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Review

Systematic review of health economic evaluation studies of dengue vaccines

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ABSTRACT

Objectives: To review the literature on economic evaluation of dengue vaccination to produce evidence to support a local cost-effectiveness study and to subsidize the decision to introduce a dengue vaccine in the Brazilian National Immunization Program. Methods: We systematically searched multiple databases (MEDLINE (via PubMed), EMBASE, SCOPUS, NHS Economic Evaluation Database (NHS EED), HTA Database (via Centre for Reviews and Dissemination – CRD) and LILACS), selecting full HEEs of dengue vaccine. Two independent reviewers screened articles for relevance and extracted the data. The methodology for the quality reporting was assessed using CHEERS checklist. We performed a qualitative narrative synthesis. Results: Thirteen studies conducted in Asian and Latin America countries were reviewed. All studies were favorable to the incorporation of the vaccine. However, the assumptions and values assumed for vaccine efficacy, safety and duration of protection, as well as the choice of the study population and the type of model used in the analyses, associated to an insufficient reporting of the methodological steps, affect the validity of the studies' results. The quality reporting appraisal showed that the majority (8/13) of the studies reported less than 55% of the CHEERS checklists' items. Conclusions: This systematic review shows that the economic evaluation of dengue vaccination did not adhere to key recommended general methods for economic evaluation. The presented cost-effectiveness results should not be transferred to other countries. It is recommended to conduct studies with local epidemiological and cost data, as well as assumptions about vaccination that reflect the results observed in clinical trials.

Contents

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1. Introduction

Dengue is the most important mosquito-borne disease worldwide, with estimated 390 million infections each year [1]. Vector control has proved to be expensive and insufficient to control dengue, pointing out to the need of using multiple strategies, including vaccines [2]. Dengue vaccine development has been a challenge mainly due to the cocirculation of four virus serotypes (DEN 1-4), limited temporary cross-protection among serotypes, and antibody-dependent enhancement disease (ADE), in which preexisting heterotypic antibodies from the first dengue infection cannot neutralize the virus during a secondary infection by a different serotype. Instead, heterotypic antibodies facilitate virus replication, resulting in increased risk of severe disease in a secondary infection. The ideal dengue vaccine must be safe, induce long-term protection to all four serotypes and do not induce ADE [3].

Currently, just one vaccine has been licensed (CYD-TDV, Dengvaxia, produced by Sanofi-Pasteur), which has been demonstrated to confer moderate protection, with higher efficacy to DEN4 (72.4%, 95%CI 58.8–81.7 and 80.9%, 95%CI 70.9–87.7, respectively in Asian and Latin America trials) and lower efficacy to DEN2 (34.7%, 95%CI 10.4–52.3 and 50.2%, 95%CI 31.8–63.6, respectively in Asian and Latin America trials [4,5]. The vaccine has also lower efficacy in children <9 years (44.6%, IC95% 31.6–55%), which justifies the vaccine has been licensed only for persons ≥9 years of age, and different performance according to the vaccinees' serostatus before vaccination, with higher efficacy in persons seropositive to dengue (81.9, 95%CI, 67.2–90%, in those aged ≥9 years) than in those seronegative to dengue (52.5, 95%CI, 5.9–76%, in persons aged ≥9 years) [6]. Longer follow-up studies (3–6 years post-vaccination) demonstrated increased risk of severe dengue among dengue seronegative vaccinees in comparison to seronegative non-vaccinated persons and confirmed protection in dengue seropositive vaccinees [7]. Based on these results, WHO recommended vaccination only in high endemic areas, with pre-vaccination serological screening to assure that only persons with evidence of past dengue infection would be vaccinated [8]. Other vaccines are in development, two of them in phase 3 trials [9,10].

Systematic reviews of health economic evaluation studies have the potential to offer policy makers, clinicians, patients and other decision makers useful information to advise decision making. They can identify the range and quality of available studies, enhance understanding of the conditions that promote effectiveness and efficiency of the intervention under evaluation, and comprehend the impact of the main parameters on the overall result [11].

Endo et al conducted a systematic review including 11 health economic evaluation studies of dengue vaccines, published in English by 2015. None of the included studies used CYD-TDV efficacy data [12]. Thus, it is necessary to update this review, including more recent studies that used the efficacy data based on CYD-TDV phase 3 clinical trials.

The objectives of this systematic review are to summarize the literature on economic evaluation of dengue vaccines to support the decision of the Brazilian National Immunization Program on the introduction of a dengue vaccine, and to inform a local model-based analysis development.

2. Methods

The systematic review was undertaken in accordance with Centre for Reviews and Dissemination – CRD) Guidelines [13] and was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [14].

A protocol was developed prior to the initiation of this review and is available from the authors on request. The protocol was not registered with PROSPERO because this register does not accept methodological reviews that do not contain at least one outcome of direct patient or clinical relevance.

2.1. Eligibility criteria

The following PICOS eligibility criteria were considered to identify relevant studies: Population (all populations); Intervention (all existing or candidate dengue vaccines); Comparators (non-vaccination or other dengue vaccine strategies); Outcomes (cases, hospitalizations, deaths, DALYs, and QALYs); Study design (full economic evaluation studies including cost-effectiveness analysis – CEA, cost-utility analysis – CUA, and cost-benefit analysis – CBA).

2.2. Information sources

The following databases were searched: MEDLINE (1946 till May week 1 2018) via PubMed, last search on 3 May 2018; EMBASE (1974 to latest issue), last search on 3 May 2018; SCOPUS (2004 to latest issue), and NHS Economic Evaluation Database (NHS EED) (1994 to March 2015) and HTA Database (1994 to 31 March 2018), via CRD, last search on 3 May 2018 and LILACS (1992 to latest issue), last search on 3 May 2018. Additionally, the references of included articles were hand-searched to identify any additional studies, and grey literature (conference abstracts, books, dissertations, etc.) was searched through Google Scholar.

2.3. Search strategy

Specific search strategies for each database included descriptors and free terms to increase sensitivity (Annex 1).

2.4. Study selection process

Two researchers (ABS and PCS) with experience in methodological reviews and health economic evaluation worked independently at all stages of article screening and selection. The search results in the various databases were merged with the EndNote reference management software and the duplicate references were removed. The two researchers (ABS e PCS) screened titles and abstracts and excluded not relevant studies. Then, they screened full-text studies. All screening disagreements were discussed, with any outstanding disagreements resolved by an independent third reviewer with experience in vaccines, infection diseases and health economic evaluation (AMCS). Results of the study selection process are reported using a PRISMA flow diagram (Fig. 1).

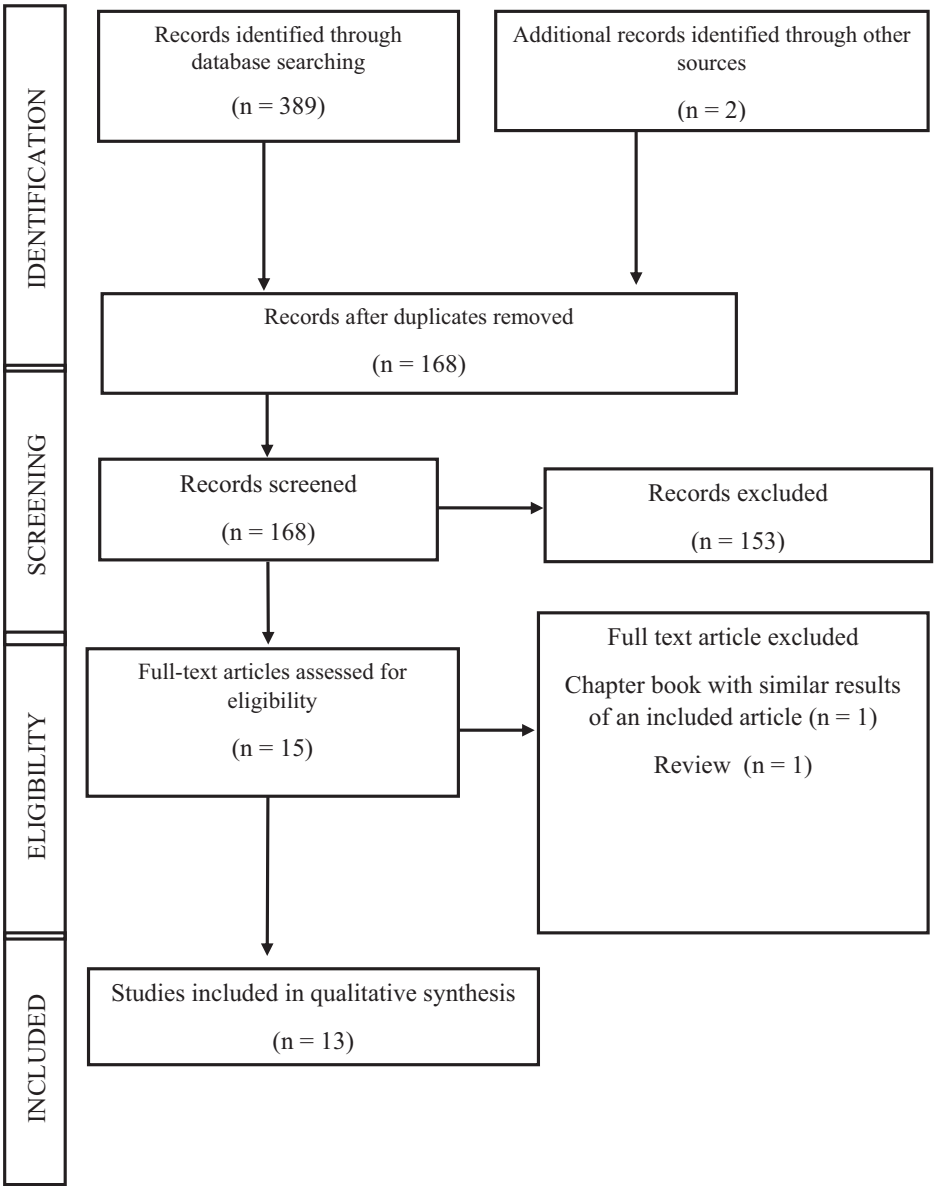

Fig. 1. PRISMA Flow diagram of selection process.

2.5. Data collection process

Two researchers (ABS e PCS) independently performed data extraction and used a beforehand piloted data extraction form, developed in Microsoft Excel 2010 spreadsheet. The following data item were extracted: title, authors and year of publication, local of study, source of funding, authors affiliation, study question, vaccine type, vaccine schedule (doses and interval between doses), target population, vaccine efficacy and source of vaccine efficacy, safety (adverse events), duration of protection, waning immunity, vaccination coverage, vaccine costs (dose, administration fee, logistics, etc.), vaccine wastage, type of economic evaluation study, comparative strategies, perspective, time horizon, decision analysis model (herd protection, vector inclusion), discount, dengue incidence, adjustment for underreporting, proportion of asymptomatic/symptomatic cases, hospitalization and case-fatality rates, currency and year of costs, included costs, summary measure, incremental cost-effectiveness ratio (ICER), sensitivity analyzes, parameters that most impacted the results of the sensitivity analyzes, and the main study conclusions.

2.6. Quality assessment

The quality of reporting of included studies was assessed using the Consolidated Health Economic Evaluation Reporting Standards – CHEERS, checklist [15]. Two researchers (ABS and PCS) applied the checklist to the included studies independently. Disagreements were resolved through discussion or arbitration of a third investigator (AMCS). A quality scoring system was not used due to its lack of validity and reliability. CRD Guidelines do not recommend its use [13].

2.7. Synthesis of results

The principal summary measure was incremental cost-effectiveness ratio. Quantitative synthesis (*meta*-analysis) was not performed. The purpose of this review was not to combine the results of individual studies and generate a pooled summary measure of the individual incremental cost-effectiveness ratios. We chose the strategy of narrative synthesis of the methodological characteristics, which were presented in summary tables.

The summary tables grouped the data extracted in: characteristics of the studies, characteristics of the vaccines studied, methodological characteristics, epidemiological and cost estimates and presentation of results and summary measures.

3. Results

3.1. Study selection

From the initial search, a total of 391 potentially relevant records were identified. After excluding duplicates, 168 records were screened. Of these, 15 full articles were assessed, two were excluded as they did not meet the eligibility criteria. One of them was a book chapter [16] with similar results of an included article and the other one was a review [17]. Thirteen full health economic evaluations were included in the review (Fig. 1).

3.2. Study characteristics

Table 1 summarizes the general characteristics of the health economic evaluation studies included. From the 13 included studies, five were from Asia [18–22] five from Latin America [23–27], three of which were undertaken in Brazil [23,25,26], and three studies considered more than one country from different continents [28–30].

Six studies conducted prior to 2016 evaluated a hypothetical vaccine [18–20,23,24,28] six studies conducted from 2016 evaluated the CYD-TDV [21,22,25–27,29] and the most recent study (2018) evaluated both CYD-TDV and a hypothetical vaccine [30].

Regarding the target population of vaccination, six studies evaluated vaccination strategies including children under 9 years [18,20,23,24,28,30], six studies evaluated the vaccine in the age range for which CYD-TDV is licensed (9 to 45 years) [21,22,25,27,29,30], one study evaluated elderly vaccination [28], and one study did not report the age group evaluated [19]. Two studies evaluated the impact of vaccination both nationwide and in areas within the country with the highest burden of dengue (hotspots) [22,24]. None of the studies considered the current WHO recommended strategy of serological screening and only vaccinate dengue seropositive persons.

Table 2 describes the characteristics of the vaccines evaluated. Six studies considered 3-dose vaccine schedules [20,22–24,26,29], two older studies considered 2-dose schedules [18,28], two studies compared both 2 and 3-dose schedules [19,30]. Three studies [21,25,27] considered the complete schedule without specifying the number of doses.

Vaccination coverage ranged from 30% to 100% and only one study did not report the coverage considered in the base case analysis [21]. Efficacy ranged from 30% to 95%; only one study considered different efficacies for dengue, severe dengue and hospitalization [24]. Five recent studies considered different efficacies according to host serostatus [21,25,27] and three studies differentiated efficacy by dengue virus serotypes [26,29,30].

Concerning safety, only one study [20], included the occurrence of minor adverse events (local pain, swelling, and fever), three did not include adverse events and nine did not report. Five studies considered the presence of ADE induced by the vaccine [21,25,27,29,30]. Only one study included waning immunity [30],

Table 1
General characteristics of the economic evaluations of dengue vaccines reviewed.

Author, year, reference	Country	Vaccine	Target population	Funding
Lee, 2018 [30]	Vietnam, Thailand and Colombia	CYD-TDV and a hypothetical new vaccine	9–29 years (both vaccines); 1–5 years (new vaccine)	The study did not receive any specific funding
Zeng, 2018 [29]	Ten countries: five in Southeast Asia and five in Latin America, where CYD-TDV phase 3 trials were conducted[a]	CYD-TDV	9–17 years	Sanofi Pasteur
Shim, 2017 [27]	Yucatán, Mexico	CYD-TDV	9–45 years	National Research Foundation of Korea (NRF)
Durand, 2017 [26]	Brazil	CYD-TDV	9–25 years	Sanofi Pasteur
Shim, 2017 [25]	Brazil	CYD-TDV	9–45 years	National Research Foundation of Korea (NRF)
Shafie, 2017 [22]	Malaysia	CYD-TDV	9–30 years Nationwide and high transmission areas	Sanofi Aventis Singapore and University Sains Malaysia
Shim, 2016 [21]	Philippines	CYD-TDV	9–15 years	National Research Foundation of Korea (NRF)
Orellano, 2016 [24]	Argentina	Hypothetical	2 years	Comisión Nacional Salud Investiga, Ministry of Health, Argentina
Durham, 2013 [23]	Brazil	Hypothetical	0–40 years	National Institutes of Health
Carrasco, 2011 [19]	Singapore	Hypothetical	Age - NR Nationwide and high transmission areas	National University of Singapore
Lee, 2011[20]	Thailand	Hypothetical	$\leq$ 1 year	National Institute of General Medical Sciences Models of Infectious Disease Agent Study (MIDAS) and the Vaccine Modeling Initiative (VMI), funded by Bill and Melinda Gates Foundation
Shepard, 2010 [28]	Southeast Asia and Panama	Hypothetical	12 months and 15–64 years	In part - Schneider Institutes for Health Policy, Brandeis University, Waltham, MA, USA
Shepard, 2004 [18]	10 countries in Southeast Asia[b]	Hypothetical	15 months	NR

CYD-TDV – the only licensed vaccine, produced by Sanofi-Pasteur (Dengvaxia®); NR – not reported.
[a] Southeast Asia countries: Indonesia, Malaysia, Philippines, Thailand, and Vietnam; Latin America countries: Brazil, Colombia, Honduras, Mexico and Puerto Rico.
[b] Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam.

Table 2
Dengue vaccine characteristics assumed in the economic evaluations reviewed.

Author, year, reference	Vaccine schedule	Vaccine coverage (%)	Vaccine efficacy (%)	Vaccine efficacy according to dengue virus serotypes (%)	Source of vaccine efficacy	Adverse events following immunization	Waning immunity	Duration of protection	Disease/Vaccine Antibody-enhanced disease
Lee, 2018 [30]	3 doses (CYD-TDV); 2 doses (new vaccine)	80 Alternative scenario: 50	New vaccine: 80 (all serotypes)	CYD-TDV: 58.4 DEN1, 47.1 DEN2, 73.6 DEN3, 83.2 DEN4	CYD-TDV phase 3 trial in LA and Asia [6]	NR	Yes (exponential decay)	Efficacy half-life: CYD-TDV: 3 years (seropositive hosts), 1 year (seronegative); New vaccine: 8 years for all	NR
Zeng, 2018 [29]	3 doses	80 (D1) 75 (D2) 70 (D3) Alternative scenario: 50	NR (by age and host serostatus)	NR	CYD-TDV phase 3 trials in Asia [4] and LA [5]	NR	NR	NR	Yes/Yes
Shim, 2017 [27]	Complete course[b]	30	According to host serostatus: 61.6 (seronegative), 79.2 (seropositive)	No	Phase 3 trial in LA and Asia [6]	NR	No	NR	Yes/Yes
Durand, 2017 [26]	3 doses	90 (D1) 67.5 (D2) 45 (D3)	NR (higher efficacy for seropositive persons)	Yes	Phase 3 trial in LA and Asia [6]	NR	NR	2.5 years (D1) 5 years (D2) 10 years (D3)	NR
Shim, 2017 [25]	Complete course[b]	Routine: 70 Catch-up: 50	According to host serostatus: 61.6 (seronegative), 79.2 (seropositive)	No	Phase 3 trial in LA and Asia [4–6,31]	NR	NR	NR	Yes/Yes
Shafie, 2017 [22]	3 doses	Routine: 95; catch-up: 95 (10–17 years); 50 (10–30 years)	55.7 – 64.5	NR	Phase 3 trial in LA and Asia [6]	NR	No	2.5 years (D1) 5 years (D2) 10 years (D3)	Yes/NR
Shim, 2016 [21]	Complete course[b]	NR	According to host serostatus: 61.6 (seronegative), 79.2 (seropositive), 90.9 (DHF)	NR	Phase 3 trial in LA and Asia [6]	NR	No	NR	Yes/Yes
Orellano, 2016 [24]	3 doses	73	General efficacy: 64.7, Severe disease: 95.5,					Hospitalization:80.3	No
Phase 3 trial in LA [5]	No	No	Lifetime	Yes/No					
Durham, 2013 [23]	3 doses	Routine childhood: 80; One-time mass vaccination: 50	General efficacy: 30 and 70	No	Authors assumption based on phase 2 trial [32]	NR	No	NR	No/No

Table 2 (*continued*)

Author, year, reference	Vaccine schedule	Vaccine coverage (%)	Vaccine efficacy (%)	Vaccine efficacy according to dengue virus serotypes (%)	Source of vaccine efficacy	Adverse events following immunization	Waning immunity	Duration of protection	Disease/Vaccine Antibody-enhanced disease
Carrasco, 2011 [19]	2 or 3 doses	75	General efficacy: 80	NR	Previous economic evaluation [18]	NR	NR	Lifetime and 10 years	NR
Lee, 2011 [20]	3 doses	100	General efficacy: 50, 75, 85 and 95	NR	NR	Major and minor AE[a]	NR	NR	Yes/Yes
Shepard, 2010 [28]	2 doses	85	General efficacy: 95	No	Previous economic evaluation [18]	No	NR	Lifetime	NR
Shepard, 2004 [18]	2 doses	85	General efficacy: 95	No	Dengue experts	No	NR	Lifetime (10 years in sensitivity analysis)	NR

NR: Not reported; D1: first vaccine dose; D2: second vaccine dose: D3: third vaccine dose; DHF: dengue hemorrhagic fever; AE: adverse events; LA: Latin America.
[a] Major and minor AE based on yellow fever and Japanese encephalitis vaccine.
[b] The author was not clear regarding the number of doses used in the model.

considering an exponential drop. In studies that reported the assumed duration of protection, it ranged from 2.5 years to 10 years or lifetime [18,19,22,24,26,28,30].

Table 3 presents the main methodological study characteristics. All studies conducted a cost-utility analysis and two of them conduct a cost-utility analysis and cost-effectiveness analysis simultaneously [20,22].

Five studies [21,22,26,27,29] were conducted from the society and health system perspectives, five [18,20,24,28,30] from the society perspective, one [25] from the health system perspective, and two [19,23] did not report the perspective taken. Six older studies [18–20,23,24,28] had a lifetime horizon, based on the life expectancy of each country, the most recent studies [21,22,25–27,29,30] published since 2016, had time horizons ranging from 10 to 30 years. Most studies [21–25,27,28] used a 3% discount rate for costs and benefits.

As for the decision analysis model, eight studies [21–23,25–27, 29,30] (most published from 2016) used dynamic mathematical models of dengue transmission, two studies [20,24] used a Markov model and three [18,19,28] did not report the model used. Nine studies (all mathematical models [21–23,25–27,29,30] and an uninformed model [19]) included herd protection in the evaluations and five studies [22,23,26,29,30] reported including the vector in their mathematical models.

Table 4 describes the epidemiological estimates adopted in the studies. Most studies (12/13) [18–28,30] reported they used local or regional surveillance data or local studies as source of epidemiologic data. Three studies [22,29,30] used data on the control group of CYD-TDV trials in the specific country and three studies [20,25,27] used data from Global Burden of Disease studies.

Seven studies [19,21,22,25–28] used an expansion factor (EF) to adjust data for underreporting in the surveillance system. In three studies [19,22,26], the EF varied according to the type of healthcare (from 1.4 to 3.4, for hospitalized cases, and from 3.2 to 3.79, for outpatient cases). In one study [19], EF also varied according to age group, from 3.8 for the youngest (<24 years) to 50 for the oldest (>55 years). In five of these studies [19,21,22,26,28], the authors justified the EF based on local or regional studies. Two studies [25,27] reported using adjustment for underreporting but did not give details on the value of EF, nor justify it. Nine studies [18–21,23–25,27,28] reported the assumed proportion of symptomatic cases among all infections, which varied from 9% to 45%, most frequently 23–24%.

Regarding the cost estimates, most studies included direct costs related to the vaccination program, hospital and outpatient treatment of the disease, and used local data sources to construct these estimates. (Table 5) One of the studies [26] included the cost of social mobilization and outreach for a new adolescent vaccine. Only one study [20] included the costs of vaccine minor adverse events treatment. The majority (10 of 13) also included indirect costs related to patient and family productivity loss and missed school days. Four studies have included the cost of dengue deaths [21,24–26].

Table 6 presents the summary measures and conclusions of included studies. The price of the vaccine dose ranged from US$0 [30], US$0.50 [18,28] to US$800 [20]. Most studies have estimated a price-per-dose threshold (the maximum cost per fully vaccinated person) for the vaccine to be cost-effective. All studies performed sensitivity analysis (univariate, multivariate or probabilistic). Vaccine price [18,19,21,24,25,27,28], coverage rate [23,25,26,30], DHF risk [18,20,28], incidence of disease [24,29], and under-reporting adjustment [22,26], vaccine effectiveness [23,29], duration of protection [22,26], and discount rate [19,24,26,30] were the parameters that most impacted the results of the sensitivity analyzes.

Only one study [30] has not used the WHO cost-effectiveness threshold (1 to 3 GDP per capita per DALY averted). Regardless of

Table 3
Methodologic characteristics of economic evaluations of dengue vaccines included in this review.

Author, year, reference	Study type[a]	Perspective	Vaccination Strategies	Time horizon	Discount rate	Model	Vector	Herd protection
Lee, 2018 [30]	CUA	Society	Routine vaccination at 9 years (R9y); R9y + catch up 10–18 years; R9y + catch up 10–29 years; Routine (1 year) + catch-up 2–5 years (just for the new vaccine)	30 years	C: 3%	Spatially individual-based dynamic mathematical model developed by Oxford/Exeter group [33]	Yes	Yes
Zeng, 2018 [29]	CUA	Health system and Society	Routine vaccination at 9 years (R9y); R9y + catch up 4 cohorts (9–13 years); R9y + catch up 8 cohorts (9–17 years)	30 years; alternative scenario: 10 years	NR	Age-structured population-based dynamic mathematical model [31]	Yes	Yes
Shim, 2017 [27]	CUA	Health system and Society	Vaccinating persons 9–45 years No Vaccination	20 years	C: 3% B: 3%	Age-structured population-based dynamic mathematical model [21]	No	Yes
Durand, 2017 [26]	CUA	Health system and Society	Routine at 9 years (R9y) + Catch-up: 10–16 years R9y + catch-up: 10–25 years No vaccination	10 years	C: 5% B: 5%	Age-structured population-based dynamic mathematical model [31,34]	Yes	Yes
Shim, 2017 [25]	CUA	Health system	Routine at 9 years + Catch up (10–18 years; 10–25 years; 10–35 years; 10–45 years) No vaccination	10 years	C: 3% B: 3%	Age-structured population-based dynamic mathematical model [21]	No	Yes
Shafie, 2017 [22]	CUA CEA	Health system and Society	1) Routine at 9 years + catchup: 10–17 years, 10–30 years (nationwide and hotspots) 2) Routine at 13 years + catch-up: 14–30 years (nationwide and hotspots)	10 years	C: 3% B: 3%	Age-structured population-based dynamic mathematical model [31]	Yes	Yes
Shim, 2016 [21]	CUA	Health system and Society	Vaccinating at 9 years Vaccinating at 9 years + Catch-up 9–15 years No vaccination	20 years	C: 3% B: 3%	Age-structured population-based dynamic mathematical model [21]	No	Yes
Orellano, 2016 [24]	CUA	Society	Routine at 2 years No vaccination Nationwide and Hotspots	Lifetime	C: 3% B: 3%	Markov cohort-based static model [24]	No	No
Durham, 2013 [23]	CUA	NR	Childhood routine vaccination Childhood routine vaccination + Catch-up 0–5 years Childhood routine vaccination + Catch-up 0–15 years Childhood routine vaccination + Catch-up 0–40 years No vaccination	Lifetime	C: 3% B: 3%	Age-structured population-based dynamic mathematical model [23]	Yes	Yes
Carrasco, 2011 [19]	CUA	NR	NR	Lifetime	C: NR B: 3%	NR	No	Yes
Lee, 2011 [20]	CUA CEA	Society	Routine at ≤1 year No vaccination	Lifetime	C: 3% B: NR	Markov cohort-based static model [20]	No	No
Shepard, 2010 [28]	CUA	Society	Routine at 15 months Catch up: 15–64 years No vaccination	Lifetime	C: 3% B: 3%	NR	No	NR
Shepard, 2004 [18]	CUA	Society	Routine at 15 months No vaccination	Lifetime	NR	NR[b]	No	No

NR: Not reported; CEA: cost-effectiveness analysis; CUA: cost-utility analysis.
[a] Categorized by the reviewers according to the summary measure presented (CUA if the summary measure was QALY or DALY).
[b] Authors informed that the model is deterministic, but they did not provide the categorization.

threshold used, all studies were favorable to the vaccination program.

The report of the 24 items recommended by the CHEERS checklist is described in (Annex 2). The older studies [18–20,23,28] reported up to 50% of the checklist items. The more recent studies (8 of 13) reported between 54.2% and 70.8% of the checklist items. The most frequently reported items were: title, background and objectives, target population and subgroups, study perspective, comparators, assumptions, analytical methods, study parameters, characterization of uncertainty, and source of funding.

All studies reported the time horizon, but only two [26,29] justified why the choice was appropriate. Most studies informed the effectiveness measures, however only two [29,30] justified why the only study chosen could be considered a sufficient source of vaccine effectiveness. Although the study outcome measure (DALY) was described in all studies, only one study [21] reported the relevance of the measure for this type of analysis.

4. Discussion

This systematic review synthesized the information available in the literature on the economic evaluation studies of dengue vaccines. All studies [18–30] favored the introduction of the vaccine, mainly where the incidence of severe dengue is high (Table 6).

Table 4
Epidemiological estimates assumptions in the economic evaluations of dengue vaccines included in this review.

Author, year, reference	Epidemiological estimates					
	Dengue incidence	Adjustment for underreporting	Proportion of symptomatic/ asymptomatic cases	Severe cases/ hospitalization	Case-fatality rate	Data sources
Lee, 2018 [30]	2 scenarios: (1) High incidence, based on the control group of CYD-TDV trials data: 2614/100,000 (Colombia), 3182 (Vietnam), 5934 (Thailand); (2) Low incidence, based on MoH data: 106 (Colombia), 112 (Vietnam), 217 (Thailand)	Not used	NR	NR	NR	Country-specific CYD-TDV trials data, surveillance data and local studies
Zeng, 2018 [29]	American countries: from 878 to 1194/100,000 (average 1079); Asian countries: from 864 to 1602 /100,000 (average 1297)	NR	NR	Country-specific, hospitalization rate varied from 4.1 to 33%	Country-specific case-fatality rate varied from 0.4 to 2.1%	Country-specific CYD-TDV trials data
Shim, 2017 [27]	Annual incidence of dengue infection: 1060/ 100,000 Annual incidence of symptomatic dengue: 539/100,000	Reported using adjustment for underreporting, but no details were given	Proportion of symptomatic cases: 0.45; Probability of seeking medical care: 0.5	Annual incidence of DHF: 12/100,000; Hospitalization rate NR	Risk of death from DHF/ DSS: 0.01	Local study and WHO global burden of dengue estimates
Durand, 2017 [26]	Base case incidence: NR	Expansion factor (EF) for outpatient case: 3.2; hospitalized case: 1.6	NR	Hospitalization rate: 8.21%	Hospitalized case fatality: 0.81%	MoH surveillance data, systematic review of local studies
Shim, 2017 [25]	Annual incidence of infection (both symptomatic and asymptomatic): 2.03% Asymptomatic 0.45 Annual incidence of dengue fever 1.07%	Reported using adjustment for underreporting, but no details were given	Proportion of symptomatic cases: 0.45	DHF: 0.029%	Risk of death from DHF/ DSS: 0.01	Local study, previous cost-effectiveness study and WHO global burden of dengue estimates
Shafie, 2017 [22]	Observed and simulated annual incidence (presented in graphic)	Expansion factor for ambulatory cases: 3.79; hospitalized cases: 1.7	NR	NR	Case fatality rate: 0.56	Surveillance data and Asian CYD-TDV trials data
Shim, 2016 [21]	Expected age-dependent incidence rates approximately 2000/ 100,000 in under-14 children (presented in graphic)	Expansion factor 7.2	Proportion of symptomatic dengue: 0.23	Probability of DHF/DSS after 2^{dary} infection: 0.0448	Risk of death from DHF/ DSS: 0.01	Local estimates
Orellano, 2016 [24]	Dengue incidence 17.66/ 100.000 (range: 0.53–71.06)	NR	Proportion of unapparent infection: 0.77	Proportion of severe dengue: 1stinfection 0.036; 2nd infection: 0.118 Hospitalization rates: dengue: 0.247 (0.154–0.340); severe dengue: 0.907 (0.779–0.974)	Death rate from severe disease in children: 0.007/1,000; in adults: 0.0045/ 1,000	Local data as reported to PAHO
Durham, 2013 [23]	Annual dengue infection incidence (both symptomatic and asymptomatic): 4.56% Annual dengue fever incidence: 1.06%	NR	Proportion of symptomatic infection: 0.23	Annual incidence of DHF/ DSS: 0.02% Probability of DHF/DSS: primary infection: 0.00245: secondary/tertiary/ quaternary infection: 0.0448	Risk of death from DHF/ DS: 0.01	Local study and regional estimates
Carrasco, 2011 [19]	Rate of recent infection: 1.2% (15–24 years) and 3.2% (45–54 years)	Expansion factor ranged from 3.8, in the youngest age group (0–24 years) to 50, in the oldest group (>55 years); Expansion factor for hospitalized cases: 1.4–3.4	Proportion of symptomatic cases (overall): 0.24–0.35	Hospitalization rate: 0.565 Hospitalized cases that are DHF: 0.358	Number of reported deaths from 2000 to 2009 (98)	National surveillance system and seroprevalence study
Lee, 2011 [20]	Baseline incidence of dengue infection: 9%	NR	Proportion of asymptomatic infection: primary infection: 91%; secondary infection: 84%	Proportion of DHF: Primary infection: 25% in children and 7.2% in adults; Secondary infection: 89% in children and 25.7% in adults	Dengue: 0.0027% DHF: 0.155%	Local study and WHO global burden of dengue estimates

(*continued on next page*)

Table 4 (*continued*)

Author, year, reference	Epidemiological estimates					
	Dengue incidence	Adjustment for underreporting	Proportion of symptomatic/ asymptomatic cases	Severe cases/ hospitalization	Case-fatality rate	Data sources
Shepard, 2010 [28]	Annual incidence rate in Panama: 1020; 791 and 636/ 100,000, in 2005, 2006 and 2007, respectively. Annual infection rate: 3.5%.	Expansion factor: 6	Proportion of symptomatic cases: 24%	Number of reported hospitalizations (456) in Panama, in 2005	Number of reported deaths (5) in Panama, in 2005	Panama Ministry of Health data and local study
Shepard, 2004 [18]	Annual infection rates: 5% (overall); 12.5% in children <15 years and 2.8% in adults.	NR	Proportion of symptomatic cases: 24%	Proportion of DHF: 6%	Case fatality rate among DHF cases: 0.8%	International data and a local study

DF: dengue fever; DHF: dengue hemorrhagic fever; DSS: dengue shock syndrome; MoH: Ministry of Health; NR: not reported; RCT: randomized control trial.

Table 5
Reported costs from economic evaluations of dengue vaccines included.

Author, year, reference	Reported costs		
	Direct	Indirect	Data sources
Lee, 2018 [30]	Vaccine wastage, Treatment cost: hospitalization and outpatient care of DF	NR	General[b] estimates
Zeng, 2018 [29]	Treatment cost: hospitalization, outpatient care, vaccine delivery costs and vaccine wastage	Productivity loss of school days and work days lost;	General[b] estimates
Shim, 2017 [27]	Treatment cost: hospitalization and outpatient care of DF and DHF	Productivity loss of both the patient and relatives, and the corresponding days of school and work days	Local[d] estimates
Durand, 2017 [26]	Vaccination program: vaccine, wastage, freight, supplies, administration, monitoring, cold chain, injection safety, operational, programmatic services, social mobilization and outreach for new adolescent vaccine Treatment cost: hospitalization and outpatient care	Indirect cost per ambulatory and hospitalized case, productivity loss and dengue deaths	Local[d] estimates
Shim, 2017 [25]	Vaccination program: vaccine, wastage, delivery, and administration Treatment cost: hospitalization and outpatient care for DF and DHF	Productivity loss and children and adults dengue deaths	General[b] and Local[d] estimates
Shafie, 2017 [22]	Vaccination program, Treatment cost: Hospitalization and outpatient care	Productivity loss of both the patient and relatives, and the corresponding days of school and work days	Regional[c] and Local[d] estimates (Malaysia and Asia)
Shim, 2016 [21]	Vaccination program, Treatment cost: hospitalization and outpatient care for DF and DHF	Productivity loss and children and adults dengue deaths	Regional[c] and Local[d] estimates (Philippines and Asia)
Orellano, 2016 [24]	Vaccination program: vaccine, vaccine transport, storage and administration Treatment cost: hospitalization, outpatient care, and laboratory practices	Absenteeism and dengue deaths costs	General[b] and Regional[c] estimates (Brazil and Asia)
Durham, 2013 [23]	Vaccination program: vaccine, vaccine delivery, and administration Treatment cost	Productivity loss	General[b] and Local[d] estimates (Thailand, Singapore and Brazil)
Carrasco, 2011 [19]	Treatment cost: hospitalization, outpatient care, transport costs, control costs	Productivity loss of parents, household services losses, elderly caregiving, school days loss	General[b] and Local[d] estimates (WHO and Singapore)
Lee, 2011 [20]	Vaccination, Treatment cost: hospitalization and outpatient care for DF and DHF, vaccine minor side effect	NR	Local[d] estimates (Thailand)
Shepard, 2010 [28]	Vaccination program: vaccine, syringes, services, contact of labor, overhead, vaccine distribution and storage for vaccine administration Treatment cost	NR[a]	Local study
Shepard, 2004 [18]	Vaccination program: vaccine, syringes, contact of labor, overhead, vaccine distribution and storage for vaccine administration Treatment cost: hospitalization, outpatient care, medications, transport costs	Parentś time seeking treatment	International literature

NR: Not reported.
[a] The model considered the school days missed by children and work days missed by adults, but there is no report of the related indirect cost.
[b] Estimates based on data from other countries.
[c] Estimates based on data of the region of the country of interest.
[d] Estimates based on data of the country of interest.

Table 6
Results of economic evaluations of dengue vaccines reviewed.

Author, year, reference	Currency/ year	Vaccine price	Summary measure	Sensitivity analyses	Threshold	Conclusion
Lee, 2018 [30]	US$/ 2014	Price[a] by fully vaccinated person: US$0–$150	Vaccine cost-effective threshold price	Univariate Scenario	0.5GDP per capita	Favorable
Zeng, 2018 [29]	US$/ 2015	US$20 per dose	ICER: Latin American countries: US$4216/ DALY averted Asian Countries: US$3751/DALY averted	Probabilistic Threshold	<1 GDP per capita 1-3GDP per capita	Favorable
Shim, 2017 [27]	US$/ 2016	Price by person fully vaccinated: Cost-saving: Health system: US$89 Society: US$163 Very cost-effective: Health System: US$140 Society: US$214 Cost-effective: Health System: US$245 Society: US$315	DALYs averted QALYs gained	Probabilistic Threshold	Very cost-effective: ICER < 1 GDP per capita; Cost-effective: ICER between 1 and 3GDP per capita	Favorable
Durand, 2017 [26]	R$/ 2016	R9/10–16 years Payer: R$187.50 Society: R$221.50 R9/10–25 years Payer: R$221.50 Society: R$216.80	Vaccine cost-effective threshold price	Probabilistic Threshold	3GDP per capita	Favorable
Shim, 2017 [25]	US$/ 2017	Price by person fully vaccinated: Health System: <1GDP 50% coverage < US$100 70% coverage < US$130 90% coverage < US$160 < 3GDP 80% coverage < US$262	Vaccine cost-effective threshold price	Probabilistic Threshold	1GDP per capita 3GDP per capita	Favorable
Shafie, 2017 [22]	US$/ 2013	Health System: US$3.58 Society: US$5.96	Vaccine cost-effective threshold price	Probabilistic Threshold	1GDP per capita 3GDP per capita	Favorable
Shim, 2016 [21]	US$/ 2016	Price by person fully vaccinated: <1GDP Health System: (A) US$66, (B)US$68 Society: (A) US$73, (B)US$74 < 3GDP Health System: (A) US$70, (B) US$72 Society: (A)US$75, (B)US$78	Vaccine cost-effective threshold price	Probabilistic Threshold	1GDP per capita 3GDP per capita	Favorable
Orellano, 2016 [24]	US$/ 2014	US$0.58 (0.51–0.65)	ICER: US$5714/DALY averted	Univariate Probabilistic Threshold	3GDP per capita	Favorable
Durham, 2013 [23]	US$/ NR	<3GDP US$534 US$314	Net benefit	Multivariate Probabilistic	US$36000	Favorable
Carrasco, 2011 [19]	US$/ 2010	3 doses conferring 10 years of immunity: US$53 2 doses conferring lifetime immunity: US$287 3 doses conferring 10 years immunity: <US$53 2 doses conferring lifetime immunity: <$US287	NR	Univariate	3GDP per capita	Favorable
Lee, 2011 [20]	US$/ 2010	3 doses: US$1.5-US$800	NR	Univariate Multivariate	3GDP per capita	Favorable
Shepard, 2010 [28]	US$/ 2005	Southeast Asia: US$0.50 (public) US$10 (private) Panama: US$5	ICER: Southeast Asia US$50/DALY saved Panama US$2069/DALY saved[b] US$2574/DALY saved[c]	Univariate Multivariate	NR	Favorable
Shepard, 2004 [18]	US$/ 2001	US$4.14[d]	ICER: US$50/DALY saved	Univariate Multivariate	1GDP per capita	Favorable

ICER: incremental cost-effectiveness ratio; GDP: gross domestic product; DALY: disability adjusted life year; QALY: quality adjusted life year; DHF: dengue hemorragic fever; DSS: dengue shock syndrome; NR: Not reported.

[a] It did not assume a single price, it estimated a threshold above which, the program would not be cost-effective.
[b] In the routine strategy (15 months).
[c] In the catch up strategy (15–64 years).
[d] Weighted average dose price in the public sector (US$ 0.50) and private sector (US$ 10).

These results must be interpreted with caution and they may not offer policy makers useful information to inform decision making, due to their low-quality reporting (Annex 2).

Contrary to our results, where the majority (8/13) of the studies reported less than 55% of the CHEERS checklists' items, a systematic review of health economic evaluation of dengue vaccine studies considered the overall quality of included studies satisfactory. They used WHO checklist, BMJ checklist and Constenla et al checklist, and got the overall average score of 59%, 73%, and 66.7% respectively. But they emphasized that some methodological issues such as data collection, discounting, analysis and interpretation of results still need improvement [12].

The economic evaluation studies mirror the technological vaccine development and can be divided in three periods: those conducted prior to the release of results from CYD-TDV phase 3 trials, which evaluated hypothetical vaccines [18–20,23,24,28], those carried out after the publication of the first CYD-TDV efficacy results [21,22,25–27], and the most recent studies performed after disclosure of increased risk of severe dengue in seronegative vaccinees [29,30]. The most recent study [30] evaluated CYD-TDV and a hypothetical vaccine due to the unsatisfactory performance of CYD-TDV.

The vaccine efficacy and price were the two parameters that most impacted the final results of the analyzes. The first-period studies that evaluated hypothetical vaccines [18–20,23,24,28] considered optimum vaccine efficacy from 70% to 95% and vaccination of children younger than 9 years. These studies assumed a low vaccine price and did not include the incidence of vaccine-induced ADE. They did not evaluate different vaccine efficacy according to viral serotype and/or host serostatus, and considered a quite optimistic duration of protection, between 10 years and lifetime. However, phase 3 trials showed a different performance of CYD-TDV, with only moderate protection, and variable performance depending on dengue virus serotypes and vaccinees' age and dengue serostatus [4,5].

The second-period studies [21,22,25–27] considered a vaccine efficacy closer to that observed in CYD-TDV phase 3 clinical trials (54.8%–64.7%) [4,5]. They evaluated only the age group for which the vaccine was recommended (9 to 45 years of age) and most included ADE in their analyses [21,22,25,27]. These studies consider the duration of protection from 2.5 years to 10 years, still an optimistic assumption, once the duration of clinical protection was not established yet. Low antibody titers were observed against all DENV serotypes after 5 years of vaccination, even though the meaning of this finding is unknown [31].

The most recent studies [29,30] evaluated countries where CYD-TDV trials were conducted, used efficacy rates based on phase 3 clinical trials, including differences in efficacy by dengue virus serotype or host serostatus. The duration of protection assumed was conservative [30] and five of them included vaccine induced ADE in the model [20,21,25,27,29]. They used parameter values closer to the results presented in clinical trials of the CYD-TDV [4–6]. One of the more recent studies proposes a more effective hypothetical vaccine to compare with the CYD-TDV [30]. However, none of the studies evaluated the current WHO recommendation for CYD-TDV of serological screening and vaccinate only the dengue seropositive persons [8]. This strategy is complex, involves unusual actions and costs in immunization programs and need to be carefully evaluated in terms of costs and feasibility. It also requires careful planning and communication. The Philippines introduced CYD-TDV in the routine schoolchildren immunization in highly endemic areas, in 2016. The program was interrupted after Sanofi's announcement, in November 2017, of an excess risk of hospitalizations/severe dengue in seronegative vaccinees in the clinical trials. More than 800,000 Philippine children aged 9–10 years had received at least one vaccine dose; 14 of them have died. Even though there was no evidence linking the deaths to the vaccine, misconceptions spread in social media led to a political and social turmoil that resulted in loss of public confidence in the vaccine and in the whole immunization program [32,33].

Vaccine price was the parameter that had the greatest impact on the sensitivity analyzes of the studies, and the one with the highest variation from US$0.50 [18,28] to US$800 [20]. The vaccine price per dose was underestimated in all studies that presenting this data [18,20,22,24,28,29]. In the Brazilian private sector, the vaccine costs approximately US$42.

Dengue incidence have also impacted the results of economic evaluations. Estimating the total number of dengue cases is challenging. Dengue is underreported worldwide, and official statistics usually underestimate disease burden. Surveillance systems sensitivity varies among countries, among different regions within a country and over time, and is usually higher for more severe cases and during epidemics [34]. Most dengue burden of disease and economic studies based on official surveillance data used some expansion factor (EF) to adjust for underreporting [34]. EF is usually estimated based on the comparison of dengue incidence rates derived from active surveillance of febrile-disease to incidence rates derived from official surveillance system [35–40]. The ratio of these two rates (the expansion factor – EF) may be used to multiply the number of notified cases to get more realistic/accurate estimates of dengue burden [34,40]. A systematic review of EF used to estimate burden of dengue in Southeast Asia estimated an overall EF of 7.6 (95% certainty level: 7.0–8.8) dengue cases for every case reported, with great variation among countries (EF ranged from 3.8 for Malaysia to 19.0 in East Timor) [35]. The Global burden study estimated a global mean expansion factor of 12.3 (6.7–20.8) [34]. However, EF may biased the burden of disease estimates, since not every country has quantified its underreporting [34,40].

CYD-TDV phase 3 trials were conducted in sites with high dengue incidence, which may not reflect the rest of the country. The global burden of dengue study [34] compared its incidence rates estimates (adjusted for underreporting) with the incidence rates derived from the control group vaccine trials data. Although the vaccine trials control group data underestimate dengue incidence for two countries (Malaysia and Indonesia), for most countries (Brazil, Colombia, Honduras, Mexico, Philippines, Thailand and Vietnam) vaccine trials control group data overestimate dengue incidence [34]. So, with the exception of the Malaysia study [22], the other two economic evaluations that used CYD-TDV trials as source of epidemiologic data [29,30] may have overestimated the burden of dengue and consequently improved the cost-effectiveness of vaccination.

Although asymptomatic cases do not lead to healthcare utilization and costs, they are important in dynamic mathematical models because they contribute to dengue transmission. The assumed proportion of asymptomatic rates also varied widely in the reviewed studies, from 9% to 45%.

There are important methodological issues involved in modeling the impact of different dengue vaccination strategies at the population level. Mathematical transmission models are challenging because of the complex dynamics of vector-borne disease, the interactions between human hosts and mosquito vectors, four co-circulating dengue virus serotypes, short-living heterotypic cross-protection and the risk of ADE (antibody dependent enhancement) [41]. Additionally, recent evidence has suggested some level of cross-immunity between dengue and Zika viruses, which is important as the endemic areas of the two viruses overlap [42,43].

Although since 2016, WHO has withdrawn the recommendation to use the 1–3 GDP-based threshold considering it is not

specific enough to support decision-making [44], only the most recent study [30] has not used this threshold to interpret cost-effectiveness ratios.

5. Conclusions

Due to their methodological and assumptions limitations, the reviewed economic evaluations of dengue vaccines do not help much decision making on introducing a dengue vaccine in a country. More studies that consider the CYD-TDV limitations and the proposed vaccination strategy with pre-vaccination serological screening are needed.

Author contributions

De Soarez PC and Sartori AMC designed the research; De Soarez PC, Silva AB, Randi BA, Azevedo LM and Sartori AMC performed the research; De Soarez PC, Silva AB, Novaes HMD and Sartori AMC analyzed the data; De Soarez PC, Silva AB, Novaes HMD, and Sartori AMC wrote the paper.

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Appendix A. Supplementary material

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