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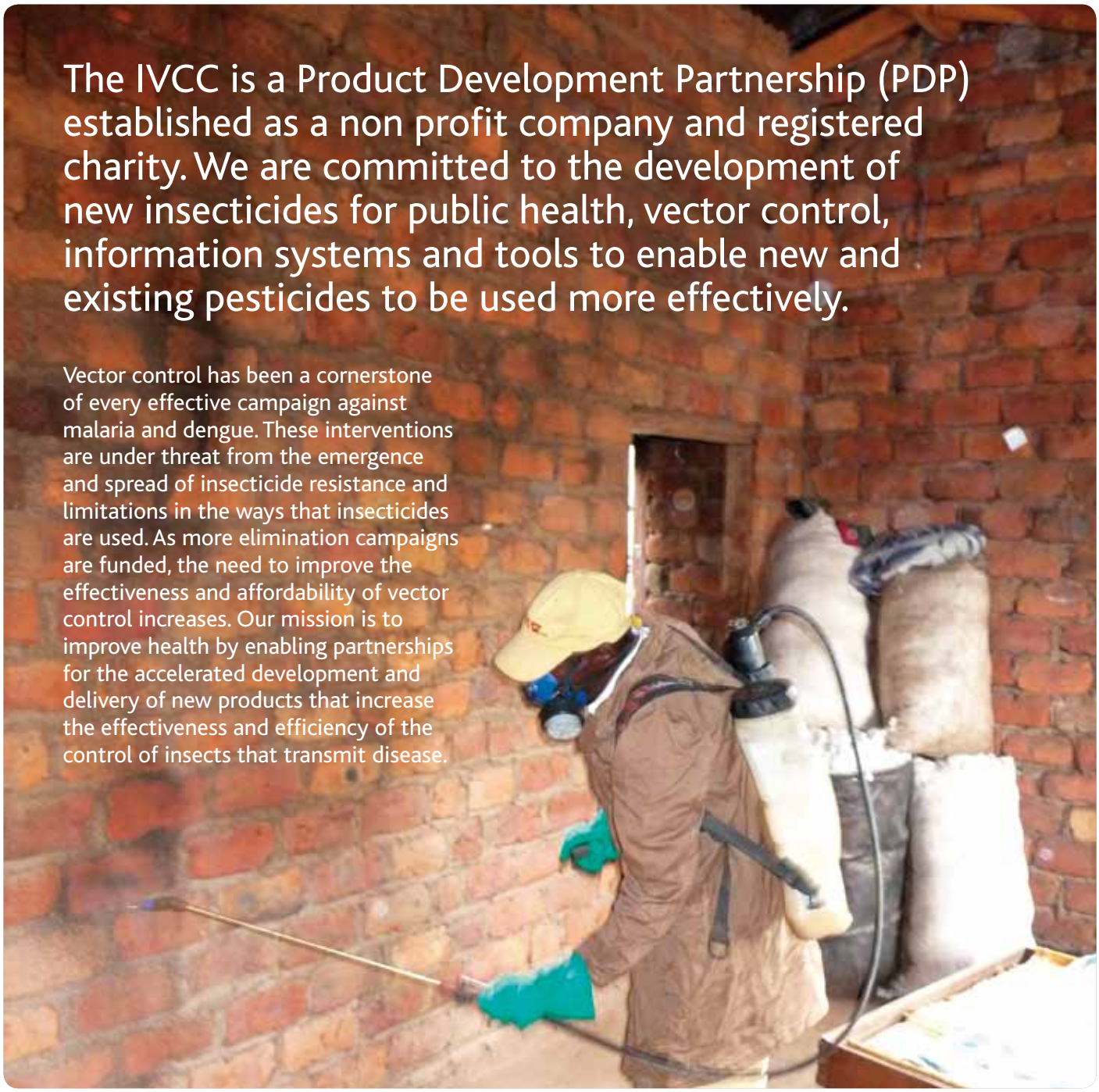
Innovative Vector Control Consortium

Working together to save lives

Annual Report 2010-2011

IVCC
COMBATING INSECT BORNE DISEASE

Contents:



The IVCC is a Product Development Partnership (PDP) established as a non profit company and registered charity. We are committed to the development of new insecticides for public health, vector control, information systems and tools to enable new and existing pesticides to be used more effectively.

Vector control has been a cornerstone of every effective campaign against malaria and dengue. These interventions are under threat from the emergence and spread of insecticide resistance and limitations in the ways that insecticides are used. As more elimination campaigns are funded, the need to improve the effectiveness and affordability of vector control increases. Our mission is to improve health by enabling partnerships for the accelerated development and delivery of new products that increase the effectiveness and efficiency of the control of insects that transmit disease.

Front cover: The Zanzibar Malaria Control Programme entomologists search for mosquito larvae in temporary breeding sites caused by the rains in Pemba Island, Zanzibar, May 2011.

Chairman's Foreword

It is encouraging that the IVCC now has concrete achievements which demonstrate the validity of the model which the founding consortium members and the founding funder, the Bill and Melinda Gates Foundation, had in mind when the original research consortium was set up. This research consortium evolved into the IVCC, established as an independent body in 2008.

On the Public Health Product side there are now two reformulated compounds which overcome forms of mosquito resistance to current products which have passed through the proof of concept phase and are now undergoing evaluation by the World Health Organization Pesticide Evaluation Scheme (WHOPES). While not yet fully approved, this means that already two product partnerships initially supported by the IVCC have reached the point that a commercial organisation is prepared to progress them entirely on their own account. These are just the first two; others are close behind. A little further behind those are two new products which show real promise of becoming the forerunners of new classes of insecticide, a more elusive goal which now looks as though it will be achievable. The partnerships have expanded rapidly and there are now agreements in place with most of the major commercial organisations working in the field which give access to libraries of tens of millions of compounds which have been synthesised by these organisations and their forerunners over decades.

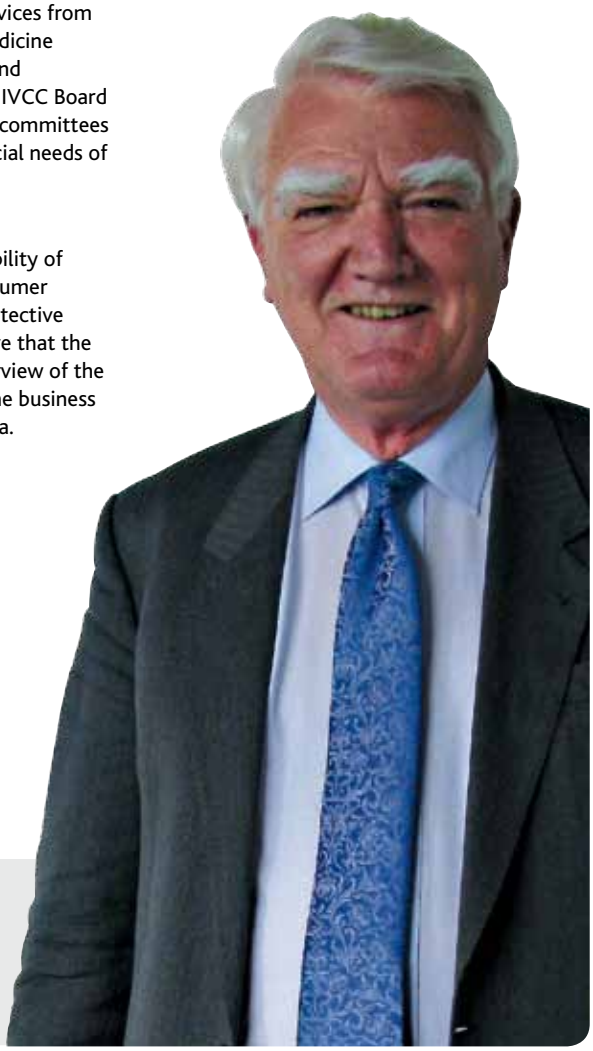
Perhaps equally important, the IVCC has developed practical software which will allow the easy monitoring of the effectiveness of campaigns against various diseases borne by insects. This is now ready for roll out. Field test kits have also been developed which can be used to check the state of treated nets. Millions of such nets have been distributed by many organisations over the past few years. It is critical to have a practical field means to inform decisions on the replacement of these nets when they have lost effectiveness.

It is equally encouraging that the IVCC is now expanding its reach and developing new areas of collaboration and operation such as the very important agreement with the Saudi Arabian Ministry of Health.

The Board consists of a mixture of members with experience and expertise in the field of insect vector control and those whose background, like mine, is essentially in business. While the detailed work is done by the all-important Scientific Advisory Committees of subject experts, the Board can assist in taking a wider view of potentially fruitful avenues. At the same time we have the fiduciary responsibility of ensuring that donor funds are well managed and that all the necessary systems are in place. While for reasons of efficiency we rely on services from the Liverpool School of Tropical Medicine (LSTM) for the delivery of finance and personnel support, members of the IVCC Board also serve on the audit and finance committees of the LSTM to ensure that the special needs of the IVCC are covered.

As the IVCC works with consumer organisations on the exciting possibility of development of products with consumer appeal while delivering a health protective advantage, we are working to ensure that the Board is well placed to provide overview of the combination of the scientific and the business side which is so essential in this area.

Sir Mark Moody Stuart,
Chairman, IVCC



The IVCC has developed practical software which will allow the easy monitoring of the effectiveness of campaigns in various diseases borne by insects.

Chief Executive Officer's Report

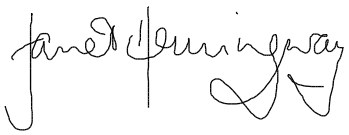
As the IVCC starts the second 5-year cycle of funding amounting to US$50m (£31m) from the Bill and Melinda Gates Foundation, a number of major events have emphasised the need for such a vector control product development partnership.

As malaria control efforts have been ramped up throughout much of Africa, the disease burden has been reduced. However, a predictable but unwanted side effect of this is the rapid increase of pyrethroid resistance in the two most serious African mosquito vectors. The situation with resistance is now sufficiently critical for WHO to convene an international oversight group to advise on the appropriate response.

The first products supported by IVCC came into operational use in 2011. Both products are likely to have a significant impact on monitoring and managing pyrethroid resistance. The Malaria Decision Support System is being adopted by the malaria control programmes in Bioko and Equatorial Guinea, and the entomological modules of the programme are being used to co-ordinate resistance management efforts in Zambia. The choice of alternative insecticides for indoor residual spraying will also increase in 2011 with the first of the IVCC supported long lasting non-pyrethroid IRS formulations being brought to market.

Meanwhile the scope and reach of the IVCC has expanded, with an expert group convened to establish the parameters for testing new vector control paradigms, and funding from DfID to assess up to four new interventions against mosquito vectors in South East Asia that predominantly feed and rest outdoors.

Translation of the decision support system into Arabic is also underway, supported by a major new initiative spearheaded by the Saudi Arabian Ministry of Health. Taken together, the IVCC portfolio of vector control products is well positioned to make a major contribution to ensuring that vector control efforts can be sustained and continue to play a vital role in the fight against malaria and vector-borne diseases.



Professor Janet Hemingway,
Chief Executive Officer, IVCC

IVCC has received $50 million from the Bill & Melinda Gates Foundation to continue its work to develop new insecticides for the improved control of mosquitoes and other insects which transmit malaria, dengue and other neglected tropical diseases.

Joint Centre for Infectious Disease Research

A new research venture with Saudi Arabia aims to advance the global response to infectious diseases.

Signing Ceremony, Left to right: Dr Amir Hassan, LSTM; Professor Janet Hemingway, Director LSTM; Professor Ziad Memish, Assistant Deputy Minister of Health, Kingdom of Saudi Arabia; HRH Prince Mohammed bin Nawaf Al Saud, Ambassador of the Kingdom of Saudi Arabia; HRH The Princess Royal, LSTM Patron; HE Dr Abdullah Bin Abdul Aziz Al Rabeeah, Minister of Health, Kingdom of Saudi Arabia; Mr James Ross OBE, LSTM Chairman; Dr Tom McLean, Chief Operating Officer, IVCC; Sir Richard Evans, LSTM President.

The Ministry of Health of the Kingdom of Saudi Arabia, the Liverpool School of Tropical Medicine and the IVCC have launched a new venture to significantly increase global efforts to control major infectious diseases such as malaria and dengue.

Led by the Ministry of Health, the partners aim to raise an additional $21.5 million to fund infrastructure, education programmes and further research activities. This initial four year agreement is viewed by the partners as being the beginning of a long-term mutually beneficial collaboration and is anticipated to continue beyond 2015.

Dr. Abdullah Bin Abdul Aziz Al Rabeeah, Minister of Health for Saudi Arabia, was presented with the Mary Kingsley Medal, the highest award which LSTM can bestow, in recognition of the Minister's outstanding contributions to medicine through his expertise in the separation of conjoined twins and in recognition of his vision in facilitating the establishment of the new Centre. His Excellency states "our vision is to develop the Joint Research Centre as a regional centre of excellence where we have a pool of world-class scientists. Science, technology and education have always been considered as key for the growth and prosperity of our Kingdom and our hope is that this partnership will also produce a step change in our ability to fight and eliminate deadly diseases in our region and around the world."

LSTM Director and CEO of IVCC, Professor Janet Hemingway, added that the Joint Centre will rapidly establish an international standard research portfolio by utilising the strengths in Liverpool and from within the IVCC to seed the Joint Centre. The Centre will also support capacity development at PhD, Masters and short course level to expand the cadre of qualified staff that the Centre can draw on.

"We applaud the commitment and vision of the Saudi Ministry of Health," said Professor Hemingway. "The Centre will not only be a research institute of the highest international standard, it will push forward the frontiers of science in order to make an important contribution to global health. We look forward to helping to nurture talents from the region and learn from their experience and knowledge."

The three main objectives of the Joint Centre are:

I. Institutional development and capacity building

II. Training of health and science professionals

III. Cutting-edge translational and operational research

With $5.5 million seed funding from the Ministry of Health of the Kingdom of Saudi Arabia, the three organisations have established a Joint Research Centre with a mission to improve health through cutting-edge research that will deliver innovative ways to control, monitor and evaluate insect borne diseases that pose a major threat in the Gulf region and around the world. As part of a larger effort to build national and regional capacity in science and technology, this Centre will be based in Jizan, Saudi Arabia.

The first phase of the joint venture will start immediately with the recruitment and training of professional staff and development of a cutting-edge laboratory facility in Jizan; the first major joint project will be to develop an Arabic version of the Malaria Decision Support System for the Arab speaking world. This platform will subsequently be extended to dengue and other vector-borne diseases.

IVCC Product Roadmap

Tom McLean answers questions about future challenges for IVCC

What are the key demands the IVCC may face in the next year?

Over the last year we have taken on a number of the challenges whose resolution is essential if we are to deliver the roadmap. Firstly, we have broadened our scope to include new categories and paradigms in vector control, as well as our work in insecticides and information systems and tools. Secondly, we have taken on a series of tasks around external relations, supporting policy development and resistance management strategy for the vector control community. Expanding an organisation like this to take on the new tasks needed to deliver the roadmap is always a challenge in that we need to fill some rather unusual roles with highly talented people.

Looking beyond that expansion, the new challenge will be to ensure that we achieve the right balance in the work that we do to smooth the path for introduction of new products and paradigms. Access has been a controversial topic for many product development partnerships and we will need to identify the roles in which an independent voice like IVCC can make a real difference in supporting policy, funding strategy and capacity development without trying to take on the whole task ourselves. Events like the IVCC stakeholder forum allow us to engage with the wider community.

Is funding still a primary concern for the IVCC?

We are grateful that a number of funding events in the last year have secured the next immediate stages of IVCC. However, we still need to continue to bring on new funders to secure the future of the IVCC, and to broaden the scope of new funding. The really important events from the last year have been the renewal of the Bill and Melinda Gates grant, which we feel is a great affirmation of what we delivered against our targets in the first five years of the IVCC. The recent venture with the Kingdom of Saudi Arabia's Ministry of Health has also provided another key supporter for IVCC. We would like to give recognition to a number of other funders such as the Department for International Development, Comic Relief and the European Union. A recent report from PolicyCures indicates that vector control R&D funding needs to increase by a factor of 3 in order to meet the RBM global malaria action plan. The key challenge continues to be finding donors who are enthusiastic to fund insecticide development.

Tom McLean,
Chief Operating Officer, IVCC

The IVCC Roadmap details the major vector control products that will be needed in the market in the next decade. Without these malaria elimination will not be possible.

New Active Ingredients (AIs)

IVCC's long term objectives call for the creation of three new active ingredients that are unaffected by current resistance mechanisms by 2020. The portfolio to achieve that outcome requires three major screening and development programmes supported by two screening programmes to account for the high risk of attrition in the lead programmes. With the projects now actively running and in the late stages of contract development this portfolio is now complete and further screening opportunities will be held in reserve in case of excess attrition. Following considerable success in the screening phases, the focus of these projects is shifting towards development of the hits.

Formulations and Re-purposing

The two key formulation projects initiated in 2007 for long lasting indoor residual sprays have successfully completed their development phase and are now progressing through the regulatory phases. Field trials of these formulations has highlighted the necessity for such products. Further trials of insecticide combinations which will mitigate the effects of pyrethroid resistance are underway. These are expected to lead to projects yielding products in 2016 that will bring alternative agricultural insecticides to bear on the vector control market.

New Paradigms Product Categories and Target Product Profiles (TPP) for Vector Control

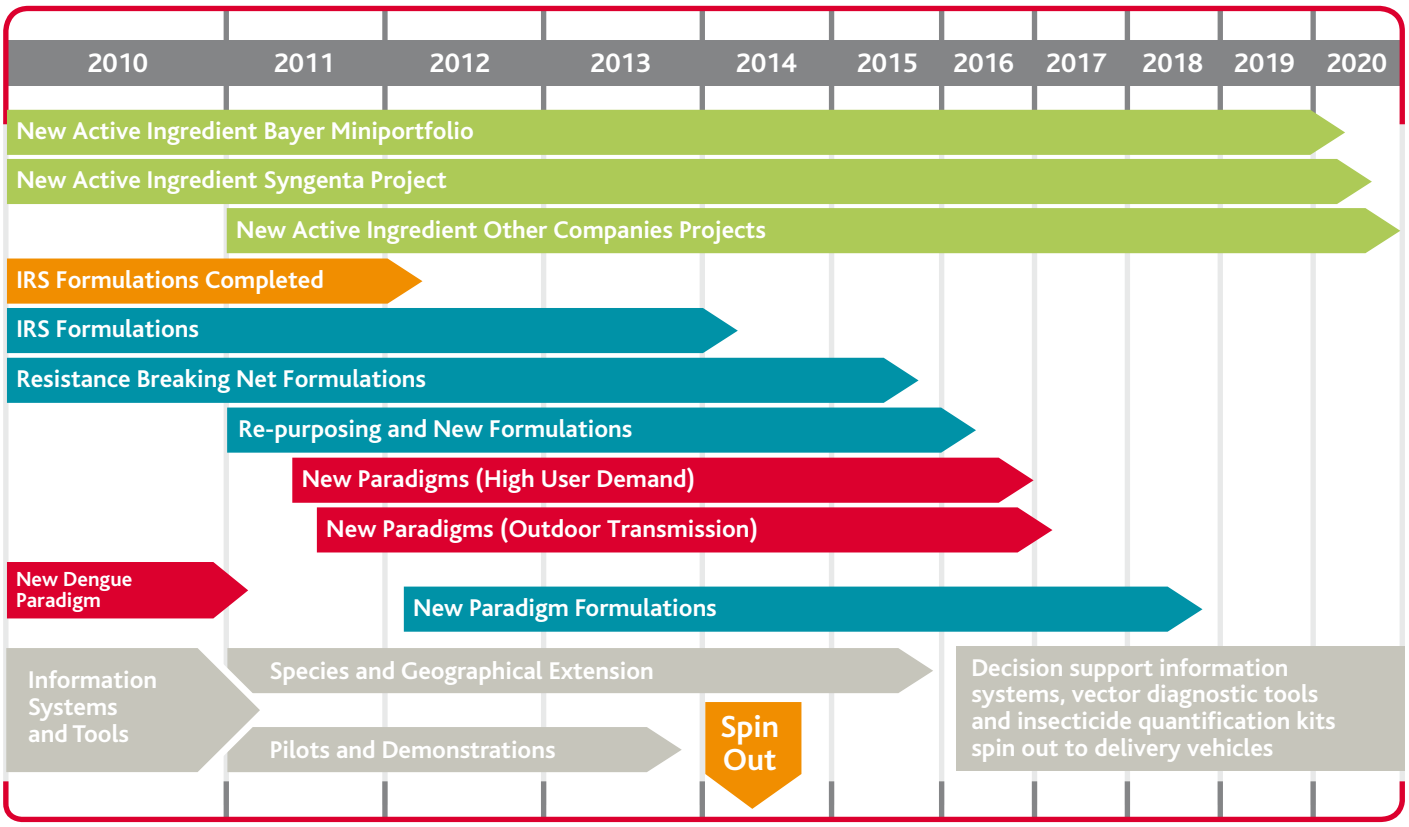
In collaboration with the Framework 7 funded AvecNet programme, work has begun on screening of potential new paradigms and product categories with the intention of taking the most successful of them to large scale randomised controlled trials. Further work on identifying new paradigm opportunities has been funded by DfID in Cambodia. A coherent, efficient process for the validation and adoption of new paradigms and product categories has been designed by a group of experts in the field spanning epidemiological and entomological expertise with economic, industrial, policy and user perspectives. Broader consultation on this process will bring it into wider acceptance. The crucial outcome of all these studies is to ensure that Target Product Profiles are created that will lead to whole classes of new products developed by industry.

Information Systems and Tools

The IVCC projects in information systems and tools have reached their targets for the first phase, creating a functional Decision Support System for malaria, with the dengue version close behind, and the technologies for insecticide quantification ready for implementation as commercial kits. Key current activities for both these tools are pilot trials to demonstrate the impact that they have on disease control programmes when used in the field. The vector population monitoring tools are widely disseminated and numbers of users of those tools continues to grow.

IVCC Strategic Roadmap

We have broadened our scope to include new categories and paradigms in vector control, as well as our work in insecticides and information systems and tools.



Recent progress and the challenges ahead

Major Product Development events

- Key Formulation Projects with Syngenta and Bayer successfully complete development stage, and enter regulatory phase.
- New Active Ingredient screening shows promising progress confirming the potential of the chemical libraries of our major partners.
- Successful pilot trials of insecticide quantification kits in Vanuatu and Malawi show that they can be used in the field.
- Malaria Decision Support System completed and going into pilot trial

(Details of these and other projects can be found in the project sections)

Renewal and Diversification of the funding portfolio

- Bill and Melinda Gates Foundation Awards IVCC $50 million second round funding for new Active Ingredients, Formulations and New Paradigms in Vector Control.
- Saudi Arabia Ministry of Health, Liverpool School of Tropical Medicine and IVCC Research Centre for Infectious Diseases focuses research on information systems and tools.
- European Union Framework 7 €12 million AvecNet project to validate new paradigms in vector control.
- DfID grant of £1.2 million to IVCC to assess new paradigms in vector control as part of the campaign to control artemisinin resistance in Cambodia.

(Details of these funding events can be found in the finance section)

Syngenta: A personal perspective

We are actively seeking additional new collaborative ideas and thus in many ways the IVCC partnership has become a core partner in Syngenta's product development process for vector control.

Andy Bywater is project leader for Syngenta's collaboration with IVCC in establishing a long-lasting non-pyrethroid IRS Formulation. Here he gives us his personal insight into the inner workings of the Actellic CS project.

Given Syngenta's long experience with the vector control market and our relationship with customers and programmes, it was apparent that resistance to pyrethroids was becoming a serious issue. Hence, there was clearly a growing opportunity for alternatives to pyrethroids but the current state of the art technology was not providing the long lasting residual performance which customers wanted.

We believed we could improve upon existing products by leveraging our experience with the long lasting Icon®10CS formulation, which utilises micro-encapsulation technology to lengthen residual effect. The active ingredient in Actellic®300CS, pirimiphos-methyl, was chosen because it offers a non-pyrethroid option to the IRS tool set with the ability to overcome the resistance mechanisms occurring in vector mosquitoes.

The development of Actellic 300CS within Syngenta was initiated prior to the involvement of the IVCC. However, we felt that an opportunity existed to accelerate the product development via support from the IVCC. The IVCC provided valuable access to field trials alongside technical advice from the ESAC, both of which played a vital role in the development of this product.

Syngenta led all the product development activities including formulation design and testing, safety studies, laboratory screening and the preparation of the registration dossier in addition to conducting our own field trials. This development activity is typical of any new formulation project within Syngenta but in this case complemented by IVCC involvement.

The major challenge was the development of a stable formulation which also delivered long lasting activity via encapsulation. The pirimiphos-methyl active ingredient is particularly difficult to encapsulate and can be degraded by a number of the processes used in formulation production. In addition, not all micro-encapsulated formulations are the same and there are many design options that need to be balanced to achieve the optimum performance and safety required by the customer.

However, following the intensive efforts of our formulation chemists and a multi-disciplinary team, we now have a stable formulation that has been shown to deliver long lasting control of pyrethroid resistant mosquitoes in the field.

Actellic 300CS provides the vector control community with a new long-lasting tool for use in IRS and will deliver an opportunity for the management of insecticide resistant mosquitoes. In addition, the long lasting efficacy means that programmes will have the benefit of fewer applications so application and material costs are reduced. We see this product as highly complementary to existing pyrethroid products for IRS and nets and therefore expands the toolbox available to programme managers as they develop integrated vector management strategies.

For Syngenta, Actellic 300CS adds a highly complementary product to the range which enables us to meet our commitment of contributing to the health and quality of life of the communities in which we work. The success with this project to date has assisted the initiation of other key collaborations such as our new insecticide research project with the IVCC.

There are two key tasks that are currently ongoing. Firstly, we are in the process of submitting the registration dossier for Actellic 300CS to the appropriate regulatory authorities in countries across Africa. The timeline for registrations is country specific but we expect registrations to begin to be granted during 2011.

In addition, we will also have to complete the WHOPES evaluation of Actellic 300CS. Phase II trials are currently underway in Asia-Pacific and Africa to complement the field data that we already have available from the IVCC and other WHO collaborating centres.

Following completion of Quality Assurance testing, we anticipate that Actellic 300CS will be available in Africa during the last quarter of 2011. A broad registration plan is underway to ensure the product is available at the earliest opportunity in African territories and in parallel registrations which will be initiated in Latin America and Asia Pacific. The precise dates of local availability will vary according to local registration timelines.

I would consider Actellic CS to be a good example of product development. We are particularly proud of the customer and stakeholder engagement at the beginning of the project which helped shape the early concepts and design of Actellic CS. And whilst we had some considerable technical challenges, those early inputs have resulted in a final product delivered by a committed and innovative multidisciplinary Syngenta team. Overall, the project has been a great team effort and we see this continuing as additional partners come on board to help accelerate the availability of the product in the disease endemic countries.

Syngenta is committed to providing innovative customer solutions and involving stakeholders in key activities within the product development process. The IVCC has proven to be a complementary, engaged and enthusiastic partner in this process and we are pleased to have been involved from the early days of the Consortium. One measure of success is that we have already extended our relationship with the IVCC by committing to extend our insecticide research collaboration into its second phase. We are actively seeking additional new collaborative ideas and thus in many ways the IVCC partnership has become a core partner in Syngenta's product development process for vector control.

Andy Bywater,
Project Leader
Syngenta

Actellic®300CS provides the vector control community with a new long-lasting tool for use in IRS and will deliver an opportunity for the management of insecticide resistant mosquitoes.

Bayer CropScience: A personal perspective

Arnd Voerste is a project manager working for Bayer CropScience and is playing a pivotal role in the exploration of new active ingredients in conjunction with the IVCC. Here he describes the project he is involved in; a typical day in the life of a Bayer CropScience project manager; the highs and lows, and the impact of his and Bayer's work on a humanitarian level, as well as what the future has in store for Vector Control.

For more than 50 years Bayer CropScience has participated in the fight against vector-borne diseases. Through our business operation Bayer Environmental Science we provide a unique portfolio of product solutions to combat diseases such as malaria, dengue, leishmaniasis, sleeping sickness and Chagas disease and we are committed to invest significantly into R&D partnerships with organisations such as the IVCC.

The Bayer & IVCC Product Portfolio

Currently we are running several projects together with the IVCC. These include the development of innovative LLIRS formulations for known insecticides and the search for completely new active ingredients with new modes of action. Personally, I am project manager for the latter, our New Public Health Insecticides Discovery Platform [PHI].

In this PHI project, we have established a dedicated team of Bayer CropScience experts working on the discovery of a new public health insecticide for malaria vector control. Our target is to identify new classes of insecticides with new modes of action, to serve as tools for the management of insect pests in the face of upcoming resistance problems with established products. It is a great honour for me personally to be responsible for such a task.

In 2009, we started the project at Bayer CropScience by building completely new laboratories to house the project activities and by recruiting new scientists to run the PHI tasks. A new mosquito screening cascade had then to be established to cope with the large number of compounds which we wanted to investigate. In order to address the issue of resistance in malaria vector control, different resistant mosquito strains had to be acquired, reared and their resistance mechanisms characterised using biochemical, molecular and electrophysiological methods. It was already an exciting time with a unique opportunity to build something new from scratch together with my team.

More than one million compounds from our Bayer CropScience substance library have since been tested against mosquitoes using a high throughput screening approach. The identified hits have been further assessed in advanced biological test systems and are now being structurally optimised by our chemists. We are very happy that our approach has already delivered several new hit classes with promising efficacy levels, which are currently undergoing further improvement.

A Personal Perspective

My own role in our PHI project is the co-ordination of activities and communication with the IVCC. Further administrative work like reporting and budgeting also belongs to this job. Strategies and plans are regularly discussed in our interdisciplinary team, results and achievements are shared and many new ideas are generated on these occasions. The major research work for this project is, of course, done by the team members during their day-to-day tasks in the different laboratories.

Since I have further tasks in my position as Head of our Insecticides Screening & Entomology Group at Bayer CropScience, there is seldom such a thing as a "typical PHI-day" in this job. Some days are however devoted entirely to the PHI project, when all the new results are brought together on a quarterly basis in order to discuss our progress jointly with the IVCC and members of the ESAC. Everybody then contributes their piece to the puzzle to come closer to our final target and we receive great support from IVCC and ESAC. I am very happy to have such a dedicated team that is eager to present something new on every occasion. There is hardly a meeting without some exciting news or significant step forward.

At the same time, I try never to forget that setbacks are also something one has to be able to cope with in research work. It was hard when we had to terminate our IVCC co-operation on modified insecticides in March, a project I had also been responsible for since 2008. The PHI project in its first year has so far run very successfully and real frustration has never come up yet. But, of course, progress is never as fast as one may have hoped for. Setbacks, like the need to terminate a hit class, have to be expected, and patience is a very important attribute.

The Role of IVCC

We have experienced tremendous support from the IVCC to smooth our way towards finding an innovative public health insecticide for the fight against malaria. As a team we have set ourselves challenging goals. We target only fast acting molecules with rapid "knock-down" activity against mosquitoes, we do not accept unwanted modes of action or those already threatened by resistance and we search only for new products meeting stringent safety standards. This takes time, but I am convinced that this approach is worthwhile and that it will result in finding a sound solution for malarial vector control.

For me personally, the best thing about working on such a project is to experience the high acceptance and dedication that the topic of fighting malaria commands. There is also the team which started work enthusiastically

Arnd Voerste,
Project Manager
Bayer CropScience

Our target is to identify new classes of insecticides with new modes of action, I am very happy to have such a dedicated team which is eager to present something new on every occasion.

Bayer CropScience

Science For A Better Life

once the project agreement had been signed, and it is a great joy to be part of it. But there is also the support and interest of others in our company, especially in Research. Assets, capacities and know-how have been donated to the project because people are convinced that we are doing the right thing to contribute to sustainable development in some of today's poorest countries.

Natural sciences for me are a powerful toolbox able to create products and solutions for all kinds of problems. In the PHI project team, we brought the different scientific disciplines together to work on a great target. With its potential for directly improving the living conditions of millions of people throughout the world and for saving lives one day, the PHI project work is one of the most exciting applications of natural sciences that I have been involved in.

The Bigger Picture

Of course, we are only contributing a tiny piece to the whole solution, and many other people, companies and organisations are dedicated to the fight against malaria. This challenge with its direct effect on people's lives is really creating a special dedication which is driving our work forward and I can sense this spirit every day in my team.

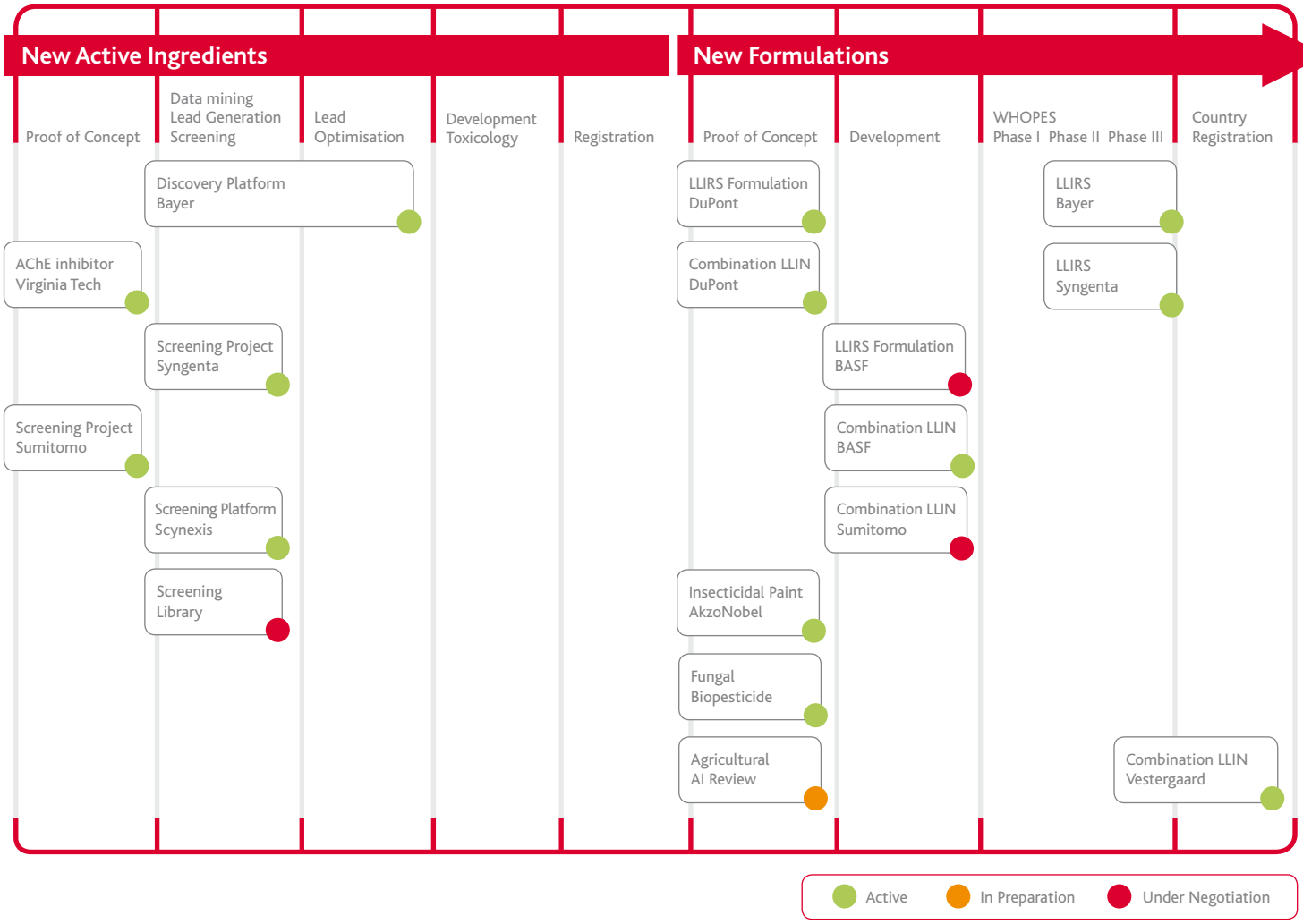
Another great thing for me in this project is that I got to know the international community of vector control experts of IVCC; ESAC and Bayer CropScience and learned a lot from them about malaria control. Members of the IVCC and the ESAC, especially Robert Sloss, Colin Ruscoe and Trevor Perrior, have become valuable and highly appreciated partners of our project. Only through our PHI project have the doors to this exciting community been opened for me and I know that this network of contacts will remain in place even beyond the time-frame of this project. I am also sure that I, personally, will keep a special connection to the topic of malaria vector control, and will follow up developments in the field even after completion of my projects.

Our project so far comprises the early discovery phase, and once this has been completed successfully I hope that we can move to the next phase with selected compounds. We are also currently assessing further options for public-private-partnerships at Bayer CropScience and I would be happy if such novel approaches would open up new opportunities for me to continue my work in the world of vector control.

IVCC Public Health Insecticides Portfolio

The IVCC now has a healthy portfolio of projects with major industrial partners, with a number of new projects under negotiation.

Our current portfolio:



Active Ingredient Projects

Project leader: Steve Ward, Liverpool School of Tropical Medicine (LSTM)
Partners: Bayer, LSTM, University of Liverpool
Contact: robert.sloss@liv.ac.uk

Resistance Breaking Insecticides:

This project focused on the synthesis and development of a novel insecticide based on a known insecticide backbone with the potential to control malaria vectors and crop pests, including those with an acquired cytochrome P450 dependent (monooxygenase based) resistance mechanism. The project used novel chemistry and approaches that were patented by the industrial partner. Utilising a known insecticide backbone as a starting template increased the probability of producing molecules with appropriate development characteristics and ensured that the new insecticide could be produced using existing plant capacity, thereby potentially reducing the cost of development and production.

In the first phase of the project, 200 lead compounds were synthesised and activity was demonstrated against resistant strains of mosquito for some of these compounds. The most active compounds were optimised and taken through further secondary screening programmes with a range of agricultural pests as well as continued screening against resistant and susceptible mosquito strains to select candidates for development.

The project was completed in December 2010. The IVCC concluded, following a recommendation from the External Scientific Advisory Committee, that whilst compounds were produced that showed enhanced activity against resistant mosquito strains with the oxidase resistance mechanism, the level of enhanced activity was not high enough to justify taking the project forward in competition with other leads. The project did deliver some novel chemistry and did prove the hypothesis that it was possible to synthesise new compounds in this class of chemistry that show improved activity against oxidase resistant mosquito strains.

Project leader:
Arnd Voerste, Bayer
Partners: Bayer, Medical Research Council SA, LSTM, London School of Hygiene and Tropical Medicine (LSHTM)
Contact: robert.sloss@liv.ac.uk

Bayer Public Health Insecticides Discovery Platform:

This project is focused on the discovery of at least one novel contact insecticide class, with a novel mode of action, and the potential to control malaria vectors. The new molecules are screened to ensure that they will not be affected by known resistance mechanisms in order to help mosquito control programmes manage resistance issues. The project is making use of Bayer's historic chemical library to generate potential leads in order to develop totally new active ingredients for vector control insecticide products.

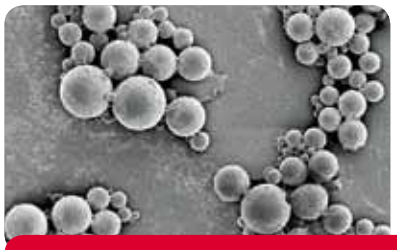
The project involves researching the chemical library for potential vector control insecticides using any data that has already been collected to identify compounds that may have activity against mosquitoes. The compounds that have been selected have then been screened for activity against mosquitoes and their mode of action determined. The most interesting compounds from the initial screening programmes will be used to direct analogue synthesis to optimise the activity of a class of chemistry against adult mosquitoes whilst minimising the potential toxicity.

The aim for the end of this project is the identification of field candidates with the potential to match the IVCC Target Product Profile for a new insecticide active ingredient. Final optimisation of selected candidates according to the IVCC TPP requirements in terms of activity profile, mode of action, safety/toxicity profile, scale-up potential and predicted cost of goods will then be the subject of a subsequent project.

The initial 3 year project began in September 2009. Several interesting classes of chemistry have already been identified. This project is the first phase in the development of a new active ingredient for vector control that will take approximately 10 years to deliver a product to the market.

Actellic®300CS, has demonstrated effective control of pyrethroid resistant mosquitoes on treated construction materials for more than eight months.

Active Ingredient Projects cont.



Project leader:
Andy Bywater, Syngenta
Partners: Syngenta, LSHTM
Contact: robert.sloss@liv.ac.uk

Syngenta Vector Control New Active Ingredient Screening Project:

This project was aimed at identifying one or more lead areas of novel chemistry free from cross-resistance to existing chemistries used for adult mosquito control and which are suitable for optimisation and potential development into products for the control of adult mosquitoes via appropriate delivery systems.

The project involved reviewing the available data from Syngenta's historic chemical collection and existing insecticide development projects to select compounds and classes of chemistry that have potential as vector control insecticides without any potential toxicological issues. A total of 23,000 compounds were selected for screening. These compounds were subsequently screened in a novel adult mosquito assay, developed for this project by Syngenta, to produce a portfolio of compounds and chemical class hits to be reviewed as potential areas of chemistry to optimise in a later project.

Fourteen percent of the compounds screened had activity against adult mosquitoes and a number had high levels of activity (i.e. a complete kill at 0.2ppm). Some of these highly activity compounds were from well scoped areas of insecticide chemistry while others are novel areas of chemistry.

The project has identified a wide range of contact active insecticidal chemistry. Within this there are chemical classes which possess:

- The potential to achieve cost-effective control of adult mosquitoes at viable application rates
- Distinct modes of action to current vector control products
- Molecules that are not susceptible to current resistance mechanisms
- Indicated acceptable toxicological and environmental properties

Syngenta have now instigated a project with IVCC to take these to the next phase; to chemically optimise the leads areas in order to identify a product for full development and commercialisation.

Project leader: Terry Marquardt
Partners: Scynexis, IVCC
Contact: robert.sloss@liv.ac.uk

SCYNEXIS New Active Ingredient Screening Project:

This project started in January 2011 and aimed at identifying one or more lead areas of chemistry with a novel mode of action, unaffected by insecticide resistance mechanisms found in mosquitoes, and with potential for optimisation and developing into vector control insecticides.

SCYNEXIS screened their collection of 75,000 compounds in a larvicide assay to select compounds for subsequent screening in adult mosquito assays against multiple species. The hit compounds from the initial adult screens were then screened against resistant strains in SCYNEXIS and in the resistant mosquito reference laboratory at the Liverpool School of Tropical Medicine.

The project was completed in July 2011. A number of hit compounds were generated but none of them showed high enough activity to take into the chemical optimisation phase.

New Active Ingredient – Proof of Concept Projects

A third company has completed a successful proof of concept screening project in which they reviewed their chemical library and screened up to 1,000 compounds from several different chemical classes against adult mosquitoes. The hit rate has been promising and we plan to agree on a full project with the company in 2011.

Virginia Tech have completed a proof of concept study to demonstrate contact toxicity of novel bivalent carbamates against susceptible and carbamate resistant strains of mosquitoes. The project did demonstrate *in vivo* activity of a bivalent carbamate against adult mosquitoes as well as some interesting results for some single site carbamates. The IVCC decided there was not enough evidence at this stage to justify supporting a full development programme in this area but the project is now being supported to the next stage by the National Institute of Health, USA.

New Active Ingredient – Projects in Development

Two other agrochemical companies have expressed initial interest in screening their chemical libraries for new vector control active ingredients. We are in late stage discussions with one of these companies to screen their chemical library for potential vector control insecticides. We expect this project to begin during 2012.

Formulation and Re-purposing Projects

Indoor Residual Sprays

Bayer Long Lasting Deltamethrin IRS Formulation:

The aim of this project was to develop a long lasting residual formulation for Indoor Residual Spraying (IRS) programmes to improve malaria vector control in disease endemic countries. The formulation uses proprietary technology to dissolve an active ingredient into a polymer. The concept is based on the idea that a polymer can be used as a barrier between an AI and an aggressive surface, to increase the probability of producing a long lasting residual formulation.

The new formulation will reduce the cost and logistical problems associated with IRS spraying in endemic countries. Long lasting formulations would allow a reduction in the number of application rounds per year, significantly decreasing the application cost. The reduction in cost achieved would reduce IRS treatments to similar operational costs as current insecticide treated material types of control. Deltamethrin was used as the AI to develop the first new formulation.

The formulation based on patented technology delivers a long lasting residual effect. In laboratory trials it has shown 12 months residual effect on concrete and wood surfaces and 9 months on mud surfaces. Experimental hut trials demonstrated up to 1 year residual activity can be achieved on thatch and concrete surfaces and up to 10 months residual activity can be achieved on mud surfaces.

Bayer took the decision to commercialise the formulation in March 2010, the dossier for the formulation was submitted to WHOPES in August 2010. The protocols for the WHOPES Phase 2 and 3 trials have been agreed, the Phase 2 trial will start in September 2011.

Syngenta Long Lasting Non Pyrethroid IRS Formulation:

The aim of this project was to develop a long lasting non-pyrethroid IRS spray formulation using proprietary technology to provide more than 6 months residual activity on all typical wall surfaces. The current level of residuality after indoor residual spraying of insecticides on house walls varies from one to six months for organophosphates, carbamates and pyrethroids and greater than six months for DDT. This necessitates varying frequency of repeat application in order to maintain protection of the population from malaria transmission. In addition, pyrethroid and DDT resistance is a major concern and increasing regulatory standards are driving the search for cost-effective alternatives to DDT.

In cases where carbamates or organophosphates are used for IRS, applications are typically made every three months which can lead to increased product and logistical costs compared to longer lasting products. Therefore, a non pyrethroid/DDT product lasting six months or more offers a practical new tool for cost-effective IRS and an opportunity to replace DDT.

To meet this challenge, Syngenta has developed a micro-encapsulated formulation of the World Health Organization Pesticide Evaluation Scheme (WHOPES) approved active ingredient, pirimiphos-methyl. In field evaluations by Syngenta and IVCC partner laboratories in Switzerland and Africa, the formulation known as Actellic®300CS, has demonstrated effective control of pyrethroid resistant mosquitoes on treated construction materials for more than eight months.

Syngenta are in the process of commercialising this formulation and it is currently being evaluated by the WHOPES. The first commercial sales of the product are anticipated in late 2011.

Bayer has developed a deltamethrin formulation based on patented technology to deliver a long lasting residual effect.

Formulation and Re-purposing cont.

Insecticide Treated Net Projects

Vestergaard Fransen "Resistance Breaking" LLIN:

Vestergaard Fransen has developed a pyrethroid based long lasting net aimed at maintaining its efficacy in areas where oxidase-based pyrethroid resistance is high. The IVCC has designed community-based trials aimed at showing whether this product has a significant impact in areas where different pyrethroid resistances are prevalent. Suitable sites in Cameroon and Côte D'Ivoire were selected and used for these trials and the entomological field work has been completed.

The data from the trials is currently being statistically analysed and the resistance status of the mosquito population is being characterised.

BASF LLIN for Resistance Management:

BASF is planning to develop a novel LLIN based on chlorfenapyr for protection against resistant and susceptible mosquitoes and to help with resistance management. This product has the potential to add a new active ingredient for use in nets to combat concerns about the increasing reports of insecticide from the field.

The project will involve the development of LLIN prototypes that will be tested in the laboratory and the best prototypes will then be tested in experimental huts to confirm the activity against field mosquito strain.

The final product is planned to be available for WHOPES evaluation in 2013.

Formulation and Re-purposing – Proof of Concept Projects

The IVCC has demonstrated that chlorfenapyr has the potential to be developed for IRS and in particular is effective against known insecticide resistant strains. BASF and the IVCC have been working on a full development project which will start in 2011.

The IVCC has tested two DuPont agricultural insecticides for their potential to be used as IRS and LLIN insecticides. These insecticides have different modes of action to those currently used in vector control. Both of these insecticides have shown some potential as vector control IRS and ITN insecticides and we are currently discussing a possible full project with DuPont.

The IVCC has completed another proof of concept study looking at alternatives to pyrethroids for ITNs. This project has produced some interesting and positive initial results and we are discussing a potential full project with the industrial partner.

A proof of concept project with Akzo Nobel has been completed which shows that modern surface coatings technology has the potential to be used to deliver long lasting insecticidal formulations (2-5 years residual activity). It will also be possible to use these paint formulations for resistance management as non-pyrethroid insecticides can be formulated in the paint. The IVCC is currently working with Akzo Nobel to develop a full proposal to develop these paints.

The IVCC has worked on a proof of concept project with Pennsylvania State University to evaluate the potential to use fungal biopesticides in IRS formulations. The study tested both the residuality of the fungal biopesticide formulations and the temperature stability of the fungus in sub-Saharan African conditions. The results were not sufficiently promising to move this to a full project.

Information Systems and Tools

To effectively control insect vectors of disease, policy makers and programme managers must have the information that allows them to choose the right control strategy for each situation. To achieve this, the IVCC is developing a range of systems and tools to support decision making in vector control programmes.

It is now widely accepted that vector control can be highly effective in reducing the burden of diseases like malaria and dengue. In fact in some cases, vector control is the only intervention proven to reduce disease levels. Effective planning, quality assurance (QA) and monitoring and evaluation are vital to ensuring that vector control measures achieve their full potential impact; and in large-scale intervention campaigns carried out in inhospitable environments, this can be a major challenge.

To help ensure that policy makers and programme managers have the information they need to plan and implement effective control strategies, the IVCC is developing a range of systems and tools to support planning, information management, decision making and QA. Many of these developments are now moving into the field, and will be on the market within the next couple of years.

At the core of our development programme are Decision Support Systems for malaria and dengue. Operated through a user-friendly computer based multi-disease interface (the DDMS), our Decision Support Systems hold a range of relevant data, which can be presented in easy to interpret graphical and map-based outputs. This helps policy makers and programme managers ensure that resources are used most effectively. We have also developed modelling software to help programme managers forecast the spread and growth of the insect vectors that spread dengue and the likely rates of disease development.

To work effectively, these systems need good quality, timely information. Part of our development work therefore has been to develop systems for the collection of field data and the integration of data already available. Accurate data on insecticide resistance and its underlying causes is one example of the information that control managers need to maintain the effectiveness of their campaigns. The IVCC's Vector Population Monitoring Tool project is developing kits that can be used in disease endemic regions for monitoring resistance and to determine its underlying molecular basis. These kits will also allow programme managers to quickly identify the vector species present and the diseases they are carrying.

To maintain high QA standards in IRS campaigns and in insecticide treated bednets and materials, the IVCC is supporting the development of a further range of test kits. The Insecticide Quantification Kit project provides a quick, simple and affordable means of measuring insecticide concentration, allowing programme managers to ensure that treated surfaces, bednets and other treated materials continue to provide the protection needed.

Information Systems and Tools cont.

Project Leader: Martin Donnelly, LSTM
Partners: Colorado State University (CSU), Rothamsted Research, Agricultural University of Athens (AUA)
Contact: m.j.donnelly@liv.ac.uk

Vector Population Monitoring Tool (VPMT):

VPMT

Vector control programme managers need up-to-date information on mosquito populations to ensure that the interventions they plan are as effective as possible. Data on mosquito species, infection status and resistance to insecticides are vital elements in planning successful interventions. However, the current means of gathering this information is costly and inaccurate. Monitoring for each of these traits is currently performed using individual tests, some of which require sophisticated equipment and expensive consumables. Furthermore, these tests are not reliable for the detection of insecticide resistance at low levels.

The IVCC has supported the development of a molecular approach to insecticide resistance detection and characterisation. This allows the underlying mechanism of resistance to be ascertained from an initial field sample of mosquitoes. Although the initial characterisation needs to be undertaken in a sophisticated laboratory, resistance markers can be identified, which allow scientists in the disease endemic countries to use simple PCR assays to reliably ascertain the mosquito species, infection status (malaria positive or negative) and insecticide resistance status.

The protocols for initial resistance detection, SNPs for tracking known mechanisms or species characteristics and platforms to undertake field screening, have been published. The system has been used to characterise the growing levels of pyrethroid resistance in numerous African locations and is already impacting on operational control decisions. For example, pyrethroid resistance was first detected in the main malaria vectors in Malawi in 2009. Subsequent analysis of the resistant mosquitoes demonstrated that this was a metabolic mechanism similar to that which has caused operation failure of pyrethroids in neighbouring Mozambique. This information prompted a change of insecticide from pyrethroids to bendiocarb for the 2011 spray season in Malawi.

The approach has now been expended to cover Middle Eastern and Asian mosquito vectors, a task that will be facilitated by the sequencing of multiple mosquito genomes by NIH.

Project Leader: John Vontas
Partners: LSTM, LSHTM
Contact: vontas@imbb.forth.gr

Insecticide Quantification Kit (IQK):

IQK

Bednets and Indoor Residual Spraying (IRS) are major control measures in the fight against malaria and other diseases carried by insects.

Apart from carrying out logistically complex and unreliable bioassays in the field, the only way to check that protection is being provided by a spray or treatment intervention is to measure the actual amount of insecticide residue remaining.

Such information is also important for local manufacturers of bednets who are now moving into the production of more technically complex Long Lasting Insecticide Nets (LLINs). Currently, the level of insecticide has to be measured using gas chromatography or high performance liquid chromatography. These methods are expensive and technically demanding, requiring skilled staff and sophisticated laboratory and insectary facilities.

This project has produced simple, cost-effective and user-friendly kits for monitoring insecticide residues on insecticide-treated materials. We now have a pipeline of simple kits for a range of relevant insecticides (including pyrethroids, DDT and carbamates), which are in the final stage of development and are currently being field trialled in Africa, Asia and the Pacific region. Work is also continuing to broaden the usability of the test kits both in terms of application and products detected.

The Insecticide Quantification Kit project provides a quick, simple and affordable means of measuring insecticide concentration.

Project Leader:
Mike Coleman, LSTM
Partners: NMCPs Malawi, Mozambique & Zambia. LSTM, Colorado State University (CSU)
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Malaria Decision Support System (MDSS):

MDSS

The effective control of malaria within a region requires programme managers to have access to the most up-to-date information on the disease in order to best direct interventions against mosquitoes. The Malaria Decision Support System (MDSS) is a computer package that collates data on disease incidence, vector populations (including density and insecticide resistance) and intervention activities and presents this information in a web-based, real-time geographical format.

The MDSS was developed in collaboration with the national Malaria Control programmes in Malawi, Mozambique and Zambia to ensure that from the outset it was tailored to fit their operational needs.

The MDSS brings together all the key indicators needed for effective vector control into one bespoke system customised for the needs of the country or region. The ability to view the outcome of interventions in a number of environmental settings and differing operational challenges further increases the usefulness of the MDSS to programme managers looking to optimise their system. Sentinel sites have been established in Malawi, Mozambique and Zambia. This is combined with survey, clinic and spray data to provide the full data set needed for the operation of the system.

The MDSS IT infrastructure is based on a multi-disease platform that currently handles both dengue and malaria and will be expanded in the near future to include leishmaniasis and filariasis. The software is compatible with most Health Information Systems, allowing countries to use this to complement and enhance their current IT systems.

A partial implementation of MDSS is being used in Zambia and Malawi. A Spanish and Arabic version is also under development for implementation in Bioko, Equatorial Guinea and Saudi Arabia in 2011.

The MDSS was developed alongside, and wherever possible, in collaboration with initiatives from other key players including the Malaria Control and Evaluation Partnership in Africa (MACEPA), the President's Malaria Initiative, the Centre for Disease Control and Prevention and the World Health Organization.

Project Leader: Lars Eisen, Colorado State University (CSU)
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Dengue Decision Support System (DDSS):

DDSS

Dengue is the most common mosquito-borne viral disease in tropical and subtropical areas of the world. More than 50 million cases of dengue fever and several hundred thousand cases of the more severe dengue hemorrhagic fever are estimated to occur each year.

Because a vaccine against dengue virus is still lacking, control of the mosquito vector is the primary option for disease prevention and control. Currently employed vector control strategies have not, however, been adequate to combat dengue and novel tools and approaches are desperately needed.

One key aim of the Dengue Decision Support System (DDSS) project is to create, optimise and distribute a system which will provide up-to-date information on all aspects of mosquito vectors and dengue to enable control programme managers to implement, evaluate and refine locally appropriate disease prevention and control strategies.

The DDSS now provides capacity for collection, management and analysis of vector and dengue data in a standardised way. Data is displayed in intuitive formats (e.g. maps, graphs, charts) to support the implementation of locally appropriate vector/dengue control programme strategies and evidence-based decision making. A framework for the DDSS has been developed and software to enable its operation is in place. The system will be available for operational implementation in 2011. The Arabic version of the platform will be developed and implemented in Saudi Arabia, where dengue is endemic and mass population movements associated with the Hajj make implementation of dengue control in urban settings logistically challenging.

The DDSS IT system operates on the same platform as the Malaria Decision support System, allowing countries with multiple vector-borne disease needs to operate and maintain one central system.

Aside from the DDSS itself, the project has developed novel strategies for proactive vector and dengue surveillance and control, including:

- 'Casa Segura' – a 'safe house' proactive vector control approach based on use of long-lasting insecticide-treated materials within the home as window curtains and door drapes. This was piloted in Mexico, producing a measurable but statistically non-significant drop in dengue transmission over the first year of the intervention. However, local demand for the impregnated materials has stimulated a local manufacturer to continue production to satisfy local demand and NIH, on the basis of the pilot data, is funding a larger scale trial over a longer period to demonstrate the potential for a statistically significant reduction in dengue transmission.
- Syndromic surveillance for rapid detection of dengue outbreaks to enable a quicker, more focused vector control intervention.

Information Systems and Tools cont.

Project Leader:
Thomas W. Scott, UC Davis
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Dengue Model (DM):

DM

Current efforts to reduce dengue burden largely focus on prescribed vector control guidelines that fail to consider variations in dengue transmission dynamics between seasons and among different locations.

Quantitative models are the best way to account for inherent variation in dengue transmission and to predict how fluctuations in local dengue mosquito vector populations will impact the incidence of disease among humans.

The IVCC has supported the development of a user-friendly computer model for simulating populations of the dengue mosquito vector *Aedes aegypti* and dengue virus transmission based on location-specific data, specifically: climate; mosquito biology and behaviour; virus factors; human demographics and immune status. Various control interventions: such as insecticide space spraying; removal of mosquito development sites; insecticide treated materials and vaccines can be introduced into the programme to assess the relative impact of individual or combined disease control strategies.

The newly developed Windows™ version of the programme has undergone extensive evaluation to confirm full functionality. Simulation results have been compared to field-derived data collected in the Amazonian city of Iquitos in Peru by the University of California, Davis and the United States Naval Medical Research Institute Detachment. Work also continues to improve the functionality and usability of the system. The validated programme will be translated into languages other than English.

The Dengue Model software will be made freely available with the Dengue Decision Support System, so that at a variety of different levels (e.g. national, regional or local) public health, vector control or government officials can contrast and select surveillance and control options that are best for their particular circumstances. The simulation programme will aid vector control programme managers, public health officials and policy makers in the development of more effective public health goals, control targets and disease reduction strategies.

Quantitative models are the best way to account for inherent variation in dengue transmission and to predict how fluctuations in local dengue mosquito vector populations will impact the incidence of disease among humans.

Quality control (QC) of insecticide interventions and assessment of metabolic insecticide resistance on Bioko Island

The Insecticide Quantification Kit (IQK) for bendiocarb was integrated into the routine surveillance of the Bioko Island vector control programme in 2011.

The IVCC activities were expanded at Bioko Island in 2010-2011, with two major objectives: to provide a robust quality assurance system for IRS that can be used on Bioko, and to establish whether metabolic resistance is present in the major vectors on the island.

The Insecticide Quantification Kit (IQK) for bendiocarb was integrated into the routine surveillance of the Bioko Island vector control programme in 2011 for monitoring the quality and residual efficacy of the Insecticide Residual Spray (IRS) applications and determining IRS residual activity over time, to immediately inform BIMCP-EGMCI about the effectiveness of the activity. The bendiocarb test comprises of a simple sticky tape, which allows rapid removal of insecticide from a small section of sprayed surface. A sample of the extract is introduced into the test tube containing a gel-strip with acetylcholinesterase (AChE) and a chromogenic enzyme substrate solution. The result is represented by a colour which is visually matched against the colour chart to estimate the insecticide residues present.

The IVCC team visited Bioko Island in 2011 during spray campaign Round 14. Eight hundred samples from both pre and post sprayed surfaces were taken and analysed at Bioko. Results show that there is close correlation of IQK concentration estimates with HPLC (cross lab validation subsequently performed at LSTM/University of Crete) and bioassays. The sticky tape sampling procedure from different wall surfaces (wood, cement etc) provides a good correlation to the active ingredients applied. A large number of *Anopheles* vectors were collected in parallel by the IVCC team during their field survey in 2011, in order to assess the presence and frequency of metabolic resistance mechanisms in the vector species on Bioko Island, by using microarrays and other modern molecular tools developed by IVCC, as a precursor to developing a resistance management strategy for the island. The IVCC team will visit Bioko Island in the second half of 2011, aiming to continue entomological and QC monitoring activities, as well as introduce the use of the IQK for bendiocarb to the local team and evaluate its utility and programmatic acceptability.

It is now widely accepted that vector control can be highly effective in reducing the burden of diseases like malaria and dengue.

Finance Report 2010/11

New Grant Awards received in 2010/11

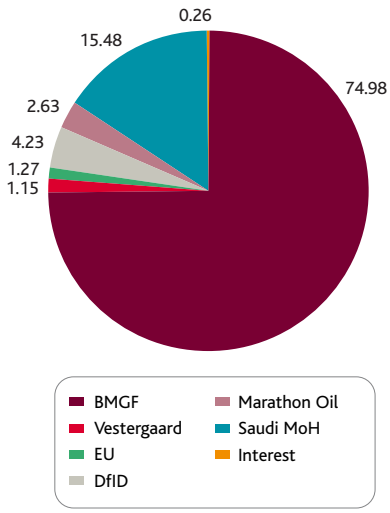
Grant awards received during the year were from a variety of funders, with the Bill and Melinda Gates Foundation (BMGF) being the largest single benefactor awarding $50m over the next 5 years. The funds will make a major contribution towards the development of new insecticide active ingredients, insecticide re-purposing and the development of new paradigms in vector control, taking us beyond bednets and sprays. A new award of $5.5m from the Saudi Arabian Ministry of Health will further the advancement of the information systems and tools programme. The funds are the initial tranche of a much larger scheme for significant capacity development in vector borne disease research and postgraduate teaching in the Kingdom.

Donor	Amount ($)	Period
Bill & Melinda Gates Foundation	50,000,000	2011-2015
Saudi Arabia Ministry of Health	5,504,439	2011-2015
Marathon Oil	289,393	2011
DfID	1,079,357	2011-2013
European Union	625,160	2011-2016

Funding Mix

Over the past few years the IVCC has been working hard to attract new donors and reduce its reliance on the Bill and Melinda Gates Foundation. As a result of these efforts, next year will see BMGF's funding reduce to 75% of the total budget, down from 96% this year and 99% the year before.

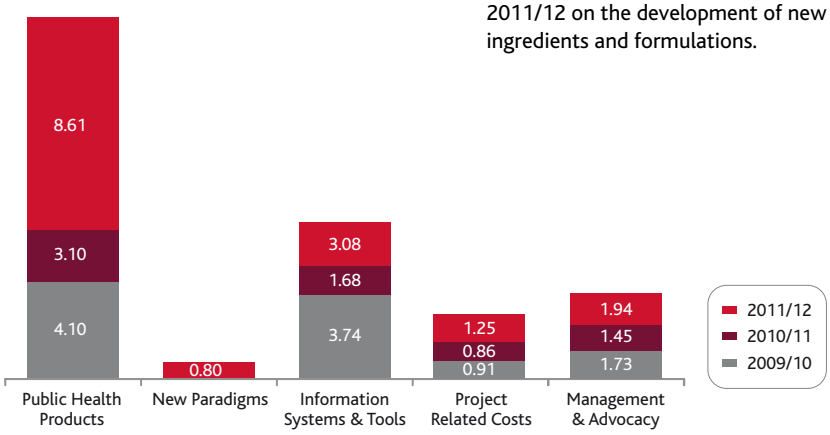
2011/12 Budget by Funder (%)



Management & Advocacy

Controlling core management costs is always a priority in any organisation. IVCC expenditure on management and advocacy fell by $279k in 2010/2011. More efficient timetabling of meetings, reductions in travel costs, staff vacancies and a general tightening of running costs helped to achieve this reduction. Several activities that are currently undertaken by senior staff within the IVCC such as fundraising, advocacy, and new paradigms portfolio management are planned to grow in importance and scope within the next year. This has caused IVCC to create specific roles within the organisation funded by our core Gates Foundation grant to deliver those objectives and we are currently actively recruiting to fill these roles in 2011.

Expenditure by Research Area ($m)



A scaling up of research activity for 2011/12 as the new active ingredient projects scale up will see an increase in product development costs. But even with four new positions filled, the M&A costs are expected to fall to 12% of overall expenditure.

As expected, interest on IVCC's investments only contributed a small return of $35k due to the historic low rates being offered on the money markets throughout the world. Active management of cash reserves will continue during 2011/12 to achieve the best returns possible in this difficult market.

Over the past 2 years, expenditure on public health products has been in line with expenditure on the development of information systems and tools, with project related and management costs remaining reasonably static over the same period. There is a significant shift in expenditure moving into 2011/12 on the development of new active ingredients and formulations.

Future Funding Secured and Projected ($m)

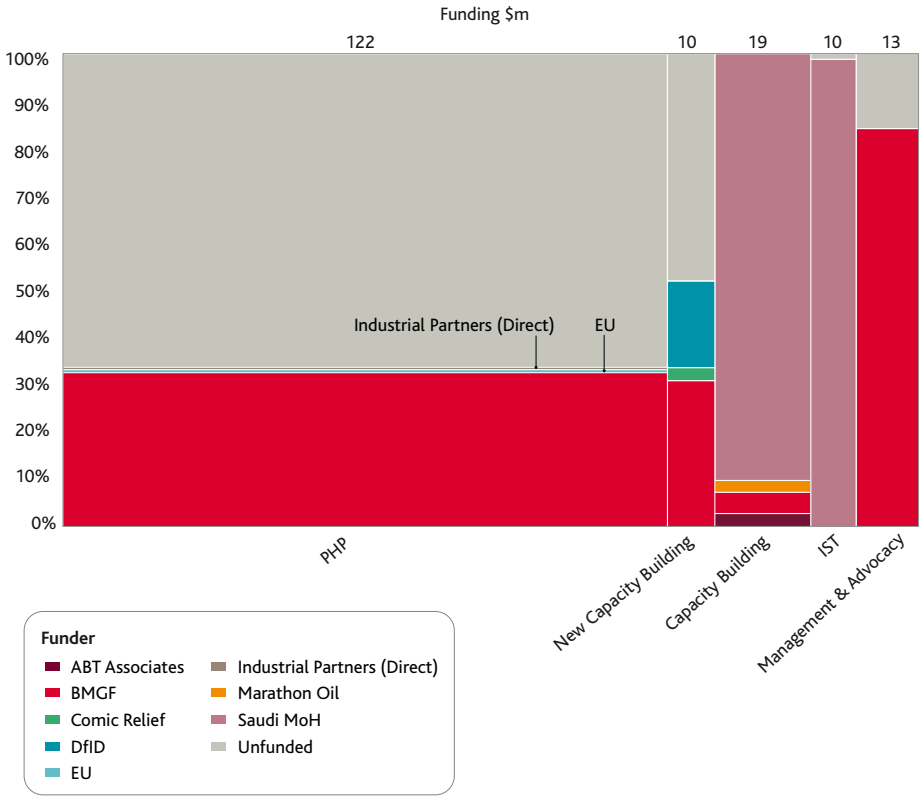
The table below shows how funding streams are distributed across all of IVCC's portfolios, and the figure to the right shows where the funding gaps are. Clearly the major gap is in the funding of the next stages of active ingredient development.

Until now the funding of active ingredient development has been structured to focus on ensuring that the early stages of AI screening and optimisation are well funded in order to fill the pipeline with enough suitable candidates to cope with the anticipated failure rates. The strategy has been particularly successful and the technical performance of the pipeline suggests that three new active ingredients are indeed achievable if suitable funding is forthcoming.

However, by the pre-trials development stages the funding rate falls short of that demanded by the cost model. Routes to coping with this funding rate include:

1. Increased co-funding from the partner companies (especially if any agrochemical applications emerge).
2. Alternative donor funding.
3. High risk (reduce the number of candidates in the pipeline and risk non delivery).

IVCC Funding Gap 2011-2015
IVCC Research Activity by Funder



Donor	PHP	New Paradigms	IST	Capacity Building	Management & Advocacy	Grand Total
Approved Funding						
BMGF	39.68	3.00	0.89		10.94	54.52
Comic Relief		0.27				0.27
DfID		1.78				1.78
EU	0.89					0.89
Industrial Partners (Direct)	0.41					0.41
Marathon Oil				0.41		0.41
Saudi MoH			2.99	2.52		5.51
Total	40.98	5.05	3.88	2.93	10.94	63.79
Projected Funding						
ABT Associates				0.50		0.50
MoH Saudi			6.93	14.56		21.49
Grand Total	40.98	5.05	10.81	15.06	10.94	85.78

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