ANNEX I

1ST ASIAN DENGUE SUMMIT (ADS): ARE WE READY FOR THE NEW VACCINE ERA?

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Abstract. This is a summary of the Proceedings of the 1st Asia Dengue Summit on evaluating the preparedness of countries for dengue vaccine introduction in the Asia - Pacific region.

INTRODUCTION

Dengue is the most common vector-borne viral infection. The global burden is increasing rapidly, driven by population growth, urbanization, globalization, and ecological changes. Dengue vaccination is needed as part of an integrated approach to dengue prevention and control that also includes vector management and improved surveillance.

A milestone in dengue control was reached with the introduction of the first dengue vaccine in Asia (Philippines) and South and Central America (Mexico, Brazil and El Salvador) in 2015-2016. The vaccine has been shown to be safe and moderately effective, particularly at reducing severe disease and hospitalization (Capeding *et al,* 2014; Villar *et al*, 2015).

The first Asia Dengue Summit (ADS) was held on 13-14 January 2015 at the Shangri-La Hotel, Bangkok, Thailand, in conjunction with the Asia Dengue Vaccination Advocacy, the Dengue Vaccine Initiative, the Southeast Asian Ministers of Education Organization Tropical Medicine and Public Health Network, and Fondation Mérieux. The goal was to explore the preparedness for dengue vaccine introduction in the Asia-Pacific region. This article summarizes the *Proceedings of the 1st ADS* on the preparedness for dengue vaccine introduction of countries in the Asia-Pacific region.

WHO PERSPECTIVE AND GUIDANCE ON DENGUE

The World Health Organization's (WHO's) Global Strategy for Dengue Prevention and Control (2012-2020) aims to reduce the burden of dengue by reducing dengue mortality by ≥50% and morbidity by ≥25% by 2020 (WHO, 2012). The Global Strategy is based on five technical elements of:

- Diagnosis and case management,
- Integrated surveillance and outbreak preparedness,
- Sustainable vector control (*Aedes aegypti* and *Aedes albopictus*),
- Future vaccine implementation, and
- Basic operational and implementation research.

Five enabling factors support the technical elements:

- Advocacy and resource mobilization,

- Partnership, coordination and collaboration,
- Communication to achieve behavioral outcomes,
- Capacity building, and
- Monitoring and evaluation.

Burden estimation, case management and surveillance

The burden estimation program involves greater access to dengue data in selected countries (Brazil, Mexico, Sri Lanka, Maldives, and Cambodia) and integration of the data into the national health information system. Burden estimation includes real-time case tracking and estimation of the economic burden of dengue during outbreaks or epidemics. To estimate the true burden of dengue disease, factors of severity (including infection, fever, disease warranting medical attention, and death), cost, age, and laboratory diagnosis need to be incorporated. The gold standard for measuring dengue incidence is active detection through serology, but hospital-based case detection is more usually done.

Diagnostic tests include immunoglobulin (Ig) M-based, dengue virus non-structural 1 (NS1) antigen-based, and combination IgM/NS1-based tests, and molecular diagnostics. Laboratory networks have been established in some regions, and the intention is to form a global network. Challenges include the varied performance of rapid diagnostic tests across populations, the need for resources for diagnostic kits, and strengthening of dengue laboratory networks.

The 2009 WHO dengue classification has been refined and treatment algorithms have been developed aimed at reducing mortality and assisting with triage. Importantly, mortality has decreased in many countries, primarily due to better hospital case management.

Integrated surveillance is important for risk assessment and situation awareness, and can support outbreak preparedness and appropriate communication. As resources are often limited, national level surveillance techniques remain a priority while ensuring sustained surveillance and early identification of disease for local response.

Early outbreak detection and prediction enables prompt intervention to moderate the impact of the outbreak. Research into outbreak response and prediction variables (rainfall, relative humidity, and temperature), and identification of key parameters for each epidemiological setting is ongoing to predict outbreaks, improve data quality, and evaluate the effectiveness of outbreak responses.

One of the key elements of the Global Strategy is 'sustainability', as tools and strategies for dengue are needed in the long term. Multiple tools for sustainable vector management are available, and tools in development include genetically modified lethal insects, Wolbachia-based *Aedes aegypti*, toxic sugar baits, and a matrix for long-term larval control (Achee *et al,* 2015).

Introduction of vaccines and combined interventions

Results of the first successful phase 3 trials of a dengue vaccine have been published (Capeding *et al,* 2016; Villar *et al*, 2016), and several other vaccine candidates are in development. Challenges to vaccine implementation include selection of the target population, the administration schedule, acceptability, affordability, and long-term effectiveness.

Dengue is no longer solely an urban disease, partly due to the role of human movement in its transmission (Stoddard *et al,* 2009). Therefore, identification of hot spots is needed for a prompt response to suppress outbreaks, and integrated surveillance is key to intervention and prevention. The impact of environmental changes needs further study, but temperature increases favor vector and virus multiplication, and climate plays a role in transmission (Colón-González *et al,* 2013). Lack of piped water may aggravate dengue incidence if domestic water storage is increased. However, vector control is sustainable with good community participation (Andersson *et al,* 2015).

Globally, the burden of malaria is declining, with many countries on the verge of disease elimination, while that of dengue continues to increase. Dengue is endemic in 128 countries and 3.9 billion people

are at risk. *Aedes albopictus* has expanded its presence into several European countries. Thus, dengue is a disease of the future, with uncertain distribution and burden.

THE DENGUE VACCINE LANDSCAPE

There have been several different approaches to developing a dengue vaccine, all of which involve the envelope (E) structural protein — the key part of the virus responsible for the antigenic distinction between serotypes. Challenges to the development of a dengue vaccine include the four antigenic serotypes that interact with each other, often in unpredictable ways, resulting in protection, cross-protection, enhancement, and interference. Technical challenges involve imprecise biological assays to measure immune response, lack of a laboratory measurement for protection, and lack of valid animal models for preclinical research. However, there is a robust vaccine pipeline, with several vaccines in preclinical development (Table 1) (Vannice *et al,* 2015).

Licensed dengue vaccine

CYD-TDV (Dengvaxia®, Sanofi Pasteur, Lyon, France) has completed phase 2b and 3 trials (Sabchareon *et al,* 2012; Hadinegoro *et al,* 2015; Capeding *et al,* 2016; Villar *et al,* 2016), and is the first dengue vaccine to be licensed. CYD-TDV is serotype-specific, with good efficacy against DENV-3 and 4, moderate efficacy against DENV-1, and poor efficacy against DENV-2. CYD-TDV has greatest efficacy against severe dengue and in older children and dengue-primed individuals. However, there was increased risk in very young children during the third year after vaccination in the Asian trial (Capeding *et al,* 2016). Given the efficacy and safety profiles, Sanofi Pasteur applied for licensure in dengue endemic countries in Asia and Latin America. In 2015-2016, CYD-TDV was licensed in Philippines, Brazil, Mexico, and El Salvador for use in 9-45-year-old individuals in endemic areas.

Vaccines in development

Two vaccine candidates at advanced stages of clinical development are TAK-003 (Takeda, Osaka, Japan) and TV003/TV005 [National Institutes of Health (NIH), Bethesda, MD, USA]. CYD-TDV, TAK-003, and TV003/TV005 are all live-attenuated vaccines and all have one or more chimeric serotype component. CYD-TDV has a yellow fever backbone and all four serotype components are chimeric (prM and E structural proteins); TAK-003 has one component that is attenuated but not chimeric (DENV-2) and three chimeric components (prM and E structural proteins); and TV003/TV005 has three attenuated components and one chimeric component (DENV-4 backbone with DENV-2 prM and E structural proteins).

There are also several vaccines at earlier development stages. GlaxoSmithKline (Brentford, UK), Fiocruz (Rio de Janeiro, Brazil), and the US Army (Walter Reed Army Institute of Research, Silver Spring, MD, USA) have collaborated on a tetravalent purified formalin-inactivated whole virus vaccine (DPIV); the US Army has developed a tetravalent dengue virus purified inactivated vaccine (TDENV-PIV) and GlaxoSmithKline has manufactured an inactivated whole virus vaccine (PIV). The V180 vaccine (Merck & Co, Kenilworth, NJ, USA) is a tetravalent recombinant protein subunit vaccine based on a truncated E structural protein (DENV-80E) that is expressed in the Drosophila S2 expression system. The TVDV vaccine (Naval Medical Research Center, Silver Spring, MD, USA) is a tetravalent DNA plasmid vaccine with genes encoding prM and E structural proteins.

IS DENGUE CONTROL POSSIBLE?

Efforts to prevent the spread of dengue virus and control dengue disease have been unsuccessful despite the many methods of mosquito control, including space spraying, perifocal control, targeted source reduction, integrated vector management, community participation, bio-control, and genetic control. However, there are some promising new approaches.

Table 1. Vaccines in active human clinical trials.

Category	Sponsor	Vaccine designation	Approach	Phase
Live attenuated	Sanofi Pasteur	CYD-TDV	YF 17D backbone and YF-DENV chimera	Phase 3 results published: safe and moderately effective Licensed in Mexico, Philippines, Brazil, and El Salvador
	Takeda	TAK-003	DENV-2 PDK-53 backbone and DENV-DENV chimera	Phase 3
	US NIH licensed to: Butantan VaBiotech Panacea Serum Institute of India Merck	TV003/ TV005	Direct mutagenesis and DENV-2/4 chimera	Phase 2 and phase 3
Protein subunit	Merck	V180	DENV 80% E protein recombinant with adjuvant	Phase 1
Inactivated whole virus	GlaxoSmithKline/ Fiocruz/US Army	DPIV	Formalin inactivated with adjuvant	Preclinical to Phase 1
DNA	US Navy	TVDV	Plasmid DNA with adjuvant	Phase 1
Heterologous prime-boost	US Army	TDENV-LAV + TDENV-PIV	Live attenuated/inactivated whole	Phase 1

DENV, dengue virus; E protein, envelope protein; NIH, National Institutes of Health; YF, yellow fever.

Vector control

New mosquito control tools include novel insecticides, genetic control methods, biological controls, spatial repellents, lethal ovitraps, and insecticide-treated materials. Residual insecticides of new non-resistant compounds could be effective replacements for dichlorodiphenyltrichloroethane that are suitable for indoor spraying and for treating oviposition sites and cryptic larval habitats. Lethal ovitraps have a place in an integrated prevention and control program, but may have a limited impact on the mosquito population. Vapor-active spatial repellents are designed to emit a chemical to prevent mosquitoes from entering an enclosed area. Insecticide-treated materials (curtains, screens) prevent human-mosquito contact, thus reducing dengue transmission (Manrique-Saide *et al,* 2015).

A new repressible dominant lethal gene has been developed for genetic control, by which all the male mosquitoes are born sterile, so cannot produce progeny. Although this method will rapidly reduce a mosquito population, it is self-limiting so needs repeated application. Trials have been promising (Harris *et al,* 2011; Carvalho *et al,* 2015).

Another positive development is a modified *Wolbachia pipientis* strain that infects *Aedes aegypti. W. pipientis* reduces transmission of the dengue virus by reducing the fecundity and survival of the mosquitoes. Several trials have been successful (Nguyen *et al,* 2015; Hoffmann *et al,* 2014).

It is unlikely that any of these methods used alone will control dengue. However, if successful at reducing the mosquito population, they will also control other mosquito-borne diseases.

Vaccination

The only licensed vaccine is CYD-TDV (licensed in Brazil, Mexico, and Philippines in 2015 and El Salvador in 2016). CYD-TDV has variable efficacy against the four DENV serotypes, with moderate overall efficacy of 56-61% (Capeding *et al,* 2016; Villar *et al,* 2015). There is increased efficacy in people who have had prior exposure to dengue infection. The vaccine has efficacy against severe disease, especially dengue hemorrhagic fever, and in reducing hospitalization. It has a good safety profile.

However, based on knowledge of dengue infection and immunity, a tetravalent vaccine may not be necessary. There is high seroprevalence in endemic countries as most people have had dengue disease at some point in their lives. Most cases of severe dengue disease occur during the first or second infections (Gibbons *et al,* 2007), and the third and fourth dengue infections tend to be mild or asymptomatic (Olkowski *et al,* 2013). Therefore, protection is most needed against the first two infections (bivalent protection).

The three lead live attenuated candidate vaccines may not provide balanced tetravalent protection, resulting in variable protection against the different serotypes. The public health rationale for use of moderately effective dengue vaccines in endemic countries is the priming effect of previous dengue infection on immunity. Most people in hyperendemic areas have already had at least one dengue infection, so vaccinees will be protected against two or more dengue serotypes and against severe disease. Other public health benefits include decreased dengue transmission, reduced magnitude and frequency of epidemics, and reduced risk of healthcare overload, resulting in better management of severe disease and decreased case fatality rate, severe disease and hospitalization, with the associated economic benefits. However, there is a lack of research on third and fourth infections and inadequate surveillance to distinguish infection sequence. Other reservations include the role of the virus strain and possible mutation, patient age as a surrogate for prior infection, temporal distribution of infections with different serotypes, and cellular immunity.

Long-term phase 4 studies might provide answers, but the vaccines could be introduced under controlled conditions and the safety and impact carefully monitored. Thus, step-wise introduction could be considered, with any safety issues being mitigated by an effective risk management program, active surveillance with high-quality laboratory support, and clinical management training. Notably, it is unlikely that vaccines alone will be effective in controlling dengue.

Integrating prevention and control

There are major challenges for dengue prevention and control in the form of expanding urbanization and increasing globalization, lack of resources to build capacity, and the need for political will for economic support and public health leadership. To support regional control of dengue, the Global Dengue and *Aedes*-transmitted diseases Consortium was formed to avoid duplication of efforts and resource use between groups. The goals are to:

- eliminate dengue as a public health problem
- promote development and implementation of innovative and synergistic approaches for prevention and control
- support the WHO global strategy for dengue control
- strengthen advocacy, capacity building, and networking
- work closely with vaccine early adopter countries
- promote integration and innovation.

Integration is a well-known concept, but synergy has been introduced to correspond with the new technologies in development. Vector control continues to be needed to reduce the mosquito population and vaccination will increase herd immunity; combining these technologies with clinical management, therapeutics, and community engagement forms a targeted control program (Fig 1). Targeted control programs use research to develop integrated vaccination and vector control, with the addition of tools suited to individual ecological environments. Importantly, none of the new tools are likely to be effective if used alone, and effective dengue prevention and control requires integration of vaccines with mosquito control and enhanced surveillance.

MODELING AS A PUBLIC HEALTH TOOL

Computer modeling is an underutilized research method with many useful applications. Models can test the empirically untestable with no ethical constraints, and questions can be answered that would not be possible in real-world research. Use of detailed modeling in the field of public health is a relatively new concept, although appropriate models can be constructed.

Models may be intuitive or quantitative and use input and output to answer a question. Quantitative models are more sophisticated, and are used to answer specific questions or those with more serious consequences. Statistical models are used to describe patterns, while mechanistic models predict and explain patterns. Mechanistic models are more complicated than statistical models, but are also more powerful.

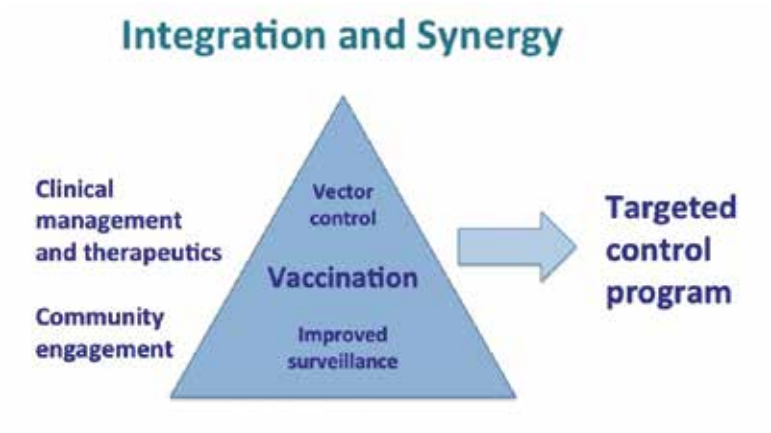

Fig 1–Global Dengue and *Aedes*-transmitted diseases Consortium paradigm using new tools to control dengue.

All quantitative models have a similar structure of inputs (parameters), interactions between variables, and outputs. Parameters could include information about the speed of an event or duration of an infectious period. The interaction between variables could include transmission of disease by mosquitoes, perhaps on a seasonal basis. Outputs are the information produced by the model that can be compared to the real world, such as projected epidemic size.

There are several different approaches to model the spread of disease. Compartmental models (in which people are represented as counts in susceptible, infectious, and recovered groups) are the simplest type, while network models represent explicit population structure. Agent-based models are the most realistic, but also the most complicated to construct and interpret (Table 2).

Independent comparative modeling

A good model is one that makes sense, fits well to the data, is applied in ways that stay close to the fitted data, and is predictive. However, when constructing dengue models, events are being predicted that may be decades in the future. The data needed to test such ambitious forecasts are often unavailable. Thus, independent, comparative modeling can be the best option. Comparative modeling involves independent modelers, using different methods and assumptions, but collaborating and comparing results. If the results between groups are similar they are likely to be predictive (Penny *et al,* 2016). On-going dengue modeling work includes comparative modeling of dengue vaccine impact, supported by the WHO.

Epidemiology modelers working in isolation from clinicians, virologists, entomologists, and public health officials may produce models that are academically interesting, but are poorly informed, unrealistic, and cannot produce reliable predictions. Therefore, modelers need to be kept informed of the important questions and provided with accurate data to produce reliable results. Equally, modelers must specify their data needs to provide accurate answers for public health decision-making. Thus, modelers and clinical and public health communities must work together.

GLOBAL DENGUE VACCINE CONSIDERATIONS AND RECOMMENDATIONS

The WHO has supported the process of dengue vaccine development, and provided guidance and scientific consensus. During the pre-registration period, the WHO engaged in activities to support global vaccine guidance and introduction by developing regulatory standards. More recently, a dedicated technical advisory group consulted on the pivotal clinical trial results on behalf of the WHO to better understand the complex data from the trials and to ascertain the data needs for public health/policy recommendations. Post-registration, the most important activity is to provide recommendations for vaccine introduction and use, as well as guidance for monitoring vaccine effectiveness and safety.

Guidance for new vaccine introduction and use

The WHO Vaccine Position Papers include global recommendations for use of a specific vaccine (or vaccine class) (WHO, 2016a). Development of a position paper starts before registration of a vaccine by

Table 2. Model types by complexity.

Compartmental models	Network models	Agent-based models
Long history Most mathematically tractable Everyone in a compartment is the same Deterministic/stochastic	Structured population Sometimes mathematically tractable Population structure is important and 'known' Deterministic/stochastic	Most detailed and flexible Arbitrarily realistic Hard to understand Computationally intensive Stochastic

national regulatory authorities and is issued after a vaccine is licensed. Position papers are endorsed by the Strategic Advisory Group of Experts (SAGE) on Immunization and published in The Weekly Epidemiological Record (WHO, 2016b). The information includes review of the evidence for key policy questions and review of the quality of evidence using the Grading of Recommendations Assessment, Development and Evaluation process. The position papers are updated regularly as new knowledge becomes available.

Much of the recommendation development is done by a dedicated SAGE working group, with input from other WHO advisory groups on specific issues. A background paper is produced and discussed by SAGE at an open meeting. The recommendations are reviewed by the WHO Director General, and tendered for broad stakeholder consultation before a position paper is developed. The process is rigorously evidence based, transparent, and inclusive. All the information that is critical for decision-making by SAGE is in the public domain or will be made public at the time of the SAGE meeting. The SAGE Working Group on Dengue Vaccines was established in March 2015.

Key considerations for policy

Key considerations for dengue vaccine policy include safety, efficacy, and programmatic aspects (Table 3). As the dengue vaccine is new, there may not be sufficient data to answer all the considerations, hence a need for mathematical modeling to inform and underpin policy recommendations. Comparative modeling of dengue vaccine public health impact will provide additional information for SAGE recommendations by assessing various vaccination scenarios and their impact on public health.

Comparative modeling of dengue vaccine impact has evaluated the following parameters: routine introduction at 9 years; catch-up vaccination at 10-17 years; Asian and Latin-American reference country scenarios and different transmission intensities; and vaccine impact on infection, clinical cases, severe cases, and death. The vaccine impact was modeled overall, by age group, and by 10- and 30-year time horizons. An exploratory economic evaluation was also done, although this will be more accurate if done by each country to suit their specific circumstances. The economic evaluation included traditional cost-effectiveness analysis (costs per clinical case and costs per disability-adjusted life year averted); delivery costs adapted from human papillomavirus vaccine delivery experience; and literature appraisal of the broader economic impact.

WHO global policy on dengue vaccine

In April 2016, recommendations on the use of the CYD-TDV vaccine were discussed by SAGE (WHO, 2016b). The first WHO Vaccine Position Paper on dengue vaccines was published in July 2016 (WHO, 2016a).

Table 3. Key considerations for dengue vaccine policy.

Parameter	Consideration
Vaccine safety	Reactogenicity and serious adverse events, adverse events of special interest Long-term safety and risk of hospitalization/severe dengue
Vaccine efficacy	Overall, by age, by serostatus, by serotype Efficacy against laboratory-confirmed dengue, severe disease Duration of protection
Programmatic aspects	Dose scheduling Co-administration Vaccine introduction strategies, including outbreak response Vaccine impact and cost-effectiveness Criteria for country decision-making

Development of vaccine policy is done at the global, regional, and national levels. The global recommendations from the WHO are intended to inform country decision makers and provide general orientation.

Considerations for vaccine introduction (Table 4) include disease factors (high morbidity with low mortality, outbreaks and burden on health system, school or work absenteeism, and alternative or additional preventive methods, *ie,* vector control) and vaccine factors (availability, price, programmatic costs, economic impact, national budget and vaccine affordability, and funding gaps and sustainability) (WHO, 2014a). The strength of the immunization program and the health system in the country are also considered. Important considerations include overall readiness for a new vaccine, school readiness, and implementation readiness (WHO, 2013), as well as tracking of vaccination status. Lessons can be learned from other vaccination programs in this age group such as human papillomavirus (HPV).

The use of both vector and vaccination strategies is essential, and communication, community mobilization, and advocacy remain important for both vector control and vaccination.

CURRENT SCHOOL-BASED VACCINATION PROGRAMS AND PLANS IN ASIA

School-based human papillomavirus vaccination program in Malaysia

Malaysia has low uptake of cervical cancer screening and delayed diagnosis and treatment, with most women seeking treatment at stage 2 or above. Thus, there is a need for cervical cancer prevention measures. When the WHO endorsed the HPV vaccine, Malaysia made it available to all girls aged 13 years (WHO, 2014b), with the aim of reducing the incidence of cervical cancer.

The vaccine was made available in the private sector in 2006, and implemented into the public healthcare system in 2010. The strategy was to deliver the vaccine as part of the Cervical Cancer Prevention and Control Program and integrate it into the Expanded Program of Immunization (EPI). The operational policy was for voluntary free school-based HPV vaccination delivery to Malaysian schoolgirls at age 12-13 years, with a target of three doses for 95% of the target population, which was exceeded at 98% completion. There was strong commitment and support from the Ministry of Education (MoE).

Factors contributing to the success of the HPV immunization program included:

- Political will and commitment,
- Public trust in the Malaysian EPI,
- Availability of school health services infrastructure,
- Existing strong relationship with the MoE,
- Effective risk communication strategy,
- Addressing religious issues, and
- Competitive procurement mechanism.

Integrating the HPV vaccine into the School Health Program made it part of the immunization package. The guiding principles of adding a new program into the school health service are:

- New service introduction must not affect existing services performance,
- Implementation must be approved by the MoE,
- Implementation must not interfere with the school schedule, and
- Participation must be voluntary, with parental approval.

There are several factors to consider before integrating a new vaccination program into school health activities (Table 4). Preparation and planning is key to the success of the program.

School-based immunization program in Philippines

There are many advantages of school-based immunization programs. Booster doses can be given to ensure high levels of protection, some vaccines are more effective if delivered at a specific age, and compliance is high. The current vaccinations delivered to Philippines schoolchildren are measles-rubella, tetanus-diphtheria, HPV and a deworming program.

Table 4. Factors to consider when integrating a new vaccination program into school health activities.

Factor	Requirements
School health infrastructure and resources	Initial budget to include implementation, *eg*, cold-chain, transportation Resource mobilization
New program objectives and expected impact	Long-term/short-term impact Coverage (>95% for HPV)
Capacity building	Training and introduction phase Updates (*eg,* policy changes)
Monitoring and evaluation	Track implementation and impact
Dealing with public expectation	Health promotion campaign budget Crisis management Demand for service
Parental acceptance	Confidence in new program Vaccine safety and efficacy Vaccine combination (*eg*, HPV and tetanus toxoid)
Will the new program effect students' performance	Which cohort to choose from (consideration of examinations, prophylaxis status of HPV vaccine)
Compliance to schedule/follow-up	Completion within one schooling period (timing of doses)

HPV, human papillomavirus.

Guidelines for the implementation of school-based immunization were introduced in 2015. The guidelines comprise both general and specific recommendations on the vaccine use, storage and transport, immunization safety, recording and reporting, and AEs following immunization. The Department of Health (DoH) provides the vaccines and immunization logistics for routine distribution, training, and pharmacovigilance reporting. The Department of Education facilitates the implementation in schools, informs participants, screens students, and submits reports to the local health units. Other governmental and local level departments organize the vaccination team and provide healthcare personnel. The Parents–Teachers Association plays a role in raising awareness.

There are several components to the dengue prevention and control program, including surveillance, integrated vector management, case management, social mobilization and communication, outbreak response, and research. The existing dengue case definition and case fatality rate is based on the recommendations of the WHO. Laboratory surveillance will enable monitoring of serotypes circulating in different areas. Mechanisms for sharing data are in place (UNITEDengue; https://www.unitedengue.org/index.html). Dengue surveillance is incorporated into an integrated disease surveillance system.

An evidence-based integrated vector management strategy has been implemented with community involvement. Vector resistance is monitored regularly. There is laboratory support for case management and a referral network system in both the public and private sectors. Communication for behavioral impact (COMBI) training has been implemented and the COMBI approach disseminated and promoted. There is a dengue outbreak standard operating system and national early warning/dengue surveillance system. Tools and strategies for dengue control and case management will be evaluated regularly.

Philippines is the first country in the Asia-Pacific region to register the dengue vaccine, on 22 December 2015. The vaccine will be delivered via the school-based immunization program to children aged 9 years, in accordance with the results of the phase 3 trials (Capeding *et al,* 2014; Villar *et al,* 2015).

Table 5. Expanded program of immunization in Thailand and Indonesia.

Age	Thailand	Indonesia
Birth	BCG, HB1	HB
1 month		BCG, OPV1
2 months	OPV1, DTP-HB1	DPT-HB-Hib 1, OPV1
3 months		DPT-HB-Hib 1, OPV2
4 months	OPV1, OPV2, DTP-HB2	DPT-HB-Hib 1, OPV3, IPV
6 months	OPV3, DTP-HB3	
9 months	MMR1	Measles
1 year	JE1-2	
18 months	OPV4, DTP4	Measles, DPT-HB-Hib
30 months	MMR2, JE3	
4 years	OPV5, DTP5	
7 years	BCG, dT, OPV, MR	
12 years	dT	
Pregnant women	dT	
Healthcare personnel and risk groups	Influenza	

BCG, Bacillus Calmette–Guérin; dT, diphtheria and tetanus; DTP, diphtheria, tetanus, and pertussis; HB, hepatitis B; Hib, *Haemophilus influenzae* type b; IPV, inactivated polio vaccine; JE, Japanese encephalitis; MMR, measles, mumps, and rubella; MR, measles and rubella; OPV, oral polio vaccine.

The vaccine will be implemented in three highly endemic regions with high-risk populations. Training of healthcare providers, active surveillance for AEs following immunization, and a recording and reporting system will be implemented. Good communication will be needed to explain why only certain regions have the vaccine. The DoH will provide all logistical items. Prevention strategies will continue in conjunction with the vaccine implementation initiative.

Operational research will include a post-authorization phase 4 study and collection of data on access to care, cost-effectiveness, and policy to support expansion of the vaccine to other parts of country.

School-based immunization program in Bangkok, Thailand

The Bangkok Metropolitan Administration healthcare providers run 68 public health centers, which are responsible for school-based vaccination, and eight hospitals. The Ministry of Public Health has 36 hospitals and 135 health units, and there are 95 hospitals and 466 clinics run by private healthcare providers. Thailand has a very full EPI (Table 5).

There are several optional vaccines recommended by the Infectious Disease Society of Thailand, including whooping cough (pertussis), *Haemophilus influenzae* type b, and HPV. School-based vaccination is well accepted with high coverage. Strengthening of capacity building is an important step for a successful school-based vaccination program.

School-based immunization program in Indonesia

The Indonesian constitution states that health is the right of all Indonesian people. Routine immunization services are available for infants, children younger than 5 years, schoolchildren, and women of childbearing age. Additional immunization is done for catch-up programs and campaigns, national immunization days, and outbreak response. Optional immunization includes those vaccines not provided by the government.

The policy and operational strategy is to achieve:

- high immunization coverage, that is equally distributed via a static and accessible EPI service and services in hard-to-reach areas,
- continuous quality improvement through skilled personnel, quality vaccine and cold chain system, and correct vaccination procedure,
- community mobilization and participation.

The target for the EPI is shown in Table 5.

The Usaha Kesehatan Sekolah (SHP) runs health education, health service delivery through schools, and the Bulan Imunisasi Anak Sekolah (School Immunization Month Program; BIAS). The objective of the school immunization program is to provide long-term protection against EPI target diseases of measles, diphtheria, and tetanus. The BIAS is a well-designed program, with operational guidelines for health workers and teachers, roles and responsibilities of each Ministry, health center budgets, and vaccine and supplies provided by central government. There is high coverage in all schools where the program is conducted. There are cost and financing issues, with limited resources for operational costs, monitoring and evaluation, and advocacy to local government. However, coverage is >90%.

The role of the Ministry of Health is development of policy and guidelines for technical matters, preparation and implementation of immunization services at schools, and monitoring and evaluation. The role of the MoE is mobilization of teachers in public and private schools to support the program, and coordination with schools and parents. The role of the Ministry of Religion is socialization and mobilization of teachers in faith-based public and private schools. The role of the Ministry of Home Affairs is advocacy to local governments for logistics and supplies and operational costs for program implementation.

The challenges include how to institutionalize the BIAS, improve parents' awareness, and integrate new vaccines such as dengue into the program. However, global disease elimination and eradication is a public health strategy.

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