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INTRODUCTION

From November 3-4, 2015, experts in the public health field, academia, vaccine producers, insecticide industries, epidemiologists, and communications convened to discuss how best to tackle dengue disease, the fastest-spreading vector-borne viral disease in the world. Participants hailed from countries across Latin America and the Caribbean, where the incidence of dengue increased five-fold between 2003 and 2013. In all, 120 scientists, physicians and policy makers from 16 countries participated in the First Regional Dengue Symposium, held in Rio de Janeiro, Brazil. Dengue is transmitted by two species of mosquito, Aedes albopictus, and its primary vector, Aedes aegypti. Both are claiming new territories as climate warms, but Ae. aegypti is particularly well adapted to live in close proximity to its favorite species, Homo sapiens. The denser the human population, the warmer and wetter the climate, and the poorer the sanitation, the more likely the mosquito is there, spreading disease—and not only dengue. Ae. aegypti transmits a host of other viruses. Some of these, including Chikungunya and zika, have symptoms similar to dengue, and are considered emerging diseases.

Thirty presentations covered a host of issues viewed as crucial to confronting the dengue upsurge. Issues of dengue disease burden and economic costs; health communications; vector control strategies; prospective vaccines and vaccine introduction; and the intersection of vaccine and vector control strategies were all on the table.

The only dengue control measure currently available is effective case management and control of its vector, which has proven difficult to maintain over time. The Pan American Health Organization (PAHO) has developed an Integrated Strategy for Dengue Prevention and Control (EGI-Dengue), which increasingly guides an integrated response to disease outbreaks. However, every component of EGI-Dengue needs to be strengthened.

A vaccine against dengue is widely anticipated as a new and crucial disease control measure, but questions remain about how much of a contribution vaccines will make as part of an overall vector-borne disease prevention and control strategy. By bringing together the vector control and vaccine communities, the Symposium provided the opportunity to explore in-depth the risks and possibilities of combining both. It highlighted the fact that not only is there no one simple answer to dengue. Complementary and integrated strategies are needed.

Symposium organizers noted that the LAC Region has entered a transition period during which evidence will be even more important as new vaccines become available. Decisions about vaccine introduction, the balance and funding of control approaches, the goal of dengue and vector control will rely on complex, interlocking sets of scientific evidence. Successful prevention and control of dengue will also rest, as much as anything, on skilful communications in raising awareness; communicating evidence to engage and empower leaders; gaining and maintaining public confidence; and generating political will and partnerships to finance both sustainable immunization and vector control programs.

“Vaccination will not be a replacement for vector control, rather it will provide synergistic effects to reduce transmission.”
BURDEN OF A DISEASE ON THE MOVE

Dengue has increased globally 30-fold over the last 50 years, according to the World Health Organization (WHO). It is prevalent in over 100 countries, with evidence of transmission in 141 countries and territories.

Overall, 3.9 billion people—about half the world’s population—are at risk in dengue-endemic countries. Up to 390 million people are infected by dengue. Of these infections, some 96 million or about 25 percent of them are symptomatic; about 500,000 people with severe dengue require hospitalization; and there are up to 25,000 deaths per year.

The number of reported cases of dengue in the Americas rose from 1.54 million between 1980 and 1989, to 8.98 million between 2010 and 2015. Figure 1 shows Brazil, Mexico, Colombia, and Venezuela have the region’s highest caseloads, with all other countries combined representing 20-30 percent of the regional dengue burden of disease. Most recently, the greatest increase has been in the Andean region.

Dengue has more than a 400-year history in the region, having been introduced through the English Caribbean during the transatlantic slave trade, with the first epidemic of dengue occurring in 1635 in Martinique and Guadalupe Island. Public health measures successfully combatted Ae. aegypti for several decades in the mid-twentieth century, as part of a massive continent-wide campaign against yellow fever, yet another virus transmitted by the mosquito. But these efforts ultimately waned, and Ae. aegypti made a comeback. Today dengue is the most reported vector-born disease in the Americas, followed by Chikungunya.

Although dengue can affect people of any age, the highest number of cases is in adolescents and young adults. With as yet no vaccine or cure for dengue, the upward trend of dengue disease represents high economic, political and social impacts.

Three social or environmental components correlate to the burden of dengue disease:

- The percentage of urban population with access to improved sanitation: the higher the percentage, the lower the incidence of dengue;
- The illiteracy index: the lower the literacy of a country, the higher the incidence of dengue;
- The GINI index of inequality: the greater the disparity of income distribution, the higher the incidence of dengue.

FIGURE 1. Dengue in America, 2006 — 2014
Symptoms of Dengue

Symptoms of dengue fever include a sudden onset of fever, severe headaches, eye, joint, and muscle pain, and a rash that typically appears on the hands, arms, legs and feet three to four days after the fever begins. Some patients with dengue recover relatively quickly, while others progress to severe dengue. For these patients, the worst part of dengue—its “critical phase”—begins 24 to 48 hours after fever drops.

Severe dengue can include hemorrhage and collapse of the circulatory system, or dengue shock syndrome. Increased vascular permeability allows blood plasma to leak out of capillaries. This, together with heart dysfunction and dehydration, can trigger shock, and lead to multi-organ failure and death within 24 hours.

Fortunately, improved recognition of the warning signs of severe dengue and improved treatment has lowered the risk of death. The rapid and careful administration of intravenous fluid replacement can be crucial to survival. Today, most patients recover from severe dengue, although symptoms such as fatigue and depression persist for up to ten months in about 10 percent of patients.

FIGURE 2. Dengue symptomatic cases globally, 2013

Economic Burden of Dengue

According to a study by Shephard et al., dengue cost the world USD 8.89 billion in 2013. This study assessed the cost of dengue across 141 countries and territories that have evidence of dengue transmission.

The study considered the costs associated with 58.4 million symptomatic dengue episodes reported in 2013 (as seen in figure 2). Of these, 10.5 million (18 percent) were hospitalized; 28.1 million (48 percent) were ambulatory; and 19.7 million (34 percent) occurred outside healthcare system, and there were 13,586 fatalities. Some 5.6 million cases, or 9.7 percent of the global total were from the Americas region.

The costs were uneven. Regionally, the greatest burdens were in Southeast Asia, East Asia and Oceania, which together accounted for 54 percent of the cost. The LAC region accounted for 19.5 percent, and South Asia accounted for another 19 percent. The rest of the world made up the remaining 7.4 percent of global costs.

The top ten countries with highest aggregate cost of dengue illness represented 82 percent of the total global cost. Of these, Indonesia was the highest; Brazil and Mexico were the only LAC countries in the top ten.

The study found that prevention costs using conventional strategies, such as outdoor spraying, added considerably to the total cost. However, there have been few economic evaluations. One, in Brazil, found that the country spent US$505 million on such strategies in 2013, and that the cost increased 50 percent during outbreaks.

The aggregate cost of dengue, including prevention, was US$1,233 billion in Brazil and US$413 million in Mexico in 2013. In Brazil it is estimated that direct and indirect costs combined rose from US$370.8 million in 2009 to US$1,227 billion in 2013 (illustrated in figure 3).

In addition to the direct costs (medical care and travel), and indirect costs (value of lost time and productivity), other costs accrue from the treatment of “persistent dengue,” — symptoms that can continue more than ten months after the onset of acute disease. Less data are available on costs associated with effects on health system congestion and tourism — for instance during the World Cup in Brazil, and upcoming concerns for the Olympics.
INTEGRATED STRATEGY FOR DENGUE PREVENTION AND CONTROL IN LATIN AMERICA AND THE CARIBBEAN

Between 2001 and 2013, PAHO passed a series of resolutions to guide the fight against dengue, leading to the emergence of an Integrated Management Strategy for Dengue Prevention and Control (EGI-Dengue). Today, 32 countries in the region have adopted the strategy, and an international technical task force assists with its technical implementation.

The strategy has six interlinking components: social communication, laboratory and diagnostics, patient care, epidemiological surveillance, integrated vector management, and environment. The strategy has been updated over time, and the most recent update envisions vaccines as a major new component, and approaches communication as a cross-cutting issue.

Social Communication

From the elimination of polio in 1994, to the elimination of rubella in April 2015, communication and advocacy has played a vital role in every victory over disease in the Americas.

In the case of rubella and congenital rubella syndrome, a disease that can cause autism, blindness, and other birth defects in newborns, effective communications of disease impacts and vaccine benefits engendered the support of Presidents and Ministers. In 2008, Mexico’s President Felipe Calderón personally launched a mass rubella elimination campaign. With similar campaigns across Latin America and the Caribbean, there was a

FIGURE 4. Samples of media coverage on rubella elimination/April 29-30, 2015

Bye-bye, rubella! ¡Adiós rubéola!
98.5 percent reduction in rubella across the region, and in April 2015, the region was declared rubella-free.

Likewise, Vaccination Week—a core strategy in the Americas—relies heavily on communications for its success. As reported by the United Kingdom’s *Guardian* newspaper: “The first Vaccination Week in the Americas was in 2003 and since then more than 465 million people of all ages have been vaccinated against diseases such as measles, rubella, yellow fever, diphtheria, tetanus, polio and influenza. The media campaigns for the week include endorsement from popular Latin American celebrities.”

Communications experts at the Symposium reported on the role of communications in diverse circumstances, and noted the communications challenges that would accompany introduction of dengue vaccine. They shared invaluable tools to assist with public health and vaccination campaigns.

Among these tools is Communication for Behavioral Impact (COMBI), an approach developed by PAHO and updated in 2011. It is based on lessons learned from projects in 15 countries across the Americas.

Its five core strategies are:

1. Advocacy public relations/administrative mobilization.
2. Community mobilization.
3. Sustained appropriate advertising.
4. Interpersonal communication.
5. Promotion at points of sale in the community, where people can get information and take the actions to prevent and control dengue.

COMBI approaches social communication as a process of social interaction that promotes behavioral change. It is based on the free, voluntary and equal exchange of information, and takes account of community, group and individual values. It clearly identifies behavioral objectives; investigates their feasibility; develops and tests messages and materials; and establishes a system for monitoring and evaluation.

With financing supplemented by CDC, DFID and CIDA, PAHO has held COMBI sub-regional workshops; and has trained coaches in Central America, the Dominican Republic, Belize, the English Caribbean and the Andean sub-region. They have introduced new educational tools, including a children’s game that has more than 44,000 on-line entries.

Going forward, challenges to the effective communication regarding dengue include:

- Ensuring the sustainability of community actions in its prevention and control;
- Identifying and monitoring valid indicators of behavior change;
- Gaining of sustained support from the Ministries of Health and local government;
- Overcoming the belief that health education is only important to the health sector;
- Strengthening communication on risk and crises related to outbreaks or epidemics of dengue.
Strengthening Laboratory Diagnostics

As the incidence of dengue and other diseases transmitted by Ae. aegypti increase, the region’s dengue-dedicated laboratory network must play a key role in rapidly identifying and responding to outbreaks; improving clinical management; and providing the data needed for research and assessments of vaccine impact, including data on dengue’s evolving genetic profile.

Dengue comes in four serotypes (Denv1, Denv2, Denv3, and Denv4), and each serotype has five genotypes. The impact on disease severity is serotype specific. Both serotype and genotype distribution is changing. Vaccine introduction will affect serotype distribution further.

Symposium participants heard how RELDA, the Dengue Laboratory Network of the Americas, has grown since its official launch in 2009. Its goal is to strengthen technical and scientific capacities of national laboratories; approve common diagnostic protocols; promote the exchange of knowledge and technology; strengthen the Quality Management Systems, and generally integrate scientific and technical capacities for rapid outbreak response.

Today RELDA includes 30 countries. RELDA has a central coordinator; four regional coordinators; a technical secretary; and an advisory technical committee. Molecular surveillance is an important aspect of RELDA’s work. RELDA is helping 20 national laboratories strengthen their use of molecular methods, such as real-time PCR. RELDA operates VIGENDA, the Genetic Surveillance of Dengue in the Americas, and feeding genotype information into a Dengue Genomic Map. The data will provide scientific information for vaccine introduction and assessment of vaccine impact.
RELDA is aggressively pursuing advanced methods of diagnosis and epidemiologic surveillance. Among the new approaches being implemented or developed are:

- Simultaneous detection of antibody (IgM and IgG) and the virus’ non-structural protein (NS1) antigen, which increases the accuracy of diagnosis;
- Technology to simultaneously detect dengue and Chikungunya; the ability to simultaneously identify zika and dengue will also be available soon; and the methodology can be applied to surveillance of infected mosquitoes as well as humans.
- Surveillance techniques (now used in Mexico) that identify dengue virus and its serotypes in mosquitoes. Early detection of dengue in mosquitoes can enable epidemiologists to anticipate and prepare for community outbreaks;
- Application of the same approach to Chikungunya virus.
- Other technology being developed includes the use of nano-fluids; the use of immunological markers to interpret severe forms of the disease, and a sophisticated entomo-virological mix of laboratory technologies.

Many of the new technologies will be presented at an upcoming RELDA meeting in Panama in 2016, including diagnostic panels covering multiple diseases (dengue, Chikungunya, yellow fever and zika viruses) transmitted by the same mosquito.

Improving Patient Care to Lower Mortality

In Peru, a high mortality dengue outbreak occurred. A group of clinical experts went to the country to advise on patient care in order to reduce mortality.

Such efforts are paying off. The Patient Care component of the EGI-Dengue has made significant advances, including through: the introduction of new WHO guidelines of dengue classification; establishment of a regional technical group affiliated with the International Technical Expert Group on Dengue; reorganization of health services and provision of clinical management training, and work with scientific societies to develop a unified approach to dengue treatment and outbreak response.

Symposium presenters reported on progress in each of these areas.

**WHO dengue classification guidelines:** In 2009, WHO reclassified dengue. The previous 1997 classification had considered dengue as three distinct syndromes: of dengue fever, dengue hemorrhagic fever, and dengue shock syndrome. The new guidelines treat dengue as a continuum of disease, reclassifying it as dengue without warning signs, dengue with warning signs, and severe dengue. A new, deeper articulation of clinical warning signs gives health care providers essential tools to identify patients in danger of developing severe disease.

In 2010, PAHO adopted the 2009 guidelines for the Americas, and a second update will soon address issues related to dengue and chronic disease, as well as dengue in the elderly, newborns and infants, and during pregnancy.

“The impact of the new classification has been on capturing severe dengue cases using warning signs, and the great value of these warning signs is that they are clinical. We don’t always need the laboratory.”

**Expert group:** The region’s clinical expert group has developed clinical guidelines; advised countries on the reorganization of health services; and provided direct training. During 2015, the group helped Brazil set up national clinical guidelines; provided training in clinical management in the Caribbean; and trained providers in the Dominican Republic in classification and treatment of dengue.

**Treatment:** Experts emphasize that dengue is a curable disease when treated early, and that success depends upon the prompt identification of warning signs and the correct management of fluids administered to the patient. The approach requires a focus on primary care, strong clinical management and teamwork; and frequent examination of the patient; improved training of health personnel; and public education.

Going forward, the Patient Care component of EGI-Dengue will work on providing continuing medical education, which is crucial given the high turnover of human resources; improving medical record keeping; establishing medical audits; and following up with health units on outbreak contingency plans. Training in understanding the clinical warning signs will also lessen dependence on laboratory diagnosis, which is often not available in a timely way.
Epidemiological Surveillance

Improvements in the Epidemiology component of the integrated dengue strategy has enabled more countries to systematically collect and disseminate data on dengue. As reported at the Symposium, epidemiologic newsletters are now published weekly in more than 20 countries, and mechanisms are in place to issue alerts. Improved reporting is contributing to a data base that will ultimately provide crucial data for both understanding the burden of disease and guiding vaccine introduction and monitoring.

Eight countries across the region are participating in a pilot surveillance project. The pilot in Mexico, El Salvador, Costa Rica, Panama, Colombia, Peru, Brazil and Argentina will work on the standardized use of dengue case definitions, in conformity with WHO’s 2009 classifications; use both national and sentinel surveillance; and report on environmental and insect indicators, as well as disease and pathogen indicators. The objectives of sentinel surveillance are to characterize clinical illness, viral serotypes, and to monitor the effectiveness of clinical management.

In 2014, Brazil adopted the new WHO dengue classification system, and chose the hyper-endemic areas of Fortaleza and Ceará as the sentinel area in which to evaluate the new case classification. That experience suggests that although the revised scheme is more sensitive to the diagnosis of severe dengue, and beneficial to triage and case management, issues with applicability remain because not all warning signs are equally monitored.

Initial recommendations from these studies include: training of medical and nursing professionals to improve the quality of clinical records and recognition of warning signs, with an emphasis on primary care; including a check list in the medical record to improve data recording and routine data analysis.

Additional tools also need to be developed to meet project objectives in sentinel sites. For example, routine-surveillance would benefit from an online tool that records and analyzes data; more timely reporting of cases and classification of cases; and expanding the confirmation of cases by laboratory criteria.
INTEGRATED VECTOR MANAGEMENT

The only control measure currently available for dengue is control of its vector: the Ae. aegypti mosquito. But efforts to eliminate or control the mosquito have failed to have the desired impact over more than 60 years of effort.

Starting in 1947, early efforts to drive down the mosquito were aimed at combatting yellow fever, another disease transmitted by Ae. aegypti. Indeed, by 1962, unprecedented commitment had vanquished the mosquito from more than 20 countries in the region. But lagging efforts—in part due to an over-emphasis on yellow fever vaccine to combat disease—led to the mosquito’s resurgence.

The symposium heard reports on vector biology and behavior; challenges to Integrated Vector Management today; and developments in vector control tools. Throughout the presentations and discussion, speakers aired various perspectives on the relationship of vaccination and vector control in preventing dengue and other viral diseases spread by its primary vector, Ae. aegypti.

Vector Biology, Behavior and Dengue Transmission

Dengue is transmitted when an Ae. aegypti mosquito bites a dengue-infected person. The mosquito ingests the virus along with its blood meal. The virus incubates and replicates in the mosquito over the next 10 to 12 days, ultimately spreading to its salivary glands. Thereafter, the next person bitten by the infected mosquito will become infected and acquire dengue symptoms four-to-13 days later.

The most significant recent dengue epidemics occurred in Southeast Asia, the Americas and the Western Pacific. But as the climate changes, and more temperate areas warm, increases in rainfall and humidity favors extending the potential range of Ae. aegypti to new areas.

Increasing urbanization also favors the spread of Ae. aegypti. The mosquito is commonly found around homes and workplaces, and particularly thrives in unsanitary conditions. It breeds in artificial containers such as tires and water tanks, and underground septic tanks. Immature stages of Ae. aegypti—eggs, larvae and pupae—are found in these water-filled habitats, mostly in close association with human dwellings and often indoors.

Once they emerge as adults, the mosquitos have a flight range in or around the houses of about 400 meters, but usually no more than 100. Although they bite most frequently during the day, since they breed indoors they are capable of biting anyone at any time. The climatic stability of indoor habitats also increases the mosquitos’ longevity. Female Ae. aegypti that are infected with dengue virus are hyperactive—they fly more often and feed up to 50 percent more often than non-infected mosquitos, which also affects the transmission of dengue. In addition to dengue, Ae. aegypti spread yellow fever, West Nile virus, and emerging diseases like Chikungunya and zika, the latter of which has been associated with an increasing number of babies born with microcephaly, a condition that stunts the growth of the baby’s skull and brain.
Challenges with Integrated Vector Management (IVM)

In 2008, the WHO and PAHO launched Integrated Vector Management (IVM) in the region. IVM approaches vector management as a decision-making process that is evidence based and that considers all the tools available for control in relationship to the vector’s behavior, its distribution, and local conditions. Key elements of IVM are: advocacy, social mobilization and legislation; collaboration within and among different sectors (health, sanitation, environment); integration of chemical and non-chemical approaches; and capacity building.

Advocacy, policy and social mobilization strategies often rely on inter-sectoral collaboration. For example, after Brazil passed legislation for the proper disposal of tires, a massive disposal program was carried out with the help of the recycling industry. The program collected 3.2 million tires between 1999 and 2015, and eliminated prolific breeding grounds for the dengue vector, as seen in figure 6.

IVM’s evidence-based decision making heavily relies on entomological surveillance. One tool that is available to efficiently generate good quality data on mosquito infestations is the Rapid Index Survey of Ae. aegypti (LIRAa). It uses a simplified method of collecting information based on area samples (blocks or houses). Brazil, Paraguay, Uruguay, and other countries have successfully used LIRAa to identify areas at highest risk of outbreaks. Vector control experts also carry out surveillance using ovitraps, which mimic the preferred breeding site for container breeding of Ae. aegypti. Egg samples are collected from the traps and tested to identify potential dengue risks.

Integrated management of vector activity includes improved sanitation and control of the environment through the physical elimination of breeding sites. Up to 60 percent of breeding sites can be eliminated with the participation of the community, families, schools and work places.

One factor influencing IVM today is widespread insecticide resistance (illustrated in figure 7), including to insecticides such as DDT, temephos, Malathion, permethrin and others. This growing problem highlights the need for the development of new pesticide ingredients.

A case study of Mexico noted insecticides being used to help control an outbreak in Villa Hermosa, Tabasco, turned out to be largely useless, as they killed only 40 percent of mosquitos. The finding prompted Mexico to conduct a national study of insecticide resistance, using biological material collected from more than 154,000 adult mosquitos in 62 localities. The results prompted shifts in the insecticides being used. However, it was noted that strong pressure from insecticide companies and corruption need to be addressed.

Other ongoing challenges to IVM stem from inadequate training in the use of insecticides; failure to evaluate mosquito susceptibility prior to insecticide use; and the use of damaged equipment.

**FIGURE 6.** National legislation for the proper disposal of tires in Brazil (policy development and implementation)
El Salvador
- temefos, malathion, fenthion, pirimiphos-methyl, fenitrothion, chlordane, deltamethrin, lambda-cyhalothrin, beta-cypermethrin, and cyfluthrin
  (Rodríguez et al., 2007; Bisset et al., 2009)

Nicaragua
- temefos, malathion, fenthion, pirimiphos-methyl, fenitrothion, chlordane, deltamethrin, lambda-cyhalothrin, beta-cypermethrin, and cyfluthrin
  (Rodríguez et al., 2007)

Costa Rica
- temefos, malathion, fenthion, pirimiphos-methyl, fenitrothion, chlordane, deltamethrin, lambda-cyhalothrin, beta-cypermethrin, and cyfluthrin
  (Perich et al., 2003; Rodríguez et al., 2007; Bisset et al., 2012)

Panama
- pirimiphos-methyl, and temefos
  (Echevers et al., 1975; Bisset et al., 2003; Rodríguez et al., 2007)

Colombia
- DDT, etofenprox, lambda-cyhalothrin, permethrin, bendiocarb, temefos, and fenitrothion
  (Fonseca-Gonzalez et al., 2011; Ocampo et al., 2011)

Peru
- temefos, malathion, fenthion, pirimiphos-methyl, fenitrothion, chlordane, deltamethrin, lambda-cyhalothrin, beta-cypermethrin, and cyfluthrin
  (Vargas et al., 2006; Rodríguez et al., 2007)

Mexico
- organophosphorus compounds, carbamates, and some pyrethroids
  (Flores et al., 2006)

Cuba
- fenthion, temefos, chlorpyrifos, deltamethrin, cypermethrin, lambda-cyhalothrin
  (Rodríguez et al., 2010; Bisset et al., 2011)

Dominican Republic
- DDT, malathion, propoxur, permethrin, and deltamethrin
  (Mekuria et al., 1991)

Puerto Rico
- malathion
  (Field et al., 1984)

Trinidad and Tobago
- fenthion, malathion and temefos
  (Polso et al., 2011)

Martinique
- Bti, temefos, deltamethrin
  (Marcobe et al., 2011)

Venezuela
- fenthion, malathion, temefos, pirimiphos-methyl, chlordane, fenitrothion, deltamethrin, lambda-cyhalothrin, beta-cypermethrin, and cyfluthrin
  (Rodríguez et al., 2007; Pérez et al., 2009)

Brazil
- temefos, cypermethrin
  (Melo-Santos et al., 2010; Lima et al., 2011)

Argentina
- temefos
  (Biber et al., 2006; Linás et al., 2010)
Current Vector Control Tools
Current vector control tools fall into two categories: tools for insect surveillance and those for insect control. Surveillance methods include the collection of eggs using classic ovitraps; collections of lava; and collections of adults using a variety of traps. Monitoring of insecticide resistance is done using bioassays developed by WHO and the United States CDC.

The classic ovitrap approach has been strengthened with the additional use of a web platform and digital image processing combined with geographic information system tools. The combined use of resources allows experts to more rapidly assess risk levels of dengue transmission, based on the estimation of local populations of infected mosquitoes. They also allow more rapid dissemination of the information to guide public health measures.

Insecticide strategies consist of indoor residual spraying; insecticide-impregnated bed nets to stop nighttime bites; and outdoor spatial spraying to kill adult mosquitoes.

Indoor and outdoor spraying each have their pros and cons. Outdoor spraying allows larger areas to be covered in less time with less labor. However, the insecticide does not reach all the mosquitoes, and success depends on favorable weather conditions. Indoor spraying reaches all mosquitoes where they are resting and can be applied using Ultra Light Volumes (ULV). On the other hand, this strategy covers only small areas. One example of a successful integrated approach to vector control comes from Acapulco, Mexico, where the use of long lasting insecticide-treated house screens was effectively combined with the targeted chemical treatment of mosquito breeding-sites.

The strategies and equipment used to apply chemical controls have not varied much during recent years, although there have been some improvements in controlling flow, droplet size, and weight. Further modifications of equipment could improve the efficiency and effectiveness of spraying.

Innovative Vector Control Approaches
Among the innovative possibilities presented at the Symposium were biological control using Wolbachia bacteria; the breeding and release of transgenic mosquitoes; and new molecules for pesticide development; and advances in the use of spraying equipment.
**Wolbachia** is an intracellular bacteria that is present in 20-65 percent of insects, including some species of mosquitoes that bite humans—but not in *Ae. aegypti*. Because *Wolbachia* can block dengue virus inside the mosquito, scientists are working on breeding *Ae. aegypti* that contain the bacteria. These *Wolbachia*-containing mosquitoes would be released into the environment to interbreed with wild mosquitoes, ultimately giving rise to *Ae. aegypti* populations incapable of transmitting dengue. Scientists are conducting pilot projects in four neighborhoods in Rio de Janeiro, Brazil. Other studies are underway in Australia, Vietnam, China and Indonesia.

**Transgenic mosquitoes:** Scientists have bio-engineered *Ae. aegypti* to contain a lethal gene that kills immature mosquitoes before they reach adulthood and breed. Researchers at the University of São Paulo have produced millions of these mosquitoes using technology developed by the British company Oxitec. By releasing transgenic male mosquitoes into the environment to breed with wild females, the mosquito population can be repressed. Pilot projects in Itaberaba and Mandacaru have succeeded in doing so. In Bahia, Brazil, suppression reached 80 percent. However, the technique requires a large laboratory to produce the requisite four to six million eggs weekly, in order to release 1.5 million insects per week.

Scientists are exploring the use of another molecular approach known as RNAi, which can turn off targeted genes. They hope to use it to silence genes that cause insecticide resistance, or genes involved in mosquito reproduction.

**New insecticides:** New molecules are also being developed to expand the choice of insecticides. One, Actellic 300CS, which is already used against malaria, is an organophosphate considered ideal for resistance management. A new microencapsulated long-term formulation can remain intact for six months. Mosquitoes who come in contact with the formulation transport the insecticide with them, and expose other mosquitoes to its effects. Scientists are developing other new adulticides and larvicides as well.

**Equipment advances:** Improvements in equipment used to spray insecticide could also improve its efficiency. For example, some equipment uses “defectrodes” that adhere the insecticide to the walls, decreasing the amount of insecticide needed.

A renewed interest in electrohydrodynamic (EHD) spraying was instigated by a need for a light-weight, low-powered sprayer for vector control in combat zones by the US military. One such piece of equipment was designed to apply sprays at ultra low volume (ULV) rates down to 0.5–1.0 ml/m2 compared with existing practice of 30–40ml/m2. Today, lighter and electrically powered equipment is in development.
DENGUE VACCINE INTRODUCTION

Speakers reported on the status of six dengue vaccine candidates. One of these, the CYD-TDV vaccine from Sanofi-Pasteur, has largely completed Phase 3 clinical trials, and the manufacturers are applying for registration in up to 20 countries with endemic disease. The other five candidates are in various stages of development, as Phase 1 and Phase 2 trials are conducted. Figure 10 illustrates the current dengue vaccine pipeline.

All of the vaccines under development are quadrivalent—aiming to protect against all four dengue serotypes. Ideally, any vaccine would have roughly equal efficacy against all four serotypes.

Participants noted that we have entered the start of a transition period where evidence becomes even more important as vaccines become available. Countries will be challenged with setting priorities, and deciding whether to introduce an available vaccine, with its particular profile of strengths and weaknesses, or to wait for other candidates as they become available.

Vaccine Pipeline

Speakers reported on safety, efficacy, potential time of availability, projected dose schedules, and age of vaccination. However, they did not comment on the potential price range, despite the importance of this issue to the feasibility of vaccine introduction.

Takeda Pharmaceuticals Limited—TDV Candidate

Japan-based Takeda Pharmaceuticals is developing a live-attenuated tetravalent dengue vaccine (TDV). Phase 2 studies are underway to assess safety and tolerability in adults and children 1.5 to 45 years old, and to establish dose schedule. The trials began in 2010, and 360 participants are now enrolled in clinical trials in the dengue endemic countries of the US/Puerto Rico, Colombia, Singapore and Thailand.

The candidate vaccine elicited a tetravalent immune response in the majority of participants, with levels of seroconversion of at least 80 percent to all four dengue serotypes after two doses. The strongest response was to Denv-1 and Denv-2, the weakest was to Denv-4.

The safety profile was strong: there were no systemic adverse events; no discontinuations due to Adverse Events; no related Severe Adverse Events; no constellation of symptoms suggestive of dengue fever, and no deaths.

A formulation has been selected for ongoing and future studies, including a Phase 3 efficacy study that is in preparation. Takeda is optimistic about a one dose schedule, and is working to determine what specific populations might need a second dose. After the Phase 3 study, there will be a one-year follow up for efficacy, and a five-year follow up for safety. They expect to have data available for prequalification by late 2017. Takeda did not comment on price.

US National Institutes of Health—TV003 and TV005

The TV003 and TV005 live-attenuated tetravalent dengue vaccine candidates were developed through the NIH and are being tested in partnership with Merck Pharmaceuticals. The vaccines are currently in Phase 1 clinical trials.

Studies in dengue-naïve adults (18-50 years old) living in Baltimore, Maryland, or Burlington, Vermont, elicited a strong tetravalent antibody response in 90 percent of subjects without previous dengue exposure.

The main adverse outcome of clinical trials has been a vaccine rash. Of 74 subjects who developed a rash, 73 were mild and one was moderate (wild-type dengue can produce a bad rash). In the vaccine trial, the rash was predictive of tetravalent antibody response. When 41 vaccinated volunteers were challenged with attenuated DENV-2 virus, TV-003 provided 100 percent efficacy against viremia and rash.

An age de-escalation study is now underway, with the final cohort of younger children (age 1-4 years) having received their vaccination in November 2015, and another is planned in Dhaka, Bangladesh.

Instituto Butantan—TV003 Adapted for Brazil

Instituto Butantan, a public sector Brazilian biomedical research center, has licensed the NIH TV003 candidate for use in Brazil, with the goal of introducing routine immunization for all children two to six years old.

Like TV003, the Brazilian formulation is a live-attenuated tetravalent vaccine. The vaccine aims to produce sustained protective immunity against all
four serotypes. It aims to protect against symptomatic disease after one dose in at least 80 percent of cases.

A Phase 2 trial is underway and will proceed through two steps. The first step bridged the NIH formulation and Butantan’s, showing similar results. The second step includes 250 additional participants, 200 of whom had previously been exposed to dengue. The preliminary safety results are strong and similar to those of the NIH. Cellular immunity was generated at day 91, eliminating the need for a booster.

Butantan has now requested approval to proceed with a Phase 3 trial designed to be carried out in 14 research studies in 13 cities in Brazil. The trial aims to represent the country’s diversity: in areas of high and low endemicity, and areas in which flavivirus co-infection is common. The trial will enroll over 17,000 volunteers, from two to 59 years of age. All volunteers will be followed for five years, paying special attention to warning signs of possible severe disease.

While expecting to file for registration in 2017, Butantan is scaling up in the meantime. It has created production process for TV003 for 10-doses packages, and is projecting a capacity of 50 to 60 million doses produced per year, inclusive of vaccine for export to other countries.

As a non-exclusive licensee of the NIH vaccine for all Latin America, and a public institution with no marketing costs, Butantan expects their vaccine to cost less than those produced by commercial pharmaceutical companies.

**GSK—DPIV**

GSK is collaborating with the Brazilian government’s FIOCRUZ institute and the U.S. Army to develop DPIV as a tetravalent vaccine derived from whole virus that has been purified and inactivated. There is no risk of transmission, reversion or viral interference due to virus inactivation. They adapted the approach after work with a live dengue vaccine candidate failed to elicit equal immune responses among all serotypes.

DPIV is intended as a two-dose vaccine, able to be administered across a broad age range, starting at just 10 weeks of age. It is intended to be co-administered with other vaccines in the National Immunization programs.

Phase 1 trials exposed 160 subjects to one of the four DPIV formulations with no Severe Adverse Events or safety signals. The trial showed that DPIV induces a high-tittered tetravalent neutralizing antibody response in dengue-naïve and dengue-experienced subjects, and induces a lasting B memory immune response.

Investigators are starting a Phase 2 trial, with formulation studies expected to start in 2016.

**Merck—V180 and V181**

Merck’s V180 vaccine candidate is a recombinant, truncated envelope glycoprotein (DEN-80E) expressed for all four dengue virus serotypes in Drosophila S2 insect-cell culture. The virus’ envelope protein is key target for virus-neutralizing antibody. As a soluble subunit vaccine, V180 will likely require adjuvant in flavivirus-naïve populations.
In its first human trial, V180 P001 was tested in 98 flavivirus-naïve, healthy young adults 18-to-49 years old in Australia who received three injections in one-month intervals. All formulations tested were generally well tolerated, and there were no severe adverse events.

Formulations containing adjuvant were highly immunogenic inducing seroconversion in 85.7-100 percent of subjects, depending on the serotype. Non-adjuvanted formulations were less consistent in inducing seroconversion. Titers declined over time for all formulations after the third dose but generally plateaued above baseline for adjuvant formulations.

The V181 vaccine candidate is an NIH live attenuated vaccine for all four dengue virus types. It has been tested as both monovalent and tetravalent formulations in more than 1,000 volunteers in US Phase 1 studies, and Phase 2 studies are ongoing in Brazil and Thailand.

Next steps for both vaccines include a clinical trial in collaboration with the NIH to evaluate recombinant V180 as a booster to V181, and Merck-sponsored clinical trials of the live attenuated virus vaccine.

Sanofi-Pasteur—CYD-TDV
Sanofi-Pasteur’s 20 years of research in developing dengue vaccines has produced the most advanced dengue vaccine candidate, CYD-TDV (Capeding, 2014, Lancet. Villar, 2015, N Engl J Med. Hadinegoro, 2015, N Engl J Med.). It is a tetravalent recombinant live attenuated vaccine. Sanofi has conducted clinical trials involving more than 40,000 individuals, with nearly 29,000 of them having received at least one dose of vaccine. Sanofi has conducted 25 studies in 15 countries, primarily focused in endemic areas of the Americas and South and Southeast Asia.

Pool data from Phase 3 clinic trials show 93 percent efficacy against severe dengue; 80 percent efficacy against hospitalized dengue, and 65 percent efficacy against laboratory-confirmed dengue in general populations 9 to 16 years of age.

Efficacy in both Latin America and Asia was higher in participants who had been previously exposed to dengue (sero-positives) than in participants who had not (sero-negatives).

In Latin America, where trial participants were 9-to-16 years of age, there were no age differences related to efficacy. In Asia efficacy varied by age, with the youngest age group of two-to-five year olds having the lowest efficacy, and the highest efficacy in 12-to-14 year olds.

Overall in Latin America, efficacy was 95 percent against severe dengue; there was an 80 percent reduction in dengue hospitalizations; and 60 percent efficacy against any laboratory-confirmed dengue.

The primary safety measure for the Phase 3 trials was laboratory-confirmed dengue hospitalizations during three years of follow-up to vaccination. The pooled data shows that among children 9-to-16 years of age the rates of hospitalized dengue are lower in vaccinees as compared to placebos. However, in Asia the youngest children (two-to-five years old) who were vaccinated had higher rates of hospitalized dengue during the third year of follow up than did children in the placebo group.

For this reason, Sanofi is seeking registration for vaccination beginning at age nine, up through age 60. Sanofi envisions routine immunization for all children at nine years of age, ideally combined with catch-up vaccination in several older cohorts when the vaccine is first introduced. This would provide indirect protection to an even larger population, and have the fastest and most dramatic impact on reducing disease.

The company has applied for registration in 10 countries heavily impacted by dengue, and plans to file in a total of 20 countries by the end of 2015. Sanofi anticipates filing for WHO prequalification in the next 18 months to two years.*

Sanofi is proposing Phase IV impact studies to assess program impact on dengue burden and vaccine effectiveness. Surveillance using high performing diagnostics serves as the foundation for these activities. Other open questions pertain to whether and how much vaccine protection wanes over time, and whether CYD-TDV can be safely co-administered with HPV vaccine, which is targeted at the same adolescent age group.

Beyond clinical development, Sanofi anticipates conducting long-term surveillance and post-licensure activities, including economic studies. It plans to produce up to 100 million doses of CYD-TDV a year, which will be packaged as a freeze-dried vaccine in single dose and five-dose presentations.

*During the production of this proceedings, Dengvaxia®, Sanofi Pasteur’s dengue vaccine, received approval for limited marketing in Mexico, Philippines, Brazil and El Salvador. The national regulatory agency of each country granted the approval, which applies specifically to individuals between the ages 9 and 45 years living in dengue-endemic areas in these countries.
VACCINE INTRODUCTIONS: PAST, PRESENT AND FUTURE

Across the region of the Americas, almost 16 million children are born every year, and year over year, they have had access to a growing array of vaccines to protect against disease and ensure they get a healthy start on life.

PAHO and ProVac

In 2015, PAHO is celebrating 38 years of its Expanded Immunization Program (EPI). During that time, most countries have achieved overall coverage of greater than 90 percent for DTP3, which is the universal marker of vaccination program performance. In the past nine years, almost all the countries have introduced new vaccines and now use either pneumococcal or rotavirus conjugated vaccines, as well as the HPV vaccine to prevent cervical cancer.

As a result, mortality rates are dramatically down. In Colombia, for example, pneumonia mortality rate has dropped by nearly 30 percent. And, this year, the entire region celebrated the elimination of rubella and congenital rubella syndrome.

Through all of this, PAHO offers support, from the beginning of the vaccine introduction to final assessments of their impact. PAHO supports surveillance, interpretation of evidence, vaccine introduction design and evaluation, and vaccine financing through the Revolving Fund. Its research and policies help guide public health vaccination strategies across the region.

PAHO promotes the technical excellence of EPI at all levels, and helps strengthen national technical advising committees (NITAGs). In the Americas, 23 out of 35 countries now have a national technical advising committee to support the decision-making process in national immunization programs.

PAHO works with countries before the introduction of a new vaccine, to ensure financing is sustainable, and the goals of vaccination can be met without interruption. Today, 25 countries have legislation that strengthens the finances of national vaccination programs, and last year PAHO’s Revolving Fund purchased vaccines worth US$573 million for regional use.

Another PAHO program that offers critical support to countries is ProVac, which PAHO initiated to strengthen national capacity to make informed decisions about vaccine introduction, in particular with the support of economic evidence.

ProVac’s current focus is on four vaccines: rotavirus, pneumococcal conjugate, HPV and Influenza. In the future, it will expand this portfolio to also concentrate on dengue, meningococcal, and Hepatitis A vaccines, among others.

ProVac works to strengthen NITAGs; develops tools for economic evaluations; and trains multi-disciplinary teams in their use. Countries collect the data to populate the tools and analyze the results. ProVac also supports advocacy for evidence-based decision making. To date, more than 30 cost-effectiveness analyses have been completed.

Going forward, ProVac will integrate the cost-effectiveness disease models into a single platform called UNIVAC that countries will be able to use to compare the cost-effectiveness of different vaccines.

Such an assessment is an important—but only one—consideration for introducing a vaccine. Other considerations for a country include social, operational and programmatic; and technical dimensions. Ultimately, ProVac will be able to deliver analysis of all of these considerations as one evidence package which can be used to assess acceptability, perception of risk, political will, and equity.

ProVac is now working with WHO to share its lessons with other regions and to transfer tools and methods that help countries link technical discussions to resource allocation decisions.

For general information, technical documents and articles go to: www.paho.org/provac.

WHO and Dengue Vaccines

Addressing the conference, a WHO-HQ representative made clear that WHO is in the process of reviewing the evidence to make recommendations about the use of dengue vaccines, but does not currently have a
position. Official WHO recommendations will be issued following the April 2016 meeting of WHO’s Strategic Advisory Group of Experts on Immunizations (SAGE), during which the principal WHO advisory committee on immunization will make recommendations to WHO. The recommendations made by SAGE will be publicly available the following week.

By mid-2016 the first WHO Vaccine Position Paper on Dengue Vaccines should be published. WHO Vaccine Position Papers make global recommendations for use of a vaccine and are issued only after a vaccine is licensed by a functional NRA and reviewed by SAGE. The Papers are published in WHO’s Weekly Epidemiological Record and include a review of the evidence related to key policy questions.

In addition to providing global guidance on optimal vaccine use, WHO supports many activities around dengue vaccines that occur both before in the clinical development stage and post-registration. The WHO representative emphasized that countries make the ultimate decision about vaccine introduction and use. Several speakers addressed the many factors that enter into such an evaluation, which will vary by country and setting. These include vaccine characteristics, programmatic concerns, and public health impact. Programmatic concerns include whether or not a new vaccine fits with the current childhood schedule, the duration of immunity and need for booster shots, and the geographic distribution and transmission intensity of the disease. The impact of a vaccination program on disease, including potential outbreaks, is also important. Do frequent or worsening epidemics tend to overwhelm clinical resources? Are other intensive or expensive interventions needed to combat the disease? All of these features contribute to estimating the public health value of a vaccine.

**Dengue Vaccine: Modeling Potential and Assessing Impact**

Several speakers addressed the crucial issues of modeling vaccine impact prior to introduction and assessing actual impact after introduction. Vaccine impact models can provide an important source of data for decision makers, and only through assessing actual impact can public health authorities evaluate vaccine benefits and costs. Yet, as a vector-born disease, dengue poses unique challenges to both modeling and assessing impact.

### Modeling Vaccine Impact in the Yucatan

Researchers presented the results of a model used to assess the potential impact of Sanofi-Pasteur’s CYD-TDV vaccine in Mexico’s Yucatan. The model takes account of every individual in the population. The tool models households, schools and other units where people may mix and encounter infectious mosquitoes. It also follows every infected mosquito in the Yucatan, using data reported from 1979 to 2013 on the total number of dengue cases.

Based on the efficacy data determined in the Phase 3 clinical trials, researchers used this model to evaluate the potential impact of the CYD-TDV vaccine. They found that with routine vaccination of children, overall effectiveness that starts at nearly zero percent goes up to about 50 percent, preventing roughly 1,000 cases of dengue per 100,000 population. If a one-time catch-up (conducted up to age 30) is added to routine vaccination of nine-year-olds, the effectiveness immediately starts at 50 percent and goes up to 75 percent, preventing double the number of severe cases after 20 years.

However, as the model is run out over a long period, effectiveness begins to weaken, because the proportion of dengue-naïve people in the population goes up, and the CYD-TDV vaccine is less effective in dengue-naïve people than in people previously exposed to dengue. In addition waning of protection of CYD-TDV is not yet known.

Therefore, researchers ran the model to account for different rates of waning. They found that booster vaccination can compensate for much, but not all, of the waning. However, when the model assumed vaccine waning but no compensatory booster vaccine, within four years dengue rates were higher than if there had been no vaccination at all.

Similarly, the model considered the impact of vector control, simulating past dynamics from 1878 to 2013, and projecting forward with a variety of vaccination and vector control scenarios. The model showed that as vector control improves over time the number of people susceptible to dengue grows, ultimately resulting in large outbreaks. Furthermore, if vector control is practiced for ten years and then stopped, dengue becomes a larger problem than if there had never been vector control.

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However, the combination of vaccination and even modest vector control provides an effective dengue control strategy. A decrease in the adult mosquito population by 10 percent results in a pattern that looks a lot like routine vaccination plus catch up. Data suggests that countries implementing effective vector control should not stop because of potential rebound effect.

The Value of Vaccines Beyond Efficacy and Safety

Experts at the Symposium argued that vaccine efficacy and safety provide only a partial snapshot of a vaccine’s true public health value.

Vaccine efficacy (VE) is based on the percentage reduction of disease in a vaccinated group of people compared to an unvaccinated group, with laboratory confirmation of the biological cause of the disease.

But another—and some argue better—measure of vaccine impact is Vaccine Preventable Disease Incidence (VPDI). VPDI is measured using a formula that incorporates the background rate of disease to determine how many actual cases of the targeted disease are prevented for every one hundred thousand people vaccinated.

For example, a study of rotavirus vaccine and acute gastroenteritis showed that vaccine efficacy was 80 percent against confirmed rotavirus, but only 54 percent against any inpatient acute gastroenteritis. But, the incidence of preventable disease was three-fold higher when considering acute gastroenteritis from any cause than when only considering etiologically confirmed rotavirus. In other words, vaccine efficacy calculation missed two out of every three cases of rotavirus that the vaccine was actually preventing.

Vaccine efficacy can be misleading as a sole monitor of vaccine impact in other ways as well. One example cited suggested that public health impact actually can be greater in settings where the vaccine efficacy is lower. A comparison of rotavirus vaccine impact in South Africa and Malawi found that even thought VE was higher in South Africa (77 percent) than in Malawi (49 percent); many more cases of rotavirus were averted in Malawi because of the much higher incidence of rotavirus in that country. When viewed through the lens of VPDI, rotavirus vaccine prevented 4,200 cases per 100,000 vaccinated children in South Africa, and 6,700 cases per 100,000 vaccinated children in Malawi.

Designing Post-Introduction Impact Assessment Studies

To evaluate the impact of vaccination on disease and vaccine performance as measured by vaccine effectiveness, several study designs, from the most basic to more complex are available. Observational studies compare disease incidence pre- and post-vaccination and rely on national and sentinel surveillance systems. But, according to several presenters, a less common but potentially more informative study design is a group randomized study, such as a community/cluster-randomized study.

Epidemiologists in Mexico are designing such studies now. They are designed to shed light on the vaccine’s overall impact, especially its indirect effects and herd immunity. Typically, Phase 4 studies go beyond the relatively narrow findings of Phase 3 clinical trials to gain information on indirect effects (the effects of widespread vaccination on people who are not vaccinated), and overall effects (population-wide reduction in disease incidence.)

In a post-introduction cluster-randomized trial, the unit of analysis is not individuals, but the cluster, which could be a state, city, neighborhood, households or schools. Everyone enrolled in the Phase 4 would receive the vaccine as it is intended and approved for the population. So, if a country decides to vaccinate every nine-year-old with dengue vaccine, everyone in the trial would likewise be vaccinated at nine years of age.

Clusters are randomized to capture the impacts of additional interventions, such as catch-up vaccination in older age groups, or the implementation of specific vector control measures. Then outcomes are compared among clusters. In Mexico, researchers are preparing now by conducting dengue transmission baseline studies in three cities in the Yucatan: the capital Merida, the port city of Progreso, and the more rural city of Ticul.

Practical Considerations for Dengue Vaccine Introduction

The Sanofi-Pasteur CYD-TDV vaccine is likely to become the first vaccine of proven safety and efficacy available to prevent dengue. Other vaccines are moving through the pipeline and at least some number of these will certainly become available in the years ahead.

Given the relatively near-term prospect of CYD-TDV registration, countries are evaluating a variety of
practical considerations related to dengue vaccine introduction. These include issues related to vaccinating adolescents: with the possibility of school-based vaccination campaigns; vaccinating adults in campaigns and at health centers; possible co-administration of dengue vaccine with HPV and tetanus vaccines; other logistical issues; and vaccine price and financing.

Adolescent and School-Based Vaccination

Although school-based immunization is the most plausible approach to reaching a large cohort of nine-year-olds, it can be challenging, in part because not all children are in school. There are approximately 117 million children and adolescents in Latin America and the Caribbean that are school aged, and of these 15.6 million do not attend school or attend only sporadically, and 6.5 million are not enrolled in school at all. Irregular attendance becomes an even bigger problem given CYD-TDV’s three-dose schedule.

Consent is also an issue. As reported in a recent position paper by the Society for Adolescent Medicine, vaccination in adolescents lags behind that in younger children. A requirement to obtain parental consent could further limit the rapid deployment of vaccines.

However, some countries, including Colombia and Brazil, require refusals from parents who do not want their children vaccinated, rather than requiring consent. This approach seems to streamline the process and support vaccination. In Brazil, only five percent of parents refused HPV vaccination for their daughters, and many of those parents later reversed their decision and actually asked that their daughters be vaccinated.

WHO pointed out that when vaccination is delivered, it is part of an integrated set of health interventions aimed at the adolescent age group. Therefore, issues of consent need to be considered across all interventions.

HPV Co-Administration and the Carmen de Bolivar Episode

When HPV vaccine is administered to adolescent girls, it prevents the development of cervical cancer later in a woman’s life. As a result, across the Americas and the world, countries have introduced the vaccine for girls. CYD-TDV could be administered to girls and boys of the same age, raising the possibility of efficient co-administration of the two vaccines. Several countries shared their experience with HPV introduction, drawing lessons for CYD.

Colombia’s experience was particularly instructive. The country decided to introduce HPV vaccine based on its cost effectiveness and the large burden of disease from cervical cancer, which kills approximately 3,000 women in Colombia every year.

The vaccination campaign started strong, reaching almost 98 percent of 9-17 year old girls with a first dose. The safety record was also strong: there were fewer than 2 to 7 adverse events for every 100,000 vaccinations.

But that initial success was not sustained. In the second round of vaccination, 80 percent of girls received their first dose, and in 2015, the percentage of girls receiving a second dose plummeted to 20 percent, then only slowly recovered to its current 41 percent.

School Readiness for Vaccination

WHO has produced a school vaccination readiness assessment toolkit. It notes that, among other things, readiness requires:

- Education for school authorities, teachers and administrators, as well as communities and parents;
- A compulsory education policy for the targeted age group;
- School health services, including things as simple as access to clean water and a location for children to be vaccinated;
- Good access to a healthcare facility should there be any kind of an adverse events requiring urgent medical attention;
- A waste disposal plan at the schools;
- Good enrollment data and a plan for administering vaccine to absent and out of school children.

Immunization programs for adolescents also need to take account of adolescent development and psychology, as experience with the HPV vaccine has shown. School vaccination delivery strategies are not easy, they are not simple, and they are not cheap. But, they do have the ability to achieve high coverage.
The abrupt decline is attributed to the Carmen de Bolivar episode, in which 15 girls at a religious school in Carmen de Bolivar began fainting. For a month, the girls would faint or have convulsions every two or three days. Within weeks, parents began blaming the vaccine. A chorus of vaccine detractors joined, including some medical experts, and media coverage fed the frenzy. Within approximately three months, some 600 girls in several other schools had at least one similar episode.

Health authorities quickly diagnosed the episode as a massive psychogenic event: a propagation of symptoms in a social group, with no organic cause, but with an unsubstantiated generalized belief in the population that the vaccine was the cause.

The situation slowly stabilized, as public health workers assuaged fears about the vaccine. Ultimately, the press acknowledged that there was no evidence that the vaccine was at fault. But by then the damage was already done.

Among the lessons shared from Colombia's Carmen de Bolivar episode were:

- Surveillance systems for vaccine adverse events need to be prepared for chronic reactions, not only severe, acute reactions;
- The public health system must be prepared to anticipate, detect, evaluate and solve such problems quickly. The Carmen de Bolivar community of 30,000 people had previously been subjected to forced relocations and extreme violence. Health authorities did not have the capacity to anticipate the severity and rapid spread of the community reaction across this psychologically vulnerable population.
- Fear mongering on social media must not go unanswered. Public health education should create and popularize trusted social media sites that provide accurate vaccine information.

In some ways, Carmen de Bolivar was a wake-up call for the public health community to be prepared for such episodes with adolescent vaccination. At the same time, it does not detract from the overall success experienced with adolescent vaccines including Hepatitis B, tetanus toxoid combinations and HPV.

Adult Vaccination, Logistics, and Price

As CYD-TDV registration is being sought for persons 9-60 years of age the possibility also exists that vaccination of adults will be considered, as it may help reduce the overall burden of disease.

Adult vaccination is not new, and in recent years PAHO has expanded its emphasis from childhood vaccination to family vaccination that includes all age groups. The Vaccine Weeks of the Americas are one example of this approach, and have greatly increased adult vaccine uptake, especially for influenza.

However, logistical and financial challenges loom large, starting with the sheer scale of the effort. The current quarterly Vaccine Weeks schedule does not coincide with the recommended CYD-TDV vaccine schedule. In the case of school-based vaccination, workload for vaccinators would more than double.

The potential vaccine price presents another concern. The large volumes needed, especially with the inclusion of catch-up vaccinations, would quickly escalate costs and call for the identification of new funding. Countries are already spending millions of dollars on vector control, and participants repeatedly stressed that vaccine purchases cannot come at the expense of vector control.

Vaccine price is still unknown, but several countries, including Mexico and Colombia, conducted vaccine cost-effectiveness studies. Based on these studies, when the Colombian government decided it may not be able to introduce CYD, despite its clear need.

The Colombian presenter reinforced the need to wait for the vaccine to be less expensive in order to think about an introduction.
BRAZIL: PLANNING FOR VACCINE INTRODUCTION

Brazil typically reports approximately 1.8 million cases of dengue per year. Usually, only 30 percent of reported cases were confirmed through laboratory tests; the remaining 70 percent are diagnosed based on clinical criteria.

With its high burden of dengue, in 2013 Brazil initiated studies to provide the needed data to make an evidence-based decision about vaccine introduction.

Researchers reviewed approximately 5.5 million dengue cases reported in the surveillance system of 4,500 municipalities that had at least one dengue epidemic between 2000 and 2014. The analysis revealed a progressive increase in dengue incidence over the last 15 years, especially in younger age groups.

The study identified key risks of hospitalization and death from dengue, including:

- Young age—children six to ten years of age were most vulnerable;
- Infection with Denv-2 and Denv-3;
- Risk highest among country’s poorer northeast regions;
- Treatment delays of longer than five days often resulted in hospitalization
- Risk of death approximately three times higher in pregnant women than non-pregnant women, and increased with gestational age.

Data has been used to model the predicted impact of vaccines, ranging in efficacy between 25 and 100 percent when deployed in epidemics. The model suggested that a vaccine of any efficacy reduces the number of dengue cases. However, if the use of lower-efficacy vaccines (less than 60 percent efficacy) is accompanied by a 10 percent relaxation in vector control, the model suggested that dengue disease incidence would rise, not fall. The findings highlight the complexity of dengue prevention and control, and the need for thorough considerations of all aspects of potential vaccine introduction and its intersection with other control measures.
CONCLUSION

The Symposium reviewed progress and challenges in dengue prevention and control from several different angles. Chief among these was the need to consider vaccination as a complement to vector control as reflected in WHO and PAHO policy. Communication challenges associated with vaccine introduction were also prioritized. Educating the public on the importance of dengue prevention, including vector control efforts, such as eliminating breeding sites near homes and appropriate spraying programs, were highlighted as a key strategy.

Introduction of a dengue vaccine in Latin America, will require careful communications to appropriately set expectations about vaccine impact and availability, supply capacity, number of doses required, price and other factors. As dengue continues to threaten the region, the public health community will be challenged to maintain vaccine coverage if multiple doses are needed. Effective treatment also requires that the public—as well as health-care providers—be better informed about dengue signs and symptoms. Even the waning of fever should never be considered an all-clear signal, but rather a marker for increased vigilance for the signs of severe dengue that may follow.

To overcome dengue, countries must act now: collecting the evidence needed, and accelerating action across all six components of the Integrated Strategy for Dengue Prevention and Control. *Ae. aegypti* mosquitoes and dengue are on the move and continue to be a rapidly expanding public health threat to the people of the Americas.