PROCEEDINGS OF THE WORKSHOP ON
“DEVELOPING STRATEGIES FOR MEETING THE CHALLENGE
OF EQUITABLE VACCINE INTRODUCTION IN THE
AMERICAS: WITH A FOCUS ON DENGUE VACCINE
FINANCING”

22-23 JULY 2013,
PAHO, WASHINGTON D.C., U.S.A.
Table of Contents

List of Abbreviations and Acronyms ........................................................................................................5
Acknowledgements........................................................................................................................................6
Foreword..........................................................................................................................................................8
Executive Summary.........................................................................................................................................9
  Background ..................................................................................................................................................12
  Goals and objectives .................................................................................................................................12
  Pre-workshop activities .............................................................................................................................13
  Structure of the workshop .........................................................................................................................13
  Topics discussed during the workshop ....................................................................................................14
  Expected outcomes of the workshop .......................................................................................................14
Workshop - Day 1..........................................................................................................................................15
  Introductory remarks and overview ........................................................................................................15
  Lessons learned from previous vaccine introductions by PAHO ..........................................................15
Part I: Understanding the need for a dengue vaccine ..............................................................................18
  Epidemiology of dengue in the region .......................................................................................................18
  Economic burden of dengue in the Americas .........................................................................................20
  Question and answer (Q&A) session ........................................................................................................21
  Discussion of vector control strategies for dengue ..................................................................................22
    Discussion session on vector control strategies ..................................................................................22
    Q & A session ........................................................................................................................................24
  Country perspective on demand for a new vaccine ..............................................................................25
    Brazil .....................................................................................................................................................25
    Mexico ....................................................................................................................................................26
    Q & A session .......................................................................................................................................27
Dengue vaccines in the pipeline ..................................................................................................................28
  The development of DENVax ...................................................................................................................28
  Merck Dengue Vaccine Program .............................................................................................................28
  Sanofi Pasteur Dengue Vaccine Project: Phase II stage – Q2 2013 status .........................................29
  Clinical evaluation of the NIAID live attenuated dengue vaccine .......................................................29
  Instituto Butantan: Division of Clinical Trials and Pharmacovigilance .............................................30
  Tetravalent Dengue Purified Inactivated Vaccine (DPIV) .................................................................30
  Q & A session .........................................................................................................................................33
Part II: Important considerations for dengue vaccine introduction .........................................................34
  Hurdles for equitable and timely introduction of vaccines with focus on dengue .................................34
Potential economic impact of new vaccine introduction for dengue .................................................. 35
Q & A session ........................................................................................................................................... 37
Workshop - Day 2 ..................................................................................................................................... 39
Part III: What will it take to finance dengue vaccine in the Americas? .............................................. 39
Financing vaccines in Mexico ................................................................................................................ 39
Financing strategies used in the Americas for other vaccines .............................................................. 41
Strategy session I - Recommendations of financing options for dengue vaccine ............................... 43
  What are specific financing strategies that are suited to specific countries and the region? .......... 43
How can existing mechanisms be leveraged to ensure timely and equitable introduction of dengue
  vaccine in the region? .............................................................................................................................. 45
Are there other innovative financing strategies that can be applied in the context of dengue vaccines in
  countries of the region? ........................................................................................................................... 46
Strategy session II: Key actions that can advance recommendations .................................................. 51
  Specific areas that require government attention ................................................................................ 51
  Potential roles for international and regional organizations and players ........................................ 52
  Next steps to accomplish recommendations ...................................................................................... 52
Conclusions ............................................................................................................................................. 55
References .............................................................................................................................................. 59

ANNEX 1. Pre-workshop survey to experts .............................................................................................. 60
ANNEX 2. Post-workshop survey to Manufacturers ................................................................................ 67
ANNEX 3. Workshop Agenda .................................................................................................................. 68
ANNEX 4. Background document: Challenges of dengue prevention and control ............................. 72
ANNEX 5. Background document: Lessons learned from previous vaccines in the Americas .......... 77
ANNEX 6. Background document: Cost of Vaccine Introduction in the Americas ............................. 82
ANNEX 7. Background document: Financing uptake of new dengue vaccines ................................. 85
ANNEX 7.1 Pooled Procurement ........................................................................................................... 89
ANNEX 7.2 Background Papers for Policy Brief #4: Domestic Taxes ................................................ 91
ANNEX 7.3 Background Papers for Policy Brief # 4: Regional Taxes ................................................ 93
ANNEX 7.4 Background Papers for Policy Brief # 4: Multilateral Loans ............................................. 95
Tables and Figures

Tables

Table 1: Topics covered during the workshop.................................................................14
Table 2: The Revolving Fund – Key figures.................................................................16
Table 3: Strategic dengue vaccine introduction plan in Brazil......................................26
Table 4: Characteristics of vaccines in development......................................................31-32
Table 5: Advantages and disadvantages of domestic taxation......................................49

Figures

Figure 1: Changes in vaccine legislation and funding..................................................17
Figure 2: Distribution of dengue morbidity by country in the Americas.......................19
Figure 3: Factors affecting the economic burden of dengue in the Americas.............21
Figure 4: Tools used in comprehensive dengue..........................................................22
Figure 5: Dengue incidence in Singapore pre-/post-vector control............................23
Figure 6: Potential dengue vaccine introduction scenarios in Mexico.........................26
Figure 7: IVAC's Dengue vaccine integrated model.....................................................36
Figure 8: Vaccine introduction process in Mexico.......................................................40
Figure 9: Objectives and composition of the Revolving Fund....................................42
Figure 10: Performance based model for dengue vaccine introduction.......................47
List of Abbreviations and Acronyms

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>ANVISA</td>
<td>National Health Surveillance Agency</td>
</tr>
<tr>
<td>CeNSIA</td>
<td>National Center of Health for Children and Adolescents</td>
</tr>
<tr>
<td>DFATD</td>
<td>Department of Foreign Affairs, Trade and Development (formerly the Canadian International Development Agency or CIDA)</td>
</tr>
<tr>
<td>DHF</td>
<td>Dengue hemorrhagic fever</td>
</tr>
<tr>
<td>DPIV</td>
<td>Tetravalent Dengue Purified Inactivated Vaccine</td>
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<tr>
<td>DVI</td>
<td>Dengue Vaccine Initiative</td>
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<tr>
<td>EPI</td>
<td>Expanded Program on Immunization</td>
</tr>
<tr>
<td>GAVI</td>
<td>GAVI Alliance (formerly The Global Alliance for Vaccines and Immunisation)</td>
</tr>
<tr>
<td>GSK</td>
<td>GlaxoSmithKline</td>
</tr>
<tr>
<td>IDB</td>
<td>Inter-American Development Bank</td>
</tr>
<tr>
<td>IVAC</td>
<td>International Vaccine Access Center</td>
</tr>
<tr>
<td>IVI</td>
<td>International Vaccine Institute</td>
</tr>
<tr>
<td>JHU</td>
<td>Johns Hopkins University</td>
</tr>
<tr>
<td>LAC</td>
<td>Latin America and the Caribbean</td>
</tr>
<tr>
<td>MMR</td>
<td>Measles, mumps and rubella (vaccine)</td>
</tr>
<tr>
<td>NIAID</td>
<td>National Institute of Allergy and Infectious Diseases</td>
</tr>
<tr>
<td>NIH</td>
<td>National Institute of Health</td>
</tr>
<tr>
<td>NITAGs</td>
<td>National Immunization Technical advisory groups</td>
</tr>
<tr>
<td>MoF</td>
<td>Ministry of Finance</td>
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<tr>
<td>MoH</td>
<td>Ministry of Health</td>
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<tr>
<td>NGO</td>
<td>Non-governmental organization</td>
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<tr>
<td>PAHO</td>
<td>Pan-American Health Organization</td>
</tr>
<tr>
<td>PNI</td>
<td>Programa Nacional de Inmunización (In English, National Immunization Program)</td>
</tr>
<tr>
<td>SUS</td>
<td>Sistema Único de Saúde (in English, Integrated Health System)</td>
</tr>
<tr>
<td>USAID</td>
<td>United States Agency for International Development</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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</table>
## Acknowledgements

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Legal

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¶ Communications/administrative oversight
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Foreword

Dengue is a painful and sometimes fatal disease spread by the bite of a mosquito. Individuals who are infected with dengue often have painful headache, skin rash and debilitating muscle and joint pains. In especially severe cases, it can lead to circulatory failure, shock, coma and death. Though early and effective treatment can ease symptoms, there is no specific cure available for dengue. The mosquito’s diurnal feeding habits and ability to breed even in small bits of stagnant water have limited the effectiveness of control strategies, which are often expensive and provide limited relief.

The last decade has witnessed substantial progress in the clinical development of several dengue vaccine candidates. This development has advanced to the point where it is likely that there will be at least one vaccine available for use in dengue-endemic countries in the near future. The development of financing strategies to meet the challenge of equitable vaccine introduction in the Americas is therefore particularly timely.

To lay the groundwork for the introduction of a dengue vaccine, experts from various bilateral organizations, public health agencies, Ministers of Health, and program managers convened on July 22-23 2013 in Washington D.C. During this time strategies for meeting the challenge of vaccine financing in countries in Latin America and the Caribbean were reviewed, with dengue vaccines serving as the example. In the present document we provide a synopsis of the main discussion points during the two-day workshop, including the recommendations on financing options and an action plan to advance these options.

We hope this document will pave the way for continued and open discussions regarding vaccine financing and the rapid introduction of dengue vaccines in the region of the Americas, where dengue reaches epidemic proportions.

*JHU’s IVAC, IVI, Sabin & PAHO*
*August 26 2013*
*Washington D.C.*
Executive Summary

On July 22-23, the International Vaccine Access Center (IVAC) at Johns Hopkins University (JHU), in collaboration with the International Vaccine Institute (IVI), the Sabin Vaccine Institute and the Pan-American Health Organization (PAHO), convened a two-day workshop to solicit input from key stakeholders in the Latin American and Caribbean (LAC) region about how to efficiently and effectively finance the introduction of dengue vaccines in the region.

Given the fiscal reality facing many countries, especially regarding the ability to appropriate funding for new vaccine introduction, there is a need to explore financing options beyond diverting funds from existing government budgets. Discussions on the second day of the workshop focused on the most effective means of accomplishing this, with a specific focus on the introduction of a dengue vaccine in the Americas.

Experts made three preliminary recommendations:

- The creation of an integrated dengue management fund that would combine existing pooled procurement mechanisms (e.g. PAHO, UNICEF) with financing mechanisms (e.g. low interest multilateral loans of the World Bank, Inter-American Development Bank [IDB]) to ensure that dengue control and prevention strategies are properly financed. The proposed plan would leverage the procurement capability and experience of PAHO’s Revolving Fund with the financial capacity of multilateral organizations to make low rate loans, resulting in a combined procurement-financing mechanism. The plan comprises strengthening of the overall dengue control and prevention system that entails a robust dengue surveillance system, vector control system, disease management, immunization financing laws, infrastructure (e.g. cold chain), and regulatory capacity. Financing sources include but are not exclusive to national or sub-national governments, foundations and trusts. Key to strengthening the overall dengue management systems is making improvements to the dengue evidence base and establishing a common research agenda for dengue control and prevention. Health system strengthening is also key to improving dengue management. The fundamental role that communication and collaboration between countries, development partners and public health agencies will play in the development of such combined mechanism for region wide introduction is key. This mechanism will require coordination of existing public-private regional health partners and financing sources will include but are not exclusive to development partners.
The creation of a performance-based financing model for dengue vaccine introduction where resources and infrastructure funding are frontloaded to accelerate the introduction of new vaccines. The proposed plan has three primary aims: (i) to support the equitable introduction of efficacious vaccines; (ii) to strengthen vaccine infrastructure; and (iii) to develop the human resource capacity of countries to deliver vaccines. In this model resources are frontloaded to accelerate the introduction of new vaccines based on a shared referential vaccine schedule. Infrastructure funding is also frontloaded to improve cold chain capabilities (maintenance, distribution, management, and logistics) and develop human resource capacity in vaccine delivery and management. The model is based on direct vaccine purchase via a pooled mechanism such as PAHO’s Revolving Fund.

(Only relevant to specific countries) The creation of additional funds for immunization financing by increasing an existing domestic tax or imposing a new tax on the purchase or use of specific goods or services, or preserving existing social security systems. The proposed plan includes, but is not limited to, the following core elements: (i) road consumption taxes (e.g. VAT/GST); (ii) taxes on specific products, especially those with harmful health effects like tobacco or alcohol (‘sin taxes’); (iii) sector-specific taxes generally levied on profitable sectors/larger corporations, especially in the financial, resource and telecommunications sectors. The funds raised from domestic taxes can go into consolidated government revenues, or be ‘hypothesized’ (i.e. earmarked) for a specific cause, such as immunization campaigns or vaccine financing.

In consideration of these recommendations the following next steps were proposed:

- Hold a follow-up regional meeting next year, where the focus is on dengue control and prevention financing with an emphasis on refining the expert recommendations of an integrated financing strategy.
- Establish a working group at the follow-up workshop with expertise in health economics, financing, public health and public policy, and business to continue driving the process forward, in parallel to a forum to discuss and prioritize financing vaccine introduction.
- Through the regional meeting, continue to engage Ministers of Finance, vaccine manufacturers, public and private providers, business groups, representatives from bilateral organizations and other key stakeholders in discussions relevant to health systems (and vaccine) financing to address cross-cutting issues and provide additional input in the follow-up regional meeting.
- Begin a process of extensive consultation with Ministers of Finance and Ministers of Health to determine their needs and interest – this could be done via regional consultations or on a country basis before the regional meeting is held.
Other steps include:

- Assist in the generation of cost-effectiveness and budget impact evidence, and present it to the relevant Ministries when available;
- Once consultation with the appropriate country representatives is undertaken, help support any proposed financing plans between the country, PAHO and/or bilateral organization – this would need to be developed with the working group; and
- Help to improve communication internally, specifically between Ministers of Health and Ministers of Finance through consultation, as any financing scheme will require coordination between both entities.

These expert recommendations can provide significant advantages to the current vaccine financing system in the region. There is still significant work to be done in this area. We hope that the implementation of these and other recommendations will herald the rapid introduction of a dengue vaccine in the Americas, a region plagued by frequent, severe dengue outbreaks.
Background

The last two decades have witnessed an unprecedented increase in the incidence and severity of the dengue virus worldwide. This is particularly true in the Americas, where dengue has become one of the most urgent public health concerns facing the region. From 1995 to 2010, more than 30 countries in the Americas reported a total of 10,589,435 cases of dengue (PAHO / WHO, 2010). In 2010 alone, more than 1.5 million cases were reported in Colombia, Venezuela, Brazil, Honduras, Guadeloupe and Puerto Rico.

In addition to a heavy epidemiological burden, dengue also inflicts a considerable economic burden in terms of the direct costs of illness and indirect costs on health systems and society (e.g. lost productivity). The total cost associated with dengue illness in the Americas has been rising steadily in the last decade, and was estimated at US$ 2,150 million as of 2010 (Shepard et al 2011). Brazil accounts for the greatest proportion (40%) of this burden. A prospective study published in 2009 estimated that the economic burden of dengue in that country could be upwards of US$350 million annually ($835 million in international dollars) (Suaya et al 2009). The same study concluded that the total annual economic burden of dengue could potentially be as high as US$ 1,076 million ($1,749 in international dollars) for El Salvador, Guatemala, Panama, and Venezuela. Argentina, Panama, Uruguay, and Venezuela are South American countries that also bear a high dengue burden per hospitalized case. Anticipated rises in hospital and ambulatory costs in the region will only further increase the economic burden of dengue on households and health systems in the future (Shepard et al 2011).

Compounding the effect of this dramatic increase in incidence and cost is the fact that current prevention and control methods have proven to be costly and of uncertain effectiveness. Dengue vaccines currently in development may provide a viable complement to these strategies.

Goals and objectives

The overarching goal of this workshop was to examine strategies for meeting the challenge of vaccine financing in the Americas with a specific focus on dengue vaccines.

The objectives of the workshop were therefore twofold: (i) to identify promising approaches to financing dengue vaccines that assure equitable and rapid introduction; (ii) to develop a set of key actions that can advance these options.
Pre-workshop activities

Several pre-workshop activities were performed to prepare for the workshop. These included: (i) identifying gaps in the area of vaccine financing; (ii) conducting pre-workshop surveys to assess countries’ experience with dengue; (iii) developing background documents that address issues related to dengue including the challenges of dengue control and prevention, lessons learned from previous vaccine introduction, financing uptake of new vaccine introduction and costs associated with vaccine introduction. The output from these pre-workshop activities can be found in Annexes 1-5.

Structure of the workshop

The objective of day 1 was to frame the issues relevant to dengue, offering the opportunity for leading experts from a variety of backgrounds to become familiar with dengue and dengue vaccines specifically. Day 1 served as a forum for stimulating discussion on the unique challenges involved in vaccine financing in the region. Over 30 experts attended the first day of the workshop. The workshop opened with participant introductions and an overview of dengue, which included a discussion of the epidemiology of dengue and current vector-control strategies. Individual countries (Brazil and Mexico) then presented on their respective experiences with dengue, followed by presentations by manufacturers regarding the status of dengue vaccines currently in development. The presentations concluded with the current challenges to dengue introduction and a discussion on the impact of vaccine introduction using economic modeling.

During the second day leading experts met to identify a set of approaches for financing dengue vaccines and to develop an action plan that can advance these options in countries in the Americas. In addition, an analysis of the financing mechanisms that have been successfully applied in countries of the region was presented. The day was split into two strategic sessions that were limited to experts and researchers who have conducted considerable work on dengue and have a background in financing vaccine introduction in the region.
**Topics discussed during the workshop**

Various topics were discussed during the two-day workshop. Table 1 summarizes these topics.

**Table 2: Topics covered during the workshop**

<table>
<thead>
<tr>
<th>Day 1</th>
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<tbody>
<tr>
<td>Overview of the epidemiology of dengue in the region</td>
<td>Financing strategies used for other vaccines</td>
</tr>
<tr>
<td>Overview of the economic burden of dengue in the region</td>
<td>Financing strategies that are suited to specific countries</td>
</tr>
<tr>
<td>Challenges of dengue vector control strategies</td>
<td>Existing mechanisms that can be leveraged to ensure equitable and timely introduction of a dengue vaccine</td>
</tr>
<tr>
<td>Demand for dengue vaccine in the Americas (country perspectives)</td>
<td>Other innovative strategies that can be applied in the context of dengue vaccines</td>
</tr>
<tr>
<td>New and emerging dengue vaccines</td>
<td>Next steps that need to be taken to accomplish the recommendations made in strategy session one</td>
</tr>
<tr>
<td>Hurdles for equitable and timely introduction of vaccines with focus on dengue</td>
<td>The role that key international and regional players and advocates can play to facilitate the adoption of these recommendations</td>
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| Potential health and economic impacts of dengue vaccine introduction | Expected outcomes of the workshop

The expected outcomes of this workshop were to provide:

- Recommendations for vaccine financing options;
- Agreement on key actions that can advance these options;
- Proceedings document providing a synopsis of the two day deliberations; and
- Peer-reviewed paper outlining recommendations on financing options

What follows is a summary of the issues discussed during both days of the workshop and recommendations for dengue vaccine financing.
Workshop - Day 1

The impetus on Day 1 was to frame the issues relevant to dengue vaccine financing. The following session provides an overview of each presentation and highlights of key discussion points and/or recommendations.

**Introductory remarks and overview**

*Speakers:* Prof. Peter Figueroa, University of the West Indies (Chair)
Dr. Dagna Constenla, John Hopkins University, International Vaccine Access Center (JHU’s IVAC)
Dr. Jon Andrus, Pan-American Health Organization (PAHO)
Dr. Vittal Mogasale, International Vaccine Institute (IVI)

The first day of the workshop began with opening remarks by Prof. Peter Figueroa, the chair of day one of the workshop. Prof. Figueroa stressed the significance of dengue fever (DF) and dengue hemorrhagic fever (DHF) in the Americas, especially with respect to the increasing severity and burden of the disease.

Introductory statements by Dr. Dagna Constenla and Dr. Jon Andrus followed Prof. Figueroa’s remarks. Dr. Constenla briefly outlined the purpose of the workshop and the challenges faced by countries as they consider new vaccine adoption. Dr. Andrus expanded on Dr. Constenla’s remarks by stressing the importance of preventing dengue as a regional priority and the pivotal role that vaccine financing will play in increasing access to the new vaccine. Dr. Mogasale then presented an overview of the Dengue Vaccine Initiative (DVI) and its role in laying the groundwork for dengue vaccine introduction in endemic areas. He also briefly discussed the need to focus on issues related to financing a new dengue vaccine and potential lessons learned from the Americas that might be applicable to Southeast Asia.

**Lessons learned from previous vaccine introductions by PAHO**

*Speaker:* Dr. Cuauhtémoc Ruiz Matus, PAHO

The first discussion of the afternoon was led by Dr. Ruiz and focused on lessons learned from previous vaccine introductions in the Americas and the pivotal role that the PAHO played in improving access to these vaccines.

Dr. Ruiz began by explaining how most countries in the region consider immunization to be a public health good that should be universally accessible regardless of income level. He emphasized the leadership role that PAHO has taken in promoting this concept in the region, namely through the ProVac Initiative and the Revolving Fund. The intended goal of the ProVac Initiative is to strengthen national capacity for decision making by assisting in the development
of tools for economic analysis and providing in-person technical training and support, while the Revolving Fund works to provide a mechanism for technical cooperation in the joint procurement of vaccines, syringes and related supplies for participating countries in the region. As a result of PAHO’s leadership role over 80% of the birth cohort in the Americas are in countries that include the pneumococcal and rotavirus vaccines in their national schedule. Dr. Ruiz also discussed the significant increase in the number of antigens circulating from 1979 to 2012, countries that have access to new vaccines, and trends in vaccine purchases in the region (Table 2). Currently, more than USD 200 million of PAHO’s USD 500 million budget for the Revolving Fund is being spent on newly developed vaccine purchases.

Table 2: The Revolving Fund – Key figures

<table>
<thead>
<tr>
<th></th>
<th>1979</th>
<th>2012</th>
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<tbody>
<tr>
<td>Antigens</td>
<td>8</td>
<td>28</td>
</tr>
<tr>
<td>Countries &amp; Territories</td>
<td>8</td>
<td>40</td>
</tr>
<tr>
<td>Purchases (US$ million)</td>
<td>2.3</td>
<td>512</td>
</tr>
<tr>
<td>Capital Fund (US$ million)</td>
<td>1.5</td>
<td>100</td>
</tr>
</tbody>
</table>

Reproduced from Dr. Ruiz’s slide presentation, July 22 2013

According to Dr. Ruiz, countries must be prepared, and able, to undertake vaccine related expenditures for several years beyond the initial introduction period. Moreover, they must also consider other costs of immunization and program management, including programmatic costs, infrastructure investments, and capacity needs. Dr. Ruiz explained that prior to vaccine introduction it is essential that these expenditures are determined and accounted for.

Two prequisites identified as necessary for the Revolving Fund to achieve economies of scale in vaccine introduction on an individual country level include self-sustaining financing and strong vaccine legislation. Vaccine legislation usually takes the form of a line item in the budget guaranteeing financing or explicitly defining the Revolving Fund as the procurement mechanism for vaccines (i.e. Peru, Panama, Honduras, Costa Rica, and Bolivia). Some countries in the region also have immunization laws which define vaccination as a public health good and establish free or universal vaccination as a right for all citizens (i.e. El Salvador).

“When countries in the Americas make the decision to introduce these vaccines it is because they are sure that they can maintain the sustainability of the introduction of the vaccine, not only for the first year but as a regular part of the national program.”

-- Dr. Ruiz from PAHO

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operational aspects of such programs. The group was then provided with an overview of the relative correlation between the number of vaccine laws in the region and the proportion of the Expanded Program on Immunization (EPI) costs covered by national funds (Figure 1).

**Figure 1: Changes in vaccine legislation and funding sources in the region from 1987-2010**

Key points from Dr. Ruiz’s presentation include:
- The need for robust surveillance at the national and regional level in order to provide data on disease burden and inform vector control strategies.
- The significance of collaboration at a regional level between countries that face a high dengue disease burden. Early experiences in individual countries might provide valuable lessons for countries with delayed dengue vaccine introduction.
- The pivotal role played by PAHO’s Revolving Fund in facilitating new vaccine adoption in several countries in the region.
- The importance of a clearly defined communication plan at the national and sub-national level that allows for the efficient and appropriate implementation of disease prevention and control strategies. Dr. Ruiz used the example of the H1N1 epidemic in the Americas to illustrate the impact of inadequate communication on outbreak control. The significance of providing accurate information to both infected populations and, most importantly, health workers was also emphasized.
- The considerable impact of national vaccine laws on facilitating sustainable financing for vaccines by explicitly recognising immunization as a legal right and clearly identifying sources of financing.
- The need to consider financing challenges that go beyond vaccine costing concerns. While affordable prices are important in providing access to vaccines, there are other costs that can undermine the long-term sustainability of an immunization program, including: implementation and rollout costs, expenditures related to cold-chain...
maintenance, remuneration for health workers, costs of training community health workers, etc.

- The significance of providing sufficient technical support to countries so that they can generate robust evidence to justify vaccine adoption. Such support is especially critical for smaller countries.
- The benefits of introducing vaccines at a universal level (impact evaluation, reliable coverage, and equity) and the importance of obtaining accurate surveillance and disease burden data pre- and post-introduction to monitor the impact.

Part I: Understanding the need for a dengue vaccine

The following section provides an overview of the presentations on the current epidemiologic and economic burden of dengue in countries of the region, followed by presentations on vector control strategies and the demand for dengue vaccine based on country perspectives. In addition, key discussion points and/or recommendations are also highlighted.

Epidemiology of dengue in the region

Speaker: Dr. Jose Luis de San Martin, Dengue Regional Consultant, PAHO

Dr. de San Martin presented an overview of the epidemiological profile of dengue in the Americas. Approximately 40 countries report dengue case estimates to PAHO, and almost all of the countries in the region are dengue endemic. According to Dr. de San Martin, the burden of dengue is highly concentrated in eight countries within the region (Mexico, El Salvador, Panama, Puerto Rico, Colombia, Peru, Argentina and Brazil) which account for close to 90% of reported cases. Brazil alone incurs over 50% of the dengue disease burden, followed by Mexico and Venezuela (Figure 2). Dr. de San Martin speculated that the rise in the number of dengue cases reported and the number of countries reporting transmission, particularly from 2008-2010, could be a result of multiple strains circulating in the region at the same time. Despite this increased incidence (over 200 cases per 100,000 in some countries), the case fatality rate associated with dengue in the Americas has remained relatively low compared to other dengue endemic areas. Dr. de San Martin also brought up the interesting point that the countries with the greatest morbidity associated with dengue (Brazil, Venezuela, Mexico) did not necessarily suffer from the highest case fatality ratio (Dominican Republic). This disparity in outcomes reflects the impact that varying degrees of primary care and disease response can have on mortality levels.

According to Dr. de San Martin, the relatively substantial dengue burden observed in the Americas could be a result of more robust surveillance systems, capable of reporting epidemiological data more accurately, rather than, or in addition to, increasing prevalence.
Interestingly, a lower number of dengue cases have been reported since 2011, although this trend could be attributable to the new World Health Organization (WHO) case definition of dengue. Further contributing to this decrease in incidence and fatality are the efforts of PAHO to improve the recognition of dengue warning signs and train primary healthcare workers with the purpose of early detection.

Figure 2: Distribution of dengue morbidity by country in the Americas 2003-2008

A lack of accurate surveillance infrastructure in other parts of the world could also be resulting in severe under-reporting, thereby making it seem as though the incidence in the region is significantly higher by comparison.

Dr. de San Martin concluded by highlighting two areas that warrant increased attention in the future:

- Surveillance systems: Surveillance systems in the region will need to be improved. PAHO is currently monitoring and evaluating a new model for surveillance in eight countries (Mexico, El Salvador, Panama, Puerto Rico, Colombia, Peru, Argentina and Brazil). The system should be ready for

“Latin America currently has good surveillance systems; nevertheless, we recognize that these systems will need to be improved in the face of new vaccine introduction.”

-- Dr. de San Martin from PAHO
use by end of 2013, with a more extensive region wide rollout expected.

- Integrated approach: It is essential that any new approach to dengue prevention, including a vaccine, be coordinated within existing vector control and disease management programs. The emphasis with this approach should be the standardization of surveillance systems throughout the region. The moderately successful introduction of a yellow fever vaccine, which was not part of an integrated process, was used to underscore the importance of integration. PAHO is currently working with the CDC to strengthen environmental control and vector management in the region in an effort to implement a comprehensive control strategy.

Economic burden of dengue in the Americas

*Speaker*: Prof. Donald Shepard, Brandeis University

Prof. Shepard discussed the economic impact of dengue in the Americas and the importance of estimating costs accurately at the national and regional level. The role of cost-effectiveness research and costing analysis and their potential to be key drivers of decision making in new vaccine introduction was emphasized. To this end, it is imperative that researchers adopt robust methodology in their analysis and identify the best sources for data collection as a priority. The focus of the presentation was largely on the present challenges of estimating the true cost of dengue.

According to Prof. Shepard, while there is little doubt that the economic burden imposed by dengue is significant, it is challenging to accurately quantify this burden at the household and population level. The probable cause of such inaccurate data estimates is underreporting, largely due to the difficulty of diagnosing dengue in resource poor settings. In order to measure the economic costs of dengue precisely, the actual number, or a reasonable estimate, of cases on an annual basis must be determined. Since this information is not widely available, a product of poor reporting systems and gaps in surveillance, researchers must apply an “expansion factor.” An expansion factor calculates the approximate number of actual dengue cases by using the estimates for disease burden in the region.

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“Surveillance systems are designed to monitor trends in a disease, not pick up every case. Even if they were intended to do that, they’re run by humans with obligations besides counting cases. An expansion factor takes the potential for human error into account.”

-- Prof. Shepard from Brandeis University
Prof. Shepard mentioned a capture-recapture study in Puerto Rico as one method of obtaining an expansion factor. This approach represents a specialized situation in which two independent data sources were required. Cohort studies are another possible source of data for calculating expansion factors. Studies from Nicaragua, Brazil, and Colombia were presented by Prof. Shepard as examples of applications of this methodology based on a study he conducted with colleagues (Shepard et al 2011). Ambulatory care costs and the expansion factor for dengue fever were the two variables that were found to impact the cost-of-illness for dengue the most (Figure 3).

**Figure 3: Factors affecting the economic burden of dengue in the Americas 2007-2010**

Prof. Shepard concluded by emphasizing the impact that accurate expansion factors have on calculating realistic aggregate costs of dengue and the importance of reliable and transparent methodology in estimating these factors. He also stressed the fact that the sizable aggregate burden of dengue will only continue to increase without an effective control and prevention strategy.

**Question and answer (Q&A) session**

The first Q&A session focused on the current state of surveillance systems in the Americas and the impact these systems have on incidence and cost estimates. Participants generally agreed that higher dengue incidence rates in the Americas are a result of an increase in both the quality of surveillance systems (as evidenced by Brazil, Mexico, and El Salvador) and the overall number of cases occurring. Higher case numbers were also attributed to a greater diversity of serotypes circulating within countries at any given time. Dr. Ruiz indicated that a specific country level platform for surveillance systems would not be developed by PAHO; rather a more general based platform (such as that used for influenza) would be tested and validated in 8 pilot countries.
countries. Three options were presented for countries looking to implement this final product: incorporate it into an existing platform, use it in conjunction with PAHO surveillance systems, or replace or parallel the new platform with the current system.

Other topics addressed in less detail included: extending PAHO interest-free 60-day loans and the information needed on a country level to generate expansion factors for more accurate dengue cost estimates. Concerns about the current lack of alignment between PAHO surveillance systems and CDC surveillance systems were voiced by Dr. Margolis, who noted that the lack of coordination between the two presented a major challenge to evidence consolidation and should be addressed.

Discussion of vector control strategies for dengue

This discussion centred on the challenges involved in the successful implementation of vector control strategies for dengue in the Americas.

Discussion session on vector control strategies
Speaker: Dr. Harold Margolis, Centers for Disease Control and Prevention, Puerto Rico

Dr. Margolis began his presentation by outlining the challenges involved in the successful implementation of vector control strategies for dengue. Although dengue is a disease that remains concentrated within specific communities, transmission occurs year round and traveling individuals spread the disease from one community to another. The significant proportion of these individuals remaining asymptomatic (75 percent) presents another difficulty in disease burden estimation.

Figure 4: Tools used in comprehensive dengue

Getting governments to schedule vector control interventions at the most effective times was mentioned as another challenge. Vector control is more effective when the disease is on a downward trend; however, most countries increase vector control measures only when incidence rises. At this point, Dr. Margolis said, it is generally too late to make a significant impact on the rapid spread of the disease.
The presentation included an overview of primary (vector control, vaccines) vs. secondary (diagnostics, case management) methods of dengue prevention along with the different types of mosquito that spread dengue, the importance of studying adult mosquitoes, and other ways in which dengue proliferates (Figure 4). The importance of using dengue as an endpoint for vector control methods, rather than the reduction in dengue indicators, when measuring the impact of any vector control program was also highlighted.

"The reality is that we do have a lot of vector control but I don’t know that we have anything that says that we have prevented dengue outbreaks once they start, or that we have actually suppressed dengue. We really have a partially effective prevention strategy."

-- Dr. Margolis from CDC Puerto Rico

control and prevent the spread of dengue. This strategy can, however, be very difficult to implement on the ground. The level of vertical and horizontal collaboration between various sectors that is required for the successful implementation of an integrated vector control strategy is extremely difficult to coordinate and, more importantly, maintain in the long term.

Figure 5: Dengue incidence in Singapore pre-/post-vector control

According to Dr. Margolis, the sustained commitment of resources and need to include sectors of society not normally engaged in public health (necessity of regulations and engineering controls in addition to addressing cultural norms) will be critical as well.
The presentation concluded with the example of Singapore, a country that went to significant lengths to combat dengue – using integrated vector control, spending substantial resources on improving prevention strategies, passing laws for specific budget line items for financing – and yet still suffers from regular outbreaks (Figure 5). It is important, however, not to prematurely conclude that vector control was ineffective in this scenario, as there are a number of factors that contribute to the effectiveness of an integrated approach.

While integrated vector control and vaccine introduction are important aspects of dengue prevention, neither will be sufficient by itself. These two approaches are most effective when combined, and a dengue vaccine could provide a much needed complement to existing vector control efforts in the fight against dengue.

Q & A session

In this Q&A session the relevance of expansion factors, given the dramatically improved quality of surveillance data from many countries in the region, was brought up again. The point was made that even in countries with high quality surveillance (i.e. Singapore) the reporting rate for dengue is still below 30 percent, highlighting the continued role that expansion factors will play in disease burden estimation. Available evidence indicates that the stronger a country’s health system, the greater the proportion of dengue cases that will be captured through surveillance and the lower the necessary expansion factor. The discussion on expansion factors led to a discussion on the need for additional cohort studies in the region to supplement the disease burden data gathered from surveillance systems.

The degree of collaboration between PAHO and the GAVI Alliance was covered as well. Aside from GAVI’s purchasing of vaccines through the Revolving Fund (with all countries paying the same price regardless of GAVI designation) experts agreed there is little overlap due to the small number of GAVI eligible countries in the region (a total of 6, with 5 in the process of graduation). Given the GAVI board’s decision not to support the introduction of a dengue vaccine for the next five years led many participants to relegate their position in the discussion to that of an outsider. Other discussants noted that the continued inclusion of GAVI in the discussion is important, as they can provide critical resources aside from funding in the form of advice and experience with vaccine introduction.

The problem of bias in the data was mentioned, especially in reference to the reporting of DHF and the recommendation was made that PAHO countries report incidence rather than case counts. The reason for the low mortality rates from dengue in the Americas was ascribed to the rapid response of technical advisory groups, a country level focus on the highest risk regions, and excellent case management at the primary care level.

Protecting Health, Saving Lives—Millions at a Time
Additional topics brought up, but not addressed in detail, included the readiness of health systems to absorb the added cost of a dengue vaccine roll out, where the extra financing for this rollout will come from, and how countries compare dengue interventions and make the decision to introduce a vaccine.

**Country perspective on demand for a new vaccine**

Two countries shared their perspective on the demand for a dengue vaccine: Brazil and Mexico. This session was organized in an effort to better understand the viewpoint of countries in the region regarding the need for a dengue vaccine.

**Brazil**  
*Speaker:* Dr. Carla Domingues, Ministry of Health in Brazil

Dr. Domingues discussed Brazil’s publicly funded health care system, known as Sistema Único de Saúde (SUS). She explained the structure of the system and the current immunization landscape, which is characterized by universal access to vaccines and high coverage rates.

According to Dr. Domingues, dengue is a notifiable disease in Brazil and is a national health priority for the government due to its high prevalence and political implications. The national surveillance system used at the municipal level (the lowest level of service provision in Brazil) is passive surveillance. The need to strengthen the existing surveillance system at this level in order to actively collect better data on dengue in Brazil was emphasized by Dr. Domingues.

The presentation concluded by outlining Brazil’s strategic plan for the introduction of a dengue vaccine (Table 3). The plan, according to Dr. Domingues, includes a focus on pre-licensing issues (ideal dosage, efficacy etc.) and post-licensing questions (target groups, long term adverse events, etc.). Given the high profile of dengue in the country, Dr. Domingues asserted that Brazil is at the forefront of vaccine adoption in the region.

“It is imperative that surveillance systems are improved at the municipal level so that vaccine efficacy in adults (the group most affected by dengue) can be established.”

--- Dr. Carla Domingues from MoH in Brazil
Table 3: Strategic dengue vaccine introduction plan in Brazil

<table>
<thead>
<tr>
<th>Pre-licensing focus</th>
<th>Post licensing focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Assessment of number of vaccine doses and protection</td>
<td>• Target areas and groups</td>
</tr>
<tr>
<td>• Interval between doses</td>
<td>• Vaccine Adverse Event Report System by the National Immunization Program (PNI) and need to improve current strategies</td>
</tr>
<tr>
<td>• Efficacy in adults</td>
<td>• Monitor long term adverse event</td>
</tr>
<tr>
<td>• Role of previous Yellow Fever Vaccination</td>
<td></td>
</tr>
</tbody>
</table>

Mexico

*Speaker:* Dr. Pablo Kuri-Morales, Secretariat of Health, Ministry of Health, Mexico (via Elluminate)

Dr. Kuri-Morales presented on Mexico’s plans for vaccine introduction. He stressed the importance of taking a proactive approach given the burden of disease in Mexico and the country’s role in the region as a pioneer in the area of immunization. Mexico’s national strategy includes recommendations from a panel of experts in order to develop a plan that can be adopted immediately following licensure. Experts on the panel represent various fields of vaccinology, including epidemiology, regulatory mechanisms, clinical care, and economic/financial experts (Figure 6).

Dr. Kuri-Morales presented on Mexico’s plans for vaccine introduction. He stressed the importance of taking a proactive approach given the burden of disease in Mexico and the country’s role in the region as a pioneer in the area of immunization. Mexico’s national strategy includes recommendations from a panel of experts in order to develop a plan that can be adopted immediately following licensure. Experts on the panel represent various fields of vaccinology, including epidemiology, regulatory mechanisms, clinical care, and economic/financial experts (Figure 6).
fields of vaccinology, including epidemiology, regulatory mechanisms, clinical care, and economic/financial experts (Figure 6).

According to Dr. Kuri-Morales, Mexico intends to include the new dengue vaccine in its national immunization schedule as soon as it is available for distribution. However, Mexico’s introduction strategy will use a targeted approach by focusing on the areas of highest dengue transmission and age groups most at risk. It is imperative that a dengue vaccine is used in conjunction with, not in replacement of, existing prevention and control methods. Dr. Kuri-Morales said that in order to accomplish this there should also a focus on strengthening epidemiological surveillance and the etiologic aspects of dengue control and prevention.

Dr. Kuri-Morales concluded by acknowledging the need to conduct further cost-effectiveness analyses and adopt better communication strategies on a national and sub-national level. Additional introduction challenges, with respect to sufficient human resources, adequate health systems capacity, and financial resources for vaccine purchase and distribution, are also anticipated.

**Q & A session**

In this discussion session the increased demand for dengue evidence amongst countries in the region, despite the lack of a licensed vaccine, was brought up. Experts argued that countries could not afford to wait until the vaccine is in place to make financial and operational decisions, as this would significantly delay roll out. Some experts indicated that, given the sizable amount of vaccines needed to inoculate children under 5 in countries like Brazil with just one dose (2 million total doses), it may be more prudent to take the conservative approach of only vaccinating the youngest cohort and observing the subsequent impact on disease burden.

Overall, there seemed to be agreement that proactive action is necessary with the introduction of a dengue vaccine, especially given the politically sensitive nature of the disease in the Americas. Experts used the example of the extensive preparation that went into developing introduction plans for an HIV vaccine that was never fully developed to emphasize caution. The surprising results of the Sanofi Pasteur Phase IIb trials were also brought up, with experts using these results to make a case for an integrated approach to dengue management, consisting of improved health systems and vector control in addition to vaccine introduction. It was noted

> "Using an expert panel, Mexico has developed a proactive approach that will allow us to take a leadership role in the introduction of a dengue vaccine in the region."

> -- Dr. Pablo Kuri-Morales from MoH in Mexico

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that although vector control is important, it has only been shown to be 25 percent effective, and the Sanofi Pasteur trials were conducted in an area of Thailand with extensive vector control. Experts also indicated that the limiting factor in dengue vaccine introduction would be constrained supply as opposed to constrained resources.

**Dengue vaccines in the pipeline**

This session was designed to allow manufacturers in the process of dengue vaccine development to present on the current status of their work. The following are highlights of these presentations.

**The development of DENVax**

*Speaker: Dr. Jorge Osorio, Takeda Pharmaceutical Company*

The Takeda vaccine in development is a live attenuated prototype that is currently enrolled in phase II clinical trials. The dengue 2 backbone was chosen as the base for this vaccine in order to increase protection against the DENV-2 serotype. Two phase I trials have been conducted in the U.S. and Colombia and have successfully demonstrated the safety and immunogenicity of the tetravalent model in non-human subjects. It is expected that the vaccine will be administered in two doses, three months apart. Efforts are currently underway to develop a version where both doses could be administered on the same day, which would significantly reduce administration costs. In the phase I trials that have been conducted thus far the vaccine was safe and well tolerated with no meaningful adverse reactions. Age descending (adults, adolescents, school age, and young children) phase II trials are being conducted in Puerto Rico, Singapore, Thailand, and Colombia. In addition, phase Ib studies are being conducted to look into the possibility of introducing a vaccine that could be administered in reduced dose intervals using alternative routes of transmission (intra-muscular, sub-cutaneous, and needle free). Results so far support the safety and immunogenicity of the vaccine in exposed and unexposed individuals of varying age groups and the efficacy of the rapid immunization regimen. In order to maximize production upon licensure a scalable, robust manufacturing process for production of phase 2b/3 materials has been developed and the studies are being prepared to be conducted 2014.

**Merck Dengue Vaccine Program**

*Speaker: Dr. Beth-Ann Coller, Merck*

The Merck vaccine is currently in phase I clinical testing in Australia (adults), with safety, immunogenicity, and efficacy having been effectively demonstrated in pre-clinical trials. A recombinant envelope produced in insect cells is being used in vaccine production because of the native conformation and greater yields associated with the system. This vaccine is designed
to be administered in three doses. At present the schedule will likely be 0, 1, 6 months as this appears to offer advantages in both the magnitude and durability of response versus the 0, 1, 2 schedule with responses following the first 2 doses of vaccine on the 0, 1, 6 month schedule being similar to that induced by 3 doses on the 0, 1, 2 month schedule.

Sanofi Pasteur Dengue Vaccine Project: Phase II stage – Q2 2013 status
Speaker: Dr. Jose Noguera, Sanofi Pasteur

The dengue vaccine that is furthest along in the pipeline is being developed by Sanofi Pasteur, and is widely regarded as the leading candidate for early licensure. Dr. Noguera began his presentation by noting the main challenges in dengue vaccine development including the lack of an animal model, variety of serotypes, and varying epidemiological burden. The Sanofi Pasteur vaccine is a recombinant LAV (Life Attenuated Viral) vaccine, with a yellow fever backbone and, unlike many other vaccines in development, does not contain an adjuvant. This vaccine is by far the most widely studied, with 45,000 individuals having participated in trials across 15 countries, with encouraging safety information, and a satisfactory immune response (PRNT50).

The results of the phase IIb trial in Ratchaburi, Thailand exhibited low efficacy against the DENV-2 serotype. Dr. Noguera emphasized that this is a phase IIb study, with a sample size of 4,002 participants, in the very specific context of this location. The results in the PP (Per-Protocol) analysis did not pass the statistical significance test, and, given the high number of observed cases, they decided to consider the efficacy per serotype. The results for DENV 1, 3, and 4 were in a range consistent with Sanofi’s assumed overall efficacy of 70%.

Two large phase III trials are currently being conducted in ten countries with results expected by the second half of 2014, which will have important implications regarding the future of the vaccine. In addition to its favorable position in the later stages of clinical development, the Sanofi Pasteur vaccine also has the benefit of sufficient capacity to be produced in large quantities (100 million doses/year) upon licensure. Dr. Noguera concluded by stressing the importance of continuing research into the etiology of dengue, as understanding this complex disease will be critical to the licensure of a safe, efficacious vaccine.

Clinical evaluation of the NIAID live attenuated dengue vaccine
Speaker: Dr. Catherine Luke, National Institute of Allergy and Infectious Diseases (NIH)

The National Institute of Allergy and Infectious Diseases (NIAID) vaccine demonstrated both safety and an extremely high level of immunogenicity (79% of naïve subjects had a tetravalent antibody response) in phase I trials. The vaccine did not appear to benefit significantly from a booster, as most subjects appeared to be “protected” against a boost, although a booster could
increase antibody durability. The NIH prototype is being shared with licensing partners as part of a technology transfer. These partners include Butantan (Brazil), Biologica E Ltd (India), Panacea Biotec (India), Vabiotech (Vietnam), and GSK. The vaccine is currently in a phase II pilot study (two dose), and a main study (one dose) being conducted in adults. The pilot study is designed to determine safety in different age groups at varying dose intervals.

**Instituto Butantan: Division of Clinical Trials and Pharmacovigilance**

*Speaker:* Dr. Ricardo Palacios, Instituto Butantan

Dr. Palacios began with a background of Instituto Butantan, which is a state-owned research organization in Brazil attached to the Secretary of Health of the State of São Paulo. Since the Butantan vaccine was developed using the NIH prototype it shares many of the same target product profile characteristics (single-dose, live attenuated vaccine, safe, and greater than 75 percent protection). Phase II trials have already been conducted using a unique lyophilisation process and formulation developed at Instituto Butantan. Dr. Palacios emphasized that most of the initial production costs at Instituto Butantan would be fixed (85 percent), and the ability to affordably scale up their unique lyophilization process will be critical to affordability.

Butantan is one of the manufacturers with significant existing production capacity; with the ability to theoretically produce 500,000 doses per year at their pilot plant (lyophilisation will be a limiting factor). Following completion of an industrial plant currently in design, Butantan will be able to produce about 100 million doses per year operating at full capacity. Challenges facing Butantan in terms of licensure include: WHO pre-qualification, a lack of experience in the use of products abroad, and finding a balance between local and international demand. Dr. Palacios also noted the challenge of the varying age distribution of cases for dengue. In Brazil over 50 percent of classic and severe cases occur in 20-59 year olds rather than children, while in other countries the burden is mostly on younger individuals.

**Tetravalent Dengue Purified Inactivated Vaccine (DPIV)**

*Speaker:* Dr. Alexander Schmidt, GlaxoSmithKline

DPIV is the result of a collaboration between Fiocruz (MoH Brazil), GSK, and the US Army, with technology transfers playing a critical role in this process. Vaccine administration is expected to be two doses, given four weeks apart. Trials thus far have shown the vaccine to be highly immunogenic, safe, and suitable for co-administration, with no viral interference between serotypes. Phase I trials are currently underway in the US and Puerto Rico, with burden of disease studies planned for Brazil (2013), Mexico (2014), and the Asia-Pacific region (2014). The decision to switch from a live attenuated vaccine to a non-replicating inactivated vaccine was made because it is highly efficacious and durable. An adjuvant was also used to further enhance
immune response, expedite onset of protection, and induce durability. Dr. Schmidt noted that there will be plenty of room for multiple vaccine manufacturers, as it would be difficult for any single manufacturer to meet global demand, especially given current capacity.

Table 4 provides an overview of the characteristics of the various dengue vaccines under development. This information was derived from a post-workshop survey that was administered to all participating industry representatives.

**Table 4: Characteristics of vaccines in development**

<table>
<thead>
<tr>
<th></th>
<th>Sanofi Pasteur</th>
<th>NIH</th>
<th>Takeda</th>
<th>Merck &amp; Co</th>
<th>Butantan</th>
<th>GSK</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Estimated cost of production</strong></td>
<td>Too early to provide an estimate</td>
<td>$0.51-$1.75 per dose when producing 15 M doses per year; $0.20-$0.70 per dose when producing 60M doses per year</td>
<td>Unknown</td>
<td>Unknown</td>
<td>60 million doses = US$.20* - US$.70**</td>
<td>Unknown</td>
</tr>
<tr>
<td><strong>Supply projections</strong></td>
<td>100 million doses/year starting in 2016 (1 billion doses/decade)</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Current capacity: 500,000 doses/year, planned capacity: 100 Million doses/year</td>
<td>Will depend on demand</td>
</tr>
<tr>
<td><strong>Price structure</strong></td>
<td>Too early to provide an estimate; SP will make a balance bet’ development capacity, demand, vaccine profile.</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td>For the Price structure, additional costs besides production will be considered</td>
<td>GSK tiered pricing approach</td>
</tr>
<tr>
<td><strong>Target population</strong></td>
<td>Clinical development plan in 2-60 yo. Two phase 3 trials : APAC: 2-14 yo; LATAM: 9-16 yo</td>
<td>Country-dependent</td>
<td>All age groups</td>
<td>Subjects at risk in endemic areas and travellers to those areas</td>
<td>All age groups</td>
<td>Six months of age and above</td>
</tr>
</tbody>
</table>
Table 4: Characteristics of vaccines in development (continued)

<table>
<thead>
<tr>
<th>Trial status</th>
<th>Sanofi Pasteur</th>
<th>NIH</th>
<th>Takeda</th>
<th>Merck &amp; Co</th>
<th>Butantan</th>
<th>GSK</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 phase II trials</td>
<td>8 phase III trials.</td>
<td>Phase II clinical trials, pilot study (2 doses)</td>
<td>Phase II age descending trials (Puerto Rico, Colombia, Singapore, and Thailand). Three Phase Ib trials done (U.S. &amp; Colombia) to assess viability reduced dose interval/needle vaccine. Phase 2b/3 in 2014</td>
<td>Currently in phase I clinical trial (Australia)</td>
<td>Currently in Phase II clinical trial (Sao Paulo), lyophilized</td>
<td>Phase I clinical trial currently underway (U.S. and Puerto Rico)</td>
</tr>
<tr>
<td>Safety</td>
<td>No increase in severe cases, good safety info &gt; 40,000 subj. received &lt; 1 d, and &gt; 26,000 w/3 doses.</td>
<td>Safety assessed after single dose of tetravalent vaccine</td>
<td>Safe and well tolerated, no meaningful adverse reactions</td>
<td>Currently in phase I clinical trial (Australia)</td>
<td>Safety assessed after single dose of tetravalent vaccine</td>
<td>Acceptable safety profile</td>
</tr>
<tr>
<td>Vaccine schedule</td>
<td>Clinical Development Plan based 6-12mo schedule</td>
<td>Unknown</td>
<td>Day 0 and day 90</td>
<td>Clinical Development Plan based on single-dose schedule</td>
<td>As needed in key countries</td>
<td></td>
</tr>
<tr>
<td>Vaccine Presentation</td>
<td>Freeze dried w/no adjuvant or preservative</td>
<td>Lyophilized (reconstituted to liquid for injection)</td>
<td>Subcutaneous and Intradermal by needle &amp; syringe</td>
<td>Recombinant Envelope Glycoprotein</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Dose Schedule</td>
<td>Clinical Development Plan based 6-12 month schedule</td>
<td>1 or 2 doses</td>
<td>2 dose</td>
<td>3 dose schedule</td>
<td>1 dose</td>
<td>2 doses 4 or CDP defined</td>
</tr>
<tr>
<td>Expected Licensure Date</td>
<td>First license planned by 4Q15.</td>
<td>2017 in Brazil</td>
<td>2017</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Q & A session

One of the first, and most salient, questions directed at vaccine manufacturers concerned how companies will ensure affordable pricing given that dengue primarily affects middle-income countries in the region. Dr. Luke from the NIH stressed that affordable pricing will be dependent on the actions of in-country manufacturers. She emphasized the need to establish cost effectiveness evidence to help influence vaccine pricing. Dr. Palacios from Butantan noted their intention to attempt to license a one-dose vaccine to promote affordability, while Dr. Schmidt of GSK indicated that public-private partnerships and tiered pricing would be used to maintain affordable pricing in global markets. Companies responded to questions about their ability to ensure supply in a similar manner, noting that they would produce as much as current capacity will allow and act responsibly. In addition to concerns about lower seroconversion rates with DENV2 for the most advanced vaccines, the need for further study on the interaction between yellow fever and the measles, mumps, and rubella (MMR) vaccine was also brought up. Overall there was agreement that more detailed answers to these questions would not be available without a target product profile.

Another question directed at the manufacturers related to timing of licensure. It was estimated that a Sanofi Pasteur vaccine could be ready for licensure as early as 2017, although it was argued that this would be highly dependent on future clinical trial results. Following behind Sanofi Pasteur in terms of vaccine development were the Takeda, NIH, and Butantan vaccines. All are somewhere in phase II trial status and have experienced encouraging results thus far. Vaccine manufacturers still in the earlier (phase I) stages of development include Merck and GSK. None of the vaccine candidates have exhibited adverse effects thus far.

All of the vaccine manufacturers present expressed concerns over supply constraints, with many, including Sanofi Pasteur, indicating their intention to construct new production facilities in the near future. There was agreement amongst the representatives present that, given the likely sizable demand, it would be extremely difficult for any one manufacturer to meet global dengue vaccine needs.
Part II: Important considerations for dengue vaccine introduction

The second part of the workshop was designed to cover a discussion on the important considerations for dengue vaccine introduction, including the inherent challenges and the potential economic impact of a dengue vaccine. Below are highlights of this discussion.

Hurdles for equitable and timely introduction of vaccines with focus on dengue

*Speaker:* Dr. Jon Andrus, PAHO

Dr. Andrus’s presentation provided an overview of the hurdles for equitable and timely introduction of vaccines. He focused on the following issues: i) how a new dengue vaccine will compete with other vaccines in terms of MoH priorities; ii) price and affordability concerns; iii) equitable and sufficient vaccine distribution within individual countries and the region as a whole; and iv) challenges of misinformation and political/public criticism. Two other key areas identified as lacking in information were dengue etiology and disease burden. Dr. Andrus noted that any deficiency in information regarding technical, programmatic, and social criteria represents an obstacle in vaccine introduction.

The ProVac Initiative and the importance of country-owned evidence generation were also highlighted. According to Dr. Andrus, the ProVac tool has proven to be useful in identifying incremental cost-effectiveness and promoting the effective use of communication tools. The evidence generated by ProVac can be used to influence political will, aid negotiations with other ministries (especially finance), accelerate vaccine introduction, and impact the overall culture of decision making at the country level (quality evidence becomes a prerequisite for decision making).

Dr. Andrus highlighted the criteria that is used for decisions around vaccine introduction, which include technical criteria (e.g. disease burden, vaccine characteristics, adverse events, cost-effectiveness analysis); programmatic and operation criteria (e.g. supply, logistical and operational questions, financing strategies); and social criteria (e.g. risk perception, political commitment, equity in access). One of the main challenges in dengue vaccine introduction is that this health intervention must compete with other new vaccines (e.g. HPV, IPV) and public health priorities. According to Dr. Andrus, vaccine price and costs associated with vaccine
introduction are of primary concern. An additional challenge is vaccine backslash and misinformation.

**Potential economic impact of new vaccine introduction for dengue**

*Speaker: Dagna Constenla, JHU’s IVAC*

Dr. Constenla focused on three main aspects of new vaccine introduction in her presentation. These included: i) models developed to forecast the potential demand and impact of new vaccines in terms of economic and disease outcomes; ii) the importance of developing an investment case for new vaccines; and iii) the need for a dengue vaccine integrated model. The presentation began with an overview of current models and methodologies being used by researchers to study the economic impact of vaccines against dengue. A global and regional literature review conducted by JHU earlier, as well as several studies performed in Southeast Asia, were described in detail. Recently, research papers have used models to look at the economic costs, benefits, and overall impact (in terms mortality and morbidity reductions) of a new dengue vaccine. The need to extend the scope of cost effectiveness work on dengue beyond vector control, especially towards studying vaccine impact, was emphasized by Dr. Constenla.

> *Integrated analysis of public and private sector returns for investment in a vaccine is a critical tool to bridge the public and private sectors, develop new interventions and achieve health impact.*

> -- Dr. Constenla from JHU’s IVAC

Dr. Constenla further explained the importance of developing an investment case for dengue vaccines using a hypothetical example. She described the need for improved values on model parameters, including information about market demand, anticipated impact, and costs (purchasing, delivery, development and production, and the ability/capacity to borrow fiscal resources). This information, she indicated, can be used to refine existing models or develop new ones to provide the most accurate data demonstrating the potential returns of vaccine introduction to ministries of health and finance.

The dengue vaccine integrated model and its role in providing countries with predictions of the potential impact of a dengue vaccine when used in local contexts (Figure 7) was also discussed. According to Dr. Constenla, the dengue vaccine integrated model is a tool to inform decision-making that connects the mathematical models of dengue epidemiology and demand
forecasting to provide a comprehensive picture of a new dengue vaccine’s potential in terms of supply, demand, health benefits, and cost. The model is divided in three modules. The first module – the demand module - estimates the number of doses of vaccine that would be needed over a given period to satisfy demand. The public health module is based on disease burden data and uses epidemiological simulation to predict the impact of a vaccine in terms of the cases, and disability-adjusted life years (DALYs) that would be averted with a given uptake scenario. The third module – the financial module - calculates the investment needed to achieve the public health impact described above, based on information entered by the user on vaccine price and implementation costs.

**Figure 7: IVAC's Dengue vaccine integrated model**

Dr. Constenla finished with a discussion on future funding needs for dengue vaccine adoption. Using conservative assumptions of high efficacy of vaccine (upwards of 75% against severe disease), high coverage rate, and vaccine price of $5-15 per vaccine course, dengue vaccine would avert up to 1.4 million cases and 51 million disability adjusted life years (DALYs, a measure of disease burden or health gap, disability, rather than health benefit) annually by 2030. Based on the same assumptions, Dr. Constenla indicated that countries outside the Americas would require USD 6.4 billion to fund a new dengue vaccine. Within the region fiscal resources up to USD 1 billion would be needed.
The importance of adopting financing strategies that ensure the availability of sufficient funds beyond the first few years of vaccine purchase and include the total costs of increasing access to vaccines for entire populations (maintaining the cold-chain, remuneration for health workers, transportation of vaccines in a timely manner, etc.) was also stressed by Dr. Constenla. At the regional and global levels, outputs from the dengue vaccine integrated model could be used to develop guidelines for vaccine use, to anticipate demand, and to secure appropriate financing.

Q & A session

In this final Q & A session of the day experts responded to the optimistic assumptions included in the forecasts made regarding vaccine cost-effectiveness. Some experts noted that even supposing tetravalent protection of 70 percent, it will take 10 years to reduce dengue incidence by 50 percent. Dr. Schmidt wondered how any elected official could survive such a scenario (spending significant amounts of money without instant results) given the political sensitivity surrounding dengue and continuously evolving political environments. According to experts, the question of political feasibility highlighted the importance of health systems strengthening as a component of integrated dengue management, as this would provide concrete results more quickly than solely vaccine introduction. Experts noted that it is much more politically palatable to introduce a vaccine than to strengthen health systems, and used the example of Argentina to illustrate the need for both. Other experts brought up the communication issues between the MoH and MoF in most countries, observing that the two ministries often don’t express themselves in similar terms, inhibiting cooperation. This, experts expressed, is an area where multilateral organizations could prove to be very helpful in generating open dialogue between countries and these organizations.

Another common concern expressed during this session was the need for transparency on the part of manufacturers regarding the price of a potential dengue vaccine, especially considering its implications for the cost-effectiveness of the vaccine. The importance of maintaining price transparency throughout the introduction process was underscored by participants, especially given the impact that the price of the first dengue vaccine will have on future demand and overall vaccine uptake.

Some experts commented on dengue management as a comprehensive concept and emphasized that all aspects of control and prevention must be strengthened, not just vaccines. Experts underscored the need to generate a very simple model for countries to start analysing these programs with local level data, since it is difficult to ensure accuracy with extrapolated data. The example of ProVac’s UniVac model was used as a tool that may help ensure country level specificity using local data in an integrated health systems approach.
Additional comments indicated that current government strategies for purchasing and assuring access to recommended vaccines have not addressed the relationship between the financing of vaccine purchases and the stability of the global and regional vaccine supply. Experts agreed that financial incentives are necessary to protect the existing supply of vaccine products, as well as to encourage the development of new vaccine products. In addition, it was mentioned that the vaccine recommendation process does not adequately incorporate consideration of a vaccine’s price and societal benefits. More efforts should be made to ensure improvement in this area.

The proceedings for Day 1 of the workshop ended with closing remarks by Prof. Peter Figueroa, who provided a synopsis of the day’s discussions. This included:

- A discussion of Pan-Americanism which seeks to create, encourage and organize relationships, associations and cooperation between the countries in the region in common interests;
- Lessons learned from the introduction of other vaccines in the Americas, especially the impact of the lag between vaccine introduction in countries of the region;
- The key epidemiological issue in assessing disease burden of the amount of underreporting of dengue cases, exacerbated by the fact that 75% of individuals are asymptomatic;
- PAHO’s general mandate to improve surveillance, clinical management, and vector control as a part of integrated dengue management;
- The importance of using an expansion factor on an individual country basis;
- The low level of impact and relative effectiveness associated with vector control;
- Country level perspectives on the part of Brazil and Mexico to provide insight into the activities of two immunization vanguards in the region;
- Manufacturer updates on the status of vaccine development, with the earliest licensure date estimated to be 2017;
- The challenges countries in the region face in introducing a dengue vaccine in an equitable and timely manner; and
- The potential economic impact of new vaccine introduction for dengue.

“There’s clearly a lot more work to be done in the preparation for dengue vaccine introduction going forward.”

-- Prof. Figueroa from University of West Indies
Workshop - Day 2

The second day of the workshop began with opening remarks and a review of the presentations by the moderator, Dr. John Andrus. A key conclusion of the first day’s deliberations, that the overall financing of health systems, not solely immunization financing, will be critical to dengue prevention and control, was highlighted. Much of the discussion on day two, which was guided by several strategic questions, pertains to this topic of broader dengue management (and health systems) financing strategies. The following pages summarize these discussions.

Part III: What will it take to finance dengue vaccine in the Americas?

To address this question, lessons learned from financing the introduction of new vaccines in individual countries of the region were highlighted.

Financing vaccines in Mexico

*Speaker: Dr. Jesus Felipe Gonzalez, Ministry of Health in Mexico*

The first presentation on day two was focused on Mexico’s experience financing new vaccines. Dr. Gonzalez began by mentioning the key factors that Mexico considers prior to vaccine introduction: type of intervention (universal, targeted, etc.), vaccination schedule, efficacy, legal and regulatory aspects, financial support, overall costs (treatment, introduction, etc.) and burden of disease.

The role of technical experts in testing a new vaccine before introduction to determine the potential for adverse effects was stressed by Dr. Gonzalez. Vaccine introduction in Mexico begins with a committee of technical experts who are responsible for making an official recommendation on a new vaccine to the national immunization council. The council then takes a vote and if introduction is approved the National Center of Health for Children and Adolescents (CeNSIA) is notified of impending implementation (Figure 8).

According to Dr. Gonzalez, fundamental sources of financing for vaccine introduction include taxation and the social security and social protection through health programs. Taxation, in particular, plays a large role in providing funding for vaccines. This financing scheme is unusual for the Americas, where taxation is generally not a politically viable means of financing.

Rotavirus vaccine introduction in Mexico in 2006 was used to illustrate the vaccine approval process. A unique aspect in Mexico’s introduction of the vaccine was their targeting of the highest risk groups in the country first, rather than aiming for universal coverage.
Dr. Gonzalez concluded by emphasizing the strength of Mexico’s immunization program, especially with regard to its surveillance system capacity, and the role that taxes play as the program’s principal form of funding. The country’s experience with rotavirus introduction was addressed further by Dr. Tapia, who brought up the impact of cost benefit studies on justifying vaccine introduction and the role of Mexico’s surveillance system in generating quality evidence for these studies. Applying the targeted method utilized by Mexico in other endemic countries in the region was mentioned as a potential strategy for dengue vaccine introduction. Dr. Tapia noted that a targeted introduction provides additional benefits in terms of the useful experience gained in handling the vaccine and administering it on a smaller scale before universal introduction. Hence, this targeted introduction is not just a valuable financial strategy but also beneficial in that all of the training, cold chain, etc. is prepared by the time universal introduction of the vaccine is applied.

“The introduction of the rotavirus vaccine was a very academic, evidence based, decision, with the analysis done largely independent of the Ministry of Health. The expert committee was really the crucial part.”

-- Dr. Gonzalez from the MoH in Mexico

Following Dr. Gonzalez’s presentation there was a brief period of discussion. The first point brought up was the ability of Mexico to piggyback off the price previously negotiated by Brazil.
for a rotavirus vaccine. Experts agreed that negotiating on a large scale is always a preferable method of procurement, and countries should cooperate to achieve this.

This segued into a conversation on the unique position of Brazil in the region, in terms of vaccine production. In addition to possessing specific legislation guaranteeing a budget for vaccines, Brazil also has the potential to produce their own vaccines, and acts largely independently of other countries in the region regarding procurement.

Experts agreed that this level of independence is highly beneficial for Brazil, but can come at a cost to other countries when technology sharing is constrained by national use. Dr. Domingues noted that efforts have been made on the part of Brazil to free up this constraint, using the example of vaccine donations to Haiti. The government of Brazil currently has a cooperation agreement with Haiti whereby epidemiologic outbreak equipment as well as BCG, MMR, DTP, oral polio, and rabies vaccines are donated to Haiti. Brazil has also supported the strengthening of Haiti’s cold chain system, and hired four professional teams to help the Haitian MoH organize immunization and surveillance activities. Haiti assists these activities by making an annual report of their vaccine needs, with Brazil donating based on their budgeting and supply capacity. The willingness of Brazil to donate vaccines and resources to Haiti is a prime example of the Pan-American spirit that pervades in countries of the region.

**Financing strategies used in the Americas for other vaccines**

*Speaker: Dr. Jon Andrus, PAHO*

Dr. Andrus began his presentation by describing the two purchasing mechanisms available through PAHO’s Revolving Fund. The first of these mechanisms is the 60-day rule, which is similar to a credit card in that it contains a certain amount that countries can draw upon, with the requirement that this drawdown be repaid within 60 days. This mechanism is currently used by 32 countries in the region and can help mobilize the resources needed for introduction in countries that may not have adequate financial resources immediately available. The other mechanism discussed is a pre-payment option, available for countries that are able to pay for vaccine purchases prior to delivery. The 3.5% interest charged by PAHO for both types of loans is credited back to the fund, allowing it to expand its capital/loan capacity over time (Figure 9).
The next topics Dr. Andrus covered were the importance of explicit legislation in securing vaccine funding and the immense variability in the quality of this legislation throughout the region. Dr. Andrus indicated that there is room for improvement in this area of work and the implementation of such legislation will require long-term vision on the part of policy makers. He asserted that the best vaccine laws ensure a line item in the budget and include an operational component for strengthening the authority of technical advisory groups. According to Dr. Andrus, 26 countries in the region currently have vaccine laws. Implementation in other countries will require discussion, mobilization, and consensus. PAHO experts stationed in country have greatly facilitated this process. Participants noted that vaccine legislation is an area where there is clearly room for more work and discussion, potentially using the convening power of PAHO.

The presentation concluded with Dr. Tapia bringing up useful lessons from Mexico’s vaccine legislation experience, where there was sufficient fiscal space, but no legal obligation, to introduce the vaccine. In this instance the resources of the Mexican Society of Public Health were used to draft legislation. Going forward Mexico’s experience could serve as a useful example to countries outside the region looking to secure vaccine financing, particularly in Africa and Asia. Participants expressed significant interest in the possibility of organizing a forum where such lessons could be presented and discussed.
Strategy session I - Recommendations of financing options for dengue vaccine

The first portion of the second day’s strategic session focuses on key strategic questions that will lead to recommendations of financing options for dengue vaccine.

*What are specific financing strategies that are suited to specific countries and the region?*

**Country level strategies**

Participants were quick to mention the importance of establishing immunization financing laws in countries to ensure that immunization programs are properly financed. This measure would address a fundamental problem facing many countries in the region, which is a lack of additional room in the fiscal budget to finance new vaccines.

In 1980, only two countries in the region had established immunization laws. By 2009, 26 countries had written some form of immunization financing legislation, and countries were financing 99% of their routine immunization costs. Key aspects of immunization financing laws were highlighted, including: financial (existence of a budget line item for the purchase of vaccines and for the EPI program, existence of a mechanism for the purchase of vaccines, and tax exemption for the purchase of vaccines); declaratory (universal vaccination free of charge, vaccination as a public good guaranteed by the state); and operative (penalties for failure to vaccinate and the existence of the EPI, a national vaccination framework, and a National Vaccination Advisory Committee) components. Two countries in the region with strong immunization financing laws, which could serve as a model for others, are El Salvador and Bolivia. El Salvador, in particular, benefitted from having a MoH that advocated strongly for legislative action. Brazil also has a detailed legislative clause guaranteeing a budget for vaccines.

Experts agreed that explicit laws might not always be necessary. The example of many Caribbean countries that use other innovative methods to ensure coverage (i.e. mandatory vaccination for school entry) was presented to illustrate this point. In addition, experts indicated that while vaccine legislation is important, the presence of a separate line item in the budget is probably

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“A lot of smaller countries have serious problems with finding fiscal space in the budget for vaccine introduction, so it is important that there is specific legislation that protects access to vaccination programs.”

- Dr. Roberto Tapia from Carlos Slim Institute

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Protecting Health, Saving Lives—*Millions at a Time*
more important to ensure immunization programs are properly financed. Experts added that it is important to develop strategies on an individual country or sub-regional basis. In a region with an established history of vaccination, such as the Caribbean, focusing efforts on legislation may not be the best use of resources.

The idea of amending vaccine legislation is not necessarily new. The challenge facing most countries in the region is the ever-changing political climate. Most experts felt that one may not always have the opportunity to wait until the next election to suggest such changes. The question of what countries would need to do specifically to improve immunization legislation was raised by various experts, but not directly addressed in the context of this workshop, and remains unanswered.

Another important point raised during this strategy session was the option for some countries to pursue technology transfers. This applies to countries like Brazil who have the capacity to produce the vaccine internally. These transfers allow a country to manufacture the vaccine and, depending on the terms of the contract, potentially export the vaccine to other countries in the region. The NIH dengue vaccine prototype transfer to Butantan in Brazil is an example where such a mechanism can successfully hasten the development and introduction of a vaccine.

Public-private partnerships were also mentioned as a possible strategy that could be employed throughout the region. These partnerships might take a variety of forms. For instance, in some countries private entities are responsible for the application, but not supply, of vaccines. In other countries, such as Trinidad and Tobago, the private sector played an active role in the introduction of the HPV vaccine. The prospect of holding private sector entities that bear partial responsibility for the spread of dengue (i.e. mining companies) liable by requiring that they supply funds commensurate with the costs of their activities was proposed as another method of obtaining additional financing.

On an individual level it is also important that countries communicate the importance and need for vaccines to their respective populations. Participants noted that the message of vaccine cost-effectiveness is not always communicated well. This is an area for improvement. If the population at an individual level understands the benefits of vaccination they are more likely to put additional pressure on politicians to introduce new vaccines.

The need to develop individual country strategies, rather than apply a general introduction strategy for the entire region, was acknowledged by most participants in the workshop. A basic reason for this is that a country’s ability to introduce a vaccine is not solely a function of economic size and growth, but also the relative epidemiologic burden of dengue. Certain
strategies may also be more relevant to specific groups of countries (e.g. Mesoamerica region, Southern cone region, Caribbean region, GAVI-eligible countries) rather than the region as a whole, and the need to create standardized definitions for sub-regions was emphasized.

**Regional strategies**

A potential regional financing strategy would be for countries to engage in coordinated negotiations to purchase dengue diagnostic tools and reagents, the price and quality of which are currently an impediment to surveillance strengthening. The purchasing of reagents by the Revolving Fund was mentioned as a possible way to promote affordable and homogenous diagnoses across countries, allowing for easier disease burden comparison as well.

**How can existing mechanisms be leveraged to ensure timely and equitable introduction of dengue vaccine in the region?**

A major topic spanning both days of the workshop that was discussed in more detail during this part of the session was the importance of focusing on the financing and strengthening of a country’s health system in addition to vaccine procurement. Leveraging the procurement capability and experience of PAHO’s Revolving Fund with the financial capacity of multilateral organizations such as The World Bank and the Inter-American Development Bank (IDB) to make low rate loans would provide a way to realize both goals. Participants expressed great interest in, and agreement on the viability of, this as a possible tool for vaccine financing and health systems financing as a whole.

The PAHO Managed Strategic and Global Funds were identified as potential entry points for such a strategy. Two countries in the region (i.e. El Salvador and Colombia) currently have a loan agreement with the World Bank. PAHO is not directly involved in these negotiations.

When considering using multilateral loans as a financing mechanism the need for countries to make their intention to distribute the money into the Revolving Fund explicit was emphasized. This will be important not only in ensuring that the funding goes towards dengue control and prevention, but also in maintaining the specificity of the Revolving Fund. The feasibility of such a scheme will vary on a country-by-country basis, as this typically can only be done through legal pathways.

A caveat to this financing method is the stipulation that low interest rate loans have to be paid at some point. It was widely agreed that these loans are not a sustainable means of funding long-term immunization programs. The problem, therefore, would not necessarily be the
collaboration between participating organizations, but the ability of countries to repay/maintain loan payments.

Other existing mechanisms mentioned include employing the financing capacity of local governments and social security programs. Local governments are often held accountable for the provision of vaccines. This, combined with the intense political pressure associated with dengue, could induce local governments in high incidence areas to introduce the vaccine separately from the national government. Mexico City and Bogota both successfully introduced vaccines on a smaller scale prior to countrywide rollout.

The experiences of Brazil and Mexico were brought up to highlight the importance of preserving social security systems as a potential procurement mechanism for vaccines. While conference members acknowledged the role that such programs play, they also questioned their viability as a financing tool, particularly considering the already significant expense and shifting demographic profile of many countries in the region.

Are there other innovative financing strategies that can be applied in the context of dengue vaccines in countries of the region?

This session focused on innovative strategies that could be used to help finance the uptake of a dengue vaccine. Two financing strategies were discussed in this context: performance-based financing model and domestic taxation.

Dr. Tapia, from the Carlos Slim Health Institute, provided an example of an innovative performance-based financing model. The incorporation of funding for infrastructure enhancement, critical to vaccine delivery and improved vaccine coverage, is particularly unique. There are three primary aims of this model: support the equitable introduction of efficacious vaccines, strengthen vaccine infrastructure, and develop the human resource capacity of countries to deliver vaccines. In this model resources are frontloaded to accelerate the introduction of new vaccines based on a shared referential vaccine schedule. Infrastructure funding is also frontloaded to improve cold chain capabilities (e.g. maintenance, distribution, management, logistics) and develop human resource capacity in vaccine delivery and management. The model is based on direct vaccine purchase via a pooled mechanism such as PAHO’s Revolving Fund.

In Figure 10 resources are frontloaded in year one with an additional non-repayable bonus (10 percent of total investment) provided for infrastructure. For the first five years countries are not required to make any loan payments, allowing them to find fiscal space in the budget to do so.
In the second year the country begins progressively self-financing vaccine purchases, with complete financial independence at year five. Another non-repayable bonus of 10 percent may be awarded at year six, conditional upon the country’s performance (coverage rates, self-financing, etc.). The country would also begin incrementally repaying their debt at this time (at 0 percent or low interest rate). At the end of loan repayment the country would be eligible for a final 10 percent bonus with criteria similar to that for the bonus in year 6 (coverage rates, self-financing, etc.). The five-year time period given to countries to repay their loan illustrates a responsible way that countries could finance vaccine introduction, even if they don’t necessarily have the fiscal resources to do so immediately.

**Figure 10: Performance based model for dengue vaccine introduction**

![Performance based model for dengue vaccine introduction](image)

Courtesy of Dr. Tapia, July 22-23 2013

Dr. Tapia mentioned that the timeline could be adjusted depending on the relative ability of countries to pay back the loan. Experts agreed that the model would be attractive from a cost effectiveness standpoint because the deaths and illness averted by the time that repayment began would outweigh the cost. Participants also felt that it would be useful to present this model to organizations such as The World Bank and the IDB for feedback regarding feasibility.

This model has already been applied successfully in the construction of roads and schools and for health systems strengthening. There are a few countries that have used this performance-based model for health systems strengthening. Haiti is the first low-income country in which health service providers (national nongovernmental organizations) were contracted and remunerated according to their performance (which was measured by the attainment of some coverage rates) (Eichler et al 2007). This model is also being developed in several African countries. Rwanda is one of these countries. The Rwandan experience has inspired neighbouring countries like Burundi and the Democratic Republic of the Congo to apply this model in their countries (Meessen et al 2011). Today, more than 20 countries are in the process of introducing...
or scaling up performance-based financing in Africa. Performance-based financing also fits into the Millennium Development Goals aid paradigm and global efforts for rapid progress on a few key indicators.

Another example of a financing strategy that can be applied in the context of dengue vaccines in countries of the region is domestic taxation. This model consists of taxes designed to raise new funds for health, either by increasing an existing tax, or imposing a new tax on the purchase or use of specific goods or services. Common options for raising additional funds include: broad consumption taxes (e.g. VAT/GST); taxes on specific products, especially those with harmful health effects like tobacco or alcohol (‘sin taxes’); and sector-specific taxes generally levied on profitable sectors/larger corporations, especially in the financial, resource and telecommunications sectors. The funds raised from domestic taxes can go into consolidated government revenues, or be ‘hypothesized’ (i.e. earmarked) for a specific cause, such as immunization campaigns or vaccine financing.

There are many examples where domestic taxation schemes have been successfully used to raise new funds for a specific purpose, including in health (WHO, 2010). These are listed below:

**VAT schemes (additional levy on top of existing VAT rate)**

- Chile: The country uses 1% of its VAT to fund health (total rate 19%).
- Bolivia: One of the main sources of funding for the Universal Mother and Child Insurance (SUMI) in Bolivia are Municipal tax transfer payments (CTM).
- Ecuador: The National Maternity and Child Insurance (SNMI) implemented in Ecuador in 2000 through the Free Maternity and Child Care Law mandates that 3% of special consumption tax (ICE) is to be used to finance SNMI. Funds for SNMI have more than doubled between 1995 and 2005 from nearly US$8 million to US$20 million due solely to the allocation of this special tax.

**Earmarked tobacco and alcohol taxes**

- Several countries within the region are raising funds for tobacco prevention and control activities through taxation of tobacco products. These “tobacco taxes” have been implemented successfully in Costa Rica, Ecuador, and Panama.
- Costa Rica raised taxes by 6.5% in early 2012 to fund tobacco control and other health promotion activities.
- Similarly, Panama doubled its tax rate on tobacco products and assigned the resulting “tax funds” to the National Cancer Institute and the Ministry of Health for the prevention and treatment of diseases attributable to tobacco products. Additionally, almost 20% of these...
funds were earmarked for the National Customs Authority (ANA) to fund its activities on the prevention of illicit trade of tobacco.

- Ecuador – which is considered a leader in implementing tobacco taxes – also adopted a universal tax on all tobacco products.

Other taxes
- Argentina: has instituted a levy on mobile phone subscriptions to fund elite sport.

Although taxation is undoubtedly an effective fundraising method, there are a number of reasons why this approach may not be successful at a regional level. Historically taxes in the region have been extremely regressive and politically unpopular, a sentiment echoed by the country level representatives at the workshop. Participants also noted the difficulty of earmarking funds for a project as specific as vaccine coverage without an explicit line item in the budget, since taxes generally go toward the national budget and not individual items. Table 5 lists the advantages and disadvantages of domestic taxation.

Table 5: Advantages and disadvantages of domestic taxation

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>High revenue</td>
<td>Politically unpopular (particularly during recession/slowdown)</td>
</tr>
<tr>
<td>High predictability</td>
<td>Require legislative change</td>
</tr>
<tr>
<td>Low transaction costs</td>
<td>The tax revenues can be difficult to ring-fence to vaccine purchase – may be used for other government priorities.</td>
</tr>
<tr>
<td>Highly sustainable</td>
<td>Consumer-based taxes hit the poorest consumers the hardest</td>
</tr>
<tr>
<td>Knock-on health gains from “sin taxes” on alcohol/cigarettes</td>
<td>Sector-specific taxes may dis-incentivise business investment in emerging economies</td>
</tr>
<tr>
<td></td>
<td>Some countries in the Americas already have a specific health care tax</td>
</tr>
</tbody>
</table>
Key financing recommendations

- The creation of an integrated dengue fund that would combine existing pooled procurement mechanisms (e.g. PAHO, UNICEF) with financing mechanisms (e.g. low interest multilateral loans of the World Bank, IDB) to ensure that dengue control and prevention strategies are properly financed. The proposed plan consists of incorporating existing financing mechanisms with existing procurement mechanisms resulting in a combined procurement-financing mechanism. The plan comprises strengthening of the overall dengue control and prevention system that entails a robust dengue surveillance system, vector control system, disease management, immunization financing laws, infrastructure (e.g. cold chain), and regulatory capacity.

- The creation of a performance-based financing mechanism for vaccine introduction where resources and infrastructure funding are frontloaded to accelerate the introduction of new vaccines. In this model resources are frontloaded to accelerate the introduction of new vaccines based on a shared referential vaccine schedule. Infrastructure funding is also frontloaded to improve cold chain capabilities (maintenance, distribution, management, and logistics) and develop human resource capacity in vaccine delivery and management.

- (Only relevant to specific countries) The creation of additional funds for immunization financing through the growth of existing domestic taxes or the levy of new taxes on the purchase or use of specific goods or services or the preservation of social security systems. Examples of domestic taxes include taxes on specific products or sector-specific taxes. The funds raised from domestic taxes can go into consolidated government revenues, or be earmarked for a specific cause, such as immunization campaigns or vaccine financing.
Strategy session II: Key actions that can advance recommendations

The second strategy session on day two focused on translating the broad recommendations outlined in session one into actionable next steps that could be pursued after the workshop. An attempt was also made to identify potential roles that key actors would play in this process.

Specific areas that require government attention

One area identified by participants where government attention could aid vaccine introduction and health system improvement is the strengthening of national regulatory agencies (NRAs). This could be done by increasing the authority of agencies regarding production and their capacity to receive and analyse information on vaccine performance. Brazil’s regulatory agency, the National Health Surveillance Agency (ANVISA), illustrates how a strong NRA can successfully assist in the rapid and equitable implementation of vaccines. Other countries currently in the process of adding similar capacity to their NRAs include Colombia, Argentina, and Mexico. The need for these agencies to gain WHO recognition was stressed, particularly in countries with the capacity to produce vaccines, as this recognition can greatly accelerate the introduction process. Participants also emphasized the need for these agencies to be open and transparent, particularly in negotiations.

Another area where government intervention could facilitate vaccine introduction would be in securing vaccine funding through legal channels (i.e. in the form of a budgetary line item) as mentioned in earlier sessions. Governments could also play a role in funding disease cost and cost effectiveness studies, which are important, especially when determining what kind of vaccine rollout to pursue.

The involvement of MoF will be central in ensuring that a dengue vaccine is financed and introduced in a timely and equitable manner. MoFs can ensure that a line item is specifically set aside in the budget for vaccine procurement and administration. The relationship between MoH and MoF is particularly important because the MoH is critical in relaying the importance of vaccine funding to the MoF through generation of evidence, and is often the only organization responsible for doing so. Without effective action on the part of MoH there will be little incentive on the part of MoF to focus on dengue. Cooperation amongst MoH in individual countries in the development of a homogenous surveillance platform will be important as well. Using the same epidemiologic indicators would help facilitate comparison of disease burden between these countries.
Potential roles for international and regional organizations and players

As mentioned previously, one of the main developments to come out of the workshop was the interest on the part of many participants in developing financing strategies in collaboration with multilateral organizations. This collaboration will be especially important given the renewed emphasis many representatives placed on strengthening health systems overall as a means of dengue control.

Recent meetings between the director of PAHO and the heads of the World Bank and IDB (on July 15th and July 25th respectively) to discuss potential projects indicate that progress is being made in opening communication channels between these organizations. Although the focus of these talks was primarily on non-communicable diseases, the highly political nature of dengue in the region could make it a subject of future meetings.

Workshop participants also emphasized the need for increased funding from grant-making foundations, such as the Bill and Melinda Gates Foundation. This need was reinforced by calls for a strengthening of communication channels amongst various stakeholders to better convey the need for dengue research funding.

Next steps to accomplish recommendations

The day two discussions brought up a number of steps to accomplish these recommendations.

Key steps to advance these options

- Hold a follow-up regional meeting next year, where the focus will be health systems financing with a focus on refining the expert recommendations on an integrated financing strategy;
- Establish a working group at the follow-up workshop with expertise in health economics, financing, public health and public policy, and business to continue driving the process forward, in parallel to a forum to discuss and prioritize financing vaccine introduction;
- Through the regional meeting, continue to engage Ministers of Finance, vaccine manufacturers, public and private providers, business groups, representatives from bilateral organizations and other key stakeholders in discussions relevant to health systems (and vaccine) financing to address cross-cutting issues and provide additional input in the follow-up regional meeting; and
- Begin a process of extensive consultation with Ministers of Finance and Ministers of Health to determine their needs and interest – this could be done via regional consultations or on a country basis before the regional meeting is held.
Additional steps include:

- Provide in-country scientific and technical experts to facilitate discussion and eventually the adoption of new vaccine laws;
- Continue supporting technology transfers to emerging markets;
- Make overtures to multilateral organizations in order to determine their willingness to offer low-rate loans to countries that carry the risk of inability to repay/maintain payments;
- Refine current disease burden and cost effectiveness models/studies to illustrate the benefits of dengue vaccine introduction;
- Strengthen surveillance systems by developing and implementing specific guidelines and a homogenous platform;
- Strengthen national regulatory authorities, especially through WHO recognition;
- Increase and improve communication, especially to development partners, such as the Bill and Melinda Gates Foundation, conveying the need for additional funding for dengue research;
- Improve communication internally, specifically between MoH and MoF, as any financing scheme will require coordination between both entities;
- Establish a basic science research agenda (primarily addressing the need for additional research on epidemiology, serotype, and age distribution) for dengue;
- Set up networks of diagnostic labs regionally to assess disease burden;
- Improve communication and coordination between key actors using research as a platform to create a more concrete network of experts/country representatives;
- Encourage vaccine manufacturers to continue their work on disease burden estimates and surveillance; and
- Encourage the sharing of technology and resources through the continued promotion of regional solidarity in the form of Pan Americanism.

Feedback from the World Bank and IDB will be critical in determining the feasibility of many of the financing schemes suggested at this workshop. It would be extremely useful for these organizations to open their portfolio to financing schemes that involve health systems loans in conjunction with vaccine procurement, as this is not currently the case.

Strengthening overall regional, in addition to national, surveillance systems is another critical step in enabling countries to determine disease burden and be in a favourable position for rolling out a new dengue vaccine. Related areas requiring attention are the establishment of a more accurate/specific clinical definition of dengue, the improvement of dengue diagnostic techniques, and the creation of a common research agenda for the region (serological, epidemiological, and age distribution studies).
Improving surveillance systems will address the extreme variability in the disease burden of dengue across the region. It is essential that accurate epidemiological data is available to determine the burden of dengue in individual countries and the region. A standardized research agenda used throughout the region would be a critical element for accurately determining this burden. Research data can help identify which age strata/populations are most affected by dengue, with subsequent vaccination strategies being targeted towards these groups. Using this data would provide the additional benefit of making vaccine introduction more affordable and providing training for health workers prior to universal roll out. Accurately quantifying disease burden is also critical to performing cost effectiveness studies, which play an important role in defining the price that a country is able to pay and communicating this information to manufacturers. The establishment of this price is fundamental in negotiations, especially on an individual country level.

Instituting explicit and specific region-wide guidelines for surveillance strengthening will be fundamental to improving evidence generation. For example, a sentinel approach nested within a national surveillance system with age-specific and regional data collection would be very powerful. Unfortunately many governments do not have access to the technical guidance needed to implement this. The prolonged time required for setting up epidemiological surveillance systems and gathering evidence make it critical that countries cooperate to share information and perform studies. An example of information sharing would be cost effectiveness studies conducted at a regional level by extrapolating information from dengue endemic countries that do have strong surveillance systems. Participants cautioned, however, that it is important to remain cognizant of the sensitive nature of surveillance strengthening. Much of this sensitivity is attributable to the fact that such activities (e.g. improving research, creating laboratory networks, etc.) are often funded by manufacturers and this support is usually contingent on country purchases of specific vaccines. Instances where manufacturers supported evidence generation in the region include Sanofi Pasteur’s funding for influenza, dengue, meningococcal disease, and pertussis surveillance and Merck’s rotavirus vaccine donations to Nicaragua to demonstrate feasibility of introduction even in the poorest countries. Getting manufacturers to continue to participate in these types of activities, possibility out of corporate responsibility, could be an additional source of funding/data.

Improved communication and coordination between key actors using research as a platform to create a more concrete network of experts/country representatives will be another important step in dengue prevention and control. This could take the form of new partnerships, such as the Partnership for Dengue Control (PDC) whose mission is to promote the development and implementation of innovative, integrated and synergetic approaches in the prevention and control of dengue, while maintaining transparency through independence. Annual Dengue
Prevention Board Meetings or periodic dengue-related meetings amongst experts would help promote this as well. Participants noted that historically the focus of these meetings has not been on applied public health strategies, meaning that not all key stakeholders have been represented. Improved communication would similarly help experts review and standardize the basic science research agenda. Better communication strategies will be important in building support at a local level for the introduction of a dengue vaccine. MoH will need to reinforce existing support by effectively communicating the value of a dengue vaccine to both the population, resulting in political pressure for implementation, and to the MoF, resulting in secure funding.

Further research into the social and cultural context of dengue and its effect on disease transmission and the potential impact of technology transfers could provide additional insight into developing an integrated dengue management plan. Related to this is the need to define common regions within the Americas, as it is unlikely that accurate disease burden and cost effectiveness studies will be conducted in each individual country.

Conducting serosurveys in specific countries would be another way to advance the recommendations made at the workshop. The extent to which the revolving fund can support reagent procurement will impact this and needs to be determined.

More economic analysis, possibly by experts at ProVac and DVI, will be needed to assess the impact of dengue vaccine introduction. Specific outputs that DVI will focus on to help meet these goals include new manufacturer and country level surveys, an updated Strategic Demand Forecast incorporating multiple suppliers, a potential follow up workshop, a published manuscript, the continued support of regulatory agencies, and possibly the reconvening of a working group comprised of initial workshop participants. Encouraging vaccine manufacturers to continue their work on disease burden estimates and surveillance is another step that will be important in meeting the aims of the workshop. Participants agreed that a contingency plan would need to be developed in the event that the front running Sanofi Pasteur vaccine suffers another setback, and/or other manufacturers experience similar phase II clinical trial results.

Conclusions

There were several discussions during the two-day workshop. Key points from these talks include:

- The need for a wholly integrated approach to dengue prevention and control, comprised of robust health systems, vector control, disease management, and vaccine introduction;
The need to integrate financing strategies that extend beyond just vaccine procurement to health systems strengthening;

The fundamental role that communication and collaboration between countries, development partners and public health agencies will play in the development of financing strategies for region wide introduction;

The incorporation of the vaccine purchasing power of the Revolving Fund with the capacity of multilateral organizations such as the World Bank or International Development Bank (IDB) to make low interest loans that could serve as a powerful financial tool for overall health systems strengthening;

The need for overall health systems strengthening that will include surveillance, immunization financing laws, infrastructure (e.g. cold chain), and regulatory strengthening, to guarantee that immunization programs are properly financed;

The need to explore the potential role that PAHO’s and UNICEF’s pooled procurement mechanisms can play in the purchasing of homogenous reagents and diagnostic tools to promote standardized and accurate disease burden estimates;

The impact of Pan-Americanism in promoting regional solidarity and cooperation in all aspects of dengue prevention and control;

The need to improve the dengue evidence base and establish a common research agenda, which will be largely reliant on increased recognition from non-governmental organizations (NGOs) and multilateral organizations in the form of funding and research;

The relative ability of countries to divert funds from existing government budgets;

The need for further research into the prospect of using immunization financing legislation as a method of securing vaccine financing;

The political feasibility of tax increases at a regional or domestic level to provide funding;

The need for more accurate disease burden and cost estimates, especially considering the unanimous agreement on the part of experts regarding the considerable degree of underreporting in dengue incidence rates and uncertainty surrounding the cost of dengue;

The need to explore the potential application of financing strategies that have been used effectively on an individual country basis to the rest of the region;

The need to make overtures to multilateral organizations to determine their willingness to offer low rate loans to countries that carry the risk of inability to repay or maintain payments; and

Vaccine donations from countries with excess capacity, technology transfers, domestic public-private partnerships, and vaccine-specific legislation are examples of effective financing methods that could be expanded to other countries in the region.
The dialogue on both days of the workshop provided important insight into vaccine financing in the Americas. One of the most significant, and interesting, developments was the general consensus amongst participants that securing funding for health systems strengthening will be just as important as vaccine procurement in the introduction of a dengue vaccine. This will be especially pertinent going forward, since vaccine financing has thus far been predominantly focused on financing vaccine procurement. The need for an integrated approach has been largely unaddressed in the literature and is an area that requires additional exploration. The issue of maintaining existing vector and disease management programs as a part of an integrated health systems approach was also brought to light as a result of this workshop.

Further contributions to the topic area were made in the evolution of the idea of leveraging the vaccine purchasing power of the Revolving Fund with the capacity of a multilateral organization such as the World Bank and IDB to make low interest loans for overall health systems strengthening.

The importance of surveillance systems, and potential methods for improvement, was also brought up repeatedly as a health systems component that will play a critical role in vaccine introduction. Related to this was the need for more accurate disease burden and cost estimates, especially considering the general consensus amongst experts that dengue incidence rates were severely underreported. The potential for extrapolating individual country level financing strategies that have proven successful to the rest of the region was also explored.

Vaccine donations from countries with excess capacity, public private partnerships, and vaccine specific legislation were all used as examples by individual countries of effective financing methods that could be expanded to other countries in the region.

The overarching influence of Pan-Americanism regarding the development of a dengue financing strategy was evident throughout the workshop. This emphasis on preserving regional solidarity was a common sentiment expressed on both days of the workshop, and was reinforced through participant’s calls for cooperation and sharing regarding many aspects (technology, research, resources) of vaccine introduction.

A final, and major, area of contribution from the workshop concerns the need for more dialogue on vaccine legislation and the most effective ways to use this as a method of securing vaccine financing. Participants on the second day of the workshop noted that this is an area where there is clearly room for more work, potentially utilizing the convening power of PAHO. The experience of Mexico in collaborating with public health entities to draft legislation guaranteeing vaccine access was mentioned as another area for future research, particularly regarding
applications outside the region (especially in Africa). These future areas of work illustrate the need for a forum where such lessons could be presented and discussed.

Current financing strategies for immunization have had substantial success, especially in improving immunization rates for young children. However, significant disparities remain in assuring access to recommended vaccines across geographic and demographic populations.

In sum, substantial increases can be expected to occur in public and private health expenditures as new vaccine products become available. Although these cost increases will be offset by the health and other social benefits associated with these advances in vaccine development, the growing costs of vaccines will be increasingly burdensome to all health sectors. Alternatives to current vaccine pricing and purchasing programs are required to sustain stable investment in the development of new vaccine products and attain their social benefits for all.
References


ANNEX 1. Pre-workshop survey to experts

PRE-WORKSHOP SURVEY

Developing Strategies for Meeting the Challenge of Equitable Vaccine Introduction in the Americas: With a focus on Dengue Vaccine Financing

Venue: Pan-American Health Organization (PAHO)
Date: July 22-23, 2013

Overview of the pre-workshop survey:
We are delighted that you are participating in the workshop hosted by the John Hopkins’ University’s International Vaccine Access Center (JHU’s IVAC), in collaboration with the International Vaccine Institute (IVI), the Sabin Vaccine Institute and the Pan-American Health Organization (PAHO), on financing for dengue vaccines. We prepared the survey attached to this document in order to solicit input from stakeholders. The motivation behind this survey was the desire to ensure that the financing strategies discussed on Day 2 (July 23) of the workshop would be in line with the main concerns and issues faced by decision makers in the region. In designing this survey we had anticipated that responses to our questionnaire would help identify key areas of concern/interest prior to the workshop and help us design strategy sessions that were focused and well developed.

Please note, the main purpose of this survey was to provide us with a quick landscape of the concerns and challenges in the region with respect to the future introduction of a dengue vaccine. We do not intend for the responses to this survey to be used for quantitative analysis or substantive research. Correspondingly, the areas of concern identified by respondents should not be taken as representative of the entire region or encompassing the entire gamut of potential challenges. This survey was meant only to guide the framework for the discussion sessions on Day 2, not to characterize regional issues with respect to dengue vaccine introduction in their entirety.

We recognize that the sample size of respondents is limited (total number of respondents = 6) and that we cannot make any inferences from these results. Additionally, responses are qualitative and not quantitative; respondents were not asked to rank answers or apply numerical values to answers. We hope to expand this work in the future and to bolster our questionnaire substantively.

Lastly, we would like to thank all those who answered our survey. Your responses provided us with valuable insight that allowed us to better facilitate productive discussions during the closed-door session on Day 2 of the workshop. We are therefore very appreciative for your assistance.

To view the original survey, please refer to Appendix 5. If you have questions or concerns regarding the survey, please contact Dr. Dagna Constenla at dconsten@jhsph.edu.
COMPILATION OF RESPONSES TO PRE-WORKSHOP SURVEY

Developing Strategies for Meeting the Challenge of Equitable Vaccine Introduction in the Americas: With a focus on Dengue Vaccine Financing

OBJECTIVE:
In preparation for the financing workshop focused on dengue vaccine introduction in the Americas, we prepared a pre-workshop survey (Appendix 1) to solicit input from key stakeholders attending the second day of the workshop. The impetus of this workshop is to identify a set of approaches to financing dengue vaccines in countries of the region and to develop an action plan that can advance these options in these countries.

Please note: the number of respondents is limited in number [total number of respondents = 5; countries represented: Brazil (1), Honduras (1), Mexico (2), and Regional expert (1)] and therefore no inferences should be drawn from the results. The main purpose of this survey is to develop guidelines to direct focused discussions on financing strategies.

RESULTS:
SECTION I. Challenges and opportunities for dengue vaccine introduction
In this section we wanted respondents to identify the key factors (both positive and negative) that influenced access to new vaccines in their respective countries. We were also interested in the solutions that countries had developed to address constraining (negative) factors.

A) Respondents identified the following constraining factors:
   1) Financing limitations:
      ○ Limited funding capacity.
      ○ Affordable pricing of the vaccine.
      ○ Lack of availability of financial capacity.

   2) Restrictions imposed by limited health systems capacities:
      ○ The challenge is to maintain high vaccines coverage, considering the large number of
        vaccines currently on the vaccination calendar. The limited abilities of the vaccination
        teams hinder the ability to maintain coverage rates.
      ○ Workforce training challenges: With every new vaccine introduction, vaccination teams
        need to be trained, number of professionals available for vaccination activities have to
        be identified, and new hires must be made when necessary. A sufficient workforce is
        key; programmatic errors are more often when the vaccination teams are not properly
        trained.

   3) Regulatory hurdles:
      ○ No specific details provided

   4) Insufficient evidence in support of the vaccine:
      ○ The lack of technical information related to the new vaccine (recommended schedules
        price per dose, presentation, etc.) can undermine support for the vaccine.
5) Lack of policy support:
   ○ A lack of support from policy makers for the prioritization of overall health prevention further challenges new vaccine adoption.

8) The factors listed below were identified as enabling new vaccine adoption:
   1) Prior experience with vaccine introduction:
      ○ Being early adopter with strong epidemiological information and very good infrastructure is a substantial advantage for successful new vaccine introduction.

   2) Technical capacity:
      a. A nationally recognized body – such as a National Vaccination Council – that provides recommendations to governing bodies, such as the Ministry of Health is crucial in providing the technical capacity required to inform decisions regarding new vaccine adoption.

   3) Countries’ ability to access sufficient products:
      a. A strong internal manufacturing capacity for vaccine production is key in ensuring sufficient quantities are available for public production.
      b. A decision-making process that takes into account regional and social inequalities further improves access to all citizens nationwide.

   4) Separate line item in budget:
      a. Sustainability: once a decision has been made to introduce a new vaccine, if a “budget law” of a country ensures the fiscal resources needed, it guarantees the sustainability of the national immunization program for the acquisition of all vaccines.
      b. Existence of a Vaccine Act: This also ensures the financing of EPI vaccines and sustainable supplies according to the national scheme.

5) Concerns related to equity issues:
   a. Ensuring equitable access: details vary by country, but the overarching idea that emerges is the importance of a decision making structure which ensure equitable access for all people.

6) Legitimacy/support from public:
   a. The acceptance and adherence of the population to the immunization activities is very important. Similarly, the support of scientific and medical societies that provide technical background and expertise to national immunization programs are key in ensuring wide support for the vaccine program.
   b. Demonstrated efficacy of the vaccine and the social acceptability of vaccination as a public policy further improves the chance that the vaccine will be adopted.
   c. Evidence of the burden of the disease and its costs further bolsters public support.
   d. Identification of the problem of dengue as a public health problem by decision makers and community builds a case for the need for a new vaccine.

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7) Features of the vaccine that make it affordable and effective play an important role, such as low cost of the vaccine, ease of vaccine administration, and evidence on the efficacy and safety of the vaccine.

II. The two main factors that were identified as solutions to the challenges posed by new vaccine introduction were:

i) Political commitment:
Not surprisingly, respondents identified a long tradition of prioritizing vaccine adoption as making their countries better suited to adopting a new dengue vaccine. Additionally, the compliance of vaccine producers with the standards requirements by national regulations to register a vaccine is also helpful in getting vaccines to the market.

ii) Efforts to gain support of national, regional, and international technical experts were mentioned as being extremely important in generating support for new vaccine adoption within government. Such support can be in the form of:
   a. Evidence generation for financial feasibility analysis
   b. Economic studies on cost-benefit studies
   c. Recommendations supporting vaccine adoption from PAHO/WHO
   d. Developing criteria analysis to document technical and programmatic feasibility

SECTION II: Recommendations of financing options for dengue vaccine
This portion of the questionnaire asked respondents to describe the financing strategies implemented by their country to introduce previous vaccines and discuss the possibility of applying the same strategies to dengue vaccine adoption.

When asked to identify previous strategies that have been successful in previous vaccine introductions, respondents mentioned the following conditions as having played a pivotal role:
1) Identifying explicit funding sources:
   a. Strengthening/ MODIFYING LAWS TO ENSURE THAT FINANCIAL SUPPORT FOR NEW AND EXISTING VACCINES.
   b. Existence of strong political support and commitment to immunization programs.
   c. Identifying explicit fixed and recurring costs associated with vaccine purchase and delivery
   d. Use of PAHO’s Revolving Fund
   e. Fiscal resources provided by the Ministry of Finance based on very strong data and benefit analysis.
   f. Mobilizing domestic financial resources for the acquisition and distribution of new vaccines, including the recurring costs of maintaining a supply chain.

2) Technical committees review need for vaccine, which allows decision makers to justify the need for resources through strong evidence generation based on analysis.

3) Advocacy within ministries of health and finance
   a. The creation of a multidisciplinary team on the topic related to new vaccine adoption.
   b. Discussing analysis for decision making related to vaccine introduction with national
advisory councils and other health authorities.

c. Strategic advocacy efforts targeting administrative authorities within Ministries of Health and Finance.

Survey respondents identified the following strategies as being potentially effective for dengue vaccine adoption:

1) Develop recommendations for dengue vaccine introduction through the establishment of expert groups or “dengue committees”:
   - Strong and very well presented recommendations from international multilateral organizations and expert technical groups addressing the technical, operational, and logistics aspects to organize the implementation of a new dengue vaccine according to the supply capacity of the public laboratories will be extremely useful.

2) Change/strengthen existing laws to ensure sufficient funding of new vaccines:

3) Include lessons learned from previous new vaccine introductions:
   - Previous experiences with other new vaccines can be applied to the introduction of dengue vaccine, since management has been successful, ensuring its sustainability.

4) Financing mechanisms:
   - Generation of a finance mechanism that could allow middle-income countries to accelerate vaccine purchasing (very poor countries can benefit from GAVI and developed countries have their own resources, but developing countries that are middle income with substantial disease burden do not currently have a mechanism in place).

5) Adopting evidence based strategies for introduction:
   - Setting priority areas with high endemicity and the most vulnerable groups (higher risk of getting sick or dying), similar to strategies already adopted with influenza vaccination and well accepted by the population.

6) Strengthen surveillance systems:
   - Strengthen epidemiological surveillance of dengue, to generate evidence.

7) Assimilate information on new vaccine into existing communication strategies for dengue prevention and control programs:
   - Provide pre-vaccine communication strategy to visualize the vaccine as an additional intervention for the prevention of disease.

SECTION III: Key actions that can advance these recommendations

The main focus of this section was to identify 2-3 areas/issues that country governments must focus on to ensure equitable introduction of dengue vaccine. Additionally, respondents were asked to discuss next steps/recommendations for dengue vaccine adoption.
The following actions/conditions were identified by respondents as being indispensable to promoting the adoption of a dengue vaccine:

1) Conduct financial feasibility analysis to address concerns related to sufficient funding and affordability:
   a. Identify the direct and indirect cost to the health system and households due to dengue.
   b. Ensure availability of sufficient fiscal resources; lack of funding is the main barrier to new vaccine introduction. If need be, mobilize financial resources.

2) Generate evidence to demonstrate need for a dengue vaccine:
   a. Solid epidemiological data and well-studied burden of disease
   b. Reinforce epidemiological surveillance, prepare social communication messages, and prepare regulatory reviews of the vaccine dossier.

3) Political and scientific will is essential to be an early adopter country

4) Identify priorities areas for vaccine introduction
   a. The priority areas for the introduction of the dengue vaccine are those with high endemicity and the priority population is those most vulnerable to the disease.

When asked what steps they thought ministries of health and national governments must take to accomplish the recommendations outlined in the previous section, respondents outlined the following actions:

1) Adopt an active approach to vaccine introduction
   o Instead of a passive approach that entails waiting for a new vaccine on the market, countries need to have an active participation in the development of a solid working plan for the analysis and introduction of the new vaccine.

2) Prioritize on integration of health systems
   o Key important areas that need to be integrated are surveillance systems, laboratory infrastructure, vaccination programs, regulatory procedures, and communications.

3) Establish a committee to identify priorities and analyze all technical, operational and logistics aspects, including the definition of priorities, to organize the vaccine implementation is essential.

4) Identify financing and regulatory strategies that will aid in vaccine introduction.

5) Focus advocacy efforts to generate support for the vaccine and to ensure affordability
   a. Advocacy by multilateral organization, such as WHO, PAHO / Revolving Fund, targeted at vaccine producers to obtain low prices of the new vaccine.
   b. Advocacy and sub-regional bodies where Presidents of countries involved, Ministers of Health to prioritize introduction of dengue vaccine
Lastly, respondents identified the following key players and advocates who can facilitate the successful adoption of these recommendations in their respective countries: Health and finance authorities, research organizations, national regulatory authority, NGOs, and scientific societies.

The following actions by key players identified above were mentioned as being useful to vaccine introduction for dengue:

1) Technical experts that generate evidence in support of the new vaccine should play an active role in advocating for the adoption of the vaccine:
   a. Since a group of experts was convened to carry out the analysis of how to prepare the country to introduce a dengue vaccine, and this group included social, governmental, academic and regulatory experts we would need them to continue working and fine tuning the implementation proposal.
   b. Support of organized groups that generate scientific opinion on political authorities through public pronouncements on media, forums, conferences, etc.
   c. To accelerate the introduction of the vaccine information should be made available to: -
      - Medical College of Honduras
      - Medical Societies
      - Association of Economists

2) Ensure that the new vaccine is affordable, particularly for low-income countries with constrained resources:
   a. Ensuring that the vaccine has a cost that can be absorbed by the national immunization program in developing or underdeveloped countries or by donors is very important.

3) Organized groups (civil society groups, municipal corporations, etc.) should ensure that the public is well-informed regarding the new vaccine
   a. Once the vaccine available, social communicators can play an important role in generating public opinion for the introduction of the vaccine in organized groups such as civil society groups (trusts, water boards, local health committees, and community groups), health committees, and municipal corporations.

The last section of the survey asked respondents to provide any additional ideas or points they felt were important to consider for dengue vaccine adoption. Respondents stressed the importance of continuing to focus on vector control programs and ensuring that a new vaccine is integrated into a new program (versus implementing vaccine introduction in a disconnected silo approach).
ANNEX 2. Post-workshop survey to Manufacturers

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ANNEX 3. Workshop Agenda

Developing Strategies for Meeting the Challenge of Equitable Vaccine Introduction in the Americas: With a Focus on Dengue Vaccine Financing

Venue: Pan-American Health Organization (PAHO)
525 23rd Street NW, Washington, D.C. 20037
Date: July 22-23, 2013

In January 2013 the World Health Organization (WHO) ranked dengue the world’s fastest growing tropical disease. The Americas, in particular, have suffered an increasing burden of disease associated with dengue, with 1.6 million cases reported across the region in 2010 alone. An effective and affordable dengue vaccine will play a critical role in reducing the human and economic costs of the disease by preventing millions around the world from getting sick. To introduce and implement a dengue vaccine in a timely and equitable manner, countries need to assess their needs and current capacities and develop effective immunization and financing strategies.

The John Hopkins’ University’s International Vaccine Access Center (JHU’s IVAC), in collaboration with the Dengue Vaccine Initiative (DVI), the Sabin Vaccine Institute and the Pan-American Health Organization (PAHO), has convened a two-day workshop to solicit input from key stakeholders about how to effectively and efficiently finance the introduction of dengue vaccines in the Americas.

Workshop Day 1 (July 22, 2013) – Room 1017, 10th floor
11:00 A.M. – 5:30 P.M.

Moderator: Prof. Peter Figueroa, Public Health, Epidemiology and HIV/AIDS, University of the West Indies, Kingston, Jamaica.

OBJECTIVE: To frame the issues relevant to vaccine introduction in the Americas, with focus on dengue vaccine financing.

11:00 A.M.  Registration and light lunch
Lunch will be served in Room 1013 (10th floor) following registration

11:30 A.M.  Introductory remarks
Prof. Peter Figueroa, University of the West Indies, Kingston, Jamaica
Dr. Dagna Constenla, JHU’s IVAC, Baltimore, MD, U.S.A.
Dr. Jon Andrus, PAHO, Washington DC, U.S.A.
Dr. Ciro de Quadros, Sabin Vaccine Institute, Washington DC, U.S.A.
Dr. Vittal Mogasale, International Vaccine Institute (IVI), Seoul, South Korea

11:55 A.M.  General introductions
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<tr>
<th>Time</th>
<th>Session Title</th>
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<tbody>
<tr>
<td>12:05 P.M.</td>
<td>Lessons learned from PAHO’s experience with new vaccine introduction</td>
<td>Dr. Cuauhtémoc Ruiz Matus, Senior Advisor on Immunization, PAHO</td>
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<td>12:25 P.M.</td>
<td>Overview of epidemiology of dengue in the region</td>
<td>Dr. Jose Luis de San Martin, Dengue Regional Consultant, PAHO/WHO</td>
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<td>12:45 P.M.</td>
<td>Overview of economic burden of dengue in the region</td>
<td>Prof. Donald Shepard, Schneider Institutes for Health Policy, Heller School, Brandeis University</td>
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<td>1:05 P.M.</td>
<td>Q&amp;A Session</td>
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<td>1:20 P.M.</td>
<td>Challenges of dengue vector control strategies</td>
<td>Dr. Harold Margolis, Chief-Dengue Branch, Centers for Disease Control and Prevention (CDC)</td>
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<td>1:40 P.M.</td>
<td>Q&amp;A Session</td>
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<td>1:55 P.M.</td>
<td>Demand for dengue vaccine in the Americas: a country perspective</td>
<td>Dr. Carla Domingues, Coordinator, National Immunization Program, Ministry of Health, Brazil Dr. Jesus Gonzalez, Director of Epidemiology, Ministry of Health, Mexico Dr. Diego Garcia, PAI Coordinator, Ministry of Social Protection, Colombia</td>
</tr>
<tr>
<td>2:40 P.M.</td>
<td>Q&amp;A Session</td>
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<tr>
<td>2:55 P.M.</td>
<td>Coffee Break</td>
<td></td>
</tr>
<tr>
<td>3:10 P.M.</td>
<td>New and emerging dengue vaccines</td>
<td>Dr. Beth-Ann Coller, Vaccines Research Department, Merck and Company Dr. Jose Noguera, Director, Vaccination Policy and Advocacy, Dengue-Americas, Sanofi Pasteur Dr. Ricardo Palacios, Division of Clinical Trials and Pharmacovigilance, Instituto Butantan Dr. Catherine Luke, Staff Scientist (Core), National Institute of Allergy and Infectious Diseases Dr. Alexander Schmidt, Vaccine Discovery &amp; Development, GlaxoSmithKline Dr. Jorge Osorio, Vice President of Research, Takeda Pharmaceutical Company</td>
</tr>
<tr>
<td>4:10 P.M.</td>
<td>Q&amp;A Session</td>
<td></td>
</tr>
</tbody>
</table>
Part II: What are important considerations for dengue vaccine introduction?

4:25 P.M.  Hurdles for equitable and timely introduction of vaccines with focus on dengue
Dr. Jon Andrus, Deputy Director, PAHO

4:45 P.M.  Potential health and economic impacts of dengue vaccine introduction
Dr. Dagna Constenla, Director - Economics & Finance, JHU's IVAC

5:00 P.M.  Q&A

5:15 PM  Synopsis of Day 2 and closing remarks
Prof. Peter Figueroa, University of the West Indies, Kingston, Jamaica

7:00 PM  Dinner
Marcel's Restaurant
2401 Pennsylvania Avenue NW, Washington DC 20037

Workshop Day 2 (July 23, 2013) – Closed Session (Room 1017, 10th floor)
8:00 A.M. – 6:00 P.M.

Moderator:  Dr. Ciro de Quadros, Executive Vice President, Sabin Vaccine Institute

OBJECTIVES: (i) To identify a set of 3-5 recommendations of financing options that would facilitate equitable and timely introduction of dengue vaccine and (ii) To develop a set of key actions that can advance these recommendations.

7:30 A.M.  Continental breakfast will be served in Room 1013 (10th floor)

8:00 A.M.  Welcome & summary of Day 1
Dr. Ciro de Quadros, Executive Vice President, Sabin Vaccine Institute

Part III: What will it take to finance dengue vaccine in the Americas?

8:20 A.M.  Financing strategies used for other vaccines
Dr. Jon Andrus, PAHO
Dr. Jesus Gonzalez, Director of Epidemiology, Ministry of Health, Mexico

9:00 A.M.  Strategy Session I: Recommendations of financing options for dengue vaccine

Questions/issues to be discussed include but are not limited to:

1) Please list financing strategies that are suited to specific countries.
2) How can existing mechanisms be leveraged to ensure equitable and timely introduction of dengue vaccine in the region?

3) Are there other innovative strategies that can be applied in the context of dengue vaccines in Latin American countries?

10:45 A.M.  Coffee break

11:00 A.M.  Discussion: review of recommendations from strategy session I

12:00 P.M  Strategy Session II: Key actions that can advance these recommendations

Questions to be discussed include but are not limited to:

1) What are the 2-3 areas/issues that you believe governments must focus on to ensure equitable introduction of the vaccine?

2) What next steps need to be taken to accomplish the recommendations you outlined in the previous session?

3) What roles can key international and regional players and advocates play to facilitate the successful adoption of these recommendations?

1:45 P.M.  Lunch

2:45 P.M  Discussion: review of recommendations from strategy session II

3:45 P.M.  Highlight of outcomes of strategy sessions and workshop discussions
Dr. Ciro de Quadros, Executive Vice President, Sabin Vaccine Institute

5:00 P.M.  Closing remarks
Dr. Jon Andrus, PAHO
Dr. Vittal Mogasale, IVI
Dr. Dagna Constenla, JHU’s IVAC
Dr. Ciro de Quadros, Sabin Vaccine Institute
ANNEX 4. Background document: Challenges of dengue prevention and control – The case for a dengue vaccine

The last two decades have witnessed an unprecedented increase in the incidence and severity of the dengue virus worldwide. This is particularly true in the Americas, where dengue has become one of the most urgent public health concerns facing the region. From 1995 to 2010, more than 30 countries in the Americas reported a total of 10,589,435 cases of dengue. In 2010 alone, more than 1.5 million cases were reported in Colombia, Venezuela, Brazil, Honduras, Guadeloupe and Puerto Rico (Figure 1). Compounding the effect of this dramatic increase in incidence is the fact that current prevention and control methods have proven to be both costly and ineffective. Dengue vaccines currently in development will provide a viable alternative to these strategies.

Public health burden and economic costs

In the past 30 years the disease burden associated with dengue has increased dramatically due to a combination of rising incidence and increasing severity. From 1980 to 2011 the number of cases per 100,000 increased from 50 to over 200 in many parts of the Americas (Figure 2). In addition to a heavy epidemiological burden, dengue has also placed a considerable economic burden on the region in terms of the direct costs of illness and indirect costs on health systems and society (e.g. lost productivity).
The total cost associated with Dengue outbreaks in the Americas has been rising steadily in the last decade (Figure 3), and was roughly US$ 2,150 million as of 2010. Brazil has incurred the greatest proportion of this burden, accounting for 40% of the total cost for dengue in the region. A prospective study conducted in Brazil in 2009 estimated that the economic burden associated with Dengue could be upwards of US$350 million annually (around $835 million in international dollars). The same study concluded that the annual economic burden of dengue is potentially as high as US$ 1,076 million total for El Salvador, Guatemala, Panama, and Venezuela (approximately $1,749 in international dollars). In 2011, experts estimated that in Colombia dengue costs accounted for more than US$54 million, which represents 0.02% of the country’s 2010 GDP. Other countries with a heavy economic burden include Argentina, Uruguay, and Venezuela. Rising hospital and ambulatory costs in the region will only serve to increase the economic burden of Dengue on households and health systems in the future.

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Challenges of vector control strategies
Unplanned and rapid urbanization has led to the creation of urban environments that are uniquely suited for A. aegypti, the mosquito species that is the primary vector for dengue transmission. Megacities such as Bogota, Buenos Aires, Mexico City, Rio de Janeiro, and Sao Paulo have given rise to overcrowded and cramped living quarters with extreme poverty and non-existent sewage systems. Moreover, insufficient water supply means that households must store water in water containers, which are model breeding grounds for A. aegypti. The emergence of these megacities combined with the deterioration of mosquito eradication and control programs in the Americas during the 1990s has greatly facilitated the rapid spread of dengue.

Currently, the region faces the challenge of developing new control programs based on outbreak response as well as preventive measures. During 2003, the Integrated Management Strategy for Dengue Prevention and Control in the Americas (IMS-Dengue, EGI dengue, in Spanish) was adopted by all countries of the region in the 44th Directive Council. IMS dengue aims to integrate different key components in dengue prevention and control in a comprehensive manner and incorporates an international Working Group on Dengue (GT Dengue internacional in Spanish) as a consortium of experts.

Main challenges - IMS Dengue evaluations

Management:
Failure to comply with the legislation concerning public policy about macro factors associated with dengue.

Surveillance:
Limited analysis for action and integration of different IMS dengue components (epidemiology, case management).
Integrated vector control:
Inadequate management of insecticides and resistance monitoring systems.
Insufficient human resources and equipment, problems arising from generational turnover of employees.
Lack of operational guidelines, limited availability of vector control tools.

Case management:
Existing technical regulations and guidelines for patient care often provide contradictory information and need regular updates.
Case definition standardization.

Laboratory:
Difficulties to standardize and decentralize dengue serological diagnosis.
Lack of criteria for sample processing during outbreaks and routine surveillance.

Communication:
Limited experience on risk communication.
Lack of financial and human resources to invest in community work.
providing technical expertise to complement existing national skills in order to reorient the control strategies at two different levels: the national and the subregional level.\textsuperscript{7} The IMS Dengue is the product of the political will of all health ministers in the region and the guide for elaborating the national strategies. Based on this strategy, countries work to strengthen all components of dengue prevention (epidemiological and entomological surveillance, vector control, laboratory, social communication, environment and patient care).

Given the lack of a licensed vaccine or specific treatment for dengue, global strategies have largely focused on vector control. In accordance with the WHO’s global strategy and PAHO’s regional recommendations for dengue prevention and control, vector control strategies must adopt an integrated approach that focuses on the epidemiological, disease surveillance, laboratory support, environmental, sanitation, and community education activities (Figure 4).\textsuperscript{6} The effectiveness of this multi-pronged approach relies heavily on vertical and horizontal coordination at the regional, national, sub-national, municipal, and community level. Political, operational, and administrative difficulties at all levels has made such coordination challenging.

**Figure 4: Integrated Management Strategy for dengue prevention and control (IMS-Dengue)**

Role of a dengue vaccine in dengue prevention and control strategies

Although vector control programs have been implemented all over the region, these approaches have had a negligible impact on dengue incidence. The high cost and relative ineffectiveness of these strategies have discouraged the public and further undermined the likelihood that vector control activities will be maintained at the household level. It has become increasingly apparent that addressing dengue will rely on vector control in conjunction with a more effective preventive measure such as a dengue vaccine.
Vaccines in clinical trial
There are four dengue vaccines in clinical trial. The most advanced candidate from Sanofi Pasteur is currently undergoing Phase III trials in 10 countries in Asia and Latin America. However, vaccine development experienced a setback during a Phase Iib trial in Ratchaburi, Thailand when the vaccine demonstrated efficacy against only three of the four dengue serotypes.

- Sanofi Pasteur CYD: tetravalent, live attenuated vaccine, 3 doses over a year. Phase I/II clinical trial.
- NIH live attenuated tetravalent (LATV) dengue vaccine: Phase I/II clinical trial.
- Inviragen DENVax (LATV) chimeric vaccine: Dosing schedule is 2 doses given 3 months apart. Phase I/II clinical trial.
- Merck sub-unit E protein vaccine: tetravalent, recombinant subunit, 3 doses 1 month apart. Phase I clinical trial. Administered with adjuvant.

A vaccine will not eliminate the need for continued investments in health systems, including early clinical diagnosis, appropriate case management, integrated disease surveillance and response, sustainable vector control strategies, and training personnel in effective outbreak response. Governments must continue to invest in all aspects of the integrated vector control strategy to effectively fight the spread of dengue. However, an affordable vaccine that is accessible to at-risk populations can play a pivotal role in easing the pressures placed on health systems and reduce the economic burden due to dengue. Most importantly, implementation of an efficacious vaccine – in tandem with effective vector control strategies – has the potential to greatly alleviate the human suffering and mortality caused by this terrible disease.

Key conclusions
- As populations migrate to areas that are conducive to A. Aegypti habitation dengue outbreaks will continue to increase in both frequency and severity.
- The direct and indirect costs associated with dengue in the Americas make it a public health priority
- Current vector control strategies are not a sufficient method of controlling the spread of dengue.
- The introduction of a dengue vaccine, combined with existing control efforts, will dramatically decrease the incidence and subsequent costs of dengue.

For comments and information, please contact Dr. Dagna Constenla (dconsten@jhsph.edu).

Disclaimer: This document was made possible with a sponsored grant from the International Vaccine Institute, a core partner of the Dengue Vaccine Initiative. Full independence of the content remains with JHU’s IVAC, along with responsibility for any errors.

Competing interests: None declared.

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1 PAHO / WHO, 2010, provided by Dr.

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ANNEX 5. Background document: Lessons learned from previous vaccines in the Americas

Lessons learned from previous vaccine introductions in the Americas

New vaccines in National Immunization Programs in the Americas
The region of the Americas is a leader in the introduction of new vaccines (Figure 1). The Pan-American Health Organization (PAHO) has been instrumental at the country level in contributing to the success of vaccine introduction in the region through: (i) collaboration at the national level to build operational capacity; (ii) strengthening epidemiologic surveillance and laboratory systems; (iii) promoting legal and financial sustainability; (iv) research and evidence generation; (v) capacity building for cost-effectiveness analysis; (vi) strengthening of the Revolving Fund; and (vii) alliances with partners. The efforts of PAHO’s ProVac Initiative have further contributed to, and complemented, these activities in the region by providing training and support in generating country owned evidence, which has proven to be a critical element in vaccine introduction in many countries.

Figure 1: New vaccines in National Immunization Programs in the region of the Americas

Lessons learned from previous vaccine introductions
Remarkable strides, possible through PAHO’s support, country commitment, and a concerted effort by both private and public sector organizations in the region, have been made towards rapid introduction of new vaccines in the Americas. What

- 90% of the birth cohort in the region is in countries that had already included the pneumococcal vaccine (60% of LAC cohort).  
- 87% of the cohort is in countries that already used the rotavirus vaccine (60% of LAC cohort).  
- By 2012, 16 countries had introduced rotavirus vaccine.  
- 23 countries and 5 territories had introduced pneumococcal vaccine.
follows is a brief description of how four countries of the region, facing similar challenges in providing health services to their population given their highly diverse populations and limited financial resources, were able to accelerate the introduction of two new vaccines (rotavirus and pneumococcal) into their routine immunization programs. An analysis of the factors that contributed to new vaccine introduction will contribute to a better understanding of how to reduce the time lag of new vaccine introduction in countries that share similar characteristics.

I. Needs assessment and addressing critical gaps prior to vaccine introduction: The successful introduction of a rotavirus vaccine in the Americas illustrates the importance of a detailed needs assessment that includes all levels of the health system. In addition, it is imperative that time is assigned for any capacity building, particularly when staff needs to be trained in the administration of the new vaccine and delivery mechanisms must be developed.

II. Strengthening technical capacity among advisory groups and regulatory authorities: Regulatory approval is crucial to new vaccine introduction in a country. PAHO provides considerable technical assistance to individual countries in lieu of domestic regulatory capacity. Countries must focus efforts on strengthening technical capacity within National Regulatory Authorities (NRAs), whose experience in oversight of clinical trials, ability to evaluate data and make licensing decisions, and capacity for safety monitoring can substantially shorten the time it takes to acquire regulatory approval. NRAs that are recognized by PAHO and have the capacity to conduct necessary assessment and monitoring functions are critical in ensuring new vaccine introduction.

III. Coordination between political and technical decisions: One of the main lessons learned from the introduction of rotavirus vaccine in countries within the region is the importance of a harmonized approach towards policy making between political leaders and technical experts. While technical experts are essential in generating evidence, close collaborations with political stakeholders can go a long way in ensuring a coordinated approach towards new vaccine introduction.

IV. Fostering relationships with technical advisory groups: New vaccines are introduced after approval is received from the National Immunization Technical Advisory Groups (NITAGS) and other technical committees. While the Ministry of Health does not accept all recommendations made by technical groups, it is rare for a vaccine to be adopted without prior approval from technical experts. NITAGs are most effective when they have standard operating procedures, declaration of potential conflicts of interest, members with diverse expertise (including a health economist when possible) and when they are at least partially independent from the Ministry of Health. The Network of Provac Centers of Excellence (COEs) established by The ProVac Initiative provides an example of a technical group that has successfully used evidence it has generated to collaborate with...
national technical teams to aid government officials regarding vaccine introduction decisions.

V. The role of public-private partnerships: The development of new vaccines is being undertaken primarily by private industry. Meaningful collaborations to ensure a reliable and sufficient supply of new vaccines at affordable prices are crucial for new vaccine introductions. Consultations between public sector authorities and the private industry can generate essential information and shared opportunities that can accelerate the introduction of new vaccines. Conversely, private sector partners can also play a constructive role in strengthening a country’s ability to adopt new vaccines. For instance, in 2006, prior to the national distribution of RotaTeq, Merck & Co. donated the three-dose, oral rotavirus vaccine for infants in Nicaragua for three years and also provided technical assistance to the Ministry of Health.7

VI. Broadening focus of national financing strategies: While most financing strategies make vaccine purchase the central focus of their approach, there have to be additional funds available to increase health system capacity for scale up of the vaccine delivery sequence. Ensuring appropriate delivery of vaccines at the lowest administrative level is a critical aspect of implementation. It is vital that a multi-dimensional financing strategy is developed so that activities beyond vaccine purchasing can be undertaken in order to ensure a stable and sustained supply.

VII. Early engagement of Ministries of Finance and Ministries of Planning: A contributing factor to Brazil’s decision to introduce the rotavirus vaccine in 2006 was the early and in-depth discussion between the Ministry of Health and the Ministry of Finance, which concluded that the economic justification for the vaccine was solid. The Ministry of Health developed advocacy documents that showed graphically the burden of disease for the two diseases locally and regionally, the savings obtainable through prevention, and the projected cost for the vaccines. In this case, the early, detailed, and continuous involvement of both Ministries expedited Brazil’s new vaccine adoption.

VIII. Established legal and political framework for immunization: Legal frameworks are critical to ensuring that an immunization program is sustainable, is provided as a public good by the state, and that everyone is afforded the right to immunization.8 A key factor that contributed to the strength and stability of vaccine decision-making in Ecuador was the 1997 Vaccine Law. The Vaccine Law guaranteed the allocation of financial resources for the purchase of vaccines and stipulates that all imported routine vaccines be purchased through the PAHO’s Revolving Fund. This allowed steady financial expansion of the program, despite political instability and changes in the national currency, thus ensuring sufficient resources and a transparent, secure mechanism for vaccine purchase.

IX. Robust disease surveillance is essential in
determining the disease burden and subsequently identifying the need for a vaccine. The Rotavirus Surveillance Network in the region, which was established in 2004, has been instrumental in providing advocates and experts with accurate data on the burden of rotavirus in the region.9

X. “Vaccine champions” can be pivotal to the adoption of new vaccines through their relentless support and advocacy efforts. The Mexico City Declaration made in July 2004 by officials from the Ministries of Health in the Americas calling upon the PAHO Revolving Fund to collaborate with the GAVI Alliance and vaccine manufacturers for the introduction of an affordable rotavirus vaccine in the region, demonstrated a commitment and a demand for the vaccine for the region.

XI. Generate sufficient evidence on efficacy and safety of a new vaccine: Prior to WHO prequalification, the rotavirus vaccines developed by GlaxoSmithKline and Merck were tested for safety and efficacy in large clinical trials in Latin America.9 Additionally, a collaborative vaccine safety study was undertaken to improve existing knowledge of the vaccine and its impact on reducing disease burden. This work relieved many of the concerns held by stakeholders in other countries regarding introduction of new rotavirus vaccine.9

XII. Strengthen technical capacity at the country level to make informed policy decisions on new dengue vaccine introduction: There is strong evidence to suggest that countries generating country-owned evidence are better able to effectively and objectively influence the decision making process on new vaccine introduction.7 This has been demonstrated on numerous occasions by the ProVac initiative, which supports nationally owned analyses that have lent support and credibility to national decision making.9 Well documented economic evidence supporting new vaccine adoption is critical in demonstrating the public health impact of a new vaccine. The presence of rigorous economic data can have a sizeable influence on advocacy efforts. ProVac has been instrumental in generating rigorous economic data in the Region. A few recommendations that have come out of regional dengue meetings are: (i) at a minimum, countries should be capable of collecting data on cost effectiveness with direct and indirect costs; (ii) countries should model the economic impacts of dengue and the results should be shared; (iii) PAHO is planning on developing ProVac tools that will allow for the evaluation of the dengue vaccine and other vaccines for vector-borne diseases. This will include a component evaluating other non-vaccines complementary health interventions to control vector borne diseases.
Case Study #4: Nicaragua

Lesson learned: The data collection and evaluation process for generating country-owned cost-effectiveness analysis helps countries build an evidence base to inform decisions on new vaccine introduction.

In 2010, the Nicaraguan Ministry of Health established a national multidisciplinary team to perform a cost-effectiveness analysis of PCV with support from PAHO’s ProVac Initiative. The data collected for the study, in particular regional estimates on disease burden and local data on circulating pneumococcal serotypes and treatment costs, alerted the national authorities of the urgency with which the country should introduce a vaccine to reduce the substantial epidemiological and economic burden of pneumococcal disease in the country. In addition to the base case result, Nicaragua presented a series of alternative scenarios to communicate the uncertainty around future GAVI co-financing and possible vaccine prices in the absence of GAVI support. The evaluation of the alternative pricing scenarios, determined by the actual prices offered through PAHO’s Revolving Fund and decreasing GAVI co-financing support, indicated that the introduction of either vaccine would be cost-effective for the price ranges considered. However, this did not imply that the country would be able to afford the long-term investments required to achieve a high-coverage vaccination program to reduce the burden of disease. Nonetheless, the process of conducting a cost-effectiveness analysis allowed the country to begin answering the questions associated with a sustainable introduction. The Ministry of Health expressed that the process of reviewing data on the impact of possible financing strategies was useful in illustrating the future role that resource mobilization will play in ensuring access to pneumococcal conjugate vaccine. By late 2010, Nicaragua decided to introduce PCV-13 due to the fact that it was the only pneumococcal conjugate vaccine approved for co-financing support from GAVI at an initial price to the country of 50.36 per dose and guaranteed for a five-year period.

Key points

- In order to streamline vaccine introduction financial support must be available to determine and strengthen existing technical and structural capacity within countries.
- Collaboration between the major actors in vaccine introduction (government officials, technical advisors, the private sector) will be essential in the development of a safe and affordable vaccine.
- Surveillance systems and other methods of gathering evidence on the economic cost, disease burden, and vaccine attributes are critical in making procurement and equitable distribution decisions.
- PAHO’s ProVac Initiative has strengthened technical capacity at the country level by providing training and support for generating country-owned evidence, which has proven to be a critical element in vaccine introduction in many countries.
- Lessons learned from countries will elucidate the best use of a dengue vaccine and provide information to facilitate the equitable and timely introduction of this vaccine in countries that need it most.

For comments and further information, please contact Dr. Dagna Constenla (dconsten@jhsph.edu).

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Competing interests: None declared.

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4 Pan-American Health Organization (PAHO) website. System for evaluation of the National Regulatory Authorities for Medicines.


6 PAHO’s Operational Guidelines for NITAGs (to be published)


Cost of Vaccine Introduction in the Americas

Strategic planning for vaccine introduction requires credible information about the cost to achieve the objectives of the vaccination program, estimate the available funding, allocate funds within the program and avoid funding shortfalls. An analysis of the costing of a vaccination program is a key step in the planning process.\(^1\)

In order to understand the cost implications of introducing a new dengue vaccine, costs for selected countries in the region are presented based on modelling done by JHU’s IVAC, using the Strategic Demand Forecasting (SDF) tool.

Figure 1. Decision space for stakeholders

SDF aids in overall strategic planning for vaccine introduction by allowing stakeholders to consider a variety of introduction scenarios. The successful introduction of a vaccine is only possible when the motivations of all three groups of stakeholders — industry, countries, and funding partners — overlap (Figure 1). SDF reveals the decision spaces within which this overlap occurs and the factors that bear influence within this space.

Cost estimates from the SDF are used to determine the cost-effectiveness of various rollout strategies and provide financiers with estimates on the value for money of a dengue immunization program. This can be done at a global level, for GAVI-eligible countries, at a regional level within the PAHO structure, or at the country level using budget impact analysis. Knowing how much an immunization program will cost allows funders to develop financing strategies prior to licensure, consequently reducing barriers to early access. The chosen financing method will impact what rollout strategies are possible and affordable in a given country and will subsequently influence global demand and prices for a dengue vaccine.

Figures 2-4 (presented in the next pages) include the full cost of vaccine implementation for each country; that is, the cost of both vaccine purchase, and vaccine delivery through the immunization program. Cost estimates are intended to be as close to real world values as possible. Individual country data on birth rates, immunization coverage, and costs of delivery are used to ensure representativeness of data. As vaccine costs are not yet known, the modelling used costs of $5-$15 per dose (in line with that of other new vaccines). The cost to Nicaragua, a GAVI country, was modelled at $0.20 per dose, the current contribution that GAVI seeks.

\(^1\)
We also sought to model the financial impact of introducing a new vaccine as realistically as possible, particularly the ‘lumpy’ nature of vaccine introduction costs. When countries implement a new vaccine they face a very high initial rollout cost, spread over a 3-5 year introduction campaign aimed at vaccinating a significant proportion of the population. This is followed by the lower, long-term ‘maintenance’ cost of vaccinating newborns each year as part of the immunization schedule. The total cost of dengue vaccine introduction is also defined by a country’s choice of vaccination strategy. Countries may choose to: (i) introduce the vaccine only in high-risk urban areas or to extend it to the entire country; (ii) cover only a subsection of the population in the initial rollout campaign (only children < 15) or rollout to adults (15-45 years). Table 1 provides a list of the current SDF model assumptions.

### Table 1: SDF model assumptions

<table>
<thead>
<tr>
<th>SDF assumptions</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td><strong>Doses, Wastage</strong></td>
<td>3, 10%</td>
<td></td>
</tr>
<tr>
<td><strong>Coverage</strong></td>
<td>Initial campaign:</td>
<td></td>
</tr>
<tr>
<td>Ages 2-4: 90%; Ages 5-9: 80%; Ages 10-14: 70%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ongoing maintenance:</td>
<td>Age 1: measles immunisation coverage for dose 1; percentage change as for DTP1 to DTP3</td>
<td></td>
</tr>
<tr>
<td><strong>Age Range</strong></td>
<td>Initial campaign: 2-14 years olds</td>
<td></td>
</tr>
<tr>
<td>Ongoing maintenance: 1 year olds</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Price per dose</strong></td>
<td>Public sector campaign price/dose:</td>
<td></td>
</tr>
<tr>
<td>$5-15 per dose for 2015-2019 GAVI</td>
<td>$0.20</td>
<td></td>
</tr>
<tr>
<td><strong>Time to achieve coverage</strong></td>
<td>3 years for initial</td>
<td></td>
</tr>
<tr>
<td><strong>Rollout costs</strong></td>
<td>Sourced from literature: initial campaign and ongoing maintenance rollout costs priced differently, with campaign costs based on HPV campaign costs in the Americas and higher than those for routine implementation</td>
<td></td>
</tr>
</tbody>
</table>

### Procurement costs of vaccine

Table 2 shows the estimated vaccine purchase cost during the first five years of use in selected countries of the region based on assumptions in the public sector, assuming $0.20 per dose for GAVI countries (Nicaragua) and $5-15 for all the remaining countries. For the first five years of use for Brazil in the 2-14-year-olds we are projecting up to 177 million doses (urban only) and up to 208 million doses (entire endemic area) at a vaccine purchase cost between $390-1,660 million and $460-1,370 million, respectively.

### Table 2. Estimated procurement costs for first five years of use

<table>
<thead>
<tr>
<th>Urban Only</th>
<th>Entire Endemic Area</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-14 years</td>
<td>15-45 years</td>
</tr>
<tr>
<td><strong>Argentina</strong></td>
<td>$(13)$</td>
</tr>
<tr>
<td>$60-150</td>
<td>$130-400</td>
</tr>
<tr>
<td><strong>Brazil</strong></td>
<td>$(77)$</td>
</tr>
<tr>
<td>$800-1,200</td>
<td>$1,800-2,660</td>
</tr>
<tr>
<td><strong>Colombia</strong></td>
<td>$(12)$</td>
</tr>
<tr>
<td>$60-180</td>
<td>$120-370</td>
</tr>
<tr>
<td><strong>Ecuador</strong></td>
<td>$(6)$</td>
</tr>
<tr>
<td>$50-80</td>
<td>$100-160</td>
</tr>
<tr>
<td><strong>Mexico</strong></td>
<td>$(44)$</td>
</tr>
<tr>
<td>$220-460</td>
<td>$400-1,200</td>
</tr>
<tr>
<td><strong>Nicaragua</strong></td>
<td>$(2)$</td>
</tr>
<tr>
<td>$0.6-1.40</td>
<td>$1.2-2.70</td>
</tr>
<tr>
<td><strong>Venezuela</strong></td>
<td>$(15)$</td>
</tr>
<tr>
<td>$70-120</td>
<td>$140-240</td>
</tr>
</tbody>
</table>

Doses in millions (in parenthesis)
Prices in million 2012 USD undiscounted
Source: JHU’s INVAC Dengue SDF, 2012 (unpublished)

#### Initial rollout costs

Costs presented in the next page are for 3-year initial rollout campaigns (urban only, and entire country) to vaccinate children aged 2-14 years (3 doses). Costs for initial rollout campaigns that would also vaccinate adults from 15-45 years (urban only, and entire country) were also calculated. These required a 5-year initial rollout period due to their much broader coverage.

Figure 2 shows the cost of annual routine vaccination for selected countries of the region. For the majority of the countries and at a vaccine price of $15 per dose the total cost of rollout in the urban and entire endemic area is less than $20 million each spread over three years. However, for countries like Brazil the same campaign would cost over $1 billion spread over three years at a vaccine price of $15 per dose. Even at the lowest modelled price of $5 per dose, this vaccine introduction

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campaign would cost Brazil $419 million over 3 years (not shown in graph).

Figure 2: Dengue immunization cost (Cost of annual routine vaccination)

Nicaragua the expense becomes significant. The impact of vaccine pricing is also made clear: the difference between a $5 per dose and $15 per dose for Brazil to vaccinate 2-14 year olds nationwide is $1.3 billion over 3 years.

Figure 4 shows the cost per selected countries of an initial rollout campaign to 15-45 year olds in urban areas and the entire country. For the majority of the countries the total cost of rollout is less than $500 million each spread over three years at a vaccine price of $15 per dose. But for Brazil the same campaign would cost over $3 billion spread over three years at a vaccine price of $15 per dose.

Figure 3: Dengue immunization cost (Cost of 2-14 yrs. catch up campaigns)

Figure 4: Dengue immunization cost (Cost of 15-45 yrs. catch up campaigns)

An initial rollout campaign among children aged 2-14 that would extend coverage across the entire country is significantly more expensive (Figure 3). Smaller and less rural countries experienced less of an increase in costs (e.g. the cost of moving to this broader strategy is much lower for Puerto Rico than Colombia), but even for a GAVI-eligible country like

Key conclusions

- An analysis of the costing of vaccine program is a key step in the planning process.
- Cost estimates from the SDF are used to determine the cost-effectiveness of rollout strategies and provide financiers with estimates on the value of a dengue immunization program.

For comments and information, please contact Dr. Dagna Constenla (dconsten@jhsph.edu).

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ANNEX 7. Background document: Financing uptake of new dengue vaccines – Challenges and opportunities

Financing Uptake of New Dengue Vaccine in the Americas – Challenges and Opportunities

Sustainable financing is one of the cornerstones of a successful vaccination program. Procuring this financing remains one of the main hurdles to new vaccine introduction and delivery in countries where vaccines are needed the most. This background document explores the opportunities and challenges countries in the Americas face on the path to introducing a dengue vaccine.

As illustrated in an earlier document, the cost of introducing a dengue vaccine is significant, but this is just one of many vaccines that countries in the region will be expected to introduce. The following pages present challenges and opportunities to generating new funding for vaccine financing. The four possible financing strategies presented are those that were considered most appropriate for vaccine financing in the region.

Challenges to financing a dengue vaccine in the Americas

Affordable pricing: The issue of affordability is the leading concern among public health officials in the region for all health interventions and a new dengue vaccine is no exception. Even though the disease burden might warrant the introduction of a new vaccine, there may be insufficient fiscal resources accessible to ministries of health to allow for vaccine introduction. Vaccine suppliers must bear in mind the fiscal limitations of governments in countries of the region when setting the price of a new dengue vaccine. Fortunately, there are several financing approaches that can ensure the affordability of a new vaccine. These include, but are not limited to, bulk procurement mechanisms (e.g. PAHO’s Revolving Fund), and mixed funding pools.

Availability of sufficient fiscal resources: It is often times challenging for governments in resource-constrained settings to find sufficient financial resources necessary for the introduction of a new vaccine. In such a scenario, governments must explore the alternative forms of financing, such as international donor support or regional pooling mechanisms to generate the necessary fiscal resources.

Experience with pricing negotiations: Contracts for new vaccines that are negotiated over a longer time period, acquired through bulk procurement strategies, and/or bundled with other products have terms that are generally more favorable for country governments. Contract negotiations are ideally placed to establish terms with manufacturers. However, if there is an absence of financing expertise within Departments of Health or if countries have not introduced new vaccines in recent years, they may face considerable challenges in negotiating favorable terms.

Ability to increase the vaccine budget to add a dengue vaccine: Having the fiscal space to include an additional vaccine to the immunization budget is an indication of political support and an assurance that dengue vaccine introduction will not harm other immunization or vector control initiatives. This ability should be
corroborated by the Ministry of Finance or National Planning Departments.

Ability to fund the implementation and delivery of a dengue immunization and existing programs: Countries should ensure that they have sufficient funding to cover the operational costs of introducing and delivering a dengue vaccine as well as maintaining existing control measures.

Ability to finance monitoring and evaluation: In addition to vaccine delivery, countries should have the ability to finance the evaluation and monitoring of vaccine impact, such as vaccine effectiveness and cost-effectiveness, and to finance post-licensure studies to evaluate the long-term safety of the vaccine.

Experience in the coordination of financing across Ministries: Countries should ideally have past experience with coordinating budgets and financing of vaccine programs across Ministries (e.g. with the Ministries of Education, of Health, of Tourism) and across public and private sectors (e.g. insurance).

**Financing strategies and procurement mechanisms for new vaccine introduction**

There are several financing strategies and potential financing models that countries in the region can adopt to ensure the availability of sufficient resources for dengue vaccine introduction. The following is not a comprehensive analysis of every option available. The focus is on approaches that are either ongoing or have already demonstrated some degree of political or practical feasibility.

**Pooled procurement** – Pooled procurement contracts allow buyers, such as countries and/or multilaterals to collectively negotiate lower prices from companies by combining their individual purchasing power into a larger bulk purchase contract on behalf of the group. The contract sets the price and volume to be supplied over a set timeframe and is designed to provide security of price and supply for the buyer, security of demand for the developer, and a lower pooled price than could be negotiated by countries on their own.

**Status:** Successfully implemented – as the Pan-American Health Organization procurement fund - and has achieved a discount of 11% on vaccine purchase (compared to buying directly from the producer).

**Revenue potential:** Pooled procurement contracts do not raise funds, but allow existing money to go further.

For a summary background on pooled procurement, please see Appendix 1.

**Regional taxes** – Taxes collected by a group of countries at the national level and pooled at a regional or international level for distribution. These taxes are generally small but on a high volume of sales or transactions and include taxes on airline tickets, Internet traffic, tobacco products, or financial exchange transactions.

**Status:** One clearly successful example globally is the air ticket levy, which has raised an average $200m per year for UNITAID. However, there is no Latin American and Caribbean regional equivalent.

**Revenue potential:** Currently, a regional air ticket levy could raise over $300m annually; this figure would be expected to grow along with the rapid rate of air travel in the region (likely over 7% per annum).

For a summary background on the regional taxes mechanism, please see Appendix 2.

**Domestic taxes** – Taxes to raise new funds for health, either by increasing an existing tax, or imposing a new tax on the purchase or use of specific goods or services. Can be broad-based (e.g. VAT) or product- or sector-specific.

**Status:** Numerous regional examples used to fund health programs. Other countries have successfully earmarked funds for health from VAT or sector-specific taxes.

**Revenue potential:** Country-dependent, but domestic taxes could raise more than $100 million annually.

For a summary background on the domestic taxes mechanism, please see Appendix 3.

**Low-interest multilateral loans** – Loans from multilateral organizations, such as the World Bank and the Inter-American Development Bank, are given to national governments at low interest rates. These loans are usually for 10-40 years at interest rates between 1% and 7%, but are typically provided for large-scale programs in a particular sector rather than for a single project such as vaccine purchase.
Status: Low-interest multilateral loans are already provided by the World Bank and the Inter-American Development Bank to a range of countries in the Americas, traditionally not for immunization.

Revenue potential: Less than $100 million.

For a summary background on the low-interest multilateral mechanism, please see Appendix 4.

Table 1. Financing options for the region

<table>
<thead>
<tr>
<th>Amount</th>
<th>Regional</th>
<th>One off</th>
<th>Annual (ongoing)</th>
<th>Successfully implemented</th>
<th>Used for health</th>
<th>Used in LAC region</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than $100m</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regional taxes</td>
<td>$200m-$1bn</td>
<td></td>
<td>√</td>
<td>√</td>
<td>√</td>
<td>√</td>
</tr>
<tr>
<td>Domestic taxes</td>
<td>$100m+</td>
<td></td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pooled procurement</td>
<td>Savings</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than $100m</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low interest</td>
<td>&lt;$100m</td>
<td>√</td>
<td>√</td>
<td>√</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Next steps/ key activities necessary prior to dengue vaccine introduction

I) Perform fiscal space analysis: Fiscal space indicates the ability of governments to provide additional funding for new activities, and is useful for international donors in determining the magnitude of support that will be required, and the level of co-financing that is possible for the introduction of a new dengue vaccine. Fiscal space analysis identifies a realistic level of support that can be expected based on economic indicators. It also signals lack of political commitment by revealing gaps between willingness to pay for a new dengue immunization program and ability to pay. Fiscal space analysis should focus on providing financial resources for the entire programmatic costs of a national level dengue immunization program, including maintaining existing vector control strategies, disease surveillance programs and monitoring and evaluation activities.

II) Estimate overall program costs: The World Health Organization (WHO) provides clear guidelines for estimating the costs of a multi-year immunization program for planning and financing purposes. These costs include the present and future costs of vaccine procurement, capital expenditures (purchase of refrigerators for cold chain, purchase of trucks for distribution), and other recurring expenditures (such as maintaining cold chain, personnel costs, equipment costs, and logistical and infrastructure costs). Prior to adoption of a new dengue vaccine, countries in the region must calculate the programmatic costs of launching a dengue immunization campaign. This is especially important for dengue immunization programs; catch-up campaigns, which will have be rolled out

for several separate age groups, will require considerable fiscal resources since they will have to be implemented independent of routine immunization programs.

III) Perform budget impact analysis: Following a calculation of overall costs, in accordance with WHO’s comprehensive multi-year plan (cMYP), a detailed analysis must be conducted to identify the impact of a new dengue vaccine on national health budgets. For instance, program costs must be compared with and without a dengue vaccine as a ratio of the government’s total annual budget for health. Additionally, a comparison can also be carried out between costs before introduction and potential costs after introduction of a dengue vaccine as a percentage of gross domestic product (GDP). While the interpretation of such appraisals can be subjective, it still reveals the relative impact of a new dengue vaccine on existing government budgets.

IV) Create a specific budget line item for dengue vaccine: Most countries in the region have a line item in national health budgets for new vaccine introduction. A specific line item in national health budgets for a new dengue vaccine introduction would ensure that there are sufficient funds available for vaccine purchase and delivery
strategies. The allocation of funds explicitly for the purpose of dengue vaccine purchase will improve financing by: i) increasing awareness among government officials of the importance of immunization as a health priority; ii) increasing transparency of funding decisions for dengue immunization programs; iii) setting up a framework for resource tracking for government expenditure on dengue prevention and control; and iv) indicating political commitment towards national dengue vaccine programs, which further bolsters efforts by vaccine advocates.  

V) Expand legal frameworks: Legal provisions can be powerful tools to ensure sustainable financing of immunization programs. This is particularly true in countries of the region where strong vaccination legislation already exists (Brazil, Colombia, Ecuador, Nicaragua, Paraguay, and Peru). Further evidence suggests that strong vaccination legislation has a positive impact on the funding and sustainable financing of immunization programs. Examples of legal provisions that will facilitate the introduction of a new dengue vaccine include, but are not limited to, legislation that guarantees a specific line item for dengue immunization programs, tax exemptions for the import of dengue vaccines and vaccine-related products, the creation of a national dengue vaccine fund (ex: Costa Rica has a national vaccine fund for routine vaccines), and/or mandating that a percentage of national health budgets are spent on dengue immunizations (ex: Bolivia has similar legislation for routine vaccines).

Points for consideration
- Funding will be needed for vaccine rollout
- ‘Demand’ as in level of community priority is driven by burden of disease and impact
- Demand, in the Strategic Demand Forecast/economic sense refers to volume (doses)
- Community demand -> filtered through financing constraints -> puts a cap on volume
- Financing needs reflect:
  - Population size/vaccine coverage
  - Vaccine strategy (urban/rural; routine/catch-up)
  - Vaccination cost (vaccine procurement [price/dose, dose schedule]; incremental rollout costs)
- Country context
- Need to consider time for implementation
- Focus on getting the vaccine to countries where need is greatest.

Concluding remarks
- Financing remains one of the main hurdles to new vaccine introduction and delivery in countries where vaccines are needed the most.
- Options for funding these new vaccines include diverting existing government funding, or finding new government funds.
- Challenges to financing a dengue vaccine in the Americas include
  - Affordable pricing
  - Availability of sufficient fiscal resources
  - Experience with pricing negotiations
- There are several financing strategies and potential financing models that countries can adopt to ensure the availability of sufficient resources for dengue vaccine adoption, including procurement mechanisms, regional taxes, domestic taxes and low interest multilateral loans.
- Other strategies should be considered to ensure timely and effective uptake of a dengue vaccine in the Americas.

For comments and further information, please contact Dr Dagna Constenla (dconsten@jhsph.edu)

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Competing interests: None declared.

2 Saxenian H et al. An analysis of how the GAVI alliance and low- and middle- income countries can share costs of new vaccines. Health Affairs, 30, no.6. 2011.
3 WHO – UNICEF guidelines for developing a comprehensive multi-year plan (mYP): Extended Programme on Immunization, Department of Immunization, Vaccines and Biologicals, WHO, 2006.
6 Ibid. Trumbo et al.
ANNEX 7.1 Pooled Procurement

Appendix 1: Pooled Procurement

Description
Pooled procurement contracts allow buyers (countries and/or multilaterals) to collectively negotiate lower prices from developers by combining their bulk purchasing power into a larger purchase commitment on behalf of the group. The contract sets the price and volume to be supplied over a set timeframe. Pooled procurement contracts are designed to provide: lower pooled price than can be negotiated by countries on their own; security of price and supply for the buyer over a defined time period; security of demand for the developer over a defined time period.

Pan American Health Organization’s Revolving Fund
The Revolving Fund has played a pivotal role in providing countries of the Americas with access to vaccines, syringes, and other related medical supplies to member countries at the lowest price. For more than 30 years, it has facilitated the uninterrupted flow of resources needed to maintain the stable functioning of national immunization programs in countries of the region. The Revolving Fund has been responsible for purchasing vaccines worth several million dollars for the region over the last decade. Most importantly, the Fund has ensured that the vaccines purchased meet the evolving needs of the region. During the 2010 H1N1 pandemic outbreak in the region, it provided vaccines worth over approximately US $100 million to countries that might not have had access in a timely manner (Figure 1).

Figure 1: PAHO Revolving Fund Annual Purchased Value By Vaccine Type 2004 - 2012

Through the Revolving Fund countries are able to gain access to products based on principles of equity and affordability; there is a single price established for a product regardless of the country’s size and economic status. Since the Revolving Fund negotiates for bulk quantities, economies of scale translate into lower prices that are affordable to countries. PAHO’s Revolving Fund has purchased vaccines for nearly 80 percent of the children born in the region and nearly half the annual birth cohort in the Americas (Figure 2). This has translated into the availability of vaccines for more than 40 countries regionally.
Other procurement mechanisms

In September 2009, Brazil’s Ministry of Health Brazil signed a contract with GSK sealing an innovative deal worth £1.5 billion, which ensures access to pneumococcal vaccines for 13 million children over a period of eight years. Under this deal, GSK provides the vaccine at €11.50 per dose and reduces to €5 in following years. Additionally, a technology transfer will take place to develop research and development capacity. This deal also includes a joint project totaling €17 million for the purpose of developing a dengue vaccine.

Status

Various forms of pooled procurement purchase contracts are already in place, including:

<table>
<thead>
<tr>
<th>Aim</th>
<th>Host/manager</th>
<th>Negotiator</th>
<th>Supplier</th>
<th>Product</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSK, Brazil pneumococcal vaccine contract</td>
<td>n/a</td>
<td>Government of Brazil and GSK</td>
<td>Single</td>
<td>Single</td>
<td>Prices higher than the GAVI negotiated price. But 65% lower than European counterparts, plus further price drops over duration of contract</td>
</tr>
<tr>
<td>PAHO Revolving Fund (39 countries and territories in Latin America and Caribbean)</td>
<td>PAHO serves as the Revolving Fund, the country contributes 3.5% of the net purchase price back into the fund (3% to be used as working capital, line of credit; 0.5% for administration costs)</td>
<td>PAHO Revolving Fund</td>
<td>Multiple</td>
<td>At least 11% savings in comparison to direct purchases from producers</td>
<td></td>
</tr>
</tbody>
</table>

Volume of potential revenue

Nil. Pooled procurement does not raise funds – instead, it allows existing money to go further.

For comments and further information, please contact Dr. Dagna Constenia (dconsten@jhsph.edu).
ANNEX 7.2 Background Papers for Policy Brief #4: Domestic Taxes

Appendix 3: Domestic Taxes

Description
These are taxes designed to raise new funds for health, either by increasing an existing tax, or imposing a new tax on the purchase or use of specific goods or services. Common options for raising additional funds include:

- **Broad consumption taxes** (e.g. VAT/GST)
- **Taxes on specific products**, especially those with harmful health effects like tobacco or alcohol (‘sin taxes’)
- **Sector-specific taxes** generally levied on profitable sectors/larger corporations, especially in the financial, resource and telecommunications sectors.

The funds raised from domestic taxes can go into consolidated government revenues, or be ‘hypothesized’ (i.e. earmarked) for a specific cause, such as immunization campaigns or vaccine financing.

Status
There are many examples where domestic taxation schemes have been successfully used to raise new funds for a specific purpose, including in health.¹

**VAT schemes (additional levy on top of existing VAT rate)**
- Chile: uses 1% of its VAT to fund health (total rate 19%).²
- Bolivia: One of the main sources of funding for the Universal Mother and Child Insurance (SUMI) in Bolivia are Municipal tax transfer payments (CTM).²
- Ecuador: The National Maternity and Child Insurance (SNMI) implemented in Ecuador in 2000 through the Free Maternity and Child Care Law mandates that 3% of special consumption tax (ICE) is to be as financing for SNMI. Funds for SNMI have more than doubled between 1995 and 2005 from nearly US$8 million to US$20 million due solely to the allocation of this special tax.³

**Earmarked tobacco and alcohol taxes**
- Several countries within the region are raising funds for tobacco prevention and control activities through taxation of tobacco products. These “tobacco taxes” have been implemented successfully in Costa Rica, Ecuador, and Panama.³, ⁴
- Costa Rica raised taxes by 6.5% in early 2012 to fund tobacco control and other health promotion activities.³, ⁴
- Similarly, Panama doubled its tax rate on tobacco products and assigned the resulting “tax funds” to the National Cancer Institute and the Ministry of Health for the prevention and treatment of diseases attributable to tobacco products. Additionally, almost 20% of these funds were earmarked for the National Customs Authority (ANA) to fund its activities on the prevention of illicit trade of tobacco.²³
- Ecuador — which is considered a leader in implementing tobacco taxes — also adopted a universal tax on all tobacco products.²³

**Other taxes**
- Argentina: has instituted a levy on mobile phone subscriptions to fund elite sport.³
- No other examples of innovative taxation mechanisms were found in the research.

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Volume of potential revenue

No information is available on the amount of revenue collected by domestic taxes.

Pros and Cons

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>High revenue</td>
<td>Politically unpopular (particularly during recession/slowdown)</td>
</tr>
<tr>
<td>High predictability</td>
<td>Require legislative change</td>
</tr>
<tr>
<td>Low transaction costs</td>
<td>The tax revenues can be difficult to ring-fence to vaccine purchase – may be used for other government priorities.</td>
</tr>
<tr>
<td>Highly sustainable</td>
<td>Consumer-based taxes hit the poorest consumers the hardest</td>
</tr>
<tr>
<td>Knock-on health gains from “sin taxes” on alcohol/cigarettes</td>
<td>Sector-specific taxes may dis-incentivise business investment in emerging economies</td>
</tr>
<tr>
<td></td>
<td>Some countries in the Americas already have a specific health care tax</td>
</tr>
</tbody>
</table>

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Competing interests: None declared.

2 Source at [http://www1.paho.org/eng/DPH/HP/FinFinC07-presdocs.htm](http://www1.paho.org/eng/DPH/HP/FinFinC07-presdocs.htm) on July 12, 2013.
ANNEX 7.3 Background Papers for Policy Brief #4: Regional Taxes

Appendix 2: Regional Taxes

Description
A regional tax is a tax that a group of countries each agree to collect nationally and then pool at the regional level for redistribution. The actual tax is usually very small but is placed on goods with a high volume of sales or transactions.

Possible sources include airline ticket sales, Internet traffic, or tobacco products. Under the airlines tax example, countries pass a law to levy a small fee on each purchase of an airline ticket made in their country. Otherwise known as the “solidarity levy on airline tickets,” this tax is paid by passengers when they buy an air ticket and airlines are responsible for collecting and declaring the tax. Solidarity airline taxes are responsible for nearly half of the funding for UNITAID, originally established as WHO’s “International Drug Purchase Facility (IPPF)” responsible for guaranteeing access to drugs and diagnostics equipment against HIV/AIDS, Malaria and Tuberculosis.¹

Chile and Brazil are both participants in UNITAID. Countries set the amount levied, depending on:
- Class of ticket: France, which is one of the founding members of UNITAID charges between €1 - €4 for economy-class tickets and between €10 - €40 for first and business-class tickets.¹
- Whether the flight is domestic or international: France also levies the solidarity tax at varying levels depending on the final destination of the traveler; charges on domestic air travel are between €1 - €10 and between €4 - €40 for international air travel.³

No information is readily available on the amount levied for airline tax in the region of the Americas.

Status
Examples of successfully implemented regional taxes are rare. The European Union is currently considering the introduction of an FTT, and a tobacco tax (the Global Solidarity Tobacco Levy) is currently under discussion as an innovative financing tool for health. There are no examples of regional taxes in the Americas. Tobacco taxes are implemented nationally.

There is one clearly successful example: the air ticket levy was first implemented in France in 2006, with funds raised going to UNITAID, an independent not-for-profit group hosted by the WHO, which uses these revenues to fund AIDS, TB and malaria-related product development and purchase.⁵ Nine countries now participate in the UNITAID airline levy, including Chile.⁴

Two possible options are applicable to vaccine financing in the Americas:
1) Persuade UNITAID to extend its remit beyond HIV/AIDS, TB and malaria to other vaccines of interest to countries of the Americas.
2) Establish an airline levy in the Americas to fund region-specific health or vaccine goals.

¹ UNITAID has 29 member countries, but Brazil and Chile are the only current Latin American members.

³ Protecting Health, Saving Lives—Millions at a Time

⁵ 855 North Wolfe Street, Suite 600 • Baltimore, Maryland 21205 • www.jhsph.edu

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Volume of potential revenue

Existing schemes
While specific figures are not available for countries in the region, European countries like France announced in January 2013 that since its establishment in 2006 the solidarity tax had raised 1 billion euros.\(^1\)

Proposed schemes
Discussions around a Financial Transaction Tax (FTT) have been gaining considerable traction within participating members of UNITAID. FT Ts would be collected on stamp duties on paper/electronic transactions and inter-bank currency transactions. Even at fairly low rates, studies estimate that a FTT could raise upwards of US$30 billion annually just within the European Union.\(^2\)

Pros and Cons

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>High potential revenue, low transaction costs</td>
<td>Taxes may be politically unpopular (particularly during recession/slowdown), and must be legislated</td>
</tr>
<tr>
<td>Once set up, funding is predictable and stable</td>
<td>Regional collaboration can be difficult to achieve, and there is a poor track record</td>
</tr>
<tr>
<td>For the airline levy: individual countries can decide what the levy will look like in their country (size of fee; domestic or international etc.)</td>
<td>An FTT (or similar) may distort markets and move transactions outside the region</td>
</tr>
<tr>
<td>Airline levy has good sustainability with no adverse effect on volumes of air traffic reported by those who have implemented it</td>
<td>For ‘Option 1’ of the airline levy, it may be difficult and slow to persuade UNITAID to extend their remit</td>
</tr>
<tr>
<td>Airline levy has a diverse source of funds, tapping into the tourist market of the Americas (as both foreign tourists and national residents pay)</td>
<td>‘Option 2’ of the airline levy may compete with the existing UNITAID model (e.g. some beneficiaries of UNITAID are in the Americas)</td>
</tr>
<tr>
<td>If option is to secure a UNITAID extension, then no new organisation needed</td>
<td>An air levy in the Americas will need a new organisation to manage it, but this is likely to be quite small (UNITAID’s operating costs are only 3.6% of total revenue)</td>
</tr>
</tbody>
</table>

For comments and further information, please contact Dr. Dagna Constenla (dconsten@jhsph.edu).

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Competing interests: None declared.


ANNEX 7.4 Background Papers for Policy Brief # 4: Multilateral Loans

Appendix 4: Low-Interest Multilateral Loans

Description
A multilateral organization (such as the World Bank or the Inter American Development Bank) provides a loan directly to a national government, at a low interest rate. Also known as concessional loans, these are typically for 10 to 40 year periods, and at interest rates of 1% to 7%.\(^1\) \(^2\) Lending terms (including grace periods, repayment terms, and up-front fees) often depend on a country’s policy and institutional performance, in terms of economic growth and poverty reduction.

Concessional loans are usually provided for large-scale programs in a particular sector (health, infrastructure, education), rather than for a single project or expenditure (such as vaccine purchase). But in some cases, a small proportion of low-interest loans have been used to purchase health products as part of a broader disease-specific or health sector program. The majority of this loan is for equipment or infrastructure upgrades, health worker training, capacity building and policy (e.g. development of national health plans).

Status
The World Bank and the Inter American Development Bank (IDB) provide various loans for health programs in countries of the region. In 2012, the World Bank Group, comprised of the International Bank for Reconstruction and Development (IBRD), International Finance Corporation (IFC), International Development Association (IDA), and Multilateral Investment Guarantee Agency (MIGA) spent US$11.8 billion in development assistance in the region.\(^3\) This included spending on large public sector projects beyond the health sector as well. A significant portion of this funding is being spent on providing assistance to health sector programs and projects. However, the total amount given for health is unknown because many projects have health as a component.

The World Bank provides development assistance to countries in the region through traditional loans and advisory services that are tailored to meet the needs of individual countries. Loans are provided through different mechanisms, depending on a country’s income level and creditworthiness. For example, the World Bank provides loans to low-income countries through the IDA and to middle-income countries through the IBRD.\(^4\) Interest rates are lower and repayment terms more generous for low-income countries.

Examples of loans including the procurement of health products:
- The Third Basic Health Care Project supported by the World Bank in Mexico has been established to improve the quality of health care services in rural and marginal urban communities by focusing on cost-effective health interventions in hospital care and emergency medical services, and providing training for HIV/AIDS prevention and control. This project is worth US$581 million and is supported in part by IBRD/IDA.\(^5\)
- The Third Rio State Fiscal Efficiency for Quality of Public Service Delivery Development Policy Loan (DPL) Program supported by IBRD/IDA in the State of Rio de Janeiro in Brazil focuses on improving various aspect of public sector delivery of

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\(^1\) See reverse for a list of countries in the region eligible for specific World Bank and IDB lending mechanisms.

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Rev. Jul 1813
services. Of the 300 million being spent, 20% is going towards improving efficiency in healthcare spending, both in regional hospitals and smaller municipality health centers.¹

- Peru’s Fourth Programmatic Social Reform Loan Project (PSRL IV), funded by the IBRD to the tune of US$100 million, supports reforms that are aimed at increasing access, transparency, and efficiency in service provision by using a Programmatic Development Policy Loan instrument.²

Countries in the Americas who are recipients of development assistance
The following countries are currently receiving, or have received, development assistance from the World Bank Group: Argentina, Bolivia, Brazil, Chile, Colombia, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Peru, and Uruguay.¹

The following countries are currently receiving, or have received, development assistance from IDB: Argentina, Bolivia, Brazil, Chile, Colombia, Costa Rica, Dominican Republic, Ecuador, El Salvador, Guatemala, Honduras, Mexico, Nicaragua, Panama, Paraguay, Peru, Uruguay, and Venezuela.²

Pros and Cons

<table>
<thead>
<tr>
<th>Pros</th>
<th>Cons</th>
</tr>
</thead>
<tbody>
<tr>
<td>Predictable and stable funding (a set amount is disbursed over a set number of years)</td>
<td>Not specifically for vaccine purchase (may need to seek vaccine funding as part of a broader health program).</td>
</tr>
<tr>
<td>Allows countries in the region to gradually assume financial responsibility over a generous timeframe</td>
<td>Must compete with other funding priorities at a national and multilateral level (World Bank and IDB funding has tended to favor infrastructure, energy, and public sector/governance programs, rather than health).</td>
</tr>
<tr>
<td>Low transaction costs (low interest rates and up-front fees)</td>
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<td>Established mechanism (no new infrastructure required)</td>
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<tr>
<td>Quick implementation (approximately six months to two years, depending on proposal and approval processes)</td>
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</tbody>
</table>

For comments and further information, please contact Dr. Dagna Constenia (dconsten@jhsph.edu).

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