# THE ESTIMATED IMPACT AND COST-EFFECTIVENESS OF DENGUE VACCINATION

**Pinyo Rattanaumpawan**

*Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand*

**Abstract.** Dengue infection is considered a significant global health threat, especially in Thailand. Dengue vaccination is one of promising methods to prevent dengue infection. Recently, the Dengvaxia™ (CYD-TDV) has become available in the market. Furthermore, some new dengue vaccines may soon become available. In this paper, we reviewed published studies focusing on cost-effectiveness of the dengue vaccine. Results from this review would help key stakeholders for making their decisions in adding the vaccine into the National List of Essential Medicines (NLEM) Thailand.

**Keywords:** cost-effectiveness analysis, dengue vaccine, health economics

## PATHOPHYSIOLOGY OF DENGUE INFECTION

Dengue virus (DENV) is a single-stranded, positive-sense RNA viruses of the genus *Flavivirus* (family Flaviviridae) (Simmons *et al*, 2012). DENV can be classified into four antigenically diverse serotypes (DENV1-4) (Simmons *et al*, 2012). Based on data of the years 1994 to 2006, the distribution of dengue serotype in Thailand was DEN-1 (36%), followed by DEN-3 (27%), DEN-2 (23%) and DEN-4 (14%) (Fried *et al*, 2010).

The primary vector of DENV is the *Aedes aegypti* mosquito, which is widely distributed in tropical and subtropical countries (Lambrechts *et al*, 2010). The clinical presentation of dengue infection can range from asymptomatic (inapparent) dengue infection, undifferentiated fever, dengue fever, dengue hemorrhagic fever, or dengue shock syndrome (Simmons *et al*, 2012).

**Correspondence:** Pinyo Rattanaumpawan, MD, MSCE, PhD, Division of Infectious Diseases and Tropical Medicine, Department of Medicine, Faculty of Medicine Siriraj Hospital, Mahidol University, 2 Wanglang Road, Bangkok Noi, Bangkok 10700, Thailand.
Tel: +66 (0) 2419 7784; Fax: 66 (0) 2419 7783
E-mail: *pinyo.rat@mahidol.ac.th*

## BURDEN OF DENGUE INFECTION

Dengue infection is considered a significant global health threat, especially in Asian countries. Not only does dengue infection results in significant morbidity and mortality, but it also results in high resource utilization. A recent study using new statistical methods and geo-located techniques was conducted to accurately predict the global burden of dengue infection (Bhatt *et al*, 2013). From that study, the global estimates of overall dengue infection and apparent dengue infection were 390 (95% CI: 284-528) and 96 (95% CI: 67-136) million per year, respectively. Of these, nearly 400 million episodes of dengue infection, approximately 70% of them occurred in Asian countries. Moreover, a recent observational study conducted in three Southeast Asian countries (Thailand, Indonesia, and Vietnam) revealed that dengue infection is the most common cause of community-acquired sepsis and severe sepsis among hospitalized patients (Southeast Asia Infectious Disease Clinical Research Network, 2017).

Dengue infection is also one of the most common causes of acute febrile illness in Thai children. A past seroprevalence study reported that 50% of 4- to 16-year-old students at a Bangkok school had antibodies to at least one dengue serotype (Burke *et al*, 1988). However, more recent

evidence reported that the crude attack rate of virologically-confirmed dengue infection among Thai children aged 2-14 years old was only 5.9 per 100 person years (Nealon *et al*, 2016).

## EFFICACY OF DENGUE VACCINE

Dengvaxia™ (Sanofi Pasteur: Lyon) the first licensed dengue vaccine is a recombinant, live-attenuated tetravalent dengue vaccine (CYD-TDV). It was approved by the Thai Food and Drug Administration in October 2016.

The vaccine efficacy has been well documented in two landmark phase III trials, namely CYD14 and CYD15. The CYD14 was conducted among 10,275 healthy children aged 2-14 years from five countries in the Asia-Pacific region including Thailand (Capeding *et al*, 2014) while the CYD15 was conducted among 20,869 healthy children between aged 9-16 years from five Latin America countries (Villar *et al*, 2015). Based on results from the long-term follow-up of these two clinical trials, the pooled vaccine efficacy against symptomatic dengue virus infection during the first 25 months were 65.6% (95% CI: 60.7-69.9) for children under 9 years of age and 44.6% (95% CI: 31.6-55.0) for the older population. Furthermore, the pooled relative risks of hospitalization for dengue were 0.84 (95% CI: 0.56-1.24) among all participants, 1.58 (95% CI: 0.83-3.02) among those under the age of 9 years, and 0.50 (95% CI: 0.29-0.86) among those 9 years of age or older (Hadinegoro *et al*, 2015).

The CYD-TDV seems to be more effective among younger or previously immune populations. Despite the relatively high vaccine efficacy, the absolute risk reduction of CYD-TDV for symptomatic dengue infection was only 0.1 - 0.2% per year (Hadinegoro *et al*, 2015). Although the CYD-TDV efficacy was not proven in two phase II trials of patients aged 2-45 years, the meta-analysis including seven studies of patients aged between 2-45 years confirmed the clinical efficacy of the CYD-TDV of 59% (95% CI 15-80), or relative risk of 0.41 [95%CI 0.2-0.85] (da Costa *et al*, 2014). Given these findings, the CYD-TDV vaccine was approved for use in patients aged 2-45 years.

## THAILAND'S NATIONAL LIST OF ESSENTIAL MEDICINES

In 2011, Thailand became an upper-middle income economy by the World Bank classification [USD4,036 - USD12,475 gross national income (GNI) per capita]. Nevertheless, affordability is still one of the important factors for policy makers to make decisions in adopting new vaccines or new treatment options. Currently, there are several mechanisms for resource-limited countries to procure vaccines at affordable prices (Burchett *et al*, 2012). For example, countries classified as low-income countries by the World Bank (USD1,025 or less GNI per capita) can secure remarkably lower price vaccines via the Global Alliance for Vaccines (GAVI) negotiation process. Furthermore, United Nations International Children's Emergency Fund established a vaccine procurement program to make some vaccines more affordable for GAVI ineligible-countries (Kaddar *et al*, 2013).

Although Thailand is not eligible for those aforementioned mechanisms, the Thai government has systematically instituted price negotiation mechanisms before adding necessary medicines and vaccines into the National List of Essential Medicines (NLEM) Thailand (Teerawattananon and Tritasavit, 2015). One of the most important steps in price negotiation is to conduct an economic analysis on such medicines or vaccines. If the given medicine does not represent good value for money, the projected price to make such medicine become good value is requested. According to the suggestion of World Health Organization (WHO), the willingness to pay (cost-effectiveness threshold) should be three times the per capita gross domestic product (GDP) per disability-adjusted life-year (DALY) averted (Bertram *et al*, 2016). Unfortunately, the threshold that is currently used for NLEM of Thailand is approximately USD 5,000 per one DALY averted or only one time of Thailand per capita GDP.

## COST-EFFECTIVENESS OF DENGUE VACCINATION IN THAILAND

There has been a number of health economic analyses evaluating the impact and economic

burden of the dengue vaccine (Shepard *et al*, 2004; Lee *et al*, 2011; Durham *et al*, 2013; Yeo *et al*, 2015; Shim, 2016; Flasche *et al*, 2016). However, the results from a study conducted in one country may not be applicable to another country due to differences in many important aspects (*ie*, the difference in vaccine efficacy across patients with differences in ethnicity, incidence of dengue infection, mortality rate or cost of treatment.

An economic analysis of the dengue vaccine using the context of Thailand was conducted in 2011 before the CYD-TDV vaccine was available in the market (Lee *et al*, 2011). The authors constructed a decision tree using the Markov model. The model started with two options to choose; vaccination versus no vaccination. Vaccinated subjects would have a lower chance of acquiring a dengue infection including asymptomatic dengue infection, dengue fever, dengue hemorrhagic fever, dengue shock syndrome and death based on vaccine efficacy. Costs for vaccination, treatment for infection, treatment for vaccine side effect and school-day or work-day missed were all calculated from the Societal perspective. Sensitivity analyses were subsequently performed using a broad range of variables such as vaccine efficacy, cumulative incidence of dengue (dengue risk) and disease characteristic (*ie*, % of hospitalization and % of outpatient visit). By using the model with a dengue risk of 5%, a vaccine efficacy of 50%, and a cost-effectiveness threshold of one per-capita GDP, the dengue vaccine would be cost-effective if the vaccination cost is less than USD 60 per course. In a situation using three times of per-capita GDP as the cost-effectiveness threshold, the dengue vaccine would be cost-effective if the vaccination cost is less than USD 200 per course. Unfortunately, the current market price of Dengvaxia™ in Thailand is approximately USD 300 per course.

## CONCLUSION

In an ideal situation, one would prefer to employ all treatment or preventive options that would increase the life expectancy of a patient. However, more than half of population in the world are in resource-limited countries. Because the CYD-TDV is currently available in the market, and some new dengue vaccines may soon become available, results from cost-effectiveness analyses would help key stakeholders for making their decisions and assisting in the price negotiation process.

## REFERENCES

Bertram MY, Lauer JA, De Joncheere K, *et al*. Cost-effectiveness thresholds: pros and cons. *Bull World Health Organ* 2016; 94: 925-30.

Bhatt S, Gething PW, Brady OJ, *et al*. The global distribution and burden of dengue. *Nature* 2013; 496: 504-7.

Burchett HE, Mounier-Jack S, Griffiths UK, Mills AJ. National decision-making on adopting new vaccines: a systematic review. *Health Policy Plan* 2012; 27(suppl): 62-76.

Burke DS, Nisalak A, Johnson DE, Scott RM. A prospective study of dengue infections in Bangkok. *Am J Trop Med Hyg* 1988; 38: 172-80.

Capeding MR, Tran NH, Hadinegoro SR, *et al*. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. *Lancet* 2014; 384: 1358-65.

da Costa VG, Marques-Silva AC, Floriano VG, Moreli ML. Safety, immunogenicity and efficacy of a recombinant tetravalent dengue vaccine: a meta-analysis of randomized trials. *Vaccine* 2014; 32: 4885-92.

Durham DP, Ndeffo Mbah ML, Medlock J, *et al*. Dengue dynamics and vaccine cost-effectiveness in Brazil. *Vaccine* 2013; 31: 3957-61.

Flasche S, Jit M, Rodriguez-Barraquer I, *et al*. The long-term safety, public health impact, and cost-effectiveness of routine vaccination with a recombinant, live-attenuated dengue vaccine (Dengvaxia): a model comparison study. *PLOS Med* 2016; 13: e1002181.

Fried JR, Gibbons RV, Kalayanarooj S, *et al*. Serotype-specific differences in the risk of

dengue hemorrhagic fever: an analysis of data collected in Bangkok, Thailand from 1994 to 2006. *PLOS Negl Trop Dis* 2010; 4: e617.

Hadinegoro SR, Arredondo-Garcia JL, Capeding MR, *et al*. Efficacy and long-term safety of a dengue vaccine in regions of endemic disease. *N Engl J Med* 2015; 373: 1195-206.

Kaddar M, Schmitt S, Makinen M, Milstien J. Global support for new vaccine implementation in middle-income countries. *Vaccine* 2013; 31(suppl): 81-96.

Lambrechts L, Scott TW, Gubler DJ. Consequences of the expanding global distribution of *Aedes albopictus* for dengue virus transmission. *PLOS Negl Trop Dis* 2010; 4: e646.

Lee BY, Connor DL, Kitchen SB, *et al*. Economic value of dengue vaccine in Thailand. *Am J Trop Med Hyg* 2011; 84: 764-72.

Nealon J, Taurel AF, Capeding MR, *et al*. Symptomatic dengue disease in five Southeast Asian countries: epidemiological evidence from a dengue vaccine trial. *PLOS Negl Trop Dis* 2016; 10: e0004918.

Shepard DS, Suaya JA, Halstead SB, *et al*. Cost-effectiveness of a pediatric dengue vaccine. *Vaccine* 2004; 22: 1275-80.

Shim E. Dengue dynamics and vaccine cost-effectiveness analysis in the Philippines. *Am J Trop Med Hyg* 2016; 95: 1137-47.

Simmons CP, Farrar JJ, Nguyen VV, Wills B. Dengue. *N Engl J Med* 2012; 366: 1423-32.

Southeast Asia Infectious Disease Clinical Research Network. Causes and outcomes of sepsis in Southeast Asia: a multinational multicentre cross-sectional study. *Lancet Glob Health* 2017; 5: e157-67.

Teerawattananon Y, Tritasavit N. A learning experience from price negotiations for vaccines. *Vaccine* 2015; 33(suppl): 11-2.

Villar L, Dayan GH, Arredondo-Garcia JL, *et al*. Efficacy of a tetravalent dengue vaccine in children in Latin America. *N Engl J Med* 2015; 372: 113-23.

Yeo HY, Shafie AA, Coudeville L, Steinberg LD, Gill BS, Jahis R. Potential health and economic impact of introducing a dengue vaccine in Malaysia: assessment using dynamic transmission modelling. *Value Health* 2015; 18: A582.