Consolidated Points for Consideration for First Introductions of Dengue Vaccines in Endemic Countries
LETTER FROM DVI

Dear Colleagues,

One of the key lessons of the last several decades of vaccine development and introduction is that developing countries will not receive the benefits of a new vaccine if planning does not start early. Here we have captured the outcomes of the 2012 Asia-Pacific and Americas Dengue Prevention Boards meetings, and included the feedback of staff of ministries of health, experts in the field and numerous partners to develop these Consolidated Points for Consideration, with the goal of helping countries interested in being among the first to introduce a vaccine to consider the steps involved in vaccine introduction, and start preparing now.

Over the last decade, very substantial progress has been made in the clinical development of several vaccines and dengue vaccine development has advanced to a point where it now seems likely that at least one vaccine will be available for use in developing countries, perhaps as early as 2015–2016. In addition, two other vaccines may be licensed in 2017 or 2018. Evidence has been mounting for some time, and a recent publication by Alan Brooks, et al. in BMC Public Health documents conclusively that planning for introduction of a new vaccine should begin several years in advance of licensure. The development of Consolidated Points for Consideration is therefore particularly timely. In addition, primarily under the DVI, very important work has been completed and is still underway to lay the groundwork for the introduction and use of new dengue vaccines. A dengue vaccine will be an important part of a comprehensive control strategy that includes prevention, treatment and vector control.

To make sure that developing countries have immediate access to new dengue vaccines, DVI has examined many issues of vaccine introduction and has sponsored a wide range of studies. A primary mechanism for conducting this work is the Dengue Prevention Boards (DPBs) in the Asia-Pacific and Americas Regions. Reports of their deliberation are available on the DVI website.

In June 2012, the Asia-Pacific Dengue Prevention Board (APDPB) meeting in Bangkok, Thailand laid out a number of Consolidated Points for Consideration to help countries determine if they wish to be first-to-introduce a dengue vaccine. The Americas Dengue Prevention Board (AmDPB) met in July 2012 in Bucaramanga, Colombia and built on that first draft, adding their own regional perspective and expertise. The final document that you find here is a consolidation and elaboration of those drafts, and incorporates inputs from a wide range of those involved in dengue and dengue vaccines. The document also includes an extensive and carefully selected list of relevant references that provide additional information and guidance.

We hope these Consolidated Points for Consideration will facilitate decision making by developing countries so that they can access the vaccine as soon as it is available.

Sincerely,

Richard Mahoney
Coordinator (retired), Policy and Access
Dengue Vaccine Initiative
A nurse in Mukdahan, Thailand shows a young girl how to search for mosquito larvae, as part of dengue control programs against the *Aedes aegypti* mosquito, which carries dengue.
INTRODUCTION

The Dengue Vaccine Initiative (DVI) is a consortium of organizations working to lay the groundwork for the introduction and use of new dengue vaccines. One of the key lessons of the last several decades of vaccine development and introduction is that developing countries will not receive the benefits of a new vaccine if planning does not start early. Waiting until a vaccine is licensed to begin planning for its introduction in developing countries has historically resulted in a delay of a decade or more before the vaccine reaches some of those most in need.

Five vaccine candidates are in clinical development (see Table 1). Two live-attenuated dengue vaccines (NIH and Inviragen) are in Phase 2 human testing and one is in Phase 3 (Sanofi Pasteur). A subunit vaccine (Merck) and an inactivated vaccine (GlaxoSmithKline) are also under development. The sixth candidate, a plasmid DNA vaccine developed by the U.S. Naval Medical Research Center, has completed Phase 1 testing. It seems likely that at least one dengue vaccine will be available for use in the relatively near future, despite the mixed results from the recent Phase 2b efficacy trial of Sanofi Pasteur’s dengue vaccine.1 But in order to ensure the vaccine is accessible by developing countries as soon as it is licensed and available, preparation must begin now.

Acknowledging that planning for introduction is a very complex undertaking and requires substantial expertise either in country or from outside, DVI has prepared Consolidated Points for Consideration, which include inputs from all four DVI member organizations (International Vaccine Institute, World Health Organization Initiative for Vaccine Research, Johns Hopkins School of Public Health International Vaccine Access Center, and Sabin Vaccine Institute), as well as the Dengue Prevention Boards, staff of ministries of health, and leading experts (see Appendix for a list of contributors). It aims to:

1. Provide a framework for countries to decide if they wish to undertake introduction activities of the first licensed dengue vaccine or other vaccines that may follow and,

2. Guide subsequent dengue vaccine adopting countries, so that the traditional lag time for vaccine introduction can be shortened and the greatest impact on public health can be achieved.

Thus, this guide is designed to help policy-makers and the national immunization program managers to assess the needs of their country and launch planning activities, as well as to serve as a reference and guide throughout their decision-making process. By the time a new dengue vaccine is available, countries considering vaccine introduction should ideally have the capacity to conduct all necessary activities which will be discussed throughout this document.

Epidemiology and Laboratory Capacity (ELC)

A key to successful vaccine introduction

- Developing adequate ELC prior to vaccine introduction is extremely important to ensure improved diagnosis, reporting, and monitoring of cases.
- Lab-based surveillance will enable countries to conduct necessary tasks, including impact modeling, post-licensure demonstration projects or Phase 4 trials, as well as evaluation of vaccine safety and effectiveness.
In order to support programs to introduce new vaccines effectively, WHO has produced several introduction guidelines. They include vaccine specific and generic ones. A draft guidance document on dengue-vaccine specific aspects of introduction has been produced by WHO, and will be finalized once more information is available on vaccine characteristics and performance.

With particular emphasis on the three most important and essential components for successful introduction of dengue vaccines, Surveillance, Regulatory Affairs, and Modeling, Consolidated Points for Consideration has been developed to address six key topics that need to be thoroughly reviewed and examined prior to introduction of a dengue vaccine:

- Regulatory;
- Evidence for Decision-making;
- Impact Modeling;
- Immunization Systems;
- Demand and Financing; and,
- Post-Licensure/Demonstration Projects.

This document contains a section for each topic, including discussion of the broader topic as well as consideration of several sub topics and specific examples. Should there be a need for more information on a topic, a selected list of publications has been compiled, and is cited throughout the text. This list of references, with links to full-text articles (free open access) or a webpage with publication details, is presented at the end of this document.

Key Messages:

- A dengue vaccine is expected to be available for use in the relatively near future.

- Countries considering introducing and implementing a new vaccine should be capable of:
  - Making licensing decisions and conducting postmarketing surveillance through the National Regulatory Authority (NRA) in coordination with the National Immunization Technical Advisory Group (NITAG);
  - Collecting and evaluating evidence for decision-making based on epidemiological surveillance; economic, policy, and social studies; and modeling;
  - Conducting impact modeling and applying its findings to develop immunization strategies;
  - Monitoring and evaluating vaccine effectiveness;
  - Establishing an information surveillance system;
  - Developing effective communication strategies; and staff training;
  - Assessing their demand and developing effective financing strategies;
  - Carrying out post-licensure/demonstration projects and sharing the results with other countries to strengthen the immunization strategies.
### TABLE 1. Dengue vaccines in development (as of November 2012)

<table>
<thead>
<tr>
<th>DEVELOPER</th>
<th>PRECLINICAL</th>
<th>PHASE 1</th>
<th>PHASE 2</th>
<th>PHASE 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>SANOFI PASTEUR</td>
<td></td>
<td></td>
<td>Currently conducting several Phase 3 trials on their live attenuated chimeric tetravalent vaccine, developed using the yellow fever virus as a backbone, in Australia and in countries in Asia and Latin America.</td>
<td></td>
</tr>
<tr>
<td>NAVAL MEDICAL RESEARCH CENTER (U.S.)</td>
<td></td>
<td>A proof of concept Phase 1 trial for DEN2 vaccine has been completed for their plasmid DNA vaccine. Five of 12 recipients of the high dose vaccine developed serum neutralizing antibodies to DENV-1. The vaccine is being reformulated with the novel adjuvant Vaxfectin to improve immunogenicity.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>U.S. NATIONAL INSTITUTES OF HEALTH (NIH)</td>
<td></td>
<td>Tested different monovalent dengue vaccine candidate vaccines to select those candidates with most favorable safety and immunogenicity profiles. TV003, the tetravalent vaccine formulation chosen for further evaluation, will begin Phase 2 trials in Thailand in flavivirus-experienced adults and children.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BIOLOGICAL E (India)</td>
<td></td>
<td>Made seed lots at scale of their live attenuated tetravalent vaccine (licensed NIH vaccine) and are reviewing their clinical development strategy.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BUTANTAN (Brazil)</td>
<td></td>
<td>Has produced different lots of their live attenuated tetravalent vaccine (licensed NIH vaccine) formulation and completed stability testing on these lots.</td>
<td>Has produced clinical lots of their live attenuated tetravalent vaccine (licensed NIH vaccine). They have received approval to begin Phase 2 testing of this product in flavivirus-naive and flavivirus-experienced adults in Brazil.</td>
<td></td>
</tr>
<tr>
<td>PANACEA BIOTECH (India)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VABIOTECH (Vietnam)</td>
<td></td>
<td>Has started production of monovalent seed lots for their live attenuated tetravalent vaccine (licensed NIH vaccine). When those have completed safety testing, they will formulate the vaccine. Currently developing their clinical trial plan.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>INVIRAGEN (Acquired by Takeda)</td>
<td></td>
<td>Entered Phase 2 clinical trials in Puerto Rico, Colombia, Singapore and Thailand for their live attenuated tetravalent vaccine. In addition, rapid immunization strategies and needleless administration are being investigated.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MERCK</td>
<td></td>
<td>Has completed a proof of concept Phase 1 trial of the recombinant subunit protein vaccine adjuvanted with Alum developed at Hawaii Biotech. They are conducting a Phase 1 trial of the tetravalent vaccine adjuvanted with ISCOM in Australia.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GLAXOSMITHKLINE</td>
<td></td>
<td>Currently in Phase 1 proof of concept testing of a purified inactivated vaccine given with novel adjuvants, originally developed by the Walter Reed Army Institute for Medical Research (U.S.), and conducting a Phase 1 study to evaluate novel methods of vaccine administration. Has signed a research agreement to develop this vaccine with Brazil’s Oswaldo Cruz Foundation.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### OVERVIEW OF POINTS FOR CONSIDERATION

**REGULATORY**
Countries considering introducing a dengue vaccine should consider:
- Capacity of the National Regulatory Authority (NRA)\(^4-^9\)
- Countries considering dengue vaccine introduction should also consider:
  - Involving WHO Recognized Regulators to Discuss Needs for a Licensing Decision
  - A Gap Analysis of the NRA
  - The NRA's Willingness to Accord Priority Review
  - The NRA's Ability to Assess Manufacturers' Risk Management Plans
  - The NRA's Ability to Assess Country Specific Issues (GMOs, etc)
  - Coordination between the National Immunization Technical Advisory Group (NITAG) and NRA

**EVIDENCE FOR DECISION-MAKING**
Countries considering dengue vaccine introduction should have the ability to undertake or participate in:
- Epidemiological Surveillance
- Economic Studies
- Policy Studies
- Social Studies
- Modeling
- Impact Assessments

**IMPACT MODELING**
Countries considering dengue vaccine introduction should consider:
- The Potential Applications of Modeling
- The Country’s Ability to Conduct Impact Modeling

**IMMUNIZATION SYSTEMS**
Prior to an introduction decision, countries considering dengue vaccine introduction should consider:
- The Recommendations of the National Immunization Advisory Group (NITAG)
- The Strategy for Vaccine Introduction
- The Budget for a Dengue Vaccine
- The Capacity for Immunization Surveillance
- The Capacity for Monitoring and Evaluation
- The Capacity of the Cold Chain and Logistics Management
- The Capacity of the Information System
- The Capacity of Communications Systems
- Training
- Cross-Sector Collaborations

**DEMAND AND FINANCING**
**Demand**
Countries considering dengue vaccine introduction should consider:
- Historical Rollout Data
- Previous Experience with Mass Immunization Campaigns or with a Vaccine Outside of the EPI schedule
- The Functioning of Management and Delivery Systems

**Financing**
Countries considering dengue vaccine introduction should consider:
- The Budget Line-Item for a Dengue Vaccine
- The Fiscal Space to Increase the Immunization Budget
- The Budget for Implementation and Delivery of a Dengue Immunization Program
- The Fiscal Space for Monitoring and Evaluation
- The Fiscal Space to Maintain Financing for Existing Vector Control
- Experience in the Coordination of Budgets across Ministries
- Experience with Price Negotiations

**POST LICENSURE/DEMONSTRATION PROJECTS**
Additionally, countries considering dengue vaccine introduction must:
- Have National Support and Community Acceptance
- Have the Technical Capacity, Resources, and Desire to Evaluate Safety and Effectiveness
- Be Willing to Share Outputs of Studies
- Have functioning Technical Collaborations
Countries considering introducing a dengue vaccine should consider:

**Capacity of the National Regulatory Authority (NRA) to:**

- Oversee Phase 3 and 4 trials;
- Make licensing decisions for innovative products, based on scientific review, especially for recombinant chimeric vaccines/genetically modified organisms;
- Evaluate data on target populations and dosing schedules, and set criteria on vaccine use for Phase 4 studies;
- Develop and validate lot release testing for innovative vaccines;
- Recognize and assure current Good Manufacturing Practices (cGMP);
- Investigate Adverse Events Following Immunization (AEFIs) from clinical trials, in routine, or catch-up campaigns;
- Perform long term safety monitoring;
- Self-assess performance of the NRA.

Ideally countries considering dengue vaccine introduction will have a WHO Regional Office recognized NRA and be capable of performing all of the above functions.

Countries considering dengue vaccine introduction should also consider:

**Involving WHO Recognized Regulators to Discuss Needs for a Licensing Decision**

Ideally an expert panel would be constituted and convened by DVI and there would be a joint review of the decision-making process involving the NRAs of first-to-introduce countries. This would support these NRAs in their decision-making process, which they would then carry out independently.

**A Gap Analysis of the NRA**

A gap analysis of all necessary NRA functions should be conducted and countries considering dengue vaccine introduction should indicate where they would need support, where they can obtain that support, and what the time frames and budget would be.

**The NRA’s Willingness to Accord Priority Review**

NRAs in first-to-introduce countries should be prepared to provide priority review for dengue vaccine. This will ensure that the NRA is capable of licensing a dengue vaccine within the timeframe for planned first-introductions.

**The NRA’s Ability to Assess Country Specific Issues (GMOs, etc)**

Some countries may have specific issues that they wish to address, and innovative vaccines may present specific challenges for NRAs, such as how to conduct an environmental impact assessment of Genetically Modified Organisms (GMOs). Countries considering dengue vaccine introduction should ensure that they are capable of addressing these issues. This might involve inter-ministerial cooperation, e.g. between Ministries of Health and Agriculture, etc.

**Coordination between the National Immunization Technical Advisory Group (NITAG) and NRA**

Countries considering dengue vaccine introduction should ensure that there is good coordination between the NITAG and the NRA. This could include ex-officio representation of each of these institutions on the advisory panel of the other. This will also ensure that both national institutions are working towards the same time frame for vaccine introduction.
EVIDENCE FOR DECISION-MAKING

Countries considering dengue vaccine introduction should have the ability to undertake or participate in:

**Epidemiological Surveillance**

At a minimum, countries should have evidence of burden of dengue disease, both outpatient and inpatient, including the **incidence**, the **age and geographical distribution**, the **serotype circulation**, and **seroprevalence** in key epidemic locales. Ideally these data should cover the past 10 years, and at a minimum two epidemic peaks.\textsuperscript{14, 24-36}

Other valuable data include mortality and disease severity.

These data are essential for establishing priorities relative to other vaccine preventable diseases, for determining priority target groups where resources and/or vaccine supply are limited, for accurately forecasting the demand and logistical requirements for a vaccine, and for assessing the impact of the immunization program on the disease.\textsuperscript{37-39}

Many dengue endemic countries do not have full epidemiological and laboratory capabilities to carry out appropriate dengue surveillance. These capabilities will have to be built up.

**Policy Studies**

A number of policy assessments targeting high ranking decision-makers and politicians should be completed to build evidence for decision-making. These would include a policy review of the importance of the disease, an assessment of the risk-benefits, the programmatic challenges (affordability and sustainability, logistical and supply), and the strategic options (routine and mass immunization, scheduling, co-administration, target age groups).\textsuperscript{56-60}

Contingency strategies should also be developed to deal with unforeseen circumstances, such as if an epidemic occurs during vaccine introduction.

**Social Studies**

A number of social dimensions should be well understood in advance of vaccine introductions. These would include evaluation of Knowledge, Attitude and Practices (KAP studies) to address public opinion and demand for a vaccine and to understand the role of the media.\textsuperscript{61-70}

**Modeling**

Mathematical and statistical models are used to integrate data and analysis from epidemiological and natural history studies into a coherent system for study of dengue transmission and control. In the case of control with vaccines, this includes the careful analysis of dengue vaccine trials, Phases 1-4. Such vaccine studies include the estimation of vaccine efficacy and effectiveness, and determination of potential immunological correlates of protection. Careful statistical analysis of prospective dengue cohort studies, coupled with routine population-level surveillance is combined with knowledge of dengue transmission to construct mathematical models for dengue transmission and control. Such a comprehensive dengue model has recently been constructed for rural Thailand.\textsuperscript{70} This model will be generalized for the use of available epidemiological data from other parts of the world.
Using epidemiological and economic data, with a model as described above, countries should model impacts of dengue vaccine deployment on disease and costs. Model outputs should include dengue virus transmission, age-specific disease attack rates, including immunization implementation costs, and cost saving. Outputs of modeling will help to better inform decision-making and encourage other countries to generate county-specific data.38, 71-73

**Impact Assessments**

Countries should have the ability to assess public health impacts and vaccine effectiveness after vaccine introduction, in addition to routine post-licensure assessments by the vaccine manufacturer. Countries considering dengue vaccine introduction should be aware that their experiences may be used to guide later-introducer countries.1, 2, 4, 8, 74-76

These countries should use uniform study designs and protocols as much as possible to assess vaccine effectiveness so that the results will be generalizable to the later introduction of vaccine.

Of note, some countries may consider building evidence iteratively and choose to first introduce a vaccine on a limited scale or area.

### IMPACT MODELING

**Countries considering dengue vaccine introduction should consider:**

#### The Potential Applications of Modeling77-80

- Integrating information from multiple sources of data to provide a transparent summary of the current dengue situation;
- Developing optimal immunizations strategies, including routine vaccination and catch-up programs;
- Determining target groups for vaccination;
- Determining Phase 4 study design;
- Determining demand forecasting;
- Assessing economic impacts from immunization (direct and indirect costs averted);
- Assessing epidemiological impacts from immunization (on infections, cases, deaths, hospitalizations);
- Assessing the synergistic impacts of other prevention/control strategies, notably vector control efforts.

#### The Country’s Ability to Conduct Impact Modeling

Countries considering dengue vaccine introduction should assess their capacity to conduct impact modeling. Data required for modeling include:36, 78, 81-88

- Vector density for the locale being modeled;
- Incidence of cases — both hospitalized and non-hospitalized — and deaths by age and gender;
  - Data should come from routine reporting and enhanced surveillance in certain regions.
- Serotype-specific susceptibility profile, by age;
  - Data from enhanced surveillance, and selected prospective cohorts and household studies.
- Natural history of infection: incubation period, infectious period, inter-serotype interaction;
- Historical distribution of each serotype by age;
- Corrective factors to ensure that under- or over-reporting of vaccination is accounted for (expansion factors);
- Impacts of other types of interventions, such as vector control activities (target control activities around the area of new cases), effects of *Wolbachia*, etc;
- Vaccination factors, overall and serotype-specific:
  - Number of dosage, duration of protection, dosage schedule;
  - Estimation of vaccine efficacy85 for susceptibility to infection (VE\_r); disease (VE\_d); infection and disease (VES\_r); and transmission to mosquitoes (VE\_t);
The Recommendations of the National Immunization Advisory Group (NITAG)

The decision to introduce a new vaccine normally follows a recommendation by the NITAG. The NITAG should therefore be prepared to review the vaccine and make a decision whether to recommend for use or not.20-22, 60, 89, 90

The Strategy for Vaccine Introduction

Countries should determine where (which geographic areas) they will introduce the vaccine and in which age groups. Strategies can be assessed with good epidemiological data and mathematical modeling. In the development of introduction strategies, countries should assess optimal strategies for utilization of initially limited quantities of vaccine and assess whether vaccines should be used (first) in urban or rural areas, in catch-up, routine or mass campaigns.90-102

Appropriate guidelines should be developed on the roles and responsibilities within the immunization system, specific to dengue immunization.

The Budget for a Dengue Vaccine

Additional funds will need to be raised to support the many activities of a dengue vaccination program. Countries should consider how the vaccination program will be financed. Financing and supply should be assured before introduction activities are initiated. Dengue vaccine should be regarded as one intervention in the context of the overall efforts for prevention and control. First-to-introduce countries should ensure availability of additional resources for immunization so that the introduction of the vaccine will not diminish a county’s ability to maintain vector control initiatives.34, 38, 57, 103-105

The Capacity for Immunization Surveillance

Critical functions of surveillance that will need to be established for a dengue vaccine include the ability to:14, 26, 35, 106, 107

- Ascertain vaccination coverage;
- Detect and report adverse events, including:
  - Trace vaccine lots to individual adverse events;
  - Detect and report using standardized definitions of adverse events; and,
  - Detect adverse events through sentinel surveillance of febrile illnesses;
- Estimation of vaccine effectiveness85, including indirect effects: Overall effectiveness (VE_{overall}); indirect effectiveness (VE_{indirect}); and total effectiveness (VE_{total}); and,
- Coverage rates by dose.

Further data describing dengue-specific annual infection rates should be collected for selected populations from routine and enhanced surveillance, and prospective cohort studies with concurrent vector density studies. Assumptions should be clearly reported, including for the natural history of infections, and for the transferability of data from a specific locale to another region. Surveillance can be a complex undertaking requiring high levels of expertise in a number of fields. Different countries undertaking these studies should use similar and coordinated protocols so that data and modeling can be combined in analysis. This will allow for generalization of results.

Technical guidance is available from a number of institutions associated with DVI.
Detect the impacts of immunization (e.g. vaccine effectiveness).

Specific surveillance for severe disease should be initiated for dengue. The surveillance capacity must be robust and may require strengthening of laboratory and sentinel surveillance. The AEFI surveillance of the immunization system must be complementary and coordinated with the pharmacovigilance of the NRA. One will NOT substitute for the other.

The Capacity for Monitoring and Evaluation

Countries considering dengue vaccine introduction should have the capacity to continuously monitor the impact of the dengue immunization program on the disease burden and to assess vaccine effectiveness. This includes the occurrence of disease in unvaccinated areas. Tracking systems should be reviewed and strengthened if necessary to ensure that everyone being vaccinated receives the appropriate doses of vaccine and that high coverage is achieved. Plans should be developed to respond to outbreaks. Diagnostic and case confirmation protocols should be developed.

The Capacity of Communications Systems

Several forms of communication strategies need to be developed, starting with clear messages on the rationale for immunizing the target population, including where (geographically) immunization will occur if a vaccine is introduced in a phased basis. Countries should develop risk communication plans to be prepared to deal with adverse events, and to counter groups opposed to vaccination.

Communications should be developed with the help of experts in mass communications.

Communications should be individually tailored to decision-makers, the health community, the general public, and the media.

Training

Complete training, including on diagnosis of the disease, vaccine administration, AEFIs, surveillance, vaccine characteristics, vaccine wastage and storages, will be required. Countries considering dengue vaccine introduction should serve as models for other countries in terms of access strategies, vaccine registries, including for high risk groups, etc. Therefore they should determine whether sufficient training has been given or have the ability to identify additional required training supports.

Cross-Sector Collaborations

Both intra-sectoral and inter-sectoral collaborations should be established to define and integrate the role of the national immunization program in dengue control. Discussions should involve actors from other control initiatives, especially with vector control departments, with NGOs, DVI, the Sabin Vaccine Institute, WHO and PAHO, clinicians, politicians, and others. Collaborations should occur for dengue control activities, for communications on dengue and dengue immunization, and for the development of public policy on dengue and dengue immunization.
DEMAND AND FINANCING

Countries considering dengue vaccine introduction should have met the minimum requirements noted under the other considerations in order to be capable of assessing their demand and finance requirements, such as the ability to conduct good disease surveillance (Evidence for Decision-making), to model (Impact Modeling), and to strategize for introduction (Immunization Systems). These considerations are not repeated here.

These countries will have determined dengue to be a priority disease, based on the health and economic burdens, and public demand for a vaccine.

DEMAND

Note: assumptions for demand are subject to variations in supply, price, and efficacy.

Countries considering dengue vaccine introduction should consider:

Historical Rollout Data

Countries with previous experience at new vaccine rollouts may benefit from lessons learned and utilize previously collected data on demand and costs to inform a dengue vaccine introduction plan.\(^{127,128}\)

The rollout plan will determine how much vaccine is to be utilized at any given time and ensure good coordination with the supply.

Previous Experience with Mass Immunization Campaigns or with a Vaccine Outside of the EPI schedule

First-to-introduce countries should have prior experience with successful implementation of mass vaccination campaigns (measles or rubella), or vaccines outside EPI schedules, such as pandemic flu, yellow fever, or HPV vaccines. In addition, campaigns or routine immunization programs should be functioning well. Previous experience with mass campaigns and other immunization programs will help to inform about the management of vaccine demand in relation to the supply.\(^{94-96,129,130}\)

The Functioning of Management and Delivery Systems

Countries considering dengue vaccine introduction should have well functioning vaccine management and delivery systems, measured by indicators such as lack of supply interruptions, high immunization coverage rates, lack of vaccine-preventable disease outbreaks, and good EPI infrastructure (such as cold chain, surveillance system, etc). Lack of supply interruptions can serve as a proxy for capacity to adequately forecast demand, but programs should be closely coordinated with the supplier to ensure that demand can be met.\(^{101,115,130-133}\)
FINANCING

Countries considering dengue vaccine introduction should consider:

The Budget Line-Item for a Dengue Vaccine
Countries considering dengue vaccine introduction should have a line item in the budget of the EPI Program, and allocate additional funds. This will ensure that lack of funding does not interrupt or otherwise disrupt introduction and maintenance strategies. It is strongly recommended that countries assess associated costs and benefits with introduction of a dengue vaccine into their national immunization program, secure a budget to ensure affordability and long-term sustainability, and actively seek for funding resources. Countries are encouraged to mobilize domestic or external funds (e.g., GAVI) to cover potential increase in the total costs of the EPI program incurred as a result of adding a dengue vaccine into the program.2, 134

The Fiscal Space for Monitoring and Evaluation
In addition to vaccine delivery, countries should have the ability to finance evaluation and monitoring of vaccine impacts, such as vaccine effectiveness and cost-effectiveness, and to finance post-licensure studies to evaluate long term safety.50, 77, 135, 136

The Fiscal Space to Maintain Financing for Existing Vector Control
The country should understand the importance of maintaining financing for existing control measures (e.g., vector control) and should not divert funds away from current control programs.

The Fiscal Space to Increase the Immunization Budget
Having the fiscal space to add 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 also be corroborated by the Ministry of Finance.

The Budget for Implementation and Delivery of a Dengue Immunization Program
In addition to having sufficient funds to purchase vaccine, countries should ensure they have sufficient funding for the implementation and delivery of a dengue vaccine. This could include school-based delivery, depending on the specific country strategy, and could represent a significant cost.38, 101, 134

Experience in the Coordination of Budgets 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, etc), and across public and private sectors (e.g. insurance).

Experience with Price Negotiations
The terms of contracts may be more favorable for countries if they are negotiated for longer terms, bundled with other purchases, or purchased by bulk procurement agencies. Countries may negotiate shared costs with suppliers for some post-licensure assessments.137
POST LICENSURE/DEMONSTRATION PROJECTS

Because there is no experience with any licensed dengue vaccines, and because of the potential for sensitizing for more severe disease, some Phase 4 trials may be requested of NRAs. Beyond requirements for Phase 4 studies, there will be questions the countries will want to answer through pilot introduction studies, such as how to introduce a vaccine to have the most impact on disease as quickly as possible. Therefore, countries considering dengue vaccine introduction should consider whether or not they have the capacity to conduct post-licensure demonstration projects or Phase 4 trials. As with surveillance, the conduct of post-licensure and demonstration projects is a complex undertaking. Technical support can be obtained from IVI and several institutions associated with the DVI.

All of the other ‘Points for Consideration’ to introduce vaccines are critical to enabling successful demonstration projects and must be met before demonstration projects can be considered.

Additionally, countries considering dengue vaccine introduction must:

**Have National Support and Community Acceptance**

Political support at the highest levels is necessary to ensure the elements needed to carry out post-licensure/demonstration projects are in place. National and local communities should be active and supportive of early introduction.

**Have the Technical Capacity, Resources, and Desire to Evaluate Safety and Effectiveness**

Countries considering dengue vaccine introduction should build on existing integrated country surveillance. Surveillance should start before the vaccine is available (such as was the case for rotavirus surveillance which started three years before vaccine availability). The country should have serotype specific surveillance, and strengthen laboratory capacity, data management and analysis capacities.

Countries should develop a manual for surveillance and develop criteria for successful surveillance based on country capacity. Countries should also have the capacity to investigate vaccine failures and to investigate specific safety signals if and when they appear. Severe adverse events should be measured within defined studies, or as part of existing surveillance.

**Be Willing to Share Outputs of Studies**

Because countries introducing dengue vaccine will generate many important lessons for subsequent introducers, they should be willing to share knowledge gained whether through positive or negative study results. Selected countries will consider conducting cohort studies which could include disease severity following immunization, length of immunity, herd protection, etc. Effectiveness of vaccine used in outbreaks and outbreak prevention studies should also be conducted. It is important to note, however, that all required doses of vaccine must be administered prior to infection but not during or after outbreaks to maximize its effects and associated benefits. Delivery of vaccines during an outbreak is unlikely to have a significant impact on the outbreak.

**Clinical Trials – Phase 4**

According to the WHO, in Phase 4 of a clinical trial, “studies are conducted after the intervention has been marketed. These studies are designed to monitor effectiveness of the approved intervention in the general population and to collect information about any adverse effects associated with widespread use.”

**Have functioning Technical Collaborations**

Because of the challenges associated with dengue vaccine introduction, it is anticipated that countries who introduce dengue vaccine will capitalize on the existing collaboration with technical agencies such as the WHO, IVI, DVI, etc and work together with inter-country institutions to enhance cooperation in the development of common guidelines, case definitions, manuals, sharing of data, etc.
CONCLUSION

After decades of waiting, the first dengue vaccine may soon be available for widespread use, with the potential to prevent dengue infection for billions of people worldwide. It is strongly recommended that endemic countries carefully use this guide to thoroughly assess and review their needs and current capacities, and develop effective immunization strategies for the successful and timely implementation of dengue vaccine.

The mission of the Dengue Vaccine Initiative is to encourage the development and use of vaccines to prevent dengue. As a consortium of organizations committed to a world without dengue, DVI is working to lay the groundwork for dengue vaccine introduction in endemic areas so that, once licensed, vaccines to prevent dengue will be swiftly adopted.

DVI is a consortium of four organizations: the International Vaccine Institute, the International Vaccine Access Center at Johns Hopkins University, the Sabin Vaccine Institute and the Initiative for Vaccine Research at the World Health Organization.
REFERENCES


APPENDIX

DENGUE PREVENTION BOARDS: AMERICAS

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

Dr. Juan José Amador
Medical Epidemiologist, Nicaragua

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

Dr. Jorge Boshell
Director
Biosafety Committee
Bone and Tissue Bank (Banco de Huesos), Colombia

Dr. Iris Villalobos de Chacon
Chief of Epidemiological Services
Hospital Central de Maracay, Venezuela

Dr. José F. Cordero
Dean of Graduate School of Public Health
Medical Sciences Campus
University of Puerto Rico, Puerto Rico

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

Dr. Eduardo Fernandez
Adjunct Professor
Community Health Sciences
Brock University, Canada

Dr. Maria Guadalupe Guzman
Head Virology Department
Director
PAHO/WHO Collaborating Center for Dengue
Pedro Kouri Tropical Medicine Institute

Dr. Harold Margolis
Liaison Member
Chief of Dengue Branch
Centers for Disease Control and Prevention, Puerto Rico

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

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

Dr. Anabelle Alfaro Obando
National Advisor in Dengue Management, Costa Rica

Dr. Steve Waterman
Liaison Member
Lead of US Mexico Unit
Division of Global Migration and Quarantine, CDC, USA
DENGUE PREVENTION BOARDS: ASIA-PACIFIC

Dr. Sri Rezeki S. Hadinegoro
Professor of Pediatric Infectious Disease
Senior Lecturer at Division of Infectious and Tropical Diseases
Department of Child Health
Faculty of Medicine,
University of Indonesia, Indonesia

Dr. Jeffrey Hanna
Public Health Physician
Tropical Population Health Unit, Australia

Dr. Jacob T. John
Advisor
Christian Medical College Hospital, India

Dr. Eng Eong Ooi
Program Director (Biological Defence)
DSO National Laboratories.
Adjunct Assistant Professor
National University of Singapore, Singapore

Dr. Paba Palihawadana
Chief Epidemiologist
Ministry of Health,
Epidemiology Unit, Sri Lanka

Dr. Simon Reid
Epidemiologist
Surveillance and Operational Research Team Leader
Public Health Division
Secretariat of the Pacific Community, New Caledonia

Dr. Pratap Singhhasivanon
Vaccine Trial Center
Faculty of Tropical Medicine
Mahidol University, Thailand

Dr. Enrique Tayag
Director IV
National Epidemiology Center
Department of Health
San Lazaro Compound, Philippines

Dr. Hlaing Myat Thu
Deputy Director and Head
Virology Research Division
Department of Medical Research (Lower Myanmar), Myanmar

Dr. Sirenda Vong
Head
Epidemiology and Public Health Unit
Institut Pasteur du Cambodge, Cambodia

DVI TECHNICAL ADVISORY GROUP (TAG)

Dr. Lulu Bravo
Executive Director
National Institutes of Health, Philippines

Dr. Jose Ignacio Santos
Professor
Experimental Medicine and Infectious Diseases
School of Medicine
Autonomous National University of Mexico, Mexico

Dr. Pratap Singhhasivanon
Dean
Faculty of Tropical Medicine,
Mahidol University, Thailand

Dr. John Vose
Consultant

Dr. Francisco Songane
Director
Partnership for Maternal, Newborn & Child Health
WHO, Switzerland

Dr. Carlos M. Morel
Scientific Director
Center for Technological Development in Health
Oswaldo Cruz Foundation
Ministry of Health, Brazil

Dr. Duane J Gubler
Professor & Director
Program on Emerging Infectious Diseases
Duke-NUS Graduate Medical School, Singapore
TECHNICAL EXPERTS: DVI STAFF AND CONSULTANTS

Dr. Ananda Amarasinghe  
Consultant Epidemiologist  
Epidemiology Unit  
Ministry of Health, Sri Lanka

Dr. Mabel Carabali  
Consultant Epidemiologist  
Dengue Vaccine Initiative (DVI)  
International Vaccine Institute, Korea

Ms. Ana F. Carvalho  
Associate Director  
Vaccine Advocacy and Education  
Sabin Vaccine Institute, USA

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

Dr. Luiz Jacintho da Silva  
Director  
Dengue Vaccine Initiative (DVI)  
International Vaccine Institute, Korea

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

Ms. Denise DeRoeck  
Consultant, USA

Dr. Shawn Gilchrist  
S Gilchrist Consulting Services Inc

Dr. Scott Halstead  
Senior Scientific Advisor  
Dengue Vaccine Initiative (DVI)  
International Vaccine Institute, Korea

Ms. Jacqueline Lim  
Epidemiologist  
Dengue Vaccine Initiative (DVI)  
International Vaccine Institute, Korea

Dr. Ira M. Longini  
Professor  
Biostatistics Department of Biostatistics  
College of Public Health and College of Medicine  
University of Florida, USA

Dr. Richard Mahoney  
Coordinator, Policy & Access  
Dengue Vaccine Initiative (DVI)  
International Vaccine Institute, Korea

Dr. Brian Maskery  
Associate Research Scientist  
International Vaccine Institute, Korea

Dr. Julie Milstien  
Consultant  
University of Maryland, USA

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

Dr. Pem Namgyal  
Medical Officer  
World Health Organization, Switzerland

Ms. Meghan Stack  
Economist  
Johns Hopkins Bloomberg School of Public Health, USA

Dr. Jonathan Sugimoto  
Research Assistant Professor  
Department of Epidemiology  
School of Public Health and Community Medicine  
University of Florida  
Staff Scientist  
Vaccine and Infectious Disease Division  
Fred Hutchinson Cancer Research Center, USA

Dr. Thomas Wierzba  
Deputy Director General  
Translational Research Division  
International Vaccine Institute, Korea
TECHNICAL EXPERTS: STAFF OF OTHER ORGANIZATIONS AND CONSULTANTS

Dr. Alan Brooks  
Senior Specialist  
Policy, Policy & Performance  
GAVI Alliance Secretariat, Switzerland

Dr. Klara Henderson  
Policy Cures, Australia

Dr. Julie Jacobson  
Senior Program Officer  
Bill & Melinda Gates Foundation, USA

Dr. Andrea Vicari  
Advisor  
Immunization Comprehensive Family Immunization Regional Project  
Pan American Health Organization  
World Health Organization, Costa Rica

Dr. Jorge Osorio  
Associate Professor  
Department of Pathobiological Sciences  
University of Wisconsin, USA

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

Dr. John Yang  
Neglected Infectious Diseases  
Bill & Melinda Gates Foundation, USA
TECHNICAL EXPERTS: DEVELOPERS

Dr. Robert Gibbons
Armed Forces Research Institute of Medical Sciences (AFRIMS), Thailand

Dr. In Kyu Yoon
Armed Forces Research Institute of Medical Sciences (AFRIMS), Thailand

Dr. Ricardo Palacios
Clinical Research Manager
Division of Clinical Trials and Pharmacovigilance
Instituto Butantan, Brazil

Dr. Diana Caceres
Medical Affairs Manager
GlaxoSmithKline (GSK), Colombia & Venezuela

Dr. Laïla El-Asmar
Senior Manager of DMVF
Vaccines Discovery & Development
GlaxoSmithKline (GSK) Vaccines, Belgium

Dr. Eduardo Ortega
Clinical R&D MA & Bio Director
PAN BI Head Office Latam
GlaxoSmithKline (GSK), Brazil

Dr. Pilar Rubio
Director of Medical Affairs
GlaxoSmithKline (GSK), Latin America & Caribbean

Dr. Alexander Schmidt
Director
Clinical Research & Translational Science Team
GlaxoSmithKline (GSK) Vaccines

Dr. Suely Tubois
Epidemiology Manager
GlaxoSmithKline (GSK), Latin America & Caribbean

Dr. Kumaran Vadivelu-Pechai
Regional Director of Medical Affairs
GlaxoSmithKline (GSK) Vaccines, Asia Pacific

Dr. Ta-Wen Yu
Director of Clinical R&D and Medical Affairs
GlaxoSmithKline (GSK) Biologicals - Vietnam, Cambodia & Lao PDR

Dr. Matt Dreitz
Manager
Clinical Operations
Inviragen, Inc., USA

Dr. Aurelia Haller
Director
Vaccine Development and Regulatory Affairs
Inviragen, Inc., USA

Dr. Jorge Osorio
Co-founder and CSO
Inviragen, Inc., USA
Associate Professor
Department of Pathobiological Sciences
University of Wisconsin, USA

Dr. Dan Stinchcomb
CEO
Inviragen, Inc., USA

Dr. Beth-Ann Coller
Vaccines Research Department
Merck and Company, USA

Ms. Lois Lockledge
Director of New Vaccines
Global Vaccines Strategy & Innovation
Merck and Company, USA

Dr. Joselita Santa Ana
Executive Director
sanofi pasteur, India

Dr. Alain Bouckenooghe
Head Clinical R&D and Medical Affairs
sanofi pasteur, Asia-Pacific
TECHNICAL EXPERTS: DEVELOPERS (continued)

Dr. Jeremy Brett  
Director of Medical Affairs and Public Policy Vaccines  
sanofi pasteur, Asia-Pacific

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

Dr. Siriporn Chirdkiatisak  
Vaccination Policy  
sanofi pasteur, Thailand

Dr. Maria de los Angeles Cortes  
Director of LATAM Regulatory Affairs  
sanofi pasteur, Mexico

Dr. Laurent Coudeville  
Health Economics Deputy Director  
sanofi pasteur, France

Dr. Carlos Espinal  
Public Health Director, Latin America  
Vaccination Policy and Advocacy  
sanofi pasteur

Dr. Juan Guillermo Lopez  
Health Economics Director  
sanofi pasteur, Mexico

Dr. Cesar Mascareñas  
Scientific and Medical Director for LATAM  
sanofi pasteur, Mexico

Dr. Fernando Noriega  
Associate Vice-President  
Head Clinical Development Latin America  
sanofi pasteur

Dr. Elsa Sarti  
Epidemiology Director  
sanofi pasteur, Mexico

Dr. Mark Simmerman  
Director of Medical Affairs and Public Policy Vaccines  
sanofi pasteur, France

Dr. Jaco Smit  
Senior Director of Global Immunization Policy  
sanofi pasteur, France

Dr. Emin Turan  
General Manager  
sanofi pasteur, Thailand

Mr. Roger Jung  
Product Manager  
SD Company

Ms. Amy Kim  
Global Marketing Manager  
SD Company
TECHNICAL EXPERTS: GOVERNMENTS OF ENDEMIC COUNTRIES

Dr. Gonzalo Lopez Casas
Director
National Institute of Health, Colombia

Dr. Guillermo Comach
Coordinador General
Laboratorio Regional de Diagnostico e Investigacion del Dengue y otras Enfermedades Virales (LARDIDEV)
Instituto de Investigaciones Biomedicas de la Universidad de Carabobo (BIOMED-UC), Venezuela

Dr. Rekol Huy
Deputy Chief of National Dengue Control Program
Head of Epidemiological Surveillance and Research Unit
Ministry of Health, Cambodia

Dr. Juan I. Arredondo Jimenez
Diretor Nacional Programa de Enfermedades Transmítidas por Vectores, Mexico

Dr. I Nyoman Kandun
Director
Indonesian Field Epidemiology Training Program
Directorate General CDC & EH
Ministry of Health Jl., Indonesia

Dr. Jehanzeb Khan
Ministry of Health, Pakistan

Dr. Chong Chee Kheong
Director of Disease Control Division
Ministry of Health
Federal Government Administration Centre, Malaysia

Dr. Jaime Lazovski
General Director
Ministry of Health, Argentina

Dr. Beatriz Londoño
Ministry of Health and Social Protection, Colombia

Dr. Carlos Eduardo Mosquera Martinez
Research and Diagnostic Coordinator
National Institute of Hygiene and Tropical Medicine, Ecuador

Dr. Charung Muangchana
Director
The National Vaccine Committee Office (NVCO)
Ministry of Public Health, Thailand

Ms. Sirlene de Fatima Pereira
Departamento de Vigilância de Doenças Transmissíveis
Secretariat of Health Surveillance
Ministry of Health, Brazil

Dr. Porntep Siriwanarangsun
Director General
Department of Disease Control
Ministry of Public Health, Thailand

Dr. Lyndon Lee Suy
National Dengue Program Coordinator
Medical Specialist IV, Emerging Diseases Program National Coordinator, Philippines

Dr. Hasitha Tissera
Public Health Specialist & Consultant Epidemiologist
Epidemiology Unit
Ministry of Health, Sri Lanka

Dr. Carlos Saenz Torres
Director of Epidemiology and in charge of Dengue and the National Immunization Programme
Ministry of Health, Nicaragua

Dr. Rosa Patricia Vidal-Vázquez
Assistant Director for Infant Health
National Center for Infant and Adolescent Health, Mexico

Dr. Than Htein Win
Deputy Director (Epidemiology), Department of Health, Ministry of Health, Myanmar