DESIGN
OF EPIDEMIOLOGICAL TRIALS FOR VECTOR CONTROL PRODUCTS

REPORT OF A WHO EXPERT ADVISORY GROUP

CHÂTEAU DE PENTHES, GENEVA,
24–25 APRIL 2017

World Health Organization

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GLOSSARY

Public health value: A product has public health value if it has proven protective efficacy to reduce or prevent infection and/or disease in humans.

Efficacy: An intervention measured when it is implemented under ideal, highly controlled circumstances; efficacy is typically measured in phase III studies.

Effectiveness: The degree of benefit of an intervention measured when it is delivered and used operationally under routine, "real-world" conditions; effectiveness is typically measured in phase IV studies.

1. EXECUTIVE SUMMARY

The World Health Organization (WHO) is mandated to provide guidance to Member States on matters of public health policy, including evidence-based policy recommendations for new vector control interventions. To that end, the Vector Control Advisory Group (VCAG) advises WHO on the value to public health of new vector control tools, including new products, technologies and approaches, intended to protect humans against pathogens transmitted by vectors. WHO recommends products for use in public health based on demonstrated evidence of their impact on diseases as well as safety and quality, but must reconcile the requirements for robust data to assess public health value with the urgent need for new tools to address critical threats (e.g. insecticide resistance and spread of Aedes-transmitted viruses). In response, WHO has called for an Expert Advisory Group (EAG) to review trial methodologies for evaluating data on the impact of new tools to prevent and control vector-borne diseases.

The recommendations developed by consensus of the Group emphasized the importance of randomized trials with robust study designs. Specific recommendations are provided on end-points, design considerations, and generation of evidence on the efficacy of long-lasting insecticidal nets (LLINs) that incorporate a non-pyrethroid class of insecticide (either alone or in combination with a pyrethroid insecticide) and on products that use indoor residual spraying (IRS) of insecticides with a novel entomological mode of action (e.g. slow-acting insecticides or insect growth regulators), which differ from the insecticides currently used for public health. The outcomes of this meeting will be used to inform the development of a WHO manual on trial designs for evaluating new vector control tools that are currently not covered by a WHO policy recommendation, for publication in 2017.

2. BACKGROUND

In accordance with WHO's mandate to provide guidance to Member States on matters of public health policy, the Organization develops evidence-based policy recommendations for new vector control tools, technologies and approaches. In 2012, an independent advisory body – the WHO Vector Control Advisory Group (VCAG) – was established to advise the Organization on the evaluation and validation of the public health value of new vector control tools, including new products, technologies and approaches, used to protect humans against pathogens transmitted by vectors.[1] VCAG reviews the potential of all new tools that target transmission of vectors-borne pathogens, such as those that transmit malaria and many neglected tropical diseases. The Group is jointly managed by the WHO's Global Malaria Programme and the Department of Control of Neglected Tropical Diseases.

Because WHO recommendations for new tools can have far reaching effects on disease control and prevention, these must be based on clear demonstration of protective efficacy through epidemiological outcomes. For example, WHO policy recommendations for malaria vector control[2] are based on robust evidence demonstrating that use of interventions such as LLINs[3] and IRS[4] reduces disease burden (morbidity and mortality). Consequently, countries have adopted these recommended interventions as part of their malaria control strategies, and this has contributed to massive declines in malaria incidence and mortality.[5]

For any new vector control tools in new product classes, WHO requires evidence from at least two well conducted, randomized controlled trials with epidemiological outcomes and follow up over at least two transmission seasons.[6] With limited funds available for disease control, Member States are required to implement the most effective interventions for their local context. Epidemiological trials should therefore be conducted in different entomological and epidemiological settings[7] in order to verify the public health value of the new product class or product variation. Two trials is the minimum number needed to assess generalizability.

Robust data are essential to assess the public health value of new product classes and to provide operational guidance. The type and extent of these data must be carefully balanced with the urgent need to make products available expeditiously to address threats

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

[2] Malaria vector control policy recommendations and their applicability to product evaluation [Information note dated May 2017]. Geneva: World Health Organization; 2017 (WHO/HTM/GMP/2017.12; http://apps.who.int/iris/bitstream/10665/255337/1/WHO-HTM-GMP-2017.12-eng.pdf).

[3] Lengeler C. Insecticide-treated bed nets and curtains for preventing malaria. Cochrane Database Syst Rev. 2004;2. CD000363; Gamble CL, Ekwaru JP, ter Kuile FO. Insecticide-treated nets for preventing malaria in pregnancy. Cochrane Database Syst Rev. 2006;2.

[4] Pluess B, Tanser FC, Lengeler C, Sharp BL. Indoor residual spraying for preventing malaria. Cochrane Database Syst Rev. 2010;4.

[5] Bhatt S, Weiss DJ, Cameron E, Bisanzio D, Mappin B, Dalrymple U et al. The effect of malaria control on *Plasmodium falciparum* in Africa between 2000 and 2015. Nature. 2015;526:207–11. doi:10.1038/nature15535.

[6] Fifth meeting of the Vector Control Advisory Group. Geneva: World Health Organization; 2017 (WHO/HTM/NTD/VEM/2017.02).

[7] Applicants are encouraged to interact with VCAG in developing trial designs for specific products.

such as insecticide resistance, outdoor transmission of malaria and rapid spread of Aedes-transmitted viruses. In response, WHO's Global Malaria Programme and the Department of Control of Neglected Tropical Diseases convened an informal Expert Advisory Group (EAG) to consider trial designs that can be used to measure the epidemiological impact of new vector control tools, and to provide timely advice to WHO on their relative value and appropriate use for policy-making. Members of the Group are international experts in epidemiology and trial design from a range of global health fields including malaria vector control, vaccines and prophylaxis, HIV, neglected tropical diseases, and epidemiology and control of Aedes-transmitted viruses.

Two background documents were provided in advance of the meeting as working material for discussion: (i) a draft manual on epidemiological trial design under development by VCAG; and (ii) a framework to evaluate second-generation LLINs prepared by the United States Centers for Disease Control and Prevention. The EAG reviewed each of these documents and concluded by consensus the relative value of different types of trial design and other considerations necessary to demonstrate public health value. Specific categories of products under evaluation by WHO were discussed including non-pyrethroid LLINs (slow acting active ingredients incorporated into LLINs) or IRS with new classes of insecticides. The consensus recommendations formulated by the Group are intended to optimize pathways for generating public health data on new vector control products.

3. MEETING OBJECTIVES

The objectives of the meeting were:

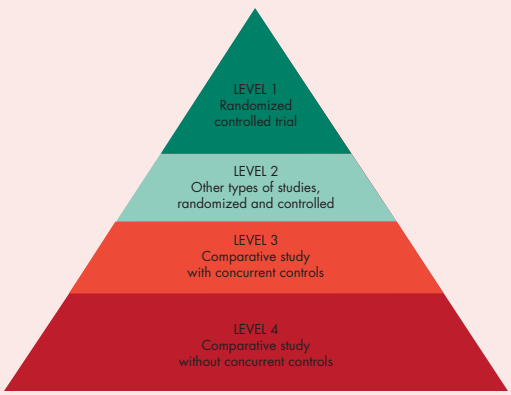
- To review the definition of "public health value" in the context of new vector control tools, technologies and approaches;
- To assess the design of epidemiological trials and substantiate their public health value, including:
  - cluster randomized trials, interrupted time series, stepped-wedge, case–control and plausibility designs
- To consider the relevance of data on the economic feasibility of new products;
- To discuss and recommend options for study designs for new vector control tools under WHO evaluation;
- To generate evidence that can be used to inform policy recommendations on the public health efficacy and operational use of new tools, including:
  - non-pyrethroid LLINs currently under evaluation
  - tools requiring different test approaches or methods (e.g. slow-acting insecticides)
  - new product classes in the VCAG pipeline
- To formulate recommendations on trial designs for which evidence-based policy decisions on vector control tools can be made. The outcome of the EAG shall be reviewed by VCAG and its recommendations contribute to the WHO manual for evaluating the public health value of new tools for vector control currently not covered by WHO policy recommendations.

4. REVIEW OF EPIDEMIOLOGICAL TRIAL DESIGNS TO SUBSTANTIATE THEIR PUBLIC HEALTH VALUE

4.1 HIERARCHY OF WHO-RECOMMENDED TRIAL DESIGNS

Box 1 summarizes the hierarchy of trial designs recommended by WHO and which type of design the Organization considers sufficiently robust to generate evidence on the efficacy and public health value of vector control products.

Box 1. Hierarchy of study designs used to evaluate the public health value of new vector control tools



Study designs recommended by WHO to assess the public health value of a new intervention or product	
Level 1. Randomized controlled trial: individual or cluster randomized	Recommended
Level 2. Randomized controlled trial: step-wedge, cross-over, factorial design	Recommended
Level 3. Non-randomized trial with control: before-and-after studies, cohort study, case–control study, cross-sectional study, time-series or interrupted time-series	Recommended on a case-by-case basis
Level 4. Trials without a control or using a historical control group: such as time series or interrupted time series without control group	Not recommended

Consensus recommendations on the hierarchy of trial designs

- Level 1 and level 2 study designs are the only designs that WHO considers acceptable to substantiate the public health value of new tools that do not fall within an already existing class and hence are not covered by a policy recommendation.

- In exceptional situations where there is no possibility of randomization, WHO will accept data generated from a trial with a "level 3" study design. Justification for this type of trial will be required and should be endorsed by VCAG before the trial is initiated.
  - The EAG noted that a full policy recommendation may not be possible in cases where a level 3 study design has been used to generate evidence. Depending on the study outcomes, additional level 1 or level 2 epidemiological studies may be needed to assess the public health value of the new vector control tool.
  - Exceptional situations where a level 3 type of study design are warranted include emergency situations such as a declared public health emergency of international concern or a humanitarian emergency, interventions against very rare disease, or clear demonstration of unusually large entomological effects ("super-interventions").

4.2 END-POINTS FOR STUDIES TO DEMONSTRATE THE PUBLIC HEALTH VALUE OF NEW TOOLS, STRATEGIES AND APPROACHES FOR VECTOR CONTROL

A clinical trial will usually specify a primary end-point as the most important outcome measure for assessing the efficacy of the intervention being evaluated. A trial might also define one or more secondary end-points that will be measured and used to confirm any conclusion that is based on the primary outcome and to help interpret the findings provided by the primary outcome. A primary end-point in a clinical trial is that for which subjects are randomized and for which the trial is powered. Secondary end-points are those that are analysed afterwards and for which the trial may not necessarily be powered or randomized.

Consensus recommendations on the hierarchy of trial designs

- Primary end-points are (in order of priority): (i) incidence of disease or infection (e.g. detection of new infections); (ii) prevalence of infection; and (iii) validated proxies of infection (e.g. sero-conversion for viral infections).
- The source of data for primary end-points can be: (i) prospective, active case detection (e.g. active follow-up of cohorts), (ii) passive reporting or case detection where robust quality-assured data are provided by the routine reporting system; and (iii) cross-sectional prevalence surveys.
- In addition to primary epidemiological data, trials must also generate robust representative entomological data to evaluate the claimed entomological effect and to finalize the target product profile for the new product class.

4.3 IMPORTANT CONSIDERATIONS FOR TRIAL DESIGN

(a) Study questions should be formulated to include a clear statement about study population.

(b) Randomization, control and intervention should be randomly allocated to individuals or clusters.

(c) Sample size should be based on powered calculations with clearly stated assumptions for both epidemiological and entomological outcomes.

(d) Studies should be blinded where possible. Where blinding of participants is not possible, outcome assessors and those conducting analysis can and should be blinded.

(e) Comprehensive baseline information should be collected on transmission and disease setting.

(f) Follow-up should occur over at least two transmission seasons.

(g) Data on entomological end-points should be collected in randomly sampled locations.

4.4 CONSENSUS STATEMENT ON MEASUREMENT OF COST EFFECTIVENESS

Collection of data on costs is encouraged during the evaluation of new vector control products, particularly during phase IV studies. While VCAG will not draw on these data to assess the public health value of a product, costing data will be useful to inform the formulation of policy recommendations and programmatic guidance. It was noted that initially costly new interventions may later benefit from economies of scale, thereby becoming considerably more affordable once they are deployed.

5. DESIGN OPTIONS FOR NEW VECTOR CONTROL PRODUCTS UNDER WHO EVALUATION

The EAG discussed trial design options to demonstrate the public health value of new vector control tools currently under WHO evaluation, particularly study design considerations for non-pyrethroid LLINs and IRS formulations with slow-acting insecticides, with reference to specific products currently under WHO evaluation.

5.1 CONSENSUS RECOMMENDATIONS ON EFFICACY TRIALS FOR NON-PYRETHROID LONG-LASTING INSECTICIDAL NETS

After review of the current status of LLINs containing a non-pyrethroid active ingredient, the EAG was of the opinion that:

- For LLINs containing a non-pyrethroid active ingredient either alone or in combination with a pyrethroid, entomological data are not considered reliable predictors of epidemiological impact. Therefore, until a policy recommendation is made that covers these new types of products, epidemiological data must be generated for the "first in class" product for all new non-pyrethroid LLINs.[1] The potential use of entomological surrogates to evaluate LLINs will benefit from further investigation to establish whether reliable correlations between entomological and epidemiological outcomes can be established. If so, WHO will consider these findings for updating product evaluation procedures for LLINs.
- Claims of public health value against insecticide-resistant vectors should be evaluated through the VCAG review process because such claims are not covered by existing WHO policy recommendation for LLINs. The following trials will be required:
    i. Laboratory and small-scale field trials to test claims of insecticide resistance according to the WHO 2017 guidelines for efficacy testing of LLINs.[2]
    ii. At least two randomized epidemiological trials conducted in different settings and ideally covering two transmission seasons. Studies should be performed in settings of high to medium insecticide resistance. The comparator should be the standard best practice used for vector control in the study area. The two studies should be conducted concurrently to minimize delays in generating evidence to assess their public health value; if the outcome is unclear or contradictory, further investigations may be required.
    iii. Requirements to collect data on attrition, fabric integrity and assessment of insecticide residual activity, as previously stipulated by the WHO Pesticide Evaluation Scheme, remain valid and should be met concurrently with phase III epidemiological studies.

[1] Malaria vector control policy recommendations and their applicability to product evaluation [Information note dated May 2017]. Geneva: World Health Organization; 2017 (WHO/HTM/GMP/2017.12, http://apps.who.int/iris/bitstream/10665/255337/1/WHO-HTM-GMP-2017.12-eng.pdf).

[2] Guidelines for laboratory and field testing of long-lasting insecticidal nets. Geneva: World Health Organization; 2017 (http://apps.who.int/iris/bitstream/10665/80270/1/9789241505277_eng.pdf).

5.2 CONSENSUS RECOMMENDATIONS ON INDOOR RESIDUAL SPRAYING FORMULATIONS WITH SLOW-ACTING INSECTICIDES AND OTHER TOOLS THAT MAY REQUIRE ALTERED OR NEW TEST APPROACHES

- Unlike LLINs, for which specifications to date are based on a single class of active ingredient (pyrethroid) and covered by current WHO policy, several active ingredients of different classes have been shown to be effective for use in IRS. WHO policy recommendations can therefore be expanded to cover a new IRS product for which entomological data are available to indicate an entomological effect that complies with the current WHO policy recommendation for IRS products. The relevant data will be generated from proof of concept in the laboratory, experimental hut studies and large-scale field trials.[1]
- IRS products for which epidemiological trials are not required before assessment by the vector control group of the WHO Prequalification Team should undergo effectiveness trials (phase IV) to verify that entomological effectiveness translates into epidemiological impact and to generate cost–effectiveness data. Effectiveness trials can be conducted during operational roll-out.
- A new IRS product for which data do not indicate a similar entomological effect to IRS products currently covered by a WHO policy recommendation will be considered a new product class. In this case, guidance on acceptable epidemiological study designs should be followed (Box 1). Close interaction with VCAG is recommended during the development of the study protocol.

5.3 CONSENSUS RECOMMENDATIONS ON ALL OTHER PRODUCTS IN NEW PRODUCT CLASSES WITHIN THE VECTOR CONTROL ADVISORY GROUP PORTFOLIO

- For any new product that does not fall into a class covered by an existing WHO policy recommendation, VCAG will assess and recommend the hierarchy of trial designs that should be applied to demonstrate the public health value of the first in class product (**Annex 1**).

[1] Methods to establish the degree of confidence in comparative effectiveness are under development by WHO.

6. CONCLUSIONS AND FUTURE ACTIONS

The consensus recommendations of the EAG were presented to the sixth VCAG meeting (Geneva, 26–28 April 2017). The outcome of its discussions will inform a WHO manual on trial design that is under development by VCAG and due for publication in 2017. This manual will provide detailed guidance to innovators on the design of phase III efficacy trials for vector control. The recommendations contained in these documents are intended to facilitate generation of the best evidence base and assessment of the most expeditious public health value for new vector control tools.

ANNEXES

ANNEX 1. NEW VECTOR CONTROL TOOLS UNDER EVALUATION BY THE VECTOR CONTROL ADVISORY GROUP

Step 3 approved / Step 3 underway

New Product - Variation	Generic Exemplar	Prototype product
ITN against IR Vector (extend ITN)	Pyr + mix/comb LLN	PermaNet 3
		Interceptor G2
Treated walls against IR Vector (extend IRS)	IRS/wall linings for IRS pop	No claim reviewed
Peri-focal residual spraying (extend IRS)	Outdoor RS	PFS formulation, Bayer
New Product Class - Chemical	**Generic Exemplar**	**Prototype product**
Attract and kill baits	Attractive Toxic Sugar Bait	Bait Station
Spatial repellents	Passive emanator	Metofluthrin or Transfluthrin
ITM for specific risk groups	ITM	Blanket, Clothes
Vector traps	Adulticidal oviposition traps	ALOT, IN2TRAP, AGO, TNK
Lethal house lures	Eave tubes	Eave tubes
Systemic insecticide	Rodent baits	Imidicloprid based bait
New Product Class - Biological	**Generic Exemplar**	**Prototype product**
Microbial control in adult vectors	Bavterial infection	wMel Wolbachia in *Ae. aegypti*
Population reduction through genetic manipulation	GMM, self limiting	OX513A *Ae aegypti* (RIDL)
	GMM, gene-drive	CRISP/Cas9 in *An. gambiae*
Population alteration of malaria vector mosquitoes	GMM, gene-drive	CRISP/Cas9 anti-parasite
SIT & incompatible insect technique (IIT)	Radiation + bacterial infection	Sterilized *Aedes* spp. + Wolbachia

ANNEX 2. AGENDA

Monday 24 April 2017	
Open Session: Full day	
09:00–09;15	Opening remarks and welcome (Dirk Engels/Pedro Alonso)
09:15–09:45	Overview of topics and objectives, framing the discussion and outputs (Raman Velayudhan/Jan Kolaczinski) Discussion
09:45–10:30	WHO pathways for policy development (information) (Raman Velayudhan) Discussion
09:45–10:30	Coffee break
11:00–12:00	Background for discussion: VCAG draft study design manual on epidemiological trials for vector control tools (Steve Lindsay)
11:30–12:30	Background for discussion: CDC draft framework to evaluate second-generation LLINs (John Painter)
12:30–13:30	Lunch break
11:30–12:30	Background for discussion: CDC draft framework to evaluate second-generation LLINs (John Painter)
13:30–17:00	Background for discussion: CDC draft framework to evaluate second-generation LLINs (John Painter)
17:00–18:00	Surrogates for epidemiological outcome a. Utility of modelling to inform study designs (Azra Ghani) b. Swiss TPH Modelling Project (Thomas Smith)
Tuesday 25 April 2017	
Closed meeting all day	
09:00 –12:30	Closed session: Development of guidance on trial designs for use in generating data required to assess public health value of new vector control tools Output – draft consensus statement on options for trial designs
12:30 –13:30	Lunch break
13:30–15:30	Closed session: Finalization of the recommendations/consensus statements
16:00–17:30	General discussion, Closure of the meeting

ANNEX 3. LIST OF PARTICIPANTS

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