Summary Meeting Report
A Critical Assessment of Vector Control for Dengue Prevention
Workshop sponsored by the Partnership for Dengue Control (PDC)
11-12 November 2013, Washington, DC

Background: Recently, the Vaccines to Vaccination (v2V) program expanded its' scope, goals, and administration from a focus on vaccines to more integrated and synergistic approaches for the prevention and control of dengue. It is now referred to as the Partnership for Dengue Control (PDC). This shift is consistent with the growing consensus among the dengue prevention community that no single intervention will be sufficient to control dengue and that sustained disease prevention will require integration of multiple intervention strategies. To that end, the mission for the PDC is to promote development and implementation of innovative, integrated, synergistic approaches for the prevention and control of dengue.

Recent results from dengue vaccine trials indicate varying levels of efficacy under field-based clinical trials. When an effective dengue virus (DENV) vaccine is commercially available, the public health community will likely continue to rely on vector control because the two strategies compliment one another. A dengue vaccine will artificially elevate herd immunity and vector control will lower the force of infection. Two examples illustrate the power of targeting the vector and pathogen for disease prevention. The first concerns reductions in malaria burden using anti-*Plasmodium* drugs in conjunction with insecticide treated bed nets (ITNs). The other involves more rapid and increased efficacy of lymphatic filariasis (LF) management when anti-parasite drugs are combined with vector control than when drugs alone are used. Guidance for this kind of intervention integration of dengue, a multi-strain pathogen with complex transmission dynamics, can be supported with mathematical and simulation models.

Purpose: Although the concept of integrated intervention for dengue prevention is currently broadly accepted, no consensus has been reached regarding the details of how a combination of approaches can be most effectively implemented to eliminate dengue virus transmission to humans. To fill that gap a vector sub-group of the PDC proposed a workstream with two components: (1) to critically review current and future vector control tools and strategies for dengue prevention and (2) to develop a plan for substantially advancing effective application of vector control for dengue prevention, including integration of vector control with other means, including vaccines, of dengue prevention. Objectives will be accomplished using a series of convened workshops comprised of multi-disciplinary panels. Although combining vector control and vaccine interventions is the long-term PDC goal, the focus of the meeting summarized in this report was to objectively draw conclusions regarding vector control where possible, identify critical gaps, and propose the most productive way forward to fill these gaps.

Framework: The workshop was structured using a series of presentations falling into three categories: (1) state-of-the-art, (2) new vector control tools and strategies, and (3) mosquito ecology and modeling (see Supplemental Table 1). Following presentations, individual breakout groups were convened to critically assess existing interventions and novel tools and strategies currently in development. Specific objectives included outlining where we are, where we need to be, what are the most promising tools and strategies, and how integration among vector control interventions should/can be accomplished. Criteria were used for assessment are summarized in Box 1.

Outcomes: Key summary points from the workshop are outlined in **Box 2**. The first and most critical is that vector control can, does, and has contributed to the management of dengue virus transmission in humans. In order for this to happen, implementation must be done thoroughly, comprehensively, and sustained; a framework that unfortunately is not followed or feasible as often as desired. The global burden of dengue is, therefore, increasing.

Ineffective implementation is likely decreasing the effectiveness of existing tools; i.e., poor local effort, erratic distribution, “making the most” of too little, etc. A critical shortfall is that there have been almost no cases where vector control for dengue management was evaluated using epidemiological metrics; i.e., virus infection rate. Because the relationship between mosquito density and disease incidence is likely not simple or linear, it is difficult to predict and challenging to assess how well existing and/or developing tools function to prevent disease. The lack of data on health impact, may be carryover from *Ae. aegypti* eradication efforts during the early 1900s to prevent yellow fever.

Existing Tools and Strategies

(see Current Tools & Strategies Spreadsheet)

A list of currently recommended vector control interventions was generated from WHO guidelines for dengue control. Using specific assessment criteria (Box 1), the panel categorized tools according to two primary uses (1) epidemic mitigation and (2) sustained mitigation. Within each category, interventions were labeled as (1) recommended, (2) effective under specific circumstances, (3) lack of sufficient data to allow adequate assessment, and (4) not recommended. The primary factor for inability to recommend a particular approach was the lack of data supporting a health impact. Two additional strategies added to the WHO list; topical repellents and legislation (regulation). The purpose of the panel discussion was not to dispute WHO guidelines, but rather to provide an objective framework to guide decision-making regarding the effective integration of existing interventions.

Of the tools/strategies assessed, those recommended for sustained mitigation include indoor sprays, preferably with residual insecticides, and perifocal spraying with residual insecticides to control adult mosquitoes. Container larvicide treatment (with insecticides and biologicals) and container removal also recommended for management of immature mosquitoes. Social mobilization campaigns (education, public relations), environmental management and legislation (enforcement and incentives) were considered effective measures for sustained control. Aerial spraying and truck ULV space-spraying were deemed as not cost-effective for routine delivery or sustained dengue transmission mitigation. On the other hand, spraying with low-flying aircraft was recognized as an approach for epidemic mitigation, under specific circumstances, in conjunction with indoor residual spray, personal repellents, such as DEET, and bed nets. Data is lacking to critical assess to what extent the last two interventions reduce dengue cases during an epidemic.

Panel noted that any vector control strategy will be site-specific based on virus and vector dynamics. Political pressures may drive implementation of highly visible activities during inter-epidemic time periods, but it is time to push-back on using interventions simply because they have been used in the past. The true public health cost-benefit must be demonstrated if we aim to reduce the public health burden of dengue on a regional or global scale. Limited resources in endemic countries must be more efficiently targeted to only those essential activities that will make an impact during specific virus transmission scenarios, even if this policy change results in implementation challenges.

Recommendations for improving sustained mitigation include creating a ‘career structure’ that will facilitate maintaining trained staff, including throughout inter-epidemic periods. This could include generating permanent positions that ensure sustainability and generate work schedules that fit community lifestyles; i.e., when community residents are home.

Although existing interventions are often not adequate for epidemic control, because of the lag between detection of elevated risk and response, epidemic response tools and strategies can reduce dengue cases. Improved surveillance efforts that guide spatial and temporal implementation of vector control activities are needed to elevate the public health impact epidemic suppression strategies. Emergency legislation for immediate access to vacant lots, households, schools, and/or offices may be required, where not currently enacted, to allow comprehensive targeting of key transmission sites.

Tools Currently Under Development

(see Tools Currently in Development Spreadsheet)

Because existing tools for suppressing dengue-vectoring mosquito populations are often judged ineffective as currently used, there has been an increase in efforts to develop new tools. Some of the new tools are being developed by technological improvement of existing approaches and others involve conceptually novel approaches that have emerged from recent breakthroughs in biotechnologies.

Workshop participants developed a list of new tools/strategies for dengue suppression that are aimed to operate based on (1) overall mosquito population reduction, (2) change the age distribution of female mosquitoes, (3) behavioral manipulation of female mosquitoes, (4) replacement of wild type mosquitoes with strains/genotypes that don’t transmit dengue virus, or (5) some combination of the above tools (see Tools Currently in Development Spreadsheet).

Each of these tools was evaluated based on a number of criteria related to (1) current stage of development, (2) predicted efficacy, (3) expected limitations, and (4) potential for integration with other tools (see Tools Currently in Development Spreadsheet). Below is a summary of workshop deliberations.

Population reduction and altered age distribution: Synthetic insecticides have long been used to suppress mosquito populations and truncate mosquito life span, but impacts on human health, lack of intrinsic efficacy, and the evolution of insecticide resistant mosquitoes are problems challenging the usefulness of this tool. Two major paths toward alleviating these problems come from investment in new chemical classes of insecticides and efforts aimed at developing “molecular insecticides” that use specially engineered nanoparticles to target insecticides at specific insect tissues and protect them from environmental degradation. There have been major investments in developing and testing new insecticides within existing chemical classes (and in new classes) with low off target effects and long residual efficacy. Some of the first products from these efforts are expected to be field-tested in the near future, while completely novel compounds should soon follow. The goal is to have a tool that is as effective at suppressing mosquitoes as was DDT (high kill and/or repellent with an effect for 6 months or more), but without the health or environmental impacts associated with DDT. It is too early to assess the potential for reaching that goal.

There are a number of tools in the pipeline that involve using insect transgenesis to suppress mosquito populations. The tool that is furthest developed is an *Ae. aegypti* strain engineered by the start-up company, Oxitec, that has conditional lethality (RIDL^{R}). The genetically engineered strain can be reared to high numbers in a laboratory or factory as long as there is tetracycline in the larval diet, but once that is removed, the subsequent generation of larvae will die. Death occurs if both parents are from the transgenic strain or if a transgenic male or female has mated with a wild mosquito in the field. Data from small-scale trials indicate that wild populations can be suppressed, but suppression takes a number of months and requires continual release of the transgenic strain. This approach is expected to work best when the initial population is at low density and is in a small area. Promising results have been obtained from field trials in small communities in Brazil. This approach could be used with other tools that would decrease population size before mosquitoes are released.

A public private partnership (Gate/Oxitec) has developed another transgenic strain in which only the females die when tetracycline is removed from the diet. Theoretically such a strain would be substantially more effective than one in which both sexes die. Results from field-cage tests in Mexico have been disappointing, but new versions of the strain may have better performance. Detailed population dynamics models indicate that mosquito suppression with this female-killing technique may be problematic in heterogeneous city settings. Some researchers question the feasibility of RIDL for large cities due to logistic challenges and concerns about cost.

Other transgenic methods that are in early stages of development could result in strains that would suppress wild *Ae. aegypti* populations based on a single release of the transgenic strain. For any transgenic strain, public acceptance is not assured.

Another tool based on novel biotechnology methods is the insertion of a microbe, *Wolbachia*, into *Ae. aegypti*. A specific application of this technology was aimed at reducing the wild *Ae. aegypti* populations and especially reducing the number of females that live long enough to transmit DENV. Field tests of this strain in Australia and Vietnam have been disappointing. New life-shorting strains are in development, but are not as encouraging as refractory strains noted below.

It is well accepted that eliminating female mosquitoes before they have completed their incubation period for DENV and become infectious should decrease DENV transmission. Trapping of female mosquitoes as they attempt to lay eggs in houses has, therefore, been considered as a potential dengue control approach for many years. Early attempts were not successful. Recent research, however, has resulted in a more efficient trap design coupled with a formulation of bacteria that produces volatile compounds that are attractive to ovipositing females. Preliminary field tests appear to have resulted in fewer human DENV infections, larger and more comprehensive trials with epidemiologic outcomes are planned.

Other tools for population suppression in early stages of development include a mosquitocidal fungus and the application of mathematical models to assist in better use of existing control tools and optimizing tools and strategies in development. Early tests of curtains impregnated with insecticide were not successful.

Behavioral manipulation: Use of repellents to keep mosquito vectors away from humans is receiving increased research attention. Field trials are being designed to evaluate new approaches for using repellents in more effective ways to interfere with mosquito-human contact and control dengue.

Refractory strains/genotypes: Some mosquito strains developed with new biotechnology methods are aimed at reducing mosquito population size. Others have been developed with the goal of interfering with and reducing DENV transmission. Furthest in development is an *Ae. aegypti* strain transfected with *Wolbachia* that is designed to block transmission to humans by inhibiting DENV infection in mosquitoes, while not substantially impacting female mosquito longevity. Field trials in Australia and Vietnam are underway, persistence of one strain is well established locally, potential for spread is being evaluated, new strains are in development, laboratory results are consistent with transmission blocking, and field trials to assess the epidemiologic impact of *Wolbachia* transfected Ae. aegypti on DENV transmission are planned for the near future.

Another approach for developing an *Ae. aegypti* strain that doesn't transmit dengue is to engineering a sequence of DNA into the mosquitoes genome that when transcribed, produces an RNA molecule that blocks DENV replication. A strain that blocks transmission of DENV-2 has been developed and shown effective in the laboratory. No field tests have been conducted. Mathematical models indicate that to spread this transgene into wild populations would require far fewer lab-reared mosquitoes than the conditional lethal RIDL approaches, but would likely require releases lasting a year. The current strain would only inhibit one of the four DENV serotypes. Efforts are underway to develop a transgenic strain that does not transmit any of the DENV serotypes.

Instead of spreading anti-dengue genes into populations through repeated releases, transgenic approaches are being developed that link an anti-dengue gene with a gene-drive mechanism that pushes the anti-dengue gene into the mosquito population based on super-Mendelian inheritance. A major effort has involved a gene drive mechanism, Medea, in which all offspring from a female die if they do not inherit the gene-drive sequence and the linked anti-dengue gene. Despite long-term efforts, this approach has not worked in the laboratory. This and other gene drive mechanisms have worked in fruit flies. It is, therefore, predicted that with more effort it should be possible to developing function in mosquitoes.

Recommendations and Next Steps

In order to address the increasing global dengue burden, there must be increased capacity for *informed* preventive versus reactive vector control efforts, either using existing or novel interventions with improved, more efficient delivery systems. Developing the conceptual basis and logistic methodologies for scaling up small-scale vector control successes to the megacities in which dengue is endemic should be a priority. Unless and until this is accomplished, dengue burden will continue to grow. Effective scaling will require accurate, validated, stochastic disease models integrating vector, health, virus, climate, and social science datasets with granularity that will support effective targeting of key spatial-temporal foci of dengue virus infection.

Because some existing vector control interventions have time lags in impact, they may reduce dengue cases, but be inadequate for epidemic control. It is anticipated that new tools in this arena will compensate for existing ones and provide strategic advantages. A critical roadblock in this regard development of a new dengue prevention tool box that is supported by a theory for dengue control, which does not currently exist, so that there is a well conceived conceptual basis for strategic innovation and rigorous intervention assessment. Similarly, there is a lack in capacity to measure the reduction from efficacy to effectiveness in the real-world as difficulties exist in modeling what we “expect” to measure due to lack of data from large-scale experimental trials. Funding for such research should be a priority moving forward.

Lastly, eliminating dengue as a public health burden will ultimately only be achieved by integrating vector control with vaccines. This integration will pose new challenges such as preparing vector control operations for variation in spatial-temporal rollout of vaccines, effective integration of entomologic measures within vaccine trials [during epidemiological characterization of study sites] to guide setting thresholds and indicators of impact as well as the need to develop guidelines for such studies for rigorous standardization across sites/trials – all of which focus on early and active engagement among stakeholders, a topic that will be posed during subsequent workshops.

BOX 1. Dengue Vector Control Assessment Criteria

Group 1: Existing vector control tools and strategies (Supplemental Table 2).

- What vector control tools/approaches are currently available?
- What works, why does it work, and under what circumstances does it work?
- What does not work and why?
- Costs and other delivery challenges
- How can best options be integrated with other interventions?

Group 2: Tools and strategies currently in development (Supplemental Table 3).

- What vector control tools/approaches are in development?
- What is most promising, how does it work, why should it prevent disease, and under what circumstances do we expect it to work?
- Steps required prior to broad scale public health application
- Costs and other delivery challenges
- How can best options be integrated with other interventions?

BOX 2. Summary Points

- Vector control for management of dengue virus transmission does work when performed "properly", but most of the time tools and strategies are not implemented “properly”.
- New vector control tools and strategies will face many of the same challenges as the old/existing interventions.
- There is a requirement for improved capacity and subsequent monitoring and surveillance data to drive the establishment of entomological thresholds required for health impact.
- Controlled experimental studies are needed to assess the health impact of dengue vector control interventions (entomological and epidemiological indicators).
- Detailed vector ecological studies are required to parameterize and validate dengue transmission models.
- Existing models indicate the potential to target vector control interventions more effectively and there is value in building more robust models to predict intervention success based on entomological, epidemiological and viral parameters.
- Close collaborations among lab, field, and modeling researchers will be needed to more adequately measure effect size of current and/or future dengue control efforts.
- Success in reducing dengue as a public health burden will require a multi-pronged approach that includes developing the underlying theory of effective dengue control, continuing to review and assess existing data and gathering new empirical data that tests fundamental concepts and strategies.

Workshop topics and corresponding speakers

Review State-of-the-Art	**New Vector Control Tools and Strategies**	**Mosquito Ecology and Modeling**
Overview of Foundation Merieux *Louise Gresham, CEO*	Combining Vaccines with Vector Control *Thomas Scott, UC Davis*	Community-based Control *Eva Harris, UC Berkeley*
Overview of Partnership for Dengue Control *Duane Gubler,* Duke-NUS Graduate Medical School, Singapore	Insecticides *Charles Wondji, Liverpool School of Tropical Medicine*	Vector Ecology and Dengue Prevention *Roberto Barrera, CDC Puerto Rico*
Dengue Vaccine Initiative and Overview of Dengue Vaccines *Georges Thiry,* International Vaccine Institute	Molecular Insecticides *Barry Beaty, Colorado State University*	Modeling Virus Serotype Interaction and Strain Variation *Deric Cummings, Johns Hopkins University*
WHO Global Strategy for Dengue Prevention *Joachim Hombach, WHO*	*Wolbachia* *Scott O'Neill, Monash University*	Modeling Cost-Effectiveness of Dengue Prevention *Donald Sheppard, Brandeis University*
Framework for Intervention Validation *Thomas McClean, IVCC*	RIDL *Hadyn Parry, OxiTec*	Predicting Surveillance and Intervention Success *Karen Campbell, San Diego State University*
Entomological Surveillance *Amy Morrison, UCDavis/NAMRU-6*	Genetic Strategies *Fred Gould, North Carolina State University*	
Current Vector Control Tools and Practices *Scott Ritchie, James Cook University*	Spatial Repellents *Nicole Achee, University of Notre Dame*	
	Lethal Ovitraps *Dawn Wesson, Tulane University*	