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Summary

In 2014, the highlights in the field of dengue vaccine development included the publication of results from two major phase III trials with the tetravalent live-attenuated chimeric dengue vaccine (developed by Sanofi Pasteur), conducted in five countries in Asia and five countries in the Americas. These trials have demonstrated that this dengue vaccine candidate provides up to 60% protection against dengue of any severity, and up to 80% against hospitalizations due to dengue in the first year of follow up after the primary series. Candidate vaccines from other developers are also progressing in clinical development. In the meantime, mathematical models, designed to estimate the potential impact of dengue vaccines on disease incidence, have demonstrated the potential effects of vaccination under different introduction scenarios and in different epidemiological settings.

With this newly available information, stakeholders need to revisit the minimum requirements for successfully launching a dengue vaccination program to complement existing preventive measures and to achieve the World Health Organization (WHO) objectives of reducing dengue morbidity by 25% and reducing dengue mortality by 50% by 2020, using 2010 figures as a baseline.


In July 2012, the Asia-Pacific and the Americas Dengue Prevention Boards (DPB) issued a report titled “Points for Consideration for First Introductions of Dengue Vaccines.” These points for consideration were designed to provide a framework to assist policy makers and national immunization program managers in determining the necessary capacities for first introductions of a dengue vaccine, and to highlight major issues to other countries wishing to subsequently adopt dengue vaccines.

The objective of the March 2015 AmDPB meeting was to refine and adapt the “Points for Consideration” based on the newly available information around dengue vaccine development and mathematical models. The Board achieved this by: reviewing the status of dengue vaccine development with all vaccine manufacturers, discussing the applications of mathematical modeling for predicting the impacts of dengue vaccination, and through the presentations of country perspectives for dengue vaccine introduction and use. The Board then held discussions in working groups to revise the “Points for Consideration.” The revisions are summarized in Table 1 of this report.

The Board noted the critical importance of linked disease surveillance and vaccination registries to monitor coverage and vaccine effectiveness, as well as pharmacovigilance to monitor vaccine safety. They also urged the standardization of age groups and case definitions of dengue disease across countries in the region to enable comparisons. They called for further analyses to understand how limited supply of vaccine might best be utilized in the first year(s) of vaccine introduction. They affirmed the importance of the Pan American Health Organization (PAHO) for supporting vaccine introductions, particularly through activities such as issuing recommendations for laboratory-based disease surveillance in the region, with an aim of standardizing the diagnostic tests.

The Board Concluded:

In General: early adopter countries must work together to generate and share data for mutual benefit, such as on vaccine effectiveness after introduction, and safety.

Evidence for Decision-Making

Epidemiological Surveillance: country data on burden of disease is essential for the development of a vaccine introduction plan, and countries that have not yet assessed their burden of disease are encouraged to do so.

Economics: assessment of the cost effectiveness of vaccination is a prerequisite for vaccine introduction and the cost of vector control programs, cost of outbreaks, and vaccination program sustainability should also be assessed.

Policy Studies: countries should review their introduction policies in light of updated regional guidelines for vaccine introduction. Capacity for vaccine safety monitoring should be enhanced and the efficiency of a vaccine in reducing burden of disease should be assessed to aid the development of vaccine policy.

Modeling

The principles for mathematical modeling of dengue transmission should be standardized. All countries in the region have the opportunity to contribute to models and should work together to enhance capacity and develop a common model. Modeling should at a minimum assess the impact of vaccination on the incidence of severe cases in addition to the impact on reducing all disease incidence.

Immunization Systems

Integrated disease surveillance, the monitoring of vaccination coverage and the conduct of pharmacovigilance need to be comprehensive and should be a condition for vaccine introduction. Early adopter countries should apply lessons learned from other vaccine introductions, including from other countries, and should develop clear communications on vaccination targets, with clear explanations for not targeting some groups, with an aim of managing the expectations of local authorities.

Demand and Financing

Short-, medium- and long-term planning is important because of the enormous uncertainty on vaccine supply in its early phases of introduction. It is very important to have clearly defined criteria for the target population.

Implementation and Post-Licensure Studies

Early-adopter countries should consider school-based vaccination programs (such as school-based HPV vaccination) to simplify implementation logistics. Countries should consider other means of integrating studies within the expanded program on immunization (EPI) with an aim of sustaining and standardizing data collection across the national immunization program. Post-licensure studies of safety and effectiveness are critical.

The meeting advanced the planning for introduction of dengue vaccines in the region. The leadership of DVI-consortium partners, and the support from Bill & Melinda Gates Foundation (BMGF) and other sponsors of dengue research and development, will be critical to enabling the successful introduction of a safe and effective dengue vaccine.
Context

In 2014, the results of Phase III trials in Asia and the Americas with Sanofi Pasteur’s dengue vaccine candidate (CYD-TDV) were published. These trials demonstrated overall vaccine efficacy (VE) against symptomatic virologically confirmed dengue of any serotype of 56.5% (95% CI 43.8–66.4%) in Asia and 60.8% (95% CI 52.0–68.0%) in the Americas. Point estimates for efficacy varied considerably by serostatus at the time of vaccination, by serotype and by country in both Asia and the Americas, and by age in Asia. No concerning safety signals were observed in the 25-month follow-up period from the first dose.

With the completion of the initial follow-up period of the Phase III clinical trials and the demonstration of 80% efficacy against hospitalization for dengue and 90% efficacy against severe dengue disease, licensing applications of the vaccine candidate have been submitted to some dengue-endemic countries for licensure, and if registered it may soon be available for introduction. 2015 will be a critical year for national regulatory authorities (NRAs). It is also critical now to prepare the scientific agenda to address remaining questions after vaccine introduction.

Important questions include how best this dengue vaccine candidate could be rolled out, which age groups could be targeted, what coverage rates could be achieved, and whether catch-up strategies could be employed. In this respect, mathematical models will continue to be particularly useful to guide policy makers.

In addition, a better appreciation of the economic burden of dengue and a clearer understanding of country perspective on dengue prevention will help to define optimal vaccine introduction strategies in the context of limited supply of a first dengue vaccine.

Given the state of advancement of candidate dengue vaccines, countries may wish to review their ability to introduce a vaccine. In 2012, the “Points for Consideration for First Introductions of Dengue Vaccines in Endemic Countries” were developed to help policy makers and national immunization program managers determine their capacity to undertake dengue vaccine introductions. In light of the potential impact of a vaccine with a moderate efficacy against serologically confirmed dengue, in the range of 56–61%, and given the variability of efficacy by serotype, age, severity and serostatus at baseline, a review of vaccine introductions strategies is warranted. This also entails a review of country capacity to introduce a new dengue vaccine.

In this context, The DVI held a 2-day consultative meeting with the Americas Dengue Prevention Board to refine and adapt the “Points of Consideration” based on newly available information.
Dengue Control in the Americas

Dengue is the most widespread vector-borne disease in the Americas. More than 2.5 billion people are at risk, and about 500,000 severe cases require hospitalization each year. In 2013, dengue cases and deaths nearly doubled those of previous years. The southern cone region reported the highest incidence rate of cases, but the Andean region reported the highest number of severe cases.

In 2003, PAHO passed a resolution urging member states to make dengue a national priority, develop a comprehensive control strategy, integrate environmental and urban planning into the national control strategy, and adopt border cooperation mechanisms. WHO and PAHO pledged their support to strengthen national strategies and mobilize resources. The resolution also encouraged the standardization of epidemiological processes and definitions in the collection of data on dengue.

The 2003 PAHO Board resolution was followed by the adoption of the COMBI strategy, then the creation of a dengue lab network in 2008, and the development of control strategy guidelines, adapted for the Americas, in 2010. A report on the “State of the Art of Dengue Control,” based on assessments in 21 countries, was presented in 2014.

The 2014 report presented a new model for integrated dengue control consisting of six components:

1) Epidemiology. Integrated disease and vector surveillance with environmental management. The objectives are to strengthen the capacity to generate quality data from countries, integrate the analyses of case detection with vector data for timely detection of outbreaks, and standardize diagnostic assays and dengue case classification.

Currently, not all countries use standardized definitions. In addition, some countries lack command and control facilities to manage large outbreaks.

To strengthen capacity, PAHO is currently supporting eight countries in the region to improve real-time detection of cases or outbreaks; improve mapping of cases by time, place and serotype; and improve reporting of deaths associated with severe or rare forms of dengue.

2) Laboratory Capability. The priority is to strengthen laboratory network capacity to generate timely and quality information through improved flow of information in the network and genomic mapping of dengue viruses in the region.

3) Case Management. The primary objective is to strengthen case management to reduce the case fatality rate, particularly in high-risk groups, such as pregnant women and the elderly. A new case management protocol has been implemented which is expected to reduce mortality by 30%.
4) Integrated Vector Control. Vector control currently has many shortcomings: vector control requires major resources and manpower, the most cost effective and sustainable vector control methods have not yet been adequately identified, and there is a lack of good vector monitoring tools and insecticide resistance monitoring. More international collaboration and research is required to improve existing vector control measures and effectively engage community participation. Some novel vector control approaches such as Wolbachia look promising, but are not yet ready for programmatic roll-out.

5) Environmental Management. Greater promotion and implementation of legal enforcement to prevent the conditions for vector breeding are needed. This requires the development of a legal framework designed to reduce most frequent breeding sites (tires, home containers, and construction sites).

6) Preparation for Vaccine Introduction. Several clinical trials are in progress. Countries need to develop realistic expectations for vaccine costs, vaccine efficacy (age and serotype-specific), and the potential impact of vaccination on disease incidence — particularly severe disease, availability of product — and prepare for public reactions to vaccine introduction. Any introduction strategy should conform to PAHO guidelines.

A decision to introduce a dengue vaccine can only be driven at the country level, but such decisions should be based on sound epidemiological and economic data.

The PROVAC initiative, established in 2006 to create the technical capacity within a country to make informed decisions about vaccine introduction, is a useful tool and may in the future strengthen country capacity for decisions about dengue vaccine introduction. Countries should follow the recommendation of WHO and PAHO for introduction strategies.

WHO’s “Global strategy for dengue prevention and control 2012–2020” has set global objectives of reducing morbidity from dengue by 25% and mortality by 50% by 2020, using 2010 as a baseline. This report emphasizes that countries should continue to strengthen strategies to eliminate vector-breeding sites and should not neglect control of other vector-borne disease.

FIGURE 1. Pilot Countries for Strengthening Dengue Surveillance in the Americas
Progress in Clinical Development of Dengue Vaccines

Several dengue vaccine candidates are in clinical development (Figure 2). Representatives from all of the vaccine developers summarized their progress made to date.

**NIH: Live Attenuated Tetravalent Dengue Vaccine**

The role of the US National Institutes of Health (NIH) is to develop technology through phase I and phase II clinical trials and then to license the technology to vaccine manufacturers.

A live attenuated vaccine candidate was pursued for dengue because of previous successes with other flaviviruses, such as yellow fever and Japanese encephalitis vaccines. The advantages of live attenuation are the inducement of both humoral and cellular responses, and antigen presentation in a native conformation, inducement of lifelong immunity, and high immunogenicity after a single dose.

The NIH construct includes full-length wild type DENV-1, DENV-3 and DENV-4 viruses that are attenuated by 30 nucleotide deletions in the 3’ untranslated region, except DENV-3 which has an additional 31 nucleotide deletion in this region. The DENV-2 component of the vaccine is a chimeric virus with the prM and E proteins of wild type DENV-2 replacing those of DENV-4 in the DEN4 30 background (see Figure 3).

Monovalent vaccines have been tested in 700 DENV-naïve adult subjects and tetravalent vaccine admixtures have been tested in 175 subjects in the U.S.

Tetravalent admixtures have been tested in two different formulations in dengue-naïve subjects: TV003 (3 log10 pfu for all dengue types) and TV005 (DENV-2 at 4 log10 pfu).

Studies in healthy flavivirus-naïve subjects given a single subcutaneous administration showed peak vaccine virus titer following administration was less than 1 log10 for each component of TV003 and slightly over 1 log for the DENV-1 and DENV-4 components of TV005. Duration of viremia was less than two days. A tetravalent neutralizing antibody response was elicited in 90% of subjects with TV005.

The candidate vaccine has been found to have a good safety profile. An asymptomatic, vaccine-associated rash occurred in 55% and 68% of TV003 and TV005 recipients respectively. The occurrence of rash correlated with a tetravalent response.

In a study to evaluate the effect of a second dose of TV003 given after 12 months, there was minimal antibody boosting (1.5–1.8 fold) in 15 recipients who received a second dose 12 months apart.

A comparison of the CD8+ T-cell responses induced by TV003 to the CD8+ T-cell responses

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**FIGURE 2. Status of Candidate Dengue Vaccines in Development**

<table>
<thead>
<tr>
<th>VACCINE CANDIDATE</th>
<th>MANUFACTURER</th>
<th>VACCINE TYPE</th>
<th>MECHANISM OF ATTENUATION OR INACTIVATION</th>
<th>CLINICAL PHASE</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYD</td>
<td>Sanofi Pasteur</td>
<td>Live Attenuated</td>
<td>Yellow Fever vaccine backbone, premembrane, and envelope proteins from wild type dengue</td>
<td>III</td>
</tr>
<tr>
<td>DENVax</td>
<td>Takeda</td>
<td>Live Attenuated</td>
<td>Wildtype DEN2 strain attenuated in primary dog kidney cells and further attenuated by mutation in N53 gene</td>
<td>II</td>
</tr>
<tr>
<td>TV003/TV005</td>
<td>NIADD and Butantan Institute</td>
<td>Live Attenuated</td>
<td>Wildtype strains with genetic mutations</td>
<td>II</td>
</tr>
<tr>
<td>TDENV PV</td>
<td>GSK and WRAIR</td>
<td>Purified Inactivated</td>
<td>Formalin inactivated</td>
<td>I</td>
</tr>
<tr>
<td>V180</td>
<td>Merck</td>
<td>Recombinant Subunit</td>
<td>Wildtype premembrane and truncated envelope protein via expression in the Drosophila S2 cell expression system</td>
<td>I</td>
</tr>
<tr>
<td>D1ME100</td>
<td>NMRC</td>
<td>DNA</td>
<td>Premembrane and envelope proteins of DENV1 are expressed under control of the human cytomegalovirus promoter/enhancer of the plasmid vector VR1012</td>
<td>I</td>
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*Status as of June of 2015.*
induced by natural DENV infection in Sri Lanka demonstrated that responses to CD8+ T cell epitopes were similar in number and magnitude between the two groups. Ex-vivo CD8+ T cells were analyzed by ELISPOT. Furthermore, 93% of CD8+ responses induced by TV003 were to conserved epitopes. Also, 97% of the total CD8+ responses induced by TV003 and natural DENV infection were to NS5 and NS3 proteins.

In a challenge study, 24 subjects received TV003 vaccine, and 24 subjects received placebo. Six months later, all 48 subjects received 3 log10 pfu of a DENV-2 Tonga/74 strain, a DENV-2 strain that caused less disease in a natural outbreak in the Kingdom of Tonga in 1978. TV003 provided 100% protection against viremia, rash and neutropenia. All placebo recipients were viremia post-challenge, 80% developed rash, and 20% developed neutropenia.

A phase II de-escalation trial is expected to enroll 294 subjects in Thailand, starting with adults (18–50 years) in Dec 2014, and de-escalating to children (1–4 years) by Sept 2015.

Butantan: Live Attenuated Tetravalent Dengue Vaccine from US NIH

The US NIH vaccine candidate TV003 will undergo field-testing in Brazil. Clinical trials have been designed to include 2–59 year olds and will include documentation of immunologic markers at baseline. It is expected that more than 80% of dengue-naïve subjects will have a tetravalent response to the vaccine.

A phase II trial of TV003 was initiated in 300 subjects in 2014. Safety data from this trial are expected to be generated in February 2015. Immunogenicity data are expected by June 2015. The trial first enrolled 50 dengue-naïve subjects in a bridging study between NIH (liquid) and Butantan (lyophilized) formulations. Subjects received two doses, six months apart. In phase IIB, 30 dengue-exposed subjects received a single dose of Butantan vaccine and 10 received placebo. A remaining 210 dengue-naïve and exposed subjects will receive one dose of dengue vaccine or placebo (see Figure 4).

In the Phase IIA study, rash was the most frequently solicited adverse event. There were no grade 3 or 4 events. In the Phase IIB, there was slightly less rash. Two cases of dengue were reported (but it is not known in which group). There were two grade 3 adverse events; one of transient neutropenia; one with symptoms that were suggestive of but found not to be dengue fever.
**Takeda: Live Attenuated Tetravalent Dengue Vaccine (TDV)**

Takeda is currently in phase II clinical development of a live attenuated tetravalent recombinant chimeric vaccine candidate using an attenuated DENV–2 backbone (see Figure 5).

Takeda’s objectives are to develop a safe and effective vaccine that elicits neutralizing serotype-specific humoral and multifunctional cellular responses, protects against infection with all four serotypes, and provides durable protection regardless of pre-existing serostatus.

In pre-clinical studies, the vaccine candidate has been found to be stable, sufficiently attenuated and well tolerated in mice and non-human primates.

In phase I clinical trials in Colombia and the US, using different dose levels, administered either subcutaneously or intradermally (with or without needle), and in different schedules, there were no safety signals. There were a few mild or moderate systemic adverse events, and none were grade 3 or 4. Local reactions predominated. There were no meaningful changes in blood chemistry.

In a separate Phase I trial, the kinetics and characteristics of CD8+ T cell responses to the backbone of the TDV candidate vaccine in flavivirus-naive individuals were analyzed. The candidate vaccine was found to elicit CD8+ T cell responses targeting the vaccine backbone (TDV-2), and reactive CD8+ T Cells produced IFN-γ, TNF-α and, to a lesser extent, IL-2. CD8+ T cells were multifunctional, producing >2 cytokines simultaneously, and were cross-reactive to the non-structural (NS) proteins from the other three DENV serotypes. The findings highlight the capacity of TDV to elicit cellular immune responses associated with protection from DENV disease.

A randomized, double-blind, placebo-controlled phase II study, with two subcutaneous vaccinations 90 days apart, was conducted in Puerto Rico, Colombia, Singapore and Thailand (Den-203). The study was designed for age de-escalation followed by expansion in 1.5–45 year olds in endemic countries (see Figure 6).

A total of 344 subjects were enrolled. The vaccine candidate was deemed to be safe with no severe adverse events, no discontinuations due to adverse events, and no constellation of symptoms related to dengue.

For all serotypes, a significant rise in GMTs was observed after the first dose and again after the second dose, but boosting was only marginal. GMTs were higher in participants who were seropositive at baseline.
Seropositivity rates against all four serotypes were high in all age groups after two doses, and in the lowest age group (1.5–5 year olds) 100% after two doses.

The study is currently evaluating safety and immunogenicity over a longer time period.

Other phase II studies are ongoing in the US, Asia and the Americas. In the US, safety and immunogenicity of three formulations of TDV in 1000 flavivirus-naïve adults, 18–49 years of age, are being assessed in a manufacturing bridging study (Den-106). Recruitment has been completed.

In Asia and the Americas, a double-blind placebo controlled study, comparing a single dose and two 2-dose schedules, is being conducted in 1800 children 2–18 years of age. First vaccinations are complete (Den-204).

A pivotal phase III trial is planned for 2015 to assess efficacy of a single dose in preventing symptomatic dengue disease (Den-301).

GlaxoSmithKline/Fiocruz/Walter Reed: Tetravalent Whole Virus Dengue Purified Inactivated Vaccine (DPIV)

Phase I trials with tetravalent whole dengue virus purified inactivated vaccine (DPIV), in 100 (mostly dengue-naïve) subjects in the continental US, and 100 (mostly dengue-primed) subjects in Puerto Rico, have been conducted comparing four different formulations of DPIV. Either 1 or 4 mcg of each dengue serotype / 0.5 ml dose were adjuvanted with alum, and 1 mcg of each dengue serotype / 0.5 ml dose adjuvanted with ASO1 or ASO3. Vaccination was given in two doses, four weeks apart. The vaccine schedule was designed to fit within the EPI schedule and be suitable for rapid outbreak control and for travelers and the military.

In dengue-naïve subjects, the highest GMTs were noted at four weeks after the second vaccine dose. At the 1 mcg dose level, GMTs were higher with ASO1 and ASO3 adjuvanted formulations than with alum adjuvant. GMTs waned and reached a plateau by month seven.

In the dengue-primed subjects, GMTs were high at baseline but vaccination nevertheless boosted titers by four or fivefold with AS01 or AS03, and twofold with alum adjuvant, and no significant waning was noted.

Given the difference in the level of GMTs and differences in the waning of GMTs between the dengue-naïve and dengue-primed subjects, a new study was developed to investigate how dosing regimens in the dengue-naïve may improve the persistence of neutralizing antibodies.

All four DPIV formulations were well tolerated in both dengue-naïve and dengue-primed subjects. More injection-site pain was noted in vaccinees than in the placebo group, but no severe adverse events were noted in the first 56 days and there have been no withdrawals due to safety. No safety signals have been noted to date.

A dose-selection study in adults in non-endemic countries is planned for 2015 to specifically look at antigen and adjuvant dose levels in dengue-naïve individuals. Clinical development will then proceed with age de-escalation and formulation selection in children. Once a final formulation has been selected, efficacy data in flavivirus-primed as well as naïve subjects will need to be generated.

Dengue epidemiological trials and clinical endpoint definition studies in dengue-endemic countries are also currently underway in Latin America and in Asia.

<table>
<thead>
<tr>
<th>PART</th>
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<th># PLACEBO</th>
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FIGURE 6. Age De-Escalation and Expansion Design of Takeda Phase II Clinical Trial
Merck: Tetravalent Recombinant Envelope Glycoprotein Dengue Vaccine (V180)

The V180 vaccine candidate is produced from recombinant truncated envelope glycoprotein (DEN-80E) from each dengue serotype. Protein is expressed in drosophila S2 cells in a native-like conformation. DEN-80E does not contain transmembrane domain or prM protein, nor some quaternary envelope epitopes.

It is likely that the V180 will need to be adjuvanted for use in flavivirus-naïve populations (but possibly not in flavivirus-experienced populations).

In non-human primate (NHP) studies, with ISCOMATRIX adjuvant, the vaccine candidate induced high titers and a well-balanced neutralizing antibody response in dengue-naïve animals. Vaccine formulations with Alhydrogel™ were less immunogenic.

V180 with ISCOMATRIX adjuvant protected dengue-naïve NHP against viremia after challenge with wild-type dengue viruses.

V180 adjuvanted with ISCOMATRIX given at zero, one and six months yielded higher peak titers and plateau than when given at zero, one and two months.

It was also noted that V180 can boost antibody responses to all four serotypes in NHPs that have had a prior exposure to a single wild-type DENV. Boosting in NHPs that received the NIH live attenuated tetravalent vaccine was higher with V180 than with homologous tetravalent vaccine.

In a phase I clinical trial in flavivirus-naïve subjects, using a dengue type 1 DEN-80E (DEN1-80E) formulated with Alhydrogel™, the vaccine was well tolerated and modestly immunogenic.

The first in-human trial with V180 was a randomized placebo-controlled dose escalation design in 98 flavivirus-naïve healthy adults (18–49 years) in Australia. Doses ranged from low (3/3/3/6 µg), to medium, (10/10/10/20 µg), to high (50/50/50/100 µg) of DEN1, DEN2, DEN3, and DEN4-80E, respectively. Three injections were given at one-month intervals. Primary safety and immunogenicity was assessed at 28 days post-third dose. Long-term safety and immunogenicity follow-up was assessed at one year post-third dose.

At one month post-dose three no serious adverse events were noted and V180 with ISCOMATRIX was highly immunogenic inducing seroconversion in 85.7–100% of subjects, depending on the serotype. Formulations with Alhydrogel™ induced seroconversion 0–62.5% and resulted in lower GMTs.
Sanofi Pasteur: Phase III Testing of a Live Attenuated Tetravalent Chimeric Yellow-Fever Dengue Vaccine (CYD-TDV)

The Sanofi Pasteur dengue vaccine candidate is a live attenuated chimeric vaccine, using a yellow fever virus backbone (see Figure 7).

Phase III testing of CYD-TDV vaccine was conducted in 9 out of 10 countries with the highest reported number of cases to WHO (see figure 8).

Three doses of CYD-TDV were given at zero, six and 12 months. Design differences between the trial in Asia and the trial in the Americas included enrollment of different age groups. In Asia, the highest incidence of dengue infection occurs in the 2–14 year-old age group; in the Americas, in the 9–16 year-old age group. Exclusion criteria included febrile illness or vaccination within four weeks prior to enrollment, or immunodeficiency, or corticosteroid-therapy.

The sample size was larger in the Americas, given a lower expected incidence of disease: 10,275 subjects in Asia and 20,869 in the Americas were enrolled.

The trial design included two phases: an Active phase (duration of 0–25 months) and a Hospital phase (duration of six years). Efficacy and safety were measured over one full year post-third dose injection during the Active phase. Adverse events and case detection was assured through active surveillance. During the Hospital phase, surveillance relies on hospital reporting.

Vaccinators were not blinded because the trial vaccine was lyophilized, but vaccinators were not involved in the study subject follow up and the subjects, the principal investigators, the caregivers and the sponsor remained blinded during the whole period of the study.

The primary endpoint of the trials was efficacy against symptomatic virologically confirmed dengue. The secondary endpoints were: efficacy against severe disease of any grade; and, efficacy per serotype, efficacy by country, efficacy by age.
strata, efficacy against dengue after one dose and efficacy according to the serostatus (in the immunological subset described below).

A subset of 1,334 vaccinated subjects and 660 controls was used to assess immunogenicity per protocol or by intention-to-treat. Immunogenicity was assessed at baseline, and one month after the second and third dose of vaccine.

Disease severity was assessed using two classifications: the 1997 WHO classification and the assessment based on 1997, 2009 and SEARO 2011 criteria, including organ failure, and reviewed by the classification done by the Independent Data Monitoring Committee.

Serotype distribution and seropositivity rates were assessed in 10 participating countries. The actual incidence rates in the control group were found to be higher than estimated: 4.7% in Asia and 2.9% in the Americas. All four serotypes circulated in all of the countries and contributed to the overall efficacy.

Protocol adherence rates were excellent in both Asia and the Americas: 96% without deviations in Asia, and 90% in the Americas (95% received three doses and 90% received three doses without any protocol deviation) with a 0.2% dropout rate in Asia and 4.5% dropout in the Americas. Ninety-eight percent of suspected cases were investigated in Asia, and 90% in the Americas.

Seropositivity at baseline was 68% in Asia and 80% in the Americas.

Efficacy results against the primary endpoint were similar for both trials: 56.5% in Asia and 60.8% in the Americas.

On both continents, efficacy was serotype-specific (Americas: 50.3% for serotype 1, 42.3% for serotype 2, 74.0% for serotype 3, and 77.7% for serotype 4; Asia: 50.0% for serotype 1, 35.0% for serotype 2, 78.4% for serotype 3, and 75.3% for serotype 4) with the type-specific confidence intervals overlapping so that the efficacy results are homogeneous between Asia and the Americas.

Secondary endpoint efficacy against severe dengue from pooled data (per protocol and intent-to-treat) was 80%.

In Asia, efficacy increased with age (intention-to-treat analyses: 33.7% at 2–5 years, 59.5% at 6–11 years, and 74.4% at 12–14 years) but in the Americas efficacy was similar across the age strata (61.7% at 9–11 years and 67.6% at 12–16 years). Efficacy was also higher in participants who were seropositive at baseline in both trials (Asia: 74.3% in seropositives versus 35.5% in seronegatives; Americas: 83.7% in seropositives versus 43.2% in seronegatives).

A post hoc analysis, for subjects from both trials over nine years of age, gave an overall primary endpoint efficacy against virological confirmed, symptomatic dengue in seropositive subjects from 9 to 16 years old (pooled analysis CYD 14 and 15) of 81.9% (CI: 67.2–90.0), 52.5% (CI: 5.9-76.1) in seronegative subjects.

The safety profile for the CYD group was similar, and not significantly different, from the safety in the placebo group at up to 25 months of follow up. No cluster in serious adverse event were seen during the first 25 months: the SAES related to the vaccine, according to the principal investigators’ criteria, were four in the vaccine group and two in the control group.

There was no cluster of adverse events of special interest and no viscerotropic or neurotropic disease. There were no vaccine-related deaths. The severity of dengue cases associated with vaccine failure was lower with less risk of hospitalization, less risk of thrombocytopenia and symptomatic plasma leakage.

Primary endpoint analysis shows that efficacy, post-third dose, was statistically significant against any serotype, meeting the primary endpoint of the study.

Based on these outcomes, a target product profile will be submitted to regulatory authorities in several countries.
Modeling Approaches and Impact of Vaccination from One Model

Models can be valuable for estimating the potential impact of vaccination on dengue prevention and virus transmission. These estimates can in turn be particularly useful for determining appropriate vaccine introduction strategies (optimal target populations, impact of catchup, etc.), and projecting the impacts of vaccination over time.

The impact of dengue interventions will depend on vaccine effectiveness and the effectiveness of vector control. Vaccine effectiveness depends on vaccine efficacy, the duration of protection, the force of infection, the mix of circulating serotypes, the level of immunity in the population and the age structure.

Several different effects can be estimated:

- **Total Effects** — synergistic effect of being vaccinated and widespread vaccination on the vaccinated.
- **Overall Effect** — the population effect, such as reduction in incidence of disease, from widespread vaccination.

The overall effect is usually what is measured for a vaccine. It is measured as:

\[ VE_{overall} = 1 - \frac{r_{vaccinated}}{r_{unvaccinated}} \]

where \( r \) is the incidence rate.

**Modeling I: Individual-Level, Stochastic, Mathematical Model in Yucatan State, Mexico**

An agent-based model was developed for Yucatan State, which has had increasingly large outbreaks of dengue, and growing numbers of dengue hemorrhagic fever over the last several years (Figure 9).

The model assumes that people stay at home, or go to work or school each day, and also

![FIGURE 9. Epidemiology of Dengue in Yucatan State, Mexico](image-url)
FIGURE 10. Agent Based Model

FIGURE 11. Nighttime Light Output in Yucatan State
assumes that mosquitoes’ flight range is limited. Uninfected mosquitoes are modeled probabilistically, whereas infected mosquitoes are modeled explicitly (see Figure 10).

For the Yucatan, household density was determined based on nighttime light output, observed from satellite imagery (Figure 11).

Workplaces and schools were clustered by household density, and mosquito movements between locations were limited to Delaunay triangulation. Mosquito populations were scaled according to the probability of daily rainfall, with weekly cases lagging behind mean rainfall.

Immunity by age was estimated based on serotype circulation. There was considerable heterogeneity by age and serotype (Figure 12).

Vaccine efficacy simulations for the Yucatan were run using assumptions based on the results from the Sanofi Pasteur phase III trial in the Americas (CYD 15).

The different vaccination strategies simulated were:

- routine vaccination of two, six, 10 or 14 year olds every year;
- routine vaccination of two, six, 10 or 14 year olds every year, with one time catch-up up to 15, 30, or 46 year olds.

All scenarios assumed no waning of immunity and 70% vaccination coverage.

The modeling showed that the effectiveness of either routine or routine + catchup strategies at preventing cases of disease, after about 20 years, was approximately the same (Figure 13).

The same pattern for effectiveness against hospitalization was observed.
However, the cumulative reduction in the number of cases per 100,000 is approximately double with catch-up strategies under both moderate and high force of infection scenarios (Figure 14). The same pattern was observed for hospitalization.

Alternate catch-up strategies, such as routine vaccination at two years and catch-up to age 15 years would take about 14 years to reach the same effectiveness as a 3–46 years catch-up strategy. Routine vaccination at two years with a catch-up at 3–30 years would be almost as effective as 3–46 year strategy and more effective after 12 years (Figure 15).

Modeling the effects of potential waning of immunity after two, five, or 10 years shows that vaccination could have potentially negative epidemiological impacts (Figure 16).

Waning would have to be addressed through vaccine-boosting strategies.

Modeling the impacts of vaccination with additional vector control shows that while vector control by itself is limited especially with high force of infection, combining routine and catchup vaccination strategies with 25% to 50% vector reduction would be highly effective (Figure 17). However, achieving vector reduction should not be assumed to equate with a proportional increase in vector control effort.

Post-licensure studies will be needed to assess the impact of vaccine introduction in different settings. In the Yucatan, in a first phase, a prospective cohort study of school children and families, using enhanced school and community surveillance, epidemiological and hospital surveillance is being planned. Case control studies will be conducted for severe disease. In a second phase, a step-wedge study will be conducted during vaccine introduction to assess vaccine effectiveness against susceptibility and disease, severe disease and infectiousness.
Modeling II: Potential Opportunities and Peril of Imperfect Dengue Vaccines

Several challenges exist for estimating the impact of dengue vaccines such as immunopathogenesis, heterogeneity in vaccine efficacy by serotype and by serostatus, specific mechanisms of action, and the potential impact of waning immunity.

The goals of modeling are to interpret results of vaccine trials; estimate the potential impact of vaccines, consistent with observations to date; identify problems or risky product profiles that could lead to an increase in clinical cases in the short or long term; develop a framework to compare alternative vaccination strategies (such as age targeting, multiple dosing, catch-up campaigns, and impact of pre-existing immunity in high and low transmission settings); and to develop a framework for study design.

One of the challenges of interpreting results of vaccine trials is understanding what the impact of a vaccine is in the absence of data on transmission. If a vaccine increases the risk of disease in the partially protected, then vaccine efficacy against clinical disease could appear smaller than against infection (Figure 18).

To overcome some of the challenges of interpreting clinical trial results, age-stratified dengue transmission models in humans and compartmental flow models of mosquitoes can be used.

One of the challenges of interpreting results of vaccine trial is understanding what the impact of a vaccine is in the absence of data on transmission.
Models should be parameterized to demographic structure, age-specific cases and serological data, as different settings have different epidemiology (Figure 19).

Different scenarios can be modeled based on the parameters selected from different settings.

Simulations show that vaccine efficacy is impacted by competition of serotypes and that vaccination changes the competition. Figure 21 shows the impact of vaccine efficacy on serotype competition under two scenarios for vaccine efficacy against DENV2.

Simulating the direct and indirect effects of vaccination, varying vaccine efficacy and transmission intensity, assuming that vaccination predisposes to some degree of immune enhancement, shows that the direct effects under some scenarios can be counterfactual, whereas being unvaccinated in a highly vaccinated population infers protection.

Given the impact on vaccine efficacy of seropositive status at baseline, simulations show that a longer time is required to reduce primary infections than secondary infections (Figure 21).

Simulating the impacts of transmission intensity shows that where there is a high force of infection, vaccination is more effective at younger ages, and where force of infection is lower, vaccination at higher ages is more effective. But effectiveness is dynamic and decreases over time, in which case target age groups may need to change over time (Figure 22).

Given that a shorter time interval between first and second dengue infections is associated with decreased risk of clinical outcome, models may also be useful in helping to determine appropriate vaccination strategies to account for waning immunity. If the length of “cross protection” between serotypes is in the one- to two-year range, a vaccine’s observed ability to “cross protect” may also diminish with time.

FIGURE 19. Differing Age-Specific Dengue Incidence in Some settings in the Americas
FIGURE 20. Impact of Vaccine Type Specific Efficacy on Serotype Competition

FIGURE 21. Impact of Vaccination on Primary and Secondary Infections

FIGURE 22. Vaccine Effectiveness by intensity of Transmission, Over Time
Economic Burden of Dengue

Dengue is a high public health priority in many countries, resulting in staggering individual, social and economic costs. The current evidence suggests that dengue costs are substantial due to cost of hospital care and lost earnings.4

Reasons for measuring cost of illness are manifold and include the need to quantify the economic importance of a disease in a country or region. A true estimate of the overall cost of dengue can be used for the following purposes and types of analysis:5

- **Raising awareness:** by demonstrating the economic impact of the disease, politicians, leaders and policy makers can become convinced of the problem and be encouraged to engage in prevention and control.
- **Planning and budgeting:** an estimate of the resources used to treat dengue can be used in an analysis of health sector expenditures and priorities to set health policy and allocate limited resources.
- **Cost-effectiveness analysis of interventions for control of dengue:** treatment costs and indirect costs of dengue can be saved if effective interventions are introduced to prevent and reduce the severity of the disease. The cost estimate is thus an integral part of a cost-effectiveness analysis of potential interventions, such as:
  - Promotion of vector-control strategies.
  - Dengue immunization.
  - Improving environmental conditions in urban and rural areas.
  - Promoting personal and domestic hygiene.

The costs of illness include the medical direct (e.g. medical visits, nurse visits, tests/exams, drugs), medical non-direct (e.g. out-of-pocket expenditure for food, lodging, transportation) and indirect costs (e.g. work/school absenteeism for patient and caregiver). The aggregate cost of disease is based on the number of cases and the costs of cases.

The incidence of dengue cases is expanding worldwide. This expansion is particularly evident in the Americas (Figure 23). But reported cases represent only the tip of the iceberg. In a study from Puerto Rico, passive surveillance detected only 42% of cases derived from a capture-recapture method,6 and, in the Sanofi Pasteur phase III trial, dengue incidence was three times higher than the rate of reported cases.

To account for underreported cases, an expansion factor (EF) can be used and derived from cohort studies from routine surveillance in the same area. In several countries in Southeast Asia it was possible to estimate an expansion factor based on a health quality index. A higher

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The incidence of dengue cases is expanding worldwide. This expansion is particularly evident in the Americas, where the annual economic burden of dengue is estimated at about $2 billion.
The quality of health was associated with a greater reporting rate of dengue episodes.

The global current number of cases is currently being assessed for 2013 using a statistical model which derived global estimates from cohort studies and a consensus panel on the number of cases from three treatment places: hospitals, ambulatory, and outside the healthcare sector. Based on this model, about 18% of all cases are hospitalized, 42% are treated in ambulatory settings and 40% remain outside of the health sector.

The costs per case can be derived from unit cost of hospital days and visits using micro-costing. Results from several countries show that indirect costs for ambulatory patients are similar to the indirect costs for the hospitalized, but direct costs for ambulatory care are considerably lower than the direct costs of hospitalization.

Using the same statistical model for 2013 global data, the estimated costs per case, by region, are shown in Figure 24.

The economic burden of dengue in the Americas is estimated at about $2 billion annually, ranging from $1 billion to $4 billion, or about $73,000 per DALY.

On a global scale, the aggregate costs amount to approximately $7.8 billion, excluding the costs associated with healthcare systems, impacts on tourism and intangibles.

A 2004 cost-effectiveness analysis for vaccination in Southeast Asia suggests that averted medical costs would offset 89% of the vaccination costs, for a cost effectiveness at about $50 per DALY. According to a study published in 2010, in Panama, vaccination may be cost saving assuming different expansion factors.

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**FIGURE 24. Estimated Costs Per Case by Geographic Region for 2013**

<table>
<thead>
<tr>
<th>REGION</th>
<th>SHORT-TERM COSTS</th>
<th>LONG-TERM COSTS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>DIRECT HOSPITAL</td>
<td>DIRECT AMBULATORY</td>
</tr>
<tr>
<td>Central Europe, Eastern Europe, and Central Asia</td>
<td>$237.78</td>
<td>$40.32</td>
</tr>
<tr>
<td>High Income</td>
<td>$9,430.32</td>
<td>$362.45</td>
</tr>
<tr>
<td>Latin America and Caribbean</td>
<td>835.64</td>
<td>102.05</td>
</tr>
<tr>
<td>North Africa and Middle East</td>
<td>$274.15</td>
<td>$45.52</td>
</tr>
<tr>
<td>South Asia</td>
<td>$229.45</td>
<td>$25.30</td>
</tr>
<tr>
<td>Southeast Asia East Asia, and Oceania</td>
<td>$287.20</td>
<td>$74.09</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>$174.50</td>
<td>$29.74</td>
</tr>
<tr>
<td>Global Average</td>
<td>$269.11</td>
<td>$55.55</td>
</tr>
</tbody>
</table>

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1 Shepard DS, Brandeis University, in cooperation with Stanaway J, Institute for Health Metrics and Evaluation.
As a dengue vaccine moves closer to reality and could eventually be used in endemic countries, it is useful to begin with an oversimplified, relatively unfavorable analysis. This simplification ignores any potential secondary benefits, such as reduction in transmission to unvaccinated persons, and assumes that vaccination were administered to everyone eligible in an entire continent. Even under these extreme assumptions, most benefit-cost ratios were at least 0.2. These would likely become favorable (i.e., exceed 1.0) under more realistic assumptions. The preliminary results, shown in Figure 25, are for this oversimplified, full scale, global vaccination. In reality, dengue vaccination programs are likely to be implemented initially only in the countries of highest risk and even then, only in urban areas where vaccination would be a priority.

Cost-benefit analyses for vector control show that genetically modified male mosquito release, assuming efficacy of 75%, could confer benefits relative to other vector-control strategies. Cost effectiveness of larviciding in two provinces in Cambodia was estimated to cost $313 per DALY from a public sector perspective and $37 per DALY from a societal perspective.

Economic burden estimates are limited in a number of ways: incompletely documented surveillance data, variable dengue classification, dissimilar reporting criteria, diverse diagnostic criteria, limited healthcare coverage, paucity of data from the private sector, under-estimation of persistent symptoms, variation in costing of dengue prevention and control, and unaccounted impacts of dengue.10

In conclusion, the increasing dengue burden has resulted in increasing health costs. Cost per episode is relatively well understood. Improved estimates of costs will depend on better information on the number and distribution of cases and more cohort studies with better description of selection in time and location. The economic value of control strategies varies with each approach and setting. Future economic studies should consider the inclusion of herd effects in their analyses.

---

**FIGURE 25. Benefit-Cost Ratios of Three-Dose Dengue Vaccination Based on Cost Per Vaccine**

<table>
<thead>
<tr>
<th>REGION</th>
<th>PER CAPITA GDP</th>
<th>BENEFITS (Illness Cost Averted per Vaccines)</th>
<th>BENEFIT-COST RATIOS BASED ON COST PER VACCINEE OF:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>$5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>OLDER VACCINE, GAVI</td>
</tr>
<tr>
<td>Central Europe, Eastern Europe, and Central Asia</td>
<td>$2,315</td>
<td>$2.45</td>
<td>0.49</td>
</tr>
<tr>
<td>High Income</td>
<td>$49,809</td>
<td>$7.89</td>
<td>1.58</td>
</tr>
<tr>
<td>Latin America and Caribbean</td>
<td>$9,462</td>
<td>$37.79</td>
<td>7.56</td>
</tr>
<tr>
<td>North Africa and Middle East</td>
<td>$6,264</td>
<td>$5.51</td>
<td>1.10</td>
</tr>
<tr>
<td>South Asia</td>
<td>$1,394</td>
<td>$13.64</td>
<td>2.73</td>
</tr>
<tr>
<td>Southeast Asian East Asia, and Oceania</td>
<td>$6,123</td>
<td>$23.24</td>
<td>4.65</td>
</tr>
<tr>
<td>Sub-Saharan Africa</td>
<td>$1,440</td>
<td>$4.97</td>
<td>0.99</td>
</tr>
<tr>
<td>Global Average</td>
<td>$7,323</td>
<td>$17.35</td>
<td>3.47</td>
</tr>
</tbody>
</table>

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Review of the 2012 “Points for Consideration” for First Introductions of Dengue Vaccines in Endemic Countries

The DVI “Points for Consideration” were originally developed to help policy makers and national immunization program managers determine their capacity to undertake dengue vaccine introductions.

With particular emphasis on three essential components for successful introduction of dengue vaccines — Surveillance, Regulatory Affairs, and Modeling — the “Points for Consideration” address six capacities that need to be thoroughly reviewed and examined in preparation of an introduction of a dengue vaccine:

1) Regulatory
2) Evidence for decision-making
3) Impact modeling
4) Immunization systems
5) Demand and financing
6) Post-licensure demonstration projects

These were reviewed in the context of the recent Phase III trial results and in light of ongoing activities to strengthen capacity in some of these focus areas. Since there is currently a regulatory working group that is focusing specifically on the regulatory issues, the “Regulatory” points for consideration were not reviewed at the Board meeting. The meeting participants divided into five working groups to review and revise the five other points of consideration. The main discussion points from the meeting are summarized below:

**Recommendations for Revisions from the Working Groups**

The outputs of the working groups are summarized and how they impact the “Points for Consideration” is summarized in Table 1.
### TABLE 1. Proposed Revisions to the 2012 "Points for Consideration on First Introductions of Dengue Vaccines in Endemic Countries"

<table>
<thead>
<tr>
<th>POINT FOR CONSIDERATION</th>
<th>PROPOSED REVISIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EVIDENCE FOR DECISION MAKING</strong></td>
<td><strong>Epidemiological Surveillance</strong></td>
</tr>
<tr>
<td>Specify that beyond capacity to conduct epidemiological surveillance, countries should attempt to:</td>
<td>Clarify the case definition used by each country as explicitly as possible, and ideally follow PAHO recommendations for case definition.</td>
</tr>
<tr>
<td></td>
<td>Harmonize age groups across countries.</td>
</tr>
<tr>
<td></td>
<td>Use age incidence as a proxy for serological prevalence if desired.</td>
</tr>
<tr>
<td></td>
<td>Identify risk groups.</td>
</tr>
<tr>
<td></td>
<td>Determine prevalence of yellow fever vaccination if appropriate.</td>
</tr>
<tr>
<td>In addition to the recommended study capacities, recommendations should include:</td>
<td>Optimizing use of existing data (i.e., incidence by age, severity, health service utilization information). Disease burden data from health services utilization is important because a decision to introduce will be based on how a vaccine should be used.</td>
</tr>
<tr>
<td></td>
<td>Mapping risk, and identifying risk factors to improve the information on the disease burden and inform decision making.</td>
</tr>
<tr>
<td></td>
<td>Using literature reviews for background information.</td>
</tr>
<tr>
<td></td>
<td>Using serological prevalence studies to complement and confirm incidence estimates from other disease-burden studies or mathematical models.</td>
</tr>
<tr>
<td></td>
<td>Reviewing vaccine indications to inform decision making.</td>
</tr>
<tr>
<td><strong>Economic Studies</strong></td>
<td>Make the capacity for conducting health economic assessments explicit, beyond the capability to collect economic data, because most countries will require these for decision making. Specify that:</td>
</tr>
<tr>
<td></td>
<td>Costing studies should be uniform and generate results that are clear and comparable between studies to inform decision making.</td>
</tr>
<tr>
<td></td>
<td>Studies should be conducted with full transparency (particularly when financed by pharmaceutical companies).</td>
</tr>
<tr>
<td><strong>Mathematical Modeling</strong></td>
<td>Impact modeling should include estimates of impacts from innovative interventions such as Wolbachia infected male mosquito release.</td>
</tr>
<tr>
<td><strong>Policy Studies</strong></td>
<td>Among the specific studies listed, specify that:</td>
</tr>
<tr>
<td></td>
<td>Current guidelines for vaccines introduction should be reviewed.</td>
</tr>
<tr>
<td></td>
<td>Sustainability of vaccine introduction should be assessed.</td>
</tr>
<tr>
<td></td>
<td>Risk-benefit assessments should be made.</td>
</tr>
<tr>
<td></td>
<td>Post-licensure studies should be conducted for surveillance of AE.</td>
</tr>
<tr>
<td></td>
<td>Evaluation of vaccine impact should be made soon after vaccine introduction to generate political will to sustain the program.</td>
</tr>
<tr>
<td><strong>MODELING</strong></td>
<td><strong>Potential Applications</strong></td>
</tr>
<tr>
<td>Specify additional applications:</td>
<td>Assessing efficacy and vaccine action for dengue vaccine candidates in phase III trials.</td>
</tr>
<tr>
<td></td>
<td>Assessing optimal number of doses, duration of protection, dosage schedule.</td>
</tr>
<tr>
<td></td>
<td>Estimating vaccine efficacy for susceptibility to infection (VES); disease (VEP); infection and disease (VESP); and transmission to mosquitoes (VEI).</td>
</tr>
<tr>
<td></td>
<td>Estimating vaccine effectiveness, including indirect effects: Overall effectiveness (VEoverall); indirect effectiveness (VEindirect); and total effectiveness (VEtotal).</td>
</tr>
<tr>
<td></td>
<td>Assessing coverage rates required by dose to achieve targets.</td>
</tr>
<tr>
<td><strong>Countries’ Capability to Conduct Modeling</strong></td>
<td>Specify additional capacities required:</td>
</tr>
<tr>
<td></td>
<td>Assess coverage rates by dose.</td>
</tr>
<tr>
<td></td>
<td>Assess transmission dynamics in different scenarios in the country.</td>
</tr>
<tr>
<td><strong>Include a New Category on ‘Engagement of Modeling Work with Decision Makers</strong></td>
<td></td>
</tr>
<tr>
<td>Countries considering dengue vaccine introduction should:</td>
<td>Survey decision makers for needs and resources.</td>
</tr>
<tr>
<td></td>
<td>Request suggestions for specific vaccine strategies to be evaluated.</td>
</tr>
<tr>
<td></td>
<td>Requests for feedback on modeled vaccine strategies with local concerns about implementation.</td>
</tr>
<tr>
<td></td>
<td>There needs to be guidance on simple analyses (survival, longitudinal, analytic results from models) that can generate similar information to models.</td>
</tr>
<tr>
<td></td>
<td>Working groups for modeling including the early adopter countries for dengue vaccine should be established.</td>
</tr>
<tr>
<td>POINT FOR CONSIDERATION</td>
<td>PROPOSED REVISIONS</td>
</tr>
<tr>
<td>-------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>IMMUNIZATION SYSTEMS</td>
<td><strong>Strategy for Vaccine Introduction (Priority)</strong></td>
</tr>
<tr>
<td></td>
<td>Specify additional requirements:</td>
</tr>
<tr>
<td></td>
<td>‣ Introduction strategy must be country-specific.</td>
</tr>
<tr>
<td></td>
<td>‣ Emphasis should be on programmatic feasibility.</td>
</tr>
<tr>
<td></td>
<td>‣ Relevant whether vaccine protects just against disease or also infection — implications for vaccination strategy.</td>
</tr>
<tr>
<td></td>
<td>‣ Good capacity for country-level decision-making in the countries.</td>
</tr>
<tr>
<td></td>
<td>‣ Working with PROVAC would be very useful.</td>
</tr>
<tr>
<td></td>
<td>‣ Strategies must be realistic and sustainable in the long term.</td>
</tr>
<tr>
<td></td>
<td><strong>Budget for a Dengue Vaccine</strong></td>
</tr>
<tr>
<td></td>
<td>This section should be reworded to specify that the budget is for the dengue control program. It should additionally specify that:</td>
</tr>
<tr>
<td></td>
<td>‣ Budget should include vector control and be managed in conjunction with vector control,</td>
</tr>
<tr>
<td></td>
<td>‣ There could be a time lag before vaccines are available through the rf, (the time required to pre-qualify a vaccine);</td>
</tr>
<tr>
<td></td>
<td>‣ Funding may be available from external organizations that have supported dengue control/vaccines. They might be able to provide some funds, as country funds are limited;</td>
</tr>
<tr>
<td></td>
<td>‣ Initial budget requirements for vaccine introduction will be large (e.g. training, roll out)</td>
</tr>
<tr>
<td></td>
<td><strong>Capacity for Immunization Surveillance</strong></td>
</tr>
<tr>
<td></td>
<td>Specify additional requirements:</td>
</tr>
<tr>
<td></td>
<td>‣ Capacity is needed to assess whether dengue cases are due to missed opportunities or vaccine failure, etc.</td>
</tr>
<tr>
<td></td>
<td>‣ Immunization surveillance should not be isolated from dengue surveillance.</td>
</tr>
<tr>
<td></td>
<td>‣ Need capacity to confirm dengue cases to avoid confusing other febrile illnesses with dengue.</td>
</tr>
<tr>
<td></td>
<td>‣ Standardization for laboratory confirmation and case definitions is critical. Goals should be set for laboratory confirmation.</td>
</tr>
<tr>
<td></td>
<td>‣ Surveillance could be regionally based, working with countries, to quickly detect impact (Role for WHO/PAHO guidance).</td>
</tr>
<tr>
<td></td>
<td><strong>Capacity for Monitoring and Evaluation</strong></td>
</tr>
<tr>
<td></td>
<td>Should be combined with immunization surveillance, and include three areas of focus:</td>
</tr>
<tr>
<td></td>
<td>‣ Disease surveillance.</td>
</tr>
<tr>
<td></td>
<td>‣ Immunization coverage.</td>
</tr>
<tr>
<td></td>
<td>‣ Vaccine safety.</td>
</tr>
<tr>
<td></td>
<td><strong>Capacity for Cold Chain and Logistics Management</strong></td>
</tr>
<tr>
<td></td>
<td>This section should additionally specify:</td>
</tr>
<tr>
<td></td>
<td>‣ Impact of product presentation size on cold chain system should be fully assessed. Optimal presentation size should be reviewed to minimize wastage (including from multi-dose policy).</td>
</tr>
<tr>
<td></td>
<td>‣ Consideration of VVMs is very important.</td>
</tr>
<tr>
<td></td>
<td><strong>Capacity of the Information System</strong></td>
</tr>
<tr>
<td></td>
<td>This section should additionally specify:</td>
</tr>
<tr>
<td></td>
<td>‣ Immunization registries are critically important. Electronic registries are a priority, with ability to link with patient records so vaccination status can be assessed even years post-vaccination.</td>
</tr>
<tr>
<td></td>
<td><strong>Capacity of Communication Systems</strong></td>
</tr>
<tr>
<td></td>
<td>This section should additionally specify:</td>
</tr>
<tr>
<td></td>
<td>‣ Social media could be very important; given the potential risks of negative publicity. There should be tracking of responses to concerns. Novel technologies (e.g., SMS) could be utilized to increase awareness.</td>
</tr>
<tr>
<td></td>
<td>‣ Key messages include:</td>
</tr>
<tr>
<td></td>
<td>† Vaccination is part of an integrative approach.</td>
</tr>
<tr>
<td></td>
<td>† Vaccinates are not 100% protected against dengue.</td>
</tr>
<tr>
<td></td>
<td>‣ Need to conduct an assessment of communications capacity of the country and plan accordingly.</td>
</tr>
<tr>
<td></td>
<td>‣ Messages on the vaccine should be integrated with messages on vector control.</td>
</tr>
<tr>
<td></td>
<td>‣ Work with health promotion departments.</td>
</tr>
<tr>
<td></td>
<td>‣ Communication will need to be adjusted to circumstances of vaccine availability.</td>
</tr>
<tr>
<td></td>
<td><strong>Training</strong></td>
</tr>
<tr>
<td></td>
<td>This section should additionally specify:</td>
</tr>
<tr>
<td></td>
<td>‣ Consider education/training outside of the medical community (e.g. journalists, political leaders).</td>
</tr>
<tr>
<td></td>
<td>‣ Medical training programs should provide a holistic view of dengue prevention and control.</td>
</tr>
</tbody>
</table>
### POINT FOR CONSIDERATION

#### DEMAND AND FINANCING

**Demand**

The “Points for Consideration” should specify additional criteria for forecasting demand, including:

- Better definition of endemic areas in dengue-endemic countries.
- Better definition of dengue cases within endemic areas.
- Clear information about product profile (e.g., vaccine to target more severe dengue cases – DHF).
- Defined threshold of seroprevalence to warrant vaccination.
- Better defined vaccine introduction strategies that consider geographic locations and age groups, prioritized by level of severity and areas of greatest impact.

**Financing**

Add a section on sustainable financing which should specify:

- Know beforehand the price of the vaccine.
- Assess the source of funding (internal versus external).
- Consider options for procurement mechanism.
- Identify complementary funding mechanisms.
  - Dengue-specific funding mechanisms, where other actors outside the public sector may have an interest.

#### POST-LICENSE STUDIES

This section should additionally specify:

- Have a clear, coherent plan on how the vaccine will be introduced/used (follow/expand PAHO guidance):
  - Defined target population.
  - Plan to deal with groups who are not targeted for vaccination (because of limited supply, etc).
- Have strong epidemiological systems to determine vaccine impact and identify safety signals long after vaccine introduction.
- Prepare for situations where vaccine effectiveness is much less than anticipated: have a communications plan prepared.
- Conduct well planned vaccine-effectiveness studies, with homogeneous clinical and epidemiological definitions.
  - Have sentinel sites with enhanced surveillance and move to PCR testing for confirmation.
  - Have pharmacovigilance plans that allow safety follow-up, linked to vaccination records.
- Issue limited licenses to control vaccine introduction by municipalities or sub-national authorities.
- Measure herd protection such as in step-wedge vaccine introduction which include areas of high, low and moderate endemicity.
Country Updates on Dengue and Perspectives on Vaccines

Countries from the Americas presented data on burden of disease, potential target groups and delivery strategies for vaccination, and the potential interface of vaccination with vector control in each of their countries.

Argentina

Only cases that meet the strict dengue case definition get reported, since several other febrile illnesses (Hantavirus, leptospirosis, etc.) occur concomitantly. Reported cases of acute febrile syndrome are subject to clinical, laboratory and epidemiological scrutiny to eliminate a diagnosis of dengue.

Dengue laboratory surveillance has been in place since 1997. Reporting, which was formerly from one administrative level to another, is now conducted in real time, which allows to conduct timely control actions for outbreaks. Diagnostic laboratories are now organized in a dengue network that reports cases on a national online system. Information is communicated on a weekly basis, and all notifications of arbovirus infections are followed up on.

Suspected cases of dengue are treated as cases until a negative lab result is available.

In 2009, there were 26,000 reported cases but an estimated 50,000 cases. Dengue was limited to subtropical regions in the north of Argentina until 2009. The 2009 outbreak, the biggest in the country, affected the central temperate region and has persisted ever since. Currently, 60 labs have NS1 IgM diagnostic capability, 14 labs perform MAC-ELISA testing for flavivirus and other arboviruses, 19 labs run RT-PCR testing for flaviviruses, and 20 labs do real-time RT-PCR testing.

Cases have occurred every year since 1998 except in 2001 and 2005. All four serotypes have circulated, DENV4 being introduced for the first time in 2010. But transmission is interrupted in winter, which means that the virus is reintroduced every year.

The median number of reported cases for the last four years is 5,000, 800 of which are confirmed or laboratory investigated. No deaths have been reported in the last few years. Different provinces have different incidence rates.

To develop a vaccination strategy, more information is needed on the incidence of illness and repeated infections. More information on the potential availability of a vaccine is also needed.

A dengue vaccine would need to fit into the national immunization schedule, but the appropriate timing still needs to be determined. A possible strategy is to target risk groups, according to outbreaks, but a proper vaccine distribution plan would need to be developed.
Dengue is a growing problem that now puts a huge burden on the healthcare system, especially during outbreaks. DENV1 resurged in 2010, and in 2014 DENV1 co-circulated with DENV4 (Figure 26).

Incidence rates in adults are higher than in younger age groups, especially in the last few years. The median age of death is 30 years but is increasing.

Hospital-based data and surveillance reports from ten municipalities between 2008 and 2013 help to fill in gaps in knowledge about epidemiology in Brazil. Based on these sources, about 40,000 hospitalizations are estimated to have occurred, but sensitivity analyses puts this estimate at about 70,000.

Dengue seroprevalence surveys are planned for 2015, in 63 cities over all regions of the country, for a total of about 65,000 samples from all age groups. In addition, a study with Sao Paolo University on cellular immunity in dengue is ongoing. And a mathematical modeling study is slated for completion in 2016.

Current challenges for vaccine introduction include developing robust surveillance. There is huge pressure from municipalities and strong public demand during outbreaks for a vaccine. There is concern that municipalities may procure vaccines on their own or that states may introduce vaccine irrespective of a national strategy. This could put the sustainability of vaccination at risk if states don’t have recurrent funding for vaccine procurement and implementation.

To address these issues, Brazil will align its position with the WHO position, which is to assess the risks and potential impacts of vaccination on public health.

An independent national advisory committee, made up of vaccination and vector control experts, will interpret the results from the Sanofi Pasteur phase III trials and develop key questions and perspectives for clarification.

The advisory committee will meet with Sanofi Pasteur to clarify issues and then propose recommendations to be presented to the Ministry of Health (MoH) as an external opinion.

**FIGURE 26.** Probable Cases of Dengue and Hospitalizations in Brazil, 1986–2014
The largest dengue epidemic occurred in 2010 (Figure 27) and the greatest lethality in 2013 (Figure 28).

The vector is persistent in most parts of Colombia and all four dengue serotypes co-circulate. Hyperendemicity occurs during the last months of year.

Fifty-nine municipalities account for 80% of dengue cases. Forty-seven percent of cases occur under 15 years of age.

Colombia has an integrated strategy for dengue prevention and control. The emergence of Chickungunya has led to better collaboration between national institutions. Management in municipalities are at the top political level (mayor), involving infrastructure and education services, and potentially immunization.

To achieve integration, the program has been reorganized to align with the priorities of policy makers. Surveillance is a critical component of intelligence, and in addition to knowledge management (cost, impact studies, etc.), needs to inform program management.

There is a need to standardize monitoring to make outcomes comparable. And dengue costs need to be assessed to project the sustainability of a vaccination control program.

Health promotion needs to be included in the COMBI strategy and risk communications further developed for dengue vaccination. Criteria for new vaccine introduction include good vaccination coverage, setting and achieving eradication and elimination targets, securing resources to sustain a program, ensuring sufficient vaccine supply of a safe
vaccine, quality disease surveillance and sufficient cold chain capacity.

Criteria for decision-making on vaccine introduction include political and technical aspects (priority, burden of disease, efficacy of vaccine, affordability) and the programmatic feasibility.

In Colombia, the immunization program is completing its transition from 'child' immunization to “family” immunization. This presents an opportunity to use vaccination as a means to ensure quality by institutional strengthening and integrated care.

**Dengue affects mostly adults.**
The median age is 30 years. It occurs predominantly along the coast where 40% of the population resides.

Dengue has been circulating for 21 years but has increased over the last five years. There was an important epidemic in 2013 (Figure 29). No DENV4 has circulated in the last five years.

Hospitals are overloaded with dengue cases during outbreaks thereby overwhelming health care systems and draining insurance companies. But plans to introduce a vaccine are not advanced.

**Dengue began in 1988** starting with the introduction of DENV1, then DENV2, followed by DENV4, Asian DENV2 and DENV3. DENV1 was highly prevalent until 2012, when DENV2 and DENV4 began to co-circulate (Figure 30). Many areas now have two or three co-circulating types. All four serotypes are likely to co-circulate in 2015.

Dengue occurrence is highly seasonal, occurring during rainfall (the winter months). In 2012 there were more than 17,000 cases. The most affected age group is 20–49 year olds but the disease is most severe in preteens and young children. There were 12 deaths in 2014.

For diagnosis, blood samples are sent to the lab in less than five days. For cases of more than six days of fever, an ELISA IgM is performed. Confirmation with real time RT-PCR is made for positives results, and quality control conducted for negatives.

MoH is currently studying the need for a dengue vaccine and exploring options for integrating dengue vaccination. Possibilities for integration include the vector control institution for malaria eradication.

**Honduras**

Dengue was introduced in 1978.

Four serotypes have been present since 2010, with a predominance of DENV2 and DENV4. *Ae aegypti* is present across the entire country and expansion of cases is occurring. There are case reports from all provinces. Epidemics occur from June to November at the time of the rainy season.

Forty thousand cases were reported in 2014. The two largest cities, Tegucigalpa and San Pedro Sula, are the most affected.

Routine confirmation is with MAC-ELISA. But most cases do not present and physicians may not send samples because the turnaround time for lab results is longer than the length of fever. But severe cases are often virologically confirmed.

For 2011, there were 13,838 cases. For 2012, there were 22,243 cases. For 2013, there were 40,993 cases. For 2014, there were 10,299 cases. For 2015, there were 725 cases.

**FIGURE 29.**
The mean age for hospitalized cases is 21 years. There were 17 deaths in 2013. The case fatality rate was around 2.6%.

In 2015, 678 cases have so far been reported, mainly in the low transmission seasons (five times more cases than in the previous year). If the same pattern of transmission continues, an epidemic is anticipated after June.

Vector control is the focus of prevention and control. Larvicides (mostly temefos) are used for larval control. Pyrethroids and organophosphates are used in adult spraying programs. Clean-up campaigns to eliminate discardable breeding sites are periodically programmed.

Recently health education has been emphasized, to improve community compliance for removal or cleaning of water containers and environmental cleanups. Education is primarily targeted at school children.

Honduras does have an integrated control strategy, following PAHO guidelines, and will seek to integrate a vaccine. Clinical trials of Sanofi Pasteur vaccine have been conducted in Honduras in 9–16 year olds.

Exposure to infection has been reported in children under one year. At school age, children become increasingly exposed to the vector. Adults have mostly been previously exposed.

Barriers to vaccine adoption include limited information on progress of vaccine development available to the medical community and the MoH, competition from other diseases (Chikungunya), availability of funding, and the transition from a vector-based control program to vaccination.

Outstanding issues to be resolved before vaccine introductions include the need for additional studies, the appropriate number of doses and vaccination schedule, the fit with the existing vaccination schedule and the capability to distinguish dengue from other febrile illnesses.

Next steps include public health trials in larger populations, improving the quality of case
confirmation, defining the licensing process, licensing, reviewing the evidence and obtaining WHO and US Food and Drug Administration (FDA) opinions.

Municipal authorities need to be involved in dengue control, but expectations need to be managed.

**Mexico is ranked fourth in the world** for the number of dengue cases reported annually.

Reported incidence is 10 times lower than what has been seen from active surveillance. So if a dengue vaccine is introduced, it will be very important to understand the impact. Severe dengue is a better indicator because of lesser confusion with other diseases.

In Mexico, the age of highest incidence is now in 5–14 year olds but this has shifted from the previous decade (1990–1999) when the highest incidence was in 15–24 year olds (Figure 31).

There are not many seroprevalence studies for Mexico, but, in 1996, 59.9% in the Yucatan were seropositive and in 2006 82% from the same state were seropositive.

Mexico has initiated the regulatory process for the introduction of a vaccine. With a successful universal immunization program for over 40 years, it was felt that logistics and strategies for dengue vaccine introduction could be easily integrated.

Still needed are seroepidemiological prevalence stratification studies for defining vaccination target groups and high-risk regions and cities. Epidemiological and entomological criteria for the evaluation of vaccine impact need to be made uniform. The expansion of the immunization program needs to be designed to account for the availability of the vaccine (only 100 million doses of vaccine available globally). Modeling and cost-benefit studies need to be completed.

**FIGURE 31.** Shifting Age-Related Incidence of Dengue in Mexico, 1990–1999 and 2000–2009, respectively
Puerto Rico has different characteristics from many other dengue-infected countries. In Puerto Rico, dengue is endemic and all four serotypes are circulating.

The key steps for introducing a vaccine are regulatory (a vaccine needs to be approved by the FDA); and decision-making [needs to be recommended by Advisory Committee on Immunization Practices (ACIP)]. The latter is a challenge because ACIP recommends vaccine at a national level for the United States, not regionally. But there is a precedent with Hepatitis A vaccine that was first recommended for southern border states and later expanded nationally.

Thus ACIP could recommend dengue vaccination for Florida, Texas and Puerto Rico. The enactment of the Affordable Care Act provides the authority for first-dollar coverage of any vaccine recommend by ACIP. Therefore any private or public insurance will cover the cost of the vaccine. In Puerto Rico, it will cover 95% of the population and the Vaccines for Children Program will cover children without health insurance or with partial insurance.

In Puerto Rico, there is good immunization system infrastructure. However, training of healthcare providers, community education and outreach, and enhanced surveillance for dengue (to be able to distinguish between seropositivity from natural infection or from dengue vaccination) are needed. A potential mechanism for training is to insert dengue vaccine training as part of the required continuing education courses required for licensed physicians (20 hours on dengue and Chickungunya will be included).

Dengue re-emerged in 1989 but there were earlier reports from the 1950s, 60s and 70s. Between 1989 and 1990, 12,000 cases with 70 fatalities were reported.

Now, more than 100,000 cases occur in a year (Figure 32). All four serotypes co-circulate.

The highest incidence is in children less than one year old, and between 7 and 15 years. Cases are increasing with time. The incidence rate is as high as 1,062 per 100,000 population. There is a high public demand for a vaccine. DENV2 kills children so there is political will to introduce a vaccine. Venezuela would need to model the estimated reduction in cases. Vaccination would be integrated with and complement vector control (larval insecticide resistance is as high as 30% in some areas).
Conclusions of Dengue Prevention Board

When first licensed, the supply of dengue vaccines will be limited to 4 to 6 countries. Therefore, the first countries to introduce a dengue vaccine will need to allow others to learn from their experience.

Evidence for Decision-Making

Epidemiological Surveillance
- Country data on burden of disease is essential for countries to develop their plan for vaccine introduction. Those that already know their burden of disease are encouraged to develop a vaccine introduction plan.

Economics
- Economic studies are another key element in developing and monitoring introduction of the vaccine, a capacity that is limited throughout the region in some countries. Countries are encouraged to develop capacity to collect data on cost of health services (public and private), and other expenses related to dengue control and treatment of disease.
- Based on previous experiences, it is recommended that economic studies be conducted in advance of decision making. These studies are important for decision makers in order to project the investments required to introduce the vaccine.
- Limited studies are available by country on costs (direct & indirect) related to dengue control and burden of disease. Countries are encouraged to consider conducting such studies.
- Economic studies should be uniform and generate results that are clear to decision makers, and comparability between studies should be reviewed.
- There should be transparency in the conduct of studies (particularly when financed by pharmaceutical companies.
- Assessment of cost effectiveness is essential and should be a requirement for countries considering dengue vaccine introduction.
- The cost of vector control programs and cost of outbreaks should be assessed as basic information independently and in addition to other cost assessments.

Policy Studies
- Countries should review their introduction policies in light of updated regional guidelines for vaccine introduction.
- Sustainability of vaccine introduction should be assessed.
- Policy decisions for vaccine introduction should include a careful risk/benefit assessment. If a decision to introduce is made, vaccine safety monitoring should be enhanced and vaccine impact on reducing the burden of disease should be assessed.
Models
- The principles of modeling should be standardized.
- All countries can participate in modeling, particularly with other more-experienced countries, and with academic institutions.
- Countries should build capacity for modeling.
- Teamwork is key for successful modeling.
- Models should focus on the impact of vaccination on severe disease.

Immunization Systems
- Countries should integrate dengue surveillance with vaccination coverage surveillance, immunization registries and pharmacovigilance for vaccine safety.
- Countries without surveillance need to develop such capacity.
- Experiences in implementation should be shared for better decision making by other countries.
- Countries should share information on new developments in their countries.
- Communication regarding individuals not targeted for vaccination needs to be developed, and local authorities need to be educated in order to manage expectations.
- Key messages of a communication plan should include:
  - “Vaccination is part of an integrated approach to prevent dengue, that also includes vector control.”
  - “Vaccines are not 100% protective against dengue.”
- Messages on the vaccine should be integrated with those on vector control.
- Communications plans on the introduction of the vaccine should include:
  - A strong and effective communication approach to those not targeted for vaccination.
  - A clear plan to address multiple targets for communication (e.g. policy-makers, health care professionals, the general public, community leaders, opinion/thought leaders).
- Considerations should be given to new channels of communication, such as social media, since they can have more reach. Social media may also serve as a screen to monitor and detect negative messaging on vaccine introduction early on.
- Novel technologies (e.g. SMS) should be utilized to increase awareness.
- Positive and negative messages, such as those circulated by social media, should be tracked and a process to respond effectively should be well-established.
- Collaboration and partnership are encouraged with health promotion departments and NGOs with this type of capacity.
- Countries should have a process to monitor and adjust communication messages based on vaccine availability.
Demand and Financing

Demand
- Short, medium and long-term planning are important because of the enormous uncertainty on vaccine supply in its early phases of introduction.
- It is very important to have clearly defined criteria for the target population based on:
  - A clear definition of endemic areas in dengue-endemic countries based on geographic locations, by age groups and level of severity that can project where the impact of the vaccine may be the greatest.
  - A standardized definition of dengue cases, and severe dengue within endemic areas.
  - Specific information on the product profile (e.g. vaccine target more severe dengue cases–DHF).
  - A defined threshold of seroprevalence.

Financing
- In order to ensure sustainable financing it is recommended that countries consider:
  - The price of the vaccine.
  - The source of funding (internal versus external).
  - The procurement mechanism that may be feasible.
  - Identifying complementary funding mechanisms, such as dengue-specific funding mechanisms where other non-traditional partners outside the public sector may be potentially involved.

Post-Licensure Studies
- Safety and effectiveness studies should be conducted, exploring a range of outcomes and time periods since vaccination.
- Countries should study the combined effect of vaccination and vector control on preventing dengue.

Implementation
- Countries should consider school-based immunization programs to facilitate implementation logistics.
- Countries should examine strategies to best integrate dengue vaccination immunization in the context of the EPI with an emphasis on sustainability of the program and of standardizing best practices.

Countries should study the combined effect of vaccination and vector control on preventing dengue.
## Appendix 1: Agenda and Speakers

<table>
<thead>
<tr>
<th>Time</th>
<th>Event</th>
<th>Presenters/Advisors</th>
</tr>
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<tbody>
<tr>
<td>8:30–9:00 AM</td>
<td>Executive session of Dengue Prevention Board — (Closed session for Board Members) DPB members only.</td>
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<tr>
<td>9:00–9:10 AM</td>
<td>Opening Remarks</td>
<td>Colombian MoH/Colombian NIH&lt;br&gt;Dr. Alma Morales&lt;br&gt;Advisor Family, Gender and Life Course&lt;br&gt;PAHO WHO Representative</td>
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<tr>
<td>9:10–9:20 AM</td>
<td>Introduction</td>
<td>Prof. Annelies Wilder-Smith</td>
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<tr>
<td>9:20–9:40 AM</td>
<td>PAHO Perspectives</td>
<td>Dr. Wilmer Marquiño and Dr. Gabriela Rey</td>
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<tr>
<td>9:40–11:45 AM</td>
<td><strong>SESSION I: THE DENGUE VACCINE CANDIDATES IN THE PIPELINE</strong></td>
<td>Presenters:&lt;br&gt;1. Dr. Steve Whitehead&lt;br&gt;2. Dr. Ricardo Palacios&lt;br&gt;3. Dr. Kwasi Amfo&lt;br&gt;4. Dr. Alexander Schmidt&lt;br&gt;5. Dr. Mic McGoldrick</td>
</tr>
<tr>
<td>9:40–11:45 AM</td>
<td>Update and perspectives of vaccines currently in clinical development (20 min per presentation &amp; ~ 5 min for discussion)</td>
<td>1. NIH&lt;br&gt;2. Butantan&lt;br&gt;3. Takeda&lt;br&gt;4. GSK&lt;br&gt;5. Merck</td>
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<tr>
<td>11:45–11:55 AM</td>
<td><strong>COFFEE BREAK</strong></td>
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<tr>
<td>11:55 AM–12:50 PM</td>
<td>Presentation of Phase 3 data by Sanofi Pasteur</td>
<td>Dr. Sandra O. Besada</td>
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<tr>
<td>12:50–1:20 PM</td>
<td>Q&amp;A and discussion</td>
<td><strong>Facilitator:</strong> Dr. Anna Durbin</td>
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<tr>
<td>1:20–2:20 PM</td>
<td><strong>LUNCH</strong> Location: Instituto Nacional de Salud de Colombia</td>
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<tr>
<td>2:20–2:55 PM</td>
<td><strong>SESSION III: POINTS FOR CONSIDERATION</strong></td>
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<tr>
<td>2:20–2:55 PM</td>
<td>Modeling I: Presentation of impact of vaccination using one model.</td>
<td>Dr. Ira Longini</td>
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<tr>
<td>2:55–3:20 PM</td>
<td>Modeling II: Presentation of other modeling approach and impact of vaccination based on another model</td>
<td>Dr. Derek Cummings</td>
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<tr>
<td>3:20–4:00 PM</td>
<td>Q&amp;A and discussion</td>
<td><strong>Facilitator:</strong> Dr. Kirsten Vannice</td>
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<tr>
<td>4:00–4:20 PM</td>
<td><strong>COFFEE BREAK</strong></td>
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<tr>
<td>4:20–4:50 PM</td>
<td>Economic burden of dengue</td>
<td>Prof. Don Shepard</td>
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<tr>
<td>4:50–5:20 PM</td>
<td>Q&amp;A and discussion</td>
<td><strong>Facilitator:</strong> Dr. Dagna Constenla</td>
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<tr>
<td>5:20–6:00 PM</td>
<td>Points for Consideration: Implications of the recent data in light of the identified points for consideration for dengue vaccine introduction</td>
<td><strong>Facilitator:</strong> Jacqueline Lim</td>
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<tr>
<td>6:30 PM</td>
<td><strong>DINNER</strong> Hosted by DVI Location: Holiday Inn Bogota Airport</td>
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## DAY 2  Tuesday, March 17

### SESSION I: PRESENTATION BY COUNTRIES

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Presenters</th>
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</table>
| 8:30 AM – 12:00 PM | Presentation on vaccine introduction and use in countries. Presenters to include data from burden of disease, target groups, delivering strategy, and interface with vector control (10 min presentation + 5 min Q&A) | Argentina— Ana Maria Briggiler  
Brazil— Giovanini Coelho  
Colombia — Jose F. Valderrama  
Costa Rica — Anabelle Alfaro Obando  
Cuba — Maria Guzman  
Ecuador — Mary Regato A.  
Honduras — Eduardo Fernandez  
Mexico — Jorge F. Mendez-Galvan  
Nicaragua — Juan Jose Amador  
Puerto Rico — José F. Cordero  
Venezuela — Iris Villalobos de Chacon |

**Facilitator:** Jacqueline Lim  
**Presenters:** DPB member from each country

### COFFEE BREAK

10:20 – 10:40 AM

### LUNCH

12:00 – 1:00 PM  
Location: Instituto Nacional de Salud de Colombia

### SESSION II: WORKING GROUPS

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Facilitators</th>
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| 1:00 – 2:50 PM | WORKING GROUP SESSION  
We propose four working groups to each select a country as example, and address the following question: “Considering the current situation and experience gained, what should be done next to evaluate the benefit of vaccination and to aid country decision-makers on introduction and use?” | Dr. Mabel Carabali & Jacqueline Lim  
Dr. Anna Durbin  
Dr. Ira Longini  
Dr. Dagna Constenla  
Dr. Kirsten Vannice & Ana Carvalho |

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Rapporteur for each group</th>
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<tbody>
<tr>
<td>2:50 – 4:30 PM</td>
<td>Presentations by the groups (15 min per presentation + 5 min Q&amp;A)</td>
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### COFFEE BREAK

4:30 – 5:20 PM

### Closed meeting among DPB members to prepare conclusions

### CLOSING SESSION

<table>
<thead>
<tr>
<th>Time</th>
<th>Activity</th>
<th>Rapporteur for DPB</th>
</tr>
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| 5:20 – 6:00 PM | Report by the Dengue Prevention Board                                    | Prof. Annelies Wilder-Smith  
Colombian MoH/NIH |

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<th>Time</th>
<th>Activity</th>
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<tbody>
<tr>
<td>6:00 – 6:20 PM</td>
<td>END — Closing remarks and adjourn</td>
</tr>
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</table>
Appendix 2: List of Meeting Participants

**BOARD MEMBERS**

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

**Dr. Juan Jose Amador**  
*unable to attend*  
National Coordinator and Research Team Leader, Nicaragua  
Boston University  
Boston, United States

**Dr. Antonio Arbo**  
*unable to attend*  
Chief of Pediatrics  
Institute of Tropical Medicine  
Public and Welfare, Ministry of Health  
Asuncion, Paraguay

**Dr. Jorge Boshell**  
Director Biosafety Committee  
Bone and Tissue Bank (Banco de Huesos)  
Biosafety Bone and Tissue Bank Cosmas and Damian Foundation  
Bogota, Colombia

**Dr. Ana Maria Briggiler**  
Chief Division Diagnosis, Pathogenesis, Treatment and Prevention  
INEVH  
Argentina

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

**Dr. Giovannini Coelho**  
Coordinator of the National Dengue Control  
Ministry of Health  
Brazil

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

**Dr. Delia A. Enria**  
*unable to attend*  
Director, INEVH (Instituto Nacional de Enfermedades Virales Humanas)  
Argentina

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

**Dr. Maria Guadalupe Guzman**  
*unable to attend*  
Head Virology Department  
Director, PAHO  
WHO Collaborating Center for Viral Diseases  
Pedro Kouri Tropical medicine Institute  
Havana, Cuba

**Dr. Jorge F. Mendez-Galvan**  
National Research  
Children’s Hospital of Mexico “Federico Gomez”  
Mexico D.F., Mexico

**Dr. Anabelle Alfaro Obando**  
Technical Expert Group on Dengue Attention  
Pan-American Health Organization  
Costa Rica

**Dr. Mary Regato**  
Chief  
Dengue National Reference Centre  
National Institute for Research in Public Health  
Guayaquil, Ecuador

**DVI COLLABORATORS**

**Dr. Mabel Carabali**  
Epidemiologist  
International Vaccine Institute

**Ms. Ana Carvalho**  
Director, Special Projects  
Vaccine Advocacy and Education  
Sabin Vaccine Institute  
Washington DC, United States

**Dr. Dagna Constenla**  
Director, Economics & Financing  
International Vaccine Access Center  
Johns Hopkins Bloomberg School of Public Health  
Baltimore, United States

**Dr. Anna Durbin**  
Associate Professor  
International Vaccine Access Center  
Johns Hopkins Bloomberg School of Public Health  
Baltimore, United States

**Dr. Shawn Gilchrist**  
Writer/Editor  
S Gilchrist Consulting Services Inc

**Dr. Tom Hladish**  
Research Scientist  
University of Florida  
Gainesville, United States

**Dr. Joachim Hombach**  
*unable to attend*  
Senior Advisor in the Department of Immunization  
Vaccines and Biologicals  
World Health Organization  
Geneva, Switzerland

**Mr. Jung Seok Lee**  
Associate Research Scientist  
International Vaccine Institute  
Seoul, South Korea
Mr. Kang-Sung Lee  
Associate Researcher  
International Vaccine Institute  
Seoul, South Korea

Ms. Jacqueline Lim  
Acting Program Leader, Dengue  
International Vaccine Institute  
Seoul, South Korea

Dr. Ira Longini  
Professor of Biostatistics  
College of Public Health and Health Professions, and College of Medicine  
University of Florida  
Gainesville, United States

Ms. Soo Hyun Rah  
Coordination Administrator  
International Vaccine Institute  
Seoul, South Korea

Dr. Diana Rojas  
University of Florida  
Gainesville, United States

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