

International Health Lecture 2012

Introduction

This is a summary of the Academy of Medical Sciences' 2012 International Health Lecture on '*Health Impacts of Product Development Partnerships*' that was delivered by **Professor Janet Hemingway CBE FRS FMedSci, Director of the Liverpool School of Tropical Medicine**, at the Wellcome Collection on 28th May 2012. Professor Hemingway's biography can be found in annex 1. A list of attendees can be found in annex 2.

Lecture summary

This summary may be read alone or alongside Professor Hemingway's slides that are available as a pdf on our website. The summary is also accompanied by an audio recording of the lecture.

The Innovative Vector Control Consortium (IVCC) is a Product Development Partnership (PDP) working to develop new strategies to control mosquitoes, the vectors of malaria.¹ Two other PDPs - the Medicines for Malaria Venture and the Malaria Vaccine Initiative - are developing new drugs and vaccines for malaria.^{2,3} The work of the IVCC forms the 'third side of the triangle' to a comprehensive approach to malaria control.

Slide
3

The need for PDPs to tackle malaria

Over the last fifty years there has been market failure in the development of new malaria diagnostics, malaria treatments and methods of vector control. In the 1950s, the state of the art in vector control was indoor residual spraying with a Hudson Sprayer, using wettable powder with a DDT concentration of 2000mg/m². This exact same approach was still being recommended by the World Health Organisation (WHO) in 2006, 50 years later. A step change in innovation is needed to develop sophisticated and widely marketable products, as has been seen with advances in so many other facets of our daily lives. Industry does not have the incentives to develop new products for the control of vectors of tropical diseases, and work in academia alone will not bring products to market and into operational use. Innovative approaches are urgently needed to provide links between skills in academia and industry, as are incentives for new product development. PDPs can help achieve these goals.

5

One important reason for market failure in the field of public health insecticides is the small potential size of the market in monetary terms - smaller in fact than the market for insecticides for use on golfing greens! A study conducted by the Bill & Melinda Gates Foundation and Boston Consulting Group estimated that eradication of malaria would cost \$4-6 billion a year until completion (current spending stands at \$2 billion a year).⁴ Vector control represents about a third of this cost, the vast majority of which is taken up by the cost of insecticides, especially where indoor residual spraying is used. PDPs provide the 'push' to get new products to market in areas where the market will not provide this alone.

6

¹ <http://www.ivcc.com/>

² <http://www.mmv.org/>

³ <http://www.malariavaccine.org/index.php>

⁴ Personal communication to the speaker

The IVCC is the only product development partnership (PDP) working in vector control and so covers a lot of ground, with four key synergistic and overlapping objectives: 7

1. Formulation and repurposing of existing insecticides. Repurposing is difficult, as the most recent insecticides developed for agricultural use are drawn up through the plant, and so only target insects that feed on these plants. This makes them useless for mosquitoes that feed on humans. However, it is possible to make better formulations of existing products.
2. Strategy and best practice: information systems and tools so that insecticides are properly used.
3. New paradigms in public health vector control.
4. Novel sustainable public health products: new active substances that are hoped to reach the market by 2020. These may cost anything between \$200-700 million to develop – the estimate is so wide because no one has made an insecticide specifically for the public health market before.

Formulation of new insecticides and reformulation of existing insecticides 8

Slide 8 shows IVCC's public health insecticides portfolio, and the current stage of development for each product. The time span shown on the slide is around ten years. All major agrochemical companies are involved, and the IVCC have identified new insecticide classes by screening the libraries of chemical compounds held by these companies. The next year will see the first reformulated products coming to market, with several more at earlier stages of development. The new classes of insecticide that are under development will reach the market in 4-5 years' time at the earliest, and so there must be a continued emphasis on best use of existing products. No new public health insecticides are being developed outside of IVCC's portfolio; this resource therefore represents all products in development for vector control.

Reformulating insecticides can extend their active duration from 6 to 12 months so indoor residual spraying needs to be done less frequently. We have to persuade buyers to take this into account when assessing value and making purchasing decisions. The cost of insecticide is partly driven by the number of steps required in manufacture. DDT is the least expensive insecticide (requiring one simple manufacturing step). Malathion is of intermediate expense (requiring three manufacturing steps). Pyrethroids were the most expensive, taking 15-16 steps to produce, although their price has tumbled following competition in the marketplace and streamlined production, so their cost is now lower than other insecticide classes with the exception of DDT. Because PDPs 'de-risk' industry involvement in developing new products, the agreement from industry is that they will keep the prices of new products as low as possible. 9

Quality assurance 10

Insecticide diagnostic and quantification methods are important in the planning and ongoing evaluation of operational programmes. Insecticide treated nets and indoor residual spraying are major control measures in the fight against malaria, but quality assurance systems are crucial for checking that the right insecticides are in the right place at the right concentration. Methods are needed to ensure that impregnated bed nets are not counterfeit (insecticide is invisible and odourless) and that insecticides distributed for indoor residual spraying are not diverted for agricultural use. Quality assurance systems are needed to check that the concentration of insecticide on a wall after it has been treated is adequate, providing valuable feedback to sprayers on quality of coverage. These systems can also be used to assess the length of time that an insecticide lasts after spraying. Methods for use in this area need to be appropriate to the setting – high-performance liquid chromatography (HPLC) and gas chromatography are not readily available in many resource limited settings. The WHO recommends that if HPLC and gas chromatography are not available, bioassays should be used to detect insecticides *in situ*, but this approach is unworkable (see steps involved, slide 11).

Bioassay methods for detecting insecticide *in situ* currently involve susceptible mosquito larvae being harvested, transported and reared into adult mosquitoes in an insectary, transported back to the site in question (a step in which many mosquitoes 11

die due to the heat) and finally brought into contact with the treated surface. This process is complicated, expensive, time consuming and subject to much variation (e.g. susceptibility of the mosquitoes to the particular insecticide being used).

Simple diagnostic and quantification systems are needed that provide results in minutes. IVCC has been sponsoring the development of simple tests for measuring insecticides *in situ*. These involve samples being taken with tape from an insecticide treated wall and combined with reagent(s) in the test kit, to produce a simple visual readout. The colour intensity on the readout indicates the concentration at which a particular insecticide is present. The kits have been specifically developed for ease of use by people in the field with no specialist knowledge or training, with minimal manipulation steps.

Insecticide quantification kits (IQKs) have been developed for use with DDT, pyrethroids (type II) and organophosphates/carbamates (slide 12 shows the steps involved with each of the three kits). All tests work in minutes, all cost less than \$1 a time, and all give easily interpretable visual results. **12**

The DDT test kit performed well in an evaluation in Bihar, India - concentrations reported by the IQK correlated very well with HPLC results. This IQK is now being calibrated and taken forward with support from the Wellcome Trust for programmatic implementation in India. **13**

Slide 14 presents work done in the Solomon Islands to measure concentrations of lambda cyhalothrin (a pyrethroid) using an IQK. Samples were taken from high, middle and lower areas on walls in 30 houses after spraying. The darker the red in the heat map on the right, the greater the concentration of insecticide. This approach is valuable in providing immediate feedback to spraying teams on coverage and allows for mop-up operations where spraying has been inadequate. **14**

The IQK for bendiocarb (a carbamate) was integrated into the routine surveillance of the Bioko Island vector control programme, and resulted in improved performance of sprayers. **15**

The utility of the IQKs lies in their ability to identify concentrations of insecticide above or below meaningful thresholds (rather than exact quantification of insecticide concentration, as with HPLC). In the example given in slide 16, houses with levels of insecticide at $<0.1\mu\text{g}/\text{cm}^2$ would fail the test, those with concentrations from $1-5\mu\text{g}/\text{cm}^2$ have been sprayed but inadequately, and those with a concentration of $>10\mu\text{g}/\text{cm}^2$ have been sprayed adequately to control mosquitoes. **16**

There has been positive feedback on the IQKs from spray supervisors. Feedback focuses on further simplification and ease of use. The next challenges are for manufacturers to take these up, and to get IQKs recommended by the WHO as the preferred method for insecticide quality assurance. This is difficult, as the status quo (HPLC, gas chromatography and bioassays) has been the standard for so long. **17**

Vector population monitoring

Vector population monitoring is key for establishing whether an insecticide will still work, whether resistance has developed in a population, whether resistance is important to vector control strategies, and if so to guide what action should be taken. Methods are therefore needed for people with little prior knowledge or training to identify an insect's species, infection status and insecticide resistance status. **18**

We already have markers to detect species and infection status using molecular Polymerase Chain Reaction (PCR) approaches. Monitoring resistance to insecticides is a particular challenge: resistance can develop in multiple ways, some of which matter to vector control strategies (in operational terms) and some of which don't. When the Presidential Malaria Initiative was launched in 2005, there were pockets of resistance to pyrethroids in six African countries (see map on slide 19). Seven years later, there are pockets of pyrethroid resistance almost everywhere else. **19**

Last week, the WHO and Roll Back Malaria Partnership launched a Global Plan for

Insecticide Resistance Management to tackle pyrethroid resistance on an international level – this is urgently needed.⁵

The map in slide 20 shows increasing pyrethroid resistance in Mexico from 2000 to 2007; it demonstrates the speed at which insecticide resistance increases and spreads – resistance needs to be detected rapidly and the vector control strategy adapted accordingly. Diagnostics for resistance management need to give answers to the questions: ‘have I got resistance and is it important operationally?’ within weeks, not months or years. **20**

Diagnostics for insecticide resistance cannot be ‘off the shelf’ because resistance can develop in so many ways. Although insecticides act on only a few target sites, possible metabolic pathways are complex involving around 190 cytochrome P450 enzymes, ~60 esterases, ~35 glutathione transferases, plus transporters and cuticle genes. The genes important for conferring resistance in a particular setting need to be identified and then monitored. **22**

The figure in slide 23 shows which cytochrome P450 enzymes are important in the metabolism of deltamethrin, and are therefore potentially important in the development of resistance. **23**

An experimental approach was used to establish insecticide resistance to deltamethrin and bendiocarb among mosquitoes in Bioko, Equatorial Guinea. Bioassays were conducted among three groups of mosquitoes: one group were exposed to deltamethrin for one hour, one group to bendiocarb for 10-15 minutes, and one group were unexposed (controls). Subsequent DNA extractions enabled identification of mosquito species and infection status. RNA extractions, analysed using microarrays, were used to identify genes that were over-expressed in the survivors (compared with susceptible mosquitoes) and which may therefore play a role in insecticide resistance. **24**

The bioassays indicated low resistance to bendiocarb in this population of mosquitoes, but some resistance against deltamethrin (40% mortality after one hour). **25**

Genes transcribed differentially by susceptible mosquitoes and other groups were identified by comparing the results from the microarrays. Over-expressed genes are shown in green on the volcano plot (see slide 28). There were no significant differences in gene transcription among the three groups of mosquitoes from Bioko. **26-28**

Slide 29 lists the comparative expression of various genes by the different groups of mosquitoes, as established via the microarrays. The substantial over-expression of oxidative stress genes in all groups is part of a normal stress response; these will not confer resistance to pyrethroids. **29**

Overall, the results show that genes for common known pyrethroid metabolising enzymes are not significantly over-expressed in this mosquito population from Bioko, and that no other putative detoxification genes were up-regulated. **30-31**

⁵ http://www.who.int/malaria/vector_control/ivm/gpirm/en/index.html

The next question to ask is: were survivor mosquitoes more likely to be infected with malaria than those that were susceptible to pyrethroid? The survivors actually had a lower infection rate than fully susceptible mosquitoes. Therefore, despite seeing some pyrethroid resistance on bioassay, this work shows that pyrethroids can still be used as part of an effective malaria control strategy in Bioko. This has important implications for programme planning, as continued use of pyrethroid (vs. use of bendiocarb alone) represents a saving of around £600,000 a year and allows for combination approaches. Although this work required the use of high-tech equipment and had to be done out-of-country, it will only need to be repeated every 3-4 years to monitor the situation and update policy as appropriate.

Summary

In the last six years, the work of IVCC has stimulated industry to develop new insecticides and diagnostics for use in controlling insect vectors of disease. The first new insecticide developed for public health use for 35 years is expected to reach the market in the next year or so, and advances in field diagnostics that allow the quantification of insecticides have received positive feedback. Both of these advances were made possible by the IVCC. Genomic and genetic information enables the monitoring of significant insecticide resistance in the field, to inform effective vector control policies. We must learn the lessons of the past and ensure that proper insecticide management processes are in place from day one when new insecticides come to market. A step change in solutions available on the market will hopefully occur in the next few years, with major improvements in technological solutions available to control insect vectors of disease worldwide.

Questions

Are these solutions scalable at a national level, and are they sustainable? Apart from the Bill & Melinda Gates Foundation and industry, who is providing funding to develop and adopt these technologies?

IVCC's work in Tanzania and Equatorial Guinea is being integrated with the national control programmes already in place. Both countries are willing to adopt cost-effective new technologies under existing funding mechanisms. This is essential for ensuring national scalability. Cost must be carefully considered at the development stage along with rationalisation of sample collection to answer specific questions. As far as sustainability is concerned, it is clear that not all PDPs can survive. The Bill & Melinda Gates Foundation is supporting a number of PDPs, but industry is being asked to increase their contributions or the model will not be sustainable in the longer term. This raises questions about how to share resources so that PDPs working in this area can be as cost-effective as possible.

You have talked about 'push' factors to bring new products to market; how can these be incorporated with 'pull' factors to generate demand for products and increase uptake when they become available?

It is important to develop products that people actively want, rather than products that require behaviour change and that people have to be persuaded to use. We are aiming for the 'iPod of vector control' (see slide 4). Consumer involvement from the start is particularly important in this regard. Uptake of diagnostics in particular could be challenging. Mosquitoes don't respect national boundaries, and so we need a global programme with sentinel sites for insecticide resistance - this raises new problems of how to fund such a programme and how to effectively share data to 'pull' new technologies into use globally.

What about the use of several insecticides in combination to reduce the chances of resistance developing? Is any work being done to develop combination formulation products?

IVCC is aiming to get several new classes of insecticides with different modes of action to market at the same time to stimulate the use of combinations that are important to reduce the risk of resistance developing. The major problem with using more than one insecticide concurrently is the

increase in cost involved, particularly in settings where the cost of insecticide is already prohibitive. For bed nets, a patchwork mosaic pattern can be used to impregnate several different insecticides into the same net without increasing cost. For indoor spraying, annual rotation of insecticide can reduce the risk of resistance developing while keeping cost at a minimum.

How have you got programmes accepted at government level in participating countries?

National settings are complex with numerous players. A key part of our success is to work as partners with national programmes from the start, and we are doing this in Mozambique, Malawi, Zambia, Peru and Mexico. We hope that these 'early adopter' countries will advocate new technologies and encourage uptake among other countries. A wide range of funding strategies are used by national governments for vector control programmes. Some programmes are supported by the Global Fund to fight AIDS, Tuberculosis and Malaria, some by the Presidential Malaria Initiative, some by public funds (where these are sufficient) and some by industry. Every country is different and we use a wide range of models and approaches to engage different national governments.

What about the problems around insecticide toxicity for spraying? Both short-term poisoning, and long-term health implications, e.g. neurological damage?

The current safety standards for new insecticides coming to market are rigorous for both human health and environmental protection (DDT, if new to the market today, would not comply). Our new insecticides must comply with the European and Japanese systems and also the US Environmental Protection Agency standards. Toxicology testing is conducted on sprayers to ensure that they are not picking up high doses of insecticides, but compliance with protective clothing can be a real problem as such garments are often hot and uncomfortable. We need to think about how safety can be built into systems from the start, and in particular how the amount of insecticide we use can be minimised so that we achieve control of the vector in question with minimal risk to human health. One approach we are investigating is the use of tiny emanators that release very low doses of insecticide into a room, sufficient to kill mosquitoes but with minimal risk to human health.

How have you persuaded so many different companies to produce so many different products as part of a PDP?

We won't be able to take all products through to market – this would be unaffordable, and the market is not big enough – we are aiming for three new classes of insecticide to allow for new combination approaches. Companies are sometimes happy to help with the development of products by screening their chemical libraries, but not with manufacture and the IVCC is open to this opportunity. Other companies are keen to be involved as part of their social responsibility agenda, and we have to make sure that companies make a small profit or at least break even to keep them involved. Support often comes from the top of companies.

Do mosquitoes change behaviour due to selection pressure from insecticides (e.g. stay away from walls, bite outside, bite earlier in the evening)?

This is very difficult to quantify. In the 1960s and 1970s, observations from Cambodia, Thailand and Vietnam suggested that mosquito behaviour had changed (from indoor to outdoor biting) following insecticide use. Later on, when molecular biology approaches became available, these showed that the mosquitoes biting outdoors were actually a different species. In Tanzania there is some evidence to suggest that the use of impregnated bed nets has triggered a shift to biting earlier in the evening. However, there are many complexities and we may again be looking at a different species or subspecies which is not susceptible to the insecticides being used. This is why ongoing monitoring and surveillance is so important, to establish whether or not real changes in the mosquito population are occurring.

Annex 1: Professor Janet Hemingway's Biography

Professor Janet Hemingway CBE FRS FMedSci is Director of the Liverpool School of Tropical Medicine and the International Director of the Joint Centre for Infectious Diseases Research, Jazan, Saudi Arabia. She is distinguished as an international authority on insecticide resistance in insect vectors of disease, and CEO of the Innovative Vector Control Consortium. Her studies on resistance management have transformed the use of insecticide by disease control programs, and her promotion of evidence-based monitoring and evaluation strategies for insecticide resistance has guided and improved international policy on vector control strategies for onchocerciasis, malaria and other vector borne diseases.

Professor Hemingway's rigorous scientific approach to resistance analysis has contributed to a greater understanding of resistance, its impact and spread and has minimised its effect in increasing human mortality and morbidity. She was elected a Fellow of the Academy of Medical Sciences in 2006 and of the Royal Society in 2011 and was awarded a CBE for services to the Control of Tropical Disease Vectors in 2012.

Annex 2: Attendees

Dr Fiona Adshead

Prya Agrawal

Dr Stuart Anderson
London School of Hygiene and Tropical Medicine

Dr Sarah Arbe-Barnes
APTIV Solutions

Professor Rifat Atun
Imperial College London

Heather Bailey
Academy of Medical Sciences

Ify Chijieko-Nwauche

Edwina Chin
Policy Cures

Íde Cremin
Imperial College London

Professor Simon Croft
London School of Hygiene and Tropical Medicine

Pam Das
The Lancet

Bismarck Dinko

Professor Hazel Dockrell
London School of Hygiene and Tropical Medicine

Professor Ten Feizi FMedSci
Imperial College London

Professor Alan Fenwick
Imperial College London

Hazel Forde
London School of Hygiene and Tropical Medicine

Professor Sir Charles George FMedSci
Stroke Association

Will Greenacre
The Wellcome Trust

Zaeem Ul Haq
Save the Children

Dr Wendy Harrison
Imperial College London

Baroness Helene Hayman GBE PC
House of Lords

Dr Teresa Hill
University College London

Teddy Tun Win Hla
University College London

Dr Richard Horton FMedSci
The Lancet

Rebecca Howell-Jones
Health Protection Agency

Professor Sanjeev Krishna FMedSci
St. George's, University of London

Danica Kwong
Policy Cures

Paul Lansdell
London School of Hygiene and Tropical Medicine

Anna Lawrence-Jones
The Wellcome Trust

Professor Irene Leigh OBE FRSE FMedSci
University of Dundee

Roni Liyanage
Policy Cures

Dr Lena Lorenz
London School of Hygiene and Tropical Medicine

Catherine Luckin
Academy of Medical Sciences

Dr Richard Malham
Academy of Medical Sciences

Linan Mao
University College London

Professor Patrick Maxwell FMedSci
University College London

Dr Ruth McNerney
London School of Hygiene and Tropical Medicine

Dame Bridget Ogilvie AC DBE FRS FMedSci

Dr Mary Oguike
London School of Hygiene and Tropical Medicine

Dr Adriana Pacheco-Coral
University College London

Professor Catherine Peckham CBE FMedSci
University College London

Nico Petty
Chatham House

Professor Baron Peter Piot CMG FMedSci
London School of Hygiene and Tropical Medicine

Becky Purvis
Association of Medical Research Charities

Lois Reynolds
Queen Mary, University of London

Dr Nick Rousseau
Department for Business Innovation and Skills

Arthy Santhakumar
Chatham House

Dr Emma Savage
Health Protection Agency

Professor Gavin Screaton FMedSci
Imperial College London

Professor Anthony Seaton CBE FMedSci

Professor Elizabeth Simpson OBE FRS FMedSci
Imperial College London

Lesley Sims
Academy of Medical Sciences

Laurie Smith
Academy of Medical Sciences

Professor Peter Smith CBE FMedSci
London School of Hygiene and Tropical Medicine

Professor Robert Souhami CBE FMedSci
Academy of Medical Sciences

Dr Peter Staves
Health Protection Agency

Professor Tilli Tansey FMedSci
Queen Mary, University of London

Yu-Han Tsou
Taipei Representative Office in the UK

Emma Veitch
PLoS Medicine

Sir Mark Walport FRS FMedSci
The Wellcome Trust

Conall Watson
Health Protection Agency

Dr Geoff Watts FMedSci

Dr Naho Yamazaki
Academy of Medical Sciences

