Financing dengue vaccine introduction in the Americas: challenges and opportunities

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Financing dengue vaccine introduction in the Americas: challenges and opportunities

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ABSTRACT

Dengue has escalated in the region of the Americas unabated despite major investments in integrated vector control and prevention strategies. An effective and affordable dengue vaccine can play a critical role in reducing the human and economic costs of the disease by preventing millions around the world from getting sick. However, there are considerable challenges on the path towards vaccine introduction. These include lack of sufficient financing tools, absence of capacity within national level decision-making bodies, and demands that new vaccines place on stressed health systems. Various financing models can be used to overcome these challenges including setting up procurement mechanisms, integrating regional and domestic taxes, and setting up low interest multilateral loans. In this paper we review these challenges and opportunities of financing dengue vaccine introduction in the Americas.

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Challenges; financing; dengue; vaccine introduction; Americas

Review of the dengue situation in the Americas

The last two decades have witnessed an unprecedented increase in the incidence and severity of the dengue virus worldwide.[1,2] 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 region reported over 10 million cases of dengue.[3] This represents a threefold increase in the number of cases from earlier years. In 2010 alone, more than 1.5 million cases were reported in Colombia, Venezuela, Brazil, Honduras, Guadeloupe, and Puerto Rico.[3] Presently, all four dengue virus serotypes are found circulating in many of the countries in the region, showing the pernicious cycle of ill health from the mosquito vector *Aedes aegypti*.[4]

The region with the highest reported cases in 2014 was the Southern cone region with 234.7 per 100,000, followed by the Central America and Mexico region with 179.9 per 100,000, the Andean region with 173.6 per 100,000, and the Caribbean region with 87.4 per 100,000.[3] The country in the Central America and Mexico region with the highest reported lab-confirmed cases of dengue in 2014 was El Salvador with 255.15 per 100,000. In the Andean region, the country with the highest lab-confirmed cases reported in the same year was Colombia with 95.73 per 100,000. Brazil was the country with the highest reported lab-confirmed cases in the Southern cone region with 108.83 per 100,000.[3]

A paper by the Global Burden of Disease Study 2013 collaborators [4] reiterated the substantial increase of dengue cases (nearly 450%) over the past decade and compared this increase with malaria and neglected tropical diseases (NTDs). Whilst the years lived with disability (YLD) for dengue remain low compared to the ‘big three’ (malaria, tuberculosis (TB), and HIV/AIDS) and many other diseases, the percentage change over the past decade was substantial. Much of this change has been attributed to the rise of breeding sites in urban and periurban areas in the region.[4]

Review of the socioeconomic costs of dengue in the Americas

Compounding the effect of this dramatic increase in incidence of dengue is the fact that dengue places a considerable economic burden in terms of the direct costs of illness and indirect costs on health systems and society (e.g. lost productivity).[5–10] A recent review of the literature [11] reported an estimated total annual cost ranging from US$13.5 million (in Nicaragua; in 2010 values) [12] to US$56 million (in Malaysia; in 2010 values),[13] depending on the country. The majority of these costs were due to hospital care and costs associated with productivity loss.[11,14] The costs associated with dengue outbreaks are also substantial, ranging from approximately US$43 per
case in Vietnam to US$430 per case in the Dominican Republic (in 2011 values).[15]

The total cost associated with dengue outbreaks in the Americas has been rising steadily in the last decade, [11] and was estimated at US$2150 million in 2010.[14] Brazil has incurred the greatest proportion of this burden, accounting for 40% of the total cost for dengue in the region.[15] A prospective study conducted in Brazil in 2009 estimated that the economic burden of dengue could be upwards of US$350 million annually (around $835 million in International dollars).[16] The same study concluded that the annual economic burden of dengue is potentially as high as US$1076 million in total for El Salvador, Guatemala, Panama, and Venezuela (approximately $1749 in international dollars). In Colombia, in 2011, dengue costs accounted for more than US$54 million (or 0.02% of the country’s 2010 GDP).[9]

A study by Castro and colleagues [17] in Colombia estimated that the dengue epidemic costs in 2010 were US$357,189,668 while in 2012, a dengue endemic year, the total socioeconomic costs of dengue were US $313,437,342. The overall cost of dengue in Colombia in 2012 represented 0.036% of Colombia’s gross domestic product (GDP), 0.03% of the national general budget, and 0.0385% of the national health budget.[17] Another study estimated the 2011 program costs, including direct and indirect clinical case management, family out-of-pocket expenses, and prevention and control costs, to be at US$128,769,620, compared to the 2011 total program actual costs of US$113,648,671.[18] Additional information about the socioeconomic impact of dengue is provided elsewhere.[11]

The integrated management strategy for dengue prevention and control in the Americas (IMS-Dengue)

The Integrated Management Strategy for Dengue Prevention and Control in the Americas (IMS-Dengue) is a model that was developed in 2003 by the Pan American Health Organization/World Health Organization (PAHO/WHO) Regional Dengue Program and the member states [3] to address the factors that contribute to the spread of dengue transmission. The model aims to integrate different key components in dengue prevention and control in a comprehensive manner and incorporates an International Working Group on Dengue as a consortium of experts providing technical expertise to complement existing national skills and reorient the control strategies at the national and subregional levels. The IMS-Dengue is the product of the political will of all health ministers in the region. Within this framework, countries work to strengthen six components of dengue prevention and control. These include social communication, epidemiology, environment, patient care, laboratory, and the integrated vector management. The effectiveness of this multipronged approach relies heavily on vertical and horizontal coordination at the regional, national, subnational, municipal, and community levels. Political, operational, and administrative difficulties at all levels has made such coordination challenging. IMS-Dengue program (43–100%) comes from external contributions, [3] which include the US Centers for Disease Control and Prevention (CDC), the government of Spain, the Canadian International Development Agency, and the Government of Brazil.[3]

Role of vector control programs in reducing the spread of dengue transmission

A number of vector control programs have been implemented in the region, including indoor spraying, container larvicide treatment, education, and public relations.[19] Despite vector control programs efforts, dengue epidemics continue to strike. Much of the failure of these existing tools has been ascribed to: (1) a lack of personnel (entomologists, social scientists, operational vector control staff) with advanced degrees and proper training to help control dengue epidemics; (2) a lack of technical expertise at decentralized levels of services; (3) insufficient funding for vector control programs; (4) inadequate geographical coverage; (5) interventions relying mostly on insecticides; (6) difficulties in engaging communities; (7) limited capacity building; (8) almost no monitoring and evaluation; and (9) inability to effectively scale-up and predict the public health impact.[19] A framework for an integrated vaccine and vector control program, such as the IMS-Dengue, may help to break this pernicious cycle of dengue given the above challenges.

Role of a dengue vaccine in reducing the spread of dengue

There are six vaccine candidates in preclinical and clinical development. The vaccine candidate called Dengvaxia® is a live recombinant tetravalent dengue vaccine produced by Sanofi Pasteur. Dengvaxia® was evaluated as a three-dose series on a 0, 6, and 12-month schedule in Phase III clinical studies and was submitted for registration in several endemic countries. On 9 December 2015, Mexico approved Dengvaxia®, marking the first time a dengue vaccine has been licensed for use in a country. The vaccine was approved for people aged 9–45 years in areas that are highly endemic, with a dengue seroprevalence of more than 60%, making the introduction of this vaccine more
targeted. Table 1 describes various aspects of dengue vaccines in development.[20]

The development of dengue vaccines has been challenged by multiple factors, including the absence of suitable markers of protective immunity, the complex, immune-mediated responses against four antigenically distinct serotypes requiring lifelong protection to all four serotypes of dengue virus, the transient protection against a secondary heterotypic infection, the inability of the vaccine to stop dengue virus transmission, the lack of an adequate animal disease model, and the resulting uncertainty around correlates of protection.

Table 1. Characteristics of dengue vaccines in development.

<table>
<thead>
<tr>
<th>Valency</th>
<th>Sanofi Pasteur</th>
<th>Takeda Pharmaceutical Limited</th>
<th>Merck &amp; Co</th>
<th>NIAID and Butantan Institute</th>
<th>GSK, Fiocruz, and WRAIR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strategy</td>
<td>Tetravalent</td>
<td>Tetravalent</td>
<td>Tetravalent</td>
<td>Tetravalent</td>
<td>Tetravalent</td>
</tr>
<tr>
<td></td>
<td>ChimeriVax™ Platform using YF17D backbone and dengue E protein</td>
<td></td>
<td>DENAg30/DEN chimeras and noncoding 3’ ΔS0 deletion mutants</td>
<td>Attenuation by passage in primary dog kidney (PDK)</td>
<td></td>
</tr>
<tr>
<td>Estimated cost of production</td>
<td>Too early to provide an estimate</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Supply projections</td>
<td>100 million doses/year starting in 2016 (1 billion doses/decade)</td>
<td>Unknown</td>
<td>Unknown</td>
<td>Unknown</td>
<td></td>
</tr>
<tr>
<td>Price structure</td>
<td>Too early to provide an estimate; SP will make a balance bet' develop-ment capacity, demand, vaccine profile; in process of negotiating price with Mexico.</td>
<td>Unknown</td>
<td>For the price structure, additional costs besides production will be considered</td>
<td>GSK tiered pricing approach</td>
<td></td>
</tr>
<tr>
<td>Target population</td>
<td>In Mexico, target is people aged 9–45 in areas that are highly endemic</td>
<td>All age groups</td>
<td>All age groups</td>
<td>Broad and in immunocompromised individuals</td>
<td></td>
</tr>
<tr>
<td>Vaccine type</td>
<td>Live attenuated</td>
<td>Live attenuated</td>
<td>Recombinant subunit</td>
<td>Tetravalent purified inactivated vaccine Vaccine candidate moving into formulation studies in 2016</td>
<td></td>
</tr>
<tr>
<td>Trial status</td>
<td>Nine phase II trials; Two phase III trials completed. Surveillance of subjects extended for &gt;2 more years, for a total follow-up of 6 years (2017–2018).</td>
<td>Phase II age descending trials (PR, Colombia, Singapore, and Thailand). Three Phase Ib trials done (U.S. &amp; Colombia) to assess viability reduced dose interval/needle vaccine.</td>
<td>Currently in phase II clinical trial in Brazil (Instituto Butantan) and in Thailand (NIH-sponsored)</td>
<td>Currently in Phase III clinical trial planning</td>
<td></td>
</tr>
<tr>
<td>Safety</td>
<td>Five of twenty-two vaccinated Thai children developed plasma leakage and two were in shock during breakthrough dengue illnesses with none in controls*</td>
<td>Safe and well tolerated, no meaningful adverse reactions, self-limited, most common adverse effects: headache, nasopharyngitis, nausea, myalgia of short duration</td>
<td>All formulations were well tolerated</td>
<td>Safety assessed after single dose of tetravalent vaccine</td>
<td></td>
</tr>
<tr>
<td>Vaccine dose schedule</td>
<td>Clinical Development Plan based 6–12 mo schedule</td>
<td>Two doses, day 0 and day 90</td>
<td>Three doses at 1-month intervals</td>
<td>No SAEs during the first 56 days in DPIV-001 and DPIV-002; no safety signals identified to date</td>
<td></td>
</tr>
<tr>
<td>Vaccine presentation</td>
<td>Freeze dried w/ no adjuvant or preservative</td>
<td>Subcutaneous and intradermal by needle &amp; syringe</td>
<td>Recombinant envelope glycoprotein</td>
<td>Lyophilized (reconstituted to liquid for injection)</td>
<td></td>
</tr>
<tr>
<td>Expected licensure date</td>
<td>Approved by the Mexican regulatory authority (COFEPRIS) on 12/9/15</td>
<td>No earlier than 2020, given Sanofi Pasteur vaccine candidate’s safety profile</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Notes: * Individuals receiving any candidate dengue vaccine must be followed up for many years to measure vaccine efficacy and safety, certainly for the 6 years mentioned. NIAID: National Institute of Allergy and Infectious Diseases; GSK: GlaxoSmithKline; WRAIR: Walter Reed Army Institute of Research; SP: Sanofi Pasteur; PR: Puerto Rico; NIH: National Institute of Health; DPIV: Dengue purified inactivated vaccine; Mo: month; COFEPRIS: Federal Commission for the Protection against Sanitary Risks or Comisión Federal para la Protección contra Riesgos Sanitarios (in Spanish); YF17D: Yellow Fever 17D. A previously live vaccine candidate was developed by GSK/FioCruz/WRAIR that is currently not being pursued. This table describes the characteristics of dengue vaccines in the pipeline. It includes information about their potential strategy, supply projections, vaccine production costs, targeted population, efficacy, and safety. Schwartz LM, Halloran ME, Durbin A, Longini IM Jr. The dengue vaccine pipeline: Implications for the future of dengue control. Vaccine 2015;33:3293–3298.[19]
effectively fight the spread of dengue. 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 effective and safe vaccine – in tandem with effective vector control strategies – has the potential to greatly alleviate the human suffering and mortality caused by this terrible disease.

In this paper, we will review only the challenges and opportunities of financing dengue vaccine introduction in the Americas while still recognizing the importance of an integrated management strategy for dengue prevention and control in the region, which includes the need to finance vector control programs, strengthen surveillance programs, and others.

Factors facilitating vaccine introduction in the Americas

New vaccine adoption in the Americas is typically a complex process with numerous stakeholders involved, competing priorities, limited resources, and inadequate financing. There can be considerable challenges on the path toward new vaccine adoption. In spite of these challenges, several countries in the region have successfully introduced new vaccines at the national and subnational levels. Figure 1 describes the factors contributing to the successful introduction of a dengue vaccine in the Americas. What follows is a more detailed discussion on the factors facilitating vaccine introduction in the Americas.

It is critical to have sufficient technical capacity within national-level decision-making bodies to assess new vaccine adoptions. Experts who can evaluate evidence and make recommendations to decision-makers can play a critical role in rapid adoption of dengue vaccine introductions by substantially shortening the time it takes to acquire regulatory approval. In Peru, the Technical Committee and the Consultative Committee within the National Vaccine Strategy Office (ESNI) have considerable influence over decisions to introduce new and existing immunization programs. All decisions to adopt new vaccination programs must receive final approval from this committee. Technical experts within this committee are able to provide valuable input to policy-makers by critically evaluating whether the new vaccines are suitable for adoption within the country’s epidemiological, fiscal, and economic profiles. In the absence of domestic technical capacity to evaluate new vaccines, countries must depend heavily on regional or international technical capacity. This greatly undermines the rapid adoption of vaccines, because it is harder to generate

Figure 1. Factors contributing to the successful introduction of dengue vaccines in the Americas.
This figure depicts the factors contributing to the successful dengue vaccine introduction in the Americas. This includes evidence of affordability and cost-effectiveness analysis, evidence surveillance.
support for advocates and policy-makers with evaluations conducted by outside sources.

**Robust disease surveillance** is essential in determining the disease burden and subsequently identifying the need for a vaccine. Accurate data on mortality and morbidity are essential in determining the potential impact of vaccination and integrated vector control programs in reducing dengue burden and dengue transmission. An example of this is the Rotavirus Surveillance Network in Latin America, established in 2004. This program was instrumental in providing advocates and experts with accurate data on the burden of rotavirus in the region.[21] Since the establishment of the Rotavirus Surveillance Network, many countries have developed a robust disease surveillance system. Currently, data from rotavirus sentinel sites in Bolivia, Chile, Colombia, Ecuador, El Salvador, Guatemala, Honduras, Nicaragua, Panama, Paraguay, and Venezuela are being used to develop more evidence in support of the adoption of the rotavirus vaccine in those countries.[21]

**Vaccine champions** can be pivotal to the adoption of new vaccines. There are several examples of individuals within ministries of health and others who propel the adoption of a new vaccine 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 Gavi and vaccine manufacturers for the introduction of an affordable rotavirus vaccine in the region, demonstrated a commitment and a demand for the vaccine in the region.[22] Through its action, Mexico City demonstrated a commitment and a demand for the vaccine for the region. Another example of strong public support by a regional body for new vaccine adoption is PAHO’s 47th Directing Council Resolution in September 2006, which urged member nations to introduce new vaccines against rotavirus, pneumococcus, and human papillomavirus.[23] Other examples of vaccine introduction champions in the region in recent years include Dr. Cesar Cabezas, popularly known as ‘an apostolate’ of the Hepatitis B campaign in Peru, and Dr. Julio Frenk, Mexico’s former Minister of Health who’s unwavering stewardship of the rotavirus vaccine was central to the vaccine’s adoption in the country.[21, 24]

It is equally important to generate **sufficient evidence on efficacy and safety** of a new vaccine. A safe and effective dengue vaccine would signify a major advance for the control of dengue and could be an important tool for reaching the WHO goal of reducing dengue morbidity by at least 25% and mortality by at least 50% by 2020. Large randomized longitudinal clinical trials document effective and safe preventive interventions against dengue, which is key to generating support from national authorities and technical experts. Prior to WHO prequalification, earlier vaccines such as the rotavirus vaccines, developed by GlaxoSmithKline and Merck, were tested for safety and efficacy in large clinical trials in Latin America.[24, 25] This helped to accelerate vaccine introduction in countries of the region. Additionally, after rotavirus vaccine was introduced in several countries of the region, a vaccine safety study was collaboratively undertaken by the Ministries of Health of these countries, PAHO, the Centers for Disease Control and Prevention (CDC), the US FDA, Gavi, and PATH to improve existing knowledge of the vaccine and its impact on reducing disease burden.[25] This work relieved many of the concerns held by stakeholders in other countries regarding the introduction of a new rotavirus vaccine.[22]

**Early engagement between the Ministers of Finance and Ministers of Health** is key to maintaining dialogue regarding potential funding opportunities for vaccine introduction. The buy-in of the Ministry of Finance is often crucial to ensure budget availability for new vaccine introduction. In the cases of Panama and Ecuador, vaccine introduction laws were facilitated by early stakeholder engagement and mandatory allocation of funds to support new vaccine introduction.[23] The Minister of Health provided the Ministry of Finance with relevant and timely information regarding the benefits and safety of new vaccines. The Minister of Finance, in turn, was persuaded by the strong burden of disease and cost-effectiveness evidence, as well as by solid documentation that showed the positive impact of previous immunization decisions. Planning for new vaccines up to 2 years or more in advance, so that they can be accounted for in government multiyear plans and budgets, including medium-term expenditure frameworks, was helpful in obtaining budgetary resources and commitment for Panama and Ecuador.

Well-documented **economic and financing evidence** supporting new vaccine adoption is critical in demonstrating the public health impact of a new vaccine. Often, in developing countries, there is insufficient evidence to demonstrate the economic or financial impact of a vaccine-preventable disease, and there may be no requirement by the government to provide evidence of the economic benefits of vaccination. The presence of rigorous economic data or the pressure to generate this evidence can have a sizeable influence on advocacy efforts, as more informed vaccine introduction decisions can be made. For example, prior to the introduction of the Hepatitis B vaccine in Peru, cost-effectiveness studies conducted
by Peruvian researchers contributed significantly to generating evidence in support of the vaccine.[23]

Last but not least, **sufficient financial resources** for the purchase and uninterrupted delivery of vaccines are central to successful vaccine adoption. Financing strategies must also take into account the costs of effective vaccine delivery, in addition to vaccine costs. This includes finances for establishing/strengthening efficient procurement systems, adequate cold chain capacity, timely transportation, and training health-care providers in the proper maintenance and delivery of the vaccine. Identifying a source of funding for the introduction of new pneumococcal and rotavirus vaccines in Peru was crucial to ensuring that the vaccine could be universally rolled out.[21] In Peru, US$14 million in supplementary credit from a previous fiscal year were used to purchase sufficient vaccines and to strengthen the cold chain capacity. Countries in Latin America and the Caribbean that have adopted rotavirus vaccines have devoted individual budget line items for vaccine purchases and delivery.[23] In both examples, financial resources devoted to the specific purpose of new vaccine introduction were critical to the successful adoption of these vaccines.

**Challenges to financing dengue vaccine introduction**

In the following section, we discuss some of the challenges to financing dengue vaccine introduction in the Americas.

**Affordable pricing**

The issue of affordability is the leading concern among public health officials in the region for all public health interventions, [26] and a new dengue vaccine is no exception. Even though the disease burden might warrant the adoption of a new vaccine, there may be insufficient fiscal resources accessible to ministries of health to allow for vaccine adoption. While the burden of dengue in the region clearly warrants the adoption of any new vaccine that is efficacious and safe, the lack of affordability will prove to be an insurmountable hurdle. For this reason, vaccine suppliers must bear in mind the fiscal limitations of governments in the region when setting the price of a new dengue vaccine. Even if a new vaccine is deemed cost-effective at a given price, countries will still be unable to adopt the vaccine at the said price if the price proves too high from an affordability standpoint. Fortunately, there are several financing approaches that can ensure the affordability of a new vaccine. These include taxation, low-rate bilateral interest rates, and pooled funding mechanisms. These will be discussed later.

**Availability of sufficient fiscal resources**

Despite the political commitment within ministries of health and affordable pricing of a new vaccine, sometimes it can still be 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.[21]

**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.[21] Countries that have previous experience with 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 of contract with vaccine suppliers.[21]

**Fiscal space**

It is essential that before embarking on the path to dengue vaccine adoption, countries conduct a rigorous analysis of the fiscal space available to increase financial support for a new vaccine program. Fiscal space indicates the ability of governments to provide additional funding for new activities.[21] Fiscal space analysis should focus on providing financial resources for entire programmatic costs of a national-level dengue immunization program, not just for the purchase of a dengue vaccine. Fiscal space analysis is also useful for international donors in determining the magnitude of support that will be required, and the level of cofinancing that is possible, for the introduction of a new dengue vaccine. Countries at different income levels are capable of providing varying levels of financial support, independent of donor support. Fiscal space analysis allows international donors to establish cofinancing and funding levels that are aligned with individual countries’ capacity to pay, while also setting clear benchmarks for countries that are expected to move toward ownership of their dengue immunizations programs in the future.
Moreover, fiscal space analysis not only identifies the realistic level of support 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. If such gaps are revealed after a fiscal space analysis for dengue vaccines, it will indicate the need for additional advocacy or country-level conversations on the need for a new dengue vaccine.

**Financing new dengue vaccine introduction in the Americas: opportunities**

There are several existing financing strategies and potentially new financing models that countries in the region can adopt to ensure the availability of sufficient resources for new vaccines. The following is not a comprehensive analysis of every option available. The focus is on approaches that are either ongoing or have already been implemented and have demonstrated some degree of political or practical feasibility in the region.[21] Table 2 describes various financing options for the region, while Table 3 outlines the strengths and weaknesses of these options.

**Pooled procurement**

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.[21,26] 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; and security of demand for the developer over a defined time period.[21,26]

PAHO’s Revolving Fund is the most known and successful cooperation mechanism for the joint procurement of vaccines and has played a pivotal role in providing countries of the Latin America and Caribbean region with access to vaccines, syringes, and other related medical supplies to member countries at affordable prices.[21,26] For more than 30 years, the Revolving Fund has facilitated the uninterrupted flow of resources needed to maintain the stable functioning of national immunization programs in the region and has been responsible for purchasing vaccines worth several million dollars for the region over the last decade. Most importantly, PAHO’s Revolving Fund has ensured that the vaccines purchased meet the evolving needs of the region. By consistently purchasing new vaccines – which currently account for nearly half of the Revolving Fund’s vaccine procurements – PAHO has ensured that countries in the region have access to the latest vaccines and to timely supplies. Through the Revolving Fund, countries are able to gain access to products based on principles of equity and affordability.[21,26] A single price is established for a product regardless of the country’s size and economic status based on economies of scale.[21,26]

Lastly, a line of credit that allows countries to pay the Revolving Fund within 60 days is available to all member states.[21,26] This line of credit is made possible by contributions of 3% of the net purchase price by all member countries to a common fund that is utilized entirely as working capital. In addition to agreeable costs and terms of payment, PAHO’s Revolving Fund also provides members with technical expertise in the procurement, financing, and negotiation of their products. This service is especially critical for individual countries that lack the expertise to negotiate favorable terms with large manufacturers.

PAHO’s Revolving Fund is not the only procurement mechanism in the region. In September 2009, Brazil’s Ministry of Health 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

**Table 2. Financing options for the region of the Americas.**

<table>
<thead>
<tr>
<th>Financing options</th>
<th>Amount</th>
<th>Mechanism of implementation/Implementation status</th>
</tr>
</thead>
<tbody>
<tr>
<td>Greater than $100 million</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regional taxes</td>
<td>$200 m–1bn</td>
<td>*</td>
</tr>
<tr>
<td>Domestic taxes</td>
<td>$100 m+</td>
<td>*</td>
</tr>
<tr>
<td>Pooled procurement</td>
<td>Savings on purchase price</td>
<td>*</td>
</tr>
<tr>
<td>Less than $100 million</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low-interest multilateral loans</td>
<td>&lt;$100 m</td>
<td>*</td>
</tr>
</tbody>
</table>

Notes: Emptied cells signify that financing options are not applicable to the mechanism of implementation/status of implementation. The cells marked with an ‘*’ denote that financing options are applicable to the mechanism of implementation/status of implementation.

This table provides information about the financing options that are available in the region of the Americas that can potentially assist in developing sustainable vaccine introduction.
### Table 3. Pros and cons of procurement and financing mechanisms.

<table>
<thead>
<tr>
<th>Pros of procurement mechanisms</th>
<th>Cons of procurement mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Easy to set up with minimal operational and governance requirements and a short lead time</td>
<td>• Difficult to determine the best terms of the contract: price, time, value</td>
</tr>
<tr>
<td>• Provides clarity for both purchaser and developer on price and volume over a defined time period. Purchasers can negotiate a lower price from developers</td>
<td>• Can be difficult to manage unintended consequences of contracts (e.g. potential negative impact on competition)</td>
</tr>
<tr>
<td>• Compatible with most financing mechanisms</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pros of multilateral loans</th>
<th>Cons of multilateral loans</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>
<td></td>
</tr>
<tr>
<td>• Established mechanism (no new infrastructure required)</td>
<td></td>
</tr>
<tr>
<td>• Quick implementation (approximately 6 months to 2 years, depending on proposal and approval processes)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Pros of domestic taxation</th>
<th>Cons of domestic taxation</th>
</tr>
</thead>
<tbody>
<tr>
<td>• High revenue</td>
<td>• Politically unpopular (particularly during recession/slowdown)</td>
</tr>
<tr>
<td>• High predictability</td>
<td>• The tax revenues can be difficult to ring-fence for vaccine purchase – may be used for other government priorities</td>
</tr>
<tr>
<td>• Low transaction costs</td>
<td>• Consumer-based taxes hit the poorest consumers the hardest</td>
</tr>
<tr>
<td>• Highly sustainable</td>
<td>• Sector-specific taxes may dis-incentivize business investment in emerging economies</td>
</tr>
<tr>
<td>• Knock-on health gains from ‘sin taxes’ on alcohol/cigarettes</td>
<td>• Some countries in the Americas already have a specific health-care tax</td>
</tr>
</tbody>
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<table>
<thead>
<tr>
<th>Pros of regional taxation</th>
<th>Cons of regional taxation</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 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)</td>
<td>• An airline levy (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 Asian tourist market (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 the option is to secure a UNITAID extension, then no new organization is needed</td>
<td>• An air levy in the Americas will need a new organization 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>

Notes: Adapted from Policy Cures’ Innovative Financing Mechanisms for South East Asia.[27]

This table provides information about the procurement and financing mechanisms that are available in countries of the region.

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period of 8 years.[21] 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.[21]

### Regional taxes

A regional tax is a tax that a group of countries agrees to collect nationally, but with the resulting funds pooled at the regional level for redistribution.[21] They are usually a very small tax but on 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.[21,28] This tax, known as the ‘solidarity levy on airline tickets’, is paid by passengers when they purchase a flight ticket. This includes airport taxes. 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)’, which is responsible for guaranteeing access to drugs and diagnostic equipment against HIV/AIDS, malaria, and tuberculosis.[21,28] Countries set the amount levied, depending on the fare (e.g. economy class, business class) and on whether the flight is domestic or international.[21,28]

A clearly successful example of a regional tax is the air ticket levy that was first implemented in France in 2006, with funds going toward 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. Nine countries now participate in the UNITAID airline levy, including Chile and Brazil. These countries have benefited from this regional tax system to fund vaccination programs.[21] Two possible options are applicable to financing dengue vaccine introductions in the region. This includes persuading UNITAID to extend its remit beyond HIV/AIDS, TB, and malaria to dengue-endemic
countries of the region and/or establishing an airline levy in the region to fund region-specific dengue control and prevention goals.

**Domestic taxes**

These are taxes designed to raise new funds for health care, either by increasing an existing tax, or imposing a new tax on the purchase or use of specific goods or services.[21] 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.[21,29,30]

The funds raised can go into consolidated government revenues, or be ‘hypothesized’ (i.e. earmarked) for a specific cause, such as a dengue vaccine introduction or dengue prevention and control programs. There are many examples where domestic taxation schemes have been successfully used to raise new funds for a specific purpose.[21,30]

Examples of VAT schemes (additional levy on top of existing VAT rate) are many. Chile uses 1% of its VAT to fund health (total rate 19%).[21,31] In Bolivia, one of the main sources of funding for the Universal Mother and Child Insurance (SUMI) is Municipal tax transfer payments (CTM).[21] 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 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.[21,32]

Several countries in Latin America and the Caribbean 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.[21,31,32] Costa Rica raised taxes by 6.5% in early 2012 to fund tobacco control and other health promotion activities.[21,29,30] 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.[21,29] Ecuador, considered a leader in implementing tobacco taxes, adopted a universal tax on all tobacco products to fund health programs.[21,29–32]

**Low-interest multilateral loans**

Another financing initiative is the low-interest multilateral loan in which a multilateral organization (such as the World Bank or the Inter-American Development Bank (IBD)) provides a loan directly to a national government, at a low interest rate to fund new and existing health-care programs.[21,33] Also known as concessional loans, low-interest multilateral loans are typically for 10–40-year periods, and at interest rates of 1–7%.[21,33] 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 has been used to purchase health products as part of a broader disease-specific or health sector program, while the majority of the loan is for equipment or infrastructure upgrades, health worker training, capacity building, and policy development (e.g. development of national health plans).

The World Bank and the IDB provide various loans for health programs in countries in the Americas.[21] 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), undertook to spend US$11.8 billion in development assistance in the region.[21,34] This included spending in large public sector projects beyond health care. A significant portion of these monies is being spent on providing assistance to the health sector programs and projects. However, the total amount given for health care 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 (LICs) through the IDA and to middle-income countries (MICs) through the IBRD.[21,33] Interest rates are lower and repayment terms more generous for LICs.
Examples of low-interest multilateral loans include the Third Basic Health Care Project supported by the World Bank in Mexico.[21,34] This loan was 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.[34] Another low-interest multilateral loan is the Third Rio State Fiscal Efficiency for Quality of Public Service Delivery Development Policy Loan (DPL) Program supported by IBRD/IDA. This program focuses on improving various aspects of public sector delivery of services in the State of Rio de Janeiro in Brazil. Twenty percent of the US$300 million budget is spent on ensuring improvements in efficient health spending, both in regional hospitals and smaller municipalities health centers.[34] The Fourth Programmatic Social Reform Loan Project (PSRL IV) in Peru is funded by the IBRD to the tune of US$100 million to support reforms that are aimed at increasing access, transparency, and efficiency in service provision. A Programmatic Development Policy Loan instrument [34] was used to set up this loan.

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.[21,33] 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.[21,34]

Conclusions

Dengue burden is substantial. Vaccines may help reduce this burden. Funding will be needed for vaccine rollout. Given the fiscal reality facing many countries of the region, especially regarding the ability to appropriate funding for new vaccine introduction, innovative financing options need to be developed to fund vaccine introduction. These include procurement mechanisms, regional and domestic taxes, and low-interest multilateral loans.

Expert commentary

MICs face a triple challenge in affording new dengue vaccine introductions. According to recent estimates by the Institute of Development Studies (IDS), three quarters of the world’s 1.3bn people live in MICs (e.g. India, China, Nigeria, Pakistan, Indonesia),[27] in contrast to a quarter that lives in LICs (e.g. Africa). Many of the MICs are countries afflicted by dengue. In the changing and challenging vaccine environment, MICs are facing increasing financial and technical challenges to maintain the same levels of access to new vaccine introductions as their LIC counterparts, who benefit from financial and technical support for new introduction of these programs. Despite having almost no access to international assistance to run an effective dengue vaccine introduction, MICs are expected to pay significantly higher prices than LICs for many of these programs.

To meet the challenge of vaccine financing in these countries, we consider a range of financing mechanisms. Some of the new tools include 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 vaccines and other control and prevention strategies are properly financed.[21] The proposed mechanism would consist of incorporating existing financing mechanisms with existing procurement mechanisms, resulting in a combined procurement-financing mechanism. The plan would comprise 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.[21]

Another potential financing option is 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.[21] In this model, resources would be frontloaded to accelerate the introduction of new vaccines based on a shared referential vaccine schedule. Infrastructure funding would also be frontloaded to improve cold chain capabilities (maintenance, distribution, management, and logistics) and develop human resource capacity in vaccine delivery and management.[21]

A third financing option is 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.[21] 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.[21]
These recommendations could provide significant advantages to the current vaccine financing system in the region, including the implementation of an integrated health systems fund, the incorporation of a combined procurement-financing mechanism, the creation of a performance-based financing tool, and the implementation of domestic tax increases. There is still significant work to be done in this area. In the end, 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.

**Five-year view**

Within 5 years, there will be sufficient data on the safety and effectiveness of at least three dengue vaccines to allow countries to introduce a dengue vaccination program. As funding for dengue vaccine introductions remains a country responsibility and countries are continuously competing against limited resources, they will need to explore financing options to meet the challenge of financing dengue vaccine introductions. Countries will need to integrate financing strategies that extend beyond just vaccine procurement to health system strengthening. The ability of countries to strengthen their overall national surveillance systems is a critical step in enabling countries to determine disease burden and be in a favorable position for rolling out an effective dengue vaccine introduction. The overarching influence of Pan-Americanism regarding the development of a dengue financing strategy should be considered when planning the funding of vaccine introduction. In sum, substantial increases in dengue cases resulting in increases in public and private health expenditures can be expected in the medium to long term. 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 these strategies will be increasingly burdensome to all health sectors. Alternatives to current pricing and purchasing of these programs are needed to sustain stable investment in the adoption and delivery of these vaccines.

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**References**

Reference annotations

- Of interest
- Of considerable interest

3. Pan-American Health Organization (PAHO)/ World Health Organization (WHO). Number of reported cases and severe dengue (SD) in the Americas, by country; [cited


• Aspects of the revolving fund as a procurement mechanism available in the region are discussed in the paper.


• Important information about various financing mechanisms that can help to fund sustainable vaccination programs.


- A discussion about the tobacco taxes is important in the context of financing mechanisms for dengue vaccine introduction.


- A discussion about the World Bank’s low interest multi-lateral loans, one of the various mechanisms highlighted in the paper and available in countries of the region for vaccine introduction.