SECOND MEETING
OF THE
VECTOR CONTROL ADVISORY GROUP

GENEVA, SWITZERLAND
10–14 FEBRUARY 2014

World Health Organization

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INTRODUCTION

The second 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 at WHO headquarters in Geneva, Switzerland on 10–14 February 2014. The objective of the meeting was to review the dossiers and target product profiles of nine potentially novel paradigms for public health vector control.

The meeting was opened by Dr Lorenzo Savioli, Director, Department of Control of Neglected Tropical Diseases (NTDs), who updated the group on the department's activities, notably its involvement in WHO World Health Day, which would highlight the importance of controlling transmission of vector-borne diseases to public health worldwide; staffing changes, including the appointment of Dr Dirk Engels as the new director of NTD upon Dr Savioli's retirement; capacity strengthening for Vector Ecology and Management (VEM) and the Global Malaria Programme (GMP) through new staff and consultancies; and recent funding to the VEM Dengue Programme from the Bill & Melinda Gates Foundation aimed at identifying the true global burden of dengue infection. Dr Savioli recalled the important work of WHOPES and the challenge of optimizing use of its structure for vector-borne disease control. He concluded by reminding the VCAG of the importance of confidentiality during proceedings and thanked the group for its work.

Dr Raman Velayudhan, Coordinator, NTD/VEM, outlined administrative arrangements for the meeting and expanded Dr Savioli's remarks about World Health Day. The event would highlight the public health impacts of insecticide resistance and environmental change and the need for capacity building for vector-borne disease management. Commemorations would include airport displays, global SMS messages about the impact of vector-borne diseases, website development and WHO region-specific focuses.

Dr Marc Coosemans called the meeting to order. He emphasized the importance of making clear statements about the epidemiological impact and public health value of the paradigm categories that VCAG would review, in order to mobilize countries in the context of an expanding global burden of vector-borne diseases, in particular dengue and other arboviruses. Increased attention must be paid to capacity-building and environmental change in vector-borne disease control. He reiterated the NTD Director's comments about the importance of confidentiality during the proceedings.

The meeting was attended by 12 of the 13 selected members of VCAG, partners from industry, observers and special invitees (Annex 1: List of participants). Dr Marc Coosemans was appointed Chair of the meeting; Dr Ashwani Kumar, Dr Anna Drexler and Dr Emmanuel Temu were appointed as Rapporteurs. The meeting was divided into open and closed sessions (Annex 2: Agenda). The closed session (10–11 February) allowed VCAG members and the secretariat to review the dossiers presented to the Group. This was followed by a closed question and answer session between VCAG and the paradigm developers (12 February). The open session (13 February) provided an opportunity for public presentations by the paradigm developers and discussion among developers, VCAG and other stakeholders. The meeting concluded with a

closed session for VCAG to finalize the paradigm and prototype assessments for each item in the VCAG pipeline.

DECLARATIONS OF INTEREST

In accordance with WHO's policy for the management of conflicts of interest for WHO experts, the following interests and related mitigation measures were disclosed.

All 13 VCAG members submitted declarations of conflict of interests, which were reviewed and assessed by the NTD Department; for certain declarations the Office of the WHO Legal Counsel was consulted.

Of the 12 VCAG members present, nine declared no conflict of interest and two declared potential conflicts of interest. For the purpose of this meeting, however, no conflicts of interest were declared that would prevent the experts from participating in the meeting. In the future, should repellents be discussed in the VCAG, Professor Coosemans will be excused from participating in formulating recommendations in relation to repellents, due to conflicts of interest.

The support provided by the Bill and Melinda Gates Foundation for the work of VCAG is gratefully acknowledged.

SPECIAL TOPICS

Role and jurisdiction of WHOPES and VCAG (Raman Velayudhan)

The WHO Pesticide Evaluation Scheme (WHOPES) and the Vector Control Advisory Group (VCAG) have separate but complementary roles in bringing vector control products to market. WHOPES is a large-scale programme that promotes and coordinates the testing and evaluation of pesticide products within established vector control paradigms (e.g. indoor residual spraying (IRS), long-lasting insecticidal nets (LLINs), mosquito larvicides and space-spraying products)[1], assesses their safety and efficacy and sets international quality standards (WHO specifications) for these tools. WHOPES can evaluate any new tool or innovative product that complies with established vector control categories (e.g. new active ingredients or formulations for use in LLINs, combination products for standard use in IRS, or larvicides with novel mechanisms of action). In contrast, VCAG serves as WHO's main mechanism for bringing innovation in paradigms to the vector control arena. Its recommendations on policy development are submitted to the GMP Malaria Policy Advisory Committee and/or the Strategic and Technical Advisory Group for NTDs.

The role of VCAG is primarily to assess and guide the development of new, innovative vector control paradigms. In this context, a new paradigm" is a category of intervention

[1] WHO Pesticide Evaluation Scheme (WHOPES) (http://www.who.int/whopes/en/; accessed October 2014).

or class of product whose public health or epidemiological impact is as yet unproven because (i) the paradigm targets vectors or transmission contexts where the usefulness of vector control is still uncertain (e.g. vector traps for disease management); (ii) the paradigm represents a new mechanism for controlling established vectors in defined transmission settings (e.g. transgenic or otherwise modified mosquitoes); (iii) the paradigm represents the gross modification of an existing intervention to the point where it forms a new product class and/or where a new epidemiological effect is expected (e.g. products for use in areas of substantive pyrethroid resistance)[2]. VCAG evaluates these novel paradigms by investigating "first in line" prototypes for each class of intervention submitted.

Central to VCAG's function is the mandate to evaluate the epidemiological impact – in addition to the entomological impact – of novel paradigms or prototypes presented to the Group. Evaluation generates the evidence or proof of principle for the new paradigm and is a key difference in the objectives of WHOPES and VCAG. Whereas WHOPES evaluates products within established categories for which sufficient evidence exists to support public health claims and thus its recommendations on efficacy require entomological data alone, VCAG requires both entomological and epidemiological data in order to issue a recommendation.

The programmes also differ in the type of product evaluated, the kind of data required, mechanisms of data generation and the end use of the WHOPES and VCAG evaluations (*Table 1*). A WHOPES evaluation targets mature products produced on a commercial scale, requiring the submission of information such as manufacturers' internal quality assurance and control schemes, product labels, material safety data sheets, manufacturing process and batch information, and draft risk assessments and specifications. WHOPES facilitates the independent and scientifically rigorous testing of submitted products according to WHO peer-reviewed published guidelines and generates data for use in product registration. A VCAG assessment, on the other hand, targets an earlier stage of product development, taking into account a wide range of published and unpublished data to formulate recommendations, rather than adherence to and performance in a series of defined tests.

By communicating with innovators during the development of innovative tools within new paradigms, VCAG aims to shorten the timeframe between submission to the Group and a policy recommendation. Should VCAG decide that a particular paradigm has potential for vector control and issues a recommendation, this product may be deemed usable for operational vector control but may need to be evaluated by WHOPES for risk assessment and development of WHO specifications, if these were not included in the VCAG assessment. The Group is also mandated to prepare guidelines for efficacy testing and risk assessment of the new paradigms recommended.

Once VCAG has recommended a new class of product (paradigm) and guidelines have been prepared, similar products in that paradigm from other manufacturers can be submitted to WHOPES for testing, evaluation and development of WHO specifications. Thus, while WHOPES currently accepts into its programme only pesticide products, in the future other vector control tools developed under the umbrella of VCAG may be eligible for WHOPES evaluation, making use of the WHOPES structure to evaluate products in novel vector control paradigms recommended and defined by the VCAG.

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[2] WHO Vector Control Advisory Group operational procedures: "When is a paradigm or category new?" (http://www.who.int/neglected_diseases/vector_ecology/Operational_procedures_for_VCAG.pdf; accessed October 2014).

Table 1. Jurisdictions of VCAG and WHOPES in vector control innovation

	VCAG	WHOPES
	Innovative vector control paradigms	Innovative products from established vector control paradigms
Scope	Looks at "first in line" prototypes when assessing paradigms claims. Does not evaluate individual product claims.	Evaluates individual product claims for commercially produced pesticides
Evaluation	Efficacy: Requires entomological and epidemiological data Safety: Requires risk assessment Other Parameters including TPP, user compliance/acceptability, economic feasibility, manufacturing sustainability and strategic/policy role	Safety: Requires risk assessment Quality: WHO Specifications developed through JMPS Efficacy: Requires entomological data only
Data	Reviews published and unpublished data submitted by innovator	Reviews data from WHOPES supervised laboratory and field trials according to WHO testing guidelines
Outcome	Issues recommendations on the public health value of the paradigm and the associated first in line prototype to policy setting groups (MPAC/NTD-STAG)	Issues recommendations on the efficacy, safety/risk and quality standards of public health pesticides for use by member states for product registration and procurement

SUBMISSIONS REVIEWED BY VCAG FEBRUARY 2014

Paradigm	Prototype	Developer	Species targeted
Microbial control of human pathogens in adult vectors	Wolbachia	Prof Scott O'Neill, Monash University, Australia	*Aedes* spp
Vector control products for pyrethroid resistant areas	Permanet® 3.0	Vestergaard Frandsen SA, Lausanne, Switzerland	*Anopheles* spp
Vector control products for pyrethroid resistant areas	SmartPatch	EU-FP7 project consortium consisting of 5 organisations[1]. Coordinator: Matthew Thomas PhD, Penn State University	*Anopheles* spp
Spatial repellents	TBD	Dr Nicole L. Achee, ECK Institute for Global Health, Notre Dame, IN, USA	*Anopheles*, *Aedes*, *Culex* and *Phlebotomus* spp
Vector traps for disease management	ALOT	Dr Dawn Wesson, Tulane University, New Orleans, LA, USA	*Aedes aegypti*
Vector traps for disease management	In2Trap	In2Care BV, Wageningen, Netherlands	*Aedes aegypti*
Lethal house lure	Eave tubes and bricks	EU-FP7 project consortium consisting of 5 organisations[1]. Coordinator: Bart GJ Knols, PhD MBA, In2Care BV	*Anopheles* spp

[1]Consortium members: Biogents AG (Regensburg, Germany); CTF2000 Flame retardants & Chemical Specialties (Zele, Belgium); Ifakara Health Institute (Dar es Salaam, Tanzania); In2Care BV (Wageningen, Netherlands); Penn State University (University Park, PA, USA)

VECTOR CONTROL PARADIGM SUBMISSIONS REVIEWED BY VCAG*

1. MICROBIAL CONTROL OF HUMAN PATHOGENS IN ADULT VECTORS

1.1 PARADIGM

The paradigm is **microbial control of human pathogens in adult vectors**. It requires the introduction of micro-organisms into vectors to reduce or prevent biological transmission of the pathogen to humans.

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.

A critical next step is to assess the efficacy of *Wolbachia* deployments in reducing natural dengue virus transmission. A cluster randomized trial (CRT) is currently premature because: (i) medium-scale field-testing is required to select the optimal *Wolbachia* strain(s) before a formal efficacy trial is undertaken; (ii) while deployment in northern Australia has provided a basic template for release, this environment differs substantially from the large urban centres in South-East Asia where a CRT would likely be carried out, and it is crucial to retain the capacity to learn during deployment about the effectiveness of release strategies and community engagement and to adjust practice accordingly; (iii) a classical two-armed CRT would have to be large, with > 40 clusters expected to be required to detect a 50% reduction in dengue seroincidence with 90% power.

This intermediate step involves a series of well-designed observational studies to provide indirect evidence of the impact of a *Wolbachia* intervention on dengue transmission. These studies are a precursor for a CRT and will provide important epidemiological, clinical, logistical, financial and regulatory information. The collection of indirect efficacy data before the deployment methodology has been fully optimized, as would be required for a CRT, will also provide important information on effect size.

1.2 PROTOTYPE: *WOLBACHIA*-BASED BIO CONTROL

Description of the prototype

Symbiotic *Wolbachia* spp. bacteria are introduced into *Aedes* spp. mosquito populations to reduce their ability to transmit dengue viruses to humans.

Prototype claims

i. Laboratory results show that *Wolbachia* infection reduces viral replication within vector mosquitoes and eliminates or substantially delays the appearance of dengue virus in mosquito saliva, making the mosquito an incompetent vector for transmission of dengue viruses.

ii. Some *Wolbachia* strains can be passed efficiently by a female mosquito to her progeny, and are thus able to spread rapidly into wild mosquito populations. In

* See also Summary in *Annex 3*

small-scale field trials in Australia, *Wolbachia* infection was established within native wild *Ae. aegypti* populations, showing that the approach can be practically deployed at a limited scale, is stable in the field and is acceptable to communities and regulators.

iii. Community authorization and regulatory approval for pilot releases of *Wolbachia*-infected mosquitoes have been obtained in Australia, Indonesia and Viet Nam, suggesting a high probability for eventual public acceptability of *Wolbachia*-based biocontrol for eliminating dengue transmission.

iv. If this approach functions as envisaged, preliminary modelling analyses predict that it will provide an area-wide solution to dengue transmission control, capable of propagating itself without the need for reapplication or human behavioural change.

Mode of action of the prototype

Wolbachia-infected mosquitoes are released to a critical density necessary to spread through local vector populations of *Ae. aegypti*. *Wolbachia* infection is established in wild *Ae. aegypti* populations. *Wolbachia* fixation in *Ae. aegypti* populations results in the reduced ability of the population to transmit dengue virus (possibly through stimulation of mosquitoes' innate immune responses or intracellular resource competition between the bacteria and the virus within the vector).

Paradigm development stage for the prototype

Completion of Step 2: Substantial dossier of data and publications. Completion of laboratory and small-scale field trials demonstrating proof of concept and scalability.

Further development of deployment technology, including medium-scale field trials to select the optimal *Wolbachia* strain(s), refine deployment strategies (release stage, release method, release numbers), efficiencies around the approach to community engagement and regulatory approval, and indirect measures of likely impact on dengue transmission, will inform the design of randomized controlled field trials to determine epidemiological outcomes.

Summary of key studies supporting the claim

The investigators have demonstrated:

i. *Wolbachia*-infected *Ae. aegypti* reduce the level of dengue virus infection in vectors in the laboratory.

ii. *Wolbachia*-infected mosquitoes introduced into wild vector populations can result in the saturation of *Wolbachia* in populations of wild mosquitoes in the field.

Supporting documentation (summary)

Substantial submission dossier included 27 publications and summaries of relevant field-trials.

1.3 CONCLUSIONS AND RECOMMENDATIONS: *WOLBACHIA*

For paradigm

i. Assess and optimize the stability and effectiveness (balanced fitness, transmission blocking) of microbial strains.
ii. Prove ability to mass produce microbial-infected vectors.
iii. Complete risk assessment studies.
iv. Assess cost-effectiveness, community acceptability of intervention.
v. Develop a framework for large-scale implementation.
vi. VCAG Step 3 requires randomized controlled field trials in an endemic setting.

For prototype

i. Assess and optimize the system of spreading *Wolbachia*-infected *Ae. aegypti* into wild vector populations.
ii. Depending on Step 1, the VCAG encourages the investigators to carry out at least one randomized control trial (RCT) with epidemiological outcomes that would take place over several years to account for inter-annual variability in dengue transmission.
iii. VCAG recommends a post-trial evaluation to monitor the long-term stability of *Wolbachia* in the vector population.
iv. Because the effectiveness of the intervention may differ by epidemiological and entomological setting, there is a need to measure the impact of the intervention in different areas in order to generate appropriate recommendations. However, because the cost of conducting multiple *Wolbachia* RCTs may be prohibitive, the VCAG suggests that sentinel sites be established in several areas prior to and concurrent with a RCT where relevant entomological and epidemiological outcomes are regularly collected. This will permit a Phase IV *Wolbachia* intervention to be evaluated using an interrupted time-series approach if the RCT results demonstrate success.
v. The VCAG emphasizes the importance of measuring the cost-effectiveness of the intervention during the RCT.
vi. VCAG also encourages the development of a framework for scaling up this intervention.

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2. SPATIAL REPELLENTS

2.1 PARADIGM

The paradigm is **spatial repellents**. It requires that spatial repellents:

i. interrupt human–vector contact through behavioural modification in vectors induced by airborne chemicals as opposed to direct killing resulting from traditional toxicants;
ii. offer protection from a varied range of medically important vectors and nuisance pests;
iii. offer protection from day-biting, early-evening and/or outdoor vector groups;
iv. provide personal and community protection against vector-borne infections/diseases.

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 and is designing randomized controlled trials required for Step 3.

2.2 PROTOTYPE: LONG-LASTING PASSIVE EMANATOR

Description of the prototype

The spatial repellant prototype is a passive emanator releasing metofluthrin or transfluthrin in the air at low vapour concentrations. The prototype product will be effective for at least 2 weeks.

Prototype claims

In October 2012, WHOPES convened a panel of experts in Geneva, Switzerland to outline key measures and methodologies for evaluating spatial repellent products in anticipation of recommendations for their use in public health. Stakeholders included representatives from academic, industry, ministries of health and a WHO testing centre. The group defined spatial repellency as a range of insect behaviours induced by airborne chemicals that result in reduced human–vector contact (WHO, 2013). This can include movement away from a chemical stimulus, interference with host detection (attraction-inhibition) and/or feeding response.

Spatial repellency can be measured and distinguished from other chemical actions, to include contact irritancy and toxicity (Dethier et al., 1960). Many active chemical compounds exhibit two or more modes of action, but they can be classified by the concentration, dose and exposure time needed to achieve those (Grieco et al., 2007). Spatial repellents have demonstrated efficacy against insecticide-resistant populations and have the potential to limit the spread and/or emergence of insecticide-resistant alleles due to low selection pressure when considering the non-lethality of effect. Spatial repellents, combined with other interventions, have the potential to demonstrate added

protective benefit, especially in areas where traditional LLINs or IRS interventions may not offer full protection (when considering day-biting, outdoor and/or early-evening vector biting behaviour) or have reached their efficacy limits, especially in areas with residual transmission[1] (Durnez L, Coosemans M, 2013) or areas where elimination is proposed (in the case of malaria). Control and/or elimination of disease in these areas will require new approaches and this may be where spatial repellency would be most effective (Ogoma et al., 2012a; Achee et al., 2012a). Spatial repellents could be offered as stand-alone tools where no other interventions are currently in use; or, most likely, combined with existing interventions to augment their efficacy (i.e. a combination strategy), thereby tackling residual transmission, managing the spread of insecticide resistance and intervening in areas of the vector life-cycle where other interventions do not reach. Spatial repellents can also be offered for protection against other arthropods of medical importance as well as nuisance pests.

Mode of action of the prototype

Spatial repellency occurs at low vapour phase concentration; contact irritancy requires higher doses and killing requires absorption at still higher levels. Despite increased research efforts during the past several decades, the mechanism of repellency is not yet fully understood. According to the known modes of action, chemicals affecting insects are classified as controlling (i) growth and development, (ii) energy metabolism and (iii) nerves and muscles. Because contact repellents are fast-acting agents, their mechanism of action is more likely to result from the last of these three types, which may include inhibition of acetylcholinesterase (AChE), modulation of sodium channels and modulation of nicotinic acetylcholine receptors. A highly probable mechanism for repellency is the interference with the insect's chemosensory system, which governs behavioural patterns such as host-seeking, oviposition and flight from chemical irritants. For example, DEET is evidenced to modulate olfaction in insects (Ditzen et al., 2008), inhibit acetylcholinesterase activity and affect gustatory receptors (Lee et al., 2010).

If a spatial repellent response is stimulated by a lower concentration of chemical than required for either contact irritancy or toxicity, then the insect or some proportion of insects will be repelled without making tarsal contact with the chemical. Conventional wisdom in the control of arthropod vectors dictates that a repellent action will neutralize the toxic effect of a compound and thus reduce the effectiveness of the chemical. This assessment is true only if we accept the notion that chemicals function to prevent pathogen transmission solely by killing vectors. However, pathogen transmission is prevented by breaking human–vector contact where it occurs, within or outside the home. This can be achieved by creating a spatial repellent barrier that precludes a proportion of the vectors from entering the treated space and/or eliciting attraction-inhibition, thereby preventing blood-meal success.

Paradigm development stage for the prototype

Step 2 – development of proof of concept, in preparation for Step 3.

Summary of key studies supporting the claim

The investigators have provided evidence for modelling studies as well as Phase I (laboratory) and Phase II small–medium-scale field studies.

[1] Residual transmission is transmission that occurs even with good access to and usage of LLINs or well-implemented IRS and/or in situations where LLIN use or IRS are not practical. (http://www.who.int/malaria/publications/atoz/technical-note-control-of-residual-malaria-parasite-transmission-sep14.pdf?ua=1)

Modelling studies demonstrate that high coverage with spatial repellents could enhance the impact of LLINs and have the potential to confer near-complete personal protection; however, indoor use of these products could also influence the mass effect of LLINs on vector populations.

Phase I laboratory studies:

i. standard vector control compounds can exert spatial repellency, contact irritancy and toxicity, depending on the dose of exposure.
ii. spatial repellency is observed in arthropods of medical importance such as *Culex pipiens* and *Phlebotomus papatasi*.

Phase II controlled field experiments:

i. Organochlorine spatial repellents reduced mosquito (*Anopheles darlingi*, *An. vestitipennis*, and *Ae. aegypti*) entry into experimental huts compared with untreated spaces in studies in Belize, Brazil and Thailand.
ii. Exposure to metofluthrin-impregnated paper or plastic strips confers indoor and outdoor protection against *Anopheles* and *Culex* spp., resulting in > 85% protective efficacy (fewer bites, lower mosquito densities and reduced landing rates) compared with controls.
iii. Transfluthrin-treated strips conferred > 90% protective efficacy for 6 months.
iv. Concentrations of metofluthrin (0.00625% in coils) below thresholds required for toxic responses elicited up to a 58% reduction in *Ae. aegypti* entry into experimental huts.

Small-scale field studies in preparation for Phase III:

i. Two trials in China and Indonesia indicate that the use of spatially acting pyrethroids (applied according to the product's manufacturing specifications) is associated with reduced rates of mosquito biting (32–88%) in treated spaces and reduced individual malarial risk (61–80%).
ii. Replication and extension of these Phase III studies is the core work of the currently funded multi-centre programme aimed at demonstrating the protective efficacy of spatial repellent products in reducing the incidence of malaria and/or dengue will capture both epidemiological and entomological end-points

Supporting documentation (summary)

Full dossier and supporting documents include:

i. WHO: Guidelines for the efficacy testing of spatial repellents
ii. Compilation of supporting unpublished data from academia
iii. Spatial repellents for control of vector-borne diseases proposal
iv. Core malaria protocol – standardized measures and methodologies
v. Core dengue protocol – standardized measures and methodologies
vi. Reference list of supporting publications.

2.3 CONCLUSIONS AND RECOMMENDATIONS: SPATIAL REPELLENTS

If widely accepted by countries endemic for malaria and dengue, spatial repellents would supplement the current indoor LLINs and IRS tools in reducing human–vector contact and controlling the infection/diseases.

The dossier provides cumulative evidence of the potential utility of spatial repellents as a viable intervention against vectors both indoors and outdoors. The applicant presents detailed and appropriate protocols to demonstrate the proof of principle of the protective efficacy of spatial repellents against new dengue infections and the degree to which their use could reduce and/or prevent malaria.

The VCAG notes the growing challenge of outdoor malarial transmission in eliminating the disease and the potential of spatial repellents to control transmission of both early-evening and outdoor-biting anopheles; however, the data presented are inadequate to demonstrate the efficacy of repellents used outdoors.

For paradigm

i. Define the synergies/limitations/conflicts of spatial repellents when used with other interventions, including how their use indoors may affect the mass effect of LLINs/IRS on the vector population.
ii. Distinguish between household and community protection when evaluating the product and include monitoring for both effects.
iii. Clarify when and where spatial repellents can be used as a stand-alone method. When used as stand-alone intervention in an endemic disease setting in a phase III RCT, the use of a placebo may be objected to on ethical grounds.
iv. Given that the placebo arm for this paradigm will not be truly blinded, resulting changes in user behaviour should be considered and accounted for if possible.
v. Evaluate the epidemiological impact of interventions using spatial repellents, especially in diverting vectors to unprotected populations.
vi. In low-transmission areas, consider the possibility of serology for malaria (multiplex assays), which could be more sensitive than PCR prevalence.
vii. Elaborate how spatial repellents would be used to manage the spread of insecticide-resistance genes.
viii. Protective efficacy for SR outdoors must be demonstrated if it is to be included in the paradigm (outdoor use is not addressed in the planned trial design).
ix. Evaluate the potential risk for selecting SR insensitive traits in vectors and strategies to monitor this.
x. Prepare appropriate guidelines to evaluate adverse events/serious adverse events and a model risk assessment for spatial repellents, taking into account their long-term use.
xi. Consider the possible effect of spatial repellents on non-target organisms (bees, butterflies and pollinators).

For prototype

i. VCAG is seriously concerned that the existing study design is underpowered to detect the hypothesized overall 30% protective effect of the intervention. It strongly recommends that each site should be powered for an independent result.

ii. It is unclear how the Kenya site results (community diversion effect versus incidence and distance) of protective efficacy need to be demonstrated.

iii. Describe the prototype product that will be used (in this multi-centre study) to enhance evidence of the public health value of spatial repellents in general, and clarify the Target Product Profile. How representative is the prototype product for addressing the paradigm?

iv. Estimate the cost of spatial repellents. What is meant by "competitively priced"?

v. Based on the model, coverage of spatial repellents should be high. What percentage of coverage (availability and compliance) will be required?

vi. The investigators should provide information on universal coverage of nets across the entire study area for all malarious sites and for all members in the communities in those countries where nets are the standard of care. Consideration should be given to changes in coverage over the duration of the study; information on net usage should therefore be collected.

vii. A risk assessment model of the prototype should be generated.

viii. Prolonged indoor use of spatial repellents may result in accumulation of active ingredients that may simulate an IRS effect. Can this be evaluated?

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3. RESISTANCE TARGETING PRODUCTS

3.1 PARADIGM

The paradigm is a **vector control intervention** that when applied in areas of substantive pyrethroid resistance has an evident beneficial effect on public health. The paradigm could be a novel intervention or an adaptation of an existing paradigm. It has an overall effect on vectorial capacity and reduces infection or disease in humans in areas where the local vectors have substantive resistance to pyrethroids.

Status of evidence for the paradigm

Substantive portfolio of field trials with one product; other products in the WHOPES process. Clear guidance needed on the burden of proof required to support claims for interventions in this category.

3.2 PROTOTYPE: PERMANET® 3.0

Description of the prototype

A bi-treated (or combination net) LLIN with pyrethroid insecticide (deltamethrin) on the walls of the net and deltamethrin + piperonyl butoxide (PBO) on the roof of the net. Product already has a standard WHOPES interim recommendation as an LLIN against WHOPES guidelines using susceptible mosquitoes.

Prototype claims

Relative to pyrethroid-only LLINs, PermaNet® 3.0 has increased efficacy against malaria vectors with cytochrome P450-based metabolic pyrethroid resistance, even if combined with kdr.

Mode of action of the prototype

The prime mode of action is based on the reported tendency of African anophelines to approach and probe LLINs with individuals sleeping under them from the top of the net and work down. Vectors contact the synergist/insecticide combination in the roof of the net, negating major monooxygenase-based resistance mechanisms in the vectors and thereby increasing the effectiveness of pyrethroid insecticides.

The effectiveness of LLINs has been demonstrated in large-scale CRTs; what is not known is the detrimental effect of increasing levels of pyrethroid resistance in the local vector populations. Although many studies have been undertaken, no data are available to assess whether resistance affects rates of malaria transmission. Laboratory data demonstrate that resistance impacts entomological indicators such as mortality and blood-feeding. However, due to poor standardization of testing methodologies and inherent variation in field populations, no conclusions can be drawn from the field data currently available.

Paradigm development stage for the prototype

Step 3 – Substantial dossier of data and publication. This is already a mature product that has interim WHOPES approval; however, the product needs to be assessed against the recommendations to be generated by the VCAG sub-committee.

Summary of key studies supporting the claim

The manufacturers have been very careful to make a relatively modest claim that can be supported by the combined evidence from multiple studies in many areas of pyrethroid resistance. The claim is specific to the major resistance mechanism that should be interrupted by exposure to PBO on the net. The VCAG collectively considered this claim to be reasonable and supported by the evidence; however, guidance must be provided to the Group on what proof of claim is needed for products in this category. While it may be ideal to have large-scale epidemiological trials, there is a pressing requirement for guidance in this area in a format where data can be gathered to give best advice within the next 12 months.

The VCAG will convene a small working group to establish the criteria required to support basic advice on product benefits in areas of high pyrethroid resistance. It will NOT develop resistance management strategies that such products could be used within nor will they examine resistance breaking claims. The group should report back to VCAG by the end of April 2014.

Supporting documentation (summary)

A WHOPES dossier and several published documents and papers were submitted for review.

3.3 CONCLUSIONS AND RECOMMENDATIONS: PERMANET® 3.0

For paradigm

A small working group needs to be established to prepare guidelines for the minimum data needed to substantiate claims for an entomological benefit from specific vector control interventions in areas of high pyrethroid resistance, recognizing that the data on the impact on human health have not yet been generated. Given the urgency of the need for guidance this group should report back to the VCAG by the end of April 2014. Terms of reference for the group have been prepared.

For prototype

As a first in class there is significant knowledge about how to (and how not to) undertake field evaluation of a product aimed primarily at pyrethroid-resistant vector populations. The changes in methodology during product evaluation have resulted in a large body of data that have large-scale variability.

Overall VCAG supports the modest claim of the manufacturers that this combination net had increased bioefficacy compared with pyrethroid-only LLINs in areas where malaria vectors have P450-based metabolic resistance mechanisms that reduce the efficacy of pyrethroid-only LLINs.

The WHOPES phase 3 evaluation process towards full recommendation should be completed.

The VCAG notes that the product would need to be implemented with resistance monitoring that assessed the underlying mechanisms of resistance

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3.4 PROTOTYPE: SMARTPATCH

Description of the prototype

The prototype has a supplementary netting patch impregnated with non-pyrethroid insecticides placed on top of a bed net. It is a simple, cheap and easily implementable technology that can be added to existing LLINs, transforming them into combination insecticide products to control pyrethroid-resistant mosquitoes (resistance breaking) and slow resistance evolution (resistance management).

Prototype claims

i. The addition of a small insecticide-treated patch of netting (e.g. 30 x 80 cm) to the top of a bednet provides a high level of mosquito control;

ii. Use of insecticides other than pyrethroids on the patch will enable control of pyrethroid-resistant mosquitoes;

iii. The product will facilitate the development of effective insecticide resistance management strategies.

Mode of action of the prototype

The SmartPatch exploits natural mosquito behaviour to deliver a non-pyrethroid insecticide to the relatively restricted area at the top of a bednet above or over the torso area of the sleeping host, where mosquitoes focus their initial searching. A short time spent probing the piece of netting is sufficient for the mosquito to collect enough toxic material to kill itself.

Paradigm development stage for the prototype

Step 1 – early notification, awaiting completion of data acquisition to proceed to Step 2.

Summary of key studies supporting the claim

The investigators have provided entomological evidence and preliminary epidemiological evidence.

Entomology

i. Mosquitoes do land on top of the net just above the head and chest area.

ii. Bioassay results with susceptible *An. stephensi* exposed for 5 minutes on netting: knockdown with LLIN was (100%), bendiocarb (90%) and chlorfenapyr (0%); however, mortality after 24 hours was chlorfenapyr (100%); bendiocarb (80%) and LLIN (0%). Thus showing transient contact can cause high mortality with bendiocarb and chlorfenapyr.

iii. Semi-field cage studies showed that *An. stephensi* exposed to different patch sizes of LLIN (full and half) had 30% knockdown after 30 minutes of exposure.

iv. Mortality in *An. gambiae* was 20% after 2 hours, increasing to 50% for a larger patch after 6 hours and to 75% overnight (only the patch was treated, not the net).

v. Of the mosquitoes released in the big cage, 30% were attracted to the host when exposed for 1 hour (*An. stephensi*) while for *An. gambiae* it was 10–15%

vi. A field trial in the United Rebublic of Tanzania with *An. arabiensis* using a bendiocarb patch showed 62% reduction in capture overnight.

Epidemiology

A small experiment shows the number of mosquitoes that search for human bait within 1 hour.

Supporting documentation (summary)

Prototype dossier was reviewed including supporting information from entomological studies and preliminary epidemiological studies.

3.5 CONCLUSIONS AND RECOMMENDATIONS: SMARTPATCH

For paradigm

A VCAG sub-committee will be formed to prepare guidelines for defining data requirements for products to be used in areas with substantive pyrethroid resistance.

Resistance management is a process, not a product; therefore claims of resistance management will not be reviewed.

For prototype

This prototype product is in Step 1 (awaiting completion of data gathering to proceed to Step 2).

If the product is to be used in conjunction with an untreated net, it should be submitted to WHOPES for review as an insecticide-treated net (ITN). If it is to be applied in conjunction with an LLIN with a claim of benefit against resistant mosquito populations, it should be subject to the guidelines to be developed by the VCAG sub-committee

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Reference

In2Care BV. The 'SmartPatch'– a supplementary netting patch impregnated with non-pyrethroid insecticides and placed on top of a bed net to turn existing LLINs into combination, resistance breaking nets [Unpublished dossier report to the World Health Organization Vector Control Advisory Group (VCAG)]; 2013.

4. VECTOR TRAPS FOR DISEASE MANAGEMENT

4.1 PARADIGM

The paradigm is **vector traps** for disease management. These devices are designed to attract mosquitoes using appropriate lures in order to reduce vectorial capacity, resulting in decreased infection and disease in humans.

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 and is designing randomized controlled trials required for Step 3.

4.2 PROTOTYPE: ATTRACTIVE LETHAL OVITRAP (ALOT)

Description of the prototype

In this application, the ALOT protects humans against dengue vectors by attracting gravid females to a plastic trap using a combination of visual cues and a bacterial oviposition attractant/stimulant. Vectors that enter the trap come into contact with a netting material containing alpha-cypermethrin and are killed; any larvae from eggs laid in the trap are killed by the larvicide spinosad.

Prototype claims

i. ALOT protects humans from dengue vectors by targeting their egg-laying behaviour and reducing the average age of the vector population.
ii. The colour and size of the trap are visually attractive to mosquitoes.
iii. The trap reservoir contains water mixed with four species of naturally occurring bacteria that emit an odour attractive to egg-laying females.
iv. The reservoir contains a larvicide (spinosad) that kills larvae within the trap.
v. The trap is lined with a mesh fabric treated with a pyrethroid adulticide (alpha-cypermethrin, made from DuraNet LLIN) that kills adult mosquitoes on contact.

Mode of action of the prototype

The primary mode of action is based on the oviposition behaviour of gravid female *Ae. aegypti* who prefer to lay their eggs in dark containers. This behaviour is enhanced and focused in the trap by bacteria that produce chemical signals that are attractive to gravid females and may stimulate eggs to hatch, thereby avoiding dormant eggs remaining in the trap for long periods of time. The mosquito killing results from contact with the insecticide-treated netting material lining the trap; any larvae resulting from eggs laid by the females are killed by the larvicide.

The novel aspect to this trap is the identification of bacteria that produce chemical signals that are attractive to females laying their eggs. This reduces the possibility that females will lay eggs in other small containers and skip over the trap.

In areas where sufficient traps are maintained with active attractant, adulticide and larvicide, these devices could reduce the average age of the female mosquito population by targeting older gravid mosquitoes, thus depleting the local vector population of mosquitoes that are more likely to carry the dengue virus. The trap reduces vectorial capacity by reducing mosquito lifespan and human–vector contact.

The success of the trap depends on the abundance of other breeding sites in the area (i.e. competition between gravid females for oviposition sites), the attractiveness of the trap, the maintenance of its functionality, the effectiveness of the treated netting material to kill entering mosquitoes and the effectiveness of the larvicide in preventing any larvae from developing into adults.

Paradigm development stage for the prototype

Based on the supporting information provided, this prototype is in Step 2 (development of the proof of concept).

Summary of key studies supporting the claim

A field study of the ALOT was undertaken in Iquitos, Peru where there is endemic dengue transmission. Two adjacent neighborhood areas in Iquitos were selected with similar housing structure and historical levels of *Ae. aegypti* infestation and dengue transmission rates. Both areas were served by the same hospital catchment area. The control area was part of a previous entomological and febrile illness surveillance system. The primary epidemiological end-points of the survey were dengue seroincidence and clinical dengue infections. Secondary end-points included mosquito gravidity, sex ratio, house density and proportion of positive houses. Entomological outcomes were assessed through a pupal survey (inspection of households for water-holding containers) and collection of adult mosquitoes using a Prokopack aspirator.

Each day, up to 30 adult female mosquitoes were selected for parity dissections. A total of 6200 traps were placed in the ALOT area: 1417 in the core area and 4783 in the buffer zone. The number of traps per house ranged from 1 to 34, with an average of 3.1 in the core area and 3.2 in the buffer area. Trap coverage rates in the core and buffer areas were 88% (460 households) and 84.6% (1505 households), respectively, for an overall coverage rate in the ALOT area of 85.3%. In the post-intervention period, the researchers found no difference in the density of immature stages. Traps were installed during the low mosquito season, which was followed by an overall seasonal increase in mosquito density in both areas; but after the intervention, houses in the core treatment area had 43.6% fewer adult *Ae. aegypti* than those in the control area. There was no significant difference between adult numbers in the two areas before the intervention (p=0.2697). The odds of houses with *Ae. aegypti* were higher during the pre-phase (OR=1.32, 95% CI=1.12–1.54) and lower (OR=0.79 95% CI=0.73–0.87) post-intervention.

After 12 months there were 37 dengue cases in the control area compared with 10 in the ALOT area, corresponding to 0.97 and 0.26 cases per 100 person-years of follow up, respectively, and a protective efficacy of 74%.

Supporting documentation (summary)

Supporting documents include publications on the development of the attractant/stimulant, unpublished data and preliminary publication of the results of the field trial.

4.3 CONCLUSIONS AND RECOMMENDATIONS: ALOT

For paradigm

i. Impact on house occupant comfort and acceptability, theft/loss and or repurposing of traps should be assessed.
ii. Data demonstrating effect on key vectorial capacity parameters must be demonstrated.
iii. VCAG Step 3 requires randomized controlled field trials with epidemiological outcomes.
iv. Data on programmatic costs and cost-effectiveness of the prototype intervention are needed, including the frequency and method of retreating or maintaining the traps.
v. Delivery and feasibility of implementation should be evaluated and challenges identified (e.g. manufacturing, sustainability, supply chain, quality control).

For prototype

The improvement of traps with the addition of an attractant for ovipositing females is an innovation that may help these devices to find a role in dengue control. Recommendation of the intervention for programmatic implementation will require further proof of principle experiments including (but not necessarily limited to):

i. Data to support the claim that traps with attractants kill more mosquitoes in semi-field trials than traps without attractants.
ii. Trap durability in the field (effect of severe weather, animals), acceptability to the community (including frequent servicing of the trap by vector control authorities) and trap stability over time need to be demonstrated.
iii. Field assessments:

    a. Randomized control trial should include incidence of infections in humans, with appropriate comparison arm.
    b. Monitor entomological efficacy for consistency with Target Product Profile (which still needs to be developed).
    c. Assessment of potential for resistance (and cross-resistance) developing should be included in field trials.

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4.4 PROTOTYPE: IN2TRAP

Description of the prototype

The In2Trap product is an ovitrap-based, multi-impact dengue mosquito control device that can effectively lure, infect and contaminate gravid *Aedes* females and exert a lethal impact on the infected adults and their progeny (in the device and in surrounding breeding sites via autodissemination), as well as prevent dengue transmission via pre-lethal and virus-blocking impacts. The In2Trap device is a user-friendly, low-cost control tool against dengue mosquitoes that does not rely on electricity, CO2 or chemical insecticides.

Prototype claims

The device proposes a dengue vector control intervention with different attraction, contamination and mode of action mechanisms compared with existing lethal mosquito ovitraps. It is designed to attract gravid females of the typically container-breeding, skip-ovipositing *Ae. aegypti* mosquito species. The intervention is based on an attract-and-kill strategy using mosquito odour lures, a mixture of slow-killing, dengue transmission blocking bioactives (silica powder and *Beauveria bassiana*) as well as dissemination of the larvicide (pyriproxifen) by mosquitoes attracted to the trap. This device incorporates an electrostatic coating on the gauze used to present the active ingredients, which is the topic of a separate submission to the VCAG.

Mode of action of the prototype

The In2Trap device exerts a range of different impacts on the dengue vector, its progeny and dengue virus transmission:

1. Larvicidal: All larvae that emerge from eggs laid inside the In2Trap are killed by pyriproxyfen at the time the fourth-stage larva moults to become a pupa.
2. Virus-blocking: Fungal infection significantly reduces dengue virus replication inside the mosquito.
3. Larvicide spreading: Pyriproxyfen is actively disseminated to surrounding breeding sites by contaminated female dengue mosquitoes (which prefer to lay eggs in multiple sites) and subsequently kills both her own offspring and larvae already present.
4. Adulticidal: The adult female mosquito is killed by the fungus and silica within 10 days after being contaminated inside the trap.
5. Pre-lethal and transmission blocking: The fungus-infected adults show a reduced fecundity and blood-feeding propensity, which significantly reduces their vectorial capacity.

The attraction of gravid-ovipositing *Ae. aegypti* mosquitoes by itself does not constitute a new paradigm as attractive, lethal ovitraps have been described previously. However, the combination of attractive ovitrap with slow-acting, non-chemical adulticides (one of which alters virus replication dynamics) allowing dissemination by mosquitoes of a growth regulator meets the criteria for a new paradigm: 1. Characteristics sufficiently changed that

entomological effect alone is insufficient to imply epidemiological effect; 2. Validation will result in a new target product profile.

Paradigm development stage for the prototype

Based on the supporting information provided, this prototype is in early Step 2 (development of the proof of concept).

Summary of key studies supporting the claim

Laboratory studies suggest:

i. The device is attractive to ovipositing *Ae. aegypti* mosquitoes.
ii. Sufficient pyriproxifen is deposited in the device such that it is not a source of mosquitoes within a measured service period.
iii. Mosquitoes exposed to the treated gauze become contaminated with silica/fungus spores and pyriproxifen; pyriproxifen particles were observed on 50% of mosquitoes exposed to the trap.

Small-cage field tests indicate:

i. Increased rate of mortality in adult female mosquitoes exposed to the silica (75% mortality within 10 days compared with approximately 20% mortality in controls).
ii. Mosquitoes contaminated with pyriproxifen deposited sufficient material in nearby oviposition sites to reduce the percentage of larvae surviving to the adult stage (approximately 18% compared with 78% in containers not exposed to contaminated mosquitoes).

Supporting documentation (summary)

Study results are provided to:

i. Confirm the attractiveness of trap and lure compounds
ii. Demonstrate that mosquitoes entering the trap are contaminated with particles of the active compounds
iii. Demonstrate that the delayed kill active ingredients cause delayed mortality in contaminated adults
iv. Demonstrate that pyriproxifen is distributed to other, nearby oviposition sites
v. Demonstrate that a quick-kill active ingredient can be applied to the gauze, and effectively cause rapid death in exposed mosquitoes.

4.5 CONCLUSIONS AND RECOMMENDATIONS: IN2TRAP

For paradigm

i. Impact on house occupant comfort and acceptability, theft/loss and or repurposing of traps should be assessed.

ii. Data demonstrating the effect on key vectorial capacity parameters must be developed, to include demonstration of performance in representative field settings.

iii. VCAG Step 3 requires randomized controlled field trials with epidemiological outcomes.

iv. Data on programmatic costs and the cost-effectiveness of the prototype intervention are needed and should include the frequency and method of retreating or maintaining the traps.

v. Delivery and feasibility of implementation should be evaluated and challenges identified (e.g. manufacturing, sustainability, supply chain, quality control).

For prototype

i. Entomological efficacy requires further documentation, particularly to characterize the performance of the trap in large cage and open field studies, to characterize the adulticidal effects and to determine the number of devices required per unit area (and in different ecological settings).

ii. Characterize the pyriproxifen dissemination efficacy in large cage and open field experiments (proportion of containers contaminated in relation to distance form In2Trap).

iii. More information is required to characterize the effect of the fungal infection on vector competence. Can this truly be effective? Is it really needed? An effective virus replication inhibition must be demonstrated if to be included in Target Product Profile.

iv. Model the effect of delayed kill on dengue transmission dynamics to determine if the delayed kill/pyriproxifen dissemination is more effective than rapid kill. How many times can contaminated mosquitoes blood-feed before dying?

v. Reconcile that the entomological efficacy noted as acceptable in the Target Product Profile has not been achieved in small cage studies: If the device cannot meet specifications in a small cage, how will it perform in a more diverse field environment?

vi. Provide homeowner acceptance information.

vii. A WHOPES risk assessment will be required for the active ingredients and the yeast lure.

viii. The arget Product Profile contains inconsistencies that should be reconciled. Is this to be a community-based intervention or a commercial product available through pest control operators to the individual homeowner? This must be reconciled in order to permit studies of entomological efficacy and epidemiological effectiveness to be appropriately designed and interpreted.

ix. The dossier indicates that the device will perform best as a component of an integrated control effort, and may be most effective if other methods reduce the number of containers available to compete with the device. This should be quantified as part of the target Product Profile – i.e. what efforts must accompany use of this product, and what is the estimated number of other container sites with which the product can compete and be effective?

x. The proposed randomized control trials with dengue cases as an outcome are premature and should follow field trials to better evaluate entomological efficacy and effect on vectorial capacity parameters.

Reference

In2Care BV. An oviposition and contamination device for Dengue vectors based on a slow-kill adulticide and juvenile hormone analogue autodissemination mechanism. [Unpublished dossier report to the World Health Organization Vector Control Advisory Group (VCAG)]; 2013.

5. LETHAL HOUSE LURE

5.1 PARADIGM

The paradigm is the **lethal house lure**. It uses the occupants of a house to lure vectors to material treated with a bioagent that kills the vector, with an overall effect on vectorial capacity and reduced infection or disease in humans.

Status of evidence for the paradigm

The most advanced prototype in this paradigm awaiting evidence and completion of Step 2.

5.2 PROTOTYPE: EAVE TUBES AND BRICKS

Description of the prototype

A silicone coating binds a bioactive agent (e.g. an insecticide, biological agent (fungal spores), inert compound with insecticidal properties) to netting material affixed to tubes or "eave bricks" installed in the eaves of houses. The prototype requires house modifications to mosquito-proof the treated house. Odour plumes/carbon dioxide and other mosquito attractants emanating from the house occupants attract vectors to enter the tubes and bricks where they contact the bioactive agent, resulting in fast-killing of vectors.

Prototype claims

i. The silicone coating will bind bioactive agents.
ii. The binding force exerted by the coating on dry particles can be adjusted to retain particles on the coating yet enable sufficient transfer of the bioagent particles to an insect landing, resting, crawling or walking across the bioagent-treated coating.
iii. Exposure to the bioactive agents is enhanced since very short exposures to the bioactive agent are sufficient to be lethal.
iv. Occupants of houses provide the attractive stimulus to vectors, causing them to enter the tubes and bricks containing netting treated with the silicone coating to which bioactive agents are bound.

Mode of action of the prototype

The primary mode of action is based on the reported tendency of African anophelines to enter houses through the eaves, rather than through doors, windows or other openings. The eaves provide points for the introduction of interventions via "eave tubes" or "bricks" by providing an opening through which indoor air (laden with odour from occupants) reaches the outdoor environment and attracts anophelines (and other mosquito species).

The mode of action of killing depends on the characteristics of the bioactive agent deployed in the intervention. The unique attribute is the claim that the silicon-coated material universally binds a wide range of bioactive agents and the mode of action of attracting the vector to the bioactive agent (e.g. using odours from houses to attract vectors to the eaves where the bioactive agent is deployed in tubes.

The effectiveness of the intervention depends on: (i) the number of insects entering houses by routes other than eaves being low enough to pose little risk of infecting house occupants; (ii) significant house improvements being undertaken as a precondition to installing the eave tubes or bricks so that the latter are indeed the only means by which odourant attractants lure vectors to attempt to enter the house (i.e. it is assumed that the eaves have already been closed); and (iii) the tubes or bricks being installed to improve ventilation/air flow without allowing access to insects.

Paradigm development stage for the prototype

Based on the supporting information provided, this prototype is at the beginning stages of Step 2 (development of proof of concept).

Summary of key studies supporting the claim

The investigators have demonstrated

i. Preliminary data on air-flow and temperature in houses with eave tubes and bricks.
ii. Screenhouse studies showing reductions in mosquitoes recaptured of 52% (bendiocarb impregnated netting), 58% (LLIN material, Permanet 2) and 67% (bendiocarb, 1% active ingredient, in powder formulation on electrostatic coating).
iii. Laboratory bioassays demonstrating 100% kill 24 hours after exposure for both deltamethrin and bendiocarb treated netting following 3 months of eave-tube use in the field.

Safety information

Bendiocarb and pyrethroids that are approved for public health applications were used in the prototype dossier submitted for evaluation. However, the claim that any bioagent could be deployed would require risk assessment if other active or novel bioagents are used. It is not clear if the formulations of the insecticides in this dossier are approved for public health applications.

Supporting documentation (summary)

i. Mathematical modelling of the intervention
ii. Laboratory studies
iii. Three semi-field studies conducted at the Ifakara Health Institute (United Republic of Tanzania) using bendiocarb and deltamethrin
iv. Eave tubes installed in village houses to measure impacts on air-flow and duration of killing effect

5.3 CONCLUSIONS AND RECOMMENDATIONS: EAVE TUBES AND BRICKS

For paradigm

i. Data on house entry by different vectors are needed together with data on suitable house construction in different geographical areas (to estimate where the intervention will be effective). Coverage of the paradigm should not be restricted to a section of the community with better houses.
ii. Programmatic costs and cost-effectiveness estimates should include house

modification and frequency and method of re-treating or maintaining the paradigm.

iii. Impacts of the paradigm on community and individual house protection should be evaluated.

iv. Impact on house occupant comfort and acceptability needs to be assessed.

v. The evaluation should compare house improvement using the paradigm with house improvement alone.

vi. Step 3 requires a community-randomized trial with epidemiological outcomes.

vii. Paradigm delivery and feasibility of implementation during experimental phase need to be documented.

viii. Field studies in areas with insecticide resistance are required to validate the target product profile claim that the paradigm is a resistance-breaking intervention.

ix. Evaluation of the compatibility of this paradigm with recommended interventions for the diseases and vectors targeted by the paradigm needs to be undertaken.

For prototype

Use of eave tubes/bricks is a prototype for a new paradigm intervention that shows potential. However, development is at an early stage, and clarifications on effectiveness, implementation strategies, costs and impacts on vectors and malaria transmission from field studies are needed.

Recommendation of the intervention for programmatic implementation will require further proof-of-principle experiments. The product developers should review the paradigm recommendations and ensure that all recommendations are addressed. In addition, VCAG requests that subsequent submissions address the following specific concerns:

i. Data to support claims of the ability to bind and release proposed bioactive agents must be provided.

ii. Duration of effectiveness experiments under field conditions should be continued and expanded, including the impacts not only of wind but also of humidity/rain on both killing and durability. Assessment of potential damage by rodents should be included.

iii. Strategies for recharging the silicon coating need to be provided. What compounds can be recharged by the householder and what bioagents will need to be managed by a vertical programme?

iv. Field assessment

   a. Impact on temperature and air-flow inside houses with eave bricks should be continued and final data provided to support the claim of increased comfort and user acceptability in houses with eave tubes/bricks.

   b. Randomized control trial plans are required (cluster or household randomization to measure community and individual household protection): incidence or prevalence of infections in humans from trials with appropriate comparison arm, i.e. occupants of houses of similar construction, but without eave tubes and bricks, are needed. It cannot be overemphasized that failure to undertake a randomized control trial with a control arm consisting of houses with eaves

blocked (e.g. identical construction as the houses with the eave bricks will confuse the interpretation of the results and diminish the value of the experiment as any impact will be a combination of the impact of house improvements and the eave bricks).

Uncertainty in the interpretation of field trial results will jeopardize, if not exclude, any recommendation by VCAG due to confusion regarding the paradigm being tested (e.g. house improvements or house improvements with eave bricks and tubes). Alternatively, a three-armed study comparing (i) eave bricks and tubes with house improvements to (ii) house improvements alone to (iii) unimproved houses without eave bricks/tubes would allow both the paradigm of house improvements and the paradigm of eave bricks/tubes to be evaluated. LLINs should be provided and equivalent in all study arms.

c. Assessment of the potential for resistance management or effectiveness in areas with resistant vectors will need to include field trial evaluation in areas where the vectors exhibit insecticide resistance.
d. Entomological assessment of vector density and survivorship/age structure on a variety of vector species as well as their tendency to enter houses though eaves may vary and should be determined as part of the process to determine the probable areas where this intervention should be recommended.
e. Outcomes should include the impact on epidemiological end-points, such as the incidence of malaria.
f. Compliance/acceptability should include determining the acceptability of house modifications and the willingness of occupants to maintain a mosquito-proof environment, including closing doors and windows.

References

In2Care BV. A coating for delivery of powder formulations of insecticidal agents to disease vectors. [Unpublished dossier report to the World Health Organization Vector Control Advisory Group (VCAG)]; 2013.

OPEN MEETING WITH INNOVATORS

An open session of the second VCAG meeting was convened in Salle B of WHO headquarters at 09:30 on 13 February 2014. The meeting was attended by the innovators, the Innovative Vector Control Consortium (IVCC), industry partners (including CropLife and AgroCare), the VCAG members and the WHO secretariat (see List of participants in *Annex 1*).

The session began with opening remarks by Dr Marc Coosemans (chair), who welcomed participants and set the administrative agenda for the meeting. Dr Raman Velayudhan noted that this meeting constituted the first VCAG review of novel vector control products and that the open session aimed to create a forum for innovators to share information, exchange views and receive input from stakeholders.

Presentation by innovators:

- *Wolbachia* (Dr Peter Ryan). After explaining the concept of *Wolbachia* for vector-borne disease control and the biological basis of the paradigm (cytoplasmic incompatibility driving bacterial spread across populations and the development of stably infected *Aedes aegypti* that resist dengue virus infection), Dr Ryan emphasized the concept of a "natural" infection of mosquitoes. He described preliminary field releases of *Wolbachia*-infected *Ae. aegypti* in Australia and Viet Nam, characterizations of novel *Wolbachia* strains and activities to develop the release technology for use in dengue-endemic regions. Discussion points included the costs of deployment, assessment measures for the rate of spread and possibilities for the coevolution of the mosquito, bacteria and virus towards increased pathogen transmission or virulence.
- *Permanet® 3.0* (Dr Helen Pates Jamet). In areas with metabolically-based insecticide resistance, LLINs no longer meet defining performance criteria and thus nets with increased efficacy should be introduced. Permanet® 3.0 is an insecticide synergist combination net that does not comply with the LLIN TPP, and detailed field study data and resistance analysis show increased efficacy of Permanet® 3.0 over other nets. Dr Pates Jamet highlighted the difficulties in characterizing resistance, the burden of evidence needed for characterization and the challenge of interpreting net field efficacy levels without a clear comprehensive understanding of the resistance profile of an area. Policy concerns discussed included the impact of insecticide resistance on vector control interventions, the need for vector control options in situations where pyrethroid-only LLINs stop working, and WHO guidance in these areas to facilitate funding and implementation efforts.
- *Smartpatch* (In2Care). The Smartpatch concept entails a supplementary netting patch impregnated with insecticides that can potentially turn an existing net into a combination LLIN. Data on net patch size, colour and architecture were presented, showing that small net patches can significantly knock down host-seeking mosquitoes. The group discussed the potential to reduce overall net costs, to vary active ingredients used for vector control and the possibility of rotating net patches in resistance management programmes. Additional discussion points included physical parameters of the net (attachment points, washability, safe handling), user behaviour and risk assessment development.

- *Spatial repellents* (Dr Nicole Achee). Spatial repellents can be used to reduce pathogen transmission by interrupting human–vector contact. The concept may be particularly useful in situations with limited vector control options (difficult-to-treat vectors or geographical regions). The prototype is a passive emanator with a planned use of 14 days minimum that releases active ingredients into the airspace and elicits a range of behaviours at concentrations below toxic levels. Dr Achee presented entomological and epidemiological evidence supporting the paradigm and described parameters proposed for large-scale epidemiological trials. Discussion included clarification of the definition of repellency, trial management and end-point indices for monitoring, safety considerations with the accumulation of active ingredients in the environment over time and the potential for development of resistance.
- *Non-chemical insecticidal fabrics* (Dr Aureliano Salatino). The presentation detailed the company's background, production facilities, current project portfolio and business interests. The insecticidal dust application developed by the company was a safe, non-toxic alternative to traditional insecticide-treated fabrics. Discussion points included considerations of resistance development and human safety from dust exposure.
- *Eaves-based delivery system* (In2Care). Dr Bart Knolls presented an overview of the electrostatic coating of netting and the concept of coated eave tubes and bricks. He detailed entomological data supporting the paradigm claim and studies in progress. Discussion points included cost calculations and the programmatic costs for home improvement and maintenance, the economic scope of the intervention, ideas for a sustainable business model, and position as a component of integrative programme.
- *ALOT* (Dr Dawn Wesson). An overview of the ALOT trap was given, including the presentation of data from recent studies, the development of trap parameters (placement, density, physical form, chemical inclusions), results from preliminary field trials and plans for further studies. Discussion points included the trap impact on population age structure, flexibility to deal with resistant populations and placement within other vector control interventions.
- *In2Trap* (In2Care). The trap presented targets gravid *Ae. aegypti* mosquitoes with the aim of interrupting dengue virus transmission. A key concept in the development of this trap was that of PPF auto-dissemination; both late-killing and fast-killing adulticides were considered in prototype development. Trap architecture development and results from entomological monitoring studies were described. Additionally, the possibility of cross-resistance developing in populations of pyrethroid-resistant mosquitoes exposed to PPF was discussed.

Closing remarks were made by the Chair and Dr Velayudhan, who reiterated the functions of and challenges before the VCAG, and thanked the participants for their open dialogue on development of novel paradigms for public health vector control. The afternoon meeting was restricted to members of VCAG and the WHO secretariat.

ANNEXES

4.1 LIST OF PARTICIPANTS

Members of the Expert Advisory Group

Professor Thomas R. Burkot, School of Public Health, Tropical Medicine and Rehabilitation Sciences, Cairns, Australia

Professor Marc Coosemans, Unit of Medical Entomology, Institute of Tropical Medicine, Antwerp, Belgium

Dr John I. Githure, Adviser, Integrated Vector Management, Ministry of Health, Rwanda

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

Dr Immo Kleinschmidt, Department of Infectious Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom

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

Dr Kim A. Lindblade, Malaria Branch, Division of Parasitic Diseases and Malaria, United States Centers for Disease Control and Prevention, Atlanta, GA, United States of America

Professor Steven Lindsay, School of Biological & Biomedical Sciences, Durham University, Durham, United Kingdom

Dr Roger Nasci, Division of Vector-Borne Diseases, Centers for Disease Control and Prevention, Fort Collins, CO, United States of America

Professor Hassan Vatandoost, Department of Entomology and Vector Control, Teheran University of Medical Sciences, Teheran, Islamic Republic of Iran.

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

Participants

Dr Nicole L. Achee, University of Notre Dame, Notre Dame, IN, United States of America

Ms Simona Angelino, Marchi and Fildi Spa, Biella, Italy

Dr Kate Aultman, Policy Consultant (SR and ALOT)

Mr Luca Cinguino, Marchi and Fildi Spa, Biella, Italy

Dr Marit Farenhorst, In2Care BV, Wageningen, Netherlands

Dr John Grieco, Consultant, Spatial Repellents

Dr Bart Knols, In2Care BV, Wageningen, Netherlands

Dr Helen Pates Jamet, Vestergaard Frandsen S.A., Lausanne, Switzerland

Dr Peter Ryan, Eliminate Dengue Programme, Monash University, Clayton, Australia

Dr Aureliano Salatino, Marchi and Fildi Spa, Biella, Italy

Mr Mikkel Vestergaard, Vestergaard Frandsen S.A., Lausanne, Switzerland

Dr Dawn M. Wesson, Tulane University, New Orleans, LA, United States of America

WHO Secretariat

Dr Anna Drexler, Vector Ecology and Management, Department of Control of Neglected Tropical Diseases

Dr Tessa Knox, Vector Control Unit, Global Malaria Programme

Dr Abraham Mnzava, Coordinator, Vector Control Unit, Global Malaria Programme

Dr John Reeder, Director, TDR and presently Acting Director for Global Malaria Programme

Dr Lorenzo Savioli, Director, Department of Control of Neglected Tropical Diseases

Dr Emmanuel Temu, Vector Control Unit, Global Malaria Programme

Dr Yeya Timoko Toure, Special Programme for Research and Training in Tropical Diseases

Dr Raman Velayudhan, Coordinator, Vector Ecology and Management, Department of Control of Neglected Tropical Diseases

Dr Rajpal Yadav, Vector Ecology and Management, Department of Control of Neglected Tropical Diseases

Observers

The Boston Consulting Group: Mr Eric Rimmke, San Francisco, CA, United States of America

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

Innovative Vector Control Consortium (IVCC): Dr Tom McLean, Liverpool School of Tropical Medicine, Liverpool, United Kingdom

Rotam CropSciences (*representing AgroCare*): Mr Garth Drury, Lyon, France and Mr Thierry Trupin, Lyon, France

Sumitomo Chemical UK PLC: Dr John Lucas, London, United Kingdom

4.2 AGENDA

10–11 February 2014 (09:00–17:30)

Closed session for VCAG members and secretariat only

1. Opening
    - Welcome remarks – Chair
    - Administrative arrangements and introduction

2. Presentations and discussions
    - Item 1 – *Wolbachia*
    - Item 2 – PermaNet® 3.0
    - Item 3 – Spatial Repellents
    - Item 4 – ALOT
    - Item 5 – Novel fabric treatments
    - Item 6 – Vector trap
    - Item 7 – Eave tubes and bricks
    - Item 8 – Smartpatch
    - Item 9 – In2Trap

12 February 2014 (08:30–18:00)

Restricted session limited to VCAG members, Secretariat and innovators (each innovator has a time slot of 1 hour)

1. Individual product discussion and Q&A with the innovator

13 February 2014 (09:30–17:00)

1. Open session

2. Industry partners are expected to join the presentation by innovators

14 February 2014 (09:00–15:00)

Closed session for VCAG members and Secretariat only

1. Conclusions and report preparation

2. Closing

Paradigm	Description of the paradigm	No. of prototypes reviewed	Status of Prototype
Microbial control of human pathogens in adult vectors	The introduction of micro-organisms into vectors to reduce or prevent biological transmission of the pathogen to humans. Prototype: *Wolbachia*	1	Step 2*
Vector control products for pyrethroid resistant areas	The paradigm could be a novel intervention or an adaptation of an existing paradigm. It has an overall effect on vectorial capacity and reduces infection and disease in humans in areas where the local vectors have substantive pyrethroid resistance. Prototypes: Permanet® 3.0 and SmartPatch	2	Permanet® 3.0: Step 3 SmartPatch: Step 1
Spatial repellents	Spatial repellents interrupt human–vector contact through vector behaviour modification induced by airborne chemicals, offering protection (personal and community) from medically important vectors and nuisance pests. Prototype: To be determined	1	Step 2*
Vector traps for disease management	Devices designed to attract mosquitoes using appropriate lures in order to reduce vectorial capacity, resulting in decreased infection and disease in humans. Prototypes: A LOT and In2Trap	2	ALOT: Step 2* In2Trap: Step 2
Lethal house lure	The paradigm uses the occupants of a house to lure vectors to material treated with a bioagent that kills the vector. It has an overall effect on the vectorial capacity and reduces infection and disease in humans. Prototype: Eave tubes and bricks	1	Step 2

* Prototypes are completing data gathering to attain Step 2 and designing randomized controlled trials required for Step 3.

Full details on the paradigms reviewed above can be found in the Report on the Second Meeting of the WHO Vector Control Advisory Group: *http://apps.who.int/iris/bitstream/10665/137318/1/9789241508025_eng.pdf*

The newly established 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 second meeting, held in February 2014, where VCAG evaluated seven submissions at various stages of development.

Vector Control Advisory Group (VCAG)
Vector Ecology and Management (VEM)
Department of Control of Neglected Tropical Diseases (NTD)
and
Vector Control Unit (VCU)
Global Malaria Programme (GMP)
World Health Organization
Avenue Appia 20
1211 Geneva 27
Switzerland

9 789241 507455