Integrated Control of Dengue Through Vaccines and Vector Control
## CONTENTS

1  Summary

3  Context

4  Global Dengue Control Strategy

6  Vector Control Efforts in Countries of the Americas

12  New Technologies and Partnerships for Vector Control

13  Dengue Vaccine Development

17  Modeling the Impacts of Vector Control and Dengue Vaccination

19  Creating a Framework for Integrating Vector Control and Dengue Vaccination

21  Recommendations of the Dengue Prevention Board on Integration of Vector Control and Dengue Vaccination

21  Conclusions

22  Appendix 1: Speakers

24  Appendix 2: Participants

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Integrated Control of Dengue Through Vaccines and Vector Control

SUMMARY

The progress in dengue vaccine development, renewed community-based engagement, new developments in vector control, partnerships, and results from mathematical modeling of the impacts of vaccination and vector control warrant further assessment of the feasibility and benefits of integrating vector and vaccine prevention and control of dengue.

The Americas Dengue Prevention Board (AmDPB) meeting was held in Mexico City, Mexico, on 25 – 26 March, 2014, to answer the question “Assuming a dengue vaccine is licensed and introduced, how could a country integrate prevention of dengue through a vaccination program with current and/or new vector control methodologies?”

The meeting brought together vaccine experts, vector control specialists, researchers, academics, representatives of ministries of health, and vaccine manufacturers of candidate dengue vaccines. It provided the opportunity for participants to share information on country vector control efforts, on current and new vector control and vector surveillance developments, on vaccine developments, and on modeling the potential impacts of vector control and vaccination on disease incidence.
The World Health Organization notes that dengue is currently the most rapidly spreading vector-borne disease. All participating countries have experienced important increases in the incidence of dengue in recent years. In these countries, current vector control efforts are failing to prevent disease outbreaks.

However, several novel vector control tools are, or are soon to be, available (new insecticides, genetic and biologic control, spatial repellents and lethal traps) and these hold promise for greater impact on disease transmission.

A dengue vaccine is also expected in the coming years. Approaches that integrate both vector control and vaccination hold the best promise for prevention and control.

The potential impacts of integrated vaccination and vector control can be modeled and can help to better inform control strategies and vaccination rollout strategies.

Meeting participants brainstormed on all of the necessary components of a framework to integrate dengue vaccination and vector control. A list of requirements was established including minimum prerequisites for study design and appropriateness of study sites, the need for communication between sectors, for policies to guide control efforts, and for standardization of entomological and other surveillance indicators.

The meeting served to lay the basis for future collaborative and integrated approaches to dengue prevention and control.

At its conclusion the Dengue Prevention Board presented recommendations for integrating vector control with dengue vaccination. The Board concluded that integrated control presents the opportunity to:

1. **Strengthen** entomological and epidemiological dengue surveillance in countries;
2. **Standardize** disease and vector surveillance indicators across countries to evaluate vector control interventions;
3. **Enhance** collaborations between the DVI and PAHO;
4. **Determine** how to integrate vaccination in close conjunction with vector control; and,
5. **Study** the effectiveness of control efforts.

Countries considering early introduction of a new dengue vaccine are encouraged to undertake preparatory work to assess their state of readiness and capability for conducting the appropriate impact assessments of both vaccination and vector control on dengue virus transmission.
CONTEXT

Dengue is currently the most rapidly spreading vector-borne disease. Over the last 50 years, its incidence has increased more than 30-fold and dengue is now endemic in 128 countries. According to the WHO, almost 3 million cases of dengue were reported in 2013, and this was from only about 100 reporting countries. Although WHO estimates 50-100 million dengue infections each year, others have estimated the number of infections closer to 390 million each year, of which 96 million are clinically apparent. Furthermore, the risk of dengue has now surpassed the risk of malaria.

Twenty years ago, dengue primarily affected Asia and Latin America, where the vector Aedes aegypti proliferated in urban areas. But environmental changes have allowed for the spread of the vector and the virus into Europe. Today all five WHO regions are affected, and Aedes albopictus, a secondary vector, has been found in at least three EURO countries.

Aedes vector control over the last 40 years has most often been ineffective at preventing dengue outbreaks. Aedes eggs resist desiccation, breeding sites are often extremely difficult to find or to access, and insecticide resistance to pyrethrins and organophosphates has developed.

Fortunately, where case management has improved and where better diagnostics are available, case fatality rates from severe dengue have fallen.

New developments in vector control and the development of new antivirals and vaccines promise better dengue prevention and management for the future. However, no preventative or control strategy alone is likely to control dengue in the coming decade given the inadequacies of current vector control, the possibility that vaccines may have sub-optimal effectiveness, and the time required for an effective vaccine to have a population impact. Therefore, approaches that integrate both vector control and vaccination hold the best promise for prevention and control, especially with the advent of novel and effective vector control tools and paradigms. Moreover, the consequences of improved vector control extend beyond dengue to other high impact infections, such as yellow fever and Chikungunya, transmitted by Aedes aegypti, and Aedes albopictus.

The DVI held a two-day consultative meeting with its Latin America Dengue Prevention Board to identify how countries could integrate a dengue vaccination program with current and/or new vector control methodologies.

A meeting of the Asia Pacific Dengue Prevention Board was previously held in Bangkok, in October, 2013, for the same purpose and a meeting report has been published. The report has been supplemented by a needs assessment from the Boston Consulting Group, to understand what is needed for dengue vaccine introductions and the effective use of new vector control tools and to determine where there is value in an integrated approach.

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GLOBAL DENGUE CONTROL STRATEGY

The *Who Global Strategy for Dengue Prevention and Control, 2012-2020*, has a goal of reducing the global burden of disease. The strategy aims to: 1) reduce mortality by 50% by 2020; 2) reduce morbidity by 25% by 2020; and 3) estimate the true burden of disease by 2015. The strategy consists of 5 components (see Figure 1):

1. **Improvement** of diagnosis and case management;
2. **Integrated surveillance** and outbreak response;
3. **Sustainable** vector control;
4. **Future** vaccine implementation; and,
5. **Operational** and implementation research.

An action plan has been developed and several activities under each component have been completed or are ongoing. For effective implementation of the strategy, 5 enabling factors have been identified, all of which need increased resources and support from countries and the international community: advocacy and resource mobilization; partnerships, coordination and collaborations; communication to achieve behavioral outcomes (COMBI); capacity building; and, monitoring and evaluation.

In addition, a Vector Control Advisory Group (VCAG) has been established to review the public health value and epidemiological impact of new vector control tools, and to issue recommendations for their use in integrated vector management.

**The Partnership for Dengue Control** (PDC) was established in July 2013 and supports WHO’s Global Strategy. The PDC’s vision is to eliminate dengue as a public health problem, working to advance the WHO Global Strategy by accelerating innovations in vaccines, vector control, antivirals, clinical management and therapeutics, diagnostics, surveillance, and social mobilization, and by strengthening advocacy, capacity building and networking.

The first objective of PDC is to create a forum in which scientists from different domains can sit together. The goal is to develop an action plan (including an operational research agenda) to be submitted to the agencies that support and fund PDC.

The PDC functions with funding from multiple donor organizations. It anticipates being governed by an independent scientific and policy advisory committee, and it currently has a secretariat hosted by the Fondation Merieux.
GOAL: TO REDUCE THE BURDEN OF DENGUE

OBJECTIVES

➤ To reduce dengue mortality by at least 50% by 2020
➤ To reduce dengue morbidity by at least 25% by 2020
➤ To estimate the true burden of the disease by 2015

ENABLING FACTORS FOR EFFECTIVE IMPLEMENTATION OF THE GLOBAL STRATEGY

➤ Advocacy and resource mobilization
➤ Partnership, coordination and collaboration
➤ Communication to achieve behavioral outcomes
➤ Capacity building and
➤ Monitoring and evaluation

Source: Dr. Raman Velayudhan, World Health Organization
VECTOR CONTROL EFFORTS IN COUNTRIES OF THE AMERICAS

Representatives from 9 countries (Mexico, Nicaragua, Paraguay, Colombia, Venezuela, Argentina, Costa Rica, Brazil, and Puerto Rico in the US), provided an overview of the current methods used in vector control of Aedes aegypti (and Aedes abopictus) in their countries, how vector control is structured, and the impact it has.

All have recently experienced a rise in cases and in deaths from dengue in spite of vector control activities, and for several countries, 2013 was the worst year ever for dengue. All four dengue virus serotypes (DENV) have now been reported in all reporting countries.

Vector control activities vary between countries but practices include elimination of breeding sites, application of environmental management policies, larvicide application to breeding sites, residual insecticide spraying, use of screening on doors and windows, and Communication for Behavioral Impact (COMBI) (see Table 1).

Vector control activities may be implemented according to risk strategies or with other actions such as improved medical diagnosis and management through training and communication. Integrated approaches to vector control involve health, education and environmental departments, but in many countries communication challenges exist between departments/units.

Effectiveness of vector control is usually measured by reduction in vector density and not against a clinical endpoint. But countries like Mexico use entomological and epidemiological data in an integrated fashion

### TABLE 1. Vector Control Methods in Countries of the Americas

<table>
<thead>
<tr>
<th>Country</th>
<th>Elimination of Breeding Sites</th>
<th>Larval Control</th>
<th>Biological Control</th>
<th>Insecticide Spraying</th>
<th>Mesh Screening on Windows and Doors</th>
<th>Legislated Environmental Management</th>
<th>COMBI&lt;sup&gt;+&lt;/sup&gt;</th>
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<tr>
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<td>Wolbachia study</td>
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<td></td>
<td></td>
<td></td>
<td>Special project&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td>✓</td>
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<td>Temephos, spinosad, larvivorous fish</td>
<td>Bti&lt;i&gt; in larvae</td>
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<td></td>
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<td>✓</td>
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<td></td>
<td>✓</td>
</tr>
</tbody>
</table>

<i>Bti = Bacillus thuringiensis israelensis. Produces toxins which are effective in killing various species of mosquitoes.</i>

<sup>a</sup>Special project refers to a pilot project being conducted on a subnational scale.

<sup>b</sup>Legislated environmental management refers to legislation that mandates that property owners or tenants undertake steps to prevent proliferation of mosquitoes, such as through the timely disposal of containers, or enables governments to enter premises that pose a risk, such as abandoned homes, in order to remove or destroy property that enable mosquito breeding.

<sup>c</sup>Communication for Behavioral Impact.
to guide control activities. In other countries disease surveillance data is not available or communicated in real time, not allowing for outbreak prevention.

All represented countries, except Puerto Rico in the US, conduct vector surveillance and some systematically monitor insecticide resistance. Insecticide procurement is also controlled in countries like Mexico and Brazil to mitigate against the potential for insecticide resistance.

Community involvement was identified as a critical success factor for more effective vector control, through approaches such as COMBI, as recommended by the World Health Organization, although its effectiveness in preventing dengue or lowering vector density has not been evaluated.

In spite of the lack of data to support a clinical impact from vector control, countries remain committed to vector control, especially given the increase in incidence of disease in recent years. Some countries noted that they are, or soon will be, piloting novel tools in vector control, including biological tools like Wolbachia.

**The epidemiology of dengue, and the surveillance and vector control activities specific to each country are summarized below:**

**After experiencing** greater than 20,000 cases per year between 1995 and 1999, the annual number of cases of dengue has again risen in Mexico to more than 15,000 cases per year since 2005 (excluding 2011), and exceeded 40,000 cases in 2007 and 2009, and 30,000 cases in 2012 and 2013. However, unlike the outbreaks of the 1990s, the proportion of dengue hemorrhagic fever (DHF) cases has increased dramatically.

All 4 virus serotypes are present but in 2013 DENV-1 (49%) and DENV-2 (48%) were predominant.

A specific action program for dengue prevention and control is developed by the federal MoH, but implementation is the responsibility of the State vector-borne disease departments. State run dengue programs have seven components: health promotion; social participation; epidemiological and entomological surveillance; laboratory
113% RISE in dengue cases in 2013 over cases in 2012, triggering a public health red alert and emergency outbreak response.

There was a 113% rise in dengue cases in 2013 over cases in 2012, triggering a public health red alert and emergency outbreak response.

In Nicaragua, national dengue control leadership is cascaded to the 17 departments and to each municipality, where vector control personnel are organized in brigades of 5 – 8.

Control measures are primarily destruction of breeding sites, home inspections of water containers, larval control of breeding sites with Temephos, spatial and indoor spraying during the rainy season (June to November), and COMBI.

Impact is assessed by using vector surveillance such as larval surveys and monitoring of insecticide resistance, which is factored into insecticide procurement. But control efforts have not been effective at preventing recent dengue outbreaks. Vaccination is considered to be an important future component of an integrated control program.

DENV-1 and DENV-2 are the predominant circulating virus serotypes, with few cases but high susceptibility to DENV-4. Over 140,000 cases were reported in 2013, by far the greatest number to date. The trend over the last 6 years has been one of increasing numbers of cases.

Since 2007, Paraguay has had a National Plan of Entomological Surveillance and a network of entomology units with response capacity at the departmental level. Approximately 1000 personnel (70% operational and 30% administrative) implement control efforts.

diagnosis; clinical case management; risk control; and chemical vector control.

As of 2013 vector control practices consist of strengthened educational and health promotion conducted in regional campaigns. Selective elimination of vector breeding places is conducted with social participation. Integrated larval control with Temephos and spatial and indoor residual organophosphate spraying is conducted in high risk areas for a maximum period of four weeks. Weekly spraying is conducted over the entire transmission area in less than five days each week.

Mexico practices integrated management as an immediate response to the emergence of cases, involving entomological surveillance, epidemiological and virological surveillance and case management. The impact on outbreak control is measured by comparing indicators from one week before the start of integrated actions to those at four weeks later.

Given the impact of the disease, Mexico has developed a vaccine introduction strategy with an objective of creating an evidence base, by gathering data to inform introduction decisions, and by evaluating vaccine impact post-introduction. An expert group from academia, government, public health, and research organizations has been constituted for this purpose. Working groups have been established to address specific challenges such as legal/regulatory and economic/financial issues. Based on the disease burden in Mexico, the expert group suggested that the optimal age for vaccination was 2 years.

A vaccination program will not replace vector control activities, but rather contribute to an integrated control strategy.

Mexico is participating in the PAHO initiative to develop an epidemiological surveillance system to define vaccination strategies. This includes standardizing methods and case definitions.
A central laboratory identifies mosquito and other insect species, as measures of insecticide resistance.

The outcomes of surveillance are cascaded to health regions, municipal secretaries of health of the governorates, and local leaders, for appropriate actions. In the event of an outbreak, the General Direction of Vigilance of Health (DGVS) sets up a situation room, activating the Rapid Response Teams (ERR) at national and sub-national levels. The ERR are multidisciplinary and are responsible for research and activation of controls under the coordination of the DGVS.

Principal control activities include elimination of breeding sites, larvicides at breeding sites, and insecticide spraying. Spraying consists of 3 to 5 cycles and, according to level of risk, is conducted either 4 or 6 times per year.

Surveillance is essentially by larval surveys, where the house is the basic sampling unit.

The size of dengue outbreaks has been steadily rising since 1978 with a recent increase in the case fatality rate. Furthermore, the proportion of cases in children has dramatically increased compared to outbreaks in the 1980s and 1990s. All 4 serotypes of dengue virus are circulating but DENV-1 is predominant at 54% in 2013, with DENV-3 second in frequency at 28%. The emergence of insecticide resistance in *Aedes aegypti* from different areas in the country has demonstrated that they can develop resistance to all types of insecticides including DDT and pyrethroids. Only Malathion did not show resistance in adult mosquitoes.

A multidisciplinary integrated dengue control strategy, including health, education, and environmental sectors is included in the 2012-2021 public health plan in Colombia.

Entomological surveillance and control by destruction of breeding sites and waste management are the primary control activities. Community interventions based on COMBI strategies in municipalities with low coverage of water services have demonstrated efficacy. These consist of engaging social leaders, educating families and active and sustained destruction of breeding sites around homes. Vector control, based on water sources, has proved effective. Likewise, larviciding of catch basins in municipalities has shown to be effective at reducing cases of dengue.

However, limitations of vector control include insecticide resistance, lack of sustained control and issues with integration between entomological and epidemiological services.

Puerto Rico, US has seen the same trend of increasing incidence and longer epidemics as elsewhere in the Americas. But Puerto Rico did not have a defined dengue prevention plan until 2011, and this is not intersectoral. Most control activities are focused on education for personal protection from biting, delivered through the media during outbreaks. The effectiveness of this has not been evaluated.

There is no entomological surveillance conducted on the Island, except in special projects. Insecticides and larvicides are used but primarily to reduce nuisance biting. Preliminary data indicates that a high percentage of *Aedes aegypti* are resistant to pyrethroids.

However, the last 5-7 years have seen a shift from measuring larval indices to developing tools to conduct surveillance for adult mosquitoes because of cryptic breeding sites, such as septic tanks and water meters, which
are inaccessible. One trap under development is an autocidal gravid ovitrap (AGO) that captures Aedes mosquitoes with adhesives. It has been found to be comparable to BG traps, is inexpensive, and does not use insecticide. Preliminary findings suggest 4 AGO traps per home, may reduce vector density by 80%, compared to surveillance traps (non-intervention).

**Venezuela**

Dengue cases have been increasing since 1987 and increased by 32% between 2012 and 2013. All four virus serotypes are circulating but DENV-3 accounted for 43% of cases in 2013. DENV-2 and DENV-1 accounted for 29% and 18% respectively.

Venezuela has had an integrated dengue control strategy since 2004 with an objective of monitoring and reducing vector density to prevent outbreaks. On a national scale, the program is within the MoH, under the Department of Environmental Health and specifically within the Directorate of Vector Control. On an operational level, Aedes vector control falls to the State Department of Health (23 states and one capital district in all), who ensure household inspections for measuring larval indices, elimination of breeding sites, and insecticide spraying. To measure effectiveness, larval counts are made before and after interventions, and epidemiological impacts are assessed.

Principal control activities are entomological surveillance, monitoring of insecticide resistance and proper vector control by destruction of breeding sites, larviciding with Temephos, biological control of larva with Bti, and involving the community. To control adults, insecticide treated screens are used on windows and doors and fogging with organophosphates is practiced.

**Argentina**

Investigations with innovative products, such as growth inhibitors, are ongoing.

Overall, vector control has been incapable of preventing dengue outbreaks, partly because efforts have not been sustained, and resources have not been adequate. Better quality COMBI approaches and greater media impacts will be required to change human behaviors. And more government support is required to increase Aedes control effectiveness.

Like elsewhere in the Americas, dengue is spreading, with virus circulating in only 5 provinces between 1998 and 2008, but since 2009 it has been circulating in 14 provinces, and 18 provinces have documented the presence of Aedes aegypti. DENV-1, DENV-2, and DENV-4 were circulating in Argentina in 2013, and cases of DENV-3 were imported.

Vector control is conducted under the Directorate of Vector Borne Diseases (DETV) through an integrated program which includes vector control, patient management, applied geographic informatics, epidemiological surveillance and community interventions.

A Situation Room was set up in 2012 to review epidemiological data on Chagas, dengue, malaria and leishmaniasis for the whole country. In 2014, 100% of localities with a history of dengue virus transmission will be inputting entomological surveillance data for risk monitoring, all provinces will have planning strategies in development, and all provinces with dengue virus transmission will strengthen capacity for case management.

In 2014, insecticide resistance activities will spread to 10 new localities and an intermediate control laboratory will be established. Several other capacity building and program strengthening activities are planned for the provinces.
Principal challenges with dengue control include communications, managerial capacity, and the sustainability of entomological surveillance.

**Costa Rica**

Dengue has been circulating since 1993 and the number of annual cases has grown over time with an increase in the severity of cases since 2010, although reported mortality remains low.

Vector control is conducted through the Integrated Vector Management (IVM) since 2009, in an integrated manner according to the comprehensive management strategy (EGI). EGI, implemented in 2004, has not been used steadily but is put into practice during outbreaks.

Principal control activities include chemical (larvicidal Temephos, adulticidal nebulized cypermethrin and residual alphacypermethrin) and biological control, waste management, health education and promotion of community participation.

A framework for action has been developed to manage solid waste given that 90% of used tires are not appropriately discarded.

Insecticide resistance is noted.

Principal surveillance methods include entomological (larval surveys) and epidemiological field investigations. Effectiveness is measured by larval indices and decreases in dengue cases.

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**Brazil**

The current national dengue control program was launched in 2002, with integrated epidemiological and entomological surveillance, vector control, patient management, environmental sanitation, health education and social mobilization, in addition to other components. A field agent, for every 800 – 1000 premises, conducts home inspections every 60 days. Larval surveys (simplified House Index) are performed using a two stage agglomerate sampling method incorporating the Premise Index and Breteau Index.

Specific control activities include destruction or larviciding of breeding sites, and health education. Transmission blocking with insecticide spraying is used during outbreaks. Activities are supported by legislation which allows, for example, for entry onto abandoned property.

Surveillance is conducted for insecticide resistance and the National MoH is responsible for the purchase and distribution of insecticides to municipalities.

The integration of the Family Health Program with traditional vector control suggests that resources can be optimized, and there is evidence that community participation reduces larval and pupae density, but an evaluation of the national control plan suggests that objectives are not being fully met.

New control methods like Wolbachia infected mosquitoes, insecticide treated screens for doors and windows, and new traps are being tested in Brazil.

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**Insecticide resistance activities will spread to 10 new localities and an intermediate control laboratory will be established in 2014.**
NEW TECHNOLOGIES AND PARTNERSHIPS FOR VECTOR CONTROL

*Aedes aegypti* is an urban daytime feeder that breeds in water-holding artificial containers. Because of the limitation of vector control on cryptic breeding sites, and increasing resistance to pyrethroids and organophosphates, and because of primarily indoor transmission of dengue virus, novel tools and new vector control paradigms are needed. Several new technologies are available for use in vector surveillance and control.

Several new methods to sample adult *Aedes* serve as an important alternative to container-based surveillance. Backpack and handheld aspirators (eg. the Prokopac) can be used to collect adult *Aedes* within premises. The Biogents Sentinel trap (BGS trap) requires battery or main power but provides continuous and efficient captures of *Aedes aegypti* and *Aedes albopictus*. Finally, new gravid traps use either adhesives [double sticky ovitrap; autocidal gravid ovitrap (AGO)] or insecticides [(Gravid *Aedes* Trap (GAT)] to capture gravid *Aedes*. These traps are inexpensive and do not require power, making them suitable for most countries. Adult mosquitoes captured by these methods can be used to estimate population size and are also processed for viruses or presence of *Wolbachia*.

Novel methods for controlling *Aedes* populations include:

NEW INSECTICIDES

- **New synthetic pyrethroids** such as metofluthrin;
- **The insect growth regulator** *pyriproxifen* that can be auto-disseminated from resting or oviposition sites resulting in the contamination of breeding sites, decreasing the emergence rates of adults;
- **Genetic control**
  - Release of mosquitoes with a dominant lethal gene (RIDL), which renders offspring infertile (or creates flightless females) and reduces mosquito populations;
- **Biologic control**
  - *Wolbachia*-infected mosquitoes. The *Wolbachia* bacteria are sexually passed from generation to generation, and persist in infected *Aedes aegypti* populations. *Wolbachia* also reduces dengue replication in the mosquito, blocking subsequent transmission. Releases of *Wolbachia*-infected *Aedes aegypti* for 11 weeks in Cairns, Australia resulted in infection of nearly 100% of mosquitoes that have persisted for 3 years.
- **Spatial repellents and lethal traps**
  - Killing stations: New attractive lethal ovitraps (A LOT), containing an attractant and an insecticide, and the autocidal gravid ovitrap (AGO), may be effective at reducing mosquito densities, and dengue virus transmission;
  - *Pyriproxifen* auto-dissemination traps that utilize attracted wild mosquitoes to disseminate an insect growth regulator to natural breeding sites, decreasing the emergence rates of adults;
  - Insecticide emanators that release vapors of the synthetic pyrethroid metofluthrin to repel and kill *Aedes* within premises.

**THE INTERNATIONAL VECTOR CONTROL CONSORTIUM (IVCC)**

The International Vector Control Consortium (IVCC) is a non-profit NGO aiming to develop new products and new formulations (such as long-lasting insecticides, organophosphates active against resistant mosquitoes), new paradigms of application (such as for outdoor biting and resting vectors), and new diagnostic kits to measure insecticide resistance.
**DENGUE VACCINE DEVELOPMENT**

Dengue vaccine development is progressing in spite of challenges which include lack of an animal disease model, lack of correlates of protection, risk of enhanced disease with a secondary natural infection, and the challenge of interference between tetravalent vaccine strains. Six dengue vaccines are currently in clinical development: 1 in phase III; 2 in phase II and 3 in phase I (see Figure 2).

Data from clinical trials to date have not identified any concerning safety signals with the available follow up time.

A safe and effective vaccine would be an important compliment to vector control strategies, and mathematical modeling will be useful for predicting the possible impact of vaccination on dengue once a vaccine is introduced.

**FIGURE 2.**
Dengue Vaccines in Clinical Development

<table>
<thead>
<tr>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase IIb</th>
<th>Phase III</th>
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<tr>
<td>DPIV</td>
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<td>CYD-TDV</td>
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<td>Naval Medical Research Center</td>
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*Licensing agreements with Vabiotech, Biological E, Panacea Biotech  
Source: Dr. Kirsten Vannice, World Health Organization
Dengue vaccines in development are summarized below:

**SANOFI PASTEUR: CYD-TDV**
Sanofi Pasteur has reached phase III clinical development with a live attenuated tetravalent recombinant chimeric vaccine, using a yellow fever backbone (see Figure 3).

As of October 2013, approximately 30,000 subjects had received the candidate vaccine.

Phase II and III results show immunogenicity to all four virus serotypes after 3 doses of vaccine. In a phase IIb efficacy trial in about 4,000 children in Thailand, crude vaccine efficacy of 56 – 100% was shown against DENV-1, DENV–3 and DENV–4, but not against DENV–2. Overall crude efficacy was estimated to be 30% in this setting (not statistically significant) or 35% by intent-to-treat analysis. The results were surprising given the good geometric mean titers (GMT) of the plaque reduction neutralization test (PRNT) found against each serotype after 3 doses of vaccine. Scientific exploration to elucidate possible explanations in vector, host, vaccine, and virus is ongoing.

However, evaluation of vaccine efficacy may be affected by several heterogeneous factors, such as mixtures of circulating virus serotypes and entomologic and demographic factors.

Pooled safety data for the CYD-TDV vaccine, from over 5,300 individuals in 9 different clinical trials suggest that for the current follow-up time the vaccine is safe, and flavivirus sero-status does not affect reactogenicity. Follow-up will be conducted for a total of 5 years post-dose 3.

Two large scale phase III trials are currently ongoing in the Americas (over 20,000 subjects) and in Asia (over 10,000 subjects) and will generate key information on the protection profile of this vaccine. Licensure is expected by the end of 2015.

By 2016, Sanofi Pasteur expects to have the capacity to produce 100 million doses of vaccine per year.

**TAKEDA: DENVAX**
Takeda is currently in phase II clinical development of a live attenuated tetravalent recombinant chimeric vaccine using an attenuated DENV–2 backbone (see Figure 4). Approximately 600 individuals have received the study vaccine to date.

A phase II trial to evaluate safety and tolerability at 1.5 to 45 years has been completed in Puerto Rico, Colombia, Singapore, and in Thailand, with 246 subjects receiving the study vaccine subcutaneously.

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**FIGURE 3.** Sanofi Pasteur Live Attenuated Tetravalent Recombinant Chimeric Dengue Vaccine

Source: Dr. Jose Noguera, Sanofi Pasteur
in 2 doses, 90 days apart. Vaccine safety has been found to be good with no serious adverse events (AEs), no dengue-like symptoms, and no meaningful blood chemistry or hematological changes.

Results show that the candidate vaccine induces high level of neutralizing antibodies and seroconversion ≥80% to all four dengue virus serotypes, after two doses, in endemic populations.

**BUTANTAN: TV003**

Butantan is in phase II clinical development with a live attenuated tetravalent DENV-1, DENV-3, DENV-4 and chimeric DENV-2 vaccine (see Figure 5).

In phase I trials, all adverse events were found to be mild. A stepwise phase II trial in adults is now underway in Brazil in dengue naïve and exposed individuals. In step A, a lyophilized formulation of the liquid NIH vaccine will be compared to the Butantan lyophilized product in 50 subjects (20 liquid vaccine, 20 lyophilized vaccine, 10 placebo). Depending on the outcome, in step B 250 dengue naïve and exposed individuals will receive a single dose of lyophilized vaccine. The safety assessment for step A is scheduled to be completed by May 2014, then the trial will move to step B.

Preparations are underway for phase III trials in Brazil and later in other Latin American countries. These include preparations for
compliance with current Good Manufacturing Practices (cGMP), site selection, approvals from regulatory and ethical oversight bodies, and further research on surrogates for protection.

If development goes according to plan, a first dossier could be submitted for licensure in 2018. First licensure would be sought for 18 – 59 year-olds.

**GLAXOSMITHKLINE: DPIV**

GSK is in phase I clinical development with a tetravalent whole virus inactivated purified vaccine, adjuvanted with AS01 or AS03. The vaccine is produced in Vero cells, in an animal-free process.

The vaccine is in early phase I trials in 100 subjects in the US, given in 2 doses, 4 weeks apart. The usual range and types of adverse events were noted in all groups, and most were grade 1 or 2. High seroconversion to all four dengue virus serotypes were noted with the AS01 and AS03 adjuvanted formulations and high dose AIOH formulation and GMTs for the microneutralization 50 assay (MN50) were approximately 10 fold higher for the AS01 and AS03 formulations than for the low dose AIOH formulation at day 56.

A similar study has been undertaken in Puerto Rico and results will be available in October 2014.

**MERCK: DEN-80E**

Merck has entered into phase I development with a recombinant truncated envelope protein in a *Drosophila* expression model (see Figure 6).

A tetravalent vaccine will be tested in healthy flavivirus-negative young adults in Australia, formulated with and without adjuvant, given in 3 doses at 1 month intervals. This dose-ranging study is now fully enrolled and follow up will occur over 6 months and again at 1 year.

**FIGURE 6.**

Merck Recombinant Envelope Protein Vaccine (Shown Den-2 80E Protein)

Source: Dr. Stephen C. Harrison, Harvard University
MODELING THE IMPACTS OF VECTOR CONTROL AND DENGUE VACCINATION

A mathematical model with components of geographic structure and human connectivity, vector density, movements and biting habits, natural history of infection and illness in humans and mosquitoes, and serotype specific epidemiology was developed for simulating dengue virus transmission in Ratchaburi, Thailand and is described in Chao et al. PLoS Negl Trop Dis 6(10): e1878. 2012. A similar model was developed, with funding from NIH and Sanofi Pasteur, for simulating dengue virus transmission in the Yucatan, Mexico, using satellite imagery of nighttime light output to estimate population density as a function of lumens. Mosquito movements were estimated based on the literature with an 85% probability of remaining within 100 m of birth place. The extrinsic incubation period was set at 11 days with a remaining life span of 1 or more days. The mean incubation period in humans was estimated at 6 days.

The immune status used to run the model for the Yucatan State, Mexico, is shown in Figure 7. An expansion factor of 36 was used (for every case reported there are 36 infections).

The model found that for the Yucatan, the best-fit model was with 90 mosquitoes per location with 1 introduction (infection) every 20 days (see Figure 8).

In addition to simulating dengue incidence, the model can be used to estimate the impact of vaccination on dengue virus transmission according to two scenarios: an effective vaccine against all four virus serotypes; or, no protection against one serotype. Overall effectiveness will vary based on the serotype-specific incidence, and with vaccination coverage. These impacts on transmission have been modeled based on vaccination rollouts in specific age groups (see Figure 9).

These analyses show that a vaccine that protects against 3 virus serotypes would be 10-35% less effective than a vaccine that protects against all 4 virus serotypes, but could still be effective depending on the relative transmission of the circulating virus serotypes.
Furthermore, subsequent analyses of the phase IIb efficacy vaccine trial in Thailand showed that since vaccine effectiveness is affected by several heterogeneous factors, such as mixtures of circulating virus serotypes, entomologic and demographic factors, weighting for the risk of exposure to each dengue serotype can better estimate vaccine effectiveness. In Thailand, the overall vaccine efficacy of the Sanofi Pasteur CYD-TDV by intent-to-treat regression analysis was estimated to be 60% using Dr. Longini’s survival model, substantially higher than the 30% efficacy estimated by crude analysis.

Vaccination could also alter the long-term mix of circulating virus serotypes, so this should be monitored.

Furthermore, modeling shows that combining vector control with vaccination could increase intervention effectiveness. Reducing vector density can have a dramatic effect on the number of infections. Models can help estimate the relative effort to be placed in integrated vaccination and vector control strategies to optimize impact on disease with available resources.

**FIGURE 9.** Impacts of Dengue Vaccination by Roll Out Strategy
CREATING A FRAMEWORK FOR INTEGRATING VECTOR CONTROL AND DENGUE VACCINATION

A dengue vaccine may be available within the next few years. Integrating dengue vaccination with vector control would have the potential to enhance disease reduction.

And since several novel tools for vector control are now or soon to be available, a meeting was held in Washington DC, in late 2013, to critically review current and future tools for vector control, and to think about how to integrate vector control with vaccination. Vector control can lower the force of infection. But integrating vector control with vaccination will require timed vaccination rollouts in designated areas, entomologic measures during vaccine trials, and standardized indicators of vector control impact to allow for comparisons between trial sites.

Many countries do not systematically measure the impacts of vector control, so countries will need to first assess the impacts of vector control in their own settings. These should be measured in a standardized way as set by the WHO.

Likewise, countries that decide to introduce a licensed dengue vaccine early will need to plan and conduct vaccine safety and effectiveness studies. Coordination between countries in study design and implementation will be critical for meaningful analysis and extrapolation of findings. The outcomes from these studies should therefore be generalizable so that results can inform decisions in other countries. Ideally, these countries will assess the simultaneous impacts of both vaccination and vector control on disease transmission so that this data too can inform control strategies.

Three working groups, formed during the meeting, were asked to consider the following questions – “In 3 years from now: 1) vaccines will be licensed and will go for phase IV in selected countries; 2) new vector control methods will demonstrate efficacy against Aedes; 3) current vector control methods will continue.” The Working Groups were asked: “If we want integration between vaccination and vector control: 1) could field sites analyze benefits of integration; 2) if yes, how; 3) what should be done to facilitate such evaluation?”

The Working Groups identified the required elements for establishing a framework for integrating vaccine and vector control. These included minimal requirements for study sites, regulatory capacity, country commitment, monitoring and evaluation of clinical and entomological impacts, and the standardization of methods. These outputs of the Working Groups are summarized in Table 2.
TABLE 2. List of Required Elements for a Framework Integrating Vaccination and Vector Control

<table>
<thead>
<tr>
<th>Requirement</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CRITERIA FOR SELECTION OF STUDY SITES AND STUDY DESIGN</strong></td>
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</tr>
<tr>
<td>Availability of baseline data</td>
<td>Site selection should be based on availability of sufficient baseline data to evaluate the additive effects of a vaccine.</td>
</tr>
<tr>
<td>Vector control capacity</td>
<td>Site should be capable of collecting good quality data and be capable of conducting good vector control of Aedes and measuring the entomological indicators that can affect VE, including at a minimum: measure of adult mosquito densities; pre- and post-impact assessments with novel control methods such as release of Wolbachia infected mosquitoes; isolation of viruses from mosquitoes; larvae counts in containers (NB: important to note container type and density (much of which may be available from previous studies), but larval and pupal census are time consuming and often misleading); and, capacity to compare conventional vs. novel control methods; pesticide resistance if pertinent to control method.</td>
</tr>
<tr>
<td>Clinical trial capacity</td>
<td>Minimal clinical vaccine trial capacities should include: measurement of clinical endpoints, and evaluation of vaccination coverage, and good diagnostic capabilities.</td>
</tr>
<tr>
<td>Observational study capacity</td>
<td>In addition to vaccine capacity, countries should also have capacity to conduct observational studies.</td>
</tr>
<tr>
<td>Regulatory capacity</td>
<td>Site selection should be based on the regulatory strength in the study site country.</td>
</tr>
<tr>
<td>Study design</td>
<td>Introduction protocols should first be approved by regulatory and ethical review; case definitions should be standardized; prospective cohort evaluations are recommended; ideally, a control group should be included from a comparable but different city; the best data will be generated from separate study areas for: vector control; vaccination; and, integrated control; the different characteristics of countries should be considered; transmission dynamics within the study site should also be considered.</td>
</tr>
<tr>
<td>Capacity for monitoring and evaluation</td>
<td>Long-term follow up should be conducted and cases reported.</td>
</tr>
<tr>
<td>Country commitment</td>
<td>The support of the national immunization committee should be considered essential and work on a vaccine introduction strategy including scheduling should be underway in the study country and study sites should have established agreements with support groups; Brazil, Colombia, Nicaragua, and Mexico should be considered good candidates for early vaccine introductions; countries themselves should drive the demand for studies so there is no perception of commercial bias.</td>
</tr>
<tr>
<td><strong>COMMUNICATION AND COORDINATION WITH OTHER SECTORS</strong></td>
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<tr>
<td>Political leaders</td>
<td>Will require good communications to explain objectives, study methods and possible results.</td>
</tr>
<tr>
<td>Vaccine industry</td>
<td>Control activities need to be coordinated with vaccine manufacturers in hyperendemic areas to consider the potential impacts on clinical trials.</td>
</tr>
<tr>
<td>Inter-country</td>
<td>Collaborations between countries are encouraged.</td>
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<tr>
<td>International organizations</td>
<td>DVI should improve communications with PAHO on dengue vaccine introductions.</td>
</tr>
<tr>
<td><strong>STANDARDIZATION OF ENTOMOLOGICAL SURVEILLANCE</strong></td>
<td></td>
</tr>
<tr>
<td>Surveillance methods</td>
<td>Standardize surveillance approaches across countries, with emphasis on adult Aedes sampling.</td>
</tr>
<tr>
<td>Vector control indicators</td>
<td>Use standardized entomological indicators for vector control activities so that clinical, epidemiological and entomological impacts are comparable between countries.</td>
</tr>
<tr>
<td>Integrated surveillance</td>
<td>Develop the details of the PAHO integrated surveillance plan so as to integrate vector surveillance and control with vaccination.</td>
</tr>
<tr>
<td><strong>DEVELOP POLICIES FOR VECTOR CONTROL</strong></td>
<td></td>
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<tr>
<td>By assessing control</td>
<td>Assess the heterogeneity in epidemiology between countries; assess current vector control strategies for strengths and weaknesses; collect economic data from integrated control efforts, to evaluate the costs-benefits; insecticide resistance status.</td>
</tr>
<tr>
<td>To strengthen capacity</td>
<td>Consider vaccine introduction an opportunity to improve quality of surveillance (both entomological and clinical).</td>
</tr>
</tbody>
</table>
RECOMMENDATIONS OF THE DENGUE PREVENTION BOARD ON INTEGRATION OF VECTOR CONTROL AND DENGUE VACCINATION

The Americas Dengue Prevention Board considers that:

1. The initiative provides an opportunity to strengthen ongoing entomological and epidemiological surveillance and vector control efforts.

2. Integrated control provides an opportunity to standardize entomological and epidemiological indicators that countries should use uniformly to evaluate interventions.

3. Given the importance of the project, the experience, strengths and influence of PAHO for these programs, a close knit cooperation should be established between the DVI and PAHO.

4. The motivation for vector control remains high in the region, in spite of the possibility of soon having an effective dengue vaccine. It should be remembered that when vaccines are ready for introduction, they should be launched in close conjunction with vector control programs/strategies.

5. It is important to study the impacts of an integrated approach (vaccination and vector control). For this, protocols should be established to evaluate the effectiveness of these interventions in specific projects, and to develop capacity for work in this field.

CONCLUSIONS

A vaccine against dengue may be licensed within the next few years. The integration of vaccination programs with appropriate currently used or new vector control methods has the potential to eliminate dengue as a public health problem.

Still countries interested in early adoption of a dengue vaccine need to undertake preparatory work to first assess the impact of vector control in their own settings using standardized indicators, and determine in advance the appropriate methods and indicators for evaluating the impact of a vaccine, in the context of existing or new vector control efforts.

Countries that decide to introduce a dengue vaccine should adhere to the minimum standards set by the WHO for vector and epidemiological surveillance.

Modeling studies can help to better inform integrated control strategies.

The meetings with the Asia Pacific and Latin American DPB conclude DVI’s consultations with the DPBs on questions related to the integration of vaccination and vector control. The DVI wishes to thank both DPBs for their valued input and their willingness to address these important questions for a better control of dengue.
### APPENDIX 1

#### SPEAKERS

**Day 1** Tuesday, March 25, 2014

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
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</thead>
<tbody>
<tr>
<td>8:00 - 8:30 am</td>
<td>Executive session of Dengue Prevention Board - (Closed session for Board Members)</td>
</tr>
<tr>
<td>9:00 - 9:10 am</td>
<td>Opening and Introduction</td>
</tr>
<tr>
<td>9:40 - 10:00 am</td>
<td>Presentation of the Partnership for Dengue Control</td>
</tr>
<tr>
<td>10:00 am - 2:00 pm</td>
<td>VECTOR CONTROL: Current practices to control vectors in Latin American countries</td>
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<td></td>
<td>Experiences with vector control programs in Latin American countries, how programs are structured, effectiveness, and lessons learnt, 15 minutes/presentation.</td>
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<tr>
<td></td>
<td>1. Mexico</td>
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<td>2. Nicaragua</td>
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<td>3. Paraguay</td>
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<td>4. Colombia</td>
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<td>5. Puerto Rico</td>
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<tr>
<td></td>
<td>6. Venezuela</td>
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<td></td>
<td>7. Argentina</td>
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<td></td>
<td>8. Cuba</td>
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<td></td>
<td>9. Costa Rica</td>
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<tr>
<td></td>
<td>10. Brazil</td>
</tr>
<tr>
<td>10:00 - 10:20 am</td>
<td>COFFEE BREAK</td>
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<tr>
<td>12:00 - 1:00 pm</td>
<td>LUNCH</td>
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<tr>
<td>2:00 - 3:15 pm</td>
<td>VECTOR CONTROL: New, under development</td>
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<tr>
<td></td>
<td>Chaired by Dr. Tom Scott</td>
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<tr>
<td>2:00 - 2:45 pm</td>
<td>Update on new approaches and technologies, stage of development and perspectives</td>
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<tr>
<td>2:45 - 3:15 pm</td>
<td>Discussion on current and new vector control strategies</td>
</tr>
<tr>
<td>3:15 - 3:45 pm</td>
<td>COFFEE BREAK</td>
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<tr>
<td>3:45 - 6:00 pm</td>
<td>DENGUE VACCINES</td>
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<td></td>
<td>Chaired by Dr. Kirsten Vannice</td>
</tr>
<tr>
<td>3:45 - 6:00 pm</td>
<td>Update and perspectives of vaccines currently in clinical development by manufacturers (15 min per presentation + 5 min for discussion)</td>
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<tr>
<td></td>
<td>1. Sanofi Pasteur</td>
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<td></td>
<td>2. Takeda</td>
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<td></td>
<td>3. Butantan</td>
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<td>4. GSK</td>
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<td>5. Merck</td>
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<tr>
<td>6:00 pm</td>
<td>Adjourn Day 1</td>
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<tr>
<td>6:30 pm</td>
<td>DINNER hosted by DVI</td>
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</table>
# Day 2  Wednesday, March 26, 2014

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
<th>Speaker(s)</th>
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</thead>
<tbody>
<tr>
<td>9:00 – 10:00 am</td>
<td>Executive session of Dengue Prevention Board - (Closed session for Board Members)</td>
<td></td>
</tr>
<tr>
<td>9:00 – 9:45 am</td>
<td>Opening and Introduction</td>
<td>Dr. Pablo Kuri Dr. Georges Thiry</td>
</tr>
<tr>
<td>9:45 – 10:00 am</td>
<td>WHO Global Strategy for dengue prevention and control, 2012-2020 – an update</td>
<td>Dr. Raman Velayudhan</td>
</tr>
<tr>
<td>10:00 – 11:10 am</td>
<td>Presentation of the Partnership for Dengue Control</td>
<td>Dr. Duane Gubler</td>
</tr>
<tr>
<td>10:00 – 10:20 am</td>
<td>Introduction to Working Groups Session</td>
<td>Dr. Georges Thiry Dr. Tom Scott</td>
</tr>
<tr>
<td>10:20 am – 2:30 pm</td>
<td>WORKING GROUPS: Starting with the assumption that a new vaccine is licensed and introduced in a given country, each working group will discuss selected topics of integrating this vaccination with new/current vector control, Groups of around 20 people, with a leader and a facilitator assigned. Each group will address specific items, will build on information provided in reports from the two previous meetings, and generate additional, in depth analysis.</td>
<td>Leaders and facilitators to be assigned</td>
</tr>
<tr>
<td>10:00 – 10:20 am</td>
<td>COFFEE BREAK</td>
<td></td>
</tr>
<tr>
<td>12:00 – 1:00 pm</td>
<td>LUNCH</td>
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</tr>
<tr>
<td>2:30 – 4:00 pm</td>
<td>Report from working groups and general discussion</td>
<td>Co-chaired by Dr. Georges Thiry and Dr. Tom Scott</td>
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<td>- A rapporteur from each group will report analysis and recommendations</td>
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<tr>
<td></td>
<td>- General discussion</td>
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<tr>
<td>4:00 – 4:30 pm</td>
<td>COFFEE BREAK</td>
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<tr>
<td>4:00 – 4:30 pm</td>
<td>Closed meeting among DPB members to prepare conclusions</td>
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<tr>
<td>4:30 – 5:00 pm</td>
<td>Report by the Dengue Prevention Board</td>
<td>Rapporteur for DPB</td>
</tr>
<tr>
<td>5:00 pm</td>
<td>END - Closing remarks and adjourn</td>
<td>Dr. Georges Thiry Dr. Jorge F Mendez</td>
</tr>
</tbody>
</table>
| 5:00 pm        | Executive session of Dengue Prevention Board
|               | Closed session for the Board members                       |                                                 |
## APPENDIX 2
### LIST OF MEETING PARTICIPANTS

#### Board Members

**Dr. Aracely Alava Alprecht** *(unable to attend)*  
Coordinator, Investigation and Microbiological Diagnosis  
Leopoldo Izquieta Perez National Institute of Hygiene and Tropical Medicine  
Chair, Virology, Guayaquil University  
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**Dr. Juan Jose Amador**  
Medical Epidemiologist  
CDC Foundation and Boston University  
Repato Carlos Fonseca II Etapa, Chichigalpa, Nicaragua

**Dr. Antonio Arbo**  
Jefe de Pediatría  
Instituto de Medicina Tropical  
Ministerio de Salud, Pública y Bienestar Social  
Paraguay

**Dr. Jorge Boshell**  
Director Biosafety Committee  
Bone and Tissue Bank (Banco de Huesos)  
Bioseguridad, Banco de Huesos y Tejidos  
Fundación Cosme y Damián  
Colombia

**Dr. Iris Villalobos de Chacon**  
Chief of Epidemiological Services  
Hospital Central de Maracay  
Av. Principal de la Floresta y Jose Maria Varga  
Sector Las Delicias  
Venezuela

**Dr. Giovanini Coelho**  
Coordinator of the National Dengue Control  
Brazil

**Dr. José F. Cordero** *(unable to attend)*  
Dean, Graduate School of Public Health  
Medical Sciences Campus  
University of Puerto Rico  
Puerto Rico

**Dr. Delia A. Enria** *(unable to attend)*  
Director, INEVH (Instituto Nacional de Enfermedades Virales Humanas)  
Argentina

**Dr. Eduardo Fernandez** *(unable to attend)*  
Adjunct Professor  
Community Health Sciences  
Brock University  
Canada

**Dr. Maria Guadalupe Guzman**  
Head Virology Department  
Director, PAHO  
WHO Collaborating Center for Viral Diseases  
Pedro Kouri Tropical Medicine Institute  
Autopista Novia del Mediodía  
Cuba

**Dr. Harold Margolis**  
Branch Chief, CDC (Centers for Disease Control and Prevention) Dengue Branch, Puerto Rico  
Centers for Disease Control & Prevention  
Dengue Branch  
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**Dr. Jose Luis San Martin** *(unable to attend)*  
Dengue Regional Consultant  
PAHO/WHO San Jose, Costa Rica

**Dr. Jorge F. Mendez-Galvan**  
Investigador National  
Hospital Infantil de México “Federico Gómez”  
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**Dr. Anabelle Alfaro Obando**  
National Advisor in Dengue Management  
Costa Rica

**Dr. Steve Waterman**  
Lead, US Mexico Unit  
Division of Global Migration and Quarantine, CDC  
(Senior Medical Epidemiologist)  
USA
Vector Control Experts

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Secretaria de Salud  
Mexico

**Dr. Cinda Martinez**  
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Venezuela

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Vice-director  
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Ministry of Health  
Argentina

**Dr. Clara Ocampo**  
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**Dr. Silvio Ortega**  
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National Dengue Control Program  
Coordination  
Ministry of Health  
Brazil

DVI Collaborators

**Dr. Mabel Carabali**  
Epidemiologist  
International Vaccine Institute

**Ms. Ana Carvalho**  
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Vaccine Advocacy and Education  
Sabin Vaccine Institute  
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**Dr. Dagna Constenla**  
International Vaccine Access Center  
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John Hopkins Bloomberg School of Public Health  
USA

**Dr. Shawn Gilchrist**  
S Gilchrist Consulting Services Inc  
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**Dr. Joachim Hombach** *(unable to attend)*  
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Vaccines and Biologicals  
WHO  
USA

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Dengue Vaccine Initiative  
International Vaccine Institute  
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**Dr. Ira Longini**  
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College of Public Health and Health Professions, and College of Medicine  
University of Florida  
USA

**Ms. Soo Hyun Rah**  
Coordination Administrator  
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International Vaccine Institute  
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**Dr. Georges Thiry**  
Acting Director, DVI  
Dengue Vaccine Initiative  
Deputy Director General, Portfolio Management  
International Vaccine Institute  
Korea

**Dr. Kirsten Vannice**  
Scientist  
Initiative for Vaccine Research, WHO  
Switzerland

**Dr. Maria Yolanda Cervantes Apolinar**  
Medical Vaccines Director,  
Vaccines Value & Health Science  
GlaxoSmithKline  
USA
Dr. Kwasi Amfo  
Vice President and Head,  
Global Dengue and EV71 Programs  
Takeda

Dr. Esthel Van Brackel  
Vice President,  
Government Affairs & Public Policy  
GlaxoSmithKline

Dr. Miguel Betancourt Cravioto  
Director de Soluciones Globales  
Instituto Carlos Slim de la Salud

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National Institute of Public Health of México  
México

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Senior Director,  
Global Strategic Marketing for Dengue  
Takeda

Ms. Catherine Dutel  
Programmes Coordinator  
Foundation Merieux

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Global Medical Affairs  
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Dr. Duane J. Gubler  
Professor & Director  
Program on Emerging Infectious Diseases  
Duke-NUS Graduate Medical School  
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Dr. Angi Harris  
Program Officer  
Bill & Melinda Gates Foundation  
USA

Dr. April Healy  
Program Coordinator  
Bill & Melinda Gates Foundation  
USA

Dr. Pablo Kuri-Morales  
Vice-Minister of Health  
Ministry of Health, México  
México

Dr. Edith Lepine  
Director & Project Leader,  
Dengue Vaccine Development  
GlaxoSmithKline

Ms. Lois Lockledge  
Director, New Vaccines  
Global Vaccines Strategy & Innovation  
Merck

Dr. Juan Guillermo Lopez  
Health economy and vaccine access  
Sanofi Pasteur

Dr. Luis Romano Mazzotti  
Medical Affairs, Mexico  
GlaxoSmithKline

Dr. Jose Noguera  
Vaccination Policy and Advocacy  
Dengue Latin America  
Sanofi Pasteur

Dr. Jorge Osorio  
VP Research  
Takeda

Dr. Ricardo Palacios  
Clinical R&D Manager  
Division of Clinical Trials and Pharmacovigilance  
Instituto Butantan  
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Dr. Scott Ritchie  
Professorial Research Fellow  
James Cook University  
Australia

Dr. Diana Rojas, MD  
Ph.D candidate  
University of Florida  
USA

Dr. Caroline Sagaert  
Director, Disease Mapping, Vaccines Future  
GlaxoSmithKline  
USA

Dr. Elsa Sarti  
Epidemiology Latin America  
Sanofi Pasteur

Dr. Alexander Schmidt  
Director, Clinical Research & Translational Science, Vaccine Discovery & Development  
GlaxoSmithKline

Dr. Thomas W. Scott  
Professor  
Department of Entomology  
USA

Mr. Ian Shephered  
Director, Legacy Progeram, Agency for Takeda

Dr. Rodrigo De Antonio-Suarez  
Senior Manager Epidemiology-Health Economics, Latin America & México  
GlaxoSmithKline

Dr. Roberto Tapia  
Director General  
Carlos Slim Health Institute  
(Instituto Carlos Slim de la Salud)

Dr. Gustavo Sanchez Tejeda  
Program Director of Vector-Borne Transmission Diseases

Dr. Remy Teyssou  
Scientific Coordination  
Foundation Merieux

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