REVIEW ARTICLE

Systematic Review Of the Economic Burden of Dengue Infection to the Healthcare in South East Asia (SEA)

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ABSTRACT

Introduction	Dengue remains a public health threat that consumes a significant number of resources for its prevention and control. This systematic review aimed to solidify recent costing evidence in dengue management among South East Asian (SEA) countries.
Methodology	All studies conducted between 2010 and 2020 were retrieved using four international databases i.e. PubMed, Scopus, Web of Science, and Emerald Insight. The review was reported according to PRISMA guidelines. Quality assessments were done independently by two reviewers using a checklist adapted for the cost of illness studies.
Results	We identified 13 original articles representing several SEA countries. Among the common reported costing measure include total cost/ health expenditure; direct medical cost; direct non-medical cost; and indirect cost. The estimated total cost for dengue management varied between countries largely due to the difference in the total incidence of dengue cases. The estimated cost spent on dengue per capita GDP ranges from less than 0.001% to 0.1%, depending on the recorded number of dengue cases of the year. The majority of the articles focused on the economic burden from the perspective of treatment such as hospitalization and ambulatory care.
Conclusion	In a nutshell, the economic burden of managing dengue infection is costly and the evidence suggests a steady increase in health expenditure with the growing number of dengue cases.
Keywords	Dengue; Economic Burden; Cost of Illness; Cost of Program; Financing

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INTRODUCTION

Dengue is an arthropod borne disease caused by dengue virus (DENV). The primary vector of transmission is the female mosquito *Aedes sp.* This vector is very competent in transmitting the virus due to high adaptability and resilient characteristic to sustain survival.[1,2]

Its impact on public health is imminent especially to those living in tropical and sub- tropical countries. The World Health Organization (WHO) has estimated that around 390 million dengue infection occurred per year and almost a third manifested clinically.[3] Nevertheless, the illness could lead to a significant amount of mortality.

Treatment option for dengue fever remains symptomatic and supportive while admission may be indicated in patients with warning sign. In some country, regular out-patient follow-up is done to ensure close monitoring of the symptoms to prevent from rapid deterioration especially during critical phase.[4]

Apart from that, the absence of safe vaccine[5] limit the prevention activity of dengue fever to vector control program. Among the strategies highlighted for vector prevention are the use of integrated vector management (IVM) which emphasize the need for source reduction through eliminating container habitats that are favorable for oviposition as well as rational use of chemoprevention.[6]

Due to the steady increase in number of dengue infection in the South East Asia (SEA) region, the countries will inevitably face the economic burden to fund its healthcare. While some health systems channel all the financial resources to management of dengue cases, others have to make a significant allocation for the prevention and control activities. Therefore, the undertaken study was aimed at understanding the current state of the art of the SEA countries' financial distribution in dengue fever management. Furthermore, the systematic review is hoped to be able to elucidate the economic burden revolves around both cost of illness and also cost of control program. As such, the knowledge gathered can serve as useful evidence for decision-makers to update or design policies more effectively.

Overview of Health Economic Burden (Evaluation)

To assess economic burden, it is necessary to identify the measurement costs related to the illness, treatment or program under evaluation. Among the common costing components mentioned in literatures are direct, indirect, intangible, capital, recurrent and per diem costs[7–9]. Direct costs are directly representing the resources used to manage the illness. It can be regarded as the primary cost of healthcare programs that often include expenditure for medical care or treatment of the disease. Further breakdown of direct costs are direct medical cost (usually health service costs such as hospitalizations, outpatient follow-ups, medications) and direct non-medical costs (costs incurred by patients or any of the carer such as travel and meal expenses during the treatment).

METHODS

A comprehensive systematic search of the literature regarding economic burden of dengue in South East Asia was conducted between October to December 2020 following the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) flow chart.[10] The guiding questions of this systematic review were: 1) What is the cost of managing dengue disease and the vector control program? and 2) What is the cost per capita GDP spent on dengue, based on the costing study?

Data Sources and Search Strategy

The search strategy was conducted using four major English databases that include PubMed, Scopus, Web of Science (WOS) and Emerald Insight to explore and identify potentially relevant studies that reported cost evaluation and economic burden of dengue to the healthcare among SEA countries, between 1st January 2010 and 1st October 2020. Only original research articles in English and Malay from peer-reviewed publications were included. Once the available studies were identified from these databases, screening process and cross-checked were conducted by reading the titles and abstracts that was performed by the MAIAZ, SAMH, and AFNAH.

Search Terms

The search terms covered both the title and the abstract text. The keywords that were used:

"economic burden" OR "cost*"
AND
"dengue" [mh]
AND
"healthcare"[mh] OR "hospital"[mh] OR "clinic"[mh]

Using the free reference manager software Mendeley, the articles were retrieved and sorted conveniently. The tool also allows for the detection of any duplicates and organizes the references with ease, thus allowing for time optimization. All the studies that went through the screening phase had their full text recovered.

Inclusion and Exclusion Criteria

The articles were included if the original research findings related to any type of costs (i.e. direct, indirect or intangible) for dengue management or dengue vector control in SEA region following the Population, Intervention, Comparison, Outcome, Study (PICOS) type approach for systematic reviews. Population considered were all the people

diagnosed with dengue fever in SEA; the contexts of Interest/Intervention were hospitals, primary healthcare clinics, district health offices, state health offices, and federal ministries of health; the comprised Outcomes such as direct, indirect, and intangible costs from the healthcare's (provider) perspective, for example, hospital cost, treatment cost, human resources, and public health measures; and the relevant Study designs such as observational (cross-sectional or surveys) and modelling studies. Article will be excluded if it is not written in English language and focusing on other vector borne diseases such as malaria and filariasis. Comparison is not required in this review.

Data Extraction Tool

MRR and SNMA independently assessed the suitability of the full texts following the inclusion and exclusion criteria. Articles that reported outcome on cost or economic burden for dengue management and/or dengue vector program using both quantitative and qualitative methods were included for data extraction related to costs. The extracted information was tabulated in an Excel spreadsheet that was developed for summarisation. The data was divided into 3 sections, according to the types of information provided by the studies:

- Section A-General information about selected studies.
- Section B-Information on study design, population included, and the study methodology.
- Section C-Result from the study perspective including costing or economic burden.

Estimating Economic Burden And Cost Per Capita GDP For Comparison

The cost or economic burden was evaluated through the results in monetary amounts associated with the disease management and the dengue vector control program. The monetary values reported in all of the studies were in US dollar (USD) currency. However, to have a meaningful interpretation, the monetary value of each result was inflated as of 16th January 2021 through this currency converter website (http://fxtop.com/en/inflation).

Next, cost per capita gross domestic product (GDP) allowed for direct comparison between countries. It depicts how much the country spend its resources on dengue. This was calculated by first measuring the per capita cost of dengue by using the formula of: total overall expenditure (highest value) divided by total number of populations of the particular country. The population figures of SEA countries were then obtained from world population website: (https://www.worldometers.info/world-population/south-eastern-asia-population/).

Subsequently, the products (above) were divided by SEA countries specific GDP, obtained from world bank group website: (https://data.worldbank.org/indicator/NY.GDP.PCAP.CD?locations=Z4-8S-Z7).

Quality Assessment Tool

The assessment of quality for economic evaluation study was done using a checklist developed by Drummond et al. [11] that consists of 10 items, and has been adapted for use by previous studies. [9,12] Each of the items was assign with equal weight and the final score being the sum of the ten individual items. The process was done by MAIAZ and AFNAH for each of the articles included.

RESULT

The systematic review search of healthcare costs of dengue infection, began in October 2020, in the Pubmed, Web of Science (WOS), SCOPUS, and Emerald Insight found 658 references. A total of 565 articles remained after duplicates were removed. A number of 514 articles were excluded based on title and abstract screened. The remaining 51 articles were thoroughly assessed for full text review with the application of inclusion and exclusion criteria, thus leaving only with 13 articles for synthesis. The flow diagram is shown in Figure 1.

The 13 studies were published as of December 2020, of which three studies (23%) were published in 2017, two studies (15%) were published in 2010 and 2015, as shown in Table 1. Only one study (7%) analysed only the cost of the vector control program, nine studies (69%) only cost of illness, and three studies (23%) analysed both costs of vector control program and illness. Seven studies (54%) in the review include a sensitivity analysis in their measurement, of which two (15%) of them used Monte Carlo analysis tool.

Nine studies (69%) reported receiving financial support, of which five (38%) obtained the financial contribution from the Pharmaceutical Industry. Only one study (7%) made an explicit claimed of no financial support, while the remains did not mention in their articles. Apart from that, seven studies (54%) declared no conflict of interest by the author, five studies (39%) did not mention about it in the manuscript, while one study (7%) admitted having potential conflict of interest of the work done.

The duration of costing data used in the studies varied marginally. Seven studies (54%) utilised longer duration of costing data sample to allow for average and stable estimate of the cost. The range of data span between 3 years to 10 years of duration. The other studies optimised the data collected within one year period as shown in Table 2.

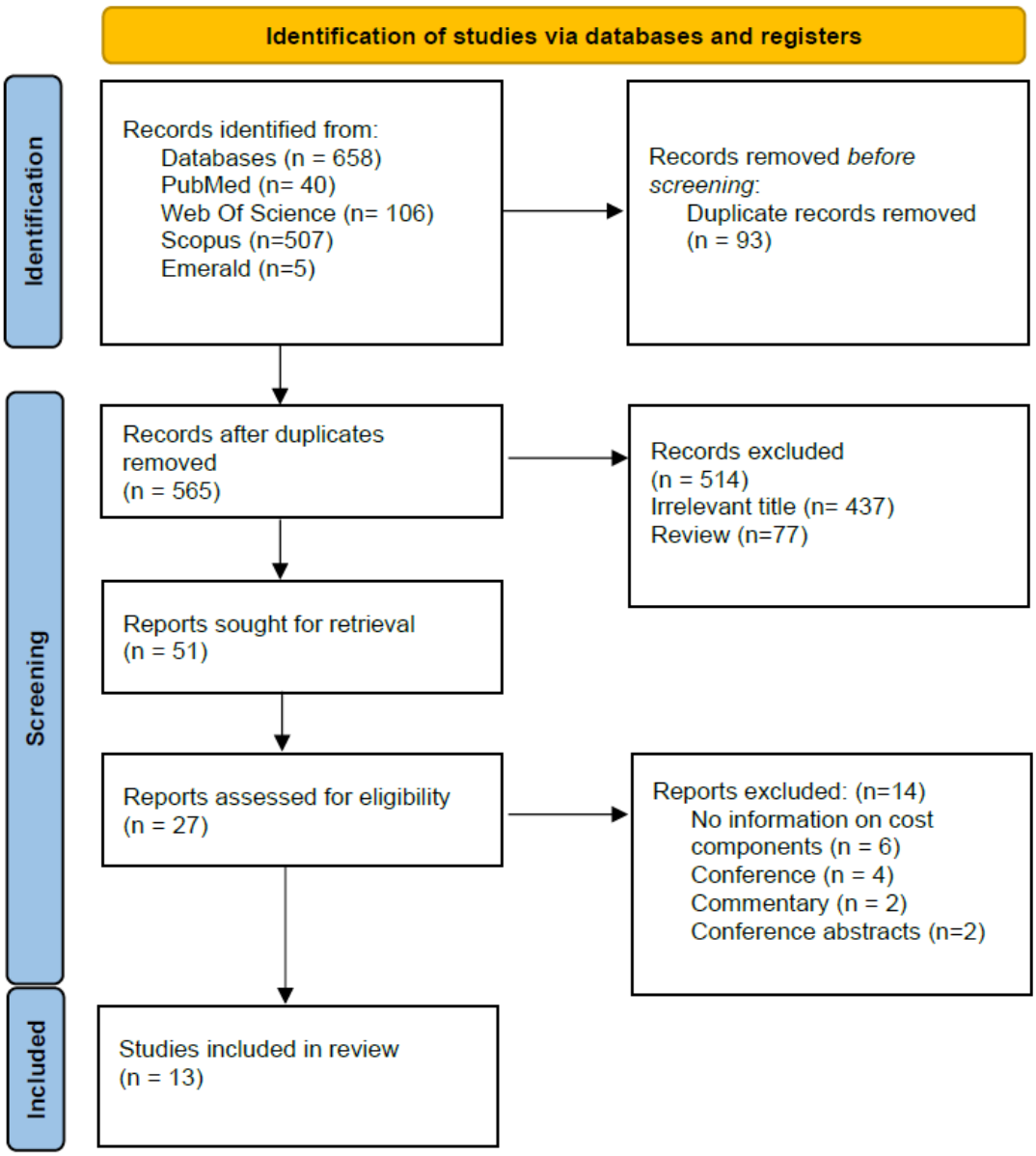

Figure 1 Flowchart of the selection of the studies included in the systematic review.

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Table 1 Characteristic of the Included Articles

Bil	Author & Year of Publication	Cost Analysis Cost of illness/ program	Sensitivity Analysis	Source of funding	Conflict of interest
1.	Beaute & Vong, 2010	Cost of Illness Cost of Program	Yes	Not mentioned	None
2.	Lee Han et al. 2010	Cost of Illness Cost of Program	Yes - Monte Carlo	Grant to the Regents of the University of California from the Foundation for the National Institutes of Health through the Grand Challenges in Global Health initiative.	Not mentioned
3.	Carrasco et al. 2011	Cost of Illness Cost of Program	Yes	National University of Singapore The ARDENT and EDEN projects were funded by the National Medical Research Council Translational Clinical Research STOP-Dengue grant	None
4.	Shepard et al. 2012	Cost of Illness	Yes	Sanofi Pasteur to Brandeis University.	Not mentioned
5.	Packierisamy et al. 2015	Cost of program	No	Sanofi Pasteur to Brandeis University. part of the STeMM Program supported by the University of Malaya/Ministry of Higher Education (UM/MOHE) High Impact Research Grant	Not mentioned
6.	Edillo et al. 2015	Cost of Illness	No	Sanofi Pasteur, Inc. to Brandeis University	None
7.	Onuh et al. 2016	Cost of Illness	No	De La Salle University-Dasmarinas through its	None

				University Research office.	
8.	Vo et al. 2017	Cost of Illness	No	Not mentioned	Not mentioned
9.	Pham et al. 2017	Cost of Illness	Yes	Not mentioned	None
10.	Tran et al. 2018	Cost of Illness	No	No	None
11.	Nadjib et al. 2019	Cost of Illness	Yes	Sanofi Pasteur	Yes
12.	Wilastonegoro et al. 2020	Cost of Illness	No	Bill & Melinda Gates Foundation	Not mentioned
13.	Donald S. Shepard et al. 2013	Cost of Illness	Yes - Monte Carlo	Sanofi Pasteur to Brandeis University.	None

Eleven studies (85%) measured cost of dengue infection in a specific country, while the other two (15%) studies attempted to compare the cost with several countries. Among the single population study, three (23%) of the articles studied the population of Vietnam, two articles (15%) each for Malaysia, Indonesia, and Philippines population, and one article (7%) each for Cambodia and Singapore population.

The method for collecting data on cost consisted of seven studies (54%) using gross-costing method and six studies (46%) used micro-costing. On the other hand, the costing component that were included in the economic evaluation were based on direct and indirect cost, of which nine studies (69%) measuring both costs. Only two studies (15%) explored the type of fund for healthcare treatment of the dengue patients.

Furthermore, the use of epidemiological sources for costing measurement were varied. Four studies (31%) utilised sampling the proportion of dengue cases to infer the cost of treating dengue, and three studies (23%) each utilising either actual number of reported dengue cases in the population, average or an estimate of dengue cases based on series of historical data or using burden of disease estimate such as disability adjusted life years (DALYs) as shown in Table 3.

Table 2 Description of Included Articles

Author & Year of Publication	Study Population	Cost component			Data Period	Method of Collecting Cost Data
		Direct Medical Cost[a]	Direct Non-Medical Cost[b]	Direct Control Cost[c] / Indirect Cost[d]		
Beaute & Vong, 2010	Cambodia	✓		✓	2006-2008	Micro costing
Lee Han et al. 2010	Malaysia Thailand	✓		✓ ✓	Malaysia: 2002-2007 Thailand: 2000-2005	Gross costing
Carrasco et al. 2011	Singapore	✓		✓ ✓	2000 - 2009	Gross costing
Shepard et al. 2012	Malaysia	✓		✓	2009	Gross costing
Packierisamy et al. 2015	Malaysia			✓	2010	Micro costing
Edillo et al. 2015	Philippines	✓		✓	2008-2012	Gross costing
Onuh et al. 2016	Philippines	✓		✓	2009-2014	Gross costing
Vo et al. 2017	Vietnam	✓			2013-2015	Micro costing
Pham et al. 2017	Vietnam	✓	✓	✓	2015-2016	Micro costing
Tran et al. 2018	Vietnam	✓	✓	✓	2017	Micro costing
Nadjib et al. 2019	Indonesia	✓	✓	✓	2014-2015	Micro costing
Wilastonegoro et al. 2020	Indonesia	✓	✓	✓	2018	Gross costing
Donald S. Shepard et al. 2013	Cambodia Vietnam Malaysia Thailand Singapore	✓	✓	✓	2001-2010	Gross costing

[a] Direct medical cost includes costs that directly attributable to patient care such as hospitalizations, medications and services

[b] Direct non-medical cost includes all costs not directly related to medical services such as transportation, meals and informal care

[c] Direct control cost includes all costs directly attributable to vector control such as inspection, enforcement & fumigation, and household insecticides

[d] Indirect cost includes reduction of work productivity, reduction of household services, loss of schooling, and increased need for caregivers

Table 3 Economic Burden and Costing Analysis of Included Study

Author & Year of Publication (Country)	Total / Aggregated Cost (Converted to 2021)	Unit Cost (Converted to 2021)	Cost per GDP (Converted to 2021)	Epid data/ sources	Total population 2020	Country GDP	Payment Coverage
Beaute & Vong, 2010 (Cambodia)	Total Cost 2006 - USD 7,149,872 2007 - USD 17,876,928* 2008 - USD 4,122,219 Direct Cost 2006 - 4,258,854 2007 - 7,969,737 2008 - 4,122,219 Vector Control Cost 2006 - 619,457 2007 - 619,457 2008 - 619,457	Direct Medical Cost - Public Hospital = USD 83.01 - Private Clinic = USD 24.78 - Health Centre = USD 40.88 - Pharmacy = USD 6.19 Direct Control Cost - USD 619,457	USD 1.07 (0.07%)	DALYs (estimated) 2006 - 5,603 2007 - 16,330 2008 - 3,397	16,718,965	1,643.1	Public - 50% User fees - 30% in public services & 100% in private Others - 20%
Lee Han et al. 2010 (Malaysia & Thailand)	N/A	Total Medical Cost per case <u>Malaysia</u> - Hospitalised - USD 1,565 - Ambulatory - USD 217 <u>Thailand</u> - Hospitalised - USD 258.5 - Ambulatory - USD 75.2 <u>Malaysia</u> Direct Medical Cost per case - Hospitalised - USD 1,369 - Ambulatory - USD 352 Indirect Medical Cost per case - Hospitalised - USD 197 - Ambulatory - USD 173	M = USD 2.77 (0.02%) T = USD 0.67 (0.009%)	Reported dengue cases Malaysia 2002 - 32,767 2003 - 31,545 2004 - 33,895 2005 - 39.654 2006 - 38,556 2007 - 50,341	(M) 32,365,999 (T) 69,799,978	(M) 11,414.2 (T) 7,806.7	N/A

		Thailand Direct Medical Cost per case - Hospitalised – N/A - Ambulatory – N/A Indirect Medical Cost per case - Hospitalised – N/A - Ambulatory – N/A Aedes Control Malaysia - USD 31.62 Thailand – USD 33.11 R&D Malaysia - 0.80 Thailand – 0.76		Thailand 2000 - 18,617 2001 - 139,327 2002 - 114,800 2003 - 62,767 2004 - 38,367 2005 - 34,291			
Carrasco et al. 2011 (Singapore)	Total cost ranges from: USD 76,050,161 to USD 190,125,401. Range 42%-59% of the cost was for control program	N/A	USD 32.5 (0.05%)	DALYs	5,850,342	65,233.3	N/A
Shepard et al. 2012 (Malaysia)	Total Annually USD 69.17m Direct Cost - Hospitalised - USD 19.04m - Ambulatory - USD 3.82m Private - 45.1% (USD 31.17m) Public - 54.9% (USD 37.99m)	Average cost per bed-day - USD 271.52 Average out-patient visit - USD 51.98	USD 2.51 (0.03%)	Derivative for dengue cases using Expansion Factor (Delphi method) = 157,140 cases both private & public in 2009	32,365,999	11,414.2	N/A

Packierisamy et al. 2015 (Malaysia)	Total - USD 88.59m Federal level -USD 2.07m State level - USD 4.82m District level - USD 81.69m → Inspection of premise USD 21.11m → entomological surveillance USD 6.51m → Fogging USD 26.9m → Larviciding 15.69m → Health education USD 11.46m	Total - USD 1,918 Federal level - USD 44.88 State level - USD 104.45 District level - USD 1,769.38	Total - USD 3.23 (0.03%) Federal level - USD 0.07 State level - USD 0.18 District level - USD 2.98	Reported number of cases	32,365,999	11,414.2	N/A
Edillo et al. 2015 (Philippines)	Total Direct Medical Cost - Hospitalised : USD 351,874,410 - Ambulatory : USD 41,152,519 Public Direct Medical Cost - Hospitalised : USD 131,958,819 - Ambulatory : USD 14,643,497 Private Direct Medical Cost - Hospitalised : USD 224,532,079 - Ambulatory : USD 26,509,023	Total Direct Medical Cost - Hospitalised : USD 652.12 - Ambulatory : USD 154.28 Public Direct Medical Cost - Hospitalised : USD 447.61 - Ambulatory : USD 101.79 Private Direct Medical Cost - Hospitalised : USD 891.51 - Ambulatory : USD 215.72	USD 3.59 (0.1%)	Average annual number of dengue cases for the years 2008–2012	109,581,078	3,485.1	N/A

Onuh et al. 2016 (Phillipines)	Average hospitalisation cost = USD 2,849,503 Average annual productivity cost loss = USD 17,342	Average annual cost per patient USD 910,169 Average annual productivity cost loss per patient = USD 78.09	USD 0.03 (0.0007%)	DALY - Years of Life Lost	109,581,078	3,485.1	N/A
Vo et al. 2017 (Vietnam)	Total cost (2013-2015) USD 89,486.4* 2013 : USD 23,594.7 2014 : USD 23,955.7 2015 : USD 41,935.99	Total cost per case (2013-2015) USD 53.42 2013 : USD 61.6 2014 : USD 49.4 2015 : USD 52.15	USD 0.001 (0.00003%)	Reported number of cases Total = 1,672 2013 = 383 2014 = 485 2015 = 804	97,338,579	2,715.3	N/A
Pham et al. 2017 (Vietnam)	N/A	Total cost - USD 152.89 Direct medical cost - USD 51.7 Direct Non-medical cost - USD 45.11	USD 0.001 (0.00001%)	Selected 168 number of cases	97,338,579	2,715.3	N/A
Tran et al. 2018 (Vietnam)	N/A	Total Cost In-patient Cost - Direct medical cost: USD 138.7 - Direct Non-medical cost: USD 20.78 - Indirect Cost: USD 92.44 Out-patient Cost - Direct medical cost: USD 28.65 - Direct Non-medical cost: USD 9.23 - Indirect Cost: USD 46.27	USD 0.001 (0.00001%)	Selected 225 number of cases	97,338,579	2,715.3	N/A

Nadjib et al. 2019 (Indonesia)	Total cost (extrapolated) USD 418,340,039.27 →In-patient : USD 389,419,671 → outpatient : USD 28,810,612	Direct medical cost (Based on Province) Yogyakarta a) In-patient - Public : USD 244.64 - Private : USD 366.92 b) Out-patient - Public : USD 8.05 - Private : USD 29.26 - Puskesmas : USD 3.64 Bali a) In-patient - Public : USD 251.95 - Private : USD 377.89 b) Out-patient - Public : USD 22.04 - Private : USD 30.87 - Puskesmas : USD 18.36 Jakarta a) In-patient - Public : USD 446.79 - Private : USD 272.87 b) Out-patient - Public : USD 25.69 - Private : USD 36.00 - Puskesmas : USD 15.95	USD (0.03%)	1.11	Selected 615 number of cases	273,523,615	4,135.6	N/A
Wilastonegoro et al. 2020 (Indonesia)	Estimated National burden - Hospitalised : USD 326.45m - Ambulatory : USD 41.35m	For Non-fatal case - Average : USD 53.99 - Hospitalised: USD 338.68 i) direct medical cost: USD 279.11 - Ambulatory: USD 24.04 i) direct medical cost : USD 15.95 Fatal case average : USD 96.83	USD (0.02%)	0.98	Selected 67 number of cases	273,523,615	4,135.6	Medical scheme - 14% Others subsidies- 10% Household resources -65% Family & Friends contribution- 11%

Donald S. Shepard et al. 2013 (Cambodia, Vietnam, Malaysia, Thailand, Singapore)	In-Patient Direct Medical Cost a) Cambodia : USD 57.52 b) Vietnam : USD 56.28 c) Malaysia : USD 722.23 d) Thailand : USD 625.16 e) Singapore : USD 2,443.21 Out-Patient Direct Medical Cost a) Cambodia : USD 9.31 b) Vietnam : USD 11.82 c) Malaysia : USD 267.49 d) Thailand : USD 156.29 e) Singapore : USD 444.92	N/A	Average data 2001-2010	N/A

* 2007 Cambodia dengue epidemic outbreak had an impact to general health care consumption
m: million

Table 4: Quality assessment of economic evaluations using the Drummond checklist

Study	Research question well defined?	Comprehensive description of alternatives?	Effectiveness of program established?	Important & relevant costs & consequences for each alternative identified?	Costs & consequences measured accurately & appropriately?	Costs & consequences valued credibly?	Costs & consequences adjusted for differential timing?	Incremental analysis of costs & consequences performed?	Allowance made for uncertainty in estimates?	Presentation & discussion of study results include all issues of concern to users?	Score
Beaute & Vong, 2010	✓	✓	✓	×	✓	✓	×	×	×	✓	Average
Lee Han et al. 2010	✓	✓	✓	✓	×	×	✓	×	×	✓	Average
Carrasco et al. 2011	✓	✓	✓	×	×	✓	×	×	✓	✓	Average
Shepard et al. 2012	✓	✓	✓	✓	✓	×	✓	×	✓	✓	Good
Packierisamy et al. 2015	✓	✓	✓	✓	✓	×	×	×	✓	✓	Average
Edillo et al. 2015	✓	✓	✓	✓	×	×	✓	×	×	✓	Average
Onuh et al. 2016	✓	✓	✓	×	×	✓	✓	×	✓	×	Average
Vo et al. 2017	✓	✓	✓	×	✓	×	×	✓	×	✓	Average
Pham et al. 2017	✓	✓	✓	✓	✓	✓	×	×	×	✓	Average
Tran et al. 2018	✓	✓	✓	×	✓	×	×	✓	×	✓	Average
Nadjib et al. 2019	✓	✓	✓	✓	✓	×	×	×	×	✓	Average
Wilastonegoro et al. 2020	✓	✓	✓	✓	✓	×	×	×	×	✓	Average
Donald S. Shepard et al. 2013	✓	✓	✓	✓	✓	✓	×	×	✓	✓	Good

The total cost spent on dengue illness program varied widely between countries. For example, in Cambodia, data showed the total estimates around USD 4 million to USD 17 million. On the other hand, for a developed country such as Singapore, cost ranges between USD 76 million to USD 190 million. On top of that, financial resources spent for dengue vector control activity also varied significantly. Malaysia for example spent in total USD 88.9 million, while Cambodia spent in total less than USD 1 million. Although the total figure and the cost per case seems broad, the estimated cost per capita GDP were marginally the same, as it ranges between less than 0.0001% to 0.1%.

Study Quality

The performance of the studies based on the assessment using Drummond 10-point checklist for economic evaluation showed satisfactory result as shown in **Table 4**. All the studies scored more than 50% 'Yes' from the total items in the checklist. Two studies reported the highest percentage of "Yes" (80%) from the checklist [13,14]. As such, all the authors concluded that the costs of dengue are of great impact on the economy and there is a need for further evaluation studies to benefit the decision makers. Hence, pursuing this systematic review is pertinent.

DISCUSSION

This systematic review is perhaps the first to compile all available reports on economic analyses of dengue management in SEA region that is known to be burdened by the disease, from 2010 to December 2020. Nevertheless, this study contributes to the understanding of economic burden faced by the healthcare in managing the illness as well as the dengue vector control activity. The synthesis analysis allows the depiction of the overall costs of managing dengue infection in several SEA countries, the different costing components evaluated, and epidemiological approach used that influenced the cost estimation.

The ongoing research about dengue infection continue to provide new evidence. Particularly in last few decades where advancement in preventive medical field is taking the limelight.[13,14] The growing interest in disease prevention will definitely give benefit in term of the opportunity cost. Our review captured many recent literatures on cost analysis and economic burden of dengue that can be averted if there is a safe and efficacious dengue vaccine program[13,14] Despite the previous Dengvaxia vaccine (CYD-TDV) from Sanofi and Pasteur to have potential adverse effect on the seronegative group,[15] continuous effort is mandatory to improvise the potential vaccine candidate. Thus, requiring countries to actively monitor the health economics and disease burden as recommended by WHO. [16]

Comparison of Studies' Methodology

Due to the nature of acute communicable disease transmission, the epidemiological data sources that is mostly appropriate for use is disease incidence.[17] The number of dengue incidence used in costing measurement may varies, for example by using the actual total number, average estimation from historical trend, selected number of samples and used of burden of disease estimates such as DALYs. Regardless of modalities used, a justifiable and sound measurement is an important tool to evaluate the intervention strategies done for the particular year and serve as the basis for subsequent planning purposes.[18–20]

Despite the heterogeneity of epidemiological data, the estimated economic burden also dependent on the methodology used. Our reviewed synthesis found different method of costing and the composition of cost items that may differ in the form of micro-costing and gross-costing. The similar situation was also experienced elsewhere, for example in a multiple sclerosis study that the variation in methodological types of costing will limit the comparability among them.[21] This is due to the difference between regulatory requirements, economic context and purpose of costing.[22]

State of Knowledge with Regard to the Cost Impact

Dengue fever is associated with substantial amount of cost including direct medical cost from hospitalisation of the severe and life-threatening cases while continuous monitoring for the remaining cases. [13-15] The latter make up a higher proportion of cases.[14] Regular visit to monitor the condition through blood parameter is very essential to target the critical phase of dengue infection.[23] However, limitation at the local setting including healthcare system differences such as resource constraints and differences in healthcare infrastructure impedes dengue management.[14] Referring to the criteria proposed by Andersson, who attempted to compare expenditure cost, it is of fundamental importance to select countries with similar parameters and health system characteristics. [24] Thailand for instance, is utilising universal health coverage to all its population while Malaysia is opting government subsidies in its public health facilities.[14]

Furthermore, each of the SEA country spent their resources based on the healthcare demand and also the guiding policy that is best suited for their current health needs.[14] This is a component of medical ethics which is distribution justice, that summarise the need for more allocation of resources on the higher burden of illness. For example, as the number of dengue cases increased, the total expenditure of the Vietnamese healthcare on dengue correlates accordingly.[25] Besides direct medical cost of treating the dengue cases, and the control program to prevent the spread or emergence

dengue incidence may need a priority too. For instance, Malaysia distributed the resources accordingly to the respected unit based on the needs for dengue control activities.[26] Similarly in Singapore, they allocated between 42%-59% of the total dengue expenditure on vector control program.[27]

This systematic review has its own strength, primarily due to the electronic databases used for article search. Secondly, the several numbers of countries included in the analysis better view of dengue burden and its economic impact. The countries experiencing the similar tropical and sub-tropical climates and throughout rainfall provide an optimal condition for mosquito to breed. Nevertheless, the impact of climate change resulted in higher temperature will inevitably accelerate the lifecycle of a mosquito. Thus, indirectly increase number of mosquito population in the habitat. Apart from that, the standardisation of currency to the year 2021 tackle the problem of inflation differences. Furthermore, the calculated cost per capita GDP allowed for meaningful comparison of health expenditure on dengue between South East Asia countries. The main limitation of this study was due to the nature of non-standardise epidemiological sources and costing variable by the articles that resulted in heterogeneity of the outcome estimates.

CONCLUSION

Despite variation in the methodology for measuring economic burden between studies, the findings from the systematic review demonstrate that dengue infection still remain a significant public health issue that consumed significant amount of healthcare resources. If additional economic costs taken into account, such as the disruption of health systems due to seasonal clustering of dengue, the long-term effects of dengue, or morbidities linked to dengue infection, the estimated burden of dengue would have been much greater.[3,4,14,23,27] Even without accounting for these changes, these findings imply that it might be economically beneficial to investigate novel strategies for lowering the dengue burden. A strategic multi-stakeholder' collaboration should be implemented to boost financial resources and ultimately produce greater impact in managing dengue cases as well as dengue vector control program.

Competing interest
The authors declared no competing interests.

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