Title: The economic promise of developing and implementing dengue vaccines: evidence from a systematic review.

Key words: Dengue, Vaccine, Cost-effectiveness, Economic, Quality Assessment

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1. Introduction

Dengue fever is the fastest-spreading tropical and vector-borne viral disease worldwide (WHO, 2009). There is no specific treatment for it, although appropriate medical care frequently saves the lives of people suffering from severe forms (Cattand, 2006). It is estimated that about 3.97 billion individuals, 56% of the world population, inhabit areas where there is a risk of transmission of dengue fever (Brady et al., 2012). The World Health Organisation (WHO) estimates 22,000 deaths per year and case-fatality rates in adults and in children can be as high as 33% if fluid management is inadequate or delayed (Halstead and Deen, 2002). Similar to other infectious diseases, reported cases are a small fraction of estimated total cases (Bärnighausen et al., 2013). Moreover, in endemic regions, the probable dengue fever disease burden in disability-adjusted life years (DALYs) is high: 0.42 per 1,000 population (Guzman and Isturiz, 2010), an increase in years lived with disability due to dengue has been observed, highlighting its steadily growing non-fatal burden of disease (Vos et al., 2015).

The disease presents considerable economic and social disease burdens to middle and low-income countries and over the past three decades there has been an increase in incidence rates with a concomitant increase of complications and severe cases. Furthermore, studies have shown that managing dengue illness requires multiple visits to health services, resulting in missed days of school and work, medical and non-medical expenditures, and foregone household productivity and income (Torres and Castro, 2007), (Suaya et al., 2009), (Shepard et al., 2013).

Vector control programmes have been the main preventive measure adopted to prevent and control dengue fever throughout the years in endemic countries but they have proved to be largely ineffective to control dengue transmission or epidemics (Erlanger et al, 2008), (Horstick et al., 2010), (Stahl et al, 2013). Recently, the first dengue vaccine was licensed in Mexico and has been since licensed in several countries (Vannice et al., 2015). Reports and studies have shown an overall vaccine efficacy of 59.2 – 60.8% and a significant efficacy variation according to serotype, age and among those previously exposed to dengue fever (Villar et al., 2014). Other vaccine candidates are in an advanced stage of development, using a variety of technological approaches, and they represent a decisive opportunity to control the disease (Vannice et al., 2015), (Hadinegoro et al., 2015).

The implementation of a new vaccine programme is often a costly process with long-term consequences and to gain a better understanding of the potential impact on health benefits and costs of a vaccine intervention, health economic studies are frequently used for estimating future impacts on health gains and costs (Bos, 2010), (Beutels et al., 2003). Studies about cost-effectiveness, fiscal impact and financial sustainability of new vaccines, for example, have guided implementation of national immunization programmes in some countries and specific guidelines have been published by the WHO to help improve the quality of economic studies evaluating vaccination programmes (WHO, 2008), (Tucker et al., 1998).

Developing countries are considerably affected by constraints on health care budgets and frequently face difficult decisions on the allocation of health resources. In this sense, the current trend in the public sector is to encourage transparent and evidence-based policy

decisions, in order to use resources effectively and efficiently. Consequently economic evaluation has acquired greater importance among decision-makers who have been pressured to know and justify which interventions represent the best "value for money" (Andrus et al., 2007), (UNICEF, 2009), (Tozan, 2016).

The development of a safe and effective dengue vaccine is moving forward at an unprecedented rate, especially because of improvements related to reverse genetics, with a high likelihood that the challenges of vaccine development and implementation can be overcome very soon (Guy et al., 2011), (Hadinegoro et al., 2015).

As recent studies have shown safe and effective dengue fever vaccines are at final stages of development and licensing is already a reality, it is essential to carefully analyze its potential economic impacts (Halstead and Deen, 2002), (Whitehead et al., 2007), (Guy et al., 2011), (WHO, 2012) to aid forthcoming resource allocation decisions for budget holders (Tozan, 2016). We do so by reviewing the available evidence to date. We also take the opportunity to compare findings from three separate checklists for assessing the quality of economic evaluation evidence.

2. Methods

Search strategy and selection criteria

A multi-stage process was designed and undertaken to systematically select relevant publications, based on PRISMA guidelines (Moher et al., 2009). The electronic literature search was performed in six electronic databases: PubMed/MEDLINE, EMBASE, Web of Science, Global Health, Latin American and Caribbean Health Sciences Literature (LILACS) and NHS Economic Evaluation Database (NHS EED). Searches were restricted to papers published between January 1970 and February 2016 and written in English, Spanish or Portuguese. Search terms, including MeSH descriptors and free text terms, were divided into three categories: dengue fever, vaccine, and economic evidence. Search terms and results are detailed in appendices 1 and 2.

Three reviewers (IE, PZ, AP) performed an eligibility assessment on the initially retrieved results, unblinded and independently. Titles, abstracts and key words were screened to determine whether they fulfilled the inclusion criteria: 1) included economic evidence focused on dengue fever vaccine; 2) involved original data analysis; and 3) written in English, Spanish or Portuguese. Editorials, letters to editors, opinion papers, meeting reports and conference reports were excluded. After the screening process was concluded, the full texts of selected abstracts were obtained to check their fulfillment of the inclusion criteria. As a final stage to the publication selection, we hand-searched reference lists of each of the papers selected for inclusion based on the electronic search to ensure that we had not missed any key publications. See Figure 1 for the complete study selection process.

Data extraction and quality assessment

Data extraction was designed to systematically summarize key elements from selected studies (Table 1), focusing on providing sufficient detail to allow comparison and was based on two published studies (Constenla et al., 2015), (Beatty et al., 2011).

Selected publications were critically appraised by three reviewers independently using three publicly available checklists: the "Drummond BMJ checklist" (Drummond and Jefferson, 1996), (Appendix 3); the "WHO checklist" for appraising the quality of economic evaluations of immunization programmes (WHO 2008), (Appendix 4); and the "Constenla et

al. checklist" (Constenla et al, 2015), (Appendix 5). Although the three checklists share many similarities, they contain some exclusive items, categorise items differently and recommend different methodologies to grade the overall quality assessment results.

With regards to categorization of items, the "Constenla et al. checklist" (Constenla et al, 2015) divides 17 questions into three categories: study design, data collection, analysis and interpretation. It is important to note that although it is mentioned the quality checklist contains 19 questions, only 17 questions are presented in appendix 2 in Constenla et al., 2015 and questions 13 and 14 are absent.

The 35 items in the "Drummond BMJ checklist" (Drummond and Jefferson, 1996) are also categorized this way. The "WHO checklist" on the other hand, divides its 28 questions into eight sections: framing, costs, effects, modelling, discounting, uncertainty, other factors and conclusions. To recognize similarities among the checklists and to facilitate comparisons across categories, reviewers considered that: the section 'framing' and items 15 and 16 from 'modelling' corresponded to 'study design'; the sections 'costs' and 'effects' corresponded to 'data collection'; and item 17 from 'modelling', 'discounting', 'uncertainty', 'other factors' and 'conclusions' corresponded to 'analysis and interpretation' (Table 3 and Appendix 4).

In terms of grading, the "Constenla et al. checklist" assigns point values to responses according to importance. The other two checklists lack such a mechanism so, for those two, we answered each question with one of four responses: 'yes', 'partial', 'no' or 'not applicable' and assigned only unitary points for each question. The 'not applicable' answers were not considered for the overall "result" and percentages were used to evaluate responses per category.

3. Results

The electronic searches yielded 1,098 articles after removal of duplicates, of which 27 studies met the inclusion criteria on the basis of their title and abstract. These papers were then assessed in full-text, and 18 were further removed, mainly because they were not an original analysis or did not focus on dengue fever vaccine economic evidence. This resulted in only nine studies satisfying the eligibility criteria. Two further studies were identified after manual review, resulting in 11 studies, all of which were written in English, meeting the inclusion criteria for the final qualitative and quantitative analysis (Table 1).

Most studies were based on data from countries in south-east Asia, although 6 studies also presented results from America regions. There were four multi-country papers and three studies focusing on cost-effectiveness of a dengue fever vaccine were performed by the same main author (Shepard), in what can be described as a series of analyses throughout the years (1993, 2004 and 2010). It is also important to note that most included studies also referred to initial studies from this author.

The perspective of society was used in most cases and one study also discussed the manufacturer perspective (Mahoney et al., 2012). The time horizon used in all studies but one (Mahoney et al., 2012) was based on life expectancy.

Types of study designs varied across studies and cost-effectiveness analysis dominated as the methodological approach performed most frequently. Three studies (Palanca-Tan, 2008), (Hadisoemarto and Castro, 2013), (Lee et al., 2015) are willingness to pay for dengue vaccine analyses and can be classified as partial economic evaluations since they provide less detailed

information relating to description, measurement or valuation of resources associated with dengue fever vaccines. One study was a cost-description about the feasibility of producing dengue vaccines (Mahoney et al., 2012).

Secondary data sources were used in all economic evaluation studies and were frequently derived from published literature and surveillance reports. Primary data collection was undertaken in the three willingness to pay for dengue vaccine studies. Recent studies generally compared interventions like clinical management and vector control programmes with vaccination. A total of five studies analysed less complex scenarios comparing vaccination and absence of specific immunization programmes.

Most studies used some kind of economic modelling; however, no studies provided justification for the selection of a particular type of model or its key parameters. A decision tree /model was included as a figure in 4 studies (Shepard et al., 2004), (Shepard et al., 2010, (Lee at al., 2011), (Orellano et al., 2015). Similarly, discount rates were often stated, but without justification for the choice of a specific rate. Details of statistical tests and confidence intervals used in the studies were not frequently stated and only four studies (Palanca-Tan, 2008), (Durham et al., 2013), (Lee et al., 2015), (Hadisoemarto and Castro, 2013) made reference to this.

The majority of studies used and referenced cost estimates from previous studies rather than re-estimating new costs; there was considerable variation in cost measures and most relevant costs were not recent as only three studies (Mahoney et al., 2012), (Orellano et al., 2015), (Durham et al., 2013) used data from within 2-3 years prior to the study being published. Included are direct costs for medical care and vector control measures and indirect costs for lost production due to illness and absenteeism by patients and by parents caring for sick children. Indirect costs were measured and reported separately from direct cost only in two studies (Carrasco et al., 2011), (Orellano et al., 2015).

Most studies did not consider productivity changes, two studies (Carrasco et al. 2011), (Lee et al., 2011) made reference to productivity losses in its analysis, but without further discussion or specific reporting on this aspect of the analysis.

Details on price adjustments for inflation or currency conversion were neglected; four studies (Shepard, 1993), (Mahoney et al., 2012), (Durham et al., 2013), (Orellano et al., 2015) did not make reference to any such detail, and three others (Carrasco et al. 2011), (Palanca-Tan, 2008), (Shepard et al., 2004) only accounted for one item at a time (e.g. conversion but not inflation).

All included studies based their analysis on assumptions related to future or recent prospects of dengue fever vaccines derived from current scientific literature, including details about how vaccine prices where estimated, with the exception of two studies (Mahoney et al. 2012), (Lee at al., 2015). However, details of methods of synthesis or meta-analysis of dengue fever vaccines estimates were not provided by most of reviewed studies. All studies considered vaccine efficacy and coverage. Three studies varied the vaccine dose regime scenario and there was a wide variation in prices per dose among studies reviewed.

Sensitivity analysis was described by seven studies; however, only three studies (Shepard et al., 2004), (Shepard, 2010), (Durham et al., 2013) justified their choice of variables, while one study did not state the range over which sensitivity parameters were varied (Mahoney et al. 2012).

Detailed reports on incremental analysis were not a frequent finding. However, in six studies (Shepard, 1993), (Carrasco et al., 2011), (Lee et al. 2011), (Durham et al., 2013), (Lee et al., 2015), (Orellano et al., 2015) it was possible to find brief details of such an approach. Remarks on generalisability issues were another rare finding and were clearly addressed in only two studies (Carrasco et al. 2011), (Shepard, 2010). All studies' conclusions were considered to be ungeneralizable due to limited data about the vaccine and regional characteristics associated with study design and methodology.

Out of the six studies that expressed disability-adjusted life years (DALYs) as an outcome measure to evaluate economic impact or cost-effectiveness of dengue vaccines, two presented the incremental cost-effectiveness ratio in units of cost per DALY averted (Lee et al. 2011), (Orellano et al., 2015).

The results of most studies showed that the dengue vaccine could be of considerable economic value but results were conditionally linked with vaccine prices, vaccine efficacy, coverage vaccine regime (number of doses) and strategy. In some cases, vaccination could provide net cost savings. All studies presented analyses linking costs to outcomes but only one recent study (Orellano et al., 2015) clearly used cost-effectiveness thresholds for the analysis.

Potential sources of bias were not clearly stated by four studies (Shepard et al., 1993), (Palanca-Tan, 2008), (Durham et al., 2013), (Lee at al., 2015) and comparisons were made with other studies in all included papers but they were only partial in 6 studies.

All studies but one (Shepard et al., 2010) have clearly acknowledged their funding sources and authors have declared there was no conflict of interest related to financial support or authors´ affiliations. Non-profit organisations (government agency, non-profit foundation, or academic institution) were responsible for financial support in ten of eleven included articles.

Evaluating quality of evidence

Although the overall quality of included studies was considered to be satisfactory as averages for positive answers according to each of the checklists were greater than 59%, some specific methodological issues still need more attention, especially in relation to data collection and analysis and interpretation. The standard deviations show that the papers were similar in terms of their quality, with few outliers (Table 2, Table 3 and Table 4).

Furthermore, despite the different methods for scoring applied for the three checklists, as there was no penalty for partially positive answers on "Drummond/BMJ checklist" and "WHO checklist" assessments, the overall scores showed a similar pattern when compared to percentage of positive answers. The "WHO checklist" overall score was the lowest as the average was 13 (59%), while the "Drummond/BMJ checklist" average score was 23.09 (73%) and the "Constenla et al. checklist" average score was 25.05 (66.7%)

Quality assessment based on the "Drummond/BMJ checklist" (Drummond and Jefferson, 1996) revealed that on average 89.6% questions were considered applicable to selected studies, 73% responses were positive, 4.7% were considered as partial and 22.2% of the answers were negative. According to this checklist, the area in most need forimprovement is data collection, scoring an average of 7.45 (62.6 %) (Table 2).

Comparatively, quality assessment using the "WHO checklist" revealed a lower percentage of positive answers among studies (Table 3). On average, 78.5% of questions were applicable to the included studies, 59% responses were positive, 13% were marked as partial and 27.6% were negative answers. Checklist scores suggested that the areas needing improvement related to data collection, and one section (discounting) associated with analysis and interpertation of results was evaluated as the lowest percentage for the overall checklist rating by category (Table 3).

The quality assessment based on the "Constenla et al. checklist" (Table 4) required the use of a different method for scoring, but shared a higher degree of similarity, for question content and categories, with the "Drummond/BMJ checklist" rather than with the "WHO checklist". Papers on average scored 25.05 (66.7%) out of 37.5 possible points and the area in most need for improvement was data collection, scoring 6.27 (46.4%) out of 13.5.

In terms of ranking the results of quality assessment, two studies (Palanca-Tan, 2008), (Lee at al., 2015) were evaluated as the lowest quality for all checklists. Moreover, the three studies associated with less quality according to the "Drummond/BMJ checklist" and the "WHO checklist" were the same, and the study ranked as of the least quality (Mahoney et al., 2012) was not among the lower scores based on "Constenla et al. checklist".

On the other hand, ranking studies according to scores for the highest quality did not show any matching results among the three checklists, although one study (Durham et al., 2013) reached a higher percentage of positive responses for the "Drummond/BMJ checklist" and the "WHO checklist", and another study (Carrasco et al., 2011) was one of the three best evaluated using the "WHO checklist" and also the "Constenla et al. checklist".

4. Discussion

This review indicates that economic analyses of future prospects for dengue fever vaccines are few in number and, although reviewed studies display different baseline assumptions and modelling designs, relevant methodological approaches were taken and findings were similar.

Studies to date, based on economic modelling approaches, make a clear case for vaccines potentially having a substantial impact on the epidemiology of this disease, even though assumptions about vaccination programmes may vary substantially. Although analysis adjustments may be necessary as critical information may be different in the future, cost-effectiveness analysis can play an important role in the decision-making process of implementing dengue fever vaccines as it allows comparison between health burdens and health gains provided by different measures of prevention and control (Siqueira Jr et al., 2005), (Halstead, 2012).

Results indicate that economic analyses have been performed by a restricted number of authors and in few countries when considering the potentially dengue fever affected areas in the world. While this facilitates comparison and interpretation among studies, there is a risk of bias as authors' preconceptions may affect interpretation of results, interfere with a scenario's setting, and also may narrow the analysis (Kimman et al., 2006).

Although quality assessment of economic evaluations is a relatively new approach for vaccination programmes and there are no generally accepted criteria for reviewing economic evidence (Higgins et al., 2008), the overall quality of studies was considered to be

satisfactory. Further, results of critical appraisal did not show considerable differences in quality levels between three quality assessment checklists, with overall 'quality scores' being similar across checklists.

It is important to highlight, however, there is some variability among the checklists which may be related to each checklist's design and specific purpose. For some included studies, lower scores could be related to checklists' specificity. The "WHO checklist", for instance, aims to assess the quality of economic evaluations of immunization programmes, while the two other checklists aim to assess general economic evaluations.

Another explanation for some differences in quality assessment results is differences in the formulation of questions. Responses for "were appropriate comparisons made with other studies?", for example, were generally positive. On the other hand, answers for the more specific question of "have the findings been compared to other economic evaluations undertaken in the same or neighbouring countries?" were usually negative.

Although there is no consensus on whether guidelines improve the quality of the economic evaluations, studies should focus on transparency of reporting, which can be aided by the use of validated quality assessment checklists (Drummond and Jefferson, 1996). On the other hand, validity of an economic evaluation may be difficult to assess due to limitations in reporting and some authors advise it is preferable to present a checklist describing methods, results, strengths, weaknesses and the implications on their conclusions (Husereau et al., 2013). Our use and comparison of three recognized checklists has shown that the quality of reporting of economic evaluations may vary and could be potentially improved as a quality assurance mechanism (Husereau et al., 2013). However, it is important to highlight that quality assessment by checklists does not distinguish between major flaws and simple weaknesses, and simplistic interpretation of results may be misleading (Bos, 2010). Accounting for level of importance in quality assessment, as introduced by the "Constenla et al. checklist", may help overcome this limitation.

The way results of economic evaluations are reported and interpreted is extremely important. Data are inevitably specific to a context and may be subject to reinterpretation if vaccine features change considerably from what is expected at the present time. The emphasis in the reporting should reside on transparency since without a clear display of parameters used in modelling, it is hard to determine if an economic model provides an accurate description of epidemiological patterns expected prior to a vaccination programme and, therefore, if they can be used to predict future incidence and outcomes associated with introducing the vaccine (Drummond and Jefferson, 1996).

Furthermore, using uncertainty analysis throughout the process of reviewing one or more parameters will help to identify those that will have a greater impact on the results. In a scenario where the price per dose is uncertain, for instance, a threshold analysis may be less susceptible to drastic changes on results and interpretation (Tucker et al., 1998).

Relevant aspects of vaccine pricing and the total cost of vaccination per fully immunized person are important variables, expected to vary across countries according to the way costs are estimated, and affecting the cost-effectiveness analysis results (Brenzel et al, 2006). To enable evidence-based decision making, country-specific costing studies should provide updated detailed data to enable analysis where it is possible to vary key inputs, such as the mix of vaccine delivery strategies and the scale of vaccination programmes (Tozan, 2016).

Considering several promising vaccine candidates are currently in the later stages of clinical development, and the first dengue vaccine was recently licensed, it is necessary to continue dengue surveillance to ensure evaluations of vaccine performance and immunization strategies. However, the clinical development of dengue vaccines should not be forestalled by unnecessary regulatory concerns and information about the quality of vaccines on procedures for licensing can be found in various World Health Organisation documents (WHO, 2008).

Although it was not a frequent finding among the studies reviewed, future studies should also account for serotype-specific immunity, herd protection, vector-host interactions, seasonal variations in disease transmission, age-specific differences in disease incidence and severity, potential effects of dengue vaccination on outbreak control spending, income from tourism and foreign direct investment flows. As also highlighted by Tozan (Tozan, 2016), only one study (Durham et al., 2013) modelled herd immunity to capture health gains by the community, including non-vaccinees; and despite Shepard (Shepard et al., 2004) considering its relevance to future economic analysis, they excluded potential indirect benefits of vaccination from their model due to the lack of evidence. Considering such aspects in economic models is more likely to assist in choosing the most efficient and cost-effective options for health interventions (Andraud et al., 2012).

Generalisability was a neglected quality criterion. So while we identified that studies took similar methodological approaches to generating economic evidence for dengue fever vaccines, little attention was given to consider a vaccination strategy that could be adopted and adapted across the world.

Recent studies have found that when investigators have financial relationships with pharmaceutical or product manufacturers, they are less likely to criticize the safety or efficacy of these agents and economic studies are more likely to report favorable qualitative assessments and less likely to report unfavorable qualitative assessments (Friedberg, 1999). Conflict of interest was declared non-existent among all selected studies and this statement is supported by the nonprofit nature of identified funding sources.

Limitations

The first dengue fever vaccine has been recently licensed in December 2015. Information about vaccine clinical effectiveness is still uncertain and it is not possible to have standardized economic parameters to compare studies on their findings and their overall quality. However, we attempted to minimize this limitation by using three recognized checklists for quality assessment. In spite of these limitations, results from this review are useful given the imminent licensure of other dengue fever vaccines and when further research about effectiveness is available.

6. Conclusions

Despite the growing consensus that dengue fever is one of the most important emerging tropical diseases in the 21st century (Gubler, 2002), few studies have provided economic evidence about dengue fever vaccines. What exists is of satisfactory overall quality and the increasing use of checklists to assess economic evaluations will likely improve overall quality of such studies.

Although, several uncertainties still remain about effectiveness of dengue fever vaccines, preliminary cost-effectiveness studies performed so far favour the implementation of a

dengue fever vaccine immunization programme. The price per dose is the most important factor affecting conclusions about the cost-effectiveness of future programmes.

As dengue vaccines candidates have been approved for use in various countries it is extremely important to improve both the number and quality of studies in the area. Given the inherent complexity of economic analysis, it is important that future studies take on board the limitations of studies already performed to ensure the production of a reliable evidence base for decision-making.

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Conflict of interest

Authors declare no conflict of interest.

Table 1: Summary of reviewed studies

STUDY	LOCATION	ANALYTICAL APPROACH			MAIN FINDINGS
		STUDY DESIGN	MAIN PARAMETERS AND ASSUMPTIONS	OUTCOMES MEASURED	
Shepard et al., 1993	Central America, South America, the Caribbean, and South-East Asia	Cost-effectiveness analysis	Data source: Secondary data sources Interventions compared: Clinical management and vector control (environmental and vertical/pesticide) Cost elements: Direct costs for medical care, vector control measures, vaccination and indirect costs for lost production due to illness and absenteeism Vaccine: Two-dose regimen; 95% effective; 73% vaccine coverage Modelling: Deterministic model, comparing vaccination, vector control and case management. Discount rate: 0.03	DALYs averted	In a country with a developed health system, case management is the most cost-effective alternative at $ 587 per DALY, but immunization would be a valuable addition at an incremental cost of $ 4,217 per additional DALY averted. Vaccines in a country with a not developed health system would be the most cost-effective alternative at $1,440 per DALY.
Shepard et al. 2004	Brunei, Cambodia, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam	Cost-effectiveness analysis	Data source: Secondary data sources Interventions compared: Clinical management and vaccine Cost elements: Direct and indirect Vaccine: Two-dose regimen; 95% effective; 85% vaccine coverage Modelling: Deterministic, age-structured and vaccination model. Discount rate: 0.03	DALYs averted, Difference in costs (with and without vaccine)	Vaccination programmes would cost $81.7 million per year, avert $72.7 million in treatment; have net cost of $9.0 million and avert 182,000 DALYs per year. Vaccination would reduce both mortality and morbidity burdens of disease by 82%, averting 0.34 DALYs per 1,000 persons per year.
Palanca-Tan, 2008	Philippines	Cost-benefit analysis	Data source: Primary data collection from in-person interviews Survey areas: (1) Respondent and household characteristics (2) willingness to pay for a dengue vaccine and value of statistical live estimates Vaccine: 1-dose or 10-dose regimen; protection for 1 year	Willingness-to-pay (WTP) for the vaccine, had it not been provided for	The mean willingness to pay for a dengue vaccine for children 14 years old and younger was US$35 for the one-year duration vaccine and US$41 for the ten-year duration vaccine. The study's model revealed a significant

			or 10 years; prices ($2, $10, $20, $60, $100) Modelling: Two-stage regression model Discount rate: Not reported	free and Value of Statistical Life Estimates	positive income effect and a significant negative price effect.
Shepard et al., 2010	Panama and South-East Asia	Cost-effectiveness analysis	Data source: Secondary data sources Interventions compared: Clinical management and vaccine Cost elements: Direct and indirect medical costs, lost work Vaccine: Scenarios: Two-dose regimen, 95% effective, and 85% vaccine coverage. Modelling: Conceptual disease model Discount rate:0.03	DALYs averted and vaccine cost-effectiveness	In SE Asia, vaccines can be highly cost-effective at $50 per DALY. Vaccination would reduce both mortality and morbidity burdens of disease by 82%, averting 0.34 DALYs per 1.000 persons per year. In Panama, due to higher treatment costs, a moderately priced vaccine would be cost saving for both infants and adults. Vaccine can be cost-effective at $2,069 and $2,574 per DALY averted in children and adults, respectively.
Carrasco et al., 2011	Singapore	Cost-effectiveness analysis	Data source: Secondary data sources (national surveillance reports and hospital billing records) Interventions compared: Vector control programme and vaccine Cost elements: Direct and indirect medical costs, loss of work Vaccine: Scenarios: Vaccine: two or three dose-regimen scenarios; 80% effective; 75% vaccine coverage Modelling: Economic model and threshold price estimation to evaluate cost-effectiveness scenarios. Discount rate:0.03	Total costs, DALYs averted and vaccine cost-effectiveness	Results strongly support the implementation of vaccination programmes if reasonably low prices are adopted. Vaccines were cost effective under $53 for three-dose regimen and 10-year immunity or under $287 for two-dose regimen and lifetime immunity. 8.7 DALYs per 100,000. Thresholds for vaccine programme cost-effectiveness ranged from $95 to $461.
Lee et al., 2011	Thailand	Cost-effectiveness analysis	Data source: Secondary data sources Interventions compared: vaccine versus no vaccine Cost elements: Direct costs Vaccine: Scenarios: two or three dose-regimen scenarios; vaccine efficacy (50-95%);	Incremental cost-effectiveness ratio (ICER)	Dengue vaccine could be of considerable economic value even at fairly high prices and relatively low vaccine efficacy. Vaccination was highly cost-effective for

			Modelling: Markov model Discount rate:0.0 3		50% vaccine efficacy or higher up to a total vaccination cost of $60 and for most scenarios until the vaccination cost was greater than $200.
Mahoney et al., 2012	Brazil	Cost analysis of vaccine production	Data source: Primary data collection from interviews Cost elements: Direct and indirect costs Vaccine: Scenarios: 1-dose or 10-dose. Modelling: Not reported Discount rate: Not reported	Total production costs for 60 million vaccine doses; cost per dose of vaccine.	Dengue vaccine can be made available at an affordable price. Cost of production for 1-dose vials $41.6 million ($0.69 per dose) and the cost for 10-dose vials 11.8 million ($ 0.19 per dose).
Durham et al., 2013	Brazil	Cost-effectiveness analysis	Data source: Secondary data sources Interventions compared: Cost elements: Direct medical and non-medical costs and indirect costs of dengue and dengue vaccine Vaccine: Scenarios: three-dose regimen; vaccine efficacy: optimistic 70% (49 - 87%) and 30% (13.4 - 56.6%), Modelling: Deterministic, age-structured four-serotype dengue transmission and vaccination model Discount rate:0.03	Vaccine cost-effectiveness threshold	At a 70% vaccine efficacy scenario, routine vaccination coverage of 82%may be cost-effective up to $534 per individual and cost saving up to $204. At a 30% vaccine efficacy scenario, routine vaccination may be cost-effective and possibly cost-saving if total vaccination costs can be kept sufficiently low, below $237 for cost-effectiveness and below $93 for cost-saving.
Hadisoemarto and Castro, 2013	Indonesia	Cost-benefit analysis	Data source: Primary data collection from in-person interviews. Survey areas: Demographics, knowledge of dengue, attitude on prevention, prevention practice, attitude on vaccination practice, acceptance of dengue vaccination, willingness-to-pay for a pediatric dengue vaccine, potential behavior change Vaccine: Single dose regimen; safe and fully protective, prices ($1.1, $2.75, $5.5, $8.25, $11 and more than $11) Modelling: Proportional odds model and an interval regression model were employed to identify determinants	Willingness-to-pay (WTP) for the vaccine, had it not been provided for free.	Pediatric dengue vaccine would be accepted by 94.2% participants. 94.6% were willing to pay for the vaccine with a median of stated WTP of $1.94 94.7% of the participants agreed that other dengue prevention methods are no longer necessary once dengue vaccine is available.

			of acceptance and WTP, respectively Discount rate: Not reported		
Lee et al., 2015	Vietnam, Thailand and Colombia	Cost-benefit analysis	Data source: Primary data collection from in-person interviews and focus-groups Survey areas: Household characteristics, household demand analysis Vaccine: 70-95% efficacy for 10 or 30 years, three-dose regimen; safe and fully protective, prices ($2.93, 11.70, $21.94, $43.88, 268.17) Modelling: Poisson or negative binomial regression models and median WTP Discount rate: Not reported	Willingness-to-pay (WTP) for the vaccine, had it not been provided for free.	The parametric median WTP is $26.4 ($8.8 per dose) in Vietnam, $70.3 ($23.4 per dose) in Thailand, and $23 ($7.7per dose) in Colombia. Respondents place more value on vaccinating young children than school age children and adults.
Orellano et al., 2015	Argentina	Cost-utility analysis	Data source: Secondary data sources Interventions compared: Vaccine versus no vaccine, vaccine at national level and vaccine limited to high transmission areas. Cost elements: Direct and indirect costs of dengue cases, human-capital approach (cost of absenteeism and deaths), vaccine costs; Vaccine: Three-dose scheme, vaccine efficacy against dengue: 0.647 (Range: minimum 0.587– maximum 0.698); against severe dengue: 0.955 (Range: minimum 0.688–maximum 0.999); against hospitalized dengue: 0.803 (Range: minimum 0.647–maximum 0.895) Modelling: Markov model Discount rate: 0.03	DALYs averted, Incremental Cost-effectiveness ratio (ICER)	Cost of vaccination programme $ 238,815. The ICER of the vaccination program was found to be $ 5714 per DALY averted and vaccination would be cost-effective (per capita income = US$ 12,873 in 2014).

Table 2

Table 2: Quality assessment summary by category and paper, "Drummond/ BMJ" Checklist.[1, 2]

STUDY	POSITIVE ANSWERS				PARTIALLY POSITIVE ANSWERS	NEGATIVE ANSWERS
	STUDY DESIGN	DATA COLLECTION	ANALYSIS AND INTERPRETATION	OVERALL		
Shepard et al., 1993	6/7 (85.7)	9/14 (64.3)	10/13 (76.9)	25/34 (73.5)	1/34 (2.9)	8/34 (23.5)
Shepard et al., 2004	7/7 (100)	8/13 (61.5)	12/13 (92.3)	27/33 (81.8)	2/33 (6.0)	4/33 (12.1)
Palanca-Tan, 2008	7/7 (100)	6/11(54.5)	7/11 (63.6)	20/29 (68.9)	2/29 (6.9)	7/29 (24.1)
Shepard et al., 2010	7/7 (100)	9/13 (69.2)	10/13 (76.9)	26/33 (78.8)	1/33 (3.0)	6/33 (18.1)
Carrasco et al., 2011	7/7 (100)	9/13 (69.3)	9/13 (69.2)	25/33 (75.7)	2/33 (6.0)	6/33 (18.1)
Lee et al., 2011	7/7 (100)	10/13 (76.9)	10/13 (76.9)	27/33 (81.8)	1/33 (3.0)	5/33 (15.1)
Mahoney et al., 2012	5/5 (100)	6/9 (66.6)	4/14 (28.5)	15/28 (53.6)	1/28 (3.5)	12/28 (42.8)
Durham et al., 2013	7/7 (100)	8/13 (61.5)	12/13 (92.3)	27/33 (81.8)	1/33 (3.0)	5/33 (15.1)
Hadisoemarto and Castro, 2013	5/5 (100)	5/9 (55.5)	9/14 (64.2)	19/28 (67.8)	2/28 (7.1)	7/28 (25.0)
Lee et al., 2015	5/5 (100)	5/9 (55.5)	8/14 (57.1)	18/28 (64.2)	2/28 (7.1)	8/28 (28.5)
Orellano et al., 2015	7/7 (100)	7/13 (53.8)	11/13 (84.6)	25/33 (75.7)	1/33 (3.0)	7/33 (21.2)
AVERAGE	**6.36/ 6.45 (98.7)**	**7.45/ 11.81 (62.6)**	**9.27/ 13.09 (71.1)**	**23.09/ 31.36 (73)**	**1.45/ 31.36 (4.7)**	**6.81/ 31.36 (22.2)**
STANDARD DEVIATION	**0.92/ 0.93 (4.31)**	**1.75/ 1.94 (7.45)**	**2.32/ 0.83 (18.14)**	**4.27/ 2.50 (8.82)**	**0.52/ 2.50 (1.89)**	**2.13/ 2.50 (8.45)**

[1]Results are presented as 'answers/ applicable questions' for each category, followed by percentages between brackets
[2]Percentages were calculated in relation to applicable questions for each category

Table 3

Table 3: Quality assessment summary by category and paper, "WHO" Checklist.[1, 2]

STUDY	POSITIVE ANSWERS				PARTIALLY POSITIVE ANSWERS	NEGATIVE ANSWERS
	STUDY DESIGN	DATA COLLECTION	ANALYSIS AND INTERPRETATION	OVERALL		
Shepard et al., 1993	6/7 (85.7)	1/4 (25.0)	8/12 (66.6)	15/23 (65.2)	2/23 (8.7)	6/23 (26.0)
Shepard et al., 2004	6/7 (85.7)	1/4 (25.0)	7/11 (63.3)	14/22 (63.6)	4/22 (18.1)	4/22 (18.1)
Palanca-Tan, 2008	5/7 (71.4)	2/4 (50.0)	4/09 (44.4)	11/20 (55.0)	1/20 (5.0)	8/20 (40.0)
Shepard et al., 2010	6/7 (85.7)	2/4 (50.0)	7/11 (63.3)	15//22 (68.2)	3/22 (13.6)	4/22 (18.1)
Carrasco et al., 2011	6/7 (85.7)	3/4 (75.0)	6/11 (54.5)	15/22 (68.2)	3/22 (13.6)	4/22 (18.1)
Lee et al., 2011	6/7 (85.7)	2/4 (50.0)	6/11 (54.5)	14/22 (63.6)	3/22 (13.6)	5/22 (22.7)
Mahoney et al., 2012	2/6 (33.3)	1/2 (50.0)	3/10 (30.0)	6/18 (33.3)	1/18 (5.5)	11/18 (61.1)
Durham et al., 2013	6/7 (85.7)	2/4 (50.0)	7/11 (63.6)	15/22 (68.2)	3/22 (13.6)	4/22 (18.1)
Hadisoemarto and Castro, 2013	5/7 (71.4)	2/5 (40.0)	5/10 (50.0)	12/22 (54.5)	4/22 (18.1)	6/22 (27.2)
Lee et al., 2015	5/7 (71.4)	2/5 (40.0)	4/10 (40.0)	11/22 (50.0)	4/22 (18.1)	7/22 (31.8)
Orellano et al., 2015	6/7 (85.7)	3/9 (33.3)	7/11 (63.6)	16/27 (59.2)	4/27 (14.8)	6/27 (22.2)
AVERAGE	**5.36/ 6.90 (77)**	**1.90/ 4.45 (44.4)**	**5.81/ 10.63 (53.9)**	**13.09/ 22.0 (59)**	**2.90/ 22.0 (13)**	**5.90/ 22.0 (27.6)**
STANDARD DEVIATION	**1.20/ 0.30 (15.91)**	**0.70/ 1.69 (14.16)**	**1.60/ 0.80 (11.81)**	**2.91/ 2.14 (10.5)**	**1.13/ 2.14 (4.72)**	**2.16/ 2.14 (13.05)**

[1]Results are presented as 'answers/ applicable questions' for each category, followed by percentages between brackets
[2]Percentages were calculated in relation to applicable questions for each category

Table 4

Table 4: Quality assessment summary by category and paper, "Constenla et al." Checklist. [1]

STUDY	STUDY DESIGN (13) [a]	DATA COLLECTION (13.5) [a]	ANALYSIS AND INTERPRETATION (11) [a]	OVERALL (37.5) [a]
Shepard et al., 1993	11 (84.6)	6.5 (48.1)	5.5 (50)	23 (61.3)
Shepard et al., 2004	13 (100)	6.5 (48.1)	5.75 (52.2)	25.25 (67.3)
Palanca-Tan, 2008	13 (100)	3.75 (27.7)	5.25 (47.7)	22 (58.6)
Shepard et al., 2010	13 (100)	6.5 (48.1)	6.5 (59)	26 (69.3)
Carrasco et al., 2011	12.5 (96.1)	6.75 (50)	8.25 (75)	27.5 (73.3)
Lee et al., 2011	11.5 (88.4)	6.75 (50)	9 (81.8)	27.25 (72.6)
Mahoney et al., 2012	13 (100)	6.25 (46.3)	5.25 (47.7)	24.5 (65.3)
Durham et al., 2013	11.75 (90.3)	5.5 (40.7)	6 (54.5)	23.25 (62)
Hadisoemarto and Castro, 2013	13 (100)	7.75 (57.4)	6.5 (59)	27.25 (72.6)
Lee et al., 2015	13 (100)	4.5 (33.3)	4.25 (38.6)	21.75 (58)
Orellano et al., 2015	11 (84.6)	8.25 (61.1)	8.5 (77.2)	27.75 (74)
AVERAGE	**12.34 (94.9)**	**6.27 (46.4)**	**6.43 (58.4)**	**25.05 (66.7)**
STANDARD DEVIATION	**0.85 (6.56)**	**1.29 (9.60)**	**1.52 (13.86)**	**2.27 (6.07)**

[1]Scores are presented for each category according to the specific methodology (Constenla et al., 2015) followed by percentages between brackets

[a] Maximum possible score for that category.

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APPENDIX 1

Search Strategy

1) Dengue [mp=title, abstract, subject headings, heading word, original title, keyword]
2) Dengue/ or Dengue Hemorrhagic Fever/ or Dengue Shock Syndrome/ or Dengue virus /or dengue vaccine/
3) Aedes aegypti/ or Aedes/ or Aedes triseriatus/ or Aedes albopictus/
4) 1 or 2 or 3
5) vaccine$ [mp=title, abstract, subject headings, heading word, original title, keyword]
6) vaccination$ [mp=title, abstract, subject headings, heading word, original title, keyword]
7) immunization [mp=title, abstract, subject headings, heading word, original title, keyword]
8) 5or 6 or 7
9) economic$ [mp=title, abstract, subject headings, heading word, original title, keyword]
10) cost$ [mp=title, abstract, subject headings, heading word, original title, keyword]
11) utilit$ [mp=title, abstract, subject headings, heading word, original title, keyword]
12) QALY$ [mp=title, abstract, subject headings, heading word, original title, keyword]
13) QUALY$ [mp=title, abstract, subject headings, heading word, original title, keyword]
14) quality adjusted life year$ [mp=title, abstract, subject headings, heading word, original title, keyword]
15) quality-adjusted life year$ [mp=title, abstract, subject headings, heading word, original title, keyword]
16) quality-adjusted-life-year$[mp=title, abstract, subject headings, heading word, original title, keyword]
17) DALY$ [mp=title, abstract, subject headings, heading word, original title, keyword]

18) disability adjusted life year$ [mp=title, abstract, subject headings, heading word, original title, keyword]
19) disability-adjusted life year$ [mp=title, abstract, subject headings, heading word, original title, keyword]
20) disability-adjusted-life-year$ [mp=title, abstract, subject headings, heading word, original title, keyword]
21) hye$ [mp=title, abstract, subject headings, heading word, original title, keyword]
22) health$ year equivalent [mp=title, abstract, subject headings, heading word, original title, keyword]
23) hui$ [mp=title, abstract, subject headings, heading word, original title, keyword]
24) life year$ gain$ [mp=title, abstract, subject headings, heading word, original title, keyword]
25) life-year$ gain$ [mp=title, abstract, subject headings, heading word, original title, keyword]
26) life year$ save$ [mp=title, abstract, subject headings, heading word, original title, keyword]
27) life-year$ save$ [mp=title, abstract, subject headings, heading word, original title, keyword]
28) preference weight$ [mp=title, abstract, subject headings, heading word, original title, keyword]
29) resource$ adj3 use$ [mp=title, abstract, subject headings, heading word, original title, keyword]
30) resource$ adj3 utili$ [mp=title, abstract, subject headings, heading word, original title, keyword]
31) resource$ adj3 consum$ [mp=title, abstract, subject headings, heading word, original title, keyword]
32) service$ adj3 use$ [mp=title, abstract, subject headings, heading word, original title, keyword]
33) service$ adj3 utili$ service$ adj3 consum$ [mp=title, abstract, subject headings, heading word, original title, keyword]
34) treatment$ adj3 use$ [mp=title, abstract, subject headings, heading word, original title, keyword]
35) treatment$ adj3 utili$ [mp=title, abstract, subject headings, heading word, original title, keyword]

36) treatment$ adj3 consum$ [mp=title, abstract, subject headings, heading word, original title, keyword]
37) hospitali$ [mp=title, abstract, subject headings, heading word, original title, keyword]
38) inpatient adj3 use$ [mp=title, abstract, subject headings, heading word, original title, keyword]
39) inpatient adj3 utili$ [mp=title, abstract, subject headings, heading word, original title, keyword]
40) inpatient adj3 consum$ [mp=title, abstract, subject headings, heading word, original title, keyword]
41) in-patient adj3 use$ [mp=title, abstract, subject headings, heading word, original title, keyword]
42) in-patient adj3 utili$ [mp=title, abstract, subject headings, heading word, original title, keyword]
43) in-patient adj3 consum$ [mp=title, abstract, subject headings, heading word, original title, keyword]
44) hospital adj3 use$ [mp=title, abstract, subject headings, heading word, original title, keyword]
45) hospital adj3 utili$ [mp=title, abstract, subject headings, heading word, original title, keyword]
46) hospital adj3 consum$ [mp=title, abstract, subject headings, heading word, original title, keyword]
47) intervention$ adj3 use$ [mp=title, abstract, subject headings, heading word, original title, keyword]
48) intervention$ adj3 utili$ [mp=title, abstract, subject headings, heading word, original title, keyword]
49) intervention$ adj3 consum$ [mp=title, abstract, subject headings, heading word, original title, keyword]
50) healthcare$ adj3 use$ [mp=title, abstract, subject headings, heading word, original title, keyword]
51) healthcare$ adj3 utili$ [mp=title, abstract, subject headings, heading word, original title, keyword]
52) healthcare$adj3consum$ [mp=title, abstract, subject headings, heading word, original title, keyword]

53) health care$ adj3 use$ [mp=title, abstract, subject headings, heading word, original title, keyword]
54) health care$ adj3 utili$ [mp=title, abstract, subject headings, heading word, original title, keyword]
55) health care$ adj3 consum$ [mp=title, abstract, subject headings, heading word, original title, keyword]
56) expenditure$ [mp=title, abstract, subject headings, heading word, original title, keyword]
57) expense$ [mp=title, abstract, subject headings, heading word, original title, keyword]
58) burden$ adj2 disease [mp=title, abstract, subject headings, heading word, original title, keyword]
59) burden$ adj2 illness [mp=title, abstract, subject headings, heading word, original title, keyword]
60) 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or 54 or 55 or 56 or 54 or 55 or 56 or 57 or 58 or 59
61) 4 and 8 and 60

APPENDIX 2

DATABASE	RESULTS	KEYWORDS USED
Embase	**512**	Dengue – MeSH **or** Dengue fever **or** Dengue hemorrhagic fever **or** dengue virus **or** Dengue Shock Syndrome **or** *Aedes Aegypti* **And** Vaccine - MeSH or vaccination or immunization **And** economic$ - MeSH **or** cost$ - MeSH **or** economic$ **or** cost$ **or** utilit$ **or** QALY **or** QUALY **or** quality adjusted life year$ or quality-adjusted life year **or** quality-adjusted-life-year$ or DALY$ **or** disability adjusted life year$ **or** disability-adjusted life year$ **or** disability-adjusted-life-year$ **or** hye$ **or** health$ year equivalent **or** hui$ **or** life year$ gain$ **or** life-year$ gain$ **or** life year$ save$ **or** life-year$ save$ **or** preference weight$ **or** resource$ adj3 use$ **or** Resource$ adj3 utili$ **or** resource$ adj3 consum$ **or** Service$ adj3 use$ **or** service$ adj3 utili$ **or** service$ adj3 consum$ **or** treatment$ adj3 use$ **or** treatment$ adj3 utili$ **or** treatment$ adj3 consum$ **or** hospitali$ **or** inpatient adj3 use$ **or** inpatient adj3 utili$ **or** inpatient adj3 consum$ **or** in-patient adj3 use$ **or** in-patient adj3 utili$ **or** in-patient adj3 consum$ **or** hospital adj3 use$ **or** hospital adj3 utili$ **or** hospital adj3 consum$ **or** intervention$ adj3 use$ **or** intervention$ adj3 utili$ **or** intervention$ adj3 consum$ **or** healthcare$ adj3 use$ **or** healthcare$ adj3 utili$ **or** healthcare$adj3 consum$ **or** health care$ adj3 use$ **or** health care$ adj3 utili$ **or** health care$ adj3 consum$ **or** expenditure$ **or** expense$ **or** burden$ adj2 disease **or** burden$ adj2 illness
Global Health	**196**	
Medline	**214**	
Web of Science	**115**	
LILACS	**57**	Dengue **or** Dengue fever **or** Dengue hemorrhagic fever **or** dengue virus **or** Dengue Shock Syndrome **or** *Aedes Aegypti* **And** Vaccine
NHS EED	**04**	Dengue **and** Vaccine

APPENDIX 3

Quality Assessment Checklist, adapted from "Drummond/ BMJ Checklist" (Drummond and Jefferson, 1996).

	QUESTIONS	POSSIBLE ANSWERS			
		Yes	No	Partially	Non applicable
Study Design	1. Was the research question stated?				
	2. Was the economic importance of the research question stated?				
	3. Was/were the viewpoint(s) of the analysis clearly stated and justified?				
	4. Was a rationale reported for the choice of the alternative programmes or interventions compared?				
	5. Were the alternatives being compared clearly described?				
	6. Was the form of economic evaluation stated?				
	7. Was the choice of form of economic evaluation justified in relation to the questions addressed?				
Data collection	8. Was/were the source(s) of effectiveness estimates used stated?				
	9. Were details of the design and results of the effectiveness study given (if based on a single study)?				
	10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of several effectiveness studies)?				
	11. Were the primary outcome measure(s) for the economic evaluation clearly stated?				
	12. Were the methods used to value health states and other benefits stated?				
	13. Were the details of the subjects from whom valuations were obtained given?				
	14. Were productivity changes (if included) reported separately?				
	15. Was the relevance of productivity changes to the study question discussed?				
	16. Were quantities of resources reported separately from their unit cost?				
	17. Were the methods for the estimation of quantities and unit costs described?				
	18. Were currency and price data recorded?				
	19. Were details of price adjustments for inflation or currency conversion given?				
	20. Were details of any model used given?				
	21. Was there justification for the choice of model used and key parameters on which it was based?				

Analysis and interpretation of results	22. Was time horizon of cost and benefits stated?				
	23. Was the discount rate stated?				
	24. Was the choice of rate justified?				
	25. Was an explanation given if cost or benefits were not discounted?				
	26. Were the details of statistical test(s) and confidence intervals given for stochastic data?				
	27. Was the approach to sensitivity analysis described?				
	28. Was the choice of variables for sensitivity analysis justified?				
	29. Were the ranges over, which the parameters were varied, stated?				
	30. Were relevant alternatives compared?				
	31. Was an incremental analysis reported?				
	32. Were major outcomes presented in a disaggregated as well as aggregated form?				
	33. Was the answer to the study question given?				
	34. Did conclusions follow from the data reported?				
	35. Were conclusions accompanied by the appropriate caveats?				

APPENDIX 4

Quality Assessment Checklist, adapted from "WHO checklist for economic evaluation of immunization programmes" (WHO, 2008).

	QUESTIONS	POSSIBLE ANSWERS			
		Yes	No	Partially	Non applicable
Framing	1. Is there a clear statement of the study question?				
	2. Have the alternatives being compared been clearly stated?				
	3. Has a cost-utility analysis been performed? If not, has that decision been justified appropriately?				
	4. Is the perspective of the analysis clearly stated? If a societal or multiple perspectives have been adopted, have the costs and outcomes been disaggregated to allow judgments to be made from different perspectives? Are the costs and outcomes reported consistent with the perspective reported?				
	5. Are the time frame and analytic horizon clearly stated and justified?				
Costs	6. Has a summary of the expected resource use and unit costs for each alternative been provided, including a specification of the assumptions behind calculations of the costs?				
	7. If productivity losses were estimated have they been reported separately? Has their relevance been discussed?				
	8. Have the methods used to estimate them been described and justified?				
	9. Is the currency stated? If so, is the date of the currency and prices used in the model stated with details of any conversions provided?				
Effects	10. Was the evidence identified systematically?				
	11. Were the methods described? If a single study was used, was its internal validity discussed? If multiple studies were used, was the method used to synthesize the results also discussed? Was external validity of the evidence discussed?				
	12. Was appropriate evidence of vaccine safety provided or referenced?				
	13. If applicable, were the methods of valuation and source of the values described?				
	14. Are adverse events from immunization impacts likely to have a substantial impact on the results of the analysis? If so, have they been included on both the costs and effects sides of the analysis?				
Modelling	15. Are the model structure and implicit or explicit assumptions clearly described?				
	16. Is the model type (static, dynamic or stochastic) clearly stated and justified in light of likely changes to the force of infection and the role of chance in the transmission process? Have the model's strengths and weaknesses been discussed?				
	17. Has the model been validated? If so, has it been validated in as many facets of validation as possible?				
Discounting	18. Is the discount rate clearly stated and justified?				
	19. Has a sensitivity analysis been conducted to explore the impact of varying the discount rate?				

Uncertainty	20. Have the costs and effects been presented for all alternatives?				
	21. Have dominated interventions been identified and excluded?				
	22. Has sensitivity analysis been conducted to assess the robustness of the findings to changes in the value of key parameters? Has the choice of parameters and the ranges over which they have been subjected to sensitivity analysis been stated and justified?				
	23. Has the national CE threshold been used, if one exists? If there is no national CE threshold, have the results of the evaluation been classified according to the per capita national GDP of the country in question?				
	24. Have the findings been compared to other economic evaluations undertaken in the same or neighbouring countries?				
Other factors	25. Is there a discussion of other important factors in the decision under consideration?				
Conclusions	26. Is an answer given to the study question?				
	27. Do the conclusions follow from the data reported?				
	28. Are the conclusions accompanied by the appropriate caveats?				

APPENDIX 5

Quality Assessment Checklist, adapted from "D. Constenla et al. Checklist" (Constenla et al., 2015).

		QUESTIONS	POSSIBLE ANSWERS			
			Yes	No	Partially	Non applicable
Study Design	1	a. Was the research question stated and justified?				
		b. Was the patient population defined?				
		c. Was the rationale for choosing the patient population explained?				
		d. Was the viewpoint of the analysis clearly stated and justified?				
	2	a. Was the choice of comparator explained? (applicable only if CMA, CEA, CBA)				
		b. Was the reason for choosing the comparator stated? (applicable only if CMA, CEA, CBA)				
	3	a. Was a recognized type of economic analysis used? (e.g. CA, CMA, CEA, CBA, COI)				
		b. Are the methods used in the study described and justified?				
		c. Was a decision tree/model included as a figure? (applicable only if a CEA)				
	4	a. Were the primary outcome measures for the study described?				
		b) Was the rationale for choosing these measures explained?				
Data Collection	5	a. Was the choice of data capture explained and justified?				
		b. Were any limitations of the data explained?				
	6	a. Was the source of probability of clinical events given? (applicable only if CMA, CEA, CBA, COI)				
		b. Are outcome data collected at same as resource use data? (along side RCT)				
		c. Were methods to value health states or other benefits explained? (if DALYs, QALYs were used)				
	7	a. Were currency and price adjustments for inflation or currency conversion explained?				
	8	a. Was discounting clearly reported and justified?				
		b. Was the time span of data collection of all relevant costs described?				
	9	a. Were all relevant costs (direct/indirect) identified and sources of these given?				
		b. Were methods for the estimation of all relevant costs described?				
		c. Were indirect costs measured and reported separately from the direct costs?				
		d. Were all relevant costs recent? (2-3 years from when the study was published)				
	10	a. Have all assumptions been specified and listed?				
		b. Were details of any model used reported and justified?				

Analysis an interpretation of Results	11	a. Were statistical tests and confidence intervals used and justified?				
		b. Were the base results both statistically and clinically significant?				
	12	a. Were adequate sensitivity analyses conducted and the choice of variables justified?				
		b. Did the sensitivity analyses include all reasonable scenarios that might affect the study results?				
	13	Are potential sources of bias presented?				
	14	Were incremental analyses reported?				
	15	Were appropriate comparisons made with other studies?				
	16	a. Does the evidence concur with the conclusions of the study?				
		b. Does the evidence answer the research question?				
	17	a. Are the conclusions justified?				
		b. Can the conclusions be generalized?				

Figure 1

Figure 1: Study Selection Process