The Innovative Vector Control Consortium: improved control of mosquito-borne diseases

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Few new insecticides have been produced for control of disease vectors for public health in developing countries over the past three decades, owing to market constraints, and the available insecticides are often poorly deployed. The Innovative Vector Control Consortium will address these market failures by developing a portfolio of chemical and technological tools that will be directly and immediately accessible to populations in the developing world. The Bill and Melinda Gates Foundation has supported this new initiative to enable industry and academia to change the vector control paradigm for malaria and dengue and to ensure that vector control, alongside drugs, case management and vaccines, can be better used to reduce disease.

Control of vector-borne disease

The vector-borne diseases (malaria, dengue, leishmaniasis, filariasis, and Chagas disease) cause extensive morbidity and mortality, and are a major economic burden within disease-endemic countries (DECs; Table 1). Control of each of these diseases, which are all transmitted primarily in or around the home, is difficult. The optimal means of controlling any one of them is likely to be a combination of vector control, drugs, management of clinical illness and/or vaccines. Although drug and vaccine development for diseases such as malaria and dengue have received increased attention since 2000, there has been no major initiative to improve vector control. By contrast, much of the available vector control technology is more than a quarter of a century old.

Home-based vector and disease control interventions have been spectacularly successful in the past. Early efforts to control malaria during the 1950s and 1960s with spraying indoors with DDT and other insecticides achieved almost total eradication of the vector and the pathogen in many parts of the world [1–3]. These efforts simultaneously reduced levels of transmission of dengue, leishmaniasis and filariasis. Some countries, such as Taiwan, are now celebrating 40 transmission-free years of malaria. This is a massive achievement, as malaria was previously a major killer in the country [4]. More recently, insecticide-treated bednets reduced morbidity and also mortality from all causes [5,6]. In African populations that use such nets consistently, parasitaemia in young children has been reduced by 62% and overall child survival has increased by 27% [7]. This is a result of protection at the levels of the individual and the community [8]. Control of dengue vectors relies on the removal of larval breeding containers, such as old tyres or flower vases or on insecticide spraying in homes. This approach has been used successfully in some locations, but is not sustainable [9,10]. Where home-based vector control interventions have been reduced or eliminated, one or more of these diseases have re-emerged.

Limitations of current control methods

The cost of insecticide treatments is prohibitive in many settings. There are also legitimate environmental and human health concerns about the use of many older-generation insecticides, such as DDT. The result is that the number of public health insecticides available is dwindling and vector-borne disease transmission is increasing. Furthermore, early efforts to reduce indoor residual insecticide application rates have sometimes led to re-emergence of disease. For example, limiting malaria vector control applications in Mexico and India to foci of *Plasmodium* transmission was accompanied by increases in dengue and leishmaniasis transmission in untreated areas [11].

Recently, Roll Back Malaria and other international programmes have advocated increased distribution of insecticide-treated nets. African Heads of State in the Abudja declarations (a collective statement by African leaders of how Africa will improve the health and wealth of its people) stated that, by 2010, 60% of pregnant women and children under five should be sleeping under treated

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Table 1. The current burden of vector-borne diseases[a,b]

Disease	Vector	Disease burden DALYs[c] (thousands)	Deaths y^{-1} (thousands)
Malaria	*Anopheles* mosquitoes	42 280	1124
Dengue	*Aedes* mosquitoes	653	21
Lymphatic filariasis	*Anopheles* and *Culex* mosquitoes	5644	0
Leishmaniasis	Sandflies	2357	59
Chagas disease	Triatomid bugs	649	13

[a]Source of data: WHO Special Programme for Research and Training in Tropical Diseases (TDR).
[b]Only diseases that are transmitted in and around the home and that will potentially be impacted by the tools developed through this programme are shown.
[c]DALYs, disability adjusted life years.

nets in malaria-endemic areas. They are a cost-effective intervention that requires little vertical malaria control infrastructure, but pyrethroids are the only insecticides currently recommended for net treatment by the WHO Pesticide Evaluation Scheme (WHOPES). Pyrethroid resistance now threatens the viability of this technology in several DECs, well before this Abudja target has been achieved. Effective optimal control of vector-borne diseases requires that communities have accurate information, access to insecticide-treated nets, to indoor spraying technology, to improved insecticides and integrated decision support systems on which to base control applications.

The Innovative Vector Control Consortium

The Innovative Vector Control Consortium (IVCC) is an initial five-year programme, established in November 2005 and, funded by the Bill and Melinda Gates Foundation. It is a new public–private partnership designed to improve the tools and technologies available for malaria and dengue vector control. Its ultimate goal is to reduce transmission of mosquito-borne pathogens around the home through improved control of adult household vectors with innovative tools. Vector control tools that the IVCC will produce, although developed for control of malaria and dengue, are intended to be used for control of all indoor transmitted vector-borne diseases. Five partner Institutions in Africa, Europe and the USA were instrumental in establishing the IVCC.

The IVCC has two distinct objectives: (i) to produce improved insecticides and formulations; and (ii) to provide improved tools for a decision support system that will be used at the community level to reduce disease transmission. Although these can be achieved independently, they are complementary, and the major attributable benefit to disease control will come from simultaneous deployment of products from them both. Failure of earlier vector control programs, for example, was due largely to poor implementation of vector control strategies. By tackling the requirement for better insecticides and the need for better implementation systems, the IVCC will have a major effect on malaria and dengue disease control paradigms. A summary of the specific aims of the IVCC is given in Box 1.

The IVCC is advised by stakeholders and by two External Scientific Advisory Committees (ESACs). The ESACs will be asked to evaluate all potential IVCC projects against four major indicators: (i) whether the project will produce products that will be used to reduce vector-borne disease transmission, and where they will fit into current control activities; (ii) whether the product will be bought for, purchased or accepted by DECs to help them reduce disease transmission; (iii) whether there is a credible regulatory pathway for the products, and whether the outputs comply with that system; and (iv) whether the products can be sensibly produced in a format that facilitates global access to this technology.

New insecticides and formulations

There are two distinct tracks within the IVCC, the first of which aims to develop new insecticides and formulations. The second currently has four pre-selected projects to improve vector control delivery.

Rationale and product selection

No new public health insecticides have been developed for mainstream vector control in DECs for 30 years. The small market for public health pesticides, contraction of the agrochemical industry and loss of commercial public health expertise have contributed to commercial disengagement. As a result, there is a paucity of insecticide choices for public health use. New cost-effective insecticides are required for safe and effective deployment in the home to supplement and replace those currently available. These new insecticides must provide solutions to

Box 1. Aims of the Innovative Vector Control Consortium

- To develop alternatives to existing pyrethroids for insecticide-treated materials and indoor residual (long-lasting) spray treatments.
- To develop longer lasting insecticide formulations for such materials and sprays.
- To develop insecticide combinations, such as bi-treated nets and insecticide treated materials, which are useful in areas where insecticide resistance might otherwise be a problem.
- To refine and further develop an informatic tool for use at the community level that includes relevant literature, decision support software, and access to one or more central databases of entomological, epidemiological and related data in a GIS-based format.
- To develop and extend simulation and analytical models that can be used to establish the threshold levels and various entomological end points that will need to be achieved for optimal vector control and disease prevention.
- To develop a field-appropriate kit for quantifying the amount of pyrethroid insecticide remaining on insecticide-treated materials.
- To develop one or more field-appropriate tools for monitoring essential characteristics of local vector populations (e.g. insecticide resistance).

overcoming the increasing problems of resistance to current insecticides [12].

Development of new public health insecticides demands investment. The cost of developing a single new insecticide is in the range of US$70 million. The overall annual public health insecticide market – for all diseases and all developing countries – is ~US$151.2 million. Clearly, market size limits commercial-sector investment and the pipeline of new insecticide candidates is therefore small [13]. At the same time, new tools must support the move away from donor dependency. A natural corollary is that commercial partners must be engaged from the outset in the development of new insecticides and in making them available at an appropriate cost to DECs. The IVCC will engage commercial and academic partners in a dialogue with community-level health workers to stimulate and guide investment in the development of new insecticides and new, user-friendly technological tools with which to manage disease-vector control operations.

The portfolio approach

To rectify the market failure to produce new public health insecticides, the IVCC will develop a portfolio approach to produce a vibrant pipeline of potential new products for disease vector control. That is, it will attempt to support a balanced portfolio of different products that reflect market need and the potential effect that these new products could have on disease transmission, rather than just considering each potential product on its own mreits. There will be a coherent, transparent, format for project evaluation that will enable the IVCC, with the technically competent ESAC, to assess and rank each project on its merits and its ability to fulfil the stated criteria (Table 2) for inclusion in the pipeline. These criteria will ensure that new products are an improvement over currently available insecticide-based products. The IVCC will generate a balanced portfolio of projects at different stages in the development cycle with different risk-reward profiles. New insecticides for insecticide-treated materials and indoor spraying applications will include alternative active ingredients, longer-lasting formulations, and new combinations of existing insecticides.

The role of industry in the IVCC is crucial. All projects entering the pipeline require an active industrial partner at an early stage. Although the origin of the intellectual property and the exact role of the industrial partner for each product will be variable, they will, as a minimum, guide and undertake the regulatory toxicological analysis, registration, marketing and manufacture. For each product, a detailed project plan will be developed involving accurate time-lines and milestones. Projects will not be initiated or funded until this detailed programme has been evaluated and agreed. Projects that fail to meet their milestones can be terminated at annual review and replaced with alternative projects within the pipeline.

This portfolio approach will also enable responses, over time, to new product-development ideas arising from different sources. The close partnership with industry will ensure that we can foster industrial links for potential products arising primarily from academics or DECs that enter the development pipeline. Evaluation of products will be undertaken in collaboration with operational vector control programme managers. Insecticide-based products will be put through the formal WHOPES phase I–III studies [14] to ensure the acceptability and global accessibility of products before full-scale production.

Improved decision support tools for vector control

Public health programme managers apply insecticides for disease control on the basis of incomplete, often anecdotal data and/or general guidelines. For example, data about insecticide resistance in the vector population are either obtained in an *ad hoc* manner or inferred from apparent failure of vector control. The four projects that make up Objective 2 are designed to improve decision making about management of malaria and dengue vector control programs. The projects will involve an iterative approach – design followed by evaluation and then refinement – in a series of disease endemic country contexts to produce broadly applicable tools.

The new tools will contribute to improved control through: (i) more directed and efficient monitoring of entomological and epidemiological parameters related to transmission; (ii) more effective control of vector mosquitoes, through prompt, timely and focused application of insecticides, which will delay insecticide resistance; (iii) more effective and efficient use of resources; and (iv) better design and development of new-generation pyrethroids through real-time interactions between the two

Table 2. Pre-project checklist[a]

Development	Marketing	Industrialization
Industrial partnership is agreed	Market fitness has been assessed	Access to insecticide is guaranteed
Industrial partnership cost sharing is agreed	First development costs have been planned for	Access to formulation capacity is in place
Insecticide is defined	Access to potential insecticide is guaranteed	There is intellectual property protection on production process
Formulation type has been established	An improvement on the existing technical answer has been shown	Time-line has been agreed with industry
Time-line is agreed	Intellectual property protection is in place	Production plant is available
Technical dossier is in place	The relevant country is interested	Production capacity is there
Patent protection is in place	Sales projections have been made	Formulation has been selected
Concept definition has been outlined	Risk evaluation has been done	Product safety profile has been determined
Development planning is in place	Development team has been agreed	Packaging solutions have been found
		Cost of product has been estimated at +/− 10%

[a]The criteria for new public health insecticide project selection that must be in place before projects move into this program. All projects will be assessed against these criteria before funding will be awarded.

consortium arms. The expected outcome is reduced transmission of vector-borne diseases, reduced abundance of arthropod vectors, optimization of insecticide use whether sprayed or in nets, and increased empowerment of community-level public health officials and populations.

New technological tools will support improved decision making at the community level. The IVCC will develop an informatic tool that includes data, decision support software, and online access to one or more central databases of entomological, epidemiological and related data in a GIS-based format, combined with improved models of dengue and malaria transmission. This will be complemented by the development and deployment of field-appropriate kits for monitoring essential characteristics (vector abundance, species composition, infection status and insecticide resistance status) of local vector populations and quantifying the amount of pyrethroid insecticide remaining on insecticide-treated materials. Each new tool is described briefly below.

Decision support systems

Producing a successful decision support system will require answers to three interrelated questions. First, what is an acceptable level of disease risk? In practice, public health officials will usually set goals based on the individual needs of their country or region. The decision support system will therefore need to be dynamic; that is, predicted goals will need to fluctuate as transmission and successes in disease prevention rise and fall. Second, what are the mosquito densities necessary to achieve desired disease reduction goals? This will require an understanding of the relationship between mosquito density and parasite transmission to predict the public health impact of specified reductions in the abundance of mosquito vectors. Modelling the impact of different interventions (i.e. insecticides and implementation strategies) on vector populations and pathogen transmission will address this concern. Third, what is the best way to measure entomological risk? Although there are differences in the details of transmission and control between malaria and dengue, consideration of these three questions forms a conceptual basis that transcends disease-specific differences and that will be a source of useful interaction between dengue and malaria control groups.

The iterative development of the decision support system, and the collection of essential data needed to support it, will take place within the context of regional and community-level control programs in Africa (Mozambique, Malawi and Zambia) and Latin America (Peru and Mexico). These locations were selected for the initiation of project activities because they cover the two major African malaria vectors, include at least one site with transmission of both malaria and dengue, and represent the epidemiological and ecological extremes of malaria and dengue transmission. The intention is that all decision support tools will eventually be generalisable to other settings.

Operational activities in Peru and Mexico will provide data for the dengue decision support systems. They will establish, in dengue-endemic field settings, whether new insecticides combined with novel delivery systems can supersede the current inefficient and unsustainable *Aedes* control efforts, which are based on the elimination of larval development sites and on sprays for home use [15]. The importance of concentrating efforts on controlling *Aedes* in homes, as proposed by the IVCC, is supported by the fact that, during a dengue outbreak in Puerto Rico, the number of adult *Aedes* mosquitoes per household per person was the only significant risk factor [15], and the indoor application of insecticide by the Ministry of Health in Iquitos, Peru, aborted a dengue epidemic during 2002 (A.C. Morrison and T.W.S., unpublished).

Simulation and analytical models for malaria and dengue

The IVCC will develop control analytical and simulation models and establish estimates of control thresholds required to reduce or eliminate disease transmission. This, in turn, will inform and guide the development of informatic tools. Because geographical and temporal variation is expected in transmission dynamics, and thus in the control strategies necessary to prevent disease, the validity of the models for malaria and dengue will be tested in four different transmission settings to demonstrate that they can be adapted for use in most DECs. There will also be collaboration across modelling groups, so that models are validated with data and that relevant models are incorporated into the decision support informatic tool.

Population monitoring tools

Entomological input into the database will initially come from classical taxonomic, molecular and biochemical analysis of mosquitoes from sentinel (fixed) site collections. Less labour-intensive analysis of samples will increase as new vector population monitoring tools (such as the IVCC insecticide resistance diagnostic kit) are evaluated and used. The available high-tech dengue and malaria vector population monitoring systems will be replaced by simpler DNA-based high-throughput formats that can be used on dried or alcohol-preserved mosquito samples. Monitoring for parasite infection and vector species will use fixed characteristics of the parasite and vector, respectively. These will not change over time. Monitoring for insecticide resistance is more technically demanding, as this involves dealing with a dynamic set of characteristics in the vector that are expected to evolve over time. To overcome this, the microarray and low-tech DNA-based kit approaches will be continued in parallel. The high-tech approach, based on the available *Anopheles gambiae* detoxification microarray chip [16] (a chip that contains all the possible genes involved in chemical detoxification), will be used periodically to monitor field populations. Periodic screening of mosquito populations against this microarray will establish whether novel resistance genes have been selected in vector populations. If and when such genes are detected, they will rapidly be added to the simple high-throughput screen. The DNA-based high-throughput monitoring kit will be used as a routine field technique to monitor changes in frequencies of known resistance genes.

Pyrethroid quantification kit

The IVCC will produce a simple field applicable kit for monitoring insecticide residues on insecticide-treated materials [17]. This will be used for quality control of new nets and as an indicator for when re-treatment of a net is needed. Good stewardship of the new active ingredients and formulations of the IVCC, by providing communities at the same time with better decision support systems to guide and optimize product use, will extend the effective lifespan of the products, maximize their impact on disease transmission and minimize their environmental impact.

Global access issues

The only source of investment return for an insecticide registered for malaria control is through sales of the product to programme managers in malaria-endemic countries. Although small, this return can be enough (when combined with public sector inputs) to sustain insecticide manufacture and distribution. Economic feasibility and commercialization analyses will be early and important criteria for prioritization of candidate pesticides for development. Commercial partners will be expected from the outset to commit resources in kind toward the development effort, and to provide pricing and availability plans in their initial presentations. Significant effort will be spent determining the appropriate and necessary balance between commercial and non-commercial investments in public health insecticide development, to optimize accessibility.

New insecticides and formulations will be actively marketed by the commercial partners of IVCC to the public sector in DECs at an affordable cost. The External Advisory Council of the IVCC, along with stakeholders, will help to ensure that new tools are rapidly assimilated into mainstream vector control activities. The IVCC will carry out a communication and dissemination strategy designed to transfer information in a timely and informative manner to user communities and other stakeholders. The IVCC will actively distribute information on its products as they are developed, through a broad range of academic, professional and trade routes. In this way, it will reach both the public and private sectors in DECs and ensure optimum uptake of new products in a well co-ordinated manner that maximizes the potential for reducing disease transmission. However, although vector control tools produced by the IVCC will be developed on malaria and dengue platforms, they will be applicable for control of all indoor transmitted vector-borne diseases.

Conclusions: the impact of the IVCC on disease reduction

A major strength of the IVCC is its direct links with existing disease prevention programs. All its interventions will be tested within the context of these real control programs; both the new insecticide formulations and the refinement of its informatics and decision support tools will therefore be informed continuously and specifically by local control efforts. Effective implementation of the new innovative vector control tools, which will be based on rigorous evaluations in the context of DEC disease prevention programs, will contribute to: (i) more effective reduction of disease vector populations; (ii) major reduction in transmission of vector-borne disease; and (iii) more cost effective and efficient use of resources.

This approach will translate into the most important attributable benefit, reduction of disease burden and numbers of deaths from vector-borne disease. Vector control alone can reduce malaria transmission in highly endemic areas by up to 50%. In combination with improved drug and vaccine initiatives there is the potential to move towards local or regional elimination of one or more of these vector-borne diseases [18].

References

1 Gramiccia, G. and Beales, P. (1988) The recent history of malaria control and eradication. In *Malaria: Principles and Practices of Malariology* (Wernsdorfer, W.H. and MacGregor, I., eds), pp. 1335–1378, Churchill

2 Mabaso, M.L.H. *et al*. (2004) Historical review of malaria control in Southern Africa with emphasis on the use of indoor residual house-spraying. *Trop. Med. Int. Health* 9, 846–856

3 Roberts, D.R. *et al*. (2000) DDT house spraying and re-emerging malaria. *Lancet* 356, 330–332

4 Department of Health, Taiwan, eds (2005) *Malaria Eradication in Taiwan* (2nd edn), Center for Disease Control

5 Phillips-Howard, P. *et al*. (2003) Efficacy of permethrin-treated bed nets in the prevention of mortality in young children in an area of high perennial malaria transmission in western Kenya. *Am. J. Trop. Med. Hyg.* 68, 23–29

6 Lengeler, C. (2004) *Insecticide-Treated Bed Nets and Curtains for Prevention of Malaria* (Cochrane Review), The Cochrane Library Issue 1, John Wiley & Sons

7 Schellenberg, J.A. *et al*. (2001) Effect of large scale social marketing of ITNs on child survival in rural Tanzania. *Lancet* 357, 1241–1247

8 Lindblade, K.A. *et al*. (2004) Sustainability of reductions in malaria transmission and infant mortality in western Kenya with use of insecticide treated bed nets – 4 to 6 years of follow-up. *J. Am. Med. Assoc.* 291, 2571–2580

9 Rigau-Perez, J.G. *et al*. (2002) The reappearance of dengue-3 and a subsequent dengue-4 and dengue–1 epidemic in Puerto Rico in 1998. *Am. J. Trop. Med. Hyg.* 67, 355–362

10 Gubler, D.J. (1989) *Aedes aegypti* and *Aedes aegypti*-borne disease control in the 1990s: top down or bottom up. *Am. J. Trop. Med. Hyg.* 40, 571–578

11 Bora, D. (1999) Epidemiology of visceral leishmaniasis in India. *Nat. Ned. J. India* 12, 62–68

12 Zaim, M. and Guillet, P. (2002) Alternative insecticides: an urgent need. *Trends Parasitol.* 18, 161–163

13 Broadhurst, M. (1999) The influence of the molecular basis of resistance on insecticide discovery. In *Insecticide Resistance: From Mechanisms To Management* (Denholm, I., ed.), pp. 47–52, The Royal Society

14 Wright, J. (1971) The WHO programme for the evaluation and testing of new insecticides. *Bull. WHO* 44, 11–22

15 Rodriquez-Figueroa, L. *et al*. (1994) Risk factors for dengue infection during an outbreak in Yanes, Puerto Rico in 1991. *Am. J. Trop. Med. Hyg.* 52, 496–502

16 David, J. *et al*. (2005) The *Anopheles gambiae* detoxification chip: a highly specific microarray to study metabolic-based insecticide resistance in malaria vectors. *Proc. Natl. Acad. Sci. U. S. A.* 102, 4080–4084

17 Enayati, A.A. *et al*. (2005) Field evaluation of a recombinant glutathione S-transferase-based pyrethroid quantification assay. *Trans. R. Soc. Trop. Med. Hyg.* 99, 369–378

18 Breeman, J. *et al*. (2004) Conquering the intolerable burden of malaria: what's new, what's needed. A summary. *Am. J. Trop. Med. Hyg.* 71, 1–15