Global **Malaria** Programme

Fifth meeting of the Vector Control Technical Expert Group (VCTEG)

Meeting report, 14–16 November 2017, Geneva, Switzerland

World Health Organization

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CONTENTS

SUMMARY

On 14–16 November 2017, the 5th meeting of the Vector Control Technical Expert Group (VCTEG) of the WHO Global Malaria Programme (GMP) convened to review updates and progress on issues related to the implementation of malaria vector control, including programme management, and to provide advice to GMP with respect to related areas of work. The key outcomes of the meeting were as follows:

(1) Global status on insecticide resistance report: The TEG welcomed the draft report and recommended that WHO conduct additional analyses, such as for individual vector species and geographies. The report should also be revised to provide clarity on its scope and objectives, as well as to better align with standard terminology. The TEG recommended that WHO publish the report once finalized and plan for periodic status updates.

(2) Malaria Threats Map: The beta application was well received, and the TEG encouraged WHO to continue to plan for Phase II development on the basis of user feedback. The TEG indicated that it should be made clear that the Malaria Threats Map is an informational tool and is not designed to be a decision support system. The group also recommended that the feasibility of compatibility with mobile devices be explored. The TEG noted plans to improve on insecticide resistance data collation through a broader GMP effort to harmonize and decentralize data management by WHO.

(3) Decision framework for insecticide resistance management (IRM): The TEG recommended updates to the draft flowcharts and table provided and the addition of narrative in order to guide the identification of malaria vector control intervention options using available insecticide resistance information. It was noted that this should include currently available tools but also consider future tools, with subsequent updates as needed. A revised version of the draft framework will be circulated to the TEG for further input, tested based on scenarios in selected countries and refined as required.

(4) Consolidated WHO guideline for malaria vector control: At its 5th meeting, the TEG served as the Guideline Development Group tasked with developing evidence-based guidance in the form of GMP's consolidated guideline for malaria vector control. Two days of closed sessions were dedicated to reviewing the evidence summaries provided by the Cochrane Infectious Diseases Group. A draft guideline document that included the recommendations arrived at during the TEG meeting was circulated to TEG members and the WHO Secretariat. Feedback on content was requested by 15 December 2017. The TEG recommended that WHO/GMP engage with the Guidelines Review Committee in order to find ways in which the large body of evidence on vector control that does not meet the criteria set by the Cochrane Group can be explicitly included in the formulation of the guideline. The TEG reiterated that it is imperative for the guideline to adequately reflect gender, human rights and equity issues.

(5) Emerging issues: The TEG suggested a number of new or expanded areas of work for GMP. These included the development of guidance on vector control interventions and associated monitoring and evaluation requirements for elimination and prevention of reintroduction settings; prioritization/ stratification of vector control interventions considering new (potentially more costly) tools and/or in the context of challenges such as constrained resources, insecticide resistance and residual transmission; targeting of vector control tools to high-risk groups defined on the basis of human and/or vector behaviour; validation of 5x and 10x intensity concentrations for estimating vector resistance; and validity of synergist bioassays as a proxy for metabolic resistance.

BACKGROUND

The Vector Control Technical Expert Group (VCTEG) was established by the WHO Global Malaria Programme (WHO/GMP) in 2013 to:

- Formulate and propose to WHO/GMP evidence-based norms, standards and guidance for malaria vector control;
- Review evidence and make recommendations to WHO/GMP on the predicted effectiveness and appropriate mix of vector control interventions for particular situations, including the adoption of new forms of vector control following recognition of "proof of principle" by the Vector Control Advisory Group (VCAG);
- Address policy issues related to building capacity for entomological monitoring and optimization of vector control; identify gaps in evidence and suggest specific areas of priority research to improve malaria vector control; and
- Provide WHO with key strategic advice on malaria vector control.

OVERVIEW OF THE MEETING

WHO/GMP convened the 5th VCTEG meeting in Geneva, Switzerland, from 14 to 16 November 2017. During the open session on the first day, 13 VCTEG members, five temporary advisors, five observers and the WHO Secretariat discussed key issues related to the implementation of malaria vector control. Conclusions and recommendations were agreed upon during the closed sessions on the second and third day of the meeting.

The WHO/GMP Director, Pedro L. Alonso, opened the meeting by acknowledging the contributions of the VCTEG to the work of WHO/GMP and singled out the importance of the vector control guideline as a single source for comprehensive recommendation and guidance on malaria control interventions. The Coordinator of the WHO/GMP Entomology and Vector Control unit, Jan Kolaczinski, then reminded the group of their roles and responsibilities, which include signing a confidentiality agreement and declaration of interests; providing WHO/GMP with high-quality, well-considered, evidence-informed advice and recommendations; participating actively throughout the year; participating in other WHO meetings including Expert Review Groups, upon request from WHO; and conducting desk-based review of documents. The meeting objectives were then outlined as below, with Dr John Gimnig appointed as the new VCTEG chair. Three new VCTEG members were welcomed to the group: Dr Constance Bart-Plange, Dr Eunice Misiani and Dr Marcy Erskine.

Meeting objectives:

- To provide a brief update on recent key GMP initiatives in the areas of entomology and vector control;
- To present an update on the global status of insecticide resistance;
- To review and provide input for refining a beta version of an online mapping tool that includes data on vector insecticide resistance;
- To discuss and provide input on a decision framework for IRM;
- To discuss and provide input on the consolidated WHO guideline for malaria vector control.

DECLARATION OF INTERESTS

All of the invited experts completed a *Declaration of interests for WHO experts* prior to the meeting, to be assessed by the WHO Secretariat. The following interests were declared:

Dr Marc Coosemans (VCTEG member) is employed by the Institute of Tropical Medicine of Antwerp, Belgium, and received a grant from the Bill and Melinda Gates Foundation for studying the impact of repellents for malaria prevention in Cambodia, as well as repellents for the study from SC Johnson. This work was conducted from 2012–2014. He has also received six grants for the evaluation of public health pesticides from WHOPES since 2007, some of which will run through 2018.

Dr Jeffrey Hii (VCTEG member) is employed by the Malaria Consortium and has received remuneration for consulting services from WHO and from the Ministry of Health, East Timor, for work conducted in 2017. He has held a grant from SC Johnson, which ceased in 2017, to evaluate transfluthrin, and received financial support from Bayer Crop Science to attend the 4th Bayer Vector Control Expert Meeting in 2017. He holds an ongoing WHO/TDR research grant, which focused on studying magnitude and identifying causes of residual transmission in Thailand and Viet Nam (completed), and will be used to study the impact of socio-ecological systems and resilience (SESR)-based strategies on dengue vector control in schools and neighbouring household communities in Cambodia (awaiting ethical approval).

John Silver (temporary advisor) is a freelance consultant who is married to Melanie Renshaw, who was VCTEG Chair from 2013 to 2016.

Dr Steve Lindsay (temporary advisor) is employed by Durham University and received an honorarium in 2017 for giving a presentation on the importance of clinical trials for measuring the efficacy of vector control products from NIAID (the National Institute for Allergy and Infectious Diseases, USA). He has also received free bednets from Sumitomo Chemical for an ongoing trial in Burkina Faso.

The WHO Secretariat assessed the interests declared by the experts. The declared interests were not found to be directly related to the topics under discussion at the meeting. WHO is of the opinion that these declarations did not constitute conflicts of interest and that the considered experts could participate in the meeting, subject to the public disclosure of their interests.

ITEMS REVIEWED AND ARISING RECOMMENDATIONS

Update on recent GMP initiatives on malaria entomology and vector control

Jan Kolaczinski, Coordinator of the Entomology and Vector Control Unit, provided an update on relevant recent initiatives:

- **Framework for a national insecticide resistance monitoring and management plan for malaria vectors** (http://www.who.int/malaria/publications/atoz/9789241512138/): The framework was released in March 2017 in English; the Spanish and French versions were released in June and July 2017, respectively. Two webinars were held in English and Spanish in July 2017. Other supporting documents released in July 2017 include key points, questions and answers, and a presentation (all in English, French and Spanish).
- **Global vector control response 2017–2030 (GVCR)** (http://www.who.int/vector-control/publications/global-control-response/)**:** The draft document and resolution were discussed at the 70th World Health Assembly in May 2017 and positive interventions were

made by or on behalf of countries from across all WHO regions. The resolution (WHA70.16: an integrated approach for the control of vector-borne diseases) was adopted without amendment. The final GVCR was released in October 2017 in English; the Arabic, Chinese, French, Spanish and Russian versions are available in draft format, with the final versions pending. Other supporting documents released include the Lancet commentary (June 2017), an advocacy brochure (September 2017), online questions and answers (September 2017) and a thematic webpage that includes disease outbreak notifications (August 2017) [www.who.int/vector-control].

- **Framework for a national vector control needs assessment** (http://www.who.int/vector-control/publications/framework-VCNA/)**:** The document was released in November 2017 in English. Updates are anticipated, drawing on experience from operational use and from GVCR implementation and progress. Translations will be considered following revision.
- **Malaria Threats Map** (http://www.who.int/malaria/maps/threats/): The online mapping application was demonstrated during the Malaria Policy Advisory Committee (MPAC) meeting in October 2017 and released publically at the end of that month on the WHO/GMP website. The Malaria Threats Map provides a global overview of malaria vector insecticide resistance, *P. falciparum hrp2*/3 gene deletions, and results from therapeutic efficacy studies and molecular marker studies. Users can generate tailored maps based on selected criteria. The beta application is available online in English, French and Spanish. Feedback is requested on potential functionality/data issues or general suggestions for improvement, and can be delivered through an online form available in English, French and Spanish. Consultations to define specifications for Phase II development are ongoing or planned.
- **Malaria surveillance manual** (under development)**:** The malaria surveillance manual has been updated to now include a chapter (5) on entomological surveillance and response. This chapter includes a description of entomological indicators for the monitoring and evaluation of vector control interventions, and considerations for entomological surveillance by transmission setting – burden reduction, elimination and prevention of reintroduction where malaria has been eliminated. Its general emphasis is on evidence-based decision making in vector control.
- **Policy and process for vector control product evaluation** (http://www.who.int/malaria/publications/atoz/evaluation-process-vector-control-products/)**:** The WHO process for evaluating vector control products was revised in early 2017 to better meet the needs of countries endemic for vector-borne diseases. Under the revised process, the evaluation pathway to be followed is determined by whether or not a product is part of a product class with an existing WHO policy recommendation. Products covered by an existing WHO policy recommendation will follow the prequalification pathway, while all new tools, technologies and approaches will follow the new intervention pathway. For products not covered by an existing WHO policy recommendation, the VCAG will validate whether the intervention under assessment has public health value. Once public health value has been demonstrated, WHO will issue a policy recommendation.
- **Evaluation of new vector control products** (http://www.who.int/neglected_diseases/vector_ecology/resources/WHO_HTM_NTD_VEM_2017.05/): The VCAG serves as an advisory body to WHO on new tools, technologies and approaches for the prevention and control of malaria and other vector-borne diseases. The VCAG advises innovators on data requirements for the evaluation of new tools, assesses this evidence once it is generated and provides recommendations to WHO on the public health value of new tools. In 2017, the VCAG convened on 26–28 April (6th meeting) and 24–26 October (7th meeting). The VCAG manager is currently under recruitment.

- **Epidemiological trials for vector control products** (http://www.who.int/neglected_diseases/vector_ecology/resources/WHO_HTM_NTD_VEM_2017.03/en/) The WHO manual on *How to design vector control efficacy trials: guidance on Phase III vector control field trial design* was provided by VCAG. This document includes recommendations on the hierarchy of trial designs, and considerations for randomization, endpoints, and measures of cost-effectiveness.
- **Comparative effectiveness evidence review group (ERG)** (http://www.who.int/malaria/publications/atoz/requirements-vector-control-products/): This ERG was tasked with reviewing summarized laboratory and field trial data for selected new vector control products as case studies with which to develop both product-specific policy recommendations and general recommendations on the evaluation process for new vector control tools. The group recommended that the existing WHO policy for indoor residual spraying (IRS) be extended to include SumiShield® 50WG. The ERG also provided general recommendations on how to access new products that share a similar mode of action (MoA) and entomological effect as products in a class covered by WHO policy; the need to modify or refine existing guidance for the evaluation of long-lasting insecticidal net (LLIN) and IRS products; the generation of further evidence to inform thresholds of entomological efficacy; the need to revisit the public health value of space spray products; and product design for managing insecticide resistance.
- **Pyrethroid-PBO net ERG** (http://www.who.int/malaria/publications/atoz/use-of-pbo-treated-llins/)**:** WHO revised the recommendation on the deployment of pyrethroid-PBO nets following an ERG review of epidemiological data and feedback from MPAC. This recommendation now specifies that national malaria control programmes and their partners should consider the deployment of pyrethroid-PBO nets in areas where the main malaria vector(s) have pyrethroid resistance that is: a) confirmed, b) of intermediate level, and c) conferred (at least in part) by a monooxygenase-based resistance mechanism, as determined by standard procedures.[1]
- **Recommendations for universal coverage with LLINs** (http://www.who.int/malaria/publications/atoz/who_recommendation_coverage_llin/)**:** The recommendations for achieving universal coverage with LLINs for malaria control were updated following the March 2017 VCTEG meeting in order to reflect new findings on the effect of user preferences and ITN use. The document was presented at the MPAC meeting in October 2017, and inputs received at the meeting were incorporated prior to publication.
- **World Malaria Day 2017** (http://www.who.int/campaigns/malaria-day/2017/)**:** Malaria prevention featured heavily in the advocacy and communications materials formulated for World Malaria Day 2017.

Global status update on insecticide resistance

Background: An update on the status of insecticide resistance in malaria vectors was presented based on a draft report focusing on three key indicators: 1) resistance frequency based on outcomes from discriminating concentration bioassays (with outcomes of % mosquito mortality and confirmed resistance, possible resistance, and susceptibility); 2) resistance intensity based on intensity concentration bioassays (with outcomes of high intensity, moderate intensity and low intensity); and 3) resistance mechanisms based on synergist-insecticide bioassays, biochemical assays or molecular assays (with outcomes of detected or not detected; for metabolic mechanisms assessed by

[1] Test procedure for monitoring insecticide resistance in adult mosquitoes, 2nd edition. Geneva: World Health Organization; 2016 (http://www.who.int/malaria/publications/atoz/9789241511575/en/).

synergist-insecticide bioassays, with outcomes of full, partial or no involvement). At the time of the meeting, the WHO insecticide resistance database included 29 363 tests. After applying inclusionary criteria (tests with mosquitoes collected in 2010–2016 from malaria-endemic countries only; bioassays conducted via standard WHO susceptibility tests or CDC bottle bioassays) and exclusionary criteria (tests using non-standard procedures; bioassay negative control with mortality ≥20%; bioassays with <10 mosquitoes), the total number of tests included in the analysis was 17 824. Primary data were provided by national malaria control programmes and their partners, with collation and validation of data conducted by WHO staff at country, regional and headquarters levels. The vast majority of the data came from the WHO African region and were for species of the *An. gambiae* complex and *An. funestus* group, as assessed using discriminating concentration bioassays.

Resistance frequency was evaluated to identify trends by insecticide classes, vector species, region, country and over time. The outcomes confirmed resistance to four insecticide classes in all WHO regions, except for the Europe region (where monitoring was limited). The prevalence of confirmed resistance (i.e., where mosquito mortality was <90%) to pyrethroids (PY) and DDT was high in the African Region (AFR), Eastern Mediterranean Region (EMR) and the Western Pacific Region (WPR) (detected at 51–78% of sites tested) and high for PY in the South-East Asia Region (SEAR) (70% of sites). Similarly, the prevalence of confirmed resistance to organophosphates (OP) was found to be high in EMR, SEAR and WPR (55–65% of sites), but low in AFR and AMR (detected at 14–18% of sites). Carbamate (CA) resistance prevalence was moderate across all regions (23–52% of sites).

Between 2010 and 2016, a median global decline in mosquito mortality was observed in discriminating concentration bioassays with pyrethroids of 10%, signifying an increase in resistance. The greatest median decline in mosquito mortality was observed in West Africa (22% decline between 2010 and 2016). For other insecticide classes, no clear overall global decline in mosquito mortality was observed, but regional declines were observed for SEAR (to DDT, CA, OP) and EMR (to DDT). There was an especially striking decline in the mortality of *An. funestus* in discriminating concentration bioassays (36% decline for PY, 20% for DDT, and 20% for CA).

Discussion: WHO sought advice from the VCTEG on whether the draft status report is informative and how the report could be strengthened. VCTEG members acknowledged the usefulness of the report and commended WHO/GMP on the accomplishment. The TEG recommended that WHO undertake more granular analyses on resistance and temporal trends in relation to mosquito species and specific geographies. The TEG also recommended that WHO enter into discussions with the Oxford MAP group with regard to ongoing work looking at the progression of resistance in relation to vector control coverage. Questions from the VCTEG members included whether there was any evaluation of larval resistance monitoring or cross-resistance; however, WHO/GMP indicated that due to a lack of reporting of larval resistance data such an analysis would be difficult. VCTEG members raised the need for clarification on the difference between resistance frequency, level and intensity. It was suggested to distinguish between two underlying parameters: the strength of the resistance genes and the frequency of the genes. The VCTEG recommended that the report be revised to clearly articulate its objectives and scope (including what questions it aims to answer and what it is not designed to answer) and to adjust terminology on resistance indicators for clarity and consistency with standard definitions. Cross-resistance and its importance with regard to new product classifications and rotation of insecticides was also discussed. Suggestions regarding the format of the report included reducing the volume (e.g., more ‘at a glance’), making country- or regional-specific reports or overviews, and publishing it in two formats: as a scientific manuscript and in WHO report format. It was suggested that the dissemination of information be tied to the Malaria Threats Map where possible and that various fora be used to disseminate the findings. The final recommendation was that WHO should publish the report and plan for periodic updates, as is being done for the WHO/GMP drug-resistance reports.

Online Malaria Threats Map on insecticide resistance – beta version

Background: The scope, data, features and status of the newly-released Malaria Threats Map were presented. This online interactive application displays global data relevant for the prevention, diagnosis and treatment of malaria, including vector insecticide resistance, *P. falciparum hrp2/3* gene deletions, and *P. falciparum* and *P. vivax* antimalarial drug efficacy and drug resistance. The VCTEG was given a live demonstration that focused on the vector insecticide resistance component. The database for insecticide resistance consists of 18 712 tests from 82 countries; the *hrp2/3* gene deletion database consists of 125 survey areas from 24 countries; and the drug efficacy and drug resistance database consists of 1006 studies from 71 countries. The map became available on the WHO website on 31 October 2017. Phase II development is planned, for which feedback regarding issues and priorities for optimization/expansion is being sought through consultation in the context of various meetings. In the VCTEG meeting, feedback was specifically requested from members on their user experience and with regard to updates that should be considered for Phase II.

Discussion and recommendations: The beta application was well received, and the TEG encouraged WHO to continue to plan for Phase II development on the basis of user feedback. TEG members were provided with the link to the tool and the associated online feedback form, and were requested to provide feedback on their user experience with a particular focus on the tool's utility for addressing malaria programme needs. It was voiced that a mobile phone application may be useful as this may increase usage beyond technical personnel (e.g., by policy makers), given that access to mobile phones is high and convenient in most countries. The TEG therefore recommended that WHO explore the feasibility of mobile device compatibility. It was also suggested that it should be made clearer that the Malaria Threats Map is an informational tool to track the status of threats to support evidence-based decision making and that it is not intended to be a standalone decision-making system. The TEG queried the difference between the Malaria Threats Map and the IR Mapper for displaying vector resistance data and was informed that the former has more up-to-date information as it includes unpublished reports from national programmes and their partners. However, the IR Mapper includes a feature that allows countries to map their own data from a standard Excel template. WHO/GMP indicated that this function could potentially be integrated into the Malaria Threats Map in Phase II if deemed useful to national programmes. TEG members asked about the plans for updating the data hosted on the application and were advised by WHO/GMP that this will be done three to four times a year, with one large update annually in line with the World Malaria Report. It was also noted by WHO/GMP that reported data are often incomplete and may not be adequately geo-referenced; however, data quality may be improved once countries see their data on the map. Issues associated with data quality also underscored the need for ongoing improvement of data management, and the TEG was informed of WHO's plans to improve IR data collection through broader GMP efforts to harmonize and decentralize data collection to the regional level and beyond. Active consultations on the Malaria Threats Map will be held over the next 4–5 months, but feedback can be sent online anytime. The TEG will be provided with updates on these activities in 2018 once they have advanced further.

Decision framework for insecticide resistance management

Background: In line with recommendations arising from the 4th VCTEG meeting in March 2017, WHO/GMP developed a draft decision framework for IRM for discussion at the 5th meeting. The information shared with the VCTEG consisted of a revised flowchart based on Figure 3.1 in the WHO *Test procedures for insecticide resistance monitoring in malaria vector mosquitoes (2nd edition)* (http://www.who.int/malaria/publications/atoz/9789241511575/) and two potential decision guidance tools: one in the form of a table and the other in the form of a flowchart. The aim of these tools is to guide evidence-based IRM in order to maintain the effectiveness of malaria vector control in line with the GPIRM and the recent expansion of the WHO *Test procedures*.

The objectives of the decision framework are:

- To provide a clear and succinct overview of what inputs are required to support evidence-based vector control planning that aligns with good IRM practice;
- To guide countries on the data inputs that are required, the interpretation of those data, and the appropriate monitoring and control responses anticipated.

Discussion and recommendations: The group recommended that the Figure 3.1 flowchart in the *Test procedures* document be updated based on the revised flowchart shared at the meeting, and that the table format outlining resistance management options be further developed. Relevant information on IR monitoring and vector control actions captured in the flowchart should be reflected in the table. The starting point should be the vector control options that are available/may become available, with a view to revising these as new tools become available.

VCTEG members agreed that it was important to consider cross-resistance and multi-resistance mechanisms in the framework. IR mechanisms are highly complex, but intervention choices and associated IRM decisions to be made are relatively few. That being said, a good understanding of cross-resistance and underlying mechanisms is essential to inform the choice of interventions when making IRM decisions. The synergist bioassay is helpful for understanding the nature of resistance mechanisms, but it is also important to quantify the frequency and level of resistance and its relationship with underlying mechanisms. Understanding the cross-resistance spectrum is essential because some oxidase-based metabolic enzymes give strong resistance to other insecticides.

Technical issues raised for consideration in developing the IRM framework included: the accuracy of current methods for quantifying resistance; the relationship between resistance frequency (indicated by % mortality in discriminating concentration bioassays), resistance level (indicated by LD50 ratios calculated as LD50 of studied population / LD50 of susceptible strain) and resistance intensity (indicated by % vector mortality in intensity concentration bioassays with 5x and 10x discriminating concentrations); and the utility of resistance intensity as an additional indicator of resistance. WHO considers the technical issues raised to be important; addressing these may require further research and discussion among experts.

Operational issues raised concerned the geographical focus of resistance monitoring in relation to the level of malaria transmission, the cost-effectiveness of making IRM decisions, and the frequency of rotations and strategy for the deployment of interventions when implementing IRM decisions. Another point of discussion was the aim of IR monitoring across different malaria transmission settings, such as those areas with ongoing transmission (burden reduction countries), elimination and prevention of reintroduction settings. WHO considers that the operational issues related to IRM decision making, IR monitoring and strategies for the deployment of interventions can be addressed to a larger extent by national malaria strategic plans (including national IR monitoring and management plans).

A concern was raised over the lack of evidence for public health use to support the inclusion of the mosaic application of insecticides in the IRM framework and the exclusion of organophosphates for rotations. Although new formulations that include more than one active ingredient (AI) are under development, such products are likely to have a significantly higher cost than single AI formulations. Furthermore, it is not clear what proportion of AIs is required in mixture formulation to prevent or manage resistance. Regarding rotations of IRS formulations, it was mentioned that more evidence is needed to guide countries; rather than stating that countries should 'rotate', it should be specified what sequence is preferred and when and how the rotation should occur. It was clarified that the four resistance management strategies outlined in the GPIRM (rotation, mixture, mosaic and combination) were given as examples for consideration in the IRM decision framework. For example, it is feasible to implement rotation and combination strategies for resistance management with existing interventions. Also, a mixture formulation with AIs of different MoAs and mosaic application

of different AIs at geographical scale will be feasible in the near future as additional options become available.

The TEG emphasized that the aim of the IRM framework should be to assist countries in exploring options for best practice IRM implementation, not to be prescriptive about what must be done. It should include information on the operationalization of IRM, such as the frequency and timing of rotations, and considerations for prioritization in light of budgetary limitations, resistance profile (frequency, intensity and underlying resistance mechanisms), and disease burden (or changes in disease burden). Moreover, the VCTEG noted that it cannot always be assumed that a metabolic mechanism is involved based on synergist-insecticide bioassays, in which mortality is higher for the synergist insecticide than for insecticide exposure, as mosquitoes from a susceptible population may also be killed when exposed to a synergist alone.

There were several suggestions for formatting the proposed components of the IRM framework, including changing fonts, simplifying Figure 2 and splitting Figure 1 into two separate frameworks in which one considers cross-resistance. Additional detailed inputs were provided during the meeting. It was agreed that a revised version of the table would be circulated to the TEG. It was suggested that WHO should prepare an accompanying short narrative with a view to providing practical guidance on IRM decisions. An updated table with its accompanying narrative will then be tested based on scenarios in selected countries and refined as required. The guidance will ultimately be integrated into the consolidated vector control guideline currently under development. The TEG suggested that WHO should explore the development of a 'guided web/mobile application' to communicate options for IR decision-making to countries.

Current WHO recommendations for malaria vector control interventions and rationale for the development of a vector control guideline

Background: This presentation provided the rationale for the development of a consolidated malaria vector control guideline, similar to the existing guideline on malaria case management. The objectives for the vector control guideline are:

- To provide global, evidence-based recommendations on vector control strategies and tools for malaria control and elimination;
- To provide a framework for the development of specific and more detailed national vector control strategies and protocols, promoting the use of effective malaria control measures at the national level based on the best available evidence;
- To identify evidence gaps and inform a research agenda in support of the 2nd edition of the guideline.

The guideline will cover the core interventions (IRS and ITNs, LLINs), supplementary interventions (LSM and others) and the scaling back of vector control, and discuss setting and programmatic factors for selecting vector control interventions. The proposal was submitted to the GRC after the MPAC meeting in October 2016. The Guideline Development Group (VCTEG) convened in March 2017 to develop PICO questions. The Cochrane Infectious Diseases Group (CIDG) at the Liverpool School of Tropical Medicine (LSTM) was commissioned for the systematic reviews and Grading of Recommendations Assessment, Development and Evaluations (GRADE) tables. MPAC was updated on progress in March 2017. The lead writer was contracted in July 2017 and evidence summaries were received from LSTM in October 2017.

Discussion: The TEG recommended that WHO/GMP engage with the Guidelines Review Committee in order to find ways in which the large body of evidence on vector control that does not meet the criteria set by the Cochrane Group can be explicitly included in the formulation of the guideline. For IRS, for example, randomized controlled trials supporting the deployment of the intervention are limited, but a substantial body of evidence generated since the 1950s provides strong support for

the public health value of this intervention. The TEG also reiterated that it is imperative for the guideline to adequately reflect gender, human rights and equity issues. A draft document of the consolidated vector control guideline will be circulated to TEG members and the WHO Secretariat by 30 November 2017. Feedback on the content must be provided by 15 December 2017.

WHO guideline development

Background: Guidelines are the fundamental means through which WHO fulfils its technical leadership in health. Some key principles are as follows; the process of development:

- is explicit and transparent;
- is multidisciplinary and includes all relevant stakeholders;
- aims to minimize the risk of bias in the recommendations;
- involves use of evidence that is publicly available;
- ensures recommendations can be implemented in and adapted to local settings and context.

The *WHO handbook for guideline development* provides step-by-step guidance (http://apps.who.int/iris/bitstream/10665/145714/1/9789241548960_eng.pdf). All relevant evidence should be identified, synthesized and presented in a comprehensive and unbiased manner. Recommendations must be based on the best available evidence, preferably through a systematic review of scientific literature guided by specific questions using the PICO format. However, other forms of evidence should be considered as well, for example, non-randomized trials, observational studies, cohort studies and expert opinions. The guideline development process at WHO is as follows: 1. Scope the guideline. 2. Set up the Guideline Development Group and External Review Group. 3. Create declarations of interest and manage conflicts of interests. 4. Formulate questions using PICO and choose relevant outcomes. 5. Retrieve, assess and synthesize evidence (systematic review). 6. Formulate the recommendation using GRADE; include explicit consideration of the benefits and harms, values and preferences, and resource use. 7. Disseminate, implement. 8. Evaluate impact. 9. Plan for updating.

Most WHO recommendations are based on a health systems perspective as opposed to an individual patient/end-user perspective. The main factors that determine the direction and strength of public health recommendations are:

- the quality of the evidence – estimates of effect;
- the balance of benefits and harms;
- values and preferences related to the outcomes;
- resource implications;
- equity, human rights, gender and social determinants of health;
- feasibility of implementation.

If, based on these factors, there is sufficient confidence that the desirable effect of adherence to the recommendation outweighs the undesirable consequences, and further evidence is unlikely to affect the recommendation, a *strong* recommendation can be given. If there is less certainty about the balance between the benefits and harm or disadvantages of implementing the recommendation, and further evidence is needed and likely to affect the recommendation, then a *conditional* or *weak* recommendation can be given.

Discussion and recommendations: With regard to improving the guideline development process, members agreed that it is necessary to identify the gaps in guideline development and to provide feedback to the Guidelines Review Committee. A key concern voiced was related to inferring

recommendations and the generalizability of guidance based on studies conducted in specific settings. Since it is impossible to have trials for each ecological situation, it was questioned how the results from such studies should best be translated into broad(er) guidance. Moreover, although the outcomes may not be significantly altered, different study designs (individuals, households, community randomization) are put together in the Cochrane analyses. Only community designs measure public health value, while the other two provide estimates on individual protection. This difference in design will also affect the PICO criteria (population). Study designs should be stated clearly in the meta-analysis reports. Double-blind when using a placebo (e.g., for repellents) is a questionable approach, as users and investigators can very quickly identify the placebo arm. Cochrane representatives noted that the GRADE process takes into account the directness of evidence.

Guideline development is a laborious and costly undertaking; hence, revision of the document will most likely occur every 2–3 years, resulting in new guidelines every 5 years. Ad hoc reviews and updates can be conducted at any point during this period if necessitated by new evidence. Furthermore, with regard to guideline development, it was noted that weak or strong evidence does not refer to the robustness of the study, but rather to the relevance of the recommendation that is made.

Evidence review and formulation of recommendations: key interventions

Background: As part of the process of developing a comprehensive guideline for malaria vector control, the CIDG was commissioned to undertake systematic reviews and assess the quality of evidence for each malaria vector control intervention. New systematic reviews were prepared on the combined use of IRS and insecticide-treated nets (ITNs), and space spraying. Existing systematic reviews covering larviciding, use of larvivorous fish, and ITNs were updated. GRADE tables for IRS were produced based on the existing 2010 review (no new studies have been published since 2010). An ongoing systematic review on topical insect repellents was completed. Representatives of the CIDG opened the session with an introduction to systematic reviews and the use of GRADE as a systematic and explicit approach to making judgements about the certainty of evidence and strength of recommendations.

The VCTEG noted that the systematic review and GRADE processes are designed primarily for clinical trials and expressed some concerns regarding their applicability and suitability for assessing vector control interventions that involve complex ecologies. Concerns were also raised that significant bodies of evidence generated over many decades through non-randomized trials and programmatic implementation are not suitable for inclusion in Cochrane meta-analyses. A specific example discussed was IRS, which is a core intervention for malaria control that has been used successfully in malaria-endemic countries for decades, but for which few RCTs have been conducted. The VCTEG serving in its capacity as Guideline Development Group felt that this large body of historical evidence from the original implementation trials of IRS and from national control programmes should be considered in the formulation of recommendations.

Within the context of the evidence to guide the decision-making process, the subject of generalizability was raised as an important issue for vector control interventions, given the large number of vector species involved in malaria transmission across countries and regions, and their different ecologies and behaviours.

The CIDG presented the results of the systematic reviews of the core vector control interventions, namely ITNs and IRS. GRADEPro software was used to guide the discussions and generate evidence-to-decision frameworks and ultimately recommendations for each intervention.

The VCTEG noted that intensity and level (not just the frequency) of insecticide resistance may be significant in relation to the effectiveness of ITNs and IRS and should therefore be considered in any future systematic reviews of vector control interventions.

In relation to the addition of IRS in areas with high ITN coverage, the VCTEG noted that the evidence available from the relatively high-quality trials conducted to date suggests that the addition of IRS probably has little or no effect on malaria incidence or prevalence; however, it was acknowledged that any recommendation on the addition of IRS on top of ITNs may differ in situations where there is high insecticide resistance. In such cases, it may be desirable to add non-pyrethroid IRS to pyrethroid-treated LLINs in order to maintain existing levels of control, without resulting in any significant changes to epidemiological outcomes.

Evidence review and formulation of recommendations: supplementary interventions

Professor Steve Lindsay of Durham University presented on the available evidence that house screening is protective against vector-borne diseases, as well as various studies currently in progress, new tools, and the policy environment.

Following the presentation, the VCTEG concluded that the evidence is not yet available to support recommendations regarding the implementation of specific housing design interventions; however, a conditional, interim recommendation to screen and/or fill in house eaves may be worthwhile. More research on the effect of existing household design on vector-borne disease transmission in different geographical regions and different transmission settings is urgently needed, as is investment in product development, especially in relation to the durability of screening materials.

The VCTEG concluded that the issue of vector-borne diseases should be considered in all global, regional and national initiatives concerning urbanization, building healthy cities, etc.

In the second session, the CIDG presented the results of the systematic reviews of the supplementary vector control interventions, namely larviciding; introduction of larvivorous fish; space spraying; and topical and spatial repellents, including insecticide-treated clothing.

With regard to the evidence for the effectiveness of larviciding, the VCTEG noted that there is likely to be significant selection bias, as the trials have been carried out in sites already identified as being suitable locations for larviciding. Therefore, the data are not representative of all study sites where larviciding might be possible. Given that the evidence for the effectiveness of larviciding on epidemiological parameters, including prevalence and incidence, is inconclusive, the VCTEG proposed that a review considering entomological outcomes (adult mosquito density, entomological inoculation rate, etc.) may contribute useful information to aid in the development of future recommendations. No recommendations were made, as further reviews need to be undertaken.

In terms of the introduction of larvivorous fish as a malaria vector control intervention, the VCTEG noted that the available evidence is of very low quality, which makes it difficult to formulate a recommendation for or against the intervention. However, despite the lack of quality evidence, larvivorous fish are currently used in the WHO EURO region to prevent reintroduction of malaria, and used for malaria elimination in Sudan, Somalia and other countries in the EMRO region. The VCTEG concluded that the evidence is insufficiently strong to recommend that the intervention be withdrawn. The VCTEG recommended that evidence of the epidemiological effects of larvivorous fish in areas where it is currently used be collated and reviewed.

A preliminary study of the available evidence on the effectiveness of space spraying as a malaria vector control tool identified only two observational studies, both of which had a high risk of bias. As a result, it was not possible to determine whether space spraying causes a reduction in the incidence of malaria, and the VCTEG concluded that other interventions are likely to be much more effective and cost-effective. More data from well-designed, high-quality trials are needed to identify specific situations in which this intervention may prove useful.

The systematic review of topical repellents, insecticide-treated clothing and spatial/airborne repellents identified a small number of trials with a high risk of bias. Based on the evidence presented and use of the evidence-to-decision frameworks, the VCTEG concluded that the use of

topical repellents for malaria prevention is not currently recommended as a public health intervention, although it acknowledged that topical repellents may be beneficial as a tool to provide personal protection against malaria in specific population groups. Similarly, the VCTEG concluded that the use of insecticide-treated clothing for malaria prevention is not currently recommended as a public health intervention, although it may be beneficial as a tool to provide personal protection against malaria in specific population groups (refugees, military). Until more studies have been conducted and published, the available evidence on spatial/airborne repellents was insufficient to support a recommendation on the use of spatial/airborne repellents in the prevention and control of malaria.

Gerardo Zamora of the WHO Gender, Equity and Human Rights Team presented on gender equity and rights mainstreaming and WHO guideline development. He focused on implications of these areas for the malaria vector control guideline currently under development and presented the available tools and approaches for ensuring that gender, equity and rights issues are fully considered. Systematic reviews are acknowledged as being the best source of evidence on gender, equity and rights for decision making, but only 20% of systematic reviews include this analysis. PROGRESS-Plus (Place of residence, Race/ethnicity, Occupation, Gender/sex, Religion, Education, Socioeconomic position, Social capital + PLUS) is the recommended framework for analysing equity (as a proxy for GERS) in systematic reviews. Specific Gender, Equity and Rights analyses were not included in the systematic reviews commissioned for the vector control guideline.

It was noted that the malaria community currently promotes universal access in order to address some aspects of gender equity and equity of access to interventions by vulnerable groups. However, it is acknowledged that the consistent and correct usage of nets among adolescents is an issue, as it is among migrant/mobile populations. More research is needed to identify the differences in access and use of malaria vector control interventions across population groups and to understand the reasons for those differences.

The proposed full contents of the malaria vector control guideline were presented, and it was suggested that the role of vector control in malaria elimination and the IRM framework presented on day 1 be included in the guideline document.

Emerging issues

The TEG identified the following as priority areas for potential further WHO/GMP work:

a. Guidance on vector control interventions, and associated monitoring and evaluation requirements (for existing and new tools) in elimination/prevention of reintroduction settings – case studies to document the implications of scaling back vector control (especially in southern Africa);

b. Prioritization/stratification of vector control interventions with the arrival of new (more costly) tools and/or in the context of constrained resources, insecticide resistance, and residual transmission;

c. Clearer definition of terminology to use in the evaluation of new vector control products that are submitted to WHO for evaluation;

d. Targeting of vector control tools to high-risk groups defined on the basis of human and/or vector behavioural components, e.g., migrant mobile populations, human occupational groups, settings with highly zoophilic vectors, other landscape risk factors;

e. Modelling selection of resistance in relation to vector control coverage (covered above);

f. Validation of 5x and 10x discriminating dosage for estimating the level of resistance in relation to the LD50 ratio of resistant population to susceptible population;

g. Further investigation into the validity of synergist bioassay as a proxy for metabolic resistance given the complex enzyme system involved in metabolic resistance;

h. Identify modalities for the cross-fertilization of the VCAG and VCTEG in order to ensure optimal interface, for instance to improve the VCTEG's awareness of new tools that will require operational guidance, and to update the VCAG on the process and status of guideline development;

i. Support the update of former WHOPES evaluation guidance for vector control interventions in order to align with the data needs of the revised evaluation process.

MEETING CLOSURE

WHO/GMP thanked the VCTEG members and temporary advisers for their inputs and requested their ongoing support on the work in progress. The 6th VCTEG meeting will likely be convened between MPAC meetings in 2018 (planned for April and October); it was provisionally agreed to hold the meeting in June 2018. VCTEG members were advised that an online poll will be conducted to identify a suitable meeting date.

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AGENDA

PROVISIONAL PROGRAMME

Tuesday 14 November 2017		
Open session		
09.00 - 09.20	Opening remarks and welcome	Pedro Alonso
09.20 - 09.30	Declaration of interests (DOI) Appointment of Chair/Co-chair	Jan Kolaczinski
09.30 - 09.50	Overview of VCTEG • Purpose, functions and role in WHO policy setting • TOR, priorities, decision making, confidentiality • Meeting objectives and expected outcomes	Jan Kolaczinski
09.50 - 10.30	Update on recent key GMP initiatives on malaria entomology and vector control (for information)	Jan Kolaczinski
10.30 - 11.00	*Coffee break*	
11.00 - 11.10	Global status update on insecticide resistance (for information)	Tessa Knox
11.10 - 11.30	Online Malaria Threats Map on insecticide resistance – beta version (for guidance)	Tessa Knox
11.30 - 12.30	Feedback for optimising Malaria Threats Map	Chair
12.30 - 13.30	*Lunch*	

Tuesday 14 November 2017 (continued)		
Open session		
13.30 - 14.00	Decision framework for insecticide resistance management (for guidance)	Emmanuel Temu & Tessa Knox
14.00 – 15.00	Discussion	Chair
15.00 - 15.20	*Coffee break*	
15.20 – 15.40	Current WHO recommendations for malaria vector control interventions and rationale for the development of a VC Guidelines.	Jan Kolaczinski
15.40 – 16.00	Formulation of recommendations. (Factors to be considered: quality of evidence, balance of benefits and harms, values and preferences, feasibility, acceptability, strength of recommendations).	Peter Olumese
16.00 – 16.30	Equity, gender and human rights and vector control interventions	Gerardo Zamora
16.30 – 17.30	Emerging issues (prioritising topics for next TEG)	All
17.30 – 18.30	Welcome cocktail	

Wednesday 15 November 2017		
Closed session		
Session I: Evidence review and formulation of recommendations: Key interventions		
09.00 – 09.45	Introduction to systematic reviews and GRADE	Leslie Choi, Joseph Pryce, Joseph Okebe
9.45 – 10.00	*Coffee break*	
10.00 – 12.00	Long lasting insecticidal treated nets (LLINs)	Leslie Choi & Joseph Pryce
12.00 – 12.30	PBO nets (update on ongoing work)	Leslie Choi & Joseph Pryce
12.30 – 13.30	*Lunch*	
Session II: Evidence review and formulation of recommendations: Complementary interventions		
13.30 - 14.30	Indoor Residual Spraying (IRS)	Leslie Choi & Joseph Pryce
14.30 - 15.15	House improvements	Steve Lindsay
15.15 - 15.45	*Coffee break*	
15.45 – 16.45	Combining LLINs and IRS	Leslie Choi & Joseph Pryce
16.45 – 17.30	Larviciding	Leslie Choi & Joseph Pryce

Thursday 16 November 2017		
Closed session		
09.00 – 10.00	Introduction of larvivorous fish	Leslie Choi & Joseph Pryce
10.00 – 10.30	*Coffee break*	
10.30 – 11.30	Space spraying	Leslie Choi & Joseph Pryce
11.30 – 12.30	Topical and spatial repellents	Leslie Choi & Joseph Pryce
12.30 – 13.30	*Lunch*	
13.30 – 14.30	Presentation of the contents of the malaria vector control guidelines	John Silver
14.30 – 15.00	Recap on key topics for decision	Chair / Jan Kolaczinski
15.00 - 15.30	*Coffee break*	
15.30 - 17.00	Conclusions and recommendations on topics for TEG decision and guidance	Chair & TEG members
17.00 – 17:10	Meeting closure	Pedro Alonso