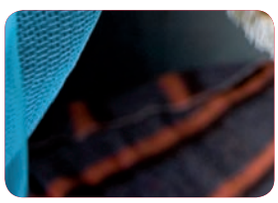
www.ivcc.com



Innovative Vector Control Consortium

A global partnership: working together to save lives

Annual Report 2007

IVCC
COMBATING INSECT BORNE DISEASE
The Innovative Vector Control Consortium

Our Mission:

To improve health by enabling partnerships for the accelerated development and delivery of new products and tools that increase the effectiveness and efficiency of the control of insects which transmit disease.

Contents:

Chief Executive Officer's Report

The Innovative Vector Control Consortium (IVCC) was established in November 2005 with an initial US$50.7 million investment from the Bill & Melinda Gates Foundation. Our aim is to stimulate industry and academia to develop new tools to better manage insect vectors of disease and to monitor and better direct these interventions.

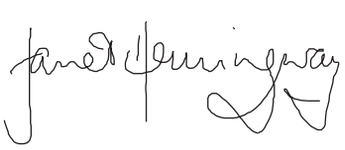
Janet Hemingway,
Chief Executive Officer, IVCC

Although insecticide-based control of adult mosquitoes within the home has been central to malaria and dengue control for over 50 years, current tools to monitor the effectiveness of these interventions are poor. Building on the pioneering work on malaria control monitoring and evaluation in southern Africa started by Dr Brian Sharp in Durban, South Africa, we are developing operational scale systems for monitoring the impact of interventions. A similar dengue decision support system should revolutionise our ability to detect and appropriately respond to dengue outbreaks. These decision support systems will allow us to rapidly assess new interventions, at scale, not only for their ability to kill insects and reduce insect population numbers but also to define the impact of these new interventions, alone or in combination, on disease transmission.

Few pesticides have been developed for public health use in the last three decades and IVCC is working with industry to overcome this inertia by providing financial, logistical and intellectual support in key areas. There are only two well validated vector control systems that impact on disease transmission: the use of Long Lasting Insecticide Treated bednets (LLINs) and Indoor Residual Spraying (IRS) of insecticide. Neither intervention is ideal, both are costly to implement and neither are well received by many disease endemic country populations. The IVCC aims both to dramatically improve these interventions and to stimulate industry to bring new interventions to the market. We know that there is a large consumer market for products such as coils, aerosols and insecticide impregnated mats to reduce mosquito biting nuisance. By interfacing between consumers, industry and other industrial and academic players, the IVCC is already stimulating the development of novel insecticide-based interventions within the home and testing the efficacy of these interventions in reducing disease transmission.

The international community is considering whether it is practical to eradicate malaria and other vector borne diseases in the foreseeable future. Achieving such ambitious goals would reduce the suffering for millions of people in disease endemic countries. If we are to make progress towards this goal the international community will need to work together to develop new appropriately priced insecticide-based interventions that are safe, effective and readily accepted by the local populations. The IVCC intends to play a major role in stimulating a paradigm shift in the way we attempt to reduce disease transmission in the home and invites donors, industry and other interested parties to join in this stimulating and rewarding mission.

Sadly up to 4 million African parents each year see their infants die of malaria. The IVCC aims to make a major contribution towards the ultimate vision that no parent should in future need watch their child die of this preventable disease.



Janet Hemingway,
Chief Executive Officer, IVCC

No new public health insecticides have been developed for mainstream vector control in disease endemic countries for **30** years

Senior Executive Officer's report

Tom McLean answers questions collected from a cross section of IVCC collaborators and stakeholders.

Q. How has the Public Health Products (PHP) industry responded to the establishment of the IVCC?

I have been greatly impressed by both the personal and corporate enthusiasm that has been shown by the insecticide teams of the global agrochemical industry for the development of new PHPs. It seems that we have touched a deep vein of desire to put their profound expertise to good use in the cause of public health. Often the research teams know exactly where to go and look for these orphaned products in their back libraries. In other cases they established data mining programmes of their huge chemical libraries to find suitable candidates. They really do want to develop these products, all they need is enough help to keep their finances respectable.

Q. The idea of long term commitments to global access for these products is new in the chemical industry. How have industry partners taken to the idea and requirements of global access?

At first the industrial partners were somewhat wary of the idea of global access fearing that we might drive them towards an economically unsustainable outcome. Now that we have all come to realise that the global access targets of affordability, availability and usability were in practice exactly what the competitive market place would demand from them in any case, they have found the requirement for global access commitments perfectly acceptable.

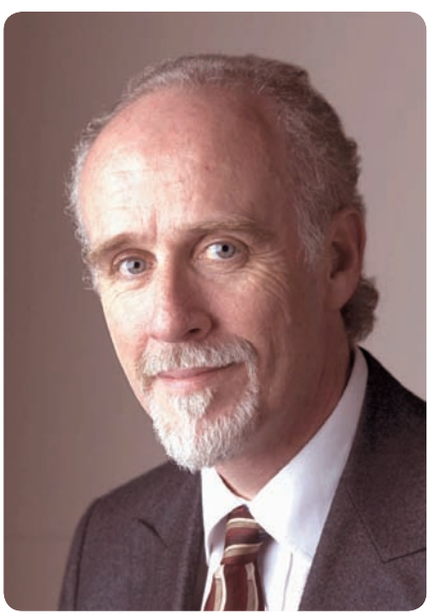
Q. The IVCC has two arms, one in development of new pesticides and the other designing Information Systems & Tools (IS&T) and validating new paradigms. What is the benefit of pursuing these two aims in the same organisation?

IS&T are the basis on which effective monitoring and evaluation of vector control programmes can be implemented. This enables the exploration of new paradigms in public health control such as the concept of 'Casa Segura' (safe house) or new approaches to consumer products that are effective in vector control. Feedback from these monitoring and evaluation and paradigm exploration activities leads to new target product profiles for reformulation of known active ingredients derived from the agricultural pesticide market or discovery of entirely new active ingredients. Our industrial partners recognise the importance of the new paradigm work taking place within the consortium and have been instrumental in donating novel products such as insecticide treated curtains to test out the new paradigms.

Q. What are the immediate and long term goals for the IVCC, and what challenges do you face?

The IVCC has already created a great deal in its IS&T program. The next step for those projects is to create a dissemination process that delivers those systems to the users who really need them.

This initial phase of the IVCC will deliver a portfolio of reformulated agricultural Active Ingredients (AIs) but it has also confirmed the need for three entirely new insecticide species with no existing resistance process to be brought to bear on the vector control market in order to create the insecticide tool set that can be guided by the decision support systems to deliver sustainable, evidence-based resistance management and effective vector control.



Tom McLean,
Senior Executive Officer, IVCC

Consultation with product development leaders of the insecticide industry has uncovered a wide range of technical opportunities for delivery of these products and they are already preparing the initiation of these projects. However, it is clear that substantial funding will be required to overcome the financial challenges that these projects face. If it turns out that those AIs have no agricultural use and therefore we have to pick up the whole tab it will cost us up to $800m over the next ten years.

Global access means making health solutions available at a price, volume and format which will **benefit people most in need** in the developing world

Organisational evolution of IVCC

The IVCC has learned a great deal about the different organisational requirements of its constituent parts during the last 24 months and the current organisational structure and governance process has evolved to meet those needs.

The Interventions Consortium (IC) is concerned with the development of Information Systems & Tools (IS&T) and the exploration and validation of new paradigms in vector control. This is a true consortium where the added value of the IVCC lies in the collaborations and skills exchange between the partners. Examples of this include:

- Exchange of key skilled workers and database design architecture between projects
- Diversification of design options and trial data sources
- Establishment of global standards in data collection models and insect resistance databases
- Increased access to strategic stakeholders and influencers and increased impact on end users.

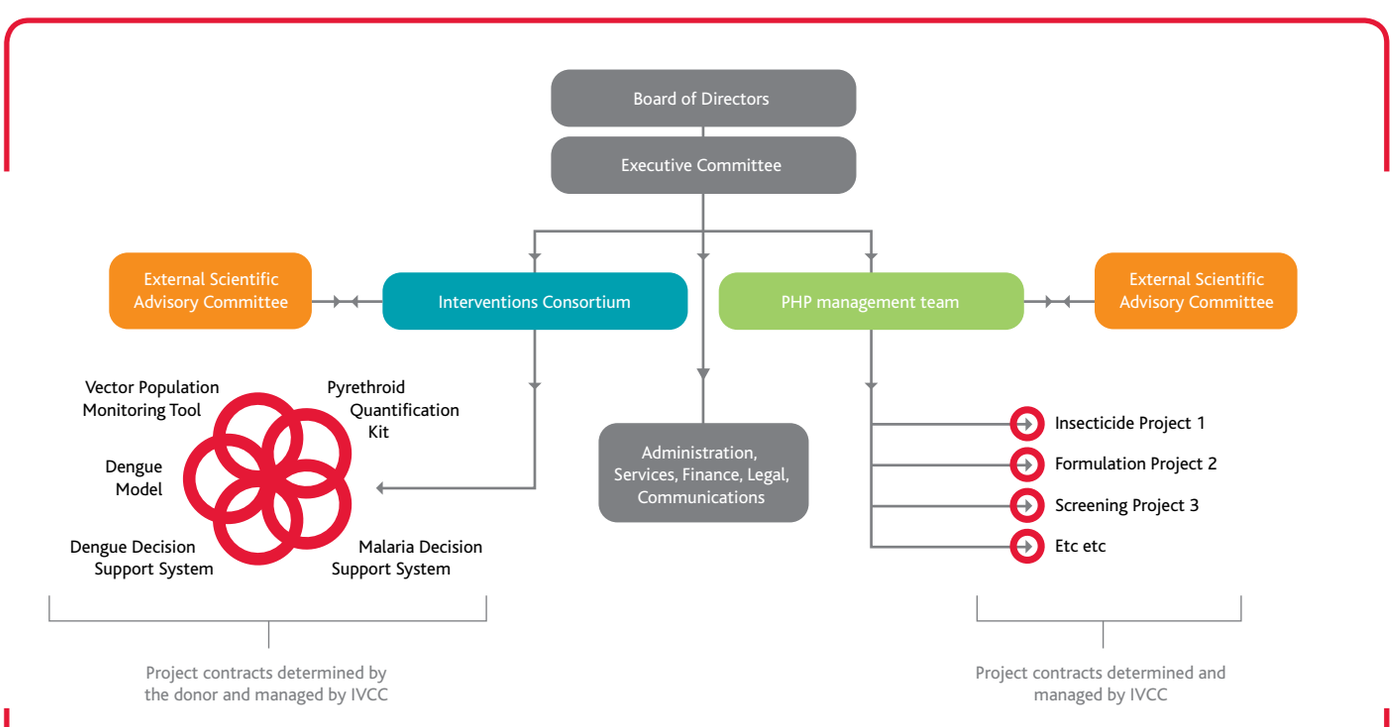
Open communication and mutual trust between the constituent projects is critical to this consortium and this is fostered by separation of the project funding and approval processes from the ongoing management and information flow within the consortium assembly. Individual projects within the IC are proposed by the participating partners (including new partners joining the consortium) to external funding bodies (such as BMGF or the Wellcome Trust). On approval these grants are then administered by the IVCC. The consortium assembly consists of the leaders of the individual projects with support from the IVCC business development team and is charged with ensuring the flow of information, skills and best practice between the partners.

The product development side of the IVCC is focused on the delivery of novel insecticide AIs and formulations through a product development partnership approach. This calls for a conventional portfolio management style which is delivered by the Public Health Products (PHP) management team. The PHP management team consists of the Portfolio Manager, Trials Manager and Project Managers who are full time IVCC staff, rather than the project representational style of the Interventions Consortium assembly.

The two management groups are advised by External Scientific Advisory Committees who are independent experts with the appropriate expertise to assess and guide the projects towards best practice.

The Executive Committee consists of the IVCC CEO and COO with the PHP Portfolio Manager and the IC Coordinator. In addition the Executive calls on the expertise of independent leaders in the fields of pesticide development and intervention validation. The Executive Committee drives the overall strategic direction of the IVCC and the raising of the substantial funds necessary to deliver its ambitious goals.

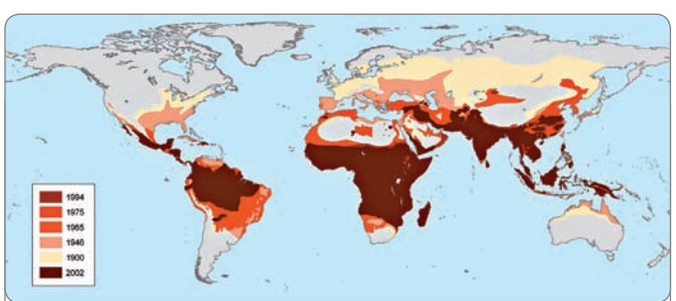
The Board of Directors represents a wide range of skills and experience of IVCC stakeholders from major donors to African industrial players and public health professionals. It is charged with ensuring that the IVCC delivers its objectives in an open, transparent and effective manner. The CEO is appointed by the Board and is ultimately answerable to them.



Why do we need IVCC?

Insecticides and Information Systems & Tools (IS&T) are crucial weapons in the fight against insect borne diseases such as malaria and dengue.

Mosquito vector control is capable of spectacular results. The malaria eradication campaigns of the mid 1900s eliminated malaria in much of the world. It was driven out of the USA, most of Europe, Latin America and Asia, and even in Sub-Saharan Africa the disease burden was reduced substantially. The eradication campaigns were discontinued because of concerns about drug and insecticide resistance and problems with sustainability.



Historical spatial limits of malaria

Historical endemicity map provided by the Malaria Atlas Project (MAP, http://www.map.ox.ac.uk), funded principally by the Wellcome Trust, UK

Over the last two decades there has been a shift away from indoor residual spraying (IRS) of insecticides towards large scale distribution of insecticide treated bednets (ITNs). Both interventions have demonstrated great success.

We need a range of longer lasting and resistance defeating insecticide products.

Insecticide	Spray	Nets	Resistance
Pyrethroids	✓	✓	✓
DDT	✓	✗	✓
Carbamates	✓	✗	✓
Organophosphates	✓	✗	✓

A major remaining issue with ITNs is the current recommendation of only one insecticide class, the pyrethroids, for net impregnation, leaving the intervention vulnerable to failure if operational levels of resistance are selected in the mosquitoes.

While insecticide choice is wider for IRS, only four classes of insecticide are registered for IRS use and resistance is already present to all classes in some mosquito populations.

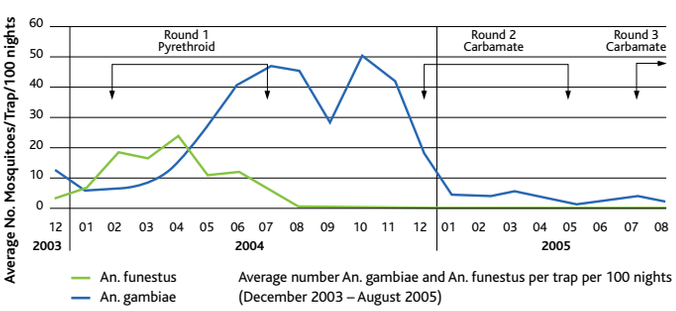
Insecticides for mosquito control are in short supply. Existing products are constrained by cost, environmental and human toxicity and resistance. In the1980s, a move away from contact toxicity and persistence, for new agrochemical products, has meant that many modern agricultural insecticides are not so easily re-purposed and no new products have been registered for the mainstream adulticide malaria Public Health Products (PHP) applications since the mid 1980s. In the long term we will need three entirely new AIs unencumbered by resistance issues.

Validation of new paradigms in vector control will diversify the options available to local control programs.

Dengue is spreading rapidly in many parts of the world. The strategy of mosquito larval source reduction and space spraying to eliminate dengue epidemics has been largely ineffective and is not sustainable. It is clear that we need to respond to potential dengue outbreaks more rapidly and efficiently than is possible at present.

IS&T are the foundation of effective monitoring and evaluation and evidence-based vector control.

Model based decision support systems have long been used as product stewardship and promotional tools in the agrochemical pesticide business. Recent evidence from effective malaria control programmes in South Africa and Mozambique demonstrates that good product stewardship also requires the deployment of IS&T to avoid the use of ineffective or resistance promoting interventions.



Graph adapted from data produced by Medical Research Council Durban, South Africa.

DID YOU KNOW? DID YOU KNOW?

An African child dies of malaria every **30** seconds

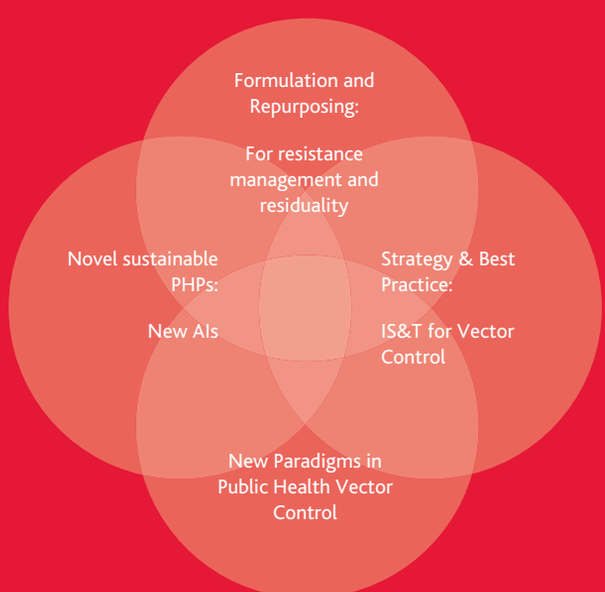
The role of IVCC

The Innovative Vector Control Consortium's strategy is to identify opportunities for the development of new products, strategies and tools for improved vector control and to enable and support those projects through developing partnerships that will provide the resources to bring them to fruition.

Key resources that overcome the major obstacles to innovation include:

- Definition of the product requirements in consultation with technical and public health experts
- Financial risk reduction by contributions to the developers to reduce their development costs
- Confidence Building
  - expert recommendations
  - market knowledge
- Insecticide testing capabilities
- Provision of enabling resources
  - registration expertise
  - key technology brokering
  - project managers

We have identified four areas where significant opportunities for effective innovation exist:



Information Systems & Tools (IS&T) are the basis on which effective monitoring and evaluation of vector control programmes can be implemented. This enables the exploration of new paradigms in public health control such as the concept of Casa Segura or new approaches to consumer products that are effective in vector control. Feedback from these monitoring and evaluation and paradigm exploration activities leads to new target product profiles for reformulation of known active ingredients derived from the agricultural pesticide market or the discovery of entirely new AIs.

Vector control intervention profile

Vector control is one of the most important weapons against insect borne disease in the developing world. Themba Mzilahowa is an intervention control specialist working in Blantyre, Malawi.

Themba Mzilahowa,
Intervention Control Specialist

The burden of malaria in Malawi is well documented and has a major impact on child mortality here. Malawi has a population of 12 million people and almost everyone is at direct risk of malaria infection. Malaria has touched every family in this country, with at least one family member affected, but it is children under five and pregnant women that carry the greatest burden of the disease. Nearly half of all infant deaths up to the age of two years are attributable to malaria infections, with surviving children continuing to be at high risk of infection up to the age of five and suffering an average of almost ten episodes of malaria every year. Shocking though this preventable tragedy is, the toll of malaria extends far beyond the numbers it kills. Malawi's economy continues to be hit very hard by the side effects of the disease. It is estimated that an average person loses 13 days of employment or school attendance per year due to malaria, resulting in a loss of productivity for both the local community and the country. Studies have estimated that malaria is responsible for the loss of more than a quarter of an average Malawian family's total annual income.

The use of insecticide treated bednets (ITNs) is the principal malaria vector control strategy in Malawi. ITNs have been in use for over a decade now and coverage is estimated at 43% of households owning at least a single net. The Malawi National Malaria Control Program (NMCP) has just begun piloting Indoor Residual Spraying (IRS) in the Nkhota kota district, a holoendemic area in central Malawi. It is hoped that in future Malawi can use both ITNs and IRS for vector control.

Malawi has just introduced Artemisinin Combination Therapy (ACT) as a first line antimalarial drug. Though ACTs are heralded as very effective against malaria and slow to be overcome by problems of drug resistance, the benefit of their use may not be realised if disease transmission pressure remains high in many parts of the country. To win the fight against malaria, we need effective, well planned and evidence-based vector control strategies. It is well known that ITNs, though simple, are very effective at reducing all-cause infant mortality and morbidity, comparing very well with IRS in terms of cost-effectiveness. Both of these strategies can be deployed simultaneously provided resources permit.

Vector control interventions in the past have lacked emphasis and expertise. That situation is changing with the introduction of the NMCP, a renewed interest in IRS as well as bednets and the roll out of the Malaria Decision Support System (MDSS). The MDSS will collect and collate data on malaria and anaemia prevalence, vector species, infection and resistance status. Eleven districts have been selected as sentinel sites: Karonga, Rumphi and Mzimba in Northern Malawi; Nkhota kota, Ntchisi and Lilongwe in the central region; and Mangochi, Machinga, Blantyre, Mwanza and Chikwawa in southern Malawi. Entomological data collection commenced in October 2007 for Nkhota kota district. Information from these sites will inform the MDSS and will help programme managers to make informed decisions on interventions and control policy. With continued, guaranteed funding to maintain large scale interventions, I am hopeful that we can make dramatic and sustainable progress in the fight against malaria.

DID YOU KNOW? DID YOU KNOW? ?

50% of all infant deaths up to the age of two years in Malawi are attributable to malaria infections

Public Health Products (PHP)

One of the key objectives of the IVCC is to develop a new range of PHPs to enable vector control programmes to effectively control the insects which transmit disease. In order to achieve this the IVCC has defined a portfolio that includes the following:

PHPs

- A new range of long lasting indoor residual spray formulations that maximises the number of insecticide classes available to allow vector control programme managers to manage resistance. This should include all insecticide classes currently recommended by WHO and any existing available agrochemical insecticides that could be repurposed for vector control.
- At least one new long lasting insecticidal net that contains an insecticide with a different mode of action from pyrethroids.
- At least three new vector control insecticide active ingredients with novel modes of action that are not affected by known vector resistance mechanisms.

The projects that have been started fit into the long lasting spray and the new active ingredient portfolio.

New Long Lasting Indoor Residual Spray

The transmission of disease by mosquitoes and other insects occurs mainly within and around the home. The spraying of insecticide-based compounds onto interior walls where mosquitoes and other insects alight, known as Indoor Residual Spraying (IRS), has been successfully used for many years and is proven to dramatically reduce the numbers of insects presenting a biting hazard. By making a formulation that will remain effective for longer than existing products, fewer spraying rounds will be necessary with less disruption to householders, shorter periods of reduced insecticide action and lower implementation costs.

IVCC is currently funding two projects to develop long lasting IRS formulations, one with the London School of Hygiene and Tropical Medicine (LSHTM) and Syngenta, the other with the Medical Research Council, South Africa, the Liverpool School of Tropical Medicine (LSTM), LSHTM and Bayer.

New Active Ingredients (AI)

Stopping the spread of diseases like malaria and dengue relies upon the effective control of mosquitoes. Insecticides are a crucial element in these control programmes but their effectiveness is increasingly constrained by the growing numbers of mosquito strains which are resistant to the active ingredient. IVCC is currently funding a project with LSTM, the University of Liverpool and Bayer to modify current active insecticide ingredients to overcome pesticide resistance.

The IVCC is looking for more projects in each of the defined sections of the portfolio.

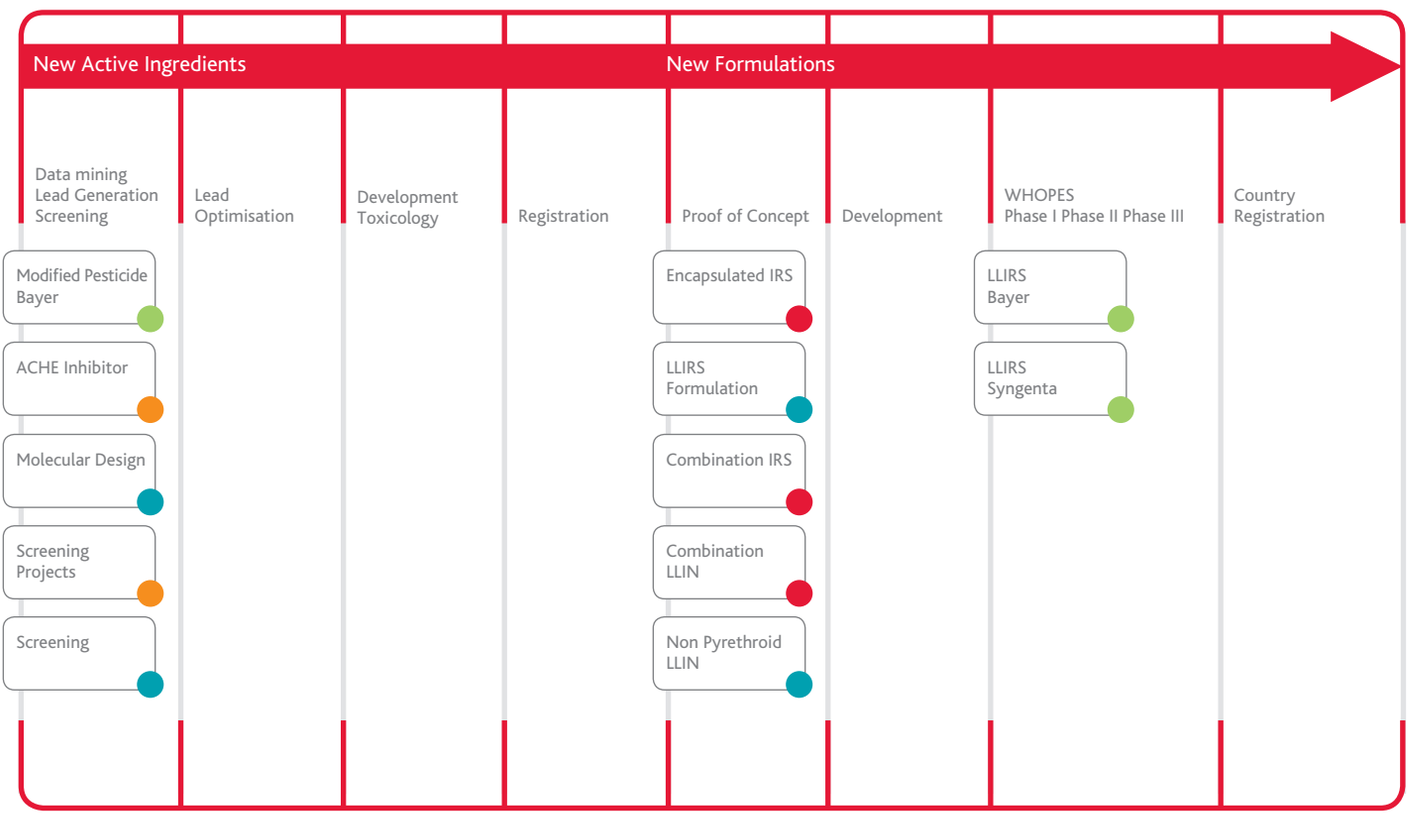
DID YOU KNOW? ?

We aim to develop longer-lasting IRS formulations which will reduce the cost of application programmes by **25%**

Pesticide field testing site in Tanzania

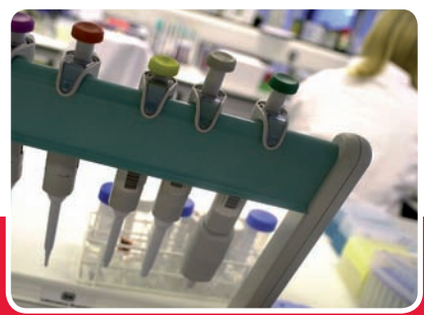
Our current portfolio:

Active · In Preparation · Opportunities · Under Negotiation



The IVCC was established with a **$50.7m** grant from the Bill & Melinda Gates Foundation

Public Health Products
PHP portfolio



Bayer potential new insecticide Active Ingredients (AI)

Project Leader: Steve Ward, Liverpool School of Tropical Medicine (LSTM)
Partners: Bayer, LSTM, University of Liverpool
Contact: robert.sloss@ivcc.com

This project is focused on the synthesis and development of at least one 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 new product will involve novel chemistry and approaches that are fully patentable. Utilising the insecticide backbone as a starting template will increase the probability of producing a molecule with appropriate development characteristics and will also help to ensure that the new insecticide could be produced using existing plant capacity, thereby reducing the cost of development and production significantly.

Over a period of 29 months up to 200 potential lead insecticides will be synthesized and screened as potential insecticides against both public health and crop pests. As promising candidates emerge from screening and appropriate resistance bioassays there will be assessments performed against the target product profile on the likely cost of goods, the ability to manufacture utilising the existing production plant and the predicted toxicity profile.

The first six months of the project will focus on the synthesis of key chemical intermediates essential for the second six month phase of analogue synthesis. During this period the pre-screen and platforms for assessing metabolic and biochemical stability will be established. The pre-screen will be performed on both susceptible and resistant strains of mosquitoes including strains with P450 resistance mechanisms and strains with knockdown resistance mechanisms.

Bayer Long Lasting deltamethrin IRS formulation

Project Leader: Volker Gutsmann, Bayer
Partners: Bayer, Medical Research Council SA, LSTM, London School of Hygiene and Tropical Medicine (LSHTM)
Contact: robert.sloss@ivcc.com

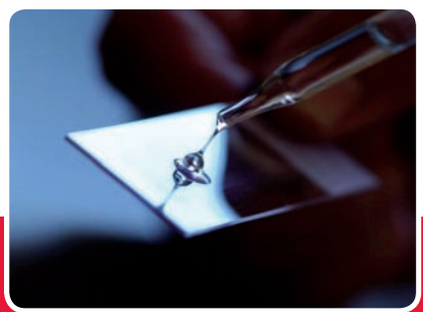
This project's aim is to develop a long lasting residual formulation for Indoor Residual Spray (IRS) programs to improve malaria vector control in disease endemic countries.

This new formulation project will utilise 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 formulations 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.

DID YOU KNOW? DID YOU KNOW?

Between 300 and 500 million people become acutely ill and more than **1 million** people die from the effects of malaria every year



Project Leader: Alex Cornish, Syngenta
Partners: Syngenta, LSHTM
Contact: robert.sloss@ivcc.com

Syngenta Long Lasting non-pyrethroid IRS formulation

Deltamethrin will be used as the AI to develop the first new formulation. This formulation work, if successful, will then be extended to bendiocarb, producing insecticides in two chemical classes that can be utilised for IRS in rotational or mosaic insecticide resistance management programs.

A number of different polymers have been formulated by Bayer and screened in an accelerated laboratory test. This has led to the identification of a lead candidate which performs better than traditional formulations and has good potential. This formulation has also been tested by Bayer to check that it does not block the sprayers currently used for IRS.

The next stage of the project is to test the lead formulation in both South Africa and Liverpool in the laboratory and in the field on several different surfaces with different strains of mosquitoes to confirm the residuality data and compatibility with spray equipment. Bayer will be working on adapting the formulation to optimise its stability and simplify the manufacturing process.

Indoor Residual Spraying is a highly effective strategy for malaria prevention as part of an integrated vector management program. The level of residuality after indoor residual spraying of insecticides on house walls varies from one to six months for organophosphates, carbamates and pyrethroids to twelve 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 would offer a practical new tool for cost-effective IRS and also provide an opportunity to replace DDT.

Syngenta has a well-established global presence in IRS primarily through the development, marketing and sales of Icon® 10WP. Syngenta are already bringing long-lasting pyrethroid-based technology to the IRS market in the form of Icon® 10CS which has shown extended effectiveness in the field beyond six months.

The Company is committed to additional innovation in IRS and are developing an improved non-pyrethroid formulation designed for extended residual performance. A lead formulation has been identified and shown promising results in initial laboratory studies performed internally at Syngenta. The lead candidate is currently being tested in Benin and Tanzania against both susceptible and resistant *Anopheles* and *Culex* strains. Laboratory and experimental hut studies will be used to determine efficacy and residuality. Studies are also being performed to assess the acceptability of the product to spray operators and residents.

WHO currently estimates there may be **50 million** cases of dengue infection worldwide every year

Interventions Consortium Information Systems & Tools (IS&T) portfolio

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.

To help those deciding when and how to act in vector control, the IVCC is developing Decision Support Systems (DSSs) for malaria and dengue. Operated through a user-friendly computer based interface, the DSSs will hold a range of relevant data, including disease incidence, the spread and density of insect populations and insecticide resistance. The systems will then present geographically based analysis of the data. This will help policy makers and programme managers ensure that resources are used most effectively.

Modelling software is being developed that will use a wide range of parameters to forecast the spread and growth of insect vector populations and the likely rates of disease development. This model will integrate with the DSS to provide programme managers with important information on the predicted need for intervention and the likely outcome of any proposed intervention.

Insecticide treated bednets are an important defence against insect borne diseases – principally malaria. To ensure they remain effective, nets must be replaced or retreated when the insecticide concentration becomes too low. The Pyrethroid Quantification Kit (PQK) being developed by the IVCC will provide a quick, simple and affordable means of measuring insecticide concentration, allowing programme managers to ensure that bednets continue to provide the protection needed.

One of the greatest potential threats to the control of insect vectors is the development of insecticide resistance among target populations. Resistance reduces the effectiveness of control measures leading to an increase in disease rates and, left unchecked, can become so widespread that vector control products can be rendered completely ineffective. Quick and reliable tests for monitoring resistance are therefore a vital tool for programme managers. The IVCC's Vector Population Monitoring Tool (VPMT) project is developing kits that can be used in disease endemic regions for monitoring resistance. These kits will also allow programme managers to quickly identify the vector species present and the diseases they are carrying.

Project Leader: Martin Donnelly, Liverpool School of Tropical Medicine (LSTM)
Partners: Colorado State University (CSU), Rothamsted Research, Agricultural University of Athens (AUA)
Contact: m.j.donnelly@liverpool.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 is funding the development of a simple molecular biology kit which will enable scientists in disease endemic countries to reliably identify the mosquito species, infection status (malaria positive or negative) and the presence of insecticide resistance genes by detecting a gene or sequence of DNA.

One example is resistance to pyrethroid insecticides. Gene mutation has resulted in the development of mosquito populations which are less vulnerable to insecticides. Bednets treated with pyrethroid insecticides are the primary method of malaria prevention in many countries so resistance to pyrethroids is of great concern for malaria control programmes. The first indication

DID YOU KNOW? DID YOU KNOW? ?

Insecticide resistance has been documented in more than **125** species of mosquito

Aedes mosquito

Project Leader: John Vontas, AUA
Partners: LSTM
Contact: vontas@aua.gr

Pyrethroid Quantification Kit (PQK):

Family sleeping under bednet

PQK

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

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

This project will produce a simple, cost-effective and user friendly kit for monitoring insecticide residues on insecticide-treated materials. Some market research was undertaken at the first phase of this project, which established that such a product would be viable in the market at the target price of less than $2 per test. The kit will comprise of a simple cartridge or filter to allow rapid removal of insecticide from a small section of net and a vial or strip test with a sensor unit and a 'traffic light' type indicator which will allow visual assessment of the amount of insecticide in the sample.

of resistance development is usually the failure of control programmes. The new kit is designed to screen the DNA of individual mosquitoes to determine whether they carry the resistance mutation, allowing programme managers to detect resistance earlier and crucially before control failure has occurred. This will give these health professionals more time to respond by changing insecticides or altering control strategies.

Provisional field testing of kits has taken place in Malawi. Malawian scientists were able to perform and score the assays in a matter of hours and to rapidly acquire a baseline of the resistance status of their mosquito populations. Following these initial positive trials the project is utilising the synergies of the IVCC by integrating the development of the kit with the Malaria Decision Support System. Project staff will be training MDSS staff in early 2008 on how to use the different tests, thereby beginning the process of getting kits into operational use. Other important milestones this year include developing the first molecular assays for metabolic resistance.

Three distinct approaches for detecting insecticides which had the potential to be adapted into a kit format were evaluated during 2007. During 2008 the final optimisation and lab test validation of the kit components and detection assays will be completed. This information, alongside IP, manufacturing and cost agreements will inform the decision on which prototype kit will be taken forward to the next stage of field trials. Refinements and optimisations based on the output from this stage are scheduled to be undertaken in close collaboration with commercial partners towards the end of 2008, with production and entry to market of a deltamethrin detection kit planned for the first quarter of 2009.

We aim to produce a simple, cost-effective and user-friendly pyrethroid quantification kit with a target market price of less than **$2** per test

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Malaria Decision Support System (MDSS):

Taking samples for a malaria indicator survey

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, the density of insect populations and insecticide resistance and presents this information in a web-based, real-time geographical format.

The MDSS is being developed in collaboration with the National Malaria Control Programmes in Malawi, Mozambique and Zambia and the Medical Research Council, South Africa. IVCC is contributing funding for this further development.

The system currently integrates a number of information systems and tools which separately monitor key aspects of malaria, including health and entomology information systems and malaria indicator surveys. Each national programme has its own regional variations and uses a variety of vector control initiatives. 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.

With support from IVCC, 19 sentinel sites have been established in Mozambique since 2006 for the collection of entomology data and two annual malaria indicator surveys have been carried out. This information has been fed back to the National Malaria Control Program allowing them to make informed decisions on the following year's control strategy.

In Malawi and Zambia the process of establishing sentinel sites has begun and over the next year base line surveys will be completed for entomology and malaria indicators.

Spatial data sets have been developed for the areas in which the MDSS is currently working and over the next year the first of the information system modules will be completed and be freely accessible to those that wish to utilise them. Ultimately, MDSS users will be able to analyse many aspects of control information in a timely fashion to make informed decisions and recommend policy change.

The MDSS is being 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 Centers for Disease Control and Prevention and the World Health Organisation.

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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.

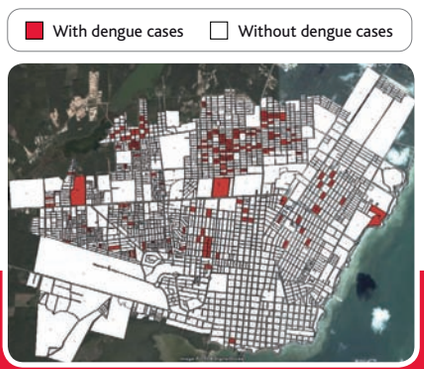
Because a vaccine against dengue virus is still lacking, control of the mosquito vector is the primary option for disease prevention and control. Currently employed vector control strategies have, however, not been adequate to combat dengue and novel tools and approaches are desperately needed.

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 will provide capacity for collection, management and analysis of vector and dengue data in a standardized way. Data will be displayed in intuitive formats (e.g. maps, graphs, charts) to support the implementation of locally appropriate vector/dengue control program strategies and evidence-based decision making. A framework for the DDSS has been developed and software to enable its operation is being developed. The system will be field tested by public health partners in Mexico in 2008/09.

DID YOU KNOW? DID YOU KNOW?

With support from IVCC **19** sentinel sites have been established in Mozambique since 2006



Distribution of city blocks with/without dengue cases in 2006 in Chetumal, Quintana Roo, Mexico

Dengue Model (DM):

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Field-derived data on dengue incidence is obtained in Iquitos, Peru

DM

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

- Use of Google Earth™ to display DDSS-generated data on an image of the physical environment
- '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. A trial programme will be implemented in Merida, Mexico, during 2008/09
- Syndromic surveillance for rapid detection of dengue outbreaks to enable a quicker, more focused vector control intervention. The feasibility of incorporating syndromic surveillance into the DDSS will be operationally tested in Merida, Mexico, in 2008/09.

The DDSS project is an international collaboration including academic partners in the United States (Colorado State University) and Mexico (Universidad Autonoma de Yucatan, Universidad Autonoma de Nuevo Leon), public health partners in Mexico (Servicios de Salud de Yucatan, Servicios Estatales de Salud de Quintana Roo, Centro Nacional de Vigilancia Epidemiologica y Control de Enfermedades, Instituto Nacional de Salud Publica), international public health partners (Pan American Health Organization, World Health Organization), and industry partners (Bayer Environmental Science, Acytex Internacional).

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.

Quantative 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 is supporting 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 is currently undergoing extensive evaluation to confirm full functionality and to construct a user-friendly interface. Simulation results will be rigorously 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. The validated program will be translated into languages other than English.

Our goal is to make the program freely available as a component of 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 program will aid vector control program managers, public health officials and policy makers in the development of more effective public health goals, control targets and disease reduction strategies.

some **2,500 million** people are now at risk from dengue

Financial Highlights

The allocation of funding from the Bill & Melinda Gates Foundation totals $50 million to be spent over a five year period. Current expenditure to date across all projects has risen to just over $15 million at the end of 2007 representing 30% of the total budget. It is anticipated that the remaining $35 million of funding will be spent evenly between 2008 and 2010, and that a substantial refinancing exercise will be undertaken in 2008/2009.

Project Finances

Based on the current financial business plan and latest projections the IVCC has allocated funding into the following three main areas:

- Public Health Products (PHP) (40%)
- Information Systems & Tools (IS&T) (45%)
- Administration (15%)

These figures are based on current funding allocations combined with future forecasted funding needs. Figure 1 breaks these down further into their respective project areas and monetary amounts.

Both PHP and IS&T are seen by the IVCC as having equal importance in achieving a successful outcome to the work being carried out in this first phase of the IVCC and the current funding reflects that. As the IS&T mature and the more costly active ingredient projects emerge, the balance of funding will shift in later phases of the IVCC.

Administration costs are always a concern and we are constantly striving to reduce costs and improve our efficiency and use of resources through regular financial reviews. These costs include the implementation of infrastructure to deliver the projects, such as a document management system and a substantial review of the governance and organisation of the IVCC.

Geographical Spend

Whilst most of the insecticide development work is based in Europe, all the field testing is performed in Africa and South America. Development of the Malaria Decision Support System (MDSS) is also being led from Africa. Consequently the IVCC has been able to place substantial research funding into organisations based in developing countries and not just the developed world. Of the funds committed so far, over one third will be spent in Africa and approximately 10% in South America.

Future Funding Needs

The long term key target for the IVCC is the development of three new active ingredients unencumbered by resistance issues. Development of new insecticide AIs costs between $150m and $250m each. The total cost to the IVCC will depend on the degree to which agricultural spin offs from these new species can be used to fund the development. In the worst case, where development costs for all three species is required, the total funding requirement would rise to $800m over 12 years. In a more optimistic scenario, where no development costs fell to IVCC, the requirement would be limited to $300m.

Figure 1 – Projected spend of the IVCC grant from the Bill & Melinda Gates Foundation

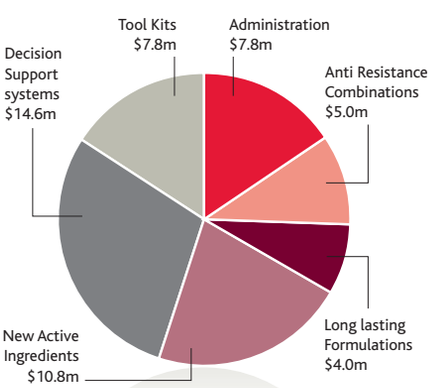


Figure 2 – Geographical split of projects supported by IVCC

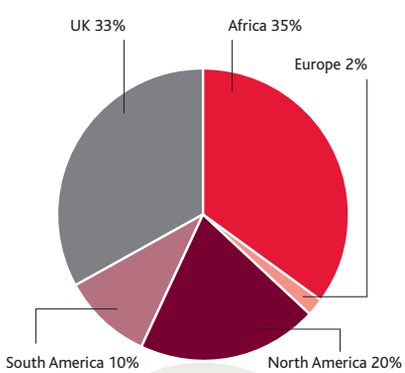
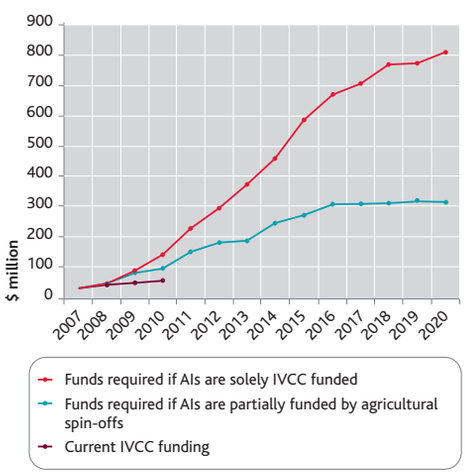


Figure 3 – Forecast of funding required to deliver IVCC's long term goals



DID YOU KNOW?

1/3 of funds so far committed will go directly to projects in Africa

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The Innovative Vector Control Consortium

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