movement and friction generated by individuals during product use.

Paradigm development stage for the prototype

Based on the supporting information provided, this prototype is in Step 1– early notification.

Summary of key studies supporting the claim

The investigators present.

1. Preliminary results on entomological efficacy, including knockdown and mortality testing, and limited repellency testing. WHO tube assays showed 100% knockdown in one hour and 100% mortality of Ae. aegypti after 5 min exposure to washed samples (up to 25 washes) (1,2). Repellency testing indicated a reduction in bites from *Ae. aegypti*, but did not demonstrate repellency due to the absence of a control and sufficient replication (3).
2. Wash durability. After 25 washes the concentration of permethrin was 64% of the original concentration (1.4 g/m^2). This concentration provided 100% knockdown at 60 min post-exposure and 100% mortality at 24 hrs.
3. Studies by Graham et al (2002) supporting acceptability of pyrethroid-treated sheets and clothing to users and protection from bites. The prototype proposed here was not tested (2).
4. Toxicological information. No significant evidence for acute oral toxicity, dermal irritation, mucous membrane irritation, skin sensitization, mutagenicity or subchronic toxicity was reported.
5. Previous published studies from Afghanistan and Kenya show the proof of principle of treated top-sheets or blankets (3,4).
6. United States Environmental Protection Agency (USEPA) for the prototype (86110-2). The prototype has passed all safety, health and environmental risk assessments required for EPA registration. Skintex MR III is the only microencapsulated permethrin product registered with the EPA.

Supporting documentation (summary)

Full dossier and supporting documents, including publications, reports and unpublished results..

3.3 CONCLUSIONS AND RECOMMENDATIONS: SKINTEX™ MR III

VCAG recognizes the public health value and importance of vector control products that protect specific populations in certain circumstances (potential for use in disaster situations), but do not necessarily contribute to community protection.

For paradigm

Previous community trials on pyrethroid-treated sheets for personal protection in Muheza (United Republic of Tanzania) did not reveal community effect. However, efficacy for personal protection should be demonstrated in an individually randomized trial with epidemiological outcome measurements such as incidence of malaria.

For prototype

Serious concerns were voiced over the utility of a pyrethroid-based product where pyrethroid resistance is increasingly a problem. VCAG recommends that the innovators follow the

guidelines for LLIN efficacy testing to demonstrate entomological efficacy of their product. VCAG recommends that the innovators consider development of a product based on a combination or non-pyrethroid AI. Evaluation and development of this prototype should strongly consider impacts of insecticide resistance. The level of protection for exposed skin outside of the blanket was also discussed. Innovators could approach IVCC to guide prototype development, under their mandate from the Bill & Melinda Gates Foundation to look at outdoor biting and outdoor resting paradigms. Innovators can work with WHO to develop guidelines to evaluate impregnated clothing for personal protection, allowing the product to be evaluated through WHOPES.

References

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4. DISCUSSION

The WHO Vector Control Advisory Group met on 12–14 November 2014 at WHO headquarters in Geneva. On the first day of the meeting an open session was held where innovators presented prototype products that they believed represented novel paradigms for broad discussion. Seven out of nine submitted products were discussed in the open session. Two products were not discussed publically. The open session was followed by private interactions between participants and the VCAG to discuss confidential information and provide individual feedback on the products. The agenda for presentations in the open session is given in *Annex 1*.

4.1 VCAG2 PARADIGM UPDATES

Developers of the paradigms reviewed in February 2014 were asked to submit single-page updates prior to the VCAG3 meeting, for the information and discussion of the Committee during the meeting. A summary of the discussion points and recommendations for these paradigms is included as follows:

1. *Wolbachia*: Updates to VCAG included: (i) ongoing monitoring of field releases for wMel and wMelPop infected *Ae. aegypti* in Australia and Viet Nam; (ii) initial assessments of potential field trial sites in various ecological and socio-cultural settings; (iii) developments in deployment methodology for *Wolbachia*-infected mosquitoes; and (iv) preparation for efficacy studies, including site suitability and feasibility studies. VCAG discussed the degree of virus blocking in the wMel-infected mosquitoes, and the need to assess how variations in blockage may effect dengue transmission. For efficacy trials, primary outcome measures could include dengue incidence in addition to seroprevalence. VCAG requested additional information on the preliminary studies leading into RCT and on the various strains of *Wolbachia* in preparation.
2. Permanet 3.0: A summary table detailing Permanet 3.0 study outcomes in comparison with pyrethroid only LLINs was presented to VCAG. The Committee discussed the relevance of data showing relative vs absolute improvement, and the utility of studies where no improvement is seen. The guidelines developed through the VCAG subcommittee should be followed to ensure the necessary data are generated to evaluate the prototype claims. The paradigm supported by this product can be moved to Step 4, and a recommendation on the paradigm (not the product) made to policy issuing bodies the WHO Malaria Policy Advisory Committee (MPAC) and the WHO Strategic and Technical Advisory Group for Neglected Tropical Diseases (STAG-NTD).
3. Smartpatch: Updates on the effects of SmartPatch on personal protection (blood-meal inhibition) were given. The WHOPES procedures for efficacy testing of LLINs can be followed to generate the data needed on this prototype, in addition to the VCAG subcommittee guidelines for evaluating claims of efficacy against insecticide-resistant mosquitoes.

4. Spatial repellents: Updates were given on the final prototype design and progress towards RCTs, including initial bridging studies in Indonesia and the United Republic of Tanzania. Concerns were raised regarding the development of tolerance to spatial repellents. The usage of nets and spatial repellents should be evaluated by observation in addition to questionnaires. The risk assessment model used should be reviewed by WHO in subsequent submissions of this paradigm to VCAG. Also, VCAG recommended that a system be put in place for early detection of adverse events in all arms of the study.
5. In2Trap: Information was given on trap sales and user acceptance, product optimizations, manufacturing and quality control measures, product registration and outcomes of initial field trials. VCAG discussed whether the traps are targeted as consumer products or as programmatic vector control interventions. Innovators should revisit the recommendations made by VCAG in the second meeting in order to sufficiently demonstrate entomological effectiveness of the trap in light of complex vector control parameters. VCAG will be developing guidelines for vector-trap assessment that may be used in generating data for this paradigm.
6. ALOT: Updates were given on ALOT efficacy trials from Iquitos, Peru, including impacts on dengue incidence and household surveys on adult mosquitoes. The developers indicated that funding constraints will delay the validation of this paradigm. VCAG noted that while pre-intervention data was excluded and significant heterogeneity in dengue incidence during the study period complicates interpretation of the results, there appeared to be an impact of the intervention in the study areas. Challenges in implementing the intervention were also discussed.
7. Lethal house lure: Updates included information on the effect of the intervention on vector house entry by species, field testing in the United Republic of Tanzania, efficacy studies for different AIs and dosages, and the results of household surveys for suitability and acceptability. VCAG discussed the paradigm update provided and expressed concerns regarding air quality inside the homes. In addition to previous recommendations, innovators should assess indoor air flow, measure particulate matter within houses and provide a plan for early clinical detection of adverse events, in particular respiratory ailments.

4.2 GUIDELINES ON LLINS TARGETING PYRETHROID-RESISTANT AREAS

On 13 November 2014, the VCAG discussed the guidelines document developed by the VCAG Subgroup following the meeting in April 2014, and made final recommendations on the document, which outlines the evidence that VCAG would expect to see to substantiate manufacturers' claims of increased efficacy of combination/mixture LLINs compared with pyrethroid-only LLINs in areas of high insecticide resistance. Major issues resolved included efficacy criteria, resistance thresholds and safety issues around resistant colonies. The full document "Guidelines for testing new LLIN products to substantiate efficacy claims in areas of high insecticide resistance" is included as *Annex 3*.

Clarifications – VCAG will not address claims of resistance management. Resistance management is a process, and evaluating the utility of individual products for this will require a burden of evidence that is beyond the scope of the Guidelines document. VCAG noted that LLIN efficacy data will relate only to the specific situations tested, and will not be generally applicable to all conditions of insecticide resistance. Nets will need to be appropriately matched to their target area based on characterization of resistance profiles of local mosquitoes prior to in-country use.

Efficacy criteria – Much discussion was given to whether the test and control LLIN should be statistically different or 25% better. It was determined that manufacturers should clearly state claims of improvement, including type (mortality, blood-feeding inhibition, etc.) and percentage, that all claims of improvement should be made with comparison to a well-documented reference strain, and that for VCAG consideration, a minimum threshold of 25% improvement (over a well-documented reference strain) should be met. Statistically relevant sample sizes for demonstrating various levels of significant difference will be given in standard operating procedures (SOPs).

Reference strains – Availability of resistant reference strains is limited to a few facilities with adequate biosafety measures and rigorous maintenance standards. The IVCC-supported Liverpool Insect Testing Establishment (LITE) has the largest number of well characterized and maintained insecticide-resistant colonies (*An. gambiae, An. funestus, Ae. aegypti* and *An. arabiensis*) used to facilitate product development. A limited number of facilities capable of testing products against resistant strains is sufficient for product development needs. VCAG noted the advantage of working with a few high-quality facilities in quality control for resistant mosquito reference strains. Other facilities may also maintain mosquito colonies with well-characterized resistance mechanisms reared under tightly quality controlled conditions. Resistant strains to be used for testing should have an RR > 10-fold threshold in order to exclude kdr-only resistance mechanisms.

Evaluation of new LLINs with fast- and/or slow-acting AIs – All test LLINs should follow standard bioassay procedures for stage 1 evaluation: exposure for 3 min and mortality score after 24 h holding time. Cone tests are used as a first pass test to determine whether an AI is fast-acting, or has an alternative mode of action (e.g. slow-acting, repellent, effects on fecundity). LLINs that fail cone tests will be tested by tunnel tests. Fast-acting compounds are assumed to maintain the personal protective function of a standard LLIN, and thus will not need to demonstrate epidemiological impact. Slow-acting insecticides/alternative modes of action deviate sufficiently from the LLIN paradigm that epidemiological evidence will need to be generated during Phase III testing , until the public health value of nets falling under this paradigm has been sufficiently demonstrated to VCAG. SOPs for all aspects of testing will be available via the VCAG secretariat and website.

Subgroup for evaluating claims of efficacy – VCAG will convene a specialist subgroup to evaluate and refine manufacturers' claims of efficacy for their products against highly pyrethroid-resistant vector populations. This process is intended to supplement the current WHOPES evaluation procedures for classical LLINs. Further, all combination/mixture LLINs submitted to VCAG with claims of increased effectiveness in areas of high pyrethroid resistance should be well advanced in WHOPES efficacy and safety evaluations and in specification development.

4.3 VCAG OPERATIONS

Internal matters to the running of VCAG were discussed on the afternoon of 14 November 2014. Subsequent VCAG meetings will follow a similar agenda to the current meeting, with innovator presentations and interactions with innovators restricted to the first day of the meeting. VCAG discussed the prescreening of submissions and modification of application procedures to better standardize the information content and quality of data presented. The following action items were identified:

1. The fourth VCAG meeting will be scheduled for mid-November 2015.
2. VCAG will move to a letter of intent (LOI) and invitation-based application system. LOIs will summarize the proposed paradigm and relevant evidence for review by the VCAG Secretariat, which will then invite applicants meeting eligibility criteria to submit full applications.
3. The VCAG Secretariat will revise instructions for applicants to improve clarity on the format and content of the LOI, application, and on data quality and presentation, including eligibility criteria for VCAG review.
4. In order to fully inform applicants, VCAG will publicize the burden of data needed to support a novel paradigm application and information on amounts of time and financial investment needed to substantiate claims of public health vector control.
5. In order to better inform applicants of current mechanisms for product evaluation, VCAG will provide references to existing paradigms and guidelines for testing products in these categories.

Additional information and clarification for applicants on VCAG procedures is given in *Annex 4*.

5. CONCLUSIONS

The third VCAG meeting concluded as follows:

1. Three novel paradigms reviewed by VCAG have potential for public health vector control.
   i. Reducing vector population through genetic manipulation, based on the prototype submitted by Oxitec Ltd for OX513A transgenic *Ae. aegypti*.
   ii. Attract-and-kill baits, based on the prototype attractive toxic sugar bait (ATSB) submitted by Westham Innovations Ltd.
   iii. A third paradigm was discussed by VCAG: "Insecticide treated materials for specific risk groups", under which the permethrin-treated blanket submitted by Pulcra Chemicals LLC might fall. This was seen as a highly beneficial tool for public health in certain circumstances. A number of recommendations were made to encourage the development of this paradigm.

2. Several submissions to VCAG comply with previously defined vector control categories and may be evaluated through existing channels (e.g. WHOPES).
   i. Larvicides: SAFE, acoustic larvicide device
   ii. IRS products: Bayer Combination IRS, Vestagaard Durable Wall Lining
   iii. Household insecticide: Candelax

3. One paradigm submission (BASF Interceptor G2) is categorized as a previously defined paradigm (LLIN for use in pyrethroid-resistant areas). Evaluation of claims of efficacy for such products will be done by VCAG itself through the actions of a subcommittee.

4. VCAG considers the paradigm "LLINs for use in areas of high insecticide resistance" to have significant public health value. All LLINs submitting claims under this paradigm must first proceed through the standard WHOPES evaluation for LLINs. A VCAG subcommittee will undertake a secondary review process for individual LLINs with claims against resistance mosquito populations. Claims will be assessed using manufacturer generated data from the guidelines and SOPs developed by VCAG. Based on previous studies on fully susceptible pyrethroid vectors, VCAG assumes that LLINs claiming personal protection against highly pyrethroid-resistant mosquitoes will protect against disease in such settings, and thus further epidemiological trials are unnecessary. However, for LLINs that offer community protection only (without personal protection), community trials (RCTs) to demonstrate epidemiological impact will be needed until sufficient evidence for the public health value of these tools has been generated. As current combinations/mixture nets are likely to be composed of pyrethroid plus another AI, VCAG notes that the presence of pyrethroid does not de facto support claims of personal protection, since this may be ineffective in cases of insecticide resistance.

5. In order to fully inform applicants, VCAG will publicize the burden of data needed to support a novel paradigm application and information on amounts of time and financial investment needed to substantiate claims of public health vector control. In order to better inform applicants of current mechanisms for product evaluation, VCAG will provide references to existing paradigms and guidelines for testing products in these categories.

6. VCAG strongly encourages innovators to work closely with an entomologist for the purposes of producing high-quality entomological data.

Table 2. Summary of submissions to VCAG in November 2014

Manufacturer/ developer	Description of the prototype	VCAG conclusions
Oxitec Ltd	Transgenic mosquito for *Aedes* control	**The paradigm is: reducing vector populations through genetic manipulation** This prototype (OX513A *Aedes aegypti*) is in late Step 2, development of the proof of concept.
Westham Innovations Ltd	Attractive toxic sugar bait (ATSB)	**The paradigm is: attract-and-kill baits** Attract-and-kill baits can be used as an effective way of suppressing vector insect populations sufficiently to have a beneficial impact on malaria and/or other insect-borne disease transmission. This prototype is in early Step 2, development of the proof of concept.
Pulcra Chemicals LLC	Permethrin-treated blanket (SkinTex)	**The paradigm is: insecticide-treated materials for specific risk groups** VCAG recognizes the public health value and importance of vector control products that protect specific populations (potential for use in disaster situations) but do not contribute to community protection. This prototype is in early Step 1, early notification, due to the need for serious modification in order to support this paradigm. The current prototype may only be of use in areas where the vectors are still susceptible to pyrethroids.
Candelax SDN BHD	Transfluthrin candle (Candelax)	Household insecticide products – previously defined paradigm. May be evaluated using the following guidelines: http://whqlibdoc.who.int/hq/2009/WHO_HTM_NTD_WHOPES_2009.3_eng.pdf
Vestagaard Frandsen	Non-pyrethroid insecticidal wall hangings (Permanet Lining)	Indoor residual spraying (IRS) – previously defined paradigm.. Under current claims, may be evaluated through WHOPES using the guidelines for IRS efficacy testing: http://whqlibdoc.who.int/hq/2006/WHO_CDS_NTD_WHOPES_GCDPP_2006.3_eng.pdf
Bayer CropScience	IRS combination insecticide (Bayer664)	IRS – previously defined paradigm. Under current claims, may be evaluated through WHOPES using the guidelines for IRS efficacy testing: http://whqlibdoc.who.int/hq/2006/WHO_CDS_NTD_WHOPES_GCDPP_2006.3_eng.pdf
InRad Corporation	Photolarvicide	Larvicide – previously defined paradigm.. May be evaluated through WHOPES using the guidelines: http://whqlibdoc.who.int/hq/2005/WHO_CDS_WHOPES_GCDPP_2005.13.pdf
New Mountain Innovations Inc.	Acoustic larvicide	Larvicide – previously defined paradigm. May be evaluated through WHOPES using the guidelines: http://whqlibdoc.who.int/hq/2005/WHO_CDS_WHOPES_GCDPP_2005.13.pdf
BASF	InterceptorG2 LLIN	Long-lasting insecticidal net (LLIN) that also falls within previously defined paradigm "Vector control products for areas with pyrethroid resistant mosquitoes". In addition to standard WHOPES testing, a VCAG subcommittee will review all LLINs that make resistance claims. Claims will be assessed using manufacturer-generated data according to the guidelines developed for this purpose by VCAG 2014.

ANNEXES

ANNEX 1. AGENDAS

Third Vector Control Advisory Group (VCAG3)
Hotel Royal (Manotel Group), Geneva, Switzerland
12 November 2014 (09:00–18:00)
AGENDA – OPEN SESSION

09:00–09:15 Opening of the meeting and welcoming remarks
Dr Dirk Engels, Director, WHO Department of Control of Neglected Tropical Diseases
Dr Pedro Alonso, Director, WHO Global Malaria Programme

09:15–09:20 Appointment of the Chairperson and Rapporteurs
Introduction of the procedure, working arrangements and objectives of the meeting
Dr Raman Velayudhan, Coordinator, WHO/VEM
Dr Abraham Mnzava, Coordinator, WHO/VCU

09:30–09:50 Self-limiting gene technology OX513A Aedes aegypti: a novel paradigm with a ready to use product. *Ms Camilla Beech, Oxitec Ltd*

09:50–10:00 Discussion

10:00–10:20 Skintex MRIII blanket. *Mr Troy Massey and Dr Raymond Mathis, Pulcra Chemicals LLC*

10:20–10:30 Discussion

10:30–11:00 Tea/coffee break

11:00–11:20 LLIN with a novel insecticide with a new MoA in combination with a pyrethroid to manage insecticide resistance. *Dr Susanne Stutz, BASF*

11:20–11:30 Discussion

11:30–11:50 Sunlight active formulated extract: a novel larvicide for malaria, filarial and dengue fever vector control. *Dr Mahmoud Abdel Kader, German University in Cairo* and *Dr Tarek A. El-Tayeb, Cairo University, Cairo, Egypt*

11:50–12:00 Discussion

12:00–12:20 Acoustic larvicide. *Mr Herbert Nyberg, New Mountain Innovations Inc.*

12:20–12:30 Discussion

12:30–14:00 Lunch break

14:00–14:20 Attractive toxic sugar bait (ATSB), from basic science to product. *Dr Gunter Müller, Westham Innovations Ltd*

14:20–14:30 Discussion

14:30–14:50 Insecticandel – reducing prevalence of malaria, lowering health care costs, improving lives. *Mr Steve Boey, Mr Michael Gurney and Professor Roslyn Sorensen Candelax SDN BHD*

14:50–15:00 Discussion

15:00–15:30 Tea/coffee break

15:30–18:00 VCAG interaction with innovators (group work)

Third Vector Control Advisory Group (VCAG3)
Room: L-14, WHO headquarters, Geneva
13–14 November 2014
AGENDA – CLOSED SESSION

13 November 2014 (09:00–17:30)

1. Updates on VCAG2 paradigms
2. Discussion of VCAG submissions in plenary
   i. Oxitec / OX513A mosquito
   ii. Pulcra / Skintex
   iii. BASF / Interceptor G2
   iv. InRad / SAFE
   v. New Mountain / Acoustic Larvicide
   vi. Westham / ATSB
   vii. Candelex / Insecticandel
   viii. Vestagaard / Wall Lining
   ix. Bayer / IRS product
3. Discussion of VCAG subgroup guidelines on LLINs for use in areas of high insecticide resistance
4. Report finalization in groups (ensure factual accuracy of the draft reports; and draft conclusions and recommendations of the meeting)

14 November 2014 (09:00–17:30)

5. Report finalization continued
6. Review/finalize conclusions and recommendations
7. VCAG housekeeping:
   i. VCAG product pipelines: when to review new information, what to do with second in line products before paradigm is finalized
   ii. Changes in report formats
   iii. Other topics for discussion
10. Closure

ANNEX 2. LIST OF PARTICIPANTS

Members of the Expert Advisory Group

Professor John C. Beier, University of Miami, Miami, FL, USA

Dr Thomas Burkot, James Cook University, Cairns, Queensland, Australia (unable to attend)

Professor Marc Coosemans, Institute of Tropical Medicine, Antwerp, Belgium

Dr John I. Githure, Adviser, Ministry of Health, Rwanda

Professor Janet Hemingway, Liverpool School of Tropical Medicine, Liverpool, United Kingdom

Dr Immo Kleinschmidt, London School of Hygiene and Tropical Medicine, London, United Kingdom

Dr Kim Lindblade, Centers for Disease Control and Prevention, Atlanta, GA, USA (unable to attend)

Dr Ashwani Kumar, National Institute of Malaria Research, Goa, India

Professor Steven Lindsay, Durham University, Durham, United Kingdom

Dr Roger Nasci, Centers for Disease Control and Prevention, Fort Collins, CO, USA

Dr Thomas W. Scott, University of California-Davis, Davis, CA, USA

Professor Hassan Vatandoost, Teheran University of Medical Sciences, Teheran, Islamic Republic of Iran

Dr Indra Vythilingam, University of Malaya, Kuala Lumpur, Malaysia

Stakeholders

BASF (Limburgerhof, Germany): Dr Susanne Stutz, Marketing Manager Business Management Global Public Health

Bayer S.A.S. (Lyon, France): Dr Frederic Schmitt, Global Project Manager / Vector Control

Candelax SDN BHD (Petani Kedah, Malaysia): Mr Steve Boey, Joint Managing Director,

Mr Michael Gurney and Professor Roslyn Sorensen

Innovative Research and development (InRad) Corporation (Cairo, Egypt): Dr Mahmoud Abdel Kader, President, and Dr Tarek Abdallah El-Tayeb, Professor Photobiology

New Mountain Innovations Inc. (Old Lyme, CT, USA): Mr Herbert Nyberg, President, and Dr Catherine B. Nyberg

Oxitec Ltd (Abingdon, UK): Ms Camilla Beech, Head of Regulatory Affairs, Dr Andrew McKemey, Head of Field Operations, and Mr Glen Slade, Head of Business Development

Pulcra Chemicals LLC (Rock Hill, SC, USA): Mr Troy Massey, Skintex Business Manager

Vestergaard Frandsen SA (Washington, DC, USA): Dr Helen Pates Jamet, Head of Entomology

Westham Innovations Ltd (Tel Aviv, Israel): Mr Amir Galili, President & CEO, Ms Orley Krinis, Dr Gunter Müller and Mr Rick O'Brien

WHO Secretariat

Global Malaria Programme (GMP):

Dr Pedro Alonso, Director
Dr Abraham Mnzava, Coordinator, Vector Control Unit
Dr Emmanuel Temu, Consultant, Vector Control Unit

Department of Control of Neglected Tropical Diseases (NTD):

Dr Dirk Engels, Director
Dr Raman Velayudhan, Coordinator, Vector Ecology and Management
Dr Rajpal Yadav, Scientist, Vector Ecology and Management
Dr Anna Drexler, Consultant, Vector Ecology and Management

Special Programme for Research and Training in Tropical Diseases (TDR):

Dr Johannes Sommerfeld, Scientist/Research Manager

Observers

Croplife International: Dr Egon Weinmüller, BASF SE, Limburgerhof, Germany

ANNEX 3. GUIDELINES FOR TESTING NEW LONG-LASTING INSECTICIDAL NET PRODUCTS TO SUBSTANTIATE EFFICACY CLAIMS IN AREAS OF HIGH INSECTICIDE RESISTANCE

Background

New long-lasting insecticidal nets (LLINs) are being developed by several manufacturers and advocated for use in areas where mosquito vectors are resistant to pyrethroid insecticides. In February 2014, the paradigm "vector control interventions for use in areas of high pyrethroid resistance" was assessed by the WHO Vector Control Advisory Group (VCAG). The paradigm was defined as a novel intervention or an adaptation of an existing product class that has an overall effect on vectorial capacity and reduces human infection or disease in areas where the local vectors have substantive pyrethroid resistance. Under this broad paradigm heading, VCAG has reviewed the data for two insecticide combination/mixture LLINs, and made a recommendation on the public health value of the paradigm of combination/mixture nets designed to have increased effectiveness in areas of high pyrethroid resistance.

The current document outlines the evidence that VCAG would expect to see to substantiate manufacturers' claims of increased efficacy of combination/mixture LLINs compared with pyrethroid-only LLINs in areas of high (RR > 10-fold) insecticide resistance.[1] VCAG will convene a specialist subgroup to evaluate and refine manufacturers' claims of efficacy for their products against highly pyrethroid-resistant vector populations. This process is intended to supplement the current WHOPES evaluation procedures for classical LLINs. Further, all combination/mixture LLINs submitted to VCAG with claims of increased effectiveness in areas of high pyrethroid resistance should be well advanced in WHOPES efficacy and safety evaluations and in specification development.

Scope

This document addresses LLINs that are designed to have greater efficacy in areas of high insecticide resistance.[2] Currently, most of these products would address resistance to pyrethroid insecticides and consist of combination/mixture nets, including pyrethroids plus another AI and/or synergist.

Objectives

As next-generation LLINs are likely to be more expensive than current LLINs, control programmes and donors will need information on whether these new nets are more effective at killing (or protecting against) insecticide-resistant populations. Current WHOPES guidelines do not require new LLINs to demonstrate superiority to in-use LLINs. Furthermore, the existing guidelines recommend that all initial testing of LLIN efficacy be performed on insecticide-susceptible mosquito populations, and new nets must demonstrate equivalency to conventional LLINs against susceptible mosquitoes, while recognizing such populations are increasingly difficult to find and resistance populations still generate useful data. In reality, new nets, particularly those not containing pyrethroids, may not perform as well

[1] This threshold (RR >10-fold) has been set to exclude mosquito strains with *kdr*-only based resistance mechanisms.

[2] For guidance, at least a 25% improvement should be achieved and the comparator reference strain must be well documented. Manufacturers should specify the percentage improvement with confidence intervals (CIs), where the CIs are based on standard errors that reflect the variation between replicates.

as conventional LLINs against susceptible mosquitoes in WHOPES tests, but may greatly outperform conventional LLINs when resistant mosquitoes are used. New nets are urgently needed to help control pyrethroid-resistant mosquito populations, but it is clear that the current testing guidelines will not generate the data needed to adequately evaluate the performance of these products against these mosquito populations, and further specifications for net evaluation need to be agreed upon.

This document aims to provide guidelines for the minimum data that need to be generated in order to assess whether next-generation LLINs are superior to current LLINs in areas of high resistance. The following assumptions are made:

1. Next-generation LLINs are primarily designed to provide enhanced protection (compared with existing pyrethroid-only LLINs pre-/post-washing) **against malaria transmitted by highly pyrethroid-resistant mosquitoes**. Hence, all tests should be performed on well-characterized pyrethroid-resistant mosquito populations. It is important to realize that the resistance ratio is pertinent to protection and should be determined.
2. Based on previous studies on fully susceptible pyrethroid vectors, one can assume that if **personal protection** against highly pyrethroid-resistant mosquitoes is observed there will be protection against malaria in such settings.
3. Next-generation LLINs are evaluated on their ability to provide enhanced protection or increased mosquito mortality in areas of high pyrethroid resistance and not on their utility as a resistance management tool.[1]

Note: *Recommendations from this VCAG subgroup on LLIN efficacy against insecticide-resistant populations will relate to only the specific situations tested, and will not be generally applicable to all conditions of insecticide resistance. Nets will need to be appropriately matched to their target area based on the resistance ratio and detailed characterization of resistance profiles of local mosquitoes prior to in-country and regional use.*

[1] Resistance management is a process, and evaluating the utility of individual products in this process will require a burden of evidence that is beyond the scope of this document.

EVALUATING LLIN EFFICACY AGAINST PYRETHROID-RESISTANT MOSQUITOES

Data generation will take a three-stage approach to reduce costs and allow the process to be stopped at each stage if increased efficacy is not apparent. These guidelines are intended to provide a general framework for evaluating next-generation LLINs. Detailed SOPs to follow will be available through the VCAG website.

1. STAGE I – LABORATORY TESTING

1.1. Objective

To demonstrate that the next-generation LLIN is significantly better at killing, reducing the reproductive capacity of and/or protecting against pyrethroid resistant mosquitoes compared to a pyrethroid-only LLIN.

1.2. What is meant by "significantly better"?

i. Next-generation LLINs should be compared to a standard WHOPES-recommended pyrethroid LLIN.[1]

ii. All laboratory testing must be performed on at least three characterized industry standard pyrethroid-resistant mosquito strains (*Appendix 1*) or comply with the documentation requirements listed in Section 1.3.

iii. Next-generation LLINs must demonstrate:
   - where insect mortality is the expected outcome, at least 25% increase in mortality compared with pyrethroid-only LLINs, following five replicates for both net types.
   - where insect mortality is NOT the expected outcome, at least 25% impact on the longevity, blood-feeding and/or reproductive output of the mosquitoes exposed to the new LLIN vs pyrethroid-only LLINs, with statistical significance.

iv. Finally, improvements over current LLINs must be maintained after the requisite number of standardized washes.[2]

It is noted that percentage improvement in Phase 1 cone tests has limited operational significance due to poor correlation (or lack of calibration) with field results; however, for guidance, **at least a 25% improvement should be achieved using a well-documented reference strain**. Manufacturers should specify claims for percentage improvement with confidence intervals (CIs), where the CIs are based on standard errors that reflect the variation between replicate tests.

1.3. What resistance strains should be tested?

i. Standard strains that represent the broad spectrum of major insecticide resistance mechanisms currently known to exist in mosquito vector populations should act as the reference test strains for next-generation LLINs. A list of the standard strains of insecticide-resistant mosquitoes which may be procured for testing is given at the end of this document.

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[1] Guidelines for laboratory and field testing of long-lasting insecticidal nets. Geneva: World Health Organization; 2013 (WHO/HMT/NTD/WHOPES/2013.1).

[2] The standard mosquito strains listed in Appendix 1 provide uniform comparators for all studies. Any alternative resistant strains used outside of those listed in Appendix 1 must comply with the documentation requirements described below.

ii. At least three strains must be tested, two of which must have major metabolic resistance mechanisms.

iii. Alternative strains: if alternative strains are used for assessment, the resistance mechanisms must be fully characterized at the time of testing. The results of the resistance profile and evidence demonstrating underlying resistance mechanisms should be documented within the dossier. The resistance level of any strain used for testing must be greater than 10-fold that of a susceptible strain of the same species at the LC^{50}. During all testing, a laboratory-susceptible strain must also be run in parallel as a control.

1.4. What method should be used?

Robust demonstration of specific beneficial entomological end-points such as increased mosquito mortality prevention of blood-feeding or reduction of reproductive output is required. This should be demonstrated by:

- Cone bioassay undertaken as specified in WHOPES guidelines.
  - Exposure should be 3 min, with knockdown recorded at 60 min and mortality at 24 h.
  - If an AI has a documented mode of action that does not result in rapid knockdown and kill (e.g. a slow-acting insecticide), the time period for evaluating mortality may be extended; however, a rationale for the testing procedures used must be provided.
  - LLINs that do not demonstrate improvements in the cone tests should be tested by tunnel bioassays (see below), which will evaluate slow-acting or mechanistically alternative compounds.[1]

- Tunnel bioassay undertaken as specified in WHOPES guidelines.
  - Tunnel assays should be used if an AI functions by repellency (requiring testing on free flying insects), or if an AI requires an exposure of greater than 3 min to give operationally representative data in cone assays.
  - Tunnel tests should use the same strains of resistant mosquitoes as the cone bioassays.[2]

- For products that have a growth regulator AIs, measurements of reproductive output (oviposition, fecundity and fertility inhibition) will be needed.

[1] Tunnel bioassays test may reveal AI toxicity which is not apparent in cone or daytime contact bioassay, as mosquitoes are exposed to the treated nets at night, mimicking natural circadian host-seeking behaviours.

[2] In some cases, resistant mosquito strains used for testing may not meet the 50% minimum blood feeding criteria for controls specified in the WHOPES guidelines. Alternative criteria can be considered on a case by case basis, however, a rationale for the testing procedures used must be provided.

Replicates for cone test

Cone tests should use standardized 2–5-day-old non-blood fed adult females only. The acceptable minimum number of replicates for each mosquito strain is as follows:

Control 1 (untreated net)	1 net x 10 replicates x 5 mosquitoes = 50 mosquitoes
Control 2 (pyrethroid-only LLIN)	4 nets x 10 replicates x 5 mosquitoes = 200 mosquitoes
Test nets	4 nets x 10 replicates x 5 mosquitoes = 200 mosquitoes
Total	450 females per strain per new LLIN to be assessed

- A minimum of one laboratory-susceptible strain and three pyrethroid-resistant strains must be tested.
- Sample size calculations should be made in advance of any experimental work and sample size should be sufficient to demonstrate the minimum effect at 5% significance levels.
- Results should be discarded if mortality on the untreated net exceeds > 10%.

Replicates for tunnel test

Tunnel tests should use standardized 5-8 day old non-blood fed adult females only. The acceptable minimum number of replicates for each mosquito strain is as follows:

Control 1 (Untreated net)	3 replicates x 50 mosquitoes
Control 2 (Pyrethroid only LLIN)	3 replicates x 50 mosquitoes
Test nets	3 replicates x 50 mosquitoes
Total	450 females per strain per new LLIN to be assessed

- Samples size calculations should be made in advance of any experimental work to clarify the size of effect expected and the minimum effect that can be detected.
- Results should be discarded if mortality on the untreated net exceeds10%.

Note on mosaic and combination nets: In the case of nets where the sides and top of the net are not treated in an identical manner (eg. differing in insecticide content and/or polymer type), data with 4 nets x 10 replicates x 5 mosquitoes for each surface type need to be generated. If the proposed mechanism of action is based on the mosquito contacting an insecticide and a synergist located on different parts of the net, accommodation should be made in the guidelines/SOPs for sequential exposure of mosquitoes to the two components; however, this must not assume that all mosquitoes will contact both parts of the net and therefore Phase II evaluation is essential to determine efficacy in field conditions.

1.5. Product quality assurance

Before laboratory, hut or community trials are undertaken, basic quality assurance should be in place to ensure that the products tested meet specifications for quality control (manufacturers or WHO, if available).

Manufacturers should provide a certificate when supplying the product for testing that states that the product meets WHO or manufacturer's specifications for quality control. Quality assurance of the nets by high-performance liquid chromatography or gas chromatography should also be undertaken before the products are tested. Independent physical and chemical analyses of the products for compliance with specifications in an accredited, qualified laboratory may be required before efficacy testing.

All net testing should be undertaken on LLINs that have been washed once and left for the WHOPES- recommended regeneration time (or the time specified by the companies against insecticide-susceptible strains), in order to correct for variations in insecticide availability due to storage conditions for the nets.

2. STAGE 2 – EXPERIMENTAL HUT STUDIES

If the new LLIN product demonstrates significant increased efficacy compared to the standard pyrethroid-LLIN against all or most of the resistant strains tested in the laboratory, Stage 2 experimental hut studies should be initiated.

2.1. Objective

To demonstrate that the candidate LLINs (prepared according to WHOPES guidelines) are significantly better at inducing mortality and/or preventing blood-feeding than a standard LLIN (or reducing fecundity and fertility of the mosquitoes if a growth regulator is involved) against local highly resistant mosquitoes.

2.2. Site criteria

Experimental hut studies need to be conducted in areas where the mosquito population has high levels (RR > 10-fold) of well-characterized pyrethroid resistance. For data to be accepted, the resistance profile and species composition of the site must be determined immediately prior to, or at the same time as, the trial.

This profiling must include:

a. WHO diagnostic dose assays for pyrethroids (deltamethrin and permethrin as a minimum).[1]
b. LC^{50} [2] for all AIs incorporated into the net. A fully susceptible strain should be used as the standard for calculating the resistance ratio of the field population. (If *An. gambiae* s.s. is the local vector, the Kisumu strain should be used).
c. If a synergist is being tested, the effect of pre-exposure to the synergist on insecticide mortality needs to be recorded. For piperonyl butoxide (PBO) this should be a one-hour exposure to 4% PBO in a standard WHO tube bioassay.
d. A baseline of the species composition (including sibling species defined by molecular markers) of vectors entering the experimental huts prior to the study.
e. Cone bioassays testing one-time washed and regenerated pyrethroid-only LLINs with local mosquito vectors must be performed prior to the study.
f. At least 100 adult females (2–5-day-old non-blood fed, non-exposed to insecticides) should be preserved in an RNA stabilizing reagent (eg. RNAlater) at the start of the study for future follow up of resistance mechanisms, if required.

Note: Suitable study sites will have a vector population that has an RR > 10-fold for one or more pyrethroids at the LC^{50} level when compared to the standard Kisumu strain. Cone tests must also show > 50% survival of resistant mosquitoes against the standard pyrethroid-only LLIN. Tests undertaken in areas with lower level resistance cannot be used to substantiate product claims against highly pyrethroid-resistant populations.

2.3. Methods

The methodology follows WHOPES guidelines for testing LLINs at the experimental hut level[1] and the same parameters are calculated (deterrency, induced exiting, blood-feeding inhibition, personal protection and mortality). If sterilizing properties are to be recorded, blood-fed mosquitoes from huts using both net types need to be kept alive and the fertility/fecundity recorded. Additional outcomes may be considered and introduced depending on the claim of the manufacturer.

Species composition of alive and dead mosquitoes should be determined if there are multiple sympatric vectors, in order to evaluate whether the net is equally effective against all.

Trials should be undertaken in at least three geographically distinct locations with different vector populations (eg. different transmission settings and/or resistance profiles) to assess whether the product is effective at multiple sites.

The trial must include comparison with a WHOPES-recommended LLIN.

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[1] World Health Organization. Test procedures for insecticide resistance monitoring in malaria vector mosquitoes.(2013). http://apps.who.int/iris/bitstream/10665/80139/1/9789241505154_eng.pdf

[2] LC50 should be determined using WHO procedures for determining intrinsic insecticidal activity, as outlined in the WHO Guidelines for Testing Mosquito Adulticides for Indoor Residual Spraying and Treatment of Mosquito Nets. http://whqlibdoc.who.int/hq/2006/WHO_CDS_NTD_WHOPES_GCDPP_2006.3_eng.pdf

3. STAGE 3 – LARGE-SCALE FIELD TRIALS

The format of the community trials will depend on whether the mixture/combination LLIN functions through personal protection of the end user or relies predominantly on creating a community effect.

i. Fast-acting and repellent compounds will maintain personal protection of the end user and thus evaluation at a household level using a household randomized design will be sufficient.
ii. For all other modes of action, including slow action, epidemiological evidence will be needed due to a loss of personal protection for first in line products, or as determined by VCAG. A community-scale randomized controlled trial (RCT) design will be required for slow-acting or non-repellent[1] insecticides or products which are expected to affect mosquito fecundity and/or fertility.

3.1. Study design for LLINs that work through personal protection

3.1.1. Objectives

To demonstrate that, **under field conditions**, the new product significantly reduces the number of blood-fed mosquitoes collected resting and exiting houses, compared to a pyrethroid-only LLIN.

3.1.2. Study methods

New products which offer personal protection can be tested at the household level with a **household randomized control design**. This type of trial is suitable, for example, for nets with a rapid acting insecticide plus a synergist.

3.1.2.1. *Pre-trial considerations*

Potential sites need to be characterized prior to trial to ascertain:

a. WHO diagnostic dose assays for pyrethroids[2] (deltamethrin and permethrin as a minimum)
b. LC50 for all AIs incorporated into the net.[3] The Kisumu susceptible strain should be used as the standard for calculating the resistance ratio of the field population if the local vectors are *An. gambiae s.s.*
c. If a synergist is being tested, the effect of pre-exposure to the synergist on insecticide mortality needs to be recorded. For PBO, this should be a one-hour exposure to 4% PBO in a standard WHO tube bioassay.
d. A 3-month baseline of the species composition (including form for *An. gambiae* s.s) of malaria vectors at the field trial site prior to the study, which should be a minimum of 3 months.

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[1] Pyrethroids lose their repellency action against pyrethroid-resistant populations and therefore combining a pyrethroid with a non-repellent insecticide or synergist would not allow a trial at household level to be a sufficient test.
[2] World Health Organization. Test procedures for insecticide resistance monitoring in malaria vector mosquitoes."(2013). http://apps.who.int/iris/bitstream/10665/80139/1/9789241505154_eng.pdf
[3] LD50 should be determined using WHO procedures for determining intrinsic insecticidal activity, as outlined in the WHO Guidelines for Testing Mosquito Adulticides for Indoor Residual Spraying and Treatment of Mosquito Nets. http://whqlibdoc.who.int/hq/2006/WHO_CDS_NTD_WHOPES_GCDPP_2006.3_eng.pdf

e. A minimum of 100 mosquitoes should be tested in each case, for a–c above.
f. Cone bioassays on one-time washed and regenerated pyrethroid-only LLINs and local vectors must be performed prior to the study
g. At least 100 adult females (2–5-day-old non-blood fed, non-exposed to insecticides) should be preserved an RNA stabilizing reagent (eg. RNAlater) at the start of the study for future follow up of resistance mechanisms, if required.

3.1.2.2. *Trial procedures*

After the baseline data above are collected, the candidate and standard net types should be randomly assigned to households and quarterly indoor and exit collections made over a transmission season. Mosquito densities will be compared between a reference pyrethroid LLIN (positive controls) and the candidate LLIN. Additionally, the mosquito densities should be noted before and after the intervention in indoor and exit collections, as well as the physiological status of female mosquitoes and any instances of delayed mortality.

Data will only be considered for trials that have been conducted in an area with documented > 10-fold pyrethroid resistance, where the resistance status has been determined at the time of the trial.

3.2. Study design for LLINs that work only through community protection.

For LLINs that work at the community rather than the individual level and that do not offer personal protection, full-scale epidemiological trials will be needed until sufficient evidence has been generated to support the paradigm so a cluster randomized design will be applicable.

Indicators of epidemiological outcome could include: incidence of malaria through active case detection, passive case detection, serology, and/or point prevalence of infection. Entomological outcomes such as human landing catch, entomological inoculation rates and parous rates should also be considered.

The design and analysis of these trials should be based on methods appropriate for cluster randomized trials and standard errors and significance tests should be estimated accordingly.

In order to facilitate assessment and to standardize testing between products and between independent trials of the same product, SOPs are being developed and example trial formats will be made available with this document through VCAG.

[1] Guidelines for laboratory and field-testing of long-lasting insecticidal nets. Geneva: World Health Organization; 2013 (WHO/HTM/NTD/WHOPES/2013.1:14–28).

[2] Pyrethroids lose their repellency action against pyrethroid-resistant populations and therefore combining a pyrethroid with a non-repellent insecticide or synergist would not allow a trial at household level to be a sufficient test.

APPENDIX 1

Standard insecticide-susceptible and insecticide-resistant strains used by industry for insecticide development and available as standards for testing via replace with Liverpool Insect Testing Establishment, Liverpool, UK. Well characterized strains from other sources may also be used (see section 1.3 above). Characterized strains from other institutions will be added to this list in due course and all the information will be made available and updated regularly on VCAG website.

Name	Species	Country of origin	Phenotype	LC50 Deltamethrin (µg/ml)	*Kdr*	Ace
Kisumu	*Anopheles gambiae*	Kenya	Susceptible	0.020	0	0
Kisumu Rdl	*Anopheles gambiae*	Kenya	Dieldrin resistant	To be determined	0	0
Akron	*Anopheles gambiae*	Benin	Carbamate resistant	To be determined	0.1	0.5
VK7	*Anopheles gambiae*	Burkina Faso	DDT resistant	0.260	0.4	0
Tiassale	*Anopheles gambiae*	Côte d'Ivoire	Pyrethroid resistant	1.590	0.9	0.4
Moz	*Anopheles arabiensis*	Mozambique	Susceptible	To be determined	0	0
New Orleans	*Aedes aegypti*	USA	Susceptible	0.004	0	n/a
Cayman	*Aedes aegypti*	Grand Cayman	Pyrethroid, carbamate and DDT resistant	9.290	0.7	n/a
FuMoz	*Anopheles funestus*	Mozambique	Pyrethroid and carbamate resistant			

kdr, knockdown resistance

ANNEX 4. CHANGES AND CLARIFICATIONS FOR VCAG APPLICANTS

VCAG application procedures

Applicants will submit a letter of intent (LOI) to VCAG that briefly describes the paradigm, the prototype, the potential public health value and the evidence supporting this application. All LOI will be screened by the VCAG Secretariat in consultation with the VCAG Chairperson to determine suitability to go before the Committee. Full applications will be submitted following an invitation by VCAG to apply.

What criteria will be used to determine which dossiers are submitted to VCAG?

Documents will be screened for completeness of the documentation and supporting material and to determine whether the submission is describing a new paradigm. In order to be eligible for VCAG review, products submitted should:

1. Either fall outside of previously defined paradigms (eg. LLINs, IRS, larvicides) or submit evidence that is sufficiently advanced that it furthers the development of the paradigm beyond what has been submitted already (e.g. if the status of evidence for a paradigm is at step 2, and the new product submits data from randomized controlled trials (RCTs) that support completion of VCAG Step 3.
2. Be targeted as a public health intervention, not a consumer product. For the most part, public health products provide community rather than personal protection. Products/prototypes described as consumer products will only be reviewed by VCAG if the applicant includes information in the TPP describing how the product could be used as a community-based intervention.
3. Be willing to generate data from RCTs to demonstrate epidemiological impact. Provide documentation supporting the potential for public health value.

A full checklist of eligibility criteria will be provided on the VCAG website (information for applicants section). In advance of application, applicants should consult the VCAG Secretariat for guidance on product eligibility and on dossier submission.

What is the burden of entomological evidence required by VCAG?

Laboratory, semi-field and small-scale field trials are required to show the entomological impact of the product. For guidance on experimental design including replicates, controls and commonly used test procedures, applicants should consult the guidelines developed by WHOPES for testing the entomological efficacy of vector control products.

LLINs: http://www.who.int/iris/bitstream/10665/80270/1/9789241505277_eng.pdf
IRS: http://whqlibdoc.who.int/hq/2006/WHO_CDS_NTD_WHOPES_GCDPP_2006.3_eng.pdf
Larvicides: http://whqlibdoc.who.int/hq/2005/WHO_CDS_WHOPES_GCDPP_2005.13.pdf

VCAG strongly encourages innovators to work closely with an entomologist for the purposes of producing high-quality entomological data.

To what extent must the applicant demonstrate public health value in the LOI?

While demonstrating the value of the paradigm will be accomplished in VCAG Step 3 (RCTs), applicants should provide justification for their claims that the submitted product will have an impact on disease. At least some documentation should be referenced in support of these claims, and such evidence provided in the full submission dossier.

What guidance will be provided to those dossiers returned to the applicant without VCAG review?

VCAG will primarily guide paradigm, not product, development. However, if the product submitted is appropriate for WHOPES, VCAG will direct the applicant to the appropriate channels and resources for such evaluation. In select cases, VCAG may also direct the developer towards sources of advice for product development or expertise in a particular area.

The WHO Vector Control Advisory Group (VCAG) supports national and global efforts to control and eliminate vector-borne diseases worldwide by strengthening WHO's capacity to assess the public health value of new vector control innovations and to develop appropriate technical recommendations. This report details the proceedings and outcomes of its third meeting, held in November 2014, where the nine submissions were evaluated, resulting in three potential new paradigms for vector control.

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and
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