Planning for the Introduction of Dengue Vaccines

Brasília, Brazil
22-23 August 2011
The Americas Dengue Prevention Board met in Brasilia on 22-23 August 2011 to identify practical and specific steps for the rational introduction of dengue vaccines. Participants included representatives of health ministries, institutions and academia from 12 countries in the Latin American region. The meeting was organized by the Dengue Vaccine Initiative (DVI), which is a consortium of the International Vaccine Institute (IVI), the International Vaccine Access Center (IVAC) at the Johns Hopkins University, the Sabin Vaccine Institute (Sabin), and the Initiative for Vaccine Research (IVR) at the World Health Organization (WHO).

Dengue is a rapidly expanding disease affecting more than 100 countries. It imposes heavy social and economic burdens on families and health systems. Vector control, although an essential part of any dengue control strategy, is largely ineffective on its own and there are no medicines for treatment. Vaccines are seen as the best means to prevent dengue. Countries in the Americas present epidemiological and clinical particularities for prevention and control of dengue, and several of these issues were presented at the meeting.

Progress has recently been made in developing safe and effective dengue vaccines, with the possible licensure of one candidate vaccine by 2015. Detailed computations indicate that the demand for a vaccine could be very large, amounting to hundreds of millions of doses each year. At the meeting, vaccine developers gave updates on the status of their candidate vaccines and their preclinical development or clinical trials. It is likely that the first adopters of dengue vaccines will be those countries in which vaccine clinical trials are being conducted. There will be important markets in both the public and private sectors, with private sector introduction likely preceding public sector adoption.

Modeling will be important for developing strategies for introducing vaccines and DVI is sponsoring the preparation of such models.

To support decision-making and policy formulation, DVI is sponsoring a wide range of studies on topics including seroprevalence, burden of disease, willingness to pay, cost of illness, financing options, and strategic demand forecasting.

A wide range of issues need to be addressed to enable the design of effective policies for the introduction and sustained delivery of dengue vaccines. These include:

- How to integrate the vaccine into existing Expanded Programs on Immunization;
- Design of catch-up campaigns;
- Delivery through other systems, such as vitamin A supplementation;
- Establishment of effective surveillance systems;
- Integration with vector control programs;
- Sustainable financing;
- Regulatory affairs and National Regulatory Authorities;
- Communications and social mobilization programs;
- Logistics and supply chain management; and,
- Training of immunization staff.

The rational introduction of dengue vaccines will require the preparation of sound investment and introduction case studies. The DVI is working in four focal countries, including Brazil and Colombia, to develop such cases. Lessons learnt from work in Asian countries have been incorporated into the Latin American studies. The cases should be helpful to other developing countries facing the challenges of vaccine introduction.

EXECUTIVE SUMMARY

It is not whether but how to introduce a dengue vaccine.

~ Luiz da Silva, IVI
Additional support is needed to harmonize the regulatory processes, to help National Regulatory Authorities to prepare for the introduction of dengue vaccine, to assess the dynamics of likely vaccine uptake, to project vaccine supply and the impact of vaccine introduction on health and the health systems, and to explore various financing mechanisms.

Advocacy for prevention and control of dengue remains essential and needs to be addressed at global, regional, national and sub-regional levels, with identification of champions and the goal of political commitment at the highest level.

The meeting provided a dynamic forum for the open and constructive exchange of information and views among the major parties concerned in the prevention and control of dengue in the region through introduction of a vaccine. Participants noted that work has started in many core areas but agreed on the need to accelerate planning to be ready for vaccine availability in just a few years’ time.

**OBJECTIVES**

The Americas Dengue Prevention Board and Dengue Vaccine Initiative (DVI) organized the meeting in order to examine ways to generate support for the rational introduction of dengue vaccines; to review the generation of data for decision-making and dengue vaccine investment cases; to discuss prospects for and issues surrounding the availability of dengue vaccines; to review country policy considerations for dengue vaccine introduction; to discuss communications and advocacy; and to involve key health ministry staff and vaccine manufacturers in the process.

DVI grew out of the Pediatric Dengue Vaccine Initiative, which was founded in 2003. DVI was launched in November 2010 as a consortium, with the International Vaccine Institute (IVI), the Sabin Vaccine Institute (Sabin), the International Vaccine Access Center (IVAC) at the Johns Hopkins University (JHU) and the Initiative for Vaccine Research (IVR) at the World Health Organization (WHO), to encourage the development of vaccines to control dengue fever and their rational introduction into public-sector programs. The consortium aims to build on past experience, with a focus on practical action. Working with committed governments, especially senior staff in health ministries, it will provide evidence for decision-making, help in policy formulation, and help ensure access to any eventual vaccine, especially for low-income populations. It will work in partnership with industry, acting as a platform for bringing together public health and industry sectors.

Dengue Prevention Board meetings provide a dynamic forum for the open and constructive exchange of views and information among government and health ministry officials, the pharmaceutical industry, academics, non-governmental organizations and others.
It is not whether but how to introduce a dengue vaccine.” Luiz da Silva, Director, DVI. That clear statement set the tone of the meeting. The Brasília meeting, and the Hanoi meeting of the Asia Pacific Dengue Prevention Board held in April 2011, represent the first time that strategic planning for the introduction of a vaccine into developing countries has been examined before the conclusion of clinical trials and vaccine licensure.

However, it was also evident that this view about how, and not if, to introduce a dengue vaccine is not held by all. Some vital decision-makers at the global level, and some national ones have little realization of the risks of dengue and severe disease, the changing clinical expression of the disease, the disease burden, and the likely impact in 10 years time if the expansion of dengue remains unchecked. Therefore there is a need to generate a broad sense of commitment beyond that held among dengue expert groups.

KeY tHeMeS

HOW TO INTRODUCE THE VACCINE

Dengue is a political and economic issue; during the meeting participants from several countries remarked that dengue has caused more resignations of health ministers than opposition parties have. In many countries where the disease is endemic, the risks and impact of dengue are well understood. Outbreaks, which cause tremendous social and economic disruption and overwhelm health services, often result in sensationalist reporting in the media, some of which use the consequences of the disease as a weapon to attack governments at local and higher levels. Outbreaks also cause problems for governance at the municipal level.

In spite of having a high priority in some endemic countries, dengue has often not received an equally high status in the global health community because of its comparatively low mortality. It is clear, however, that number of deaths alone is not the sole criterion in decisions to introduce new vaccines. Recent examples, including the introduction of pentavalent vaccines containing hepatitis B and DTP antigens, illustrate the range of factors influencing efforts to add new vaccines.

The setting of priorities for introducing a dengue vaccine will vary from country to country, and respond to the various epidemiological patterns seen within them. But it was emphasized that no standard priority setting method exists. In the absence of a standard method, different analysts come to different conclusions. This leads to several uncertainties. Whose priority is it? Which priorities should donors, countries, manufacturers, and other partners respond to?

The discipline of public health recognizes that priority setting is a complex process not reducible to a single number. Public health asks four questions: Is the disease a public health problem - is the problem real? What is the disease burden? Can something be done about it? And what are the costs of doing something about it?
RISK FACTORS

The risk factors for infection with dengue virus seem likely only to continue or expand in the near future; poverty, population growth, uncontrolled urbanization and environmental mismanagement (for instance, open-air storage of tires and poor disposal of waste and plastics) will remain leading determinants. Migration, tourism and climate change will also impact the spread of the disease. An integrated approach to prevention and control is needed and a successful vaccine will be only a part of a comprehensive solution, complementing good vector control. Moreover, the prevention and control of dengue extends beyond the health sector, and successful responses must be global rather than sectoral.

IMMUNOLOGY AND MODELING

Dengue cannot be compared with other infectious diseases for which treatments and vaccines are being developed. Unlike these other diseases, infection with a dengue virus leads not to full immunity but, in fact, potentially increases susceptibility to severe disease if a person is infected with a second serotype of the dengue virus. This makes modeling the impact of introducing a dengue vaccine more complicated than for other vaccines. Nevertheless, given substantial computing power and good models, great advances are being made, allowing various scenarios to be formulated, tested and revised.

SUPPLY AND DEMAND

The price of the vaccine will be a determining issue in country decisions to introduce and will depend substantially on the demand, the size of the market and the immunization strategy that is selected. Strategic demand forecasting is a powerful tool for assessing the likely market size and has been applied to Brazil and Colombia for 2015-2019. Although there is much enthusiasm surrounding the potential vaccines, care will be needed not to raise expectations too high; for example, vaccine supplies will need to be ensured in advance so as to meet expected demand.

~ Cuauhtemoc Ruiz Matus, PAHO
As noted earlier, politics and economics are key aspects of dengue control. Unlike the situation in most of Asia, the intervals between epidemics in countries in Latin and Central America have been long, and populations are becoming more susceptible to severe dengue. Both the epidemiological patterns and the clinical expression of the disease across the Americas differ from those in Asia, with higher mortality rates in some countries in the Americas, and illness occurring more in older age groups.

Dengue, and efforts to control the disease, has a long history in the Americas. The first resolution adopted by the Pan American Health Organization’s (PAHO) Directing Council, in 1947, endorsed a hemisphere-wide program to eradicate *Aedes aegypti*, the vector of both yellow fever and dengue. The mosquito’s eradication from 10 countries was certified in 1958. From the 1950s to the 1970s, the Americas were virtually a dengue-free zone. As a result, interest in vector control waned. Environmental concerns led to the interruption of vector control in the 1970s. That, combined with the acceleration of uncontrolled urbanization in many Latin American countries, and its associated waste management problems, resulted in the re-introduction of the mosquito, massive re-infestation, and outbreaks of dengue. In several countries the disease reappeared for the first time after many decades, and all four serotypes are now spreading throughout the Americas. In 1993 both Costa Rica and Panama recorded outbreaks for the first time in forty and fifty years, respectively, and in 1998 dengue reappeared in Argentina after a seventy year absence.

In 1979 PAHO established the Revolving Fund for vaccine procurement, a unique procurement and financing mechanism to buy vaccine syringes and cold-chain equipment. Through concentrated efforts, and with help from the Fund, poliomyelitis and measles have been eliminated.

### Dengue Incidence in the Americas, 1980–2010

**Incidence Rate x 100,000**

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980-1989</td>
<td></td>
</tr>
<tr>
<td>1990-1999</td>
<td></td>
</tr>
<tr>
<td>2000-2009</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td></td>
</tr>
</tbody>
</table>

Source: Countries report PAHO/WHO
from the region. High vaccine coverage rates for these and other diseases have been reached and maintained. In 2006 PAHO passed resolution CD47.R10, urging Member States to use the Fund to buy new and under-used vaccines. In 2010 the Revolving Fund was utilized to purchase US $504 million worth of vaccines (covering 28 antigens) for 40 countries and territories.

PAHO is currently working to implement the Regional Immunization Vision and Strategy, drawing on the experience of its ProVac Initiative to improve capacity for evidence-based decision-making, including cost-effectiveness studies. Rotavirus and pneumococcal vaccines have been successfully introduced, with more than 80% of the target populations vaccinated in 16 countries in 2010. WHO and PAHO have issued global measurement standards and practical guides for the introduction of new vaccines, sentinel surveillance, case definitions, evaluation and other aspects. PAHO has been instrumental in organizing studies and publishing evidence on the successful introduction of vaccines, recognizing that no magic formula exists but that the solution lies in a strategic vision.

There exists a good tradition of networking and collaboration, as exemplified by the network of PAHO/WHO collaborating centers and national reference laboratories for dengue in the Americas. The ProVac Initiative, which covers the period 2008-2013 and would accommodate the prospective dengue vaccine, has led to the establishment and networking of both regional centers of excellence and national teams. Extensive technical cooperation, collaboration and capacity building are ongoing, bringing together United Nations bodies, national and international development agencies, the US Centers for Disease Control and Prevention (CDC), and several donors and foundations, including the Bill & Melinda Gates Foundation.

The diversity of the Americas makes the region a good role model, and some countries will be more prepared than others for the introduction of a vaccine. In general, countries in the region enjoy high socioeconomic and educational levels. Governments generally run well-developed health programs; a regional characteristic is that immunization programs are almost all funded nationally (99% of the total expenditure of US $1,680 million in Latin America in 2007-2008). Some countries qualify for support for immunization from the GAVI Alliance. Another particularity of many countries in the region is the special role in public health played by municipalities.

These characteristics may make the region a role model for the world in introducing a dengue vaccine, with Brazil fostering and creating an agenda for the region. Brazil, facing a heavy burden of disease, is reviewing its national dengue control program, with recommendations that include reorganization of the health system to reduce transmission of dengue and revision of legal instruments and legislation. Also, Brazil seems likely to be one of the first countries to introduce a dengue vaccine.

---


Over the past few decades dengue has spread rapidly and is endemic in more than 100 countries. This spread will continue for the foreseeable future unless a vaccine becomes available. While outbreaks have been seen in countries as diverse as Cape Verde, Nepal and Bolivia, the epidemiological situation may be even more extensive. Dengue’s status in Africa, China and India is not known because of a range of factors, including poor data and some cases of dengue being counted as other febrile illnesses. WHO estimates that between 2.5 and 3.6 billion people are at risk of dengue virus infection, estimating between 50-100 million infections of dengue fever in 2010, and an additional 0.5-2.1 million cases of severe dengue. Case studies have shown major under-reporting of cases; in Cambodia and Thailand the estimated under-reporting of inpatient cases was about two-fold for children under 15 years of age, and approximately nine-fold for all cases. More than 70% of all cases are outpatient. It is likely that cases are also under-reported in Latin and Central America, with recent estimates for Colombia putting the figures at 2.3-fold for severe dengue and 9-fold for dengue fever.\(^3\)

All tropical areas of Central and South America, as well as most of the Caribbean, have been significantly affected by dengue in the past two decades. Epidemics are now being seen even in countries with no history of dengue. The massive extension of both the vector and the virus has caused serious and disruptive outbreaks, with sharp increases in the incidence of both dengue fever and severe dengue. It seems that each epidemic cycle of dengue increases in magnitude and severity of cases. Because dengue is likely under-reported to a considerable extent, the true burden of disease is not fully known.

Data for Brazil for the period of 2000-2010 show more than 4.5 million probable cases, with more than half a million admissions to hospitals in the public health system; over that period, some 54,000 cases of dengue with complications and 18,000 cases of severe dengue were recorded, along with nearly 2,200 deaths.

In 2010, the largest number of cases and deaths ever was recorded, 1.7 million cases of dengue (and 50,000 cases of severe disease) reported for Latin America, and Brazil accounting for nearly 60% of these. Many countries experienced their largest recorded epidemics last year, with reported incidence rates of more than 200/100,000 inhabitants. Outbreaks continued in 2011 in Bolivia, Brazil, Ecuador, Paraguay and Peru. New outbreaks have been reported in the Bahamas, Panama and Saint Lucia.

---

Dengue affects all age groups, and its impact varies from country to country. In some parts of the Americas the highest incidence rates are being reported in adolescents and young adults, while in others considerable mortality is seen in the over-60 year age group. In still others dengue remains a pediatric disease. This impact is influenced by the number of dengue serotypes in circulation and the intervals between outbreaks; the severity of a secondary dengue infection appears to intensify with longer intervals between infections. Moreover, coinfections with influenza and other diseases have also been observed.

All four serotypes of dengue virus are circulating within the Americas, and the dominant serotype shifts over time. The virus can spread and evolve quickly, and serotype is an important factor in severity of disease; infection with a second serotype can increase the likelihood of severe dengue, as can the order of serotype infections (e.g. infection with serotype 1 and then serotype 3, compared with infection with serotype 2 and then serotype 3).

The rapid spread and high evolution rate of the different dengue virus genotypes could be due to high transmission rates, especially in hyperendemic areas, and could be slowed by the introduction of a vaccine.

For example, dengue virus serotype 1 was introduced in Cuba in 1977 and, although serological surveys indicated that 44% of the population was infected, only mild disease was reported. Four years later, however, the first severe dengue outbreak to occur in the Americas swept Cuba, with hundreds of thousands of cases of dengue fever reported. This epidemic involved serotype 2. Nearly ten years later, a variant of serotype 2 was introduced, and is believed to have displaced the serotype responsible for the 1981 outbreak. This time, severe dengue was seen only in adults who had been infected with the serotype 1 introduced in 1977; those infected by the early version of serotype 2 appeared to be less affected. This illustrates the important interactions between type of serotype, order of infection, and timing of infections.
The variability of the disease is a challenge, as exemplified by recent epidemics in Brazil. In the three epidemics between 2002 and 2011, cases were concentrated in different states. The outbreak due to dengue virus serotype 3 in 2002 saw an increase in severe cases; that in 2008 (due to serotype 2) showed a shift of severe disease to children; and in the 2010 epidemic (due to serotype 1) more deaths occurred in elderly people with co-morbidities. Although the overall regional case fatality rate was 2.6% for the period 2000-2009, in a few countries or territories (Dominican Republic, Guatemala, and Puerto Rico) it was in the range of 12-14%. In some instances health-care workers’ lack of experience managing dengue as well as the disease’s changing clinical expression, have led to the higher case-fatality rates observed. Deaths due to dengue are often highlighted by the media.

**GENERATING DATA**

PAHO’s ProVac Initiative is supporting the formation of multidisciplinary country teams for data collection and cost-effectiveness analysis, and establishing a regional network of key centers of excellence specializing in health costing and evidence-based decision-making at national and sub-regional levels. The Initiative supports the establishment of sub-regional strategies to improve the effectiveness of research and the production of comprehensive data. Countries may select national or sub-regional data in order to estimate disease burden, program costs and cost-effectiveness by standardized methods. Thus, they may make their own decisions through careful consideration of technical, programmatic, operational and societal criteria.

In addition to its core partners, DVI works with PAHO and nongovernmental organizations such as the Carlos Slim Health Institute on these studies.

The idea of dengue investment cases is to examine the feasibility and desirability of introducing dengue vaccines in specific countries, to identify efficient and affordable vaccination strategies, to identify country-specific barriers as well as enabling factors for new vaccine introduction, and to map a path forward to vaccine introduction, if warranted by the evidence. Regional costs of dengue illness have recently been estimated: the quoted aggregated annual cost per case for the Americas as a whole was US$571 but the figure ranged from US$358 in the Southern Cone to US$627 in Brazil and US$3154 in North America. The cost per capita, including treatment, non-medical direct costs and productivity losses, was estimated to be in the range US$4.82–8.66 in tropical areas — a substantial burden, which would be even greater in high-risk groups.

---

THE VACCINES

Six vaccine candidates have been developed so far and put into clinical trials. The meeting was told that the development of one, based on a live attenuated virus, has been suspended after Phase II trials, with the development team (GlaxoSmithKline, Fiocruz and the US Army) focusing attention instead on a tetravalent inactivated virus, with clinical development due to start in 2012.

Four other vaccines are in preclinical development or Phase I trials. These include formulations that combine defined genetic mutations or deletions and chimeras, chimeric viruses based on passaged serotype 2 virus, recombinant subunit envelope proteins expressed in insect cells, and a DNA vaccine comprised of dengue envelope protein genes. The final candidate, sanofi pasteur’s tetravalent chimeric yellow fever/dengue vaccine, is showing great promise and is in Phase III trials, to assess safety and immunogenicity. Licensure is expected in 2015. Its dosage schedule comprises three injections, administered at six month intervals. Its impact and effects will need long-term monitoring and post-marketing studies. Clinical trials of the vaccine in children are being conducted in several countries in Latin America.

MODELING AND STRATEGIC DEMAND FORECASTING

Mathematical models are powerful tools for assessing the effectiveness of various vaccine-introduction strategies by exploring the interplay of key determinants of transmission. They offer a means of forecasting the impact of vaccination as well as enabling the estimation of, for instance, the proportions of populations that need to be vaccinated to ensure protection and the optimal proportions to minimize adverse effects. For example, one model shows that a vaccine will block the development of epidemics when coverage reaches 70% of the population. Challenges in modeling include the complex immunology of dengue virus infection, seasonality, and human vital dynamics.

Strategic demand forecasting helps to project future demand of a vaccine based on available information and can be used to build evidence-based decisions at all levels. Information generated from demand forecasting models enable the pharmaceutical industry to better judge manufacturing capacity. A model has been applied to the introduction of a vaccine in Brazil and Colombia using the assumptions that it would take two years to reach maximum routine coverage, there would be two-year catch-up campaigns and a price of about US$15 ($10-20) in the public sector (88% of the market in Brazil and 80% in Colombia) and US$100 ($80-120) in the private sector. The resulting forecast estimates some 250 million doses for the two countries together for the period 2015-2019: 38 million for routine doses, 148 million for catch-up vaccination of under 15 year olds, and 62 million doses for vaccination of adults. The public sector cost would be US $2,400 million over five years. It was recognized that there would be wide variance in demand estimates depending on the assumptions of variables such as coverage rate in catch-up campaigns, delays in introduction, and wastage.

Cost is likely the most important barrier to vaccine introduction, and (governments) may wait for the price to decline before introducing it.

~ Brian Maskery, IVI
and the Asia-Pacific region, and the results of the first efficacy trial are expected in 2012. The Instituto Butantan in Brazil expects its candidate vaccine, based on a virus containing gene deletions, to enter Phase II trials in late 2012 with licensure possibly in 2015.

The vaccine developers or commercial partners range from government institutions (e.g. the US National Institute of Allergy and Infectious Diseases and the Naval Medical Research Center) to a vaccine developer (Inviragen) and vaccine developers with manufacturing capacity (Instituto Butantan, Biological E, Panacea, Vabiotech and Merck). It is expected that sanofi pasteur, GlaxoSmithKline and Merck will seek regulatory approval in the countries in which their candidate vaccines are tested; others are likely to seek approval in their host countries (Instituto Butantan in Brazil, Panacea and Biological E in India, and Vabiotech in Viet Nam).

Dengue vaccines will most likely be introduced in the countries in which clinical trials have been conducted (the so-called early adopters), in particular middle-income countries with a large middle class. The need for a road map for the introduction of the vaccine was also underlined. Several countries, such as Brazil, are already working on strategic plans for vaccine introduction.

Dengue vaccines will be predominantly a public sector product, although private sector demand in middle-income countries will be the driver and entry point for vaccination programs.

Evidence continues to accumulate that markets exist (including travelers and the military) and that people are willing to pay to protect themselves and their families. Demand will rely heavily on what age cohorts are vaccinated. The role of the pharmaceutical industry in spearheading introduction of a vaccine in the private sector was highlighted, it being noted from strategic demand forecast models that in Brazil and Colombia 80 million doses would be needed for the private sector alone for the five-year period studied. Sanofi pasteur stated that its production capacity could be geared up to 100 million doses for 2015, with possible margins for increasing that capacity depending on forecast and actual demand.

In the context of vaccine regulation, WHO’s prequalification procedures remain crucial. Through its Strategic Advisory Group of Experts (SAGE) on Immunization, WHO provides recommendations and position papers for countries to use in their decision-making processes. WHO provides normative and technical support to countries in the areas of disease monitoring, outbreak control, vector control, clinical case management and vaccine development. It has recently issued a new guide on the process leading to recommendations by SAGE on immunization and the development of WHO vaccine position papers,7 and in 2009 updated its guidance on the principles and use of rapid tests for dengue.8

8 WHO Western Pacific Regional Office. Update on the principles and use of rapid tests in dengue. Manila, WHO Western Pacific Regional Office, April 2009.
In Asia, DVI has convened meetings with regulatory authorities in order to try to accelerate the process of licensing a candidate vaccine. The situation regarding regulatory review in Central and Latin American countries needs further examination, and a meeting on the topic was held in Brazil a few weeks before the Americas Prevention Board meeting. More discussions are needed to harmonize the requirements of regulatory authorities in advance of and in readiness for rapid vaccine licensure.

Individuals will benefit from vaccination but it will not be easy to demonstrate the indirect public health benefit in the short term. Second-generation vaccines may need more complex clinical trials (as there can be no placebo arm), and plans need to be drawn up.

**NATIONAL POLICY CONSIDERATIONS**

DVI is working closely with its partners, health ministries and key stakeholders in its four focal countries, Brazil, Colombia, Thailand and Viet Nam.

In Brazil DVI’s cooperation with the Ministry of Health concentrates on the strategy for prevention and control of dengue, and on health economic studies. Four vaccine candidates are being developed or tested in the country, with Phase III trials of the sanofi pasteur vaccine in several sites. With DVI’s input, the Ministry is elaborating a strategic plan for introduction of the vaccine. An advisory group, which held its first meeting in June 2011, is looking at pre-licensing and post-licensing needs from the ministry’s perspective and the plan is scheduled to be ready by July 2012. Work includes establishing effective communication channels with private and public vaccine developers, cost-effectiveness studies, identification of groups to be targeted, dosage and administration issues, monitoring of adverse events, assistance for public laboratories, and financing.

In Colombia, the highest incidence rates are seen in children less than 15 years of age. Two pharmaceutical companies (sanofi pasteur and Inviragen) are conducting vaccine trials in the country. DVI works with the Ministry of Social Protection and the Antioquia University as core partners in studies (starting in October 2011) on disease burden, seroprevalence, cost of illness, willingness to pay and healthcare utilization in order to prepare a national dengue investment case. DVI’s work on the dengue investment case in Colombia aims to provide evidence-based analyses to the National Immunization Advisory Committee, using inputs from its partners to iterate strategies based on modeled vaccine impact and cost effectiveness, financing requirements, and supply constraints. The team seeks input not just from the health sector (including pediatricians, other health professionals and prospective vaccine recipients) but also from the finance ministry, development partners and other sectors affected, such as tourism.

Dengue has caused more resignations of health ministers than opposition parties have.

~ Several speakers
Detailed presentations were given by 10 countries on their planning towards introduction of a dengue vaccine: Argentina, Brazil, Colombia, Cuba, Ecuador, Honduras, Nicaragua, Paraguay, Venezuela and the USA (including the experience of Puerto Rico and more generally the decision pathways to vaccine introduction). Issues that emerged included: the existence of specific national policies, goals and legislation, all of which entailed related resources; the need for coordination at national level and definition of responsibilities (with examples of interministerial cooperation); and the perennial problem of costs and financing. Speakers underlined the role that primary health care could play in prevention and control, the changing epidemiology and the increased risks through travel and the movement of people. With regard to the vaccine, several speakers emphasized their country’s recent experiences in successfully introducing new vaccines, but raised matters that will need consideration. Those include vaccine safety, the identification of target populations, factors affecting dynamics of vaccine uptake (from both company and state perspectives), delivery and storage systems (including strengthening the cold chain), immunization schedules, and, when the vaccine is introduced, the need to protect other immunization programs and maintain achievements made so far. Vaccination strategies would have to be sustainable, and questions such as whether vaccination should be voluntary or compulsory, and what role the vaccine would play in containing outbreaks would have to be resolved. A review of the decision-making process for vaccines in the USA concluded by emphasizing that recommendations for dengue vaccine will change over time, as exemplified by the introduction of hepatitis A vaccine. Other subjects mentioned included health records, monitoring and evaluation, logistics, the training of health-care staff, the value of political commitment at high level, advocacy, and awareness raising, and the need to ensure the dissemination of clear messages.

Vaccination must be considered as part of integrated programs, including environmental management. Surveillance systems that integrated epidemiological, entomological, environmental, clinical and laboratory data, as
Vaccination must be considered as part of integrated programs, including environmental management.

in Cuba, were vital. Improved vector control is needed, with better tools and stronger systemic management, and would benefit prevention of more diseases than just dengue (e.g. Chikungunya). Technology does offer solutions, not just in the form of one or more vaccines but through improved vector control. By itself, however, vector control has its limitations; as was emphasized several times, it is vital to integrate vector control and vaccination in an overall strategy. In 2007, the Pan American Sanitary Conference urged Member States in the region to work to address the weaknesses and threats identified by each country in the preparation of such integrated vector management strategies. Some 21 countries and four sub-regions, ranging from the Caribbean to the Andes, have integrated management strategies for prevention and control that feature vector control, environmental management, social mobilization, and epidemiological and entomological surveillance as part of the strategies.

Finally comes the perennial issue of sustainable financing. New sources of funding need to be found and innovative funding mechanisms devised. The studies under way in Colombia will provide data and evidence that will be used to prepare convincing arguments for persuading finance ministries through dengue investment cases.

**ADVOCACY**

The dramatic progress in recent years in introducing new and under-used vaccines - rotavirus, acellular pertussis, human papillomavirus, meningococcal, pneumococcal and typhoid vaccines - has been made thanks in large part to advocacy in raising awareness, mobilizing leaders, maintaining public confidence and professional knowledge, and increasing the financial sustainability of immunization programs. Actions taken include providing health-care managers at all levels with information, issuing guidelines and ensuring support for implementing immunization programs, responding rapidly and appropriately to challenges to immunization, and fostering collaboration between policymakers, researchers, industry representatives, public health officials, health-care professionals and others. It will be important to adopt a systematic approach to raising the profile and understanding of dengue by public health professionals, donors and the general public; examples cited included the running of a two-day workshop on immunization for journalists and the use of social media.

Another key to success is the identification of allies in all sectors – for example, in the media, ministries (not just health), and civil society – who will champion the prevention and control of dengue. The successful campaigns against other neglected diseases, such as filariasis, schistosomiasis and onchocerciasis, offer platforms to build on, and lessons can be learnt from countries that already accord a high profile to dengue. An area ripe for greater advocacy efforts is the reinforcement and reinvigoration of vector control and persuading decision-makers that vaccination is not the only solution.


10 Resolution CSP27.R15 on dengue prevention and control in the Americas.
Members of the Dengue Prevention Boards could assume an expanded activist role, through, for instance, preparation of reviews (access and social equity were two topics that were suggested) and networking. All participants should be able to capitalize on the sense of urgency and opportunity that pervaded the meeting. With regard to the biggest challenges of vaccine supply and price, countries in the region could and should argue more powerfully with a collective voice. It was also noted that, as governments have a limited life span, now was the time to work with both the parties in power and those in opposition in order to generate sufficient knowledge for sound policies to be developed.

**FURTHER ISSUES AND CHALLENGES**

Throughout the meeting, a common theme was that initial steps have been taken but much remains to be done in many areas: data generation (especially burden of disease), modeling, cost-effectiveness analyses, forecasting demand (and the need to come up with an agreed set of base case assumptions for models), design of vaccination strategies, examining manufacturing and supply issues, estimating costs, preparing investment cases, harmonizing regulatory processes in the region, and raising general awareness.

Many questions still need answers, and more information about the progress of clinical trials of candidate vaccines and the capacities of manufacturers is essential. Vaccination strategies will need to be examined carefully, as planning decisions will have a major impact on local manufacturers’ decisions about production capacity and potential export as well as on national policies. Renewed and alternative sources of funding are badly needed now, in the years up to the introduction of vaccine and thereafter.

At the regional level, countries can contribute towards the work of WHO’s Strategic Advisory Group of Experts on Immunization in order to ensure strong recommendations. A common regional forum or workshop on harmonizing regulatory processes would be useful, and more general information about approaches to vaccine introduction needs to be shared regionally. WHO prequalification would accelerate vaccine introduction.

Dengue vaccines are likely to be introduced slowly, country by country, initially in countries where clinical trials were conducted and in middle-income countries with a likely strong private-sector demand. The need for open and effective communication between WHO, PAHO and other regional stakeholders will increase as progress is made towards vaccine introduction.

Given the political sensitivity of dengue, health ministers will likely be the decision makers and it was observed that they will need solid data for those decisions - “in order to immunize themselves against losing their jobs”, as one participant put it.

Much progress has already been made, but there is still much work to do ... and time is short.
CHALLENGES
Numerous challenges remain. These include:

• the need to define target populations
• determining optimal dose schedules
• finding ways of introducing the vaccine into existing vaccination programs.

PRIORITY SETTING
Priority setting will vary with each country and its epidemiological and socioeconomic particularities.

• Vaccination strategies need to consider and accommodate catch-up campaigns and resolve the problems of reaching and vaccinating an adult population.
• The costs of immunization programs need to be estimated and sources of financing identified.
• Ways have to be found to cope with the likely initial domination of the market by a single manufacturer and developing countries’ lack of experience in bringing vaccines to market.
• Once the vaccine is licensed, adequate supplies of vaccine need to be assured.
PARTICIPANTS

BOARD MEMBERS

Dr. Aracely Alava Alprecht
Coordinator, Investigation and Microbiological Diagnosis
Leopoldo Izquierda Perez National Institute of Hygiene and Tropical Medicine
Chair, Virology, Guayaquil University
Ecuador

Dr. Juan Jose Amador
PATH
Nicaragua

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

Dr. Jorge Bashell
Director Biosafety Committee
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. José F. Cordero
Dean, Graduate School of Public Health
Medical Sciences Campus
University of Puerto Rico
Puerto Rico

Dr. Delia A. Emria
Director, INEVH (Instituto Nacional de Enfermedades Virales Humanas)
Argentina

Dr. Eduardo Fernandez
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
Cuba

Dr. Harold Margolis
Branch Chief, CDC (Centers for Disease Control and Prevention) Dengue Branch
Puerto Rico

Dr. Jose Luis San Martin
Dengue Regional Consultant
PAHO/WHO
Costa Rica

Dr. Jorge F. Mendez-Galvan
Investigador National
Hospital Infantil de México “Federico Gómez”
Mexico

MINISTRIES OF HEALTH GUESTS

Dr. Maria Luisa Avila Aguer
Minister of Ministry of Health of Costa Rica
Costa Rica

Dr. Jarbas Barbosa
Secretary of Health Surveillance
Ministry of Health
Brazil

Dr. Haroldo Bezerra
PAHO Consultant
Dengue Unit Technical and Non-Communicable Diseases
Brazil

Dr. Giovannini Evelim Coelho
General Coordinator
Dengue Control National Program
Ministry of Health
Brazil

Dr. Jehony Joe Real Cotto
Coordinator of Demand and Supply Process
Undersecretary of Regional Health and Island Coast
Ecuador

Dr. Jaime Lazovsky
General Director
Ministry of Health, Editorial Committee
Argentina

Dr. Miriam Morales
Vice-Minister, Ministry of Health of Venezuela
Venezuela

Dr. Maria Aparicia Palma
Sub Chief of the Honduras EPI
Honduras

Dr. Mariana Pihuave
Undersecretary of Tropical Health
Ministry of Public Health of Ecuador
Ecuador

Dr. Hugo Lopez-Gatell Ramirez
General Director
National Centre for the Epidemiological Surveillance and Disease Control
Mexico

Dr. Jairo A Mendez Rico
Head of Virus Laboratory
Instituto Nacional de Salud, Colombia
Colombia

Dr. Carlos Saenz
Director of Epidemiology and in charge of Dengue and the National Immunization Program
Nicaragua

Dr. Carlos Daniel Torres
Director of the Immunization Program of Health
Ministry of Paraguay
Paraguay

Dr. Andrea Vicari
Advisor, Immunization
Comprehensive Family Immunization Project
Pan American Health Organization/World Health Organization
Costa Rica
DVI STAFF AND ADVISORS

Dr. Mabel Carabali
Consultant Epidemiologist
International Vaccine Institute

Ms. Ana Carvalho
Associate Director
Sabin Vaccine Institute

Dr. Dagna Constenla
Associate Scientist
International Vaccine Access Center
John S. Hopkins Bloomberg School of Public Health

Dr. Scott Halstead
Senior Scientific Advisor
International Vaccine Institute

Dr. Joachim Hombach
Acting Head
Initiative for Vaccine Research
World Health Organization

Dr. Orin Levine
Professor
Johns S. Hopkins Bloomberg School of Public Health

Ms. Jacqueline Lim
Epidemiologist
International Vaccine Institute

Dr. Ira M Longini
Professor
College of Public Health and College of Medicine
University of Florida

Dr. Richard Mahoney
Coordinator
Policy & Access Unit
International Vaccine Institute

Dr. Brian Maskery
Associate Research Scientist
International Vaccine Institute

Prof. Eduardo Massad
USP, Faculdade de Medicina (Brazil)

Dr. Vittal Mogasale
Associate Research Scientist
Policy and Economic Research Unit
International Vaccine Institute

Dr. Ciro de Quadros
Executive Vice President
Sabin Vaccine Institute

Dr. João Bosco Sigueira
Federal University of Goias (UFG)
Institute of Tropical Pathology & Public Health

Dr. Luiz Jacinto da Silva
Director
Dengue Vaccine Initiative
International Vaccine Institute

INVITED GUESTS

Dr. Miguel Betancourt
Director for Global Solutions
Carlos Slim Health Institute (Instituto Carlos Slim de la Salud)

Dr. Lucia Bricks
Public Health Director
The vaccines division of sanofi aventis, Brazil
sanofi pasteur

Dr. Emmanuel Burckel
Dengue Project Leader, Latin America
sanofi pasteur

Dr. Luiz Camacho
Epidemiologist
Bio-Manguinhos / Oswaldo Cruz Foundation

Dr. Elena Caride
Viral Vaccines Program Manager
Bio-Manguinhos / Oswaldo Cruz Foundation

Dr. Roberto Tapia Conyer
Director General
Instituto Carlos Slim de la Salud

Dr. Artur Roberto Couto
Director
Bio-Manguinhos / Fiocruz

Dr. Carlos Espinal
Public Health Director, Latin America
sanofi pasteur

Dr. Germano Ferreira
Epidemiology, Global
sanofi pasteur

Dr. David FitzSimons
Editor/Writer

Dr. Laila El-Asmar
Sr. Manager, Disease Mapping and Target Product Profile (DMTPP), Belgium
GlaxoSmithKline Biologicals

Dr. Ricardo Galler
Principal Investigator on Dengue Vaccine
Bio-Manguinhos / Oswaldo Cruz Foundation

Dr. Pedro Garbes
Regional Clinical Development Director, Brazil
sanofi pasteur

Dr. Enrique Gil
Coordinator for Disease Control and Prevention and Sustainable Development, PAHO/WHO

Dr. Julie Jacobson
Senior Program Officer
The Bill and Melinda Gates Foundation

Dr. Los Lockledge
Merck and Company

Dr. Cuauhtemoc Ruiz Matus
Senior Advisor on Immigration
Pan American Health Organization (PAHO)

Dr. Tatiana Noronha
Epidemiologist
Bio-Manguinhos / Oswaldo Cruz Foundation

Dr. Eduardo Ortega-Barria
Vice President & Head
Clinical R&D and Medical Affairs
Latin America & the Caribbean
GlaxoSmithKline Biologicals

Dr. Jorge Osorio
CSO
Inviragen, Inc.

Dr. Alexander R. Precioso
Diretor Médico de Ensaios Clínicos
Medical Director of Clinical Trials
Instituto Butantan - Fundação Butantan, Brazil

Dr. Nervo Sanchez
Medical Director
Clinical R&D and Medical Affairs Brazil
GlaxoSmithKline Biologicals

Dr. Diego Victoria
PAHO WHO Representative of Brazil
# AGENDA

## DAY 1: August 22, 2011

<table>
<thead>
<tr>
<th>TIME</th>
<th>AGENDA ITEM</th>
<th>PRESENTERS</th>
</tr>
</thead>
<tbody>
<tr>
<td>8:30 – 9:00</td>
<td><strong>Session I: Opening Session</strong></td>
<td><strong>Officials of Brazil Ministry of Health, WHO, PAHO and DVI</strong>&lt;br&gt;Jarbas Barbosa</td>
</tr>
<tr>
<td>9:00 – 9:30</td>
<td><strong>Session II: Generating Increased Support for Introduction to Dengue Vaccines</strong>&lt;br&gt;Update on DVI Overview for the meeting: The importance of having a clear and accurate understanding of the complexity of dengue vaccine introduction</td>
<td>Luiz da Silva</td>
</tr>
<tr>
<td>9:45 – 10:30</td>
<td>Comparitive historical analysis of vaccine priority setting</td>
<td>Richard Mahoney</td>
</tr>
<tr>
<td>10:30 – 11:00</td>
<td><strong>Coffee Break</strong></td>
<td></td>
</tr>
<tr>
<td>11:00 – 11:30</td>
<td>The Experience of PAHO in the introduction of new vaccines</td>
<td>Cuauhtemoc Ruiz Matus</td>
</tr>
<tr>
<td>11:30 – 12:00</td>
<td>Generating support for dengue vaccines: reflections on the experience in Brazil</td>
<td>Jarbas Barbosa</td>
</tr>
<tr>
<td>12:00 – 12:30</td>
<td>The importance of constructing and implementing a Road Map for dengue vaccines</td>
<td>Roberto Tapia</td>
</tr>
<tr>
<td>12:30 – 1:30</td>
<td><strong>Lunch</strong></td>
<td></td>
</tr>
<tr>
<td>1:30 – 1:50</td>
<td>Overview of the global burden of disease of dengue: DALYS, dollars, poverty, and families</td>
<td>Luiz da Silva</td>
</tr>
<tr>
<td>1:50 – 2:10</td>
<td>The changing view of the priority of dengue disease as seen by WHO and its regional offices</td>
<td>Joachim Homback&lt;br&gt;Jose Luis San Martin</td>
</tr>
<tr>
<td>2:10 – 2:30</td>
<td>The Role of Advocacy for Immunization</td>
<td>Ciro de Quadros</td>
</tr>
<tr>
<td><strong>Session III: Data and their use</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2:30 – 3:00</td>
<td>DVI studies to generate Data for Decision Making</td>
<td>Jacqueline Lim&lt;br&gt;Mabel Carabali&lt;br&gt;Joao Basco Siquera</td>
</tr>
<tr>
<td>3:00 – 3:30</td>
<td>Vaccine Investment Case: Case Study</td>
<td>Brian Maskery</td>
</tr>
<tr>
<td>3:30 – 4:00</td>
<td><strong>Coffee Break</strong></td>
<td></td>
</tr>
<tr>
<td>4:00 – 4:30</td>
<td>Modeling the impact of dengue vaccines on burden of disease</td>
<td>Ira Longini</td>
</tr>
<tr>
<td>4:30 – 5:00</td>
<td>Approaches to modeling the impact of dengue vaccines in the Americas</td>
<td>Eduardo Massad</td>
</tr>
</tbody>
</table>
### DAY 2: August 23, 2011

<table>
<thead>
<tr>
<th>TIME</th>
<th>AGENDA ITEM</th>
<th>PRESENTERS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>Session IV: Prospects and Issues for Availability of Dengue Vaccines</strong></td>
<td></td>
</tr>
<tr>
<td>8:30 – 10:00</td>
<td>Short presentations (10 minutes each) followed by moderated discussion with developers of diagnostics and vaccines</td>
<td>Butantan, Fiocruz, GSK, Inviragen, Merck, sanofi pasteur, Alere</td>
</tr>
<tr>
<td>10:00 – 10:30</td>
<td>Factors affecting introduction and availability of dengue vaccines</td>
<td>Richard Mahoney</td>
</tr>
<tr>
<td>10:30 – 11:00</td>
<td>Strategic Demand Forecasting and Financing of dengue vaccines</td>
<td>Orin Levine</td>
</tr>
<tr>
<td>11:00 – 11:30</td>
<td>Coffee Break</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Session V: Policy Considerations</strong></td>
<td></td>
</tr>
<tr>
<td>11:30 – 11:45</td>
<td>Policy Considerations for introduction of dengue vaccines: Argentina</td>
<td>Jaime Lazovski</td>
</tr>
<tr>
<td>11:45 – 12:00</td>
<td>Policy Considerations for introduction of dengue vaccines: Brazil</td>
<td>Giovanini Coehlo</td>
</tr>
<tr>
<td>12:00 – 12:15</td>
<td>Policy Considerations for introduction of dengue vaccines: Colombia</td>
<td>J Mendez Rico</td>
</tr>
<tr>
<td>12:15 – 12:30</td>
<td>Policy Considerations for introduction of dengue vaccines: Costa Rica</td>
<td>M.L. Avila Aguero</td>
</tr>
<tr>
<td>12:30 – 12:45</td>
<td>Policy Considerations for introduction of dengue vaccines: Cuba</td>
<td>Maria Guzman</td>
</tr>
<tr>
<td>12:45 – 1:00</td>
<td>Policy Considerations for introduction of dengue vaccines: Ecuador</td>
<td>Jhony Joe Real Cotto</td>
</tr>
<tr>
<td>1:00 – 2:00</td>
<td>Lunch</td>
<td>M. L. Avila Aguero</td>
</tr>
<tr>
<td>2:00 – 2:15</td>
<td>Policy Considerations for introduction of dengue vaccines: Honduras</td>
<td>M. Aparicia Palma</td>
</tr>
<tr>
<td>2:15 – 2:30</td>
<td>Policy Considerations for introduction of dengue vaccines: Mexico</td>
<td>H Lopez-Gatell Ramirez</td>
</tr>
<tr>
<td>2:30 – 2:45</td>
<td>Policy Considerations for introduction of dengue vaccines: Nicaragua</td>
<td>Carlos Saenz</td>
</tr>
<tr>
<td>2:45 – 3:00</td>
<td>Policy Considerations for introduction of dengue vaccines: Paraguay</td>
<td>Carlos Daniel Torres</td>
</tr>
<tr>
<td>3:00 – 3:15</td>
<td>Policy Considerations for introduction of dengue vaccines: Puerto Rico</td>
<td>Harold Margolis</td>
</tr>
<tr>
<td>3:15 – 3:30</td>
<td>Policy Considerations for introduction of dengue vaccines: Venezuela</td>
<td>Iris Villalobos de Chacon</td>
</tr>
<tr>
<td>3:30 – 4:00</td>
<td>Moderator discussion: Likely scenarios for introduction of dengue vaccines</td>
<td>Luiz da Silva, Moderator</td>
</tr>
<tr>
<td>4:00 – 4:30</td>
<td>Coffee Break</td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Session VI: Communications and Advocacy</strong></td>
<td></td>
</tr>
<tr>
<td>4:30 – 5:15</td>
<td>Developing a communications/advocacy work plan for the Prevention Board</td>
<td>Ana Carvalho</td>
</tr>
<tr>
<td>5:15 – 6:00</td>
<td><strong>Session VII: Summary and Conclusions</strong></td>
<td>David FitzSimons, Luiz da Silva, Cuauhtemoc Ruiz Matus, Jose Luis San Martin</td>
</tr>
</tbody>
</table>
The mission of the Dengue Vaccine Initiative (DVI) is to encourage the development and use of vaccines to prevent dengue. As a consortium of organizations committed to a world without dengue, DVI is working to lay the groundwork for dengue vaccine introduction in endemic areas so that, once licensed, vaccines to prevent dengue will be swiftly adopted.