### **PROSPECTS FOR THE DEVELOPMENT OF A DENGUE VACCINE**

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**Abstract.** Dengue is a mosquito-borne viral disease, which is currently an important and rapidly growing health problem across the globe. Four closely related dengue serotypes cause the disease, which ranges from asymptomatic infection to undifferentiated fever, dengue fever (DF), and dengue hemorrhagic fever (DHF). Specific antiviral medications are not available for dengue, and successful treatment that is mainly supportive depends on early recognition of the disease and careful monitoring for shock. Prevention of dengue depends on the control of the mosquito vector, which has had only limited success. Development of a dengue vaccine is seen as a new tool to prevent this potentially fatal disease. The scope and intensity of dengue vaccine development has increased dramatically in the last decade. A live-attenuated tetravalent dengue vaccine based on chimeric yellow fever dengue virus has progressed to licensure in several dengue endemic countries in 2015 after its Phase III efficacy study involving more than 30000 volunteers from Asia and Latin America. Several other dengue vaccine candidates are currently being evaluated in clinical and preclinical studies including other live-attenuated vaccines, subunit, DNA purified inactivated vaccine candidates, as well as virus-vectored and virus-like particle-based vaccines. Since dengue poses a heavy economic cost to the health system and society, the potential economic benefits are associated with promising dengue prevention interventions such as dengue vaccine and vector control innovations.

Keywords: dengue, vaccine development

#### INTRODUCTION

Dengue is a mosquito-borne viral disease that is currently an expanding global problem. Successful treatment, which is mainly supportive, depends on early recognition of the disease and careful monitoring for shock.

A severity-based revised dengue classification for medical interventions has been developed by the World Health Organization (WHO) and has been adopted in most countries. Dengue is a disease entity with different clinical manifestations often with unpredictable clinical evolutions and outcomes. Four closely related dengue serotypes cause the disease, which ranges from asymptomatic infection to undifferentiated fever,

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dengue fever (DF), and dengue hemorrhagic fever (DHF). The severity of DF manifestations increases with age. DF causes fever, rash, muscle or joint pain, headache, and eye pain, but DF is rarely fatal. DHF is considered a distinct disease characterized by fever, bleeding diathesis, and increased vascular permeability leading to leakage of plasma with a tendency to develop potentially fatal dengue shock syndrome (DSS). Although shock and plasma leakage seem to be more prevalent as age decreases, the frequency of internal hemorrhage rises as age increases. Increases in liver enzymes found in both children and adults indicate liver involvement during dengue infections. Pre-existing liver diseases, which are more common in adults, such as chronic hepatitis, alcoholic cirrhosis, and hemoglobinopathies can aggravate the liver impairment in dengue patients.

Dengue with organ impairment mainly involves the liver and the central nervous system. Consistent hematological findings include vasculopathy, coagulopathy, and thrombocytopenia. Laboratory diagnosis includes virus isolation, serology, and detection of dengue ribonucleic acid. The age of dengue cases in several countries has increased from children to adolescents and adults (Thisyakorn and Thisyakorn, 2015a).

Antiviral medications are not available for dengue and successful treatment, which is mainly supportive, depends on early recognition of the disease, bleeding tendency, and careful monitoring for signs of circulatory failure. Adults have a higher prevalence of underlying diseases, eq, coronary artery disease, peptic ulcer, hypertension, diabetes mellitus, cirrhosis, and chronic kidney diseases, which should be considered in dengue management. A severity-based revised dengue classification for medical interventions has been developed and adopted in many countries (Tantawichien, 2015). Prevention using vector control has had limited success, and dengue vaccine is thus seen as one of the major tools in effectively controlling dengue diseases (Horstick and Ranzinger, 2015; Thisyakorn and Thisyakorn, 2015b).

#### DENGUE VACCINE DEVELOPMENT

Dengue virus is a positive-sense, singlestranded, 11kb RNA *Flavivirus* consisting of three structural proteins [premembrane/membrane (prM/M), envelope (E), as well as capsid (C) and seven non-structural proteins]. There are four antigenically distinct serotypes (DENV-1, 2, 3, and 4). The pathogenesis of DHF is not clearly understood. The uniqueness of the dengue viruses and the spectrum of diseases resulting from infection have made dengue vaccine development difficult.

Several different approaches have been tried to develop a dengue vaccine. Because dengue is a unique and complex disease, developing a dengue vaccine has proven equally complex. However, there is an advanced pipeline of vaccine research currently in clinical and preclinical studies including live-attenuated vaccines, subunit, DNA, purified and inactivated vaccine candidates, as well as virusvectored and virus-like particle-based vaccines. (Thisyakorn and Thisyakorn 2014a; Prommalikit and Thisyakorn 2015; Vannice *et al*, 2016).

#### LICENSED DENGUE VACCINE

The first dengue vaccine, CYD-TDV (Dengvaxia®, Sanofi Pasteur: Lyon), is a live-attenuated tetravalent dengue vaccine with a yellow fever backbone, and all four dengue serotype components are chimeric (prM and E proteins). This vaccine has now been licensed by several dengue endemic countries in Asia and Latin America for use in persons aged 9-45 or 9-60 years and is under regulatory review in several others (WHO, 2016b).

The first Phase III efficacy trial for CYD-TDV in highly dengue-endemic areas of five Asian countries in 10,275 children demonstrated that this dengue vaccine is efficacious when given as a 0-6-12 month schedule to 2-14 year-old children. The vaccine showed a 56.5% (95% CI: 43.8-66.4) overall efficacy with the contributions of each of the four serotypes, and more than 80% of severe dengue episodes were avoided with a two-third reduction in hospitalization. Higher efficacy was observed in the immunogenicity subset seropositive at baseline. A good safety profile was observed with an interesting finding that vaccine efficacy was higher for participants who were seropositive for dengue than for those who were seronegative. Furthermore, vaccine efficacy increased with age, which could be a marker of previous exposure to dengue (Capeding et al, 2014).

A second Phase III clinical trial in Latin American countries involving 20,875 children and adolescents aged 9-16 years demonstrated a 60.8% (95% CI: 52.0-68.0) overall efficacy with the contributions from each of the four serotypes. Additional results showed a significant reduction of the risk of hospitalization by 80.3%. Higher efficacy was observed in the immunogenicity subset seropositive at baseline with a good safety profile (Villar *et al*, 2015). The burdens of dengue were substantial in both regions and in all age groups. Burdens varied widely according to country, but the rates were generally higher and the disease more frequently severe in Asian countries than in Latin American countries (L'Azou et al, 2016).

Assessment of the incidence of hospitalization for virologically-confirmed dengue as a surrogate safety end point during follow-up in years 3 to 6 of two Phase III trials and a Phase IIb trial showed the risk among children 2 to 16 years of age was lower in the vaccine group than in the control group. However, the unexplained higher incidence of hospitalization for dengue in year 3 among those children younger than 5 years needs to be carefully monitored during long-term follow-up (Hadinegoro et al, 2015).

The WHO Strategic Advisory Group of Experts on Immunization (SAGE) recommends countries consider introduction of CYD-TDV in geographic settings where dengue is highly prevalent. SAGE recommends that vaccination should be considered as an integrated strategy together with communication strategy, well-executed and sustained vector control, the best evidence-based clinical care for all patients with dengue, and robust dengue surveillance (WHO 2016a). The observed vaccine efficacy against asymptomatic dengue infection is expected to translate into reduced dengue virus transmission if individuals are vaccinated in endemic areas (Olivera-Botello et al, 2016).

The WHO published its first position paper on a dengue vaccine based on the available evidence of CYD-TDV or Dengvaxia®, the only dengue vaccine to have received regulatory approval, in the Weekly Epidemiological Record. Since December 2015, Dengvaxia<sup>®</sup> has been approved by the regulatory authorities of several countries in Latin America and Asia. The WHO recommends that countries should consider the introduction of the dengue vaccine Dengvaxia® only in geographic settings (national or subnational) where epidemiological data indicate a high burden of disease, and dengue vaccine introduction should be a part of a comprehensive dengue control strategy, including well-executed and sustained vector control, evidence-based best practices for clinical care for all patients with dengue illness and strong dengue surveillance (WHO, 2016b).

naïve subjects, and in more favorable immunization schedules. Carefully designed studies in nonhuman primates should allow prioritization of preclinical candidates for human subject trials (Thisyakorn and Thisyakorn, 2014a; Thisyakorn and Thisyakorn, 2015b; Vannice et al, 2015). Future clinical development of dengue vaccine candidates needs to consider that CYD-TDV (Dengvaxia<sup>®</sup>, Sanofi Pasteur: Lyon) has been introduced into many endemic countries.

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#### DENGUE VACCINES IN THE PIPELINE

Two dengue vaccine candidates at advanced stages of clinical development are both liveattenuated vaccines and both have one or more chimeric serotype components. TDV (Takeda: Osaka) has one component that is attenuated but not chimeric (DEN-2) and three chimeric components (prM and E proteins) while TV003/ TV005 (National Institutes of Health: Bethesda, MD) has three attenuated components and one chimeric component (a DEN-4 backbone with DEN-2 prM and E proteins). Both are at Phase II and III efficacy trial stages (Asia Dengue Summit, 2016).

Increasing knowledge of dengue vaccine development is providing more insights into improved vaccine design. Recent advances in vaccine science have greatly increased the technological options for dengue vaccine development as several promising dengue vaccine candidates are in preclinical and clinical development. In parallel, molecular biology and system biology permit more specific analysis of vaccine-induced immunogenicity and safety. However, possibly the most intriguing finding in dengue vaccines over the past year comes from the first licensed CYD-TDV. There are also three inactivated whole virus dengue vaccines with incorporated adjuvants for enhancing immunogenicity at the Phase I trial stage.

The preclinical dengue vaccine pipeline covers

a broad range of approaches both in antigen

as well as in delivery and presentation. Second

generation vaccines may improve upon first

generation vaccines in overall and strain-specific

vaccine efficacy, in particular in immunologically

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#### ASIA DENGUE SUMMIT

During 13-14 January 2016, the Asia Dengue Summit (ADS) co-organized by the Asian Dengue Vaccination Advocacy (ADVA), the Dengue Vaccine Initiative, the Southeast Asian Ministers of Education Organization Tropical Medicine and Public Health Network, and the Fondation Mérieux was held in Bangkok, Thailand. This meeting focused on improving strategies for dengue prevention and control.

The ADS and the ADVA workshop presentations provided a foundation from which to form an outcome statement and call to action. Because dengue vaccine is potentially game changing, the events of 2016 will impact the future for populations in dengue endemic areas around the world.

The second part of the meeting comprised of discussions of a set of statements drafted by ADVA based on the key messages from the ADS as described below.

#### Call to action

## Within the broader context of the outcomes of the Asia Dengue Summit, we...

- Recognize that dengue continues to be a major global public health threat and the problem is growing.
- Recognize that vaccines would be a useful addition to current prevention and control efforts that, in most cases, are inadequate for full impact.
- Are aware of the licensure of the first dengue vaccine and imminent availability of other promising candidates for preventive vaccination.
- Are cognizant of the strong leadership role provided by the WHO, guided by the Global Strategy for Dengue Prevention and Control, to reduce dengue mortality by 50% and morbidity by 25% by the year 2020.
- Are informed by the urgent need for adequate resources, for integrated surveillance, for sustainable vector control methods, for adequate preparedness for vaccination

programs that include school-based vaccination, appropriate evaluation and monitoring of interventions, as well as for new methodologies and high-quality point-of-care diagnostic tests.

- Recognize the central role of good science, good communications, the media, strong political leadership, and public support.
- Are sensitive to the need to ensure equity, sustainability, ethics, and social justice.

# The co-hosts of the Asia Dengue Summit make the following call to action: we...

- Call on countries, where appropriate, to develop and implement a carefully controlled stepwise programmatic introduction of dengue vaccine(s), including school-based vaccination and catch-up campaigns, which are closely integrated with other control strategies and the needs and constraints of health systems. These activities should be based on close consideration of the country's own disease epidemiology, capacities, health infrastructure, financial resources, and decision on vaccine registration.
- Call on countries to ensure that vaccine implementation programs are monitored and tracked, and evaluated for safety, effectiveness, and acceptance through sound risk communication and management plans with good communication, active surveillance, laboratory support, and clinical management.
- Call on various related initiatives to work closely together through global efforts such as the Global Dengue and Aedestransmitted Diseases Consortium to monitor developments in vaccine and vector control implementation as well as to perform high-level advocacy with governments and international organizations for vaccine introduction in endemic countries. This should be guided by the need for better integration and synergy of strategies to avoid fragmentation and duplication.
- Call for the political will and commitment to accelerate effective dengue prevention

and control interventions, including strengthening health systems and ensuring sustainable financing.

- Call on relevant organizations and institutions to continue performing and supporting research to further enhance the impact of vaccination, including biomedical and clinical research, mathematical modeling, implementation and operational research, as well as post-licensure studies.
- Call on the WHO and other global and regional organizations and initiatives to give higher priority to dengue prevention and control, to provide continued leadership, guidance, and technical support to countries on the possible introduction of dengue vaccine, as well as to assist with implementation strategies and obtaining sustainable financial support for countries (Thisyakorn *et al*, 2014b; Asia Dengue Summit, 2016).

The 2<sup>nd</sup> ADS will be held in Manila, Philippines during 1-2 March 2017 (2<sup>nd</sup> Asia Dengue Summit, 2017).

### ASEAN DENGUE DAY

ASEAN Dengue Day is an advocacy event held every 15 June to increase public awareness of dengue, to mobilize resources for its prevention and control, and to demonstrate the region's commitment to tackling the disease. The advocacy event was agreed upon during the 10<sup>th</sup> ASEAN Health Ministers Meeting in 2010. The first regional event was held in 2011 in Jakarta, Indonesia. During 13-15 June 2016, the 6<sup>th</sup> ASEAN Dengue Day was held in Bangkok, Thailand where health experts called for collective regional action to fight the fastest-growing burden of dengue in the ASEAN region (ASEAN Dengue Day, 2016).

#### CONCLUSION

The global burden of dengue is increasing rapidly, driven by population growth, urbanization, globalization, and ecological changes. A dengue vaccine is needed as part of an integrated approach to dengue prevention and control. One dengue vaccine, CYD-TDV, has been licensed in several dengue endemic countries in Latin America and Asia since 2015 for use in 9-45 or 9-60 year-old individuals. Two other vaccines are at advanced stages of clinical development at Phases II and III. Several other vaccines are at varying stages of preclinical and clinical development.

### CONFLICT OF INTEREST

The authors declare no conflicts of intrest in preparing this article.

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