Development of Dengue Vaccines
Status Review and Future Considerations

REPORT OF THE ASIA-PACIFIC DENGUE PREVENTION BOARD MEETING
Seoul, Korea
November 21 - 22
2014

DVI is a consortium of the International Vaccine Institute, World Health Organization, Sabin Vaccine Institute, and Johns Hopkins University’s International Vaccine Access Center
Report of the Asia-Pacific Dengue Prevention Board Meeting

Development of Dengue Vaccines – a Review of the Status and Future Considerations

SUMMARY

This year, highlights in dengue vaccine development include the publication by Capeding MR et al\(^1\) on the safety and efficacy of the Sanofi Pasteur dengue vaccine candidate (CYD-TDV) in Asia, and more recently the publication by Villar L. et al\(^2\) on the outcomes of Phase III trials in Latin America. Candidate vaccines from other developers are also progressing in clinical development, as is the modeling of the impact of vaccination on dengue incidence.

In view of these updates, DVI convened a meeting of the Asia-Pacific Dengue Prevention Board (APDPB) for the purpose of: (1) reviewing the dengue vaccine Phase III clinical trial results, the progress of clinical development with other candidate vaccines, and the mathematical modeling of the potential impact of vaccination on dengue; (2) openly discussing experts’ perspectives for licensing and introducing dengue vaccines in their respective countries and in the context of the “Points for Consideration” developed in 2012 by the Asia-Pacific and Americas Dengue Prevention Boards. The Points for Consideration were originally developed to help policy makers and national immunization program managers determine their capacity to undertake dengue vaccine introductions.


The meeting allowed for information sharing from all vaccine manufacturers on the status of their candidate vaccines, and for discussion with modelers on the application of modeling to impact predictions of dengue vaccination.

The expert representatives of the Asia-Pacific countries provided their perspectives on the prospects for dengue vaccine introduction and use in their countries, including integration with vector control, and highlighted specific challenges and needs for decision-making.

The review of the Points for Consideration led to a proposal for a number of revisions or additions which are summarized in Table 1 of this report. Specifically, they should provide greater details where needed.

The Board noted:

- **the completed Phase III trials** will contribute to future dengue vaccine study design and implementation;

- **the complexities** around mathematical modeling of dengue transmission and the potential impacts of vaccination in conjunction with vector-control strategies highlight the importance of ongoing interaction between dengue experts and modelers;

- **the Points for Consideration** are too demanding of some member countries and would benefit from being revised and updated to account for the capacity of member countries to introduce a dengue vaccine;

- **differences between dengue epidemiology** in countries will require country-tailored dengue vaccine policies and implementation strategies.

The meeting provided for a fruitful exchange of knowledge and views on issues countries face in the planning and introduction of dengue vaccines.

The continuing leadership of DVI, the contributions of the partners in the DVI consortium, the support from BMGF and other sponsors of dengue research and development, will be critical to enabling the successful introduction of dengue vaccines.
Since the last APDPB meeting and since the Points for Consideration for First Introductions of Dengue Vaccines in Endemic Countries were developed, the results of Sanofi Pasteur’s dengue vaccine candidate (CYD-TDV) Phase III trials in Asia and the Americas have been made public. These trials demonstrated overall vaccine efficacy (VE) against symptomatic virologically-confirmed dengue of 56.5% (43.8 – 66.4) in Asia and 60.8% (52.0; 68.0%) in the Americas. Point estimates for efficacy varied considerably by age, by sero-status (VE 35.5% in seronegative vs. 74.3% in seropositive subjects in Asia), by serotype, and by country. No safety signals, and in particular no signs of sensitization, were observed in a 25 month follow-up period.

These results show that a vaccine that can prevent dengue cases is feasible. This candidate will be submitted by the company for licensure, and might be considered for introduction in dengue-endemic countries. Given the possible availability of a dengue vaccine once licensed, countries need to assess their capacity to plan for vaccine introduction in a timely manner. Additionally, the newly available information on VE from the Phase III trials warrants an examination of the published and presented data and the potential implications for country introductions.

In this context, DPB members/meeting attendees from the Asia-Pacific region agreed to review whether the earlier elaborated Points for Consideration for First Introductions of Dengue Vaccines in Endemic Countries continue to apply. The ‘Points for Consideration’ were originally developed to help policy makers and national immunization program managers determine their capacity to undertake dengue vaccine introductions. The newly available data on VE, available by serotype, age, and sero-status, might warrant some new considerations.

Furthermore, approaches that integrate both vector control and vaccination need to be further evaluated in light of the potential impact of a vaccine with a moderate efficacy against serologically confirmed dengue in the range of 56 – 61%.

Therefore, the DVI held a 2-day consultative meeting with the Asia-Pacific Dengue Prevention Board to:

- **review** the clinical development progress of candidate vaccines;
- **explore** the potential for mathematical modeling to project the impact of a vaccine, using the Phase III trial data, and by tailoring country or regional epidemiology.
- **discuss** DPB members/meeting attendees’ perspectives for licensing and introducing dengue vaccines in the context of the ‘Points for Consideration’ earlier developed.
**PROGRESS IN CLINICAL DEVELOPMENT OF DENGUE VACCINES**

In addition to the Sanofi Pasteur CYD-TDV dengue vaccine candidate, which has completed Phase III evaluation, development of several other dengue vaccine continues to progress. Industry representatives highlighted that the introduction of a licensed dengue vaccine might complicate the development of earlier stage dengue vaccine candidates by possibly requiring new clinical trial design to account for the use of an existing licensed dengue vaccine. It will not be ethical to randomize to a placebo group once a dengue vaccine has been introduced. Countries were encouraged to help find solutions to facilitate trials with earlier stage vaccine candidates and invite competition in the market.

**Takeda (TDV-2):** 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 1). Approximately 600 individuals have received the study vaccine to date, including about 200 children under 12 years.

In addition, a number of studies are ongoing to better ascertain the correlation between protection and cell mediated-responses.

Clinical development is currently in Phase II, evaluating safety and tolerability in subjects aged 1.5 to 45 years in Puerto Rico, Colombia, Singapore, and Thailand. 246 subjects received the study vaccine subcutaneously in 2 doses, 90 days apart. Both high and low dose formulations were found to be safe with no related serious adverse events (SAEs), no constellation of symptoms suggestive of dengue fever, and no notable blood chemistry of hematological changes.

Results show that the candidate vaccine induces high levels of neutralizing antibodies and sero-conversion ≥80% to all four dengue virus serotypes, after two doses, in endemic populations.

A pivotal Phase III efficacy study is in preparation with an expected start in 2015.

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**FIGURE 1.**

Takeda’s Live Attenuated Tetravalent Dengue Vaccine Candidate: DENV-2-Based Recombinant Vaccine

- Live, attenuated Takeda TDV-2 induces responses to DENV-2
- Recombinant approach to induce antibodies against DENV-1, DENV-3 and DENV-4
- TDV-2 backbone can induce multifunctional and cross-reactive cellular CD8+ T-Cell responses to non-structural genes

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*Ambuel et al, 2014 DOI: 10.3389/fimmu.2014.00263
*Partidos et al, ASTMH 2014; Poster No. 182
NIH/Butantan: is currently in Phase II clinical trial with a live attenuated tetravalent DENV-1, DENV-3, DENV-4 and chimeric DENV–2 vaccine (see Figure 2).

So far, all adverse events have been found to be mild. A vaccine-associated rash correlated with a tetravalent response has been noted but is asymptomatic. Sterilizing immunity to a second dose of vaccine is observed at 6 months post vaccination and there is minimal antibody boosting with a 2nd dose.

Challenge studies with a DENV-2, derived from DENV-2 Tonga/74 showed that TV003 (a formulation with each serotype at a dosage of 103 pfu) completely protected 14/14 subjects from viremia, rash and neutropenia.

A stepwise Phase II trial in adults is now underway in Brazil in dengue naïve and exposed individuals. Immunogenicity and safety data from a 1 dose protocol are expected in Q4 2014.

Once the data from this phase are available and satisfactory, the trial will progress to a Phase III in 2015.

A separate Phase II is expected to enroll 240 subjects in Thailand in December 2014 for a head to head comparison of TV003 and TV005 (DENV-2 component given at a dose of 104 PFU vs 103 PFU in TV003). If there are no safety concerns, the trial will age de-escalate down to children 1 year of age with TV005.

GlaxoSmithKline/Fiocruz/Walter Reed (DPIV): a tetravalent whole virus dengue purified inactivated vaccine (DPIV), adjuvanted with AS01 or AS03, is in in early Phase I trials in 100 subjects in the continental US and 100 subjects in Puerto Rico. Given in two doses, four weeks apart, the target profile is designed to fit within the EPI schedule, be suitable for rapid outbreak control, and for travelers and the military.

Four DPIV formulations were tolerated well in both sero-negative and sero-positive subjects. More than 90% seroconversion to all four dengue virus serotypes was noted with the AS01 and AS03 adjuvanted formulations and high dose AlOH formulation. High titer balanced GMTs were observed against all four serotypes in sero-negative subjects. The ASO3 formulation induced the highest neutralizing antibody GMTs. Waning of GMTs was observed in sero-negative subjects.

In primed subjects in Puerto Rico, the vaccine induced and boosted GMTs and no waning of GMTS was observed.

A new study planned for 2015 will specifically look at the dosing regimen in the dengue naïve.

A final formulation will be selected and then trials will proceed by age de-escalation, to generate efficacy data in flavivirus-primed as well as naïve subjects.

However, the ability to conduct efficacy trials will depend largely on the feasibility of
conducting placebo-controlled trials at a time when a licensed vaccine may have already been introduced. The potential size of trials needed may discourage investment. Discussion with the World Health Organization (WHO), national regulatory authorities (NRAs) and countries are needed to determine the Phase III design and the requirements to properly evaluate and advance a 2nd product to market.

Dengue epidemiological trials and clinical endpoint definition studies where burden of dengue is on the rise are currently underway in Latin America and in Asia.

**Sanofi Pasteur (CYD-TDV):** Sanofi Pasteur has completed clinical testing with a live attenuated tetravalent recombinant chimeric vaccine, using a yellow fever backbone (see Figure 3) in more than forty thousand subjects, of which over thirty thousand were vaccinated with the dengue candidate vaccine, the majority with 3 doses.

Results from the first 25 months of follow-up in Phase III clinical trials from Asia were published in July 2014, and from the Americas in November 2014.

Countries were selected for the Phase III studies from a list of places with the highest endemicity, based on WHO and country data, and with reasonable infrastructure and capacity for full Good Clinical Practices (GCP) and international conference on harmonization (ICH) compliance. These were, in Asia:

Indonesia, Malaysia, Thailand, The Philippines, and Vietnam; and in the Americas: Brazil, Colombia, Honduras, Mexico, and Puerto Rico.

VE was measured against symptomatic virologically confirmed dengue, irrespective of disease severity or serotype, occurring >28 days post-third injection.

The Phase III trials were targeted at ages with highest attack rates: 2–14 years in Asia; and 9 – 16 years in the Americas.

Three doses of CYD-TDV were given and 0, 6 and 12 months. Efficacy and safety were measured over one full year post-third dose injection. Safety will ultimately be tracked for a total observation period of up to 6 years for hospitalized cases, starting from 1 dose.

**RESULTS FROM PHASE III IN ASIA**

The data were published in *The Lancet* by Capeding MR et al, 2014. The efficacy was derived from 10,275 subjects and immunogenicity data from 2,000 subjects. Study compliance was high (98.8% for 3 doses) with 0.8% drop out over 2 years and 2.1% excluded from pre-protocol efficacy.

Primary endpoint analysis shows that efficacy, post-dose 3, was statistically significant against any serotype at 56.5% (43.8 – 66.4), meeting the primary endpoint of the study. Efficacy against the WHO 1997 definition of dengue hemorrhagic fever (DHF) was 88.5% (58.2 - 97.9). Point estimates of serotype-specific efficacy ranged from 35.0% for DENV-2, to 78.4% for DENV-3

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**FIGURE 3.**
Sanofi Pasteur Live Attenuated Tetravalent Recombinant Chimeric Dengue Vaccine

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YFV 17D Virus

* C

* NS

* prM

* E

** DENY-1

** DENY-2

** DENY-3

** DENY-4

** Recombinant DENY-1, -2, -3, and -4
and were statistically significant for all, except for DENV-2. Likewise, country-specific efficacy ranged from 51.1% in Vietnam to 79.0% in Malaysia but differences were not statistically significant.

VE was considerably lower in sero-negative subjects (35.5%, not statistically significant) than in sero-positives subjects (74.3%; 53-86%).

A trend of higher efficacy with age was noted, age correlating with baseline sero-positivity. As such it is possible that higher VE is more dependent on sero-status rather than age per se.

The observed safety profile up to 25 months of follow-up in vaccines has been good and not different between vaccinees and placebo.

Immune responses were good after a first dose and remained good with additional doses, as observed in prior Phase I and Phase II studies.

**RESULTS FROM PHASE III IN THE AMERICAS**

These data were published in the *New England Journal of Medicine* by Villar L et al, 2014. In the Americas, a larger sample size was used because the anticipated attack rate was about half that in Asia. 20,869 subjects were therefore enrolled for efficacy and safety, and a subset of 2,000 constituted a cohort for immunogenicity.

Primary endpoint analysis shows that efficacy, post-dose 3, was statistically significant against any serotype, and the primary study endpoint was met. VE against symptomatic virologically-confirmed dengue was 60.8% (52.0 – 68.0). The observed VE in sero-negative subjects was 43% (not statistically significant) and 84% in sero-positive subjects.

Point estimates of serotype-specific efficacy ranged from 42.3% for DENV-2, to 77.7% for DENV-4 and were statistically significant for all serotypes. Likewise, country-specific efficacy ranged from 31.3% in Mexico (where there was a higher proportion of sero-negatives) to 77.5% in Brazil but differences were not statistically significant.

Intention-to-treat analyses show 80.3% (64.7–89.5) efficacy against hospitalization, and 95.0% (64.9–99.9) against 1997 WHO DHF criteria.

A trend was noted for higher efficacy in sero-positives than sero-negatives (83.7% vs 43.2%) but no age effect was observed.

As in Asia, the observed safety profile up to 25 months of follow-up showed no difference between vaccinees and placebo.

**COMPARISON OF PHASE III OUTCOMES IN ASIA AND AMERICAS**

Age in the CYD groups (mean 8.8 years in Asia versus 12.4 years in the Americas) and baseline sero-positivity (67.7% in Asia vs 80.6% in the Americas) was one aspect of differences between the two regions.

While the point estimates of efficacy were not identical between regions, the confidence intervals for efficacy by serotype and by severity (ICDM, 1997 WHO DHF criteria, and hospitalization) overlapped between the two regions such that heterogeneity in efficacy between the regions could not be concluded.

There were no differences in safety between the regions.

**POSTSCRIPT**

Clinical efficacy is consistent between regions. Based on the achievement of the primary efficacy and safety endpoints in Phase III trials, vaccine licensure is expected by end of 2015/2016.

Discussion with WHO, NRAs and countries are needed to determine the Phase III design and the requirements to properly evaluate and advance a second product to market.5

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5 Merck is also developing a dengue vaccine candidate. Representatives were unable to attend the meeting. For more information please read “2014 Dengue Candidates in Review.”
MODELING APPROACHES AND IMPACT OF VACCINATION FROM ONE MODEL

Models can be valuable for projecting the impact of vaccination on preventing dengue, and virus transmission. These projections could be particularly useful for determining appropriate vaccine introduction strategies (optimal target populations, impact of catch up, etc), and projecting the impacts of vaccination over time.

Using an individual-level, stochastic, mathematical model, the impact of dengue vaccination was projected for Yucatan in Mexico.

The model assumed:

- approximately 400,000 households clustered in towns and urban centers;
- seasonality of dengue associated with probability of rainfall;
- risk of disease dependent on infecting serotype, age of individuals, and immune status.
- lifelong protection against each dengue virus serotype and 100% heterotypic cross protection lasting 2 years.

Approximate Bayesian computation\(^6\) was used to fit the model to historical data. The model was then used in 2 scenarios: a high force of infection (annual average \(R_0 = 3.4\)) and a moderate force of infection (annual average \(R_0 = 2.2\)). The moderate scenario, which corresponded to a mean dengue incidence (cases) of 14 per 1,000, was considered more realistic for the Yucatan.

The model was run for routine vaccination of 2, 6, 10 or 14 year-olds +/- a one-time catch up to 46 year-olds. The model shows that after about 20 years there is convergence of the attack rate for routine childhood vaccination and routine + the one-time catch-up vaccination for the high force of infection scenario. Under the moderate scenario, after 20 years, the routine + catch-up strategy still reduces more cases than the routine-alone strategy (see Figure 4).

One-time catch-up vaccination is most effective when associated with routine vaccination of 2 year-olds because the largest number of people are being vaccinated. Routine vaccination without catch up is most effective when administered to 14 year-olds (Figure 5) because the vaccine is assumed to be more effective for people who have been previously infected.

Similar qualitative results were observed for the reduction in hospitalizations and vaccine effectiveness against hospitalizations although an overall increase in effectiveness

\(^6\)ABC is a statistical procedure used to infer parameters for which empirical estimates are missing. Fitted parameters are then used to run the model (without ABC) with and without vaccines.
is observed because the vaccine is assumed to reduce disease severity.

The conclusion for the Yucatan model is that routine vaccination of children + one-time catch up up to 46 years of age result in 95% effectiveness for clinical dengue, and falls to 90% over a 20 year period, under the moderate scenario. For hospitalizations, effectiveness starts near 100% and falls to near 90%.

The best target age for routine vaccination without catch up, in the Yucatan, is 14 years. The optimal age will likely decrease for populations with a higher dengue burden (infections/year).

When most of a population is unvaccinated, vector control measures that substantially reduce the number of adult mosquitoes are quite effective. At higher vaccine coverage levels, vector control measures become less important.

Phase IV effectiveness studies will require model-based assessments coupled with empirical studies, such as cluster randomized step-wedge designs where using a control group is problematic. Instead, the time period can be used as a control by randomizing when vaccine introductions occur.

**DISCUSSION**

DPB members/meeting attendees’ primary concern was that the extensive catch-up programs suggested by the model as being necessary for effective control of dengue, using a vaccine with this Phase III profile, are unrealistic. Furthermore, dengue epidemiology is highly country-specific, and therefore modeling would not be generalizable. At the same time, it was recognized that the required data to model (e.g. GPS location of all schools, vector density data, etc) might not be available for all countries.

There was also strong interest in running alternate scenarios, such as smaller catch ups, or serotype-specific vaccine efficacies, or different epidemic potentials, or in running a regional model for Asia-Pacific countries.

Some countries also noted the political/ethical challenges of not immunizing at younger ages, in spite of potential contrary model predictions for best outcomes.

Given the interest in adapting models for country use, modelers and countries were urged to more closely engage to determine how models can be best adapted to country needs.
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 Consolidated 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. The main discussion points from the meeting are summarized below:

1. Regulatory – a support to NRAs is being led by the DVI, with WHO – a member of the DVI consortium – as technical partner. Seven countries (Brazil, Colombia, Indonesia, Malaysia, Mexico, Thailand, and The Philippines) are part of the DVI NRA network, working together for almost two years now.

A first meeting organized by DVI with these seven NRAs was held in April 2013 in Brasilia and discussed a possible common review by NRAs of vaccine license application, and ways to increase NRA capacity by bringing experts from each country or external.

In Bangkok in October 2013 and in Kuala Lumpur in July 2014, NRAs further elaborated a mechanism for common review of progress of dengue vaccine. NRA met again in November 2014. Manufacturers attended these meetings and each had close sessions with the NRA to discuss further about their progress. As per a review of a license application, one challenge is that each country has its own specific requirements and the NRA meeting specifically looked at the operational aspect of a common review of a file. A document describing the process of review has been signed by the NRA’s directors.

The DVI views this as a promising new paradigm to increase NRAs’ capacity, by working together and benefitting from the expertise of WHO and other partners.

2. Immunization systems – the DVI ‘Points for Consideration’ outlined the requirements for successful dengue vaccine introductions. These included: consulting a National Immunization Technical Advisory Committee (NITAG); having a vaccine introduction strategy; securing sufficient budget; the capacity for surveillance; monitoring and evaluating vaccination impact; sufficient logistics capacity; communication capacity; capacity for cross-sector collaborations, such as with vector control and technical agencies. Some countries also identified additional specific needs associated with dengue vaccine introductions (for example the need for halal certificates for Muslim populations).
These included adapting immunization registries to allow for dengue vaccine reporting with effective recall mechanisms. This ‘in’ turn requires training.

Vaccination of e.g. 2 year olds would also require additional vaccinator training for proper holding of children.

Since additional required capacities are currently being reviewed for inactivated polio vaccine (IPV) introduction, an opportunity exists to combine reviews with capacities required for dengue vaccine introductions. The capacities for dengue vaccination are likely to exceed those for IPV, since IPV will still fit within the EPI schedule.

DVI could play a role in identifying partners that can offer technical support, such as GAVI through Heath Systems Strengthening (HSS).

Lessons from rotavirus vaccine introduction could be looked at and possibly applied to dengue vaccine introduction, for communication with unified messages to public and private sectors, and also building trust.

Communication and advocacy were repeatedly identified throughout the course of the meeting as being critical for accelerating a dengue vaccine introduction. This included communications and advocacy with technical and political decision-makers on the potential impacts of vaccination, and communications to the public on matters such as benefits and risks of vaccination, rationale for target selection, potential impacts of vaccination, etc.

Additional guidance on the most appropriate strategies for vaccine rollout still needs to be developed by NITAGs and WHO, particularly in light of the possibility of having a licensed vaccine in 2015/2016.

3. Evidence for decision making –

These ‘Points for Consideration’ were considered to be overly demanding of countries. It was suggested that these could be reviewed with a more practical, if not realistic, approach.

A better understanding of hospital-seeking behaviors is needed to more accurately compare the economic impacts of dengue vaccination between countries.

The Phase III data published by Capeding et al and by Villar et al showed that true burden of dengue may be 2 or 3 times the current estimates, a difference between passive and active surveillance. This means that an improvement in the quality of baseline data is needed for accurately measuring the impact of dengue vaccination after its introduction.

4. Impact modeling – The Yucatan model developed in Mexico by Ira Longini and his team is available to countries in source code. However, it is not being used because it requires expertise to run. While desired by countries, tailoring country-specific inputs to the models will be challenging because it requires programming expertise. Furthermore, running this specific model would need to be done on a ‘super’ computer, as the program needs to run it several hundred times.

Modelers can indicate which data are necessary to run the model so that countries can assess whether they have the appropriate information. However, it is also acknowledged that some country data are not available, such as GPS positions of all schools.

Countries may also work with other deterministic models which are available. It may also not be necessary for every Asia-Pacific country to conduct modeling, especially if this is thoroughly performed in one or two countries.

The WHO has developed a guidance document in 2012 on the general principles of modeling which could also prove useful to countries.
5. Demand and financing - Capacity in this area in particular should be viewed in the global context of the health system. The health system should be analyzed for its capacity to support dengue vaccine introduction.

A simple health economic model for countries, to support decision-making on dengue vaccine introduction, is also needed.

6. Post-licensure demonstration projects - As previously recommended by the Points for Consideration, first introducing countries should have national support and community acceptance, technical capacity and desire to evaluate safety and effectiveness, be willing to share outputs with other countries, and have functioning technical collaborations.

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**TABLE 1.**

Summary of the Working Groups Discussion on the ‘Points for Consideration’ for Modeling

<table>
<thead>
<tr>
<th>MODELING</th>
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<tbody>
<tr>
<td><strong>PREAMBLE</strong></td>
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<tr>
<td>&gt; Limitation of existing models; limitation in data e.g., immune profile, expansion factor</td>
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<tr>
<td>&gt; Several models in the pipeline – which model should a country adopt, especially if different models conflict</td>
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<td>&gt; WHO’s experts to provide guidelines for model development</td>
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<td>&gt; Definition of vector control is different in different countries - preventive environmental management? Fogging in response to outbreaks?</td>
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<tr>
<td><strong>APPLICATIONS</strong></td>
<td></td>
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<tr>
<td>&gt; Inform public health impact</td>
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<td>&gt; Determine epidemiological impact of vaccine, with various target groups (e.g. by age), to identify vaccination strategies</td>
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<td>&gt; Cost effectiveness of vaccine for various strategies</td>
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<tr>
<td>&gt; Identify data gaps e.g. immune profile, expansion factor for each kind of models</td>
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<tr>
<td>&gt; Communication tool (policy makers/public)</td>
<td></td>
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<tr>
<td><strong>RECOMMENDATIONS</strong></td>
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<tr>
<td>&gt; Simple model that requires basic data, for adoption by any country</td>
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<tr>
<td>&gt; To facilitate country to develop country specific models/ to access modelling capacity</td>
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<tr>
<td>&gt; Detailed models that require more data for 2-4 countries</td>
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<tr>
<td>&gt; Applicable to early adopter and countries with data</td>
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<tr>
<td>&gt; Group countries according to seroprevalence/epidemiological profiles and develop detailed model for each group</td>
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<td>&gt; Funding/resource required?</td>
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<tr>
<td>&gt; Need external validation/peer review</td>
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<tr>
<td>&gt; Close interaction between country and modeler</td>
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<tr>
<td>&gt; To enable use of more realistic vaccine scenarios</td>
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<tr>
<td>&gt; Countries to provide “needs”</td>
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</tbody>
</table>

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First-introducing countries should have national support and community acceptance, technical capacity and desire to evaluate safety and effectiveness, be willing to share outputs with other countries, and have functioning technical collaborations.

**TABLE 2.**
Summary of the Working Groups Discussion on the ‘Points for Consideration’ for Immunization Systems

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<td>› Multi-dose/single dose</td>
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<td>2. <strong>VARIABLES TO CONSIDER FOR IDENTIFYING TARGET GROUP(S)</strong></td>
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<td>› Peak age incidence</td>
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<td>› Serostatus and efficacy by serostatus</td>
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<td>› Seasonality</td>
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<td>3. <strong>FEASIBILITY OF INCORPORATION INTO EXISTING SCHEDULE/PROGRAMS</strong></td>
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<td>› EPI – multiple injections at same time</td>
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<td>› Toddler years</td>
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<td>› School based – staffing</td>
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<td>› Ordering/storage/logistics/consumables</td>
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<td>› Record keeping</td>
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<td>› Surveillance: coverage/completion/AEFIs</td>
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<tr>
<td>› Training: health care workers, pediatricians, etc</td>
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<td>› School based staffing</td>
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<tr>
<td>4. <strong>WHAT WILL MAKE DENGUE VACCINE INTRODUCTION A SUCCESS STORY?</strong></td>
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<td>› Pilot study</td>
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<td>5. <strong>COMMUNICATION AND TRAINING</strong></td>
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<td>› Audiences</td>
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<td>› Professional organizations</td>
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<td>› Parents</td>
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<td>› Private sector</td>
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<td>› Media</td>
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<tr>
<td>› Issues</td>
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<td>› Moderately effective vaccine</td>
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<td>› Breakthrough cases/AEFIs</td>
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<td>› Complete schedule</td>
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<td>› Role in outbreaks</td>
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<tr>
<td>› Continuation of vector control/mobilization</td>
</tr>
<tr>
<td>› Rationale for [limited] introduction</td>
</tr>
<tr>
<td>› Communication in the event of outbreak</td>
</tr>
<tr>
<td>› Communicate successes</td>
</tr>
<tr>
<td>› Risk communication plan</td>
</tr>
</tbody>
</table>
### TABLE 3.
Summary of the Working Groups Discussion on the ‘Points for Consideration’ for Evidence for Decision-Making

#### Evidence for Decision-Making

<table>
<thead>
<tr>
<th><strong>Surveillance</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- National surveillance and demonstration project prior to introduction</td>
</tr>
<tr>
<td>- Post-introduction surveillance as follow up (country will decide)</td>
</tr>
<tr>
<td>- Need baseline evidence on burden of dengue</td>
</tr>
<tr>
<td>- Incidence by age/geographical distribution, seroprevalence, serotype</td>
</tr>
<tr>
<td>- Dengue is already integrated in the national surveillance as a notifiable disease (may need improvement for introduction)</td>
</tr>
<tr>
<td>- Use of the standard clinical case definition</td>
</tr>
<tr>
<td>- Should be identical in the national surveillance and the follow up after introduction</td>
</tr>
<tr>
<td>- Active sentinel surveillance (e.g., hospital-based surveillance to identify sero/genotypes)</td>
</tr>
<tr>
<td>- Ideal to have community-based (school-based cohorts) surveillance for longitudinal follow up (sero-prevalence)</td>
</tr>
<tr>
<td>- Laboratory confirmation on all by virology (e.g., RT-PCR for serotyping)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Epidemiological Surveillance</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Additional evidence on burden of dengue</td>
</tr>
<tr>
<td>- Follow up on final diagnosis for information on severity</td>
</tr>
<tr>
<td>- Use standardized grading of the severity: new vaccine efficacy more focused on severe cases</td>
</tr>
<tr>
<td>- Duration of hospitalization</td>
</tr>
<tr>
<td>- Monitor case fatality (should focus on death/severe cases)</td>
</tr>
<tr>
<td>- Develop capacity to share information and techniques (for evaluation) for greater consistency across countries</td>
</tr>
<tr>
<td>- Data for inter-country interpretation of data</td>
</tr>
<tr>
<td>- Quickly accessible public health informatics</td>
</tr>
<tr>
<td>- Capacity development for improved surveillance in the area in preparation for the demonstration project</td>
</tr>
<tr>
<td>- Take the cohort set up and use as the sample for demonstration (e.g., Rota in NICED, Kolkata)</td>
</tr>
<tr>
<td>- Data needed to identify immunization strategies</td>
</tr>
<tr>
<td>- Operational research to address gaps (cluster randomized study)</td>
</tr>
<tr>
<td>- Collaboration among countries</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th><strong>Other Considerations</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>- Involvement of bilateral agencies – define countries’ responsibilities with the demonstrations</td>
</tr>
<tr>
<td>- Proposal for demonstration projects</td>
</tr>
<tr>
<td>- Vaccine supply</td>
</tr>
<tr>
<td>- Operational costs</td>
</tr>
<tr>
<td>- The agencies to take the role of facilitator</td>
</tr>
</tbody>
</table>
RECOMMENDATIONS FOR REVISIONS
The meeting participants divided into three working groups to review and revise the current points of consideration. Given the limited time, the three “points” prioritized by DVI and board members for review were:

1. Immunization systems
2. Impact modeling
3. Evidence for decision making

The outputs of the working groups are summarized in Table 1-3. How these outputs impact the 2012 ‘Points for Consideration’ is summarized in Table 4.

<table>
<thead>
<tr>
<th>IMMUNIZATION SYSTEMS</th>
<th>MODELING</th>
<th>EVIDENCE FOR DECISION-MAKING</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recommend demonstration projects to test the introduction strategy</td>
<td>Include guidance on model selection and use</td>
<td>Include recommendation for demonstration projects and post-demonstration surveillance</td>
</tr>
<tr>
<td>Recommend preparing more comprehensive communication strategies and communications training specifically aimed at dengue vaccines</td>
<td>Standardize terminology, e.g. for ‘vector control’</td>
<td>Recommend the standardization of case definition and severity grading and the consistent use of evaluation techniques across the country</td>
</tr>
<tr>
<td></td>
<td>Promote greater collaboration between modelers and countries to improve on the accuracy of predictions through the use of local data</td>
<td>Recommend sentinel surveillance for sero/genotype surveillance</td>
</tr>
<tr>
<td></td>
<td>Recommend the assessment and mobilization of required funding</td>
<td>Recommend monitoring case fatality of dengue to justify need for vaccine introduction</td>
</tr>
<tr>
<td></td>
<td>Recommend external/independent validation of models</td>
<td>Recommend increased capacity to share information such as through quickly accessible electronic information</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Recommend the collection of data needed for the development of the vaccination strategy such as sero-status by age since VE may differ between sero-positives and sero-negatives</td>
</tr>
</tbody>
</table>

**TABLE 4. Proposed revisions to the 2012 ‘Points for Consideration on First Introductions of Dengue Vaccines in Endemic Countries’**
The Asia-Pacific countries 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.

* Ae aegypti is endemic * in Queensland but dengue virus is not. Small recurring outbreaks arise in north Queensland but severe dengue is very rare. The relatively low burden of disease is characterized by urban settings very heterogeneous in risk. High-risk suburbs tend to include a high proportion of transients.

In Australia, new vaccine introductions require an Australian Technical Advisory Group on Immunization (ATAGI) review of evidence. In their review, ATAGI liaises with the National Immunization Committee (NIC), Pharmaceutical Benefits Advisory Committee (PBAC), and others bodies, for additional evaluations, such as cost-effectiveness.

Funding for a new vaccine is determined by the government, based on a threshold of cost-effectiveness. The funding for a new vaccine, in turn, is made available from the National Immunization Program (NIP) or Pharmaceutical Benefits Scheme (PBS).

Given the low burden of disease in Australia, it is unlikely that a dengue vaccine would be funded for public use, but it is feasible that a vaccine could be used in the private market, for travelers or the army, or possibly in persons with previous first dengue infection.

**DENV-1 is the predominant serotype** in Cambodia since 1980, but all 4 serotypes are present with alternating predominance of serotypes DENV-2, DENV-3 and DENV-1. In 2014, DENV-1 accounted for 83% of cases. The incidence rate is from 0.7–3.0/1,000 pop with 3–5 years epidemic cycles. The annual number of cases did not appear to be trending upward in Cambodia, but this was because surveillance was not picking up cases. In the last decade, sentinel surveillance has detected considerably more cases than were being reported from passive surveillance (see Figure 6). In addition,
development, and environmental factors, or decreased vector control, may account for some of the increase in cases.

There was low number of dengue cases in 2014. All notified cases were from hospitals, with about 80 – 85% of cases from sentinel surveillance sites. None were reported from passive surveillance.

Figure 6 also shows that the case fatality rate (CFR) has been steadily declining, from 15% to 0.3% in 2013 (0.6% in 2014), in spite of the greater number of detected cases.

The national policy is to reduce the burden of dengue by integrated vector management and community activities with an objective to maintain the incidence rate ≤ 319/100,000 pop, and a CFR ≤ 0.6%.

The house index for Aedes has been evaluated at ≥40% but there is currently no routine vector surveillance in Cambodia. Cambodia is not ready for the introduction of a dengue vaccine because it still needs to better consider the evidence from vaccine trials and need a concrete plan for vector surveillance, vector control and human prevention.

In 2013, the average incidence of DHF was 43/100,000 with an average CFR of 0.73% with considerable regional variation. The incidence of DHF has climbed considerably over the last 45 years, but the CFR has fallen dramatically from 41% in 1968 to under 1% in 2013.

Indonesia has used a number of case definitions based on hospitalized DHF cases but has now adopted the 2011 WHO guidelines. These guidelines add expanded dengue syndrome and warning signs from the 2009 WHO guidelines to the 1997 WHO guidelines, to detect early signs of shock.

In Indonesia, peak incidence of dengue cases follows peak rainfall, with cases peaking in March and April (see Figure 7).

Serotype distribution is variable by locality, but all 4 serotypes co-circulate in most localities. A sero-prevalence study is ongoing to determine the true incidence in 30 clusters in urban sub-districts, in children 1-18 years old.
In addition, mathematical modeling is needed to determine appropriate age groups, based on DHF incidence, to target for vaccination. Observed incidence in under 4 year-olds is relatively stable but the incidence in those over 15 years is higher and increasing (see Figure 8).

The proportion of dengue mortality increases in older age groups (see Figure 9).

A lower birth rate over the last 10 years has reduced the number of people susceptible in younger age groups. Moreover, better infant survival may have increased the number of immune individuals in older age group. Therefore, children in primary school may be a more rational and cost effective target for immunization than infants.

Lessons can be learned from the introduction of Hib vaccine in Indonesia where from an initial ITAGI meeting it took about 14-15 years before Hib vaccine was introduced nationwide. Vaccine introduction was not simple and needed to follow a step-by-step course, starting with introduction in the private sector, then an ITAGI recommendation and vaccine studies, and may involve the development of local vaccine production by BioFarma. In order to implement dengue vaccination in less time than for Hib introduction, advocacy targeted at the immunization program manager, the MoH, the Ministry of Finance, Parliament, the National Financial Board (BAPENAS) and to policy makers will be required.

Primary needs for integrating vector control with vaccination in Indonesia, are upgrading dengue surveillance by reporting cases and grade of severity and collecting socio-economic data, expanding awareness, targeting vector control at schools and work places and tailoring vector control based on evidence. Vaccination will not replace vector control.
The number of dengue cases has been increasing since 1995 with an expected 90,000 cases and 168 deaths in 2014 (the highest number ever) (see Figure 10). The 2014 incidence equated with approximately 3,000 laboratory confirmed cases/week.

Epidemics occur in a 2 year cycle. The disease is predominantly urban.

In 2014 the predominant age group shifted from 20–24 years to 25–29 years. The predominant serotype also shifted from DENV-3 and DENV-2 to DENV-1 with variability between localities and with most states having 2 dominant serotypes.

As noted elsewhere, cases are higher in males. In Malaysia, deaths peak at 40 – 60 years, and there is over 30% seropositive by 16 years.

Based on this profile, modeling suggests that vaccinating 17 – 30 year-olds with 80% coverage could achieve reductions in cases of between 46 – 62% between 3 and 10 years. Vaccinating 13 – 17 year olds with 95% coverage, in addition, would increase the reduction on cases to 71 – 76% in the same time period.

Given an older age target group than was studied in the Sanofi Pasteur Phase III trials, bridging studies may be needed for vaccine licensure.

Vector control, post vaccination, will be restructured and converted into an environmental cleanliness and sanitation program, with community empowerment, because current vector control is not effective.

Malaysia needs to conduct a public health impact study, moving forward.
The first outbreak of dengue occurred in 1970, but dengue cases are now reported from all across the country, except in one state. All serotypes are circulating. The number of DHF cases has increased over time, but, like in other countries of the region, the CFR have fallen (see Figure 11).

Epidemics occur every 3–4 years. The highest number of cases and deaths recorded to date were 24,285 cases in 2009 and 444 deaths in 1994, respectively. During 2011 and 2012, 4738 cases and 16 deaths and 6433 cases and 27 deaths were reported. The year 2013 was an epidemic year with 20,255 cases with 84 deaths. This year 2014 (up to September) 9845 cases with 55 deaths have been reported.

Although the disease was previously predominantly urban, in recent years equal number of cases have occurred in rural areas. The 5–9 year age group is most affected.

Vector control is used aiming to reduce the number of cases of DHF and the CFR. Strategies include: establishing disease and vector surveillance; disease prevention with integrated community activities; to develop emergency preparedness capacity; establish prompt case management; increase awareness; and, improve management and technical support.

Main challenges remain: vector surveillance; source reduction, partnerships between municipal services and community participation; monitoring and evaluation of vector control; and finances.

For vaccination, Myanmar is working within the framework of the Global Vaccination Action Plan (GVAP) to ensure all people achieve the full benefits of immunization. This includes developing and introducing new vaccines and technologies.

FIGURE 11.
Cases of DHF and CFR in Myanmar, 1970 - 2012
New vaccine introductions require the support of the NRA (FDA) established in 1995, the national committee for immunization practices (NCIP) established in 2007, to conduct policy analyses to determine optimal policies, guide strategies, monitor impact, and serves as an advisory body to the MoH.

Capacity for dengue surveillance is limited. The National Public Health Laboratory (NHL) does not perform routine active surveillance, but confirms cases sent to the laboratory from hospitals (by PCR and Dengue ICT detecting NS1 antigen), and the Department of Medical Research identifies the serotypes from Yangon Children Hospital and does molecular characterization (for research purpose).

The AEFI surveillance system investigates serious AEIs (death, hospitalisation, clusters, systemic/central nervous system reactions) through the States/Regional level as soon as the information is received or as soon as possible. All investigations started within 24 hours of notification.

Dengue vaccine is not a priority for Myanmar because a vaccine is not yet commercially available and because the CFR is < 0.4%. Vaccine price is also an important consideration because of reliance on GAVI support.

However, there is a high demand for a dengue vaccine in the private sector because dengue is an important cause of hospitalization in children and a considerable source of anxiety for mothers.

There is limited serotype distribution data in the country and mild disease is highly underreported. Even clinical cases are practically not reported from the private sector, in spite of a requirement for reporting.

A descriptive prospective epidemiological study of laboratory confirmed cases of dengue in 2009 – 2010 from the top 5 regional hospitals reporting the highest numbers of cases showed that of 2103 suspected cases in 0 – 18 years, 81.6% were laboratory confirmed (range 75 – 90%). Serotype distribution was DENV-3, 33%; DENV-2, 32%; DENV-1, 31%; and, DENV-4, 9%. But DENV-4 is increasing in distribution.

However, dengue is one of the most feared diseases among physicians and parents, in spite of low mortality, creating a high public demand for testing. Cases may thus be over-reported. In one study, 17% of NS1 were positive out of more than 1,000 samples. In another study, 4% were positive in over 10,000 tests.

The most affected age group is 3 – 15 year-olds accounting for 85% of cases. A study from the 1990s found that sero-positivity was 47% by 10 years of age without any history of hospitalization for dengue.

The Philippines will introduce a vaccine in the EPI when a vaccine is available. Since the most affected age group is between 3 and 15 years, the country considers targeting vaccination at age five and above.
The economic burden of dengue in Singapore is very high, estimated at between USD$ 0.85 – 1.15 billion in direct medical costs, indirect costs such as loss of productivity, and in vector control (1,000 persons doing site inspections) in the last 10 years.

DHF surveillance has been established since the 1960s, with occasional outbreaks in the 1970s and 1980s. In the 1990s, surveillance began using immunoglobulin M (IgM) to confirm cases and in 2000s polymerase chain reaction (PCR) confirmation was introduced. Rapid tests are now available but the enhanced surveillance could have contributed to the increase in incidence rate in the last 2 decades.

The highest incidence rate is in 15 – 34 year-olds but this may be in part linked to health seeking behavior and host response to the infection. Overall sero-prevalence is relatively low in the 16 – 20 years age group at around 15% in 2013. Serotype-specific antibody prevalence in young adults (aged 16-30yrs), as measured by plaque reduction neutralization test (PRNT), were 13.4% for DENV-1, 16.3% for DENV-2, 6.7% for DENV-3, and 3.6% for DENV-4.

A long term decline in dengue sero-prevalence among older adults has been observed whereas low sero-prevalence among youths appears to be sustained.

Dengue incidence is associated with housing type. 85% of cases are from public housing but the incidence rate is higher in compound houses (which are fewer in number, 85% of the population lives in high-rise buildings). Cases correlate with weather and population density, age of buildings (higher in older buildings), and the extent of urbanization.

Vector sentinel surveillance is conducted in 34 sites with about 3,000 Gravitraps, primarily set along corridors of public housing.

Despite a low premise index, outbreaks occur (see Figure 12). Eighty percent of Ae aegypti breeding habitats are found in premises. The estimated dengue infection risk in residents by individual age from 2010 to 2013 was 5.6%.

Outbreaks have been associated with switches in predominant serotypes (see Figure 13).

Spatio-temporal dengue risk models have been used to project incidence and risk stratification in Singapore. In 2013, 86% of
large clusters were in fact located in high-risk areas.

A cross-border virus surveillance programme (UNITEDengue) with Malaysia, has shown that different viruses had driven the 2013 concurrent outbreaks in the two countries.

In the future, an integrated approach to dengue control will be adopted, integrating vaccination with vector control and surveillance of cases, virus, and vector. UNITEDengue will be expanded to monitor viruses in the region.

Vaccination could be introduced in either private or public sectors but age targets will depend on VE results.

Possible target groups for vaccination are 10 – 11 year-olds (which equates with P5 school year) at school, or in health services. Males 19 – 20 years of age could also be targeted during national military service. Females 20 – 29 years of age could be targeted at polyclinics.

The first reports of DHF in Sri Lanka date to the 1960s, but endemicity was not established until 1989.

An epidemic of 1298 clinically diagnosed DHF hospitalized cases and 54 deaths (CFR 4.2%) occurred in 1996. Since 2000, about 5,000 cases of dengue fever/DHF are reported each year with an exponential increase after 2009. However, the CFR has declined over time (see Figure 14). All four serotypes are present.

Originally dengue was predominantly an urban disease, but now the disease is spreading to semi-urban and rural areas.

Now, about 400 cases per week are reported in non-peaks and about 1,400 cases per week in peak season. Estimates indicate that about 30 infections occur in children <12 years for each reported case.

In 2013, the national incidence rate was 160 per 100,000 and 15 districts had over 100 cases per 100,000.
The most affected age group has shifted in the last 10 years from 10 – 15 years to 20 – 25 years.

In Colombo, in 2009, the sero-prevalence at 5 – 6 years was 50%, indicating a high intensity of transmission.

In children in 2009, incidence of DENV infection was found to be 8.39 (95% CI 6.56-10.53) per 100 children per year; Incidence of DENV illness was 3.38 (95% CI 2.24-4.88) per 100 children per year, for a ratio of clinically unapparent to apparent infections of 1.48.

DHF is an increasingly important problem with a mean age of 13.6 years, but case management has improved with use of ultrasound for early detection of vascular leaking in DHF. However, health system costs are important at 3.5 million US$, or $5 per individual for management and prevention.

In Sri Lanka, the National Advisory Committee on Communicable Diseases (NACCD) recommends the introduction of new vaccines. The chief epidemiologist provides the NACCD with key evidence for policy formulation. Among the required data are disease surveillance and cost effectiveness data.

The key points for decision-making on new vaccine introduction are: consistency with national policy of universal free health care for all; WHO prequalification; feasibility of incorporation into the National Program on Immunization (NPI); and economic analyses. In this respect a main obstacle for vaccine introduction is vaccine price.

There are ample opportunities to introduce a dengue vaccine in the EPI because immunization in Sri Lanka extends from 1 year to 13 years of age. The most convenient age for vaccination of a dengue vaccine would be 12 – 14 months or 18-20 months with a 3 dose schedule.

However, it would be premature to introduce a new dengue vaccine into the NPI directly. Instead a targeted introduction, in a phased manner, with intense follow up would be more appropriate.

Challenges that are anticipated include facilitating additional Phase III trials after a first vaccine has been introduced; and, continuing clinical management and vector control after vaccine introduction.

In this respect, it would be useful to have a review paper for the region from DVI on these and other related issues.
Like in other countries of the region, the incidence rate of dengue has increased since 1958, but in 2014 there was a low number of cases (see Figure 15).

The incidence in 2010 was 184.1 cases per 100,000 (or a total of 116,947 cases). All four serotypes are present.

Traditionally, dengue was a disease of young children but age-specific incidence has shifted to a peak of 15–24 years by 2013.

The highest death rate is among those over 65 years, followed by the 10-14 year-olds. CFR in 2011 was 126.25 deaths per 100,000 (over 8 months).

The economic impact of dengue in Thailand has been estimated at US$ 158 million per year or US$ 3.55 per capita per year. Cost of hospitalization for a dengue case has been estimated at US$ 573, and only 24% of cases are serologically confirmed.

Passive surveillance is used to detect cases whereas active sentinel surveillance is used for serotyping and for vector surveillance (but this is of low quality). Diagnosis is based on clinical and laboratory analysis by medical doctors using WHO 1997 criteria. Virological surveillance is performed by Thailand’s Department of Medical Science who appoint a number of hospitals from around the country to act as sentinel sites in order to monitor different serotypes. The disease is reportable in 24 hours.

Routine vector surveillance is conducted weekly at the local level, and biannually at the central level. Some areas conduct larval surveys.

There are currently 10 antigens in the EPI schedule, but several more are under consideration and others are delivered in the private sector.

The decision-making criteria used in Thailand for a new vaccine introduction are: burden of disease; priority of intervention; cost-effectiveness; programmatic feasibility; and demonstration project.

Furthermore, national advisory bodies recommend a new vaccine introduction to the National Health Security Office (NHSO). The NHSO main criteria for a decision are cost-benefit, cost-effectiveness and budget burden. The NHSO recommends to the budget bureau, which then must obtain the approval of the government for funding.

Health technology assessments suggest that a dengue vaccine could be quite cost-effective in Thailand.
In Thailand, dengue vaccine is likely to be introduced first in the private sector with a lag time of 8-10 years before it is introduced in EPI.

Dengue vaccination likely to be started in very young age group (1.5 – 2 years, largely because of the public pressure to offer vaccination to children as a priority) and then expanded with catch up.

Vector control will be integrated with vaccination but the potential impact has not been assessed.

**Dengue first occurred in Vietnam** in 1958. Now an average annual 70,000 cases occur with approximately 100 deaths. More than 50% of cases and deaths occur in children under 15 years of age. Severe outbreaks occurred in 1983, 1987, 1991, 1998 and 2010 (see Figure 16).

The dengue season starts in May and peaks in September with higher incidence in the south of the country with regional variability in the age-specific prevalence, with some regions having a predominance of cases in under 15 year-olds and others in older age groups.

Case Fatality Rate (CFR) is very low: less than 0.1% in 2013. All four serotypes of dengue are present. The vector is *Ae aegypti* 94% of the time.

The national program for dengue surveillance and control employs two general strategies: community participation together with active prevention and long-term strategies for education, community-based vector control, and environmental improvement. Near term strategies are to pilot a model, a collaborator network, and emergency response.

The community-based vector control program relies on four strategies: vertical and horizontal approaches to vector control; prioritize vector control according to container density; use mesocyclops as a biological control agent of larvae; and vector control at household level.

Vietnam’s future plan are to scale up the model; research possibility of Wolbachia as a biological control agent for dengue vector control in urban areas; dengue vaccination for a target population; conduct further research on the integration of vector and vaccine control.

**FIGURE 16**. Number of Cases and Deaths from DHF in Vietnam, 1980 – 2013

![](image)
CONCLUSIONS OF DENGUE PREVENTION BOARD

A milestone in dengue vaccine development was reached in 2014 with the successful completion of the first Phase III clinical trials. These demonstrated both safety and overall efficacy, especially against the most severe outcomes of dengue infection, in both Asia and the Americas. Other vaccine development is also progressing.

A review of the implications of these and other developments, such as in mathematical modeling, and a review of the dengue epidemiology in Asia-Pacific countries, allowed for a comprehensive discussion on the necessary steps to successfully introduce a first dengue vaccine.

The main outcomes from the discussions are summarized below.

PART I: Dengue Vaccine Candidates in the Pipeline

- Informative updates from the manufacturers:
  - Sanofi Pasteur has completed two Phase III efficacy studies
  - Takeda plans to start a Phase III efficacy study in 2015
  - Takeda and NIH are currently involved in Phase II safety and immunogenicity studies
  - GSK is planning Phase I study/II studies (formulation selection and age de-escalation)

- Important insights have been gained from the completed Phase III studies which may contribute to future dengue vaccine study design and implementation.

- The Board encourages countries to find competition-encouraging solutions to the clinical development of other dengue vaccine candidates even in the context of the availability of a licensed vaccine.

- The Board is encouraged by the ongoing development of the vaccine candidates by these manufacturers.

- The Board was grateful to DVI for facilitating the interaction with the manufacturers as this enabled subsequent discussions between members.

PART II: Modeling

- This technical presentation highlighted the complexities around mathematical modeling of dengue and the potential impacts of vaccination in conjunction with vector-control strategies.

- The interaction with the two experts in the field was appreciated by the Board members and emphasizes the importance of ongoing interaction between dengue experts and modelers.

- The Board recommends that a simple and practical model that can be customized to the needs of decision makers throughout the region be developed and made available.

- The Board also recommends that a more detailed model be made available to potential early adopters of dengue vaccine or countries with sufficient data.
PART III: Points for Consideration

- The DVI Points for Consideration document was reviewed and recognized to be very comprehensive, but demanding and perhaps beyond the scope of some of the member countries. The Board recommends that DVI considers revising and updating this document recognizing the capacity of member countries.

PART IV: Country Presentations

- Informative updates from Board members of the ten respective countries.

- These updates not only highlighted the similarities, but also the differences between countries in the region. The various settings would require different dengue vaccine policies and implementation strategies.

PART V: Working Groups

- The continuing extreme burden of dengue disease is of great concern throughout the region and it requires the urgent development and implementation of new and innovative strategies.

- The Board appreciated the opportunity provided by DVI for these presentations to be delivered and discussed during the meeting, considering the timing of the recent publications of the Phase III studies. There was a fruitful exchange of knowledge and views between the meeting participants.

ACKNOWLEDGEMENTS

The Board appreciates the continuing leadership of DVI and support from BMGF and acknowledges all who contributed to this meeting.
NEXT STEPS

The meeting was considered highly productive for preparing the next steps in dengue vaccine introduction. A number of key DVI activities in the coming months will support countries efforts to successfully plan and introduce dengue vaccines.

These include ongoing DVI efforts to convene NRAs for operationalizing the review of a dengue vaccine license application, providing further guidance to countries by making the agreed revisions to the ‘Points for Consideration,’ facilitating the dialogue between countries and modelers, and supporting countries to further elucidate the burden of dengue in the region and devise appropriate vaccine introduction strategies.

Meeting delegates acknowledged and greatly appreciated the leadership of Dr. Georges Thiry at advancing country preparedness for a dengue vaccine introduction in the region, and looked forward to continuing to make progress with his successor at DVI.
### APPENDIX 1

**SPEAKERS**

### Day 1  Friday, November 21, 2014

<table>
<thead>
<tr>
<th>Time</th>
<th>Session</th>
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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)</td>
</tr>
<tr>
<td>9:00 – 9:15 am</td>
<td>OPENING SESSION &lt;br&gt; Opening remarks and introduction &lt;br&gt; Dr. Georges Thiry &lt;br&gt; Acting Chair of the AP DPB</td>
</tr>
<tr>
<td>9:15 – 10:45 am</td>
<td>SESSION I: THE DENGUE VACCINE CANDIDATES IN THE PIPELINE &lt;br&gt; Update and perspectives of vaccines currently in clinical development (20 min per presentation + 10 min for discussion) &lt;br&gt; Presenters: &lt;br&gt; 1. Dr. Kwasi Amfo &lt;br&gt; 2. Dr. Anna Durbin (by teleconference) &lt;br&gt; 3. Dr. Alexander Schmidt</td>
</tr>
<tr>
<td>10:45 – 11:00 am</td>
<td>COFFEE BREAK @ IVI Lobby</td>
</tr>
<tr>
<td>11:00 – 12:15 am</td>
<td>SESSION II: UPDATE ON CYD-TDV &lt;br&gt; Presentation of Phase III data by Sanofi Pasteur &lt;br&gt; Dr. Alain Bouckenooghe</td>
</tr>
<tr>
<td>12:15 – 13:00 pm</td>
<td>Q&amp;A and discussion &lt;br&gt; Facilitator DVI, Dr. Georges Thiry</td>
</tr>
<tr>
<td>1:00 – 2:00 pm</td>
<td>LUNCH @ IVI Lobby</td>
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<tr>
<td>2:00 – 2:45 pm</td>
<td>Modeling: Presentation of (a) the various modeling approaches and (b) impact of vaccination using one model &lt;br&gt; Dr. Tom Hladish &lt;br&gt; Dr. Jon Sugimoto</td>
</tr>
<tr>
<td>2:45 – 3:45 pm</td>
<td>Q&amp;A and discussion &lt;br&gt; Facilitator DVI, Dr. Dagna Constenla</td>
</tr>
<tr>
<td>3:45 – 4:15 pm</td>
<td>COFFEE BREAK @ IVI Lobby</td>
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<tr>
<td>4:15 – 6:00 pm</td>
<td>SESSION III: POINTS FOR CONSIDERATION &lt;br&gt; Points to Consider: Implications of the recent data in light of the identified points for consideration for dengue vaccine introduction &lt;br&gt; Facilitator DVI, Ms. Jacqueline Lim</td>
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<tr>
<td>6:30 pm</td>
<td>DINNER hosted by DVI</td>
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<tr>
<td>Time</td>
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<td>9:00 – 12:00 pm</td>
<td><strong>SESSION I: PRESENTATION BY COUNTRIES</strong>&lt;br&gt;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&amp;A)&lt;br&gt;1. Australia&lt;br&gt;2. Cambodia&lt;br&gt;3. Indonesia&lt;br&gt;4. Malaysia&lt;br&gt;5. Myanmar&lt;br&gt;6. Philippines&lt;br&gt;7. Singapore&lt;br&gt;8. Sri Lanka&lt;br&gt;9. Thailand&lt;br&gt;10. Vietnam&lt;br&gt;Chair: DVI&lt;br&gt;Presenters: DPB member from each country</td>
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<tr>
<td>10:20 – 10:40 am</td>
<td><strong>COFFEE BREAK @ IVI Lobby</strong></td>
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<td>12:00 – 1:00 pm</td>
<td><strong>LUNCH @ IVI Lobby</strong></td>
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<td>1:00 – 2:00 pm</td>
<td><strong>SESSION II: WORKING GROUPS</strong>&lt;br&gt;<strong>WORKING GROUPS SESSION</strong>&lt;br&gt;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?”&lt;br&gt;Facilitators for DVI:&lt;br&gt;Ms. Ana Carvalho&lt;br&gt;Ms. Rebecca Van Roy&lt;br&gt;Ms. Jacqueline Lim&lt;br&gt;Dr. Dagna Constenla</td>
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<tr>
<td>2:00 – 3:20 pm</td>
<td>Presentations by the groups (15 min per presentation + 5 min Q&amp;A)&lt;br&gt;Rapporteur for each group</td>
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<tr>
<td>3:20 – 4:00 pm</td>
<td><strong>COFFEE BREAK @ IVI Lobby</strong></td>
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<td>3:20 – 4:00 pm</td>
<td><strong>CLOSING SESSION: WORKING GROUPS</strong>&lt;br&gt;Closed meeting among DPB members to prepare conclusions</td>
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<tr>
<td>4:00 – 4:40 pm</td>
<td>Report by the Dengue Prevention Board&lt;br&gt;Rapporteur for DPB</td>
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<td>4:40 pm</td>
<td><strong>CONCLUSION – CLOSING REMARKS AND ADJOURN</strong>&lt;br&gt;Acting Chair of the AP DPB&lt;br&gt;Dr. Georges Thiry</td>
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<tr>
<td>5:00 pm</td>
<td><strong>DINNER hosted by DVI</strong></td>
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APPENDIX 2
LIST OF MEETING PARTICIPANTS

Board Members

Dr. Chong Chee Keong
Director
Disease Control Division
Ministry of Health
Malaysia

Dr. Enrique Tayag (Unable to attend)
Director IV
National Epidemiology Center
Department of Health
Philippines

Dr. Hasitha Tissera
Consultant Epidemiologist
Head National Dengue Control Unit
Ministry of Health
Sri Lanka

Dr. Hlaing Myat Thu
Director (Research)
Department of Medical Research
Lower Myanmar
Myanmar

Dr. Jacob T. John (Unable to attend)
Advisor
Christian Medical College Hospital
Kamalakshipuram, Vellore
India

Dr. Jeffrey Hanna
Associate Professor
Discipline of Public Health & Tropical Medicine
School of Public Health
Tropical Medicine & Rehabilitation Sciences
James Cook University
Australia

Dr. Lee Ching Ng
Director
Environmental Public Health Division
Singapore

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

Dr. Rahma Mulya Karyanti
Head Division of Infection and Tropical Pediatrics,
Department of Child Health
Faculty of Medicine, University of Indonesia
Jakarta, Indonesia

Dr. Rekol Huy
Director of CNM (National Center for Parasitology, Entomology and Malaria Control)
Ministry of Health

Dr. Vu Sinh Nam
Deputy Director
General Administration of Preventive Medicine
Ministry of Health
Vietnam

DVI Collaborators

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

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

Dr. Dagna Constenla
Director, Economics & Finance
International Vaccine Access Center
John Hopkins Bloomberg School of Public Health
USA
Dr. Georges Thiry  
Acting Director,  
Dengue Vaccine Initiative (DVI)  
International Vaccine Institute  
Seoul  
Korea

Ms. Jacqueline Lim  
Acting Program Leader  
Dengue Vaccine Initiative (DVI)  
International Vaccine Institute  
Seoul  
Korea

Dr. Jon Sugimoto  
Staff Scientist  
Vaccine and Infectious Disease Division (VIDD)  
Fred Hutchinson Cancer Research Center  
USA

Mr. Jung Seok Lee  
Associate Research Scientist  
International Vaccine Institute  
Seoul, Korea

Ms. Rebecca Van Roy  
Communications Officer  
Sabin Vaccine Institute  
Seoul, Korea

Dr. Shawn Gilchrist  
Writer/Reporter  
S Gilchrist Consulting Services Inc

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

Dr. Tom Hladish  
Post-Doctoral Fellow  
University of Florida

Dr. Vittal Mogasale  
Head of Policy and Economic Department  
International Vaccine Institute  
Seoul  
Korea

Invited Guests

Dr. Phan Trong Lan  
Director of Pasteur Institute of Ho Chi Minh City

Dr. Rithea Leang  
Chief of Research Unit  
Assistant Manager  
National Dengue Control Program  
National Center for Parasitology and Malaria Control

Mr. Yuske Kita  
Senior Public Health Officer (Policy & Control)  
Communicable Diseases Division  
Ministry of Health Singapore

Vaccine Industry

GlaxoSmithKline

Dr. Alexander Schmidt  
Director Clin Res & Translational Science Team  
GlaxoSmithKline Vaccines

Sanofi Pasteur

Dr. Alain Bouckenooghe  
Regional Head  
Clinical R&D and Medical Affairs, Vaccines, Asia – Pacific  
Sanofi Pasteur

Dr. Jean-Antoine Zinsou  
Senior Director  
Vaccination Policy and Advocacy  
Sanofi Pasteur

Dr. Tippi Mak  
Regional Director  
Dengue Vaccine Public Policy, Vaccines, Asia-Pacific  
Sanofi Pasteur

Takeda

Dr. Jeremy Brett  
Senior Director Dengue Global Medical Affairs  
Takeda  
Singapore

Dr. Kwasi Amfo  
Global Head, Dengue and EV71 Programs  
Takeda  
Singapore