

RBM Vector Control Working Group Insecticide Resistance Work Stream

<u>Progress on 2012 Work Plan – Maureen Coetzee, University of the Witwatersrand, South</u> Africa

Updates were given on the following:

- 1. Global Plan for Insecticide Resistance Management (GPIRM): GPIRM was released in May 2012. A WHO-AFRO/African Network on Vector Resistance (ANVR) meeting was held in Cotonou Benin on 17-18th January 2013 with 14 participating countries to accelerate implementation of GPIRM in their countries and to source funding to support this. Several countries are already implementing the GPRIM, including South Africa which has developed a plan for insecticide resistance management and training courses. Bioko and Zambia are also developing plans for insecticide resistance management.
- 2. ANVR Atlas on Vector Resistance: Data from 2004-2010 has been updated with the new criteria for resistance (98-100% mortality green, 90-97% orange, <90% mortality red). These criteria have also been adopted for the draft Guidelines on Resistance Testing. The atlas is available online.
- 3. *Diagnostic dose for pirimiphos-methyl:* Tests have been conducted by AvecNet at three institutions in Europe and Africa to validate the proposed diagnostic dose.
- 4. Cochrane Review of the effect of insecticide resistance on malaria: The review is currently with the editorial team and should be published within the next three months.
- 5. The Pan-Africa Mosquito Control Association has been established and is being led by Charles Mbogo from KEMRI.

Discussion

Better data is needed from multiple sites to develop diagnostic doses for pirimiphos-methyl. Funding is being made available through WHO GMP. The implications of patchy and mediocre coverage with IRS for control were discussed. The WHO Tube bioassay for resistance monitoring has been updated and will be published shortly. This test will remain the standard, while the CDC Bottle Assay will be a useful and complementary test.



4th Insecticide Resistance Work Stream Meeting 9.00-12.00, Wednesday 30th January 2013 Auditorium, IFRC, Geneva

Chairs: Janet Hemingway and Maureen Coetzee
Rapporteur: Lucy Tusting

Cochrane Review of the effect of insecticide resistance on malaria transmission – Janet Hemingway, LSTM, UK

The review is in the final stages before being submitted for peer review. It is envisaged that the review will be published in PLoS One or PloS Medicine. The main conclusion is that there is insufficient evidence to substantiate whether insecticide resistance is having an impact on malaria transmission, although there may be some evidence on its impact on entomological outcomes. The review will be circulated to the VCWG once accepted.

Discussion

It was suggested that the review could be made available on the VCWG website if all members of the VCWG approved it. The review highlights the need to assess the extra evidence required to examine the effect of insecticide resistance on clinical outcomes, and how should this be collected. A major priority is research that demonstrates which of the approaches recommended by GPIRM are applicable in different settings, i.e. what must be done now to preserve pyrethroids for nets? A multi-country study ongoing in five countries is assessing the impact of insecticide resistance on prevalence and incidence from cohort data. It will also be necessary to continue working with countries running IR management programs to evaluate available data, as in Bioko.

It is important to draw careful conclusions since if no action is taken before evidence for any effect of insecticide resistance becomes available, it may be too late to manage resistance. It also may be damaging in terms of funding. It was queried when the next Cochrane review would be undertaken and whether it might be updated with additional categories such as nets designed for resistance management. It was clarified that the review will not conclude that there is not a resistance problem, but will state that there is insufficient evidence. The review will also be updated regularly.

Since so many studies were not eligible for inclusion, it would also be useful to characterise a minimum set of criteria for future studies to evaluate, in more detail than existing WHO guidelines.

There was some discussion of the value of conducting small-scale cage experiments to compare different resistance management strategies rather than running large-scale trials which can take years to generate data. A limiting factor may be a lack of genetic markers for resistance genes. Some new markers are being developed but the process is made difficult since markers are difficult to find. There is also a danger that the markers will be used as a substitute for full testing, for example kdr markers are sometimes used as a definitive test for pyrethroid resistance, which is not correct practice.

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Janet Hemingway described work ongoing to establish updated discriminating dosages. Data has been collated to make recommendations. It is planned that WHOPES will then set new guidelines. It is important to test dosages on susceptible strains in order to allow comparability between studies. It is important to establish the discriminating dose for new insecticides before they are used operationally.

Discussion

It was queried whether one standard insecticide per class should be selected, given that the end goal is to standardise testing for insecticide resistance. It was agreed that this is not appropriate since different insecticides within the same class have different resistance profiles and mechanisms. Clarification was requested regarding the criteria for establishing whether a particular colony can be defined as susceptible for insecticide resistance testing. Previously, WHO-collaborating centres held colonies of resistant strains, insecticides were tested on at least 10 strains and the dosage was set at double that which killed 100% *An. sacharovi*, which tends to be the most robust species. It is important to remember that changes in mortality with a discriminating dose are not evidence of resistance but simply indicate that changes may have occurred. In situations where insufficient mosquitoes are available for testing, a priority list of insecticides for testing should be drawn up. Since mosquito catches are often the limiting factor in testing, alternative trap schemes and sample sizes should always be considered.

It is necessary to have clear guidance not only on how to conduct WHO bioassays but also how to analyse, interpret and disseminate data.

It was suggested that an additional indicator to assess whether resistance is present and where mitigation strategies are effective may be useful. In response, Janet Hemingway stated that there is not likely to be a simple solution to this.

Gold standards for IR testing and data interpretation-Janet Hemingway, LSTM, UK

To examine how data from country programs can be used to inform resistance management strategies, Janet Hemingway described ongoing work in Bioko and Zambia. These case studies serve as examples of good practice and it is hoped that careful dissemination will encourage further similar evaluations.

In Bioko, IRS with deltamethrin began in 2004 which was associated with suppression of *An. funestus* but not *An. gambiae*. Bendiocarb was then introduced, with a consequent decline in *An. gambiae* and parasite prevalence, which might be explained by pyrethroid resistance (40-60% survival and high kdr frequency) in both molecular forms of *An. gambiae*. Since the introduction of IRS, *An. funestus* has virtually disappeared although *An. gambiae* M and S and *An. melas* are still present (see publications by Brian Sharp and colleagues). After seven years of the program, there is no evidence of resistance to bendiocarb while resistance to pyrethroids remains high. In 2007/8, large scale LLIN distribution was conducted but usage was low. In 2012 LLIN coverage increased. Despite dramatic reductions in prevalence, transmission has not yet been interrupted and further work is examining the reasons for this (possible explanations include the low residual efficacy of bendiocarb and its need for reapplication every 3 months, together with poor application).

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Evidence for gene flow between *An. gambiae* on the mainland and in Bioko indicates that it may not be sensible to continue with bendiocarb given high levels of resistance to bendiocarb on the mainland. Since the NMCP has carefully catalogued and stored mosquito samples, these are being revisited to examine various factors, including the premise that kdr resistant vectors have been contributing proportionally more to transmission. The data showed that kdr homozygotes were actually less frequently infected with parasites than were heterozygotes or susceptible mosquitoes.

Since the length of the deltamethrin spray round is 3 months, the data from window exit traps was disaggregated to establish which mosquitoes were collected pre- and post-spraying. These data indicate that *An. gambiae* populations declined immediately after spraying, while increasing in unsprayed houses. This suggests that, despite resistance, deltamethrin was still having an impact on *An. gambiae* during the period in which it was used for IRS. The samples have also been used to examine whether there is solely kdr resistance in Bioko. Poor correlation between kdr and survival on the discriminating dosages indicates that other resistance mechanisms are also present. Recent sampling in 2011 showed in microarray analysis that there was no difference between surviving and unexposed mosquitoes but a large difference between these two groups and the susceptible laboratory strain. None of the major P450 genes were upregulated.

In summary, although the correct decision was made to stop deltamethrin spraying, today there is only low underlying increased metabolism and some kdr resistance and this is not sufficient justification for not resuming IRS with a pyrethroid. The decision has therefore been made to reinstate deltamethrin IRS for one year with careful IR monitoring to safeguard against the introduction of bendiocarb resistance genotypes from the mainland.

In Zambia, a similar process is underway. Here, *An. funestus* has high-level metabolic resistance and *An. gambiae* has weaker resistance (both kdr and metabolic). CDC, PMI and IVCC amongst other groups have pooled data in order to stratify the country by levels of resistance and an in-country mosaic may be introduced. This work is ongoing and hindered to some extent by a lack of a strong link between resistance and prevalence data.

Discussion

The problems with using kdr as a pseudo-marker for resistance were again highlighted. Assessing for correlation between survival on the discriminating dosages and kdr prevalence is not a robust method for assessing which markers are present.

Possible reasons for a lack of reversion (kdr) in Bioko may be due to selective pressure from LLINs or agricultural pesticide use, the kdr mechanism being present for many years since DDT (implying that it does not confer a selective disadvantage) or low gene flow from susceptible mainland populations. Reversion has occurred rapidly in Zimbabwe, India and Pakistan and these data, together with data on reversion from other locations such as Sri Lanka and Gezira, Sudan will inform our understanding.

The rationale for resuming spraying with deltamethrin rather than an alternative in Bioko is that a new 12-month formulation will be assessed in a trial for the first time operationally, negating the requirement for frequent reapplication. If possible the full report from Bioko will made available in English, French and Portuguese.

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Decisions must be made regarding the need to switch from pyrethroids when resistance is detected, given that coverage may subsequently decline due to the increased costs of alternative insecticides (e.g. PMI switched insecticide in 2012 in Liberia with a consequent reduction in IRS coverage from 23% to 11%). In these settings, it is suggested that further tests are conducted to confirm which mechanisms of resistance are present and the prevalence of these.

National level entomological surveillance data will be highly valuable in the long-term and the example from Dar-es-Salaam shows the value and feasibility of community-led entomological surveillance. In general the quality of entomological data is highly variable.

In Zanzibar, there has been resistance on Pemba Island to all types of pyrethroid since 2010. In 2010, there was no evidence of DDT resistance, in 2011 survival was 3% and in 2012 at one site 25% survival was observed. Furthermore, resistance is now present where previously it was absent. A recent study shows that mortality is higher in older mosquitoes, concurring with similar work elsewhere.

The new WHO guidelines on susceptibility tests should be published both in French and English given the number of francophone countries with a resistance problem. It was suggested that WHO, together with partners such as PMI, could hold regional workshops this year to manage communication and to disseminate information in a formal manner with program managers.

Data sharing - request from ANVR - Maureen Coetzee, University of the Witwatersrand, South Africa

WHO-AFRO is responsible for maintaining the African Network on Vector Resistance to Insecticides (ANVR) database, which is used for producing maps of resistance. The data being used is largely unpublished and ANVR relies on countries providing this. It is however necessary to make it clear that sharing data with ANVR does not preclude publication in an academic format and the data will not be used unscrupulously. It may be helpful for editors of key journals to make a joint statement with WHO to clarify this.

There are plans to create a South East Asia network on insecticide resistance.

Michael Macdonald closed the meeting by highlighting the need for specific action points for 2013 to collect the evidence to guide policy over the coming years.

Actions and 2013 Work Plan

- 1. Develop a generic resistance management strategy.
- 2. Sub-regional workshops for Resistance Management Strategy Development.
- 3. A joint statement from WHO, RBM and journal editors should be made regarding publication of data.



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Agenda				
8:30 - 9:00	Coffee and tea			
6.30 - 9.00	Poster viewing			
9:00 - 9:30	Cochrane review			
9:30 - 10:30	Discriminating dosages			
10:30 - 10:45	Morning break / coffee and tea			
10.30 - 10.45	Poster viewing			
10:45 - 11.45	Gold standards for IR testing and data interpretation			
11.45 - 12.00	Data sharing – request from ANVR			
12:00 - 13:00	Lunch			
12.00 - 13.00	Poster viewing			