

5th Insecticide Resistance Work Stream Meeting
9.00-12.00, Thursday 20th February 2014
Auditorium, IFRC, Geneva

Chairs: Janet Hemingway & Maureen Coetzee
Rapporteur: Lucy Tusting

Welcome and overview of 2013 developments - Maureen Coetzee, Witwatersrand University, South Africa

Maureen Coetzee opened the meeting and gave an overview of developments in the past year. Brief highlights include the publication of the WHO guidelines on insecticide testing in 2013 which are now available online (WHO, 2013. Test procedures for insecticide resistance monitoring in malaria vector mosquitoes. Geneva, WHO. Available:

<http://www.who.int/malaria/publications/atoz/9789241505154/en/>), the launch of the Pan African Mosquito Control Association (PAMCA) at MIM Durban in October 2013 and the further development of the online insecticide resistance data base Insecticide Resistance (IR) Mapper.

Vector resistance studies in Uganda in relation to insecticide use in public health and agriculture – Tarekegn Abeku and Michelle Helinski, Malaria Consortium, UK

The objectives of the pyrethroid resistance management project were: (1) to evaluate the role of IRS using carbamates or organophosphates in pyrethroid resistance management, in order to prolong the usefulness of LLINs, (2) to understand the role of insecticides used in public health and agriculture in the spread of vector resistance, (3) to understand the impact of resistance on the effectiveness of interventions and (4) to help the Uganda Ministry of Health develop resistance management strategies. IRS was introduced in northern Uganda in 2006 first using DDT and pyrethroids and later when resistance was detected in 2009, switching to bendiocarb in 2010. The study was conducted in 45 sites in 3 groups of districts which had been exposed to different levels of IRS and LLIN coverage. The study comprised entomological surveys (pyrethrum spray catches twice at 12 houses in each site and WHO susceptibility tests), household and prevalence surveys, health facility-based morbidity studies, and data on the intensity of insecticide use in public health and agriculture. The use of agricultural pesticides differed by region, with organophosphates most commonly used overall. Indoor resting density was lowest in the group that had received IRS and highest in the group that had not received IRS or LLINs. No evidence of resistance to bendiocarb was found in any of the IRS districts. Resistance or suspected resistance to deltamethrin and permethrin was found in all districts where testing was possible. Malaria prevalence was highest in the group that had not received any major LLIN or IRS campaign, suggesting that nets appear to be providing protection despite widespread pyrethroid resistance.

Insecticide resistance in West Africa – Hilary Ranson, Liverpool School of Tropical Medicine, UK

AvecNet (<http://www.avecnet.eu/>) research on cross resistance in Cote d'Ivoire and measurement of the strength and impact of resistance in Burkina Faso was presented. In Tiassale, Cote d'Ivoire, *Anopheles gambiae* is resistant to all classes of insecticide available for IRS. There are high frequencies of the kdr mutation, insensitive acetylcholinesterase, CYP6M2 and multiple CYP6P enzymes. All of these resistance mechanisms are found elsewhere; kdr is widespread and insensitive

ace-1 is spreading in West Africa. In Burkina Faso, pyrethroid resistance is well established. Three years of WHO monitoring data show little change in resistance levels in Valle de Kou. However once resistance is established, diagnostic assays may mask drastic change in resistance levels. This study therefore investigated how best to quantify the level of resistance in the population. Different assays were evaluated. The LT50 determination showed a ten-fold increase in time to mortality in one year (July 2011 to July 2012), however very long exposure times were required for the test making it less operationally useful in this setting. In an attempt to identify an alternative indicator of resistance, mortality rates were measured in a Kisumu laboratory strain and the Valle de Kou field strain after exposure to new and used LLINs. In order to determine a threshold level for an operationally significant level of resistance, CDC bottle bioassays were conducted with deltamethrin; however datasets were highly variable. Future research should assess whether diagnostic dose assays alone are sufficient to set insecticide policy, whether it is possible to define an operationally significant level of resistance from a bioassay and how best to select source mosquitoes. Further work must also link bioassay and molecular data to resistance impact.

Cochrane review of impact of insecticide resistance – Janet Hemingway, Liverpool School of Tropical Medicine, UK

The review assessed the impact of pyrethroid resistance on LLIN effectiveness and has now been accepted, with publication due in March 2014. It was a difficult process since methodologies are not standardized; future studies must ensure compliance with guidelines. Outcomes included were blood feeding, mosquito mortality, induced exophily, deterrence, not passing through the net, knockdown and time to knockdown. Resistance levels were stratified into high, moderate and low. Overall, there was considerable variability in the data and the assays used, and therefore insufficient evidence to evaluate whether pyrethroid resistance has had any impact on the effectiveness of LLINs.

Discussion

- *Monitoring resistance:*
 - Measuring resistance is a priority for countries. The technical expertise may not exist on the ground to do so and standardized methods are still required.
 - A solution to the variability in resistance measurement would be to have a WHO collaborating centre which takes responsibility for testing.
 - As patterns of resistance change it is becoming clear that the picture is complex and evolving and that resistance can spread very quickly; the greatest risk at present is in West Africa with hotspots elsewhere. Few populations have kdr alone and it is therefore necessary to both detect other mechanisms while taking into consideration the strength of resistance that can be conferred by kdr.
 - The data already exist to inform strategy in-country; it is not clear however who should provide leadership especially given that decisions potentially will impact on lives saved.
- *Resistance management:*
 - It will be crucial to apply new insecticides only in combination with other insecticides to avoid resistance emerging. IVCC is working towards three new active ingredients, which will have no cross-resistance and will be implemented with a careful resistance management strategy.

- There is a need for clear guidance for NMCPs faced with resistance to all four classes of insecticides used for adult mosquito control.
- Technical skills must be developed in-country and there is a need for nationally-owned policies that incorporate the agricultural sector. Both WHO and the FAO should raise awareness of this amongst policy makers, perhaps also involving organisations such as CropLife.
- While GPIRM sets general principles for resistance management, guidelines for country-level implementation are needed as it is difficult to make general recommendations across all settings. Resistance management plans have been assembled for (1) Bioko and Equatorial Guinea in collaboration with Marathon Oil, published in the Proceedings of the National Academy of Sciences and on the IVCC website, and (2) Zambia, which will be available later in 2014 and good templates exist for some other countries. Guidelines for various scenarios would also help. This is being addressed by the WHO GMP and the VCTEG.
- Insecticide resistance does not always translate into control failure; countries are in great need of guidelines on which strategies to adopt and when.
- IVM can play a role in resistance management and has been recommended for years yet has not been adopted by countries.
- *Impact of resistance on LLINs:*
 - In areas of high pyrethroid resistance, the impact of resistance on net efficacy could be assessed using a randomised controlled trial with treated and untreated nets in each arm; the ethics would be debatable but could be justified by arguing equivalence between the two interventions in the presence of resistance.
 - The difficulties experienced in conducting the Cochrane Review of the impact of resistance are similar to those experienced for the Larval Source Management and LLIN reviews. Many studies are poorly designed and evaluated and therefore cannot be included in Cochrane reviews; this is a waste of resources. The CONSORT guidelines for reporting clinical trials should be replicated for entomological data.
- *Role of the Work Stream:*
 - The VCWG lacks funds but could consider having a partner who is a legally registered entity submit an Expression of Interest for a regional application to the Global Fund for funding to support the work of networks such as PAMCA; the deadline for submission of the Expression of Interest is 1 May.
 - The Global Plan for Insecticide Resistance Management (GPIRM) does not describe specific country-level plans to manage resistance, but outlines a general strategy and theory. A subgroup of VCTEG or the IR Work Stream could help guide its implementation at the field level.
 - The Work Stream can also:
 - Serve as a means of communication between research and VCTEG, and between research and NMCPs.
 - Assess whether we have sufficiently robust assays to monitor resistance.
 - Help countries adopt IVM as a resistance management strategy.
 - Document strategies being used in-country, to allow the effectiveness of different methods to be gauged in the coming years.

Work Stream priorities for 2014

1. Develop a document on best practices illustrating how 2-3 countries have implemented GPIRM.
2. Support WHO to convene country advisory groups to advise countries in developing resistance management strategies. Core members of the work stream should be identified to help examine country data and provide immediate advice; an email will be circulated after the meeting to assemble a list. Regional nuances must be accounted for so expertise should be matched. This is urgent given the upcoming Global Fund deadline.
3. Develop short advocacy or position statement on the current status of LLINs and IRS in the context of resistance and to ensure that countries are aware of GPIRM.