Institution:
UNIVERSITY OF LIVERPOOL and LIVERPOOL SCHOOL OF TROPICAL MEDICINE

Unit of Assessment:
UOA1 - Clinical Medicine

Title of case study:
Improving the Impact of Malaria Prevention Activities

1. Summary of the impact

Malaria kills around 650,000 children a year but can be prevented by killing the mosquito vectors. As mosquitoes become resistant to insecticides the prevention measures can become ineffective. Research at the Liverpool School of Tropical Medicine (LSTM) led by Professor Hemingway FRS has been instrumental in the development of current World Health Organisation (WHO) guidelines to manage resistance, and has led to improved resistance diagnostics and novel monitoring software to integrate entomological and human health outcomes. LSTM's research led to the creation of the Innovative Vector Control Consortium (IVCC) which was established as an independent Product Development Partnership (PDP) in 2008. New, longer lasting formulations of insecticides developed by IVCC are now in operational use, and several novel public health insecticides are under development.

2. Underpinning research

This case study encompasses the outputs from five academic staff; Janet Hemingway, (2001-) Director of LSTM, Hilary Ranson (2001-) Professor of Medical Entomology, Martin Donnelly, (2001-) Professor of Evolutionary Genetics, Mark Paine (2006 -) Senior Lecturer, and Charles Wondji (2005-) Research Fellow, leveraging several hundred millions of pounds of research income since 2001.

Scale up of insecticide based interventions to target the mosquito vectors that transmit malaria have resulted in a 33% reduction in malaria cases over the last decade in Africa. However, malaria prevention is currently reliant on a very small number of insecticides with only the pyrethroids approved for insecticide treated bednets. Malaria mosquitoes are rapidly developing resistance to these insecticides. There is a critical lack of alternative vector control technologies, and a further impediment to effective malaria control is often the absence of accurate timely information on which to base disease prevention measures, which can result in wasted resources and increased disease burden. New vector control tools, decision support systems and new insecticides are urgently needed to save lives in Africa. If current tools fail due to resistance, the gains in malaria prevention could be quickly eroded.

Understanding the mechanisms and spread of insecticide resistance.

LSTM leads the malaria control community in understanding the causes and consequences of the evolution of insecticide resistance in malaria vectors. Research into the molecular basis of insecticide resistance has resulted in new resistance monitoring tools and new approaches to measure the speed of spread of resistance [1]. LSTM has characterised a newly emerging resistance mechanism that confers cross resistance to multiple insecticide classes [2], and alerted the community to the presence of a population of malaria vectors in Cote d'Ivoire that has now developed resistance to all available insecticides [3]. The molecular tools developed are now being used in insecticide development to identify new, resistance-breaking chemistries. LSTM has the largest collection of characterised insecticide resistant and susceptible mosquito colonies in the world, maintained by the Liverpool Insect Testing Establishment (LITE; http://www.lite-testing-facility.com/). This facility is being used by a range of commercial partners as part of the insecticide development pipeline.

Programmatic monitoring and evaluation

LSTM has conducted evidence based monitoring and evaluation strategies for insecticide resistance in multiple countries including defining the types of insecticide resistance that have a major impact on the ability to prevent disease transmission. As an example, research into the mechanisms of resistance in Equatorial Guinea has guided and improved international policy on resistance management [4]. LSTM led a Tropical Disease Research (TDR) network on insecticide

resistance in malaria vectors in four countries, establishing protocols for longitudinal resistance monitoring and data evaluation and has worked with the Presidents Malaria Initiative (PMI), and National Malaria Control Programmes to introduce entomological monitoring and evaluation into routine control activities [5, 6]. The EU funded FP7 AvecNet project is working with IVCC and in country partners, setting new standards in quality assurance for evaluation of new insecticides in field trials.

Underpinning Research leading to product development.

a) LSTM's research on the insect detoxification systems has led to the development of simple, cost-effective and user friendly kits for monitoring insecticide residues on insecticide-treated materials. Pyrethroid Quantification Kits were initially aimed at pyrethroid insecticides used on bednets but the insecticide quantification kits (IQK^{TM}) now also encompasses diagnostics kits to monitor DDT and Carbamates used in indoor residual spraying (IRS) [7].
b) New insecticide based products to overcome the rapid selection of pyrethroid resistance in African malaria vectors are under development by IVCC and commercial partners. The LSTM led AvecNet consortium is evaluating these products in the field, including undertaking the first clinical trial of a new dual action bednet.
c) Strategic and day to day operational decisions within disease control programmes have to be based on quality information. The Disease Data Management (DDMS) was established to assist in the operational running, monitoring and evaluation of a malaria control/elimination programme. Development of a software platform that could be configured for any environment was completed in 2011 [8].

3. References to the research

1. **Riveron JM, Irving H, Ndula M, Barnes KG, Ibrahim SS, Paine MJ, Wondji CS** Directionally selected cytochrome P450 alleles are driving the spread of pyrethroid resistance in the major malaria vector Anopheles funestus. (2013) Proc Natl Acad Sci U S A. Jan 2; 110 (1):252-7. Citations: 4 Impact Factor: 9.737

2. **Mitchell SN, Stevenson B**, **Muller P**, **Wilding CS**, Egyir Lawson A, Field SG, **Hemingway J**, **Paine JI**, **Ranson H, Donnelly MJ**. Identification and validation of a gene causing cross-resistance between insecticide classes in Anopheles gambiae from Ghana. (2012) Proceedings of National Academy of Sciences, 109:6417-52. Citations: 20 Impact Factor: 9.737

3. Edi CAV, **Koudou BG, Jones CM,Weetman D and Ranson H** Multiple insecticide resistance in Anopheles gambiae mosquitoes southern Côte d'Ivoire. (2012) Emerging Infectious Diseases. 18(9): 1508-11. Citations: 5 Impact Factor: 5.993

4. **Hemingway J,** Vontas J**, Poupardin R,** Raman J, Lines J, Schwabe C, Matias A. and Kleinschmidt I. Country-level operational implementation of the Global Plan for Insecticide Resistance Management (2013) Proceedings of the National Academy of Sciences, Vol 110, Issue 23, pp. 9397-9402. (Equatorial Guinea / Bioko). Citations: 0 Impact Factor: 9.737

5. **Wondji CS, Coleman M**, Kleinschmidt I, Mzilahowa T, **Irving H**, **Ndula M,** Rehman A, **Morgan J**, **Barnes KG**, **Hemingway J**. Impact of pyrethroid resistance on operational malaria control in Malawi. (2012) Proc Natl Acad Sci U S A. 2012 Nov 20; 109(47):19063-70. Epub. Citations: 4 Impact Factor: 9.737

6. Casimiro S, **Coleman M, Mohloai P, Hemingway J**, Sharp B: Insecticide resistance in Anopheles funestus (Diptera: Culicidae) from Mozambique**.** (2006) J Med Entomol 43:267-275. Citations: 43 Impact Factor: 1.95

7. Dowd AJ, **Steven A, Morou EA**, **Hemingway J,** Vontas J. and Paine **MJI**. A simple glutathione transferase -based colorimetric endpoint assay for insecticide detection. (2009)

Enz and Micro Tech. 45, 164-168. Citations: 5 Impact Factor: 2.638

8. Eisen L, **Coleman M**, Lozano-Fuentes S, McEachen N, Orlans M, **Coleman M** Multi-disease data management system platform for vector-borne diseases. (2011) PLoS Negl Trop Dis. Mar 29; 5 (3):e1016. Citations: 7 Impact Factor: 4.716

Selected Research Awards

2005–2013. **Bill & Melinda Gates Foundation**. 'Innovative Vector Control Consortium (IVCC)'. $50,744,497. **Janet Hemingway** (PI)

2010–2016. **Bill & Melinda Gates Foundation**. **'**IVCC Product Development Partnership', $50m **Janet Hemingway**. (PI)

2011–2016. European Commission (FP7). 'African Vector Control: New Tools (AvecNet)'. €11,999,989. **Hilary Ranson**. (PI)

4. Details of the impact

The WHO estimates that insecticide resistance in African malaria vectors, if left unchecked, could potentially result in an additional 120,000 childhood deaths, rising to 250,000 as current vector control tools are scaled up [9]**.** LSTM's research is working to prevent this eventuality. Its approach to resistance analysis has contributed to the greater understanding of insecticide resistance, and has led to proactive decisions being made on insecticide use to avoid control relapses by malaria control programmes in Bioko, Zambia, Mozambique Uganda and Zanzibar. Global Malaria Programme at the World Health Organization has stated "As part of the global malaria community, LSTM has made significant contribution through their research efforts to the prevention and control measures in addressing the problem of insecticide resistance in the WHO African Region" leading to the 25% reduction in malaria mortality rates since 2000 and by 33% in the WHO African Region [10].

LSTM technical input was sought for the WHO Global Plan for Insecticide Resistance Management in Malaria Vectors 2012 (GPIRM) [9] and the recommendations for action in the GPIRM are substantially based on the research output of LSTM in identifying resistance mechanisms and means to track resistance in the field, and in helping countries to generate an evidence base for resistance management strategies. LSTM managed the only large-scale public health insecticide resistance management programme with a 7-year trial in Mexico, sponsored by industry which demonstrated that Indoor Residual Spraying (IRS) in either an annual rotation system or a village scale mosaic maintained control and extended the useful life of the insecticides.

LSTM worked directly with National Malaria Control Programmes in Malawi, Bioko, South Africa, Swaziland, Mozambique and Zambia between 2001 and present day advising on the optimal resistance management strategies. Changes in insecticide use in malaria control have occurred in each of these countries as a direct result. LSTM also supported entomological monitoring and evaluation in a further six African countries (Zanzibar, Liberia, Uganda, DRC, Ethiopia, Ghana, Mozambique and Zambia), through technical assistance to the PMI and, again, several of these countries, including Zanzibar and Uganda, have changed the class of insecticide used in as a direct result. The Co-Chair of the Roll Back Malaria Vector Control Working Group, has highlighted the increased urgency for routine monitoring of resistance and acknowledged LSTM's leading position in driving this forward, in working with country programmes, conducting evidence based monitoring and evaluation and insecticide selection [11].

Impact of product development partnership:

a. Kits for monitoring insecticide residues on insecticide treated materials. Sub-standard spraying, loss of insecticidal activity in the field and even fake bednets are all major problems facing malaria control programmes. The diagnostic insecticide quantification systems developed by LSTM are undergoing trials by AVIMA Pty (SA) for commercial production in Africa, under the brand name "Assure" [12]. They cost <$1, are easy to use and have a unique

ability to provide a rapid assessment of spray team performance, so that any problems can be rectified promptly, whether by re-spraying, retraining or improved supervision. The IQK ™ have undergone fields trials in Bioko Island (Dec 2010), Vanuatu (Nov 2010) and Ethiopia (Aug 2013). Based on the success of the Bioko trial, approximately 2000 prototype kits were ordered for the subsequent spray rounds in 2011.

b. New insecticides. The first longer lasting insecticide formulations (Actellic, Syngenta) became commercially available in 2012 and a second set was launched in 2013 (K-Othrine, BayerCropScience). These new formulations increase the residual performance of the insecticide. IVCC and AvecNet funded and managed all of the efficacy trials, both in the Laboratory (LITE) and in the African field trials sites. The new formulations make the insecticide more effective on traditional muds used in house building in rural African communities, and reduces IRS programme costs by increasing the required interval between applications (e.g Syngenta's original formulation, Actellic EC, was effective for two to three months, whereas the new Actellic CS formulation lasts for 4 – 6 months). Actellic CS is now being used in Ghana and Zambia. K-Othrine, Bayer's long lasting formulation of Deltamethrin, is now being used in Equatorial Guinea. Syngenta's Actellic CS country registrations are accessible for Ghana, Equatorial Guinea [13]**.** The IVCC annual report includes further information on industry investment in research and development. [14]

c. New software for assessing malaria control programmes. The DDMS software enables managers in countries to monitor interventions and evaluate impact in ways they have not been able to do before. They operate in both resource-poor and resource-rich environments and can be tailored to operate as a single database to an integrated system, combining data from several resources, producing maps, reports and alerts for disease outbreaks. DDMS is being implemented in Ethiopia, Mozambique and Zambia. A Spanish version of the software was produced by LSTM in 2012 and is being used by the Bioko Island Malaria Control Programme, Equatorial Guinea. This highly successful programme has reduced transmission of malaria in Bioko by more than 80% [15]**.**

5. Sources to corroborate the impact

Each source listed below provides evidence for the corresponding numbered claim made in section 4 (details of the impact).

9. Global Plan for Insecticide Resistance Management in Malaria Vectors 2012 http://whqlibdoc.who.int/publications/2012/9789241564472_eng.pdf

10. Contact: Vector Control Unit, Global Malaria Programme at the WHO. To corroborate LSTM's significant contribution to the prevention and control measures in addressing the problem of insecticide resistance in the WHO African Region leading to reduction in malaria mortality in the WHO African Region.

11. Contact: Co-Chair of Roll Back Malaria Vector Control Working Group. To corroborate LSTM's global influence and impact on resistance management strategies used in control programmes.

12. Contact: Director for Avima Pty, the company licensing the IQK in Africa. To corroborate Quantification Kits are in commercial production.

13. Syngenta's Actellic CS country registrations can be provided on request (Ghana, Equatorial Guinea.)

14. IVCC annual report 12/13, http://www.ivcc.com/documents/IVCCAnnualreport2011-12.pdf

15. Contact: Senior Officer at Medical Care Development International, who is the PI in the Bioko Island Control Project, confirming DDMS has had a major impact reducing transmission of malaria.