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Economic Evaluations of Dengue Vaccination in Southeast Asia Region: Evidence From a Systematic Review

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ABSTRACT

Objectives: To review the literature on the cost-effectiveness of dengue vaccination in Southeast Asian countries and possibly to provide recommendations on promoting dengue vaccination in this region. **Methods:** A systematic search was conducted to identify relevant articles in 3 major databases (ProQuest, American Society of Tropical Medicine and Hygiene, and PubMed). Complete economic evaluation studies, including willingness-to-pay (WTP) studies, that were conducted in any Southeast Asian country were included in this study. Systematic review, non−full-text, and non-English studies were specifically excluded. **Results:** Nine selected studies highlighted the economic evaluation of dengue vaccination in Southeast Asian countries by considering many parameters (eg, vaccine cost, vaccine efficacy, cost-effectiveness threshold, economic assessment, public acceptance, and WTP). All studies confirmed that dengue vaccine can be used as a prevention strategy to reduce the incidence rate of dengue cases by providing a variance of high cost-effectiveness values. In addition, communities provided a good assessment, acceptance, and WTP value for the vaccine. **Conclusions:** The use of dengue vaccine could reduce the burden of disease and economic burden due to dengue infection in Southeast Asian countries. The efficacy of dengue vaccine was estimated to be 50-95% for those <9 years, 9 years, and >9 years. In particular, several studies reported that dengue vaccine could be categorized as a cost-effective intervention in Southeast Asian countries within certain conditions.
Keywords: cost-effective, dengue, immunization, SEAR, vaccine.

Introduction

Over the last decade, dengue fever has been reported to be the most prevalent arboviral fever worldwide, with up to 40% of the world's population living in endemic regions and at risk for dengue infection.[1] The dengue virus, which is transmitted through mosquitoes, has been causing serious problems in several tropical countries.[2] It has been reported that during the period 2001 to 2010, the number of dengue cases in Southeast Asian countries was 2.9 million, with 5906 deaths.[3] Dengue infections were also related to 1.8 billion cases in Southeast Asian and Western Pacific countries.[4,5]

Southeast Asia is one of the regions in the world with a relatively high incidence rate of dengue infection and a short epidemic cycle of 3 to 5 years. Several studies reported that dengue fever in Southeast Asian countries was responsible for 75% of the total disease and economic burden due to dengue fever in the world.[4,6,7] In particular, an annual economic burden due to dengue infection in Southeast Asian countries was estimated to be $950 million ($1.65 per capita).[3] Several prevention strategies (eg, surveillance, vector control, and community-based disease prevention) that have been implemented in these countries could not be categorized as cost-effective interventions.[8] A national surveillance system, which was conducted to determine the incidence rates in the context of prevention efforts, could not significantly reduce the number of dengue infections.[9] Nevertheless, controlling the vector of mosquitoes or larvae remains ineffective,[10] which might be caused by the lack of support from the community in comprehensive prevention strategies.[11]

Even though several prevention strategies have been implemented in Southeast Asian countries, most countries in this region are still facing a continuous rise in the number of dengue cases.[12,13] Till now, governments are seeking the most

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effective strategies to control dengue disease transmission.[14] In the context of giving examples on the situation of dengue prevention strategies in other regions, dengue vaccination has been confirmed to be the most cost-effective strategy in reducing the number of dengue cases, specifically in countries with a high number of cases and extensive vaccination coverage.[15] Many studies on dengue vaccine, including the specific vaccine type, mode of action, immune response, and vaccine effectiveness, confirmed promising results in reducing the number of dengue infection cases.[16–18] A preliminary clinical trial study, which took into account the correlation between the vaccine use with its impact on reducing the disease severity and viral transmission, confirmed a significant number of prevented infection cases.[17] A phase III clinical trial study in a group of 9- to 16-year-old volunteers to be analyzed over a period of 25 months indicated that vaccination could reduce dengue fever (all serotypes) in most (2 out of 3) of the volunteers and reduce the length of stay.[18] In particular, a previous study confirmed that dengue vaccination in Southeast Asian countries could save medical expenses of up to $17 and highlighted that vaccination was more cost-effective than vector control strategy.[19] Another study also reported that a vaccination program could reduce 24% of dengue hemorrhagic fever cases.[20] In particular, a previous study in 10 endemic countries confirmed that dengue vaccination could be highly cost-effective and a cost-effective intervention in 3 and 7 countries, respectively, according to their gross domestic product (GDP) per-capita values.[21] Despite the fact that dengue vaccine has been licensed in several Asian countries and has proven its cost-effectiveness, a postlicensing monitoring and evaluation (eg, monitoring and registration systems for immunization, reporting, and long-term safety assessments) is still required to be implemented.[22]

Considering the results from previous studies, it can be summarized that dengue vaccine in many cases has an ability to reduce the transmission of dengue infection in the community.[23] Furthermore, the World Health Organization has confirmed the potential benefits of dengue vaccine to be implemented into the national routine immunization program in countries with high endemicity level as an effort to control dengue infection.[24–26] Nevertheless, before the introduction of dengue vaccine, economic evaluation studies should be conducted to analyze the cost-effectiveness of the vaccination program in a specific country or region, such as in Southeast Asia, which has been highlighted as one of the regions with the highest prevalence of dengue infection in the world.[27–29] The objective of this study was to systematically review all published studies on economic evaluations of dengue vaccination in Southeast Asian countries and to conduct a comprehensive policy recommendation on introducing dengue vaccine in this region.

Methods

Search Strategy

Two of the investigators (W.S. and A.A.S.) searched 3 databases (ProQuest, American Society of Tropical Medicine and Hygiene [ASTMH], and PubMed) for all published studies on economic evaluations of dengue vaccination, including willingness-to-pay (WTP) studies, in Southeast Asian countries. The search used the following keywords: "economic evaluation" OR "cost minimization" OR" "cost-effectiveness" OR "cost utility" OR "cost benefit" OR "willingness-to-pay" AND "dengue" OR "dengue fever" OR "dengue hemorrhagic fever" AND "vaccine" OR "vaccination" OR "immunization."

Table 1 – Criteria for assessing quality of economic evaluations.

Design study	Setting and location
	Type of study
	Study perspective
	Time horizon
	Discount rate
	Choice of model
Information about vaccine	Vaccine efficacy
	Vaccination strategy
	Vaccination coverage
	Duration of vaccine protection
Cost component	Direct and indirect cost
	Cost estimation
	Vaccination cost
	Source of cost
Outcome measurement	Cost-effectiveness criteria
Result	Incremental cost-effectiveness ratio
	Sensitivity analysis

Inclusion and Exclusion Criteria

All complete economic evaluation studies in English that were conducted in any Southeast Asian country according to the Association of Southeast Asian Nations and published in the period 2000 to 2017 were included in this study. Nevertheless, systematic review studies and studies available in abstracts only were excluded. From the selected studies, we extracted both qualitative and quantitative data on design study, information about vaccine, cost component, outcome measurement, and results. The required criteria of each included article are presented in Table 1.

In particular, economic results from the analyses were converted into 2016 international dollars by using purchasing power parities and deflators as measured by the annual growth rate in the country-specific GDP implicit deflator.[30] In case a study did not specify the year of cost, we assumed the year of cost to be the same as the year of publication.

Results

Literature Search

The literature search identified 162, 60, and 33 original articles in PubMed, ProQuest, and ASTMH, respectively. We selected 9, 2, and 2 articles after excluding 153, 58, and 31 articles in PubMed, ProQuest, and ASTMH, respectively, because these were pharmacological and epidemiological studies. From these 13 articles, we further excluded 4 duplicate articles. In total, there were 9 studies for final review, as presented in Figure 1.

Our 9 selected studies were from 7 different countries: Indonesia (n = 3), Singapore (n = 1), Thailand (n = 1), Philippines (n = 1), Vietnam-Thailand (n = 1), Malaysia (n = 1), and Southeast Asia (Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand and Vietnam; n = 1).[19,31–38] The oldest article that appeared from our search was from 2004, focusing on the cost-effectiveness of a pediatric dengue vaccine in 10 countries in Southeast Asia (ie, Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam),[30] and the most recent one was an article from 2017 addressing the cost-effectiveness of dengue vaccine in Malaysia.[38] The most relevant aspects of these studies are presented in Table 2.

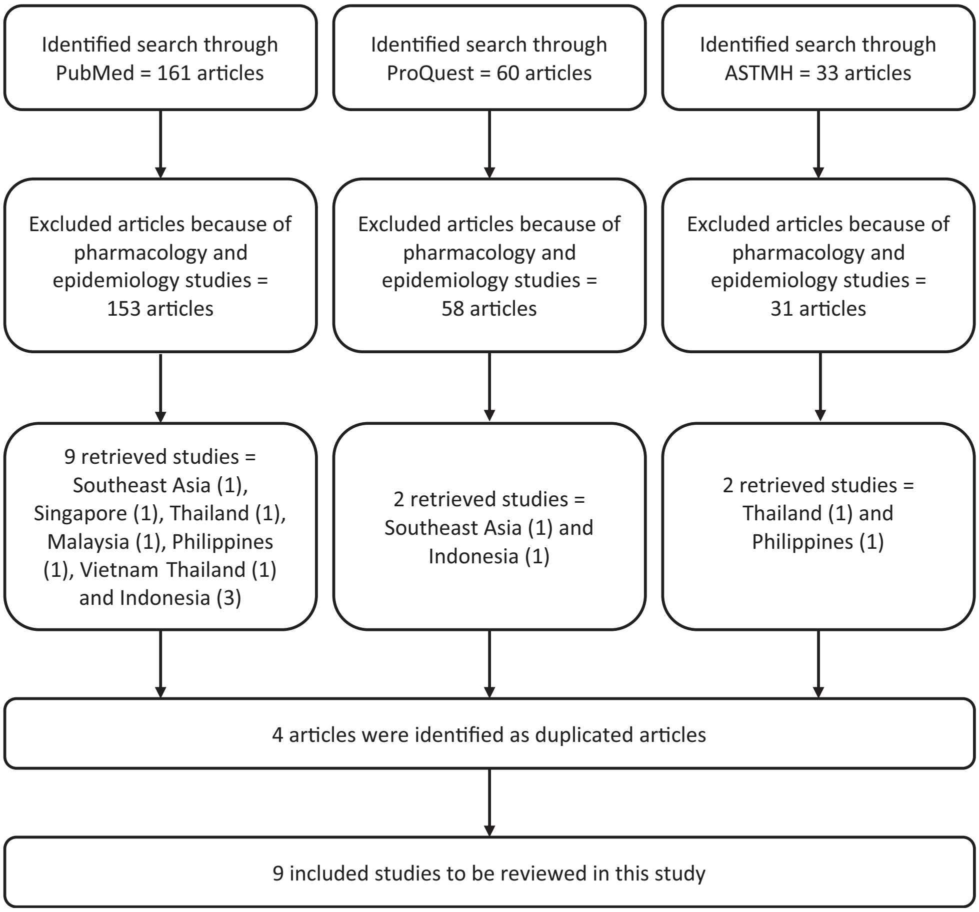

Figure 1 – Literature search from 3 databases. ASTMH indicates American Society of Tropical Medicine and Hygiene.

Assessing Economic Evaluation Studies

Study design and data collection

All selected studies, which have been conducted in specific targeted populations (eg, household, society, and public and private hospitals), provided information on the economic analysis, the acceptance, and the WTP value of the society related to the implementation of dengue vaccination in Southeast Asian countries. In particular, 4 studies applied cost-effectiveness analysis (CEA)[19,31,33,38] and other studies specifically estimated the public acceptance and the WTP value of vaccine.[34–37] The CEA studies provided the incremental cost-effectiveness ratio (ICER) by comparing a scenario of vaccination with that of no vaccination, so that the difference amount of the cost and outcome for vaccination to be implemented could be estimated.[39] Other studies considered the public acceptance and the WTP value of vaccine as the outcome parameters by taking the monetary unit into account.[39]

A study on cost-effectiveness of a pediatric dengue vaccine in 10 countries, which was conducted by Shepard et al,[19] applied a standard approach to estimating cost-effectiveness values by comparing 2 scenarios (with vaccination and without vaccination), evaluating costs and benefits in each scenario, considering cost per disability-adjusted life-year (DALY) saved, and taking vector control programs into account. A study by Carrasco et al[31] specifically calculated direct and indirect costs of hospitalized and ambulatory cases due to dengue in Singapore. Data related to indirect cost on both cases were collected by using the human-capital and friction cost methods. Two studies in Thailand and the Philippines calculated ICERs in the context of cost per DALY averted, compared with no dengue vaccination.[32,33] A study by Shafie et al[38] in 2017 evaluated the cost-effectiveness and impact of dengue vaccination in Malaysia by using a dynamic transmission mathematical model. A multicountry study, which focused on the household WTP for dengue vaccination in Vietnam and Thailand, collected the median value of WTP by assuming that 50% of the population would purchase vaccine.[34] Three previous studies in Indonesia collected parametric estimates of WTP, which are sensitive to the choice of distribution and functional forms of household demand. In particular, demographic information of participants was collected to measure the level of knowledge, attitude, and practice related to dengue vaccine and other prevention strategies.[35–40] More information about study design and data collection of selected studies is presented in Table 3.

Study perspective, time horizon, discount rate, and use of mathematical modeling

The choice of perspective in economic evaluation studies is critical because it determines the cost component that must be included in the study.[39] All the CEA studies applied societal, provider, and healthcare perspectives.[19,31,33,38] Individual perspective was applied only in those studies that focused on the public acceptance and the WTP of vaccine.[31,34–38]

Table 2 – Summary of 9 selected articles on economic evaluations of dengue vaccination in Southeast Asian countries, as published in 2000-2017.

Study	Title	Setting and location	Study objective	Type of study	Data collection and analytical methods
Shepard et al[19]	Cost-effectiveness of a pediatric dengue vaccine	10 countries in Southeast Asia (Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam)	To develop a cost-effectiveness model of dengue vaccination by focusing on children (aged 15 mo) and using societal perspective	Cost-effectiveness analysis	1. Cost-effectiveness values were derived from the cost per DALY saved 2. Vaccination of the cohort was compared with the current situation (no dengue vaccination) by considering existing vector control programs
Carrasco et al[31]	Economic impact of dengue illness and the cost-effectiveness of future vaccination programs in Singapore	Singapore	To estimate the cost of illness due to dengue infection, including economic burden within DALYs calculation, and to investigate the cost-effectiveness of vaccination program	Cost-effectiveness analysis	1. Indirect costs in hospitalized and ambulatory cases were taken into account by using the human-capital and the friction cost methods 2. Disease burden was estimated by considering DALYs
Lee et al[32]	Economic value of dengue vaccine in Thailand	Thailand	To evaluate the potential health and economic value of dengue vaccine administration in ≤1-y-old children	Cost-effectiveness analysis	1. ICER was presented in cost per DALY averted 2. Cost per avoided cases (DHF and DSS) was calculated by dividing the incremental cost with the number of averted cases
Shim[33]	Dengue dynamics and vaccine cost-effectiveness analysis in the Philippines	Philippines	To estimate the cost-effectiveness of dengue vaccination in the Philippines	Cost-effectiveness analysis	1. Incremental health effects were estimated from the differences between the incidence of dengue infection with and without the vaccination program 2. Cost-effectiveness value was presented in cost per QALY gained
Lee et al[34]	A multicountry study of the household WTP for dengue vaccination: household survey in Vietnam and Thailand	Vietnam and Thailand	To investigate the economic benefits of dengue vaccination in high-risk countries	Cost-benefit analysis	1. Median of WTP was calculated by estimating 50% of population would purchase vaccination 2. Parametric estimates of WTP were considered to be sensitive on the choice of distribution and functional form of household demand
Hadisoemarto and Castro[35]	Public acceptance and WTP for a future dengue vaccine: a community-based survey in Bandung, Indonesia	Indonesia	To assess parents' WTP for a dose of dengue vaccine	Cost-benefit analysis	1. Knowledge, attitude, and practice related to dengue, dengue prevention, and vaccination, in general, were measured 2. Public acceptance and WTP for a dengue vaccine were taken into account

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Table 2 – *continued*

Study	Title	Setting and location	Study objective	Type of study	Data collection and analytical methods
					3. Dengue vaccine acceptance was correlated with several independent variables
Harapan et al[36]	WTP for a dengue vaccine and its associated determinants in Indonesia: a community-based, cross-sectional survey in Aceh	Indonesia	To assess WTP for a dengue vaccine among community members and to investigate its correlation with explanatory variables	Cost-benefit analysis	1. A cross-sectional survey in community was applied in this study 2. A questionnaire was developed to measure participants' WTP for a dengue vaccine and to collect information on their demographic background, economic status, history of episodes of DF, knowledge, attitude, and practice regarding dengue, and attitude toward vaccination practice
Harapan et al[37]	Dengue vaccine acceptance and associated factors in Indonesia: a community-based cross-sectional survey in Aceh	Indonesia	To explore the acceptance of dengue vaccine and its correlation with explanatory variables among healthy inhabitants	Cost-benefit analysis	A response variable of dengue vaccine acceptance and a range of explanatory variables (socioeconomic status; knowledge, attitude, and practice; attitudes toward vaccination practice; history of dengue; and other demographic data) were covered in the questionnaires
Shafie et al[38]	The potential cost-effectiveness of different dengue vaccination programs in Malaysia: a value-based pricing assessment using dynamic transmission mathematical modeling	Malaysia	To evaluate the cost-effectiveness and impact of dengue vaccination in Malaysia from both provider and societal perspectives by using a dynamic transmission mathematical model	Cost-effectiveness analysis	1. Malaysian-specific data, evidence from the latest phase III studies, a collection data of long-term safety, and efficacy were collected 2. Age-structured deterministic compartment, vector-host, and serotype-specific deterministic compartment models were built to identify the optimal age of vaccination and routine vaccination strategies and/or mass catch-up vaccination strategies 3. A value-based pricing was applied as the cost-effective threshold price instead of ICER

DALY indicates disability-adjusted life-year; DF, dengue fever; DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life-year; WTP, willingness to pay.

Table 3 – Methodological characteristics of 9 selected articles on economic evaluations of dengue vaccination in Southeast Asian countries, as published in 2001-2017.

Study	Study perspective	Comparison	Time horizon	Discount rate	Choice of model	Parameters in the sensitivity analysis
Shepard et al[19]	Societal	Comparing vaccination with no vaccination and vector control program	66 y	15% (commercial sector) and 6% (public sector)	NR	Costs per dose that was based on the lowest and highest price of HBV vaccine in developing countries; use of other vaccines; degree of illness, which was based on alternative value of Gubler and Meltzer; and value of DALYs
Carrasco et al[31]	Individual	Comparing vaccination with no vaccination and vector control program	75 y	18%	NR	Symptomatic level in each age group; duration of symptoms of DHF; defect weight of DF cases; proportion of dengue cases; total estimated cost for hospital cases; hospitalization cost per day; length of stay in hospital; and currency fluctuations
Lee et al[32]	Societal	Comparing vaccination with no vaccination	1 y	3%	Markov simulation model	Vaccine costs; vaccine efficacy; risk of infection; and specific threshold value for each country
Shim[33]	Healthcare and societal	Comparing the use of vaccine (continuously on 9-y-old and 1-y-old catch-up with target of children between 9 and 15 y old) with no vaccination	20 y	3%	Mathematical model of dengue transmission and vaccination	Symptoms; disease stage; type of treatment; age-dependent vaccine efficacy; and loss of immunity
Lee et al[34]	Individual	NR	NR	NR	NR	NR
Hadisoemarto and Castro[35]	Individual	NR	NR	NR	NR	NR
Harapan et al[36]	Individual	NR	NR	NR	NR	NR
Harapan et al[37]	Individual	NR	NR	NR	NR	NR
Shafie et al[38]	Provider and societal perspectives	Comparing vaccination with no vaccination	5-30 y	0%	Dynamic transmission mathematical modeling	Geographical location; routine population age group; coverage rate; vaccine administration cost; compliance; vaccine wastage; vaccine efficacy; vaccine average duration of protection; underreporting factors; catch-up cohort coverage, catch-up cohort compliance; case-fatality rate; and treatment cost

DALY indicates disability-adjusted life-year; DHF, dengue hemorrhagic fever; HBV, hepatitis B virus; NR, not reported.

Table 4 – Vaccine information.

Study	Vaccination strategy	Duration of vaccine protection	Vaccination coverage	Measurement of effectiveness
Shepard et al[19]	2- or 3-dose vaccine at age of 9, 12, and 18 mo	10 y	70% (lowest coverage level in SEAR, according to the coverage of measles vaccination in several countries)	Vaccination was estimated to be 95% efficacious in providing lifetime protection against each dengue virus serotypes and 0.25% reduction in recipients' annual risk of infection
Carrasco et al[31]	2- and 3-dose vaccine	10 y	75%	Vaccine efficacy was estimated to be 80%, which was relatively low (compared with that in previous studies)
Lee et al[32]	3-dose vaccine	10-30 y	NR	Vaccine efficacy varied in a range of 50%-95%
Shim[33]	2 strategies: A (given to 9-y-old children) and B (given to 9- to 15-y-old children, and 9-y-old children through catch-up and routine program)	NR	NR	Vaccine efficacy was estimated to be 61.1%, 79.2%, and 90.9% against infection among seronegative group of ≥9 y old, seropositive group of ≥9 y old, and against DHF among seropositive group of ≥9 y old, respectively
Lee et al[34]	3-dose	10-30 y	NR	Vaccine efficacy 70% and 95%
Hadisoemarto and Castro[35]	NR	NR	NR	NR
Harapan et al[36]	NR			NR
Harapan et al[37]	NR	NR	NR	NR
Shafie et al[38]	3-dose vaccine at school-based (9-17 y old) and community-based age (18-30 y old); routine and catch-up strategies were taken into account	10 y	20%-80% and 90%-100% (including coverage for catch-up cohort in several strategies)	Vaccine efficacy was estimated to be 55.7%-64.5% according to pooled phase III efficacy data; relative efficacy against infection was estimated in a range of 0%-100% for ambulatory cases

DHF indicates dengue hemorrhagic fever; NR, not reported; SEAR, Southeast Asian Region.

The interpretation of results in economic evaluation studies is associated with the application of time horizon. The calculation of benefit-to-cost ratio in a long-term intervention, such as vaccination, should consider a long time horizon (>1 year). Five selected CEA studies applied 5 different time horizons: 1 year, 20 years, 65 years, 71 years, and 5 to 30 years,[19,31–33,38] whereas other studies did not take this into account. When a study applies a time horizon of more than 1 year, the health effect and cost should be adjusted with a discounting rate. Four selected CEA studies applied 4 specific discount rates: 3%, 6%, 15%, and 18%.[19,31–33,38] Other studies did not apply a discount rate (see Table 3).

From all the selected studies, only 3 studies took mathematical modeling into account.[32,33,38] A study by Lee et al[32] developed a decision-analytic Markov simulation model to estimate the cost-effectiveness value of implementing a dengue vaccine to a population of 1-year-olds or younger in Thailand from a societal perspective.[32] In addition, a study in the Philippines by Shim[33] developed an age-structured model of dengue transmission and vaccination by comparing 2 vaccination scenarios entailing routine vaccination programs both with and without catch-up vaccination. Shafie et al[38] applied a dynamic transmission mathematical model to evaluate the cost-effectiveness and impact of dengue vaccination in Malaysia. More detailed information is presented in Table 3.

Sensitivity analysis

Because economic evaluation studies should consider the uncertainty aspect of various used parameters, it seems critical to analyze the impact of these uncertain parameters by conducting a sensitivity analysis. In this study, only 5 selected studies conducted sensitivity analyses by considering various parameters, such as vaccine price, use of other vaccines, dengue diagnoses and symptoms, duration of illness, degree of dengue fever, estimated costs of illness, threshold values, vaccine mechanisms, and impacts on decreased transmission rates or dengue spread.[19,31–33] Differing with other studies, Shafie et al[38] considered more parameters in the sensitivity analyses, such as geographical

Table 5 – Cost elements.

Study	Cost estimation
Shepard et al[19]	Secondary data from medical expenses in the hospital (outpatient and inpatient cases) and primary data (travel expenses and parents' time lost)
Carrasco et al[31]	Direct medical costs (hospitalized and ambulatory cases), direct nonmedical costs, and disability weights (DF and DHF cases)
Lee et al[32]	Costs of vaccination, clinical visit, hospital visit, vaccine minor side effect, and disability weight
Shim[33]	Direct medical costs for healthcare perspective and direct and indirect costs for societal perspective
Lee et al[34]	Vaccination cost
Hadisoemarto and Castro[35]	Vaccination cost
Harapan et al[36]	Vaccination cost
Harapan et al[37]	Vaccination cost
Shafie et al[38]	Treatment and vaccination costs from provider and societal perspective

DF indicates dengue fever; DHF, dengue hemorrhagic fever.

location, routine population age group, coverage rate, vaccine administration cost, compliance, vaccine wastage, vaccine efficacy, vaccine average duration of protection, underreporting factors, catch-up cohort coverage, catch-up cohort compliance, case-fatality rate, and treatment cost.

Vaccine information

Most of the studies (n = 5) focused on the use of a 3-dose vaccine[19,31–34] and 2 of them made a further comparison between the use of 3-dose and 2-dose vaccines.[37,39] Targeted age groups varied from the ages of 6, 12, and 18 months to younger than 9, 9, and older than 9 years.[19,31–34,38] The protective duration of vaccine was estimated to be 10 years[19,31,38] and 10 to 30 years,[32,33] whereas the coverage of vaccination was estimated to be 20% to 80%, 70%, 75%, and 90% to 100%.[19,31,38] Regarding vaccine efficacy, several studies estimated the values to be 50%, 55.7% to 64.5%, 70%, 80%, and 95%.[19,32,34,38] Only 1 study specifically estimated the vaccine efficacy on the basis of age: younger than 9 years (61.6%), 9 years (79.2%), and older than 9 years (90.9%).[33] All information about vaccine is presented in Table 4.

Cost estimation

Costs or opportunity costs are defined as the value of lost opportunities as a result of resource use in an activity.[39] In economic evaluation studies, cost appears to be an important aspect to be estimated because of its limited resources in many countries, including Southeast Asian countries. All studies estimated the vaccination cost.[19,31–38] Four studies calculated direct and indirect costs because they applied a societal perspective.[19,31–33,38] In particular, 2 studies took disability weights into account[32,33] and only 1 study considered the cost of minor side effects due to vaccination (see Table 5).[32]

Primary results

All studies considered vaccine price and administration cost to estimate total vaccination cost. Shepard et al[19] applied vaccine prices of $0.50 and $10.00 for the public and private sectors, respectively. Carrasco et al[31] considered vaccine prices of $58.90 (3 doses with 10 years of immunity) and $319.00 (2 long-lived immune doses).[31] A range of $0.12 to $65.70 (total for 3 doses) was applied in Thailand.[32] Lee et al[34] considered vaccine prices at a range of $0.0004 to $0.04 and $0.16 to $39.34 in Vietnam and Thailand, respectively.[34] A WTP study in Indonesia applied vaccine prices of $0.0002 to $0.004.[35,36] Administration cost varied from $0.50 to $6.00 (see Table 6).[19]

Shepard et al[19] confirmed that the incremental cost of vaccinating 1 child against dengue would be $4.85/DALY and $39.10/DALY in the public and private sectors, respectively.[19] In particular, a study in Singapore mentioned that the thresholds for vaccination to be cost-effective in Singapore would range from $105.70 to $546.30 per dose.[31] A study in Thailand showed that vaccination would be a highly cost-effective intervention (ICER < 4289) for all scenarios under certain conditions, such as a point of vaccine price at $4.93, a dominated vaccine efficacy of at least 75%, and an administration cost of a 3-dose vaccine at $0.12 or less.[32] A study in the Philippines confirmed that dengue vaccination would be cost-effective at a WTP value of $0.15 per quality-adjusted life-year (QALY) in 69% of the model iterations. This likelihood of cost-effectiveness would increase up to 74% within an acceptability threshold of $0.46/QALY.[33] Lee et al[34] highlighted that the WTP values of vaccine were $0.004 ($0.002 per dose) and $5.56 ($1.85 per dose) in Vietnam and Thailand, respectively.[34] Hadisoemarto and Castro[35] observed that distribution of maximum WTP in Indonesia was achieved when 37.2% of participants expressed their WTP to be below $0.0003. Another study by Harapan et al[36] reported that the mean and median values of WTP on dengue vaccine were $0.001 (95% confidence interval [CI] 3.86-4.23) and $0.001 (95% CI 3.74-4.23), respectively.[36] In addition, Shafie et al[38] confirmed that the best vaccination strategy to be implemented in Malaysia was a routine vaccination program for the age of 13 years, coupled with a catch-up program for the age of 14 to 30 years. The total price per dose values of $50 491 to $95 372 and $23 843 to $44 180 were likely to be cost-effective and highly cost-effective thresholds, respectively, from the provider perspective. The highly cost-effective threshold could even be $21 038 to $24 544 by assuming no underreporting cases in Malaysia (see Table 6).[38]

Discussion

Dengue vaccination is considered to be one of the most cost-effective interventions to prevent the spread of dengue fever in many countries within certain conditions. Nevertheless, more scientific evidences regarding its potential benefits are still required because the number of its economic evaluation studies and the use of vaccine itself are still very limited. Economic evaluation studies that have been conducted in several countries applied a modeling approach to predict the economic impact of vaccination by considering several alternative scenarios.[40,41] Nevertheless, the implementation of modeling studies on the cost-effectiveness of dengue vaccine appears to be crucial before the introduction of dengue vaccine itself in each specific country. Most of the studies in this area applied a Markov simulation model and dynamic transmission model, which took herd immunity into account.[32,38,42] The models differed in assumptions and parameters related to the natural history and ecology of dengue in both humans and mosquitoes.[24]

All included studies targeted a population group that had a relatively high risk of dengue infection in all settings (hospitals, communities, or households), which can be extrapolated into the general population. Several perspectives (eg, societal, individual, provider, payer, and healthcare perspectives) were applied to estimate the cost of illness due to dengue infection. Nevertheless, the determination of perspective was based on the research

Table 6 – Primary result (in 2016 international dollars).

Study	Vaccination cost		Primary result
	Vaccine price	Administration cost	
Shepard et al[19] (in Southeast Asia 2001)	$0.50 and $10 per dose in the public and private sectors, respectively	$4.14	1. Vaccination could reduce 82% of mortality and morbidity burdens of disease by saving 0.34 DALYs/1000 population/y. 2. Incremental cost of vaccination would be 4.85/DALY and 8.28/DALY in the public and private sectors, respectively. 3. Cost-effectiveness ratio for an environmental management approach to dengue prevention and control was estimated to be 3 139/DALY.
Carrasco et al[31] (in Singapore 2010)	$58 for a 3-dose vaccine with a 10-y duration of immunity and $319 for a 2-dose vaccine with a lifetime duration of immunity	NR	1. Total economic costs in 2000-2009 were $1.01 billion and $0.95 billion from the human-capital and friction cost method, respectively. 2. Average DALYs per 100 000 population were estimated to be 8.7 (5th and 95th percentiles of 8 and 10) and 14 (5th and 95th percentiles of 13 and 16) when using constant symptomatic rates and age-dependent symptomatic rates, respectively. 3. Cost-effectiveness values ranged from $77.90 per dose (a 3-dose vaccine within a 10-y immunity) to $235.86 per dose (a 2-dose vaccine within a lifetime immunity), which were lower than the threshold for vaccination program to be cost-effective in Singapore.
Lee et al[32] (in Thailand 2010)	$0.12-$65.7 for total doses in a 3-dose vaccine	NR	1. Vaccination was estimated to be highly cost-effective (ICER < 4289) for all scenarios at a vaccine price of up to $4.93 and would dominate (less costly and more effective) in most scenarios at a vaccine efficacy of at least 75% when the total cost of a 3-dose vaccine was $0.12 or less. 2. Vaccination remained to be cost-effective (4289 > ICER < 12 868) at vaccine prices of $16.40 and $32.87 when the vaccine efficacy and infection incidence were applied to be at least 75% and ≥9%, respectively. 3. Vaccination would not be cost-effective when the incidence rate of infection was <9%, vaccination cost was >$24.65, and vaccine efficacy was <50%.

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Table 6 – *continued*

Study	Vaccination cost		Primary result
	Vaccine price	Administration cost	
			4. Vaccination was even proved to be cost-effective at a vaccine price of $65.73, vaccine efficacy of 95%, and infection risk of 15%.
Shim[33] (in Philippines 2016)	From the healthcare perspective, the threshold for vaccination to be cost-effective was estimated to be $3.90 and $4.00 for strategy A and B, respectively From the societal perspective, the threshold was estimated to be $4.00 and $4.12 for strategy A and B, respectively		From the health and societal perspectives, at WTP values of ≤$153.97 (1× GDP per capita) and $461.9 (3× GDP per capita), the likelihood of vaccination to be cost-effective would be 68%-69% and 74%, respectively.
Lee et al[34] (in Vietnam and Thailand 2012)	Vietnam: $0.0004, $0.002, $0.003, $0.006, and $0.04 Thailand: $0.16, $0.79, $2.38, $4.80, and $39.34	NR	The conservative Turnbull lower bound mean of WTP was calculated to be $1.14 and $1.85 per dose in Vietnam and Thailand, respectively. The parametric median of WTP was calculated to be $0.71 and $1.89 per dose in Vietnam and Thailand, respectively.
Hadisoemarto and Castro[35] (in Indonesia 2010)	$0.0003-$0.003	NR	A total of 94.2% of the participants expressed that they were likely or very likely to vaccinate their children. Distribution of maximum WTP was observed to be 1.8%-37.2%.
Harapan et al[36] (in Indonesia 2015)	$0.70-$14.70	NR	Most participants (87.5%) confirmed that they were willing to pay for a dengue vaccine. The mean and median values of participants' WTP were estimated to be 4.04 (95% CI 3.86-4.23) and 3.97 (95% CI 3.74-4.23), respectively. In particular, approximately 6.4% of participants were unwilling to accept a dengue vaccine even if the vaccine was provided for free, and 6.1% of participants stated that they would accept the vaccine only if it was provided for free.
Harapan et al[37] (in Indonesia 2015)	NR	NR	Approximately 37.6% and 39.7% of participants expressed that they were likely and very likely to vaccinate their children (if they had children), respectively. About 5% of participants were unable to decide. When dichotomizing vaccine acceptance into willing and nonwilling, the acceptance rate would be 77.3%.
Shafie et al[38] (in Malaysia 2013)	Direct vaccination program cost per dose from the societal perspective would be the same as that from the provider perspective ($2510)	Vaccine administration cost per dose would be $2510 and $4179 from provider and societal perspectives	The best vaccination strategy to be implemented in Malaysia was program 1, which considered a routine vaccination program for the age group of 13 y, coupled with

continued on next page

Table 6 – continued

Study	Vaccination cost		Primary result
	Vaccine price	Administration cost	
			a catch-up program for the age group of 14-30 y. The total price per dose values of $50 491-$95 372 and $23 843-$44 180 were likely to be cost-effective and highly cost-effective thresholds, respectively, from the provider perspective. Even, the highly cost-effective threshold could be $21 038-$24 544 by assuming no underreporting cases.

CI indicates confidence interval; DALY, disability-adjusted life-year; GDP, gross domestic product; ICER, incremental cost-effectiveness ratio; NR, not reported; WTP, willingness to pay.

question. In particular, cost-effectiveness values were calculated by comparing the use of vaccine with a situation of no vaccine and other scenarios (eg, vector control) to determine the best scenario or strategy in terms of cost-effectiveness values (cost/DALY or cost/QALY). Regarding the sensitivity analysis, several studies considered the mean burden of disease, total cost, and benefit-cost ratio of the vaccination program, parameters related to the lifetime immune system and duration of dengue symptoms, and discount rate.

Several studies reported the values of vaccine efficacy to be 50%, 70%, 80%, and 95%.[19,31,32,34] A study by Shim[33] specifically mentioned values of vaccine efficacy in different age groups (<9 years: 61.6%; 9 years: 79.2%; and >9 years: 90.9%). These findings, however, are correlated with the fact that vaccination could reduce the mortality, morbidity, and disease burden by 82%.[19] A previous study also reported that a potential dengue vaccine has an ability to reduce the burden of dengue disease in moderate and high endemicity areas,[24] with a rate of efficacy for symptomatic dengue during the first 25 months being 60.3% (95% CI 55.7-64.5).[43] It has also proven to be able to reduce dengue fever in 4 serotypes (by 2/3 of the total volunteers), to prevent dengue cases (from 9 dengue cases), and to reduce the length of stay (8 out of 10 cases of dengue).[18] The efficacy of the vaccine on the specific serotype was reported to be 50.3%, 42.3%, 74.0%, and 77.7% for serotypes 1, 2, 3, and 4, respectively. Furthermore, a 3-dose regimen of CYD-TDV has been confirmed to have a good safety profile in a group of 2- to 11-year-olds with a history of yellow fever vaccination and elicited robust antibody responses that were balanced against the 4 serotypes.[44] The safety and immunogenicity of CYD-TDV have also been demonstrated through independent phase I trials in the United States and Colombia,[45] which confirmed that the safety profile of the CYD-TDV vaccine was similar to that of the placebo, with no marked difference in rates of adverse events.[46] The risk in seronegative vaccine recipients was higher than in seronegative controls, and the risk of severe virologically confirmed dengue in seropositive vaccine recipients was also lower than in seropositive controls.[47] In particular, pain at the injection site, itching, and mild erythema were the most common side effects that could be found in all age groups.[48]

Even though dengue vaccine has the potential to reduce the burden of dengue disease, specifically in moderate and high endemicity areas, it has not yet been included in existing immunization programs in many countries.[24] Because an economic evaluation study is required by the government or insurance companies as a consideration on decision-making process, it should be comprehensively conducted to enable policy makers to make decisions more precisely while allocating resource and budget because in some countries, such as in Southeast Asian countries, dengue vaccination might be heavily subsidized by the government and would have an impact on healthcare policies.[49] The results on CEA of dengue vaccine in this study demonstrated that dengue vaccine can be considered as a cost-effective intervention, which might be developed and implemented in all regions.[50] It has been highlighted that the total cost of using dengue vaccine in Southeast Asia would be approximately $81.7 million annually, which could save $72.7 million compared with conventional treatment. Furthermore, about 1 million cost-effectiveness ratio of dengue vaccination would save 20 000 DALYs. The least costly or unfavorable cost-effectiveness ratio would be $683/DALY and the cost-effectiveness ratio with low vaccine efficacy would be $788 to $960/DALY, which were still lower than GDP per capita in Southeast Asian countries ($1083).[19] In particular, because vaccination is considered to be a long-term investment with high initial costs, the best vaccination strategy should be considered by the stakeholder. A study in Malaysia highlighted the potential of a routine vaccination program for the age of 13 years that was coupled with a catch-up program for the age of 14 to 30 years, which could be considered as the best vaccination strategy in the context of morbidity and mortality averted.[38]

Despite the fact that this study has several limitations, such as the high heterogeneity among the included studies, and its inability to take into account the prevalence rate in the search strategy and the cost of overcoming side effects because of its relatively low cost, policy makers in Southeast Asian countries can consider this study to review evidence from all published studies on economic evaluations of dengue vaccination in Southeast Asian countries so as to conduct a comprehensive policy recommendation on introducing dengue vaccine in this region. Nevertheless, dengue vaccination has been proven to be a cost-effective intervention in several prioritized countries within certain age groups.[26] In a country with a relatively high burden of dengue infection, vaccination appears to be a very promising intervention. Yet, vaccine price is considered to be the most influential parameter in the cost-effectiveness value.[51–53] This situation should be highlighted by policy makers in Southeast Asian countries so that dengue vaccination can be sustainably implemented in this region.

Conclusions

The implementation of dengue vaccination could reduce the burden of disease and economic burden due to dengue infection in Southeast Asian countries. The efficacy of dengue vaccine was estimated to be 50% to 95% for those younger than 9 years, 9 years, and older than 9 years. In particular, several studies reported that dengue vaccination could be categorized as a cost-effective intervention in Southeast Asian countries within certain conditions.

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