Preparing for dengue vaccine introduction in ASEAN countries: recommendations from the first ADVA regional workshop

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The independent, scientific and educational The Association of South East Asian Nations (ASEAN) Member States Dengue Vaccination Advocacy Steering Committee (ADVASC) was established in 2011 to address the practical challenges faced by ASEAN countries as they prepare for the eventual introduction of a dengue vaccine. ADVASC convened a workshop in September 2012 that drew together public health representatives and dengue experts from seven ASEAN countries in order to make practical recommendations to improve current surveillance and diagnostics for dengue to enable countries to assess consistently, and accurately communicate, the impact of a dengue vaccine. The workshop compared surveillance and diagnostic capacity in these ASEAN countries and made recommendations to streamline and harmonize key elements of these systems. In particular, attendees recommended the need for reconciliation and harmonization of the different World Health Organization guidelines, in use in ASEAN countries for case definition and surveillance of dengue.

KEYWORDS: Association of South East Asian Nations • burden • dengue • Southeast Asia • surveillance • vaccination impact • vaccine introduction

The Association of South East Asian Nations (ASEAN) comprises 10 countries in the Asia Pacific region that work together for mutual interest. These countries are economically, politically and culturally diverse, yet they share many health problems, including dengue. It has been estimated that 75% of the global dengue burden occurs in the Asia Pacific region [1], with a significant and increasing dengue burden across the ASEAN countries (Figure 1) [2]. Recognizing its public health importance, ASEAN leaders have prioritized dengue [3-5]. In addition, the WHO has set goals to improve surveillance for dengue and, by 2020, to reduce dengue morbidity by 25% and mortality by 50%. These goals could be supported by the use of a vaccine integrated with vector control within the next few years [1]. Furthermore, there are many challenges to the successful introduction of a dengue vaccine in countries with a high dengue disease burden including the development and use of disease surveillance that will permit the effectiveness of prevention and control methods to be assessed [1,6-8].

Understanding the specificities of these challenges in the Asia Pacific region, the ASEAN Member States Dengue Vaccination Advocacy Steering Committee (ADVASC), a regional independent scientific and educational committee, was established in 2011 to disseminate information and make practical recommendations about how to prepare for dengue vaccine introduction in ASEAN countries [9].

The first ASEAN member states dengue vaccination advocacy workshop

The first ASEAN Member States Dengue Vaccine Advocacy (ADVA) Workshop was held in Bangkok on 21–23 September 2012. Attendees included physicians, pediatricians, vaccinologists, immunologists and public health experts...
from eight countries across the Asia Pacific region. Representatives from seven ASEAN countries critically described the nature and extent of surveillance systems in their country and attendees considered the suitability of these surveillance systems in relation to the successful future implementation of dengue vaccination programs and assessment of vaccine impact. Attendees also considered how to overcome the identified obstacles as the first step in preparing the region for the introduction of dengue vaccines to ensure that at-risk individuals are vaccinated as early as possible. To stimulate discussion, lessons were drawn from presentations describing challenges to the adoption of other vaccines in the region.

Lessons drawn from previous vaccination programs
Successful vaccine uptake is important for achieving the necessary coverage rates in a National Immunization Program (NIP) to successfully protect a population against a given preventable disease. However, previous rotavirus and pneumococcal NIPs have been hampered by low uptake for several reasons.

Rotavirus vaccine
Rotavirus is the most common cause of severe diarrheal disease in young children, with approximately 500,000 children under the age of 5 years dying each year worldwide [10]. Despite promising data from early-adopter countries, the availability of health economic study data and a WHO recommendation for inclusion of rotavirus vaccine in NIPs, most ASEAN countries have failed to do so [11]. Attendees believed that reasons for the slow uptake of rotavirus vaccination in the ASEAN region may include the absence of regionally cohesive vaccine advocacy and purchasing power (such as Pan American Health Organization in Latin America), delay in availability of African and Asian vaccine efficacy and country-specific cost–effectiveness data [12,13]. In addition, vagaries of bureaucratic processes in relation to revealing tender prices may be an important barrier in developing cost–effective implementation strategies.

The attendees discussed these rotavirus vaccine implementation issues in relation to the implementation of a dengue vaccine in ASEAN and noted that clinical trials of a dengue vaccine were already being conducted in dengue endemic countries around the world including in ASEAN countries [14–16]. Furthermore, they suggested that the establishment of a Revolving Fund for vaccines might reduce financial barriers to the purchase of new vaccines generally in ASEAN, particularly among non-GAVI-eligible lower middle-income countries.

Pneumococcal vaccine
A case study of polysaccharide pneumococcal vaccination in adults showed that despite vaccination being recommended for all senior adults (≥65 years), those with chronic or immunocompromising medical conditions and smokers, the uptake remained low in Thailand. Similarly, studies from the USA showed only 30% uptake among high-risk adults [17]. ADVASC considered that reasons for low uptake may include a lack of understanding of the burden or importance of pneumococcal diseases in Thailand, a failure by physicians to appreciate the importance of vaccine for preventing invasive pneumococcal disease (IPD) [16] and a lack of understanding of the considerable disease prevention that a 46–59% reduction in IPD in adults represents [17]. However, the introduction of a pneumococcal protein conjugate vaccine among children has led to a herd immunity effect that resulted in a 38% decrease in the rate of IPD among elderly adults. This has renewed interest in evaluating pneumococcal protein conjugate vaccines in adults for prevention of IPD and pneumonia [18].

While recognizing that there is much greater awareness of dengue disease than IPD in the ASEAN region, attendees considered that it would be crucial to educate healthcare professionals about the benefits of dengue vaccination for adults as well as children and challenge the perception that dengue is only a pediatric disease. Healthcare professional communication and media engagement could ensure that this information is shared with patients effectively. The committee believed that, overall, advocacy to build political will and commitment among decision- and policy-makers would be key to the successful introduction of a dengue vaccination program in the region. Finally, the already-crowded public immunization schedule, coupled with health workforce shortages, health economics and allocation of resources in the ASEAN region, must also be taken into consideration when introducing any new vaccine.
Assessment of vaccine impact in ASEAN countries
ADVASC members agree with the latest WHO guidelines, which state that a harmonized effort is needed across national dengue surveillance systems to obtain the critical data on disease burden necessary to assess progress in reducing disease-associated morbidity and mortality [1].

Surveillance systems
Information was presented regarding surveillance systems in use at the time of the workshop. Attendees noted a lack of harmonization across ASEAN countries’ surveillance systems. For example, countries use a mix of WHO 1997 and 2009 case definitions and severe disease classification [19,20]. Most use only passive surveillance methods, but some, notably Malaysia, Thailand, Philippines and Indonesia, have recently implemented active surveillance methods at sentinel sites, particularly during outbreaks. Reporting is mandatory in all countries, but most reported cases come from public hospital inpatients, with fewer reports from outpatients, laboratories, private hospitals and clinics and primary care physicians. Countries collect surveillance data at all levels of the healthcare system and typically report it hierarchically to a central coordinating point. Attendees noted that Vietnam has an extensive laboratory network with tiered capacity so that district-level laboratories are responsible for sample collection and transport; provincial-level laboratories perform preliminary tests, which are then confirmed at the national level. In contrast, it was noted that Thailand employs a dual system of case- and event-based surveillance. For case-based surveillance, data are notified and reported by healthcare units from the public and private sectors. For event-based surveillance, reports are received from public health volunteers and other sources such as the media. Indonesia employs active-based surveillance using dengue officers to collect cases on a weekly basis from the government community health clinics (Puskesmas). Nevertheless, delays in reporting, and consequently, any outbreak containment response, can extend from 1 day in Singapore (with vector control response within 48–72 h) to a week or more for data collection and analysis at district or central levels in Indonesia, Myanmar and Philippines. Surveillance for dengue serotype distribution was conducted in all countries, but for some, this was limited and not systematically applied. Genotyping is also done to some extent in all countries, but, except in Malaysia, this is done primarily by academic researchers. Most countries provide regular feedback to their surveillance network (not Indonesia) and make surveillance data available to the public (not Indonesia or Vietnam).

According to the attendees, a key aim for dengue surveillance in the vaccine era would be the use of uniform case definitions, which would facilitate the comparison of data between countries.

Furthermore, high-quality sentinel surveillance from selected sites, which could be extrapolated to the wider population, might provide better estimates of dengue burden where there is under-reporting of ambulatory and private patients. They noted discrepancies regarding case classification used in different surveillance systems across the region, with most countries applying either WHO 1997 [19] or 2009 [20] criteria. In addition, some countries do not have a standard protocol for sending samples for laboratory confirmation, while other countries utilize different standard protocols. Even when a country has a clear policy detailing which cases to test, the application of this policy may vary between public and private sectors and inpatient and outpatient facilities. Attendees emphasized that a policy of representative sampling of cases of all clinical severities would ensure greater consistency and provide a more accurate estimate of disease burden, and that such a policy would be essential for estimating the impact of future dengue vaccination programs.

Clinical & laboratory diagnostics
Dengue infection can either be asymptomatic or manifest a broad spectrum of symptoms, ranging from cases of mild fever, to dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS) and dengue with unusual manifestations. Attendees discussed how differences in classification of the severity of dengue infection between centers and between countries can lead to inaccurate estimates of disease incidence from diagnostics and case reporting. The 1997 WHO dengue case classification (Figure 2) [19] describes dengue fever as fever with headache, retro-orbital pain, myalgias and/or arthralgias in the absence of plasma leakage. DHF, which involves plasma leakage and abnormal hemostasis, is further classified into Grades I–IV, with Grades III and IV also referred to as DSS.

Attendees agreed that stringent application of the 1997 WHO guidelines may lead to underdiagnosis of severe dengue cases, since the classification scheme does not fully capture dengue as a spectrum of clinical severity [21], while the 2009 guidelines (Figure 3) [20] may better aid clinicians for dengue cases triage and management. The 1997 and subsequent 2011 WHO South-East Asia Regional Office [22] guidelines, which provide information on dengue with unusual manifestations, may be more useful for public health surveillance. The attendees acknowledged, however, that the 2009 WHO guidelines are considered the standard within Western Pacific Regional Office countries.

For the purposes of surveillance following introduction of a dengue vaccine, the attendees emphasized the need for concrete and standardized case classifications uniformly adopted across the region, to provide a clear measure of disease burden. However, they realized that this may be difficult to achieve, given the diversity of the virology and genetics of dengue. Attendees also considered that it might be useful to maintain the distinction between dengue fever, DHF and DSS, to maintain comparability with historical data.

Methods for laboratory confirmation of dengue infection include direct virus isolation, viral RNA detection and antibody or antigen detection (including rapid methods), with assay selection based on the clinical timing of sample collection [23]. Most ASEAN countries appear to use a variety of these methods and ideally, both acute-phase virus or antigen detection and later-
phase antibody detection should form part of routine diagnostics. Importantly, the most appropriate test also differs according to the purpose of surveillance. Attendees highlighted the wide variation in the proportion of reported cases that undergo laboratory testing; for example, Singapore only reports laboratory-confirmed cases (serology or virus NS1 antigen positive), whereas the Philippines reports all suspect and probable cases based on clinical diagnosis alone. Most countries test the majority of fatal and severe cases but, in general, any requirement for laboratory testing must be balanced against affordability.

There is a need for better understanding of the currently unestablished correlates of dengue protection [24]. A test of vaccination status, which differentiates past dengue infection from vaccination, will also be useful for disease surveillance. However, the panel agreed that this would be methodologically difficult to achieve.

![Figure 2. Manifestations of dengue virus infection [19] WHO. Reproduced with permission from [19] © WHO 1997.](image)

![Figure 3. Suggested dengue case classification and levels of severity [20] WHO. Reproduced with permission from [20] © WHO 2009.](image)
Summary of recommendations

Surveillance

The WHO guidelines [19,20,22] should be reconciled and harmonized with the aims of extracting the features needed to undertake simplified surveillance and meeting key diagnostic criteria, such as sensitivity, inclusivity, inclusion of severe disease and unusual manifestations, predictive value and warning signs. Measures taken to ensure that information on DHF and DSS is preserved will be crucial for maintaining comparability with historical data. We feel that data should be collected at all levels of the health care system and reported to a central coordinating point according to a standard protocol. Vaccination status should be linked to improved surveillance systems in a feasible manner. It is also important to promote regional networks that provide and share beneficial data in a sustainable manner.

Diagnostics

The choice of diagnostic test should be guided by the purpose of dengue surveillance and, ideally, results of all tests should be linked to surveillance systems to provide data on case outcomes. In a setting where testing of the majority of all cases is not possible, we recommend testing at sentinel sites and representative sampling of cases of all clinical severities, which would provide laboratory-confirmed estimates of dengue burden and case severity. Although testing can be done at various levels, quality control should be maintained by a central reference laboratory. Testing and case outcomes should be placed in the context of population demographics and local epidemiology.

Research & advocacy

It is important to strengthen the evidence base through research into better vaccine formulations and areas that support the measurement of dengue vaccination impact. These include disease classification, surveillance, disease burden, vaccine efficacy and delivery and long-term safety follow-up. As the results of Phase III clinical trials are being consolidated, and possible new candidate vaccines emerge, it is important to continue work on tests evaluating vaccination status, disease transmission modeling, the health economics of dengue vaccine introduction and the impact of vaccine in the context of other preventive and control methods. It is also important to continue developing affordable, accessible, reliable and rapid diagnostic tests, as well as identifying and accurately measuring immunological correlates of protection.

The visibility of dengue and dengue vaccination within the ASEAN member states needs to be raised in the context of broader public health objectives. It is important to encourage policy action, especially in the absence of large outbreaks. Rapid sharing of information from early-adopter countries will facilitate decisions regarding dengue vaccine introduction in other endemic countries. An awareness campaign can help gain support for dengue vaccination within the community, the medical profession, the media, policy-makers and other stakeholders. Initiatives should be explored and partnerships built to ensure sustainable, long-term financing for dengue prevention and control.

In conclusion to this first ADVA Regional Workshop, ADVASC have recommended streamlining and harmonizing a number of factors necessary for successful dengue vaccine introduction in the ASEAN member states, with particular emphasis on dengue detection (i.e., diagnostics and surveillance procedures). We noted that existing health systems require further investment and have made recommendations for needed research and advocacy.

Expert commentary

The work of ADVASC is important to address the practical challenges faced by ASEAN countries as they prepare for eventual introduction of a dengue vaccine. This work attempts to bridge the gap that exists between the high-level recommendations made by inter- and non-governmental organizations and the specific challenges faced at a country and regional level. Dengue is unlike many other infectious diseases that affect the region, because all sections of society and all age groups are at risk. For vaccine to be impactful in ASEAN member states’ communities, very broad vaccination programs integrated with other dengue control interventions will be required. This first ADVA workshop drew together public health representatives from 7 of the 10 ASEAN countries along with other experts from the region in order to identify challenges and make practical recommendations about necessary improvements to current surveillance and diagnostics for dengue. The workshop highlighted the many differences that exist between countries in this capacity and recommended improvements that, if followed, should enable countries to consistently and accurately assess and communicate the impact of a dengue vaccine in the region.

Five-year view

Challenges of assessing the impact of a dengue vaccine

Dengue vaccines are in development with the anticipated introduction of a vaccine in the next few years. Methodologies needed to assess the impact of a dengue vaccination program will depend on the capacity and political will of individual countries. High-quality public health surveillance is based on strong clinical, laboratory and epidemiological capacities. Socioeconomic studies and modeling approaches can be used to evaluate projected health system and economic effects of vaccination, including treatment versus vaccination costs, rates of uptake, cost–effectiveness and vaccine delivery. Knowledge, attitudes and practice surveys can be used to assess the acceptability of the vaccine by the community.

Many countries have low capacity for these methods, and weak surveillance in particular may be part of a wider problem of a lack of investment in health services. There is a clear need for strengthening health systems in the ASEAN region and considering the health benefits of vaccination when making an investment case. Furthermore, it will be crucial to develop synergistic collaborations between various disease control modalities such as prevention, treatment, vector control and health promotion.
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Key issues

- The burden of dengue is of particular concern in Southeast Asian countries, and current tools for dengue control are limited.
- Dengue vaccines are anticipated by these countries, and the first of these vaccines may be available within the next few years.
- Association of South East Asian Nations (ASEAN) and the WHO have prioritized dengue and made recommendations for its surveillance and control.
- Nevertheless, consistent surveillance practices are not applied among ASEAN countries.
- This lack of consistency may hamper efforts to assess and subsequently communicate the impact of dengue vaccine introduction.
- The ASEAN Member States Dengue Vaccination Advocacy Steering Committee recently convened a workshop to discuss these critical issues, with a particular focus on optimally measuring vaccination impact in ASEAN countries.
- ASEAN Member States Dengue Vaccination Advocacy Steering Committee made recommendations to streamline and harmonize key factors, with a focus on dengue diagnostics and surveillance procedures.
- It was noted that existing health systems require further investment, and recommendations for research and advocacy needed were also made.

References

Papers of special note have been highlighted as:
- of interest
- of considerable interest


3. This reference defines the WHO’s goals for dengue, including both understanding the true burden of dengue by 2015 and reducing morbidity and mortality due to dengue by 2020.


8. This occasional paper by Hanna, published by the Paediatric Dengue Vaccine Initiative, comprehensively discusses issues related to dengue vaccine introduction.


15. Capeding RZ, Luna IA, Bomassang E, et al. Live-attenuated, tetravalent dengue vaccine in children, adolescents and adults in a...
dengue endemic country: randomized controlled phase I trial in the Philippines. Vaccine 2011;29(22):3863-72


**Sabchareon and others’ paper documents the first efficacy results for a tetravalent dengue vaccine.**


- These guidelines for dengue prevention and control from the South-East Asian Regional Office of the WHO provide the most complete recommendations available to date.
