Roll Back Malaria Vector Control Working Group (RBM VCWG)
12th Annual Meeting, 8-10th February 2017
Moevenpick Hotel, Rue de Pre Bois 20, 1215 Geneva

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2nd New Challenges, New Tools in Vector Control Work Stream meeting
14:30-17:30, Wednesday 8th February 2017
Co-leaders: Michael Reddy & Fredros Okumu

Updates on Work Plan - Mike Reddy, Bill & Melinda Gates Foundation and Fredros Okumu, Ifakara Health Institute

The New Tools and New Challenges for Vector Control Work Stream was set up last year to examine the limitations of our current approaches to vector control. An update on the Work Stream Activities was given:

- Consolidating evidence on New Challenges and New Tools for Malaria Control UCSF team has completed a comprehensive review of 22 vector control tools other than IRS and LLINs. The final report "Expanding the Vector Control Tool Box for Malaria Elimination" is expected in Feb 2017.
- Mutual learning and idea sharing between south-east Asia and Africa. Engagement was initiated by Dr Mike Macdonald and Dr Jeffry Hii. Fredros Okumu attended the Joint International Tropical Medicine Meeting in Bangkok in December 2016 to present the African perspective on new challenges and new tools. The Asian team has been invited to Geneva in Feb 2017. There are already groups in SE Asia working on outdoor transmission, and a joint meeting for all groups is planned through WHO-TDR.
- Symposia on New Tools and New Challenges during PAMCA conference side meeting. The VCWG-NTNC symposium covered new tools, current challenges. A second meeting was held on the last day of PAMCA to address the role of PAMCA in meeting these challenges.
- Develop draft guidelines for measuring residual malaria transmission and its drivers. The aim of this activity is to develop draft standardised guidelines to quantify malaria transmission and its drivers across different settings. A partnership was formed with VectorWorks JHU during a meeting in July 2016, to combine resources to achieve similar goals. TDR is planning a similar effort in 2017, and engagement with TDR is planned for Feb 2017 Geneva meeting. A meeting of all interested groups will then be held in Africa in late 2017.

Updates on expanding the vector control toolbox: gaps and opportunities - Allison Tatarsky & Yasmin Williams

A desk review and modelling based approach was applied to understand gaps in vector control (beyond ITNS and IRS) in order to identify potential solutions and to accelerate progress to elimination. The five work streams were:

1. Geospatial modelling to determine the extent of residual transmission. This was done in partnership with the MAP project, to identify areas where transmission does persist despite high coverage of nets.
2. A Systematic Literature Review to determine the evidence that exists to date and what gaps remain. The review looked into 21 vector control tools (excluding ITNs and IRS) and trials showing epidemiological outcomes, or entomological outcomes. Out of 17,912 abstracts, 155 studies were eligible for inclusion. Only 7 of 21 vector control tools have gone through a Phase III evaluation.
3. A technical review of aerial application to establish the potential for aerial spraying for *Anopheles* control.
4. Transmission modelling to identify the optimal combinations of tools. The Vector Control Optimisation Model simulates the addition of a new VCT into the local setting. Modular Analysis and Simulation for human Health is a model that takes into account environmental heterogeneities.
5. Case study series to help identify the enabling factors for the implementation of new tools. Case studies were taken from the US, Australia, and malaria endemic countries. Best practice showed; entomological and operational capacity; entomological intelligence linked with spatial, epidemiological and cost data; evidence-based and decentralised decision making; sustainable financing; meaningful community engagement; strong leadership and management at all levels; links with research institutions.

The outcome is an ongoing development of a shortlist of "ready" tools with potential for impact

- Environmental Management
- Larviciding
- Mosquito-proofed housing

These tools are needed immediately while R&D of other less researched tools is carried out. The RBM VCWG New Tools, New Challenges work stream was asked to consider moving beyond the traditional research models to develop a learning-by-doing approach for emerging vector control tools.

Summaries available on website: http://www.shrinkingthemap.org/what-we-do/vector-control

Discussion

- It was queried why the mapping component concentrated on SSA which has stable transmission and where elimination is not currently achievable. SSA was used for the mapping component as this area has the best available data. But the rest of the project was location agnostic. Exploring across different settings is a good research priority.
- An explanation of "learning-by-doing" was requested. A model might be to set up an intervention trial, maybe with a control, but with huge emphasis on data collection and heavy M&E. This allows methods and interventions to be adapted as needed, but does lack rigor as compared to RCTs. It may allow more rapid movement forward when facing elimination targets.

Everything you need to know about residual malaria transmission in 10 minutes – April Monroe, Johns Hopkins University Center for Communication Programs

Residual Malaria Transmission (RMT) occurs where high ITN uptake and IRS are being carried out, but malaria transmission is continuing. RMT studies are taking place in Africa (Ethiopia, Kenya, Tanzania, Ghana, Cameroon and Burkina Faso), SE Asia (Vietnam and Thailand), Americas (Brazil and Peru) and the Western Pacific (Papua New Guinea). An outline of the Special Programme for Research and Training in Tropical Diseases (TDR) was given, which aims to quantify and characterise RMT across

settings. Three more studies funded by PMI were outlined, in Zanzibar, Ghana and Ethiopia. All these groups are using different strategies to assess human behaviour, entomological and epidemiological outcomes. Other RMT activities include geospatial modelling and mapping and an entomological surveillance framework. RMT has been discussed at the Mekong outdoor malaria network workshop (Nov 2016), and a TDR investigators dissemination workshop is planned for Sept 2017 in Tanzania.

The VCWG were asked to consider the following opportunities: a dedicated forum to share results and discuss methods across groups, settings and funders, re-establishment of outdoor transmission networks in other regions, consensus building around best practiced, standardised methods/tools for use across settings.

Discussion

- It was queried whether the parasite species involved differed between different settings, which was confirmed.
- An explanation of the map presented was requested. Red areas were those predicted to have high residual transmission, so would be areas where new tools other than LLINs and IRS are necessary. Blue areas have low RMT and represent areas where LLINs might still be useful. It was confirmed that insecticide resistance was included in the model as a driver of RMT. The definition of "residual transmission" used in the model was queried. There has been some debate over the definition of RMT and it might be an issue worth discussing across the group. The working definition for the model is the same as WHO definition.
- It was queried what indicators should be measured to detect RMT. It was stated that we need a platform to discuss best practice and to bring scientists together to discuss these issues.
- Request for future meeting to have more results from on the ground research. Evaluations of new tools are required before recommending them to country programme managers. A bigger picture view of the research is needed allows a call for discussion of the work going on and comparison of methods.
- The large number of researchers in this area led to a query of whether there is duplication of work. But a lot of institutions are already collaborating, so effort is not necessarily being duplicated.

Anopheles species identification: an old and continuing challenge – Basil Brooke, National Institute for Communicable Diseases (on behalf of Maureen Coetzee)

Identification of species within complexes requires molecular identification and is becoming more necessary in order to tailor interventions to differing behaviour profiles. However, there is a tendency to rely heavily on molecular identification at the expense of morphological work. Collections from five African countries were identified morphologically, and non-vectors were put through molecular assays. It was found that it was very common to get misidentifications. These findings make it clear that there should be sound morphological identification first, before molecular assays are used. It was reported that Maureen Coetzee is planning to update the morphological keys (Gillies & Coetzee 1987) and would appreciate feedback from users of the keys.

Discussion

- It was reported that morphological identification (including voucher specimen collection) is planned in SE Asia through IP & PMI, and that the work stream should help link up these researchers to help revive these basic skills.
- It was asked whether any sequence data would be included in the work. The first step will be to produce a hard copy guide, which will be followed by an electronic version which could incorporate sequence data.

- It was asked when the guide will be available. The current dichotomous keys and the PCR are currently correct to use, but it is important that morphologically identification happens first, followed by PCR where appropriate.
- It was asked what could be proposed for storage of specimens for later identification, especially in areas where trained entomologists are rare. It was reported that this is one aspect of training courses provided by NICD, and also should be embedded in vector control programme.
- It was asked whether this key would differ from the existing IRD interactive key, and whether there was a plan to produce a simplified key. It was responded that although simplified keys are a possibility, good taxonomic skills are still required and there are no real short cuts.

Ivermectin for malaria elimination: 2016, a year of exponential growth – Carlos Chaccour, Barcelona Institute for Global Health

Three high-level assessments were made last year. A technical consultation with WHO was done to define key data that is missing before a policy recommendation can be made, and the development of a draft TPP. MPAC evaluated TPP (Sep 2016), which will be resubmitted in March 2017. MalERA refresh included endectocides in their publication from the Panel no Diagnostics, drugs, vaccines and vector control in malaria elimination and eradication. The MMV has included endectocides under TCP-6 as a new development in antimalarial target candidate and product profiles. More information is available on MESA track. The effect of ivermectin has been established on *Anopheles aquasalis, An. darlingi, An. dirus, An. minimus, An. sawadwongporni, An. campestris*. The IVERMAL trial has published partial results that show no adverse events following very large doses (9x higher than normal) and in combination with DHA-PIP. The effect on mosquito survival was longer than the drug itself lasts in the body, most likely due to metabolites. There is measurable effect for 28 days on mosquito mortality. RIMDAMAL ivermectin intervention was given to >5 years, but 20% reduction in incidence of malaria observed in under 5s. IMSEA trial 16 volunteers looked at safety of multiple drug regimens as well as mosquito mortality. The antimalarial effect of ivermectin extends to the parasite where it inhibits liver infection. There is research into formulations such as the Bellinger star-shaped pill that can release a drug over 2 weeks. Dosing is being reviewed as current weight based dosing hampers co-formulations. When used in a veterinary setting, although protective in the first instance, can reduce the efficacy of human-centred control measures and sustain R0 above 1. Future work priorities should be focussed on the technical (gaps in pharmacokinetic knowledge and dosing; metabolites; other endectocides); study design (outcomes and size: what is required to assess this intervention properly) and regulatory and policy.

Discussion

- A query was raised as to why Merck was not supporting this work. They are donating a lot of drug for LF and onchocerciasis, but this kind of work may be out of their scope at present.
- It was asked what the safety profile of ivermectin was in children given that most malaria in SSA is in children <5 years. A safety assessment has recently been submitted, but it is also important to note that the treatment in adults can give protection to children.
- It was asked whether the impact comes from mortality or sterilising. Mortality effect is short-lived, and sterility is longer lasting, but both together work to reduce malaria.

Progress on a Randomised Controlled Trial for evaluation of Eave Tubes – Matt Thomas, Penn State University

Eave tubes are an intervention where the eaves are blocked and an insert installed that doubles as ventilation and insecticide netting. The odour plume from the eave tube turns the house into a lethal lure. Window screening was also carried out. The netting uses an electrostatic charge to bind with

insecticide powder. Phase I and II are completed, and III is underway. Forty villages will be monitored over 2 years by active case detection, parasite clearance and time to first infection. Data will also be collected on entomology, the physical environment, social science and an economic analysis. Despite massive pyrethroid resistance, a pyrethroid (10% beta cyfluthrin) was selected as this was the only insecticide tested that caused 100% mortality, with no decline in efficacy after 5 months.

Discussion

- It was asked whether the trial was powered to detect an effect over and above LLINs, as this was given to the controls. The effect size was estimated from phase II work and the trial should be sufficiently powered.
- The safety of the manufacturing process of the inserts was queried. The insert are made within a closed system, and the operatives also wear all appropriate PPE.
- It was asked how the pyrethroid worked even though mosquitoes are resistant. The electrostatic charge on the netting binds the insecticide powder, which then transfers to the insect. Therefore contact with the insecticide is much more prolonged than compared to nets or IRS.
- The choice to use a pyrethroid in an area with high resistance was questioned. It was responded that the initial plan was to use a non-pyrethroid, but beta-cyfluthrin worked the best. Non-pyrethroid products did produce 100% mortality, but persistence did not last 3 months. However the product profile is very flexible and the active on the insert can be changed frequently. It was suggested that the loss of efficacy in non-pyrethroids could be due to vapour pressure, and microencapsulation may help to overcome this.
- It was asked whether dust would adhere to net and reduce efficacy. The nets are treated to saturation, so no new particles should adhere, within the lifespan of the insert.
- It was asked how long installation took. One eave tubes can be installed in about a minute. Installation of window screens is slower as windows are not standard size. With a team of 10-15 people it takes 1-2 week to treat a small village, and 3-4 weeks for a large village.

Updates on Spatial Repellents for Malaria Elimination – Neil Lobo, University of Notre Dame

Spatial repellents provide a bubble of personal protection, and could be suitable for use against day time biters and to combat resistance. Trials in China and Indonesia have shown effects on disease transmission. But results were more varied in Cambodia. More research is needed on coverage, efficacy variation with bionomics and diversion before global recommendations can be made. An update was given on an ongoing project in Indonesia and Peru to generate this evidence base. However, information on the diversion effect and insecticide resistance will be missing as these parts of the study have been discontinued. At present the results are still blinded.

Discussion

- It was reported that there is some baseline data from the African sites, but no more.
- It was asked how the study design catered for both dengue and malaria. The dengue and malaria study designs are completely different to deal with the different disease transmission dynamics. The movement of individuals was not taken into account within the dengue trial, as it is household based.
- It was asked what kind of emanatory was being used. The emanatory is Shield from SC Johnson, containing transfluthrin and lasting 3 weeks, and being replaced every 2 weeks.
- It was asked what other interventions are in place. It was responded that country level interventions are already in place as recommended, so spatial repellent effect is over and above this.
- It was asked whether indoor air concentration of transfluthrin was being monitored. It was responded that it was not.

Session 2: Feedback from the work stream meeting and discussions

A round up and highlights of the presentations was given alongside the discussion points that were raised during the meetings. These were the (1) Updates on expanding the vector control toolbox: gaps and opportunities; (2) Everything you need to know about residual malaria transmission in 10 minutes; (3) *Anopheles* species identification: an old and continuing challenge; (4) Ivermectin for malaria elimination: 2016, a year of exponential growth; (5) Progress on a Randomised Controlled Trial for evaluation of Eave tubes; and (6) Updates on Spatial repellents for malaria elimination, Neil Lobo.

Discussion and Work Plan

1. Re-examine the definition of Residual Transmission

How should the definition of residual malaria transmission take insecticide resistance into account? Is the current WHO definition appropriate? Should we just call this "persistent malaria"?

- The definition assumes maximum coverage of major tools, so remaining transmission can be considered as residual. The existing definition says the mosquitoes must be susceptible to those tools. So RMT is very difficult to define in areas with high insecticide resistance. The only purpose of RMT is to have a practical tool to guide programmes. There can be a number of explanations for the transmission remaining after LLIN/IRS scale up. While insecticide resistance is one explanation, outdoor transmission is another, so it would be desirable to have a definition that did not exclude any possible cause behind RMT.
- It was pointed out that all the maps of RMT presented, were based on modelling. The resolution of these maps is too large to be of any use to country and district programme managers, and more fine scale data is required for these operatives.
- The definition is often not used well. The common definition is more simply, what is left after interventions have been implemented. The current WHO definition constrains many practitioners, so if it not useful, it might be changed. It was suggested that when the term is used, a definition is given as to what it means in that context.
- Proposal to use the term 'operational failure' this covers IR, and also problems with roll out of tools, or inappropriate use of tools.
- The current definition has a good handle on the problem. We need to facilitate a way for countries to decide whether they have residual transmission. WHO should be challenged to provide criteria that to arrive at the definition.
  - To action: Yousif Himeidan, Manuel Lluberas, Nakul Chitnis and Christian Lengeler.

2. Joint meeting for RMT partners to share findings from Africa and SE Asia

- Objection to the sponsoring of TDR as this would exclude private sector (product manufacturers). A solution might be to have the TDR meeting, immediately followed by another meeting. Clarification was given that WHO cannot sponsor private sector attendance, but they are welcome to attend open sessions of the meeting.
  - To action: Establish consensus about methodologies for measuring residual transmission.
  - To action: Examine the value of parasite surveys in residual transmission measures.
  - To action: Develop a consensus on new tools that can be used in residual transmission settings.
  - To action: Develop a consensus on how to assess RMT in migratory communities in SEA.

3. Identify examples of vector control tools that are amenable to learning-by-doing

- A plea was made not to neglect rigorous evidence collection. Meta-analysis of vector control too often shows how badly trials are often run and, it this approach runs the risk of generating more data that cannot be used to justify recommendations. We still need randomised controlled trials to show protection against disease. Learning by doing may be more appropriate to country level M&E, post roll out. Some interventions (e.g. drainage) do not lend themselves to RCTs, so an approach like LBD may work here.
- The WHO is currently recommending some approaches that are yet to gain full robust evidence. But in order to give country managers some guidance, these were included. Although these were included now, we should still move on to provide that evidence.
- Clearest examples of LBD come from monitoring and evaluation evidence.
- Some tools have good evidence and are ready for use, but need further assessment in terms of field deployment. So here guidance can be given on the type of evidence that needs to be gathered.
    - To action: Allison Tatarsky, Pete Gething and Nakul Chitnis.

4. Update of current keys for mosquito identification

Planned work by Prof. Maureen Coetzee. In addition contributions / sharing of experiences on mosquito taxonomy and identification are requested, and sharing of sequence data and information on new species. Improved capacity for taxonomy and vector identification is required

- To action: Neil Lobo and Seth Irish.