6th Optimizing Evidence for Vector Control Interventions Work Stream Meeting
9.00-12.00, Friday 21st February 2014
Auditorium, IFRC, Geneva

Chairs: Christian Lengeler and John Gimnig
Rapporteur: Lucy Tusting

John Gimnig opened the meeting and reiterated the role of the Work Stream, which is to provide a forum for donors, the Innovative Vector Control Consortium (IVCC), Vector Control Advisory Group (VCAG) and Vector Control Technical Experts Group (VCTEG) in developing new paradigms. An overview of the agenda was given.

**LLIN-IRS interactions – an update of recent evidence – chaired by Immo Kleinshmidt, London School of Hygiene & Tropical Medicine, UK**

**Impact of insecticide resistance in Anopheles arabiensis on effectiveness of malaria vector control in Sudan – Hmooda Kafy, National Malaria Control Programme, Sudan**

The objective of the trial was to assess the impact of insecticide resistance on the effectiveness of malaria vector control in Sudan and to determine the effects of different combinations of vector control intervention combinations. The specific objectives were (1) to determine the impact of long-lasting insecticide-treated nets (LLINs) and LLINs plus indoor residual spraying (IRS) on malaria control and (2) to determine the insecticide resistance status and underlying genetic mechanisms in the primary malaria vector *An. arabiensis* in four districts of Sudan. In each arm clusters were randomised to receive either LLINs alone or LLINs with IRS. The study was designed so that the 70 clusters in each of the two study arms were balanced in terms of insecticide resistance levels and between the four study areas. Clinical data were collected through active case detection in cohorts of 200 children in each study cluster using community health workers and cross-sectional surveys. Overall, LLIN use averaged approximately 80% from 2011 to 2013. In 2012 there was no evidence of a difference in parasite prevalence (Odds Ratio 1.45, 95% confidence interval (CI) 0.61 to 3.45) or incidence (Rate Ratio 1.11, 95% CI 0.68 to 1.80) in clusters with LLINs alone compared to clusters with LLINs and IRS. The study has two more years to run. 2013 findings have not been analysed yet.

**Combined use of LLIN and IRS compared to LLIN alone for malaria control: results of a cluster randomised trial in Tanzania – Natasha Protopopoff, London School of Hygiene & Tropical Medicine, UK**

The study aimed to assess the effectiveness of LLINs and IRS for controlling malaria versus LLINs alone. The study was conducted in Kagera, Muleba district, an area of moderate transmission with two annual peaks after the long and short rains. The primary vector is *An. gambiae s.l.* The study was a two arm cluster randomised controlled trial with 25 clusters per arm. In each of two baseline and three post-intervention cross-sectional household surveys 80 homes with a total of 80 children and 20 adults were selected per cluster. The primary outcomes were parasite prevalence and entomological inoculation rate (EIR). Clinical and entomological data were collected alongside data on socio-economic and demographic variables and intervention coverage. In the baseline year, both
arms received both IRS and LLINs and in the second year, one arm received LLINs and IRS and one arm received LLINs alone. IRS coverage averaged 90% with ITN use ranging from 36-53%. Prevalence was significantly lower in the IRS+LLIN arm compared to the LLIN only arm (OR 0.43, 95% CI 0.19 to 0.97, p=0.043) as was EIR (RR 0.01 (adjusted for baseline anopheline density), 95% CI 0.00 to 0.01, p<0.001). Findings indicate that in this area of Tanzania with moderate net use and high pyrethroid resistance, it is beneficial to apply IRS with bendiocarb in addition to LLINs. A second randomised controlled trial is planned in Muleba with four arms (1) high coverage with standard Olyset® LLINs, (2) high coverage with Olyset® Plus, (3) high coverage of Olyset® and IRS with pirimiphos methyl capsule suspension (CS) and (4) high coverage of Olyset® Plus LLIN and IRS with pirimiphos methyl CS.

Does indoor residual spreading provide additional protection over current best practice alone – a cluster randomised control trial in The Gambia – Steve Lindsay, Durham University

The trial was conducted in Basse, Upper River Region, The Gambia. 35 clusters were randomised to receive LLINs alone and 35 clusters were randomised to receive DDT-IRS plus LLINs. The primary outcome was incidence of clinical malaria measured through passive case detection. A clinical cohort of 7,858 children aged 6 months to 14 years was enrolled. Cross sectional surveys were also conducted before and after the rains with entomological surveillance carried out over two rainy seasons. The study was conducted over two years (2010 to 2011). Both LLINs and IRS were deemed to be operating successfully. IRS coverage was 86% in 2010 and 83% in 2011. DDT was analysed by an independent WHO-certified laboratory and found to be satisfactory. The concentration sprayed was measured by high-performance liquid chromatography with a target dose of 2.0 g/m^2 and mean actually spray dose of 1.7g/m^2. High mortality was observed in WHO cone tests. At baseline, LLIN coverage was 46% and increased through distribution to 93% at the end of the rains in 2010 and 96% in 2011. Cone tests on LLINs had good mortality. Baseline parasite prevalence was 1.6%. In both years, there was no evidence that IRS had a protective effect, with no difference in attack rates, malaria incidence per child per month, moderate and severe anaemia and parasite prevalence between arms. These findings were corroborated by the entomology data; no difference in mosquito density (light traps and exit traps) and sporozoite rates was observed. The data indicate that the susceptibility of the vectors to DDT and permethrin used in the study area was high. However increasing resistance was detected in the second year (2011) in a few foci. In an area of seasonal, low transmission, with good LLIN coverage, there was no benefit of adding IRS.

Benin – Immo Kleinschmidt, based on published results by Corbel et al

A four arm cluster randomised control trial was conducted in Benin, with clusters randomised to receive the following interventions: (1) targeted LLIN to pregnant women and children aged <6 years (the control), (2) universal coverage with LLINs, (3) targeted LLIN plus full coverage of carbamate-IRS applied every 8 months and (4) universal coverage plus carbamate-treated plastic sheeting. Overall there were 28 clusters with 7 per arm and the primary outcome was incidence of clinical malaria in children followed for 18 months. There was no evidence of a difference in malaria incidence between any study arms. In conclusion, there is no benefit in combining IRS with targeted LLIN coverage, compared to targeted LLIN coverage alone and no benefit of universal LLIN coverage versus targeted LLIN coverage in this area of Benin. However the study may have been under-powered with only seven clusters per arm.
Discussion
A précis of the characteristics of the four trials was presented and hypotheses for the observed findings discussed. In the Tanzania trial, an analysis including only net users (i.e. accounting for generally low net use) still found a protective effect. It was suggested that passive case detection may not have been reliable in The Gambia; however any biases would have been comparable across groups, and other outcomes (parasite prevalence from cross-sectional surveys and entomological outcomes) corroborate the incidence data. One limitation of the Benin trial may have been that only one round of IRS was conducted each year, and bendiocarb has a short residual effect. The low baseline levels of transmission in the Sudan and Gambia necessitates caution in interpreting results; vector control interventions may have reached their maximum potential efficacy and other interventions may be needed in such settings. In The Gambia trial, there was a large increase in malaria in the second year, possibly due to high rainfall despite high LLIN coverage and good case detection and management. Overall the results suggest that in areas of good LLIN coverage with little pyrethroid resistance and low transmission, there is no evidence of a benefit in adding IRS. In areas of higher transmission and with high levels of pyrethroid resistance there may be added protection due to the combination. Possibly, where one intervention is compromised then it is worth adding a second. The Vector Control Technical Experts Group (VCTEG) will examine new evidence in February 2014.

Updates on alternative bioactives – Matthew Thomas, Penn State University, USA
EU-funded research on eave tubes was presented. Eave tubes are a potential new intervention which provide a high entry point for vectors at which they are targeted with bendiocarb-treated electrostatic gauze and pieces of LLIN. Experimental hut trials are ongoing in Ifakara, Tanzania. Biological actives such as fungi (Beauveria spp) could potentially be added to the eave tubes. Transient exposure (5 seconds) to Beauveria gives 100% laboratory mortality within 5-6 days which though slow is more effective than controls or permethrin. Models indicate that eave tubes with fungus could have a significant impact on EIR in Ifakara even in the absence of instant kill. Virulent Beauveria can impact on the survival and transmission potential of adult mosquitoes by reducing fitness several days before death. Insecticide resistant mosquitoes are completely susceptible to B. bassiana. The active could also be produced locally; a photograph of a facility in Benin was shown and used to treat homes at around 10 cents per house. Registration for the product is simple (dossiers already exist) and ethical permissions are in place. The next stage is to conduct a field trial if funding can be secured. Other research has focused on whether Smart Patches can be added to LLINs to improve their efficacy. A series of ‘optimization’ studies have been conducted with a single bednet with 50 mosquitoes within a controlled environment chamber. Smart Patches could provide greater product choice and improve the efficacy of compromised nets.

Discussion
It is hoped that a large cluster randomised controlled trial can be conducted to test these interventions. The longevity of eave tubes was queried; persistence of the fungus in the field has been observed for 3-6 months. The five second exposure was chosen as a conservative figure but in reality could be longer. Better mortality is achieved with focal points (i.e. eave tubes) instead of entirely screened eaves.
Redesigning the Vector Control portfolio at the Bill and Melinda Gates Foundation – Janice Culpepper, Bill and Melinda Gates Foundation (BMGF), USA

The Bill and Melinda Gates Foundation (BMGF) recently laid out its strategy for vector control for the next 25 years with the overall aim of malaria elimination. The three overarching goals are to (1) accelerate the trajectory to zero transmission by applying interventions and strategies based on the five principles of the Analytical Framework, (2) prepare for the next generation of interventions, strategies and delivery modes and (3) sustain progress by preventing resurgence in countries that are nearing elimination and helping them to achieve and sustain their current elimination goals.

Under the three goals, the five principles of the Analytical Framework are that (1) malaria eradication is the elimination of parasites from the human population, (2) complete cure at the individual level is necessary for elimination, (3) targeting asymptomatic infection is key, (4) the principles of evolutionary medicine should be the formulation of science, product development and operational development and (5) think global and act local. These are supported by six initiatives: (1) ‘eliminate’, (2) ‘infection detection’, (3) ‘achieve radical cure’, (4) ‘prevent transmission’, (5) ‘focus on the last mile’ and (6) ‘mobilise’ (i.e. advocate for political support and funding). The new strategy requires new vector control tools that can deliver complete transmission prevention, and work is ongoing with partners to ‘fill the gap’. Specifically, new active ingredients (AIs) are being investigated to combat resistance and the research portfolio is being broadened to target outdoor biting.

Discussion

The trade-offs between the short term cost and long-term savings of elimination need consideration and are being investigated by BMGF. It is important to invest in people and systems in addition to products.

VecNet Update – Tom Burkot, James Cook University, Australia

VecNet evolved from the MalERA consultation and its mission is to use spatially explicit data to understand and model the impacts of interventions on malaria transmission for control and eradication (www.vecnet.org). A demonstration of the VecNet site was given. Various tools are available including the VecNet Digital Library, which contains data, tagged citations, articles and reports that members can search and curate. The Transmission Simulator gives access to complex models. Parameters including weather data, vector species, malaria epidemiology and interventions can be entered and different malaria control scenarios simulated. The Risk Mapper, under development by the Malaria Atlas Project, is a tool for malaria control programmes for comparing the impact of LLINs and IRS over time. Other tools include the Product Impact Evaluator and Computational Intervention Portfolio Evaluator. The site is currently in beta testing and will be made more user friendly and widely available in 2014.

Revival of IVCC plans for new paradigms in vector control – Tom McLean, Innovative Vector Control Consortium (IVCC), UK

IVCC is a product development partnership that invests in research and development to overcome barriers to innovation in vector control. The portfolio includes new active ingredients, new formulations, re-purposed AIs and new paradigms. The presentation focused on new paradigms. Over the past year, an IVCC Framework for validation of new intervention paradigms and product categories has been developed, alongside a framework for rapid assessment and adoption of new vector control tools and a case study of the design of a programme for validation of the spatial
repellent paradigm. An Expert Scientific Advisory Committee has also been formed (ESAC 3). The mandate of IVCC is not to make policy, but to create the evidence to validate Target Product Profiles (TPPs), while ensuring that procedures align closely with those of VCAG. Key objectives are to achieve or develop: (1) protection from disease transmission by outdoor biting mosquitoes, (2) protection during targeted elimination campaigns and (3) protective products distributed through private sector and consumer channels. The specific strategy of IVCC is to (1) develop TPPs, to enable multiple manufacturers to design products in a particular class, (2) partner with multiple companies that have the capability to develop and deliver the products matching the TPPs, and (3) prepare for the introduction of new paradigms. Within scope could also be odour baited traps, repellents, swarms and possibly others, whereas out of scope are new designs of bednets and IRS that fit the current TPP, genetically or biologically modified mosquitoes (which lie outside the IVCC skills base) and early stage research. To be debated is housing stock improvement. The process for portfolio management will be: (1) basic research and concept development, (2) proof of concept, (3) epidemiological validation and (4) policy endorsement and adoption.

**Discussion – 2014 Work Plan and interactions with IVCC**

The main activity in previous years has been to organise the annual meeting at VCWG which is valuable in bringing partners together. In 2013, the only organised session was a session on LLINs and IRS combinations at MIM Durban. This level of activity is in line with financial and personnel resources (very limited).

The following areas of work in 2014 were proposed:

- The Work Stream regularly interacts with IVCC, and since resources are limited the Work Stream could continue to act as a forum and a link between IVCC and researchers.
- Statisticians and epidemiologists could be brought in to advise on study design. Other working groups in RBM have run training workshops to improve understanding of the issues involved in trial design; this Work Stream could convene these alongside already planned meetings.
- Since the same gaps in research seem to recur, specific questions for research should be listed and circulated, drawing on expertise within the group.

It was also noted that:

- Large annual meetings such as the American Society for Tropical Medicine and Hygiene are an opportunity to hold additional Work Stream meetings.
- The Special Programme for Research and Training in Tropical Diseases, TDR, may be a good partner for capacity building.