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Cost-effectiveness of dengue vaccination in Brazil

Custo-efetividade da vacinação contra dengue no Brasil

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Keywords:
Brazil, cost-effectiveness, dengue, dengue vaccination, transmission model

ABSTRACT

Objective: To define the economic value of a tetravalent dengue vaccine in Brazil by estimating the cost-effectiveness vaccine price threshold per dose. **Methods:** A dengue dynamic transmission model was used to estimate the public health impact of dengue vaccination and related economic parameters. Two vaccination strategies were assessed: routine vaccination at 9 years old plus either a catch-up campaign of 7 cohorts (10 to 16 years old; R9&10-16) or 16 cohorts (10 to 25 years old; R9&10-25). Brazilian-specific demographic, epidemiological and economic data were used. The economic impact over 10 years was estimated from the public payer and societal perspectives. All costs were expressed in BRL2016. **Results:** Over 10 years, the R9&10-16 and R9&10-25 vaccination strategies would prevent 9 million and 15 million dengue cases, respectively, avoiding 269,906 (95% CI: 410,097–154,653) and 434,334 (95% CI: 547,052–304,799) disability-adjusted life years. This would result in savings of up to BRL7.4 billion (US$2.1 billion) from a societal perspective with the larger vaccination program. The cost-effective vaccine price threshold per dose for the R9&10-16 and R9&10-25 strategies would be BRL187.5 (95% CI: 109–276) (US$52.1) and BRL183.6 (95% CI: 129–230) (US$51.0), respectively, from the public payer perspective, and BRL221.5 (95% CI: 129–326) (US$61.5) and BRL216.8 (95% CI: 153–271) (US$60.2), respectively, from the societal perspective. **Conclusion:** The high threshold of vaccine price per dose demonstrates the significant economic value of dengue vaccination in Brazil, even for a large program with 16 catch-up cohorts.

Palavras-chave:
Brasil, custo-efetividade, vacinação contra a dengue, modelo de transmissão

RESUMO

Objetivo: Definir o valor econômico da vacina tetravalente contra dengue no Brasil por meio da estimativa do limiar de preço custo-efetivo por dose. **Métodos:** Um modelo dinâmico de transmissão foi utilizado para estimar o impacto em saúde pública da vacinação contra dengue e os parâmetros econômicos relacionados. A análise avaliou duas estratégias de vacinação: rotina aos 9 anos, mais campanha de vacinação com 7 coortes (10 a 16 anos; R9&10-16) ou 16 coortes (10 a 25 anos; R9&10-25). Foram utilizados dados demográficos, epidemiológicos e econômicos específicos para o Brasil. O impacto econômico foi estimado em 10 anos sob a perspectiva do pagador público e da sociedade. Todos os custos foram expressos em BRL2016. **Resultados:** Em 10 anos, as estratégias de vacinação R9&10-16 e R9&10-25 preveniriam 9 milhões e 15 milhões de casos de dengue, respectivamente, evitando 269,906 (95% CI: 410,097–154,653) e 434,334 (95% CI: 547,052–304,799) anos de vida ajustados por incapacidade. Isso resultaria em uma economia de até BRL7,4 bilhões (US$2,1 bilhões) sob a perspectiva da sociedade com o maior programa de vacinação. O limiar de preço custo-efetivo por dose para as estratégias R9&10-16 e R9&10-25 seria BRL187,5 (95% CI: 109–276) (US$52,1) e BRL183,6 (95% CI: 129–230) (US$51,0), respectivamente, sob a perspectiva do público pagador, e BRL221,5 (95% CI: 129–326) (US$61,5) e BRL216,8 (95% CI: 153–271) (US$60,2), respectivamente, sob a perspectiva da sociedade. **Conclusão:** Os altos limiares de preço custo-efetivo por dose demonstram o significativo valor econômico da vacinação contra dengue no Brasil, mesmo para um programa amplo com campanha com 16 coortes.

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Introduction

Dengue is a major public health problem in Brazil (De Castro *et al.*, 2013) and evidence suggests that the geographical spread in the country is increasing, with a rise in both the number and the severity of reported cases (Teixeira *et al.*, 2013). Furthermore, recent surveillance data showed more than 1.6 million dengue cases reported in 2015, which represents an incidence of 813.1 cases/100,000 inhabitants, the highest annual incidence registered in Brazil since dengue surveillance was implemented in the 1980s by *Sistema de Informação de Agravos de Notificação* (SINAN), and the highest incidence in Latin America reported to the Pan-American Health Organization (PAHO) over the last 25 years (Pan American Health Organization, 2015). Case fatality rates as high as 18.6% were reported for dengue patients in intensive care units (ICU) and 19.6% for in-hospital patients in a recent study in Minas Gerais State in South Eastern Brazil (Amancio *et al.*, 2015).

The economic burden of dengue in Brazil is substantial. A study of the cost of dengue illness across the Americas between 2000 and 2007 estimated the burden at US$2.1 billion per year (2010 US$) in the region, with substantial year to year variation – Brazil accounted for about 40% (US$878.2 million) of the total costs (Shepard *et al.*, 2011). A study by the same group found the overall cost in 2013 in Latin America and the Caribbean to be US$1.7 billion (Shepard *et al.*, 2016). For Brazil alone, an economic burden as high as US$1.2 billion for the period September 2012–August 2013 has also been reported (Martelli *et al.*, 2015). The estimated costs per patient from a societal perspective were reported as US$173 per ambulatory case and US$448 per hospitalized case, and US$64 per ambulatory case and US$237 from a public payer perspective in Brazil (Martelli *et al.*, 2015).

The World Health Organization (WHO) has set a target of reducing the mortality and morbidity associated with dengue disease by 50% and 25%, respectively, by 2020 (Da Costa *et al.*, 2014). Vaccination is a critical pillar of the WHO's strategy towards effectively fighting dengue. Vaccines are viewed as the most cost-effective option to achieve this target (Da Veiga *et al.*, 2015).

A recombinant live, attenuated, tetravalent dengue vaccine (CYD-TDV) has been shown to be effective in reducing symptomatic, virologically-confirmed dengue in two large pivotal efficacy studies involving ≥31,000 children aged 2–16 years in Asia and Latin America (Capeding *et al.*, 2014; Villar *et al.*, 2015). A pooled analyses of these two trials in children aged ≥9 years showed that the vaccine significantly reduced the incidence of virologically-confirmed dengue by 65.6% (95% CI, 60.7 to 69.9) and hospitalizations by 80.8% (95% CI, 70.1 to 87.7) during the first 25 months (Hadinegoro *et al.*, 2015). Lower efficacy rates were observed for those younger than 9 years of age. Subsequently, CYD-TDV (Dengvaxia®, Sanofi Pasteur) has recently been approved for use (administered as three doses, 6 months apart) in individuals aged 9–45 years in several endemic countries, including Brazil.

In April 2016, the WHO's Strategic Advisory Group of Experts (SAGE) on Immunization recommended the introduction of CYD-TDV in geographic settings (national or subnational) where epidemiological data indicate a high burden of disease (World Health Organization, 2016a); this was based in part on the comparative modelling of dengue vaccine (CMDVI) report published online, which used dynamic mathematical model analyses (Flasche *et al.* 2016a) and was followed in July 2016 by the publication of the WHO position paper (World Health Organization, 2016a), and later that year by the subsequent journal publication from the CMDVI group (Flasche *et al.* 2016b).

The benefits of dengue vaccination in Brazil are expected to be considerable. Vaccination benefits based on a mathematical model suggest a 22% reduction in the number of dengue cases for a strategy consisting of routine vaccination at age 9 years and catch-up campaign to 10 years of age (1 catch-up cohort), and 92% reduction with routine vaccination at age 9 years and catch-up campaign to 40 years of age (31 catch-up cohorts) over a 10-year period in comparison with a non-vaccination scenario (Araujo *et al.*, 2016). The reduction in the number of dengue cases would lead to a significant decrease in the number of hospitalizations: up to 739,378 hospitalizations would be prevented over a 10-year period with the larger vaccination strategy compared with the scenario without vaccination (Araujo *et al.*, 2016).

The economic implications of introducing CYD-TDV in Brazil have yet to be established. The purpose of this study was to calculate the economic value of dengue vaccination in Brazil from both public payer and societal perspectives and to estimate the cost-effective vaccine price threshold per dose.

Methods

The analysis was based on a mathematical model of dengue transmission dynamics previously published by Coudeville & Garnett (Coudeville & Garnett, 2012). The model allows the assessment of disease dynamics at a population level and the impact of different dengue vaccination strategies on dengue transmission (both direct to vaccine targets and indirect for the entire population), thereby enabling the public health and economic benefits to be determined accurately. The model has been refined (Coudeville *et al.*, 2016b) as more data became available on the efficacy of CYD-TDV (Capeding *et al.*, 2014; Hadinegoro *et al.*, 2015; Villar *et al.*, 2015) and knowledge improved on dengue transmission. The model has been used to evaluate the potential public health impact of vaccination in a number of endemic countries (Coudeville *et al.*, 2016a) and has helped inform the Strategic Advisory Group of Experts on immunization (SAGE) recommendations

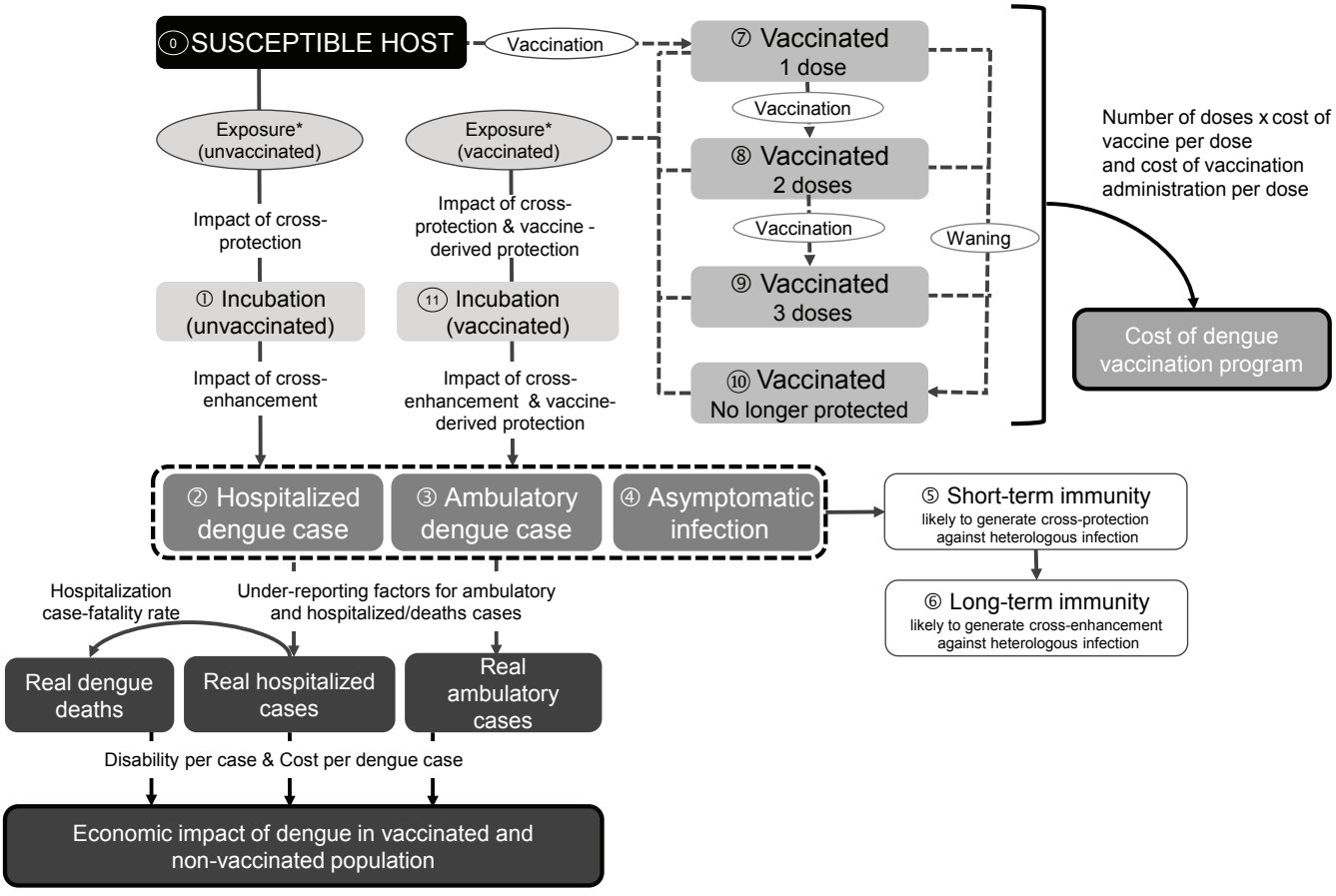
on the introduction of CYD–TDV in geographic settings with high dengue endemicity (World Health Organization, 2016b). The potential public health benefits of a dengue vaccination program in Brazil using this model have already been published (Araujo *et al.*, 2016); so the current analysis focused on the economic impact of dengue vaccination with CYD-TDV. The structure of the model with the economic components is presented in Figure 1. This model was adapted for Brazil using appropriate published or national data sources where available. The analysis focused on two extreme vaccination strategies described in Araujo et al. (Araujo *et al.*, 2016) as the most efficient strategies (in terms of cases avoided compared with doses administered) in Brazil: routine vaccination program at age 9 years plus a catch-up campaign of 7 cohorts (10 to 16 years old; R9&10-16) in one case, and 16 cohorts (10 to 25 years old; R9&10-25) in the second case.

Model inputs

Demographic, epidemiological, disease transmission, vector, vaccination and other parameters used in the model have been previously described and validated by Araujo et al. 2016 (Araujo *et al.*, 2016) and are summarized in Supplementary Table S1. In addition to these inputs, we considered Brazil-specific economic inputs in order to estimate the economic value of dengue vaccination in the country (also available in the supplementary Table S1).

Inputs related to the economic evaluation

Costs and health outcomes were discounted at 5% in line with national guidelines (http://rebrats.saude.gov.br/diretrizes-metodologicas). All economic data were denominated at January 2016 values of the Brazilian Real (BRL) using IPCA inflation rates, which are more conservative than the inflation rates in health services (FIPE Saúde; http://www.fipe.org.br/pt-br/indices/ipc/#) (Figure 2) and using exchange rates based on the Thomson Reuters database where necessary. The main source of cost data for the treatment of ambulatory and hospitalized dengue cases was taken from a previous study of the economic impact of dengue in Brazil (Supplementary Table S1) (Martelli *et al.*, 2015). The cost of vaccination other than vaccine price has been estimated from a quick literature review (supplement Table S2). The highest values



Sources: (Coudeville & Garnett, 2012; Coudeville *et al.*, 2016b).
*Following a bite by a vector infectious with dengue serotype 1, 2, 3 or 4.

Figure 1. Structure of the model: from the transmission model components to the economic components. Numbers 0 to 11 are for didactic purpose and help in describing the transmission model structure.

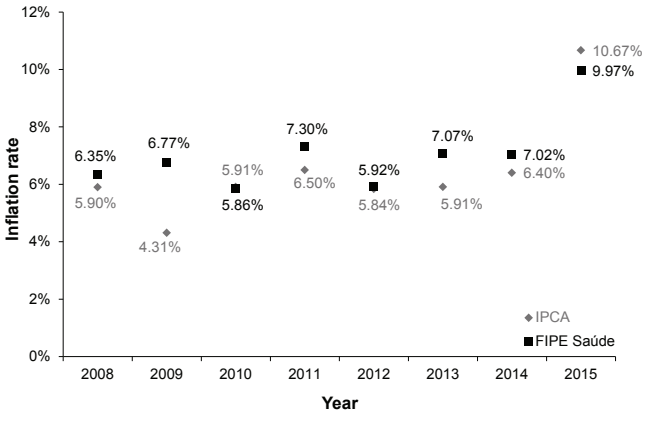


Figure 2. Conversion of all economic data into BRL January 2016 values using IPCA inflation rates, which are more conservative than inflation rates in health services (FIPE Saúde).

has been considered for dengue vaccination program to be conservative.

To calculate the Disability-Adjusted Life Years (DALYs), the classical methodology published by Fox-Rushby & Hanson (Fox-Rushby & Hanson, 2001) and Larson et al. (Larson, 2013) was considered, including a 5% discount as recommended by national health economic guidelines. To estimate the years of life with disability per non-fatal case, a literature review was performed to establish the disease burden in terms of disability weight and duration of symptoms (Supplementary Table S3). Publications that have used WHO, Global Burden of Disease (GBD) or World Bank disability values are not specific to dengue as these were extrapolated from general health states (Durham *et al.*, 2013; Lee *et al.*, 2011; Murray *et al.*, 2015; Shepard *et al.*, 2011). In addition, these health states were not ascertained in Brazil or a Latin American population. The only available disability estimates specific to dengue and Brazil were from the study published by Martelli et al. (Martelli *et al.*, 2011), which measured the daily losses in quality of life through the course of dengue infection using the visual thermometer-like scale technique. Disability weighting was calculated using 1-QoL status. The 1-QoL calculation is not ideal for estimating disability weighting, but has the merit that it provides estimates specific to dengue and Brazil and, therefore, fits well with our analysis. The disability weightings obtained from Martelli et al. (Martelli *et al.*, 2011) are close to that of the World Bank classification for class 5 (Luz *et al.*, 2009; Shepard *et al.*, 2011), which provides assurance in our estimates. The DALY lost per case was then calculated using the formula:

DALY loss per case	=	(number of days with dengue symptoms/365 days) x disability

This resulted in DALY loss per case of 0.024 for ambulatory and 0.028 for hospitalized subjects. Since there is uncertainty around these base case values, these parameters were varied in the sensitivity analysis. It is worth mentionning that the DALYs considered here do not take into consideration any persistent symptoms that occur with some dengue cases (Tiga 2016).

The time horizon of the analysis was 10 years, i.e. from 2016 (introduction of vaccination) to 2025. This time horizon is considered long enough to measure all benefits of vaccination (Ultsch *et al.*, 2016).

The vaccine was assumed to be cost effective, based on the World Health Organization's definition, if the incremental cost per additional DALY was less than 3-times the GDP per capita (World Health Organization, 2016c). GDP was taken from the IBGE (BRL28,876 per capita in 2015).

Sensitivity analysis

Parameters' uncertainties were addressed through univariate sensitivity analysis on the strategy R9&10-16 only, and through a probabilistic sensitivity analysis (PSA), using Monte Carlo simulations with 1,000 samples, on the two vaccination strategies defined (Supplementary Tables S4 and S5). Except for vaccine efficacy and annual endemicity, which have a discrete uniform distribution, all parameters were assigned to follow a triangular distribution. Although log-normal distribution would be preferable in cost parameters (Chau, 1995), triangular distribution was used due to some model development limitations. Acceptability curves were also generated in order to get the probability to be cost-effective according to the vaccine price per dose.

Results

The model shows that vaccination campaigns would lead to a decrease in the number of dengue cases, hospitalizations and deaths in Brazil (Table 1). Over 10 years of vaccination, 9 million and 15 million symptomatic dengue cases would be prevented with the R9&10-16 and R9&10-25 vaccination strategies (asymptomatic cases would also be prevented but these would not be captured in this health economic analysis), respectively, which is a decrease in symptomatic dengue cases of 49% (95% CI: 28–73) and 79% (95% CI: 55–91), respectively. Vaccination would also avoid 269,906 and 434,334 DALYs associated with dengue for the R9&10-16 and R9&10-25 strategies, respectively.

These public health benefits would generate associated economic benefits. Savings of BRL4.7 billion (US$1.3 billion) and BRL7.4 billion (US$2.1 billion) would be gained from costs associated with the disease from a societal perspective with R9&10-16 and R9&10-25 strategies, respectively, and savings of BRL1.3 billion (US$0.4 billion) and BRL2.1 billion (US$0.6 billion) from a public payer perspective (exchange rate taken for July 2016: US$1 = BRL3.60) (Table 2). Conse-

Table 1. Health outcomes over 10 years (2016–2025). Data expressed as mean values [95% CI] from the probabilistic sensitivity analysis with 1000 simulations.

Vaccination strategy	No vaccination (NV)	R9&10-16	*Incremental benefit R9&10-16 – NV*	R9&10-25	*Incremental benefit R9&10-25 – NV*
Symptomatic cases*	18,742,866 [15,489,874; 21,923,758]	9,482,650 [4,670,492; 13,894,070]	*-9,243,838 [-14,082,590; -5,251,334]*	3,810,950 [1,536,384; 8,315,765]	*-14,933,531 [-18,827,168; -1,003,233]*
Ambulatory cases	17,942,206 [14,828,240; 20,987,278]	9,082,011 [4,474,132; 13,305,587]	*-8,844,511 [-13,478,057; -5,020,300]*	3,651,289 [1,471,715; 7,968,112]	*-14,292,457 [-18,021,062; -9,949,158]*
Hospitalised cases	800,660 [661,635; 936,476]	400,639 [196,912; 587,215]	*-399,328 [-604,234; -230,212]*	159,661 [64,682; 347,652]	*-641,074 [-805,876; -452,771]*
Deaths	6,485 [5,359; 7,585]	3,245 [1,595; 4,757]	*-3,235 [-4,895; -1,865]*	1,293 [525; 2,816]	*-5,193 [-6,528; -3,667]*
DALYs	543,742 [449,268; 636,067]	273,363 [134,488; 400,617]	*-269,906 [-410,097; -154,653]*	109,456 [44,228; 238,532]	*-434,334 [-547,052; -304,799]*

* Symptomatic cases are composed of ambulatory and hospitalized cases. Hospitalized cases include deaths since it is assumed that all deaths come from hospitalized cases.

Table 2. Economic outcomes over 10 years (2016–2025) from the public payer (SUS) and societal perspectives in BRL2016. Data expressed as mean values [95% CI] from the probabilistic sensitivity analysis with 1000 simulations.

Vaccination strategy	No vaccination (NV)	R9&10-16	*Savings R9&10-16 – NV*	R9&10-25	*Savings R9&10-25 – NV*
COST OF DISEASE					
Public payer perspective					
Total cost of disease	2,704,120,973 [2,270,637,090; 3,151,004,805]	1,359,827,940 [702,880,973; 1,967,425,073]	*-1,342,086,487 [-1989444649; -797553146]*	576,764,623 [250,435,595; 1,184,951,656.]	*-2,127,580,551 [-2646774286; -1530317719]*
Ambulatory costs	2,320,781,783 [1,948,728,388; 2,704,238,785]	1,168,802,559 [603,766,811; 1,691,250,577]	*-1,150,082,796 [-1,706,929,731; -682,612,722]*	496,260,485 [215,219,928; 1,019,782,341]	*-1,824,711,500 [-2,271,134,631; -1,310,393,276]*
Hospitalisation costs	3,383,339,190 [321,908,701; 446,766,021]	191,025,381 [99,065,469; 277,613,364]	*-192,003,691 [-282,514,918; -115,628,082]*	80,504,137 [35,178,755; 163,711,288]	*-302,869,051 [-375,639,366; -220,189,433]*
Societal perspective*					
Total cost of disease	9,362,545,902 [7,631,393,479; 11,350,925,321]	4,678,960,359 [2,399,051,677; 6,983,463,303]	*-4,673,579,043 [-6,875,040,310; -2,691,815,076]*	1,978,014,798 [842,969,008; 4,126,707,295]	*-7,383,441,395 [-9,437,912,768; -5,161,654,598]*
Ambulatory costs	6,279,920,525 [4,993,754,934; 7,784,102,751]	3,161,932,447 [1,605,445,530; 4,786,544,532]	*-3,110,692,806 [-4,662,606,080; -1,725,195,659]*	1,342,762,486 [556,541,006; 2,777,586,230]	*-4,935,979,990 [-6,397,431,095; -3,379,985,566]*
Hospitalisation costs	723,492,950 [575,208,750; 896,783,950]	360,435,079 [183,601,806; 549,195,206]	*-362,223,653 [-541,046,920; -202,535,294]*	151,923,242 [63,478,260; 315,993,266]	*-571,438,367 [-738,901,864; -393,789,681]*
Premature death costs	2,359,132,427 [1,985,371,227; 2,755,439,901]	1,156,592,833 [599,274,255; 1,684,608,703]	*-1,200,662,585 [-1,753,045,037; -732,330,948]*	483,329,070 [212,453,317; 983,940,026]	*-1,876,023,038 [-2,314,248,760; -1,378,515,431]*
VACCINATION COSTS					
Cost of vaccination (other than vaccine price)	0	718,014,426 [599,143,541; 837,126,631]	*NA*	1,157,574,138 [964,716,960; 1,349,266,775]	*NA*

* Include direct costs from the public and private sectors as well as indirect costs from loss of productivity.

quently, the cost-effective vaccine price threshold per dose for the R9&10-16 and R9&10-25 vaccination strategies would be BRL187.5 (95% CI: 109–276) (US$52.1) and BRL183.6 (95% CI: 129–230) (US$51.0), respectively, from the public payer perspective, and BRL221.5 (95% CI: 129–326) (US$61.5) and BRL216.8 (95% CI: 153–271) (US$60.2), respectively, from the societal perspective (Figure 3). It is noteworthy that the vaccine price threshold between both strategies is very close meaning that increasing the the number of catch up would not significantly decrease the economic value of vacccination. Moreover, larger programs are associated with lower uncertainty (95% CI).

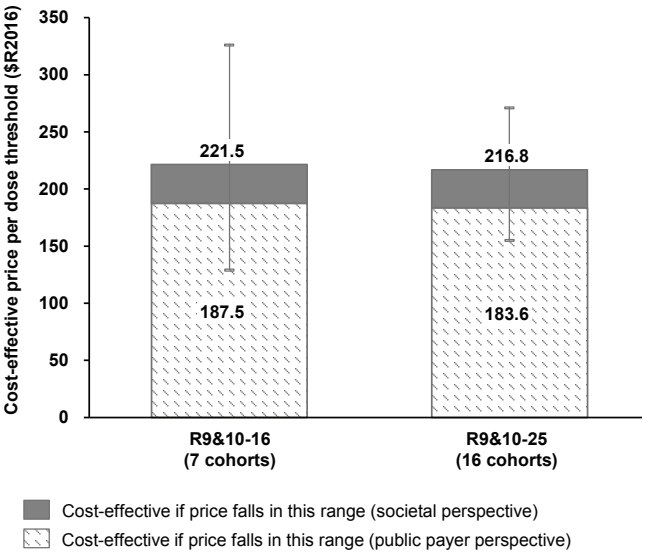


Figure 3. Cost-effective price/dose thresholds (based on 3x the GDP per capita) from the public payer (SUS) and societal perspectives over 10 years in BRL (January 2016). Average value from the probabilistic sensitivity analysis (1000 iterations).

Sensitivity analysis

The sensitivity analysis showed that the parameters with the highest impact on the results were the under-reporting factors, the duration of vaccine protection, the discount rate, and the DALYs per dengue case, as represented in the tornado diagrams for strategy R9&10-16 from both public payer and societal perspectives (Figure 4). Not surprisingly, the parameter with different impacts on public payer and societal perspectives was the 'cost of dengue disease', which had a lower impact in the public payer than in the societal perspective.

Acceptability curves showing the probability of being cost-effective according to the vaccine price per dose for both vaccination strategies from the public payer and societal perspectives are shown in Figure 5. From a public payer perspective, both the R9&10-16 and R9&10-25 vaccination strategies have a 50% probability of being cost-effective at a price per dose of BRL185 (Figure 5A). From a societal perspective, the R9&10-16 and R9&10-25 vaccination strategies have a 50% probability of being cost-effective at a price per dose of BRL219 and BRL218, respectively (Figure 5B).

Discussion

This analysis shows that dengue vaccination with CYD-TDV would be cost-effective in Brazil at prices up to BRL 184–222 (US$ 51–62) per dose, depending on the number of cohorts included in the vaccination program and the perspective of the analysis. These results confirm previous model-based analyses on the likely cost-effectiveness of CYD-TDV in Brazil; for example, Durham et al., using Phase IIb trial data, estimated that, depending on vaccine efficacy, the use of CYD-TDV might be cost-saving at US$93–204 per dose and cost-effective between US$237 and 534 per dose (Durham et al., 2013). In Colombia, a cost-effective analysis with the dengue vaccine found that all vaccination strategies tested for vaccination at 9 years of age and a catch-up campaign to 19 years of age were cost-effective with a vaccine price of US$39.03 from the public payer and societal perspectives (Rodríguez et al., 2015).

One of the key strengths of our analysis is that established country-specific data sources were used rather than making assumptions about key variables, and these were applied in an established dynamic transmission model. However, while the basic modelling approach can be applied to other countries, these results are not generalizable beyond Brazil. It is also possible that, while these data were considered representative of the whole country, this representativeness may be difficult to obtain given the size of the country and the geographical variability in the burden of dengue across the country. Despite these limitations, these findings would appear to be robust in sensitivity analyses; in general, vaccine protection duration, discount rate on health and costs and under-reporting have the greatest impact on the cost estimates. This is not surprising since under-reporting of dengue cases or any other disease to national surveillance programs is well-known and the duration of vaccine protection has yet to be fully established. Indeed, as for any vaccine, additional data collected during long-term follow-up of phase III and phase IV trials will help to refine these parameters in the future.

Although the benefits of CYD-TDV on symptomatic infection have been shown and are continually being assessed over the longer term, there is now evidence to suggest that vaccination may also prevent transmission by decreasing asymptomatic infections (Olivera-Botello *et al.*, 2016). Indeed, vaccine efficacy against asymptomatic infection was reported to be about half of that observed for symptomatic dengue. As most dengue infections are asymptomatic and likely contribute significantly to viral transmission (Bhatt *et al.*, 2013), simultaneous protection against both asymptomatic and symptomatic infections could contribute to reduced transmission and thus to greater indirect protection. This reduction in dengue transmission will have a significant public health impact at sufficient vaccination coverage. Furthermore, considering the outcomes of cost-effective analyses, it is also important to be aware that the use of vaccination may bring additional benefits beyond those considered in a typical economic evaluation, which include reduced spending on outbreak control and reduced losses in terms of tourism (Nishikawa *et al.*, 2016) and productivity (Barnighausen *et al.*, 2013). The costs associated with these activities are usually not considered in most cost-effectiveness studies, even when the societal perspective is taken, because it is difficult to measure these activities with precision.

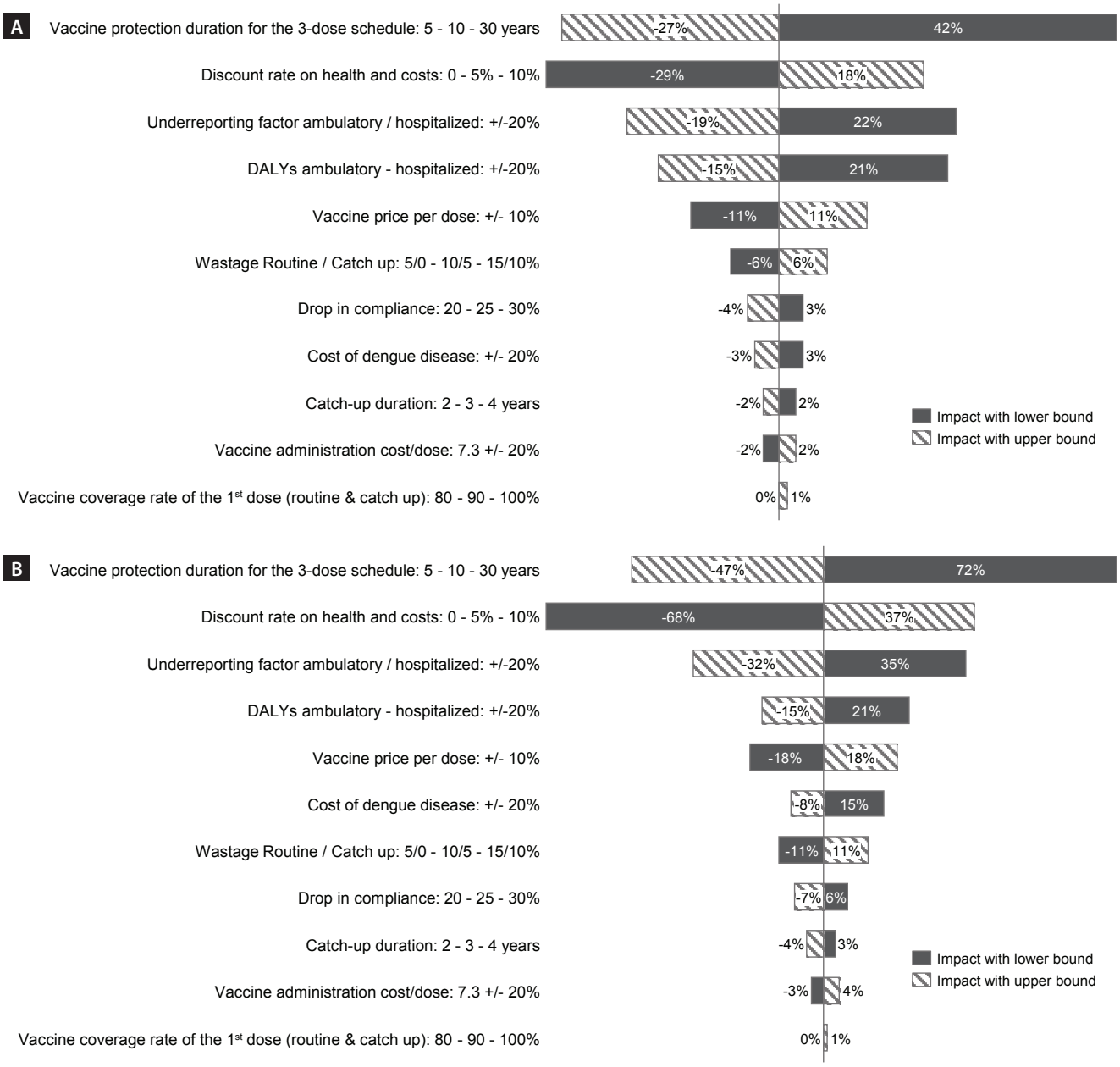


Figure 4. Univariate sensitivity analysis, represented through a tornado diagram, showing the impact of varying some parameters on the cost-effective price threshold of the strategy R9&10-16, from (A) public payer and (B) societal perspectives.

Conclusions

This analysis suggests that introducing CYD-TDV in Brazil would substantially reduce the disease and economic burden in the country, contributing to the achievement of the goals established by the WHO to reduce dengue burden. Dengue vaccination programs would be cost-effective in Brazil up to a vaccine prices of BRL 184–222 (US$ 51–62) per dose, depending on the number of the cohorts included in the vaccination program and the perspective of the analysis. The mean cost-effective price thresholds of both vaccination strategies are similar but the largest strategy (R9&10-25) averts more cases and costs of disease in absolute numbers and reduces the uncertainty in the results. The robustness of these findings was confirmed in the sensitivity analyses. These findings should help inform policy-makers about the decision regarding the introduction of dengue vaccine in public health programs in Brazil.

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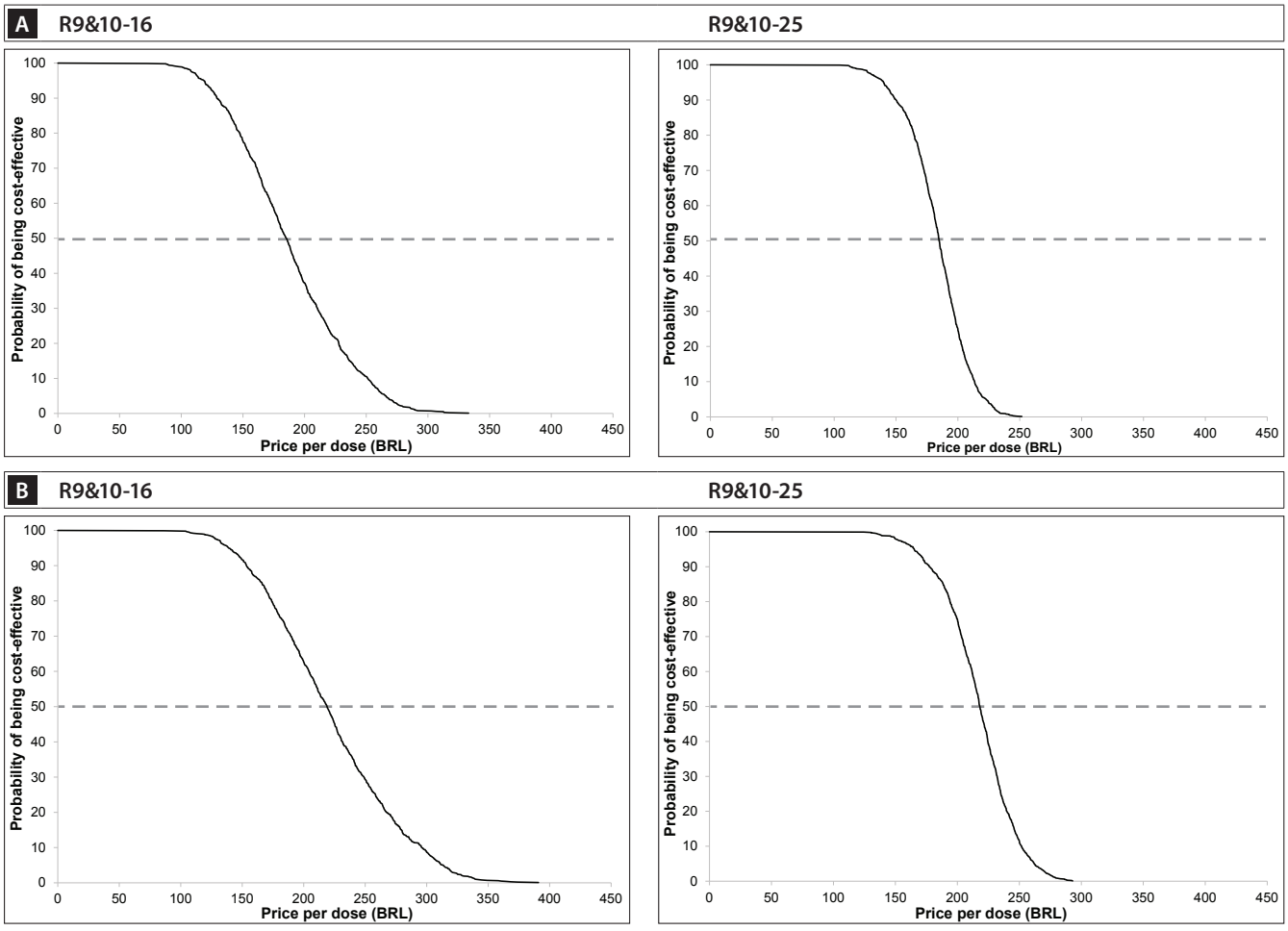

Figure 5. Acceptability curves of probability of being cost-effective according to the vaccine price per dose for R9&10-16 and R9&10-25 vaccination strategies from (A) public payer and (B) societal perspectives.

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Table S1. Parameters used to estimate the public health impact and economic impact of dengue vaccination in Brazil

Parameter	Base case	Source
Parameters related to demographics		
Total population the first year of vaccination	2016: 206 081 432	IBGE, Projeção da população por sexo e grupos de idade, em 1º de julho – 2000/2060 http://www.ibge.gov.br/home/estatistica/populacao/projecao_da_populacao/2013/ (Instituto Brasileiro de Geografia e Estatística (IBGE), 2013b)
Endemic territory	100%	Teixeira M, et al. Epidemiological trends of dengue disease in Brazil (2000–2010): a systematic literature search and analysis. PLOS Negl Trop Dis. 2013;7(12):e2520 (Teixeira *et al.*, 2013)
Population growth (%)	Average 2016–2025: 0.66%	IBGE, Projeção da população por sexo e grupos de idade, em 1º de julho – 2000/2060 http://www.ibge.gov.br/home/estatistica/populacao/projecao_da_populacao/2013/ (Instituto Brasileiro de Geografia e Estatística (IBGE), 2013b)
Age distribution	As in 2013 population	IBGE, Projeção da população por sexo e grupos de idade, em 1º de julho – 2000/2060 http://www.ibge.gov.br/home/estatistica/populacao/projecao_da_populacao/2013/ (Instituto Brasileiro de Geografia e Estatística (IBGE), 2013b)
Survival	Data 2013	Survival: IBGE, Diretoria de Pesquisas (DPE), Coordenação de População e Indicadores Sociais (COPIS) 2013: http://www.ibge.gov.br/home/estatistica/populacao/tabuadevida/2013/defaulttab_xls.shtm (Instituto Brasileiro de Geografia e Estatística (IBGE), 2013a)
Disability rate of the population	Average between male and female in 2013	Global Burden of Disease (GBD) 2013. Global, regional, and national disability-adjusted life years (DALYs) for 306 diseases and injuries and healthy life expectancy (HALE) for 188 countries, 1990–2013: quantifying the epidemiological transition.(Murray *et al.*, 2015) Supplement appendix
Parameters related to epidemiology		
Seroprevalence	CYD 15 Brazil specific data (2011–2013)	Villar L, et al. from CYD15 Study Group. Efficacy of a tetravalent dengue vaccine in children in Latin America. N Engl J Med. 2015;372(2):113-23 (Villar *et al.*, 2015)
Serotype distribution in dengue cases (% per year)	Average 2001–2014: DEN1 32% DEN2 26% DEN3 32% DEN4 9%	2001–2012: Ceará. Governo do Estado. Secretaria da Saúde. Boletins. Informe semanal da dengue - 17 de maio de 2013. Disponível em: <http://www.saude.ce.gov.br/index.php/boletins>. Acesso em: 24 maio 2013. 2010-2014: Brazil data country are porporcioned by Lucia Bricks & Dr. Giovanini on May 2013 2013: GAL-CGLAB/MoH- pdf presentation_Brasil MoH_Apresentação da Coletiva de Imprensa de Dengue_19Nov2013 442 municipalities 2014 DEN1: Epidemiological bulletin/MoH Brazil/EW16, 2015;46(5)
Monthly incidence of total dengue probable cases reported (/100,000)	Data from 2001 to 2014	Teixeira M, et al. Epidemiological trends of dengue disease in Brazil (2000–2010): a systematic literature search and analysis. PLOS Negl Trop Dis. 2013;7(12):e2520 (Teixeira *et al.*, 2013) Boletim Epidemiológico Secretaria de Vigilância em Saúde – Ministério da Saúde. Volume 46 N° 28 – 2015. ISSN 2358-9450 http://portalsaude.saude.gov.br/images/pdf/2015/outubro/01/2015-030-bol--2-.pdf Agosto 2015, Graphic presented by Dr. João Bosco at Simpósio Satélite – Sanofi, XIX Congresso Brasileiro de Infectologia Gramado, 27 de agosto de 2015, adjusted to english
Hospitalization rate reported (%)	Average 2010–2013: 8.21%	Teixeira M, et al. Epidemiological trends of dengue disease in Brazil (2000–2010): a systematic literature search and analysis. PLOS Negl Trop Dis. 2013;7(12):e2520 (Teixeira *et al.*, 2013) SIH, Update: 06/06/2014

Hospitalized case fatality rate	0.81%	Average 2010-2013 Boletim Epidemiológico Secretaria de Vigilância em Saúde – Ministério da Saúde. Volume 46 N° 28 – 2015. ISSN 2358-9450 http://portalsaude.saude.gov.br/images/pdf/2015/outubro/01/2015-030-bol--2-.pdf (Ministério da Saúde, 2015) Agosto 2015, Graphic presented by Dr. João Bosco at Simpósio Satélite – Sanofi, XIX Congresso Brasileiro de Infectologia Gramado, 27 de agosto de 2015, adjusted to english The model considered that all deaths come from hospitalizations
Under-reporting associated to reported incidence	Ambulatory cases: 3.2 Hospitalized cases: 1.6	Martelli CM, et al. Economic Impact of Dengue: Multicenter Study across Four Brazilian Regions. PLoS Negl Trop Dis. 2015;9(9):e0004042 (Martelli et al., 2015)
Parameters related to disease transmission		
Average duration of cross-protection after natural infection	15.59 months	Estimated from CYD14 and CYD15data Coudeville L, et al. Estimation of parameters related to vaccine efficacy and dengue transmission from two large phase III studies. Vaccine. 2015, Nov 21. pii: S0264-410X(15)01665-5. doi: 10.1016/j.vaccine.2015.11.023 (Coudeville et al., 2015)
Relative risk to develop a symptomatic case (as compared with primary infection	Ambulatory case (2^{nd} infection): 1.77 Hospitalized case (2^{nd} case): 1.84 Symptomatic case (3^{rd} and 4^{th} infection: 0.39	Estimated from CYD14 and CYD15data Coudeville L, et al. Estimation of parameters related to vaccine efficacy and dengue transmission from two large phase III studies. Vaccine. 2015, Nov 21. pii: S0264-410X(15)01665-5. doi: 10.1016/j.vaccine.2015.11.023 (Coudeville et al., 2015)
Relative infectivity from human to mosquito according to the severity of the infection	Severe: 4x (for all serotypes) Mild: 4x (for all serotypes) Asymptomatic: 1x	Assumptions vs. Observed efficacy for all symptomatic cases from CYD14 & 15 results (Capeding et al., 2014; Hadinegoro et al., 2015; Villar et al., 2015) Supported by other references: Yoon In-Kyu, et al. Characteristics of mild dengue virus infection in Thai children. Am J Trop Med Hyg. 2013;89(6):1081-7 (Yoon et al., 2013) Nguyen NM, et al. Host and viral features of human dengue cases shape the population of infected and infectious Aedes aegypti mosquitoes. Proc Natl Acad Sci USA. 2013;110(22):9072-7 (Nguyet et al., 2013) Carrington LB, Simmons CP. Human to mosquito transmission of dengue viruses. Front Immunol. 2014;5:290. doi: 10.3389 / fimmu.2014.00290 (Carrington & Simmons, 2014)
Duration of dengue infection (hosts)	Average duration of the incubation period (IIP): 5.5 days	De Castro Medeiros LC et al. Modeling the dynamic transmission of dengue fever: investigating disease persistence. PLoS Negl Trop Dis. 2011;5(1):e942. ISSN 1935-2727. Data: model Brazil, 5.5 days (68% CI 4–7) (de Castro Medeiros et al., 2011) Supported by other references: Rudolph 2014: recent systematic review, median at 5.3 days (95%CI: 5–5.7) Chan 2012: systematic review, 5.9 days (95%CI: 3.4–10) Bartley et al. The seasonal pattern of dengue in endemic areas: mathematical models of mechanisms. Transactions of the royal society of tropical medicine and hygiene (2002) 96, 387-397: 5 days (2–12) (Bartley et al., 2002)
	Average duration of the infectious period: 4.5 days (3–6)	Bartley et al. The seasonal pattern of dengue in endemic areas: mathematical models of mechanisms. Transactions of the royal society of tropical medicine and hygiene (2002) 96, 387-397 (Bartley et al., 2002) De Castro Medeiros LC et al. Modeling the dynamic transmission of dengue fever: investigating disease persistence. PLoS Negl Trop Dis. 2011;5(1):e942. ISSN 1935-2727. Model 4.5 days (68% CI 3–6).(de Castro Medeiros et al., 2011)

Duration of dengue infection (vectors)	Minimum duration of the incubation period (EIP): 8 days Average duration of the incubation period (EIP): 12 days	Bartley et al. The seasonal pattern of dengue in endemic areas: mathematical models of mechanisms. Transactions of the Royal Society of Tropical Medicine and Hygiene 2002;96:387-397 (Bartley et al., 2002) Data: 12 days (8-20) for duration of latent period in vector
Parameters related to vector data		
Vector life expectancy	14.49 days	Andraud M, Hens N, Beutels P. A simple periodic-forced model for dengue fitted to incidence data in Singapore. Math Biosci. 2013;244(1):22-8. ISSN 0025-5564 (Andraud et al., 2013) Fouque F, et al. Aedes aegypti survival and dengue transmission patterns in French Guiana. J Vector Ecol. 2006;31(2):390-9. ISSN 1081-1710 (Fouque et al., 2006)
Maximum lifetime	30 days	Coudeville L, Garnett GP. Transmission dynamics of the four dengue serotypes in southern Vietnam and the potential impact of vaccination. PLoS One. 2012;7(12):e51244. ISSN 1932-6203 (Coudeville & Garnett, 2012) Castanha PMS et al., Force of infection of dengue serotypes in a population-based study in the northeast of Brazil. Epidemiol. Infect. 2013;141:1080-8 (Castanha et al., 2013)
Ratio vector/ Host	2	De Castro Medeiros LC et al. Modeling the dynamic transmission of dengue fever: investigating disease persistence. PLoS Negl Trop Dis. 2011;5(1):e942. ISSN 1935-2727. Model: 4.5 days (68% CI 3–6) (de Castro Medeiros et al., 2011)
Daily biting rate	0.67 (0.33–1)	Bartley et al. The seasonal pattern of dengue in endemic areas: mathematical models of mechanisms. Transactions of the royal society of tropical medicine and hygiene. 2002;96:387-97 (Bartley et al., 2002) Other sources: 0.7 used in Durham et al. 2013 (Durham et al., 2013)
Vector population density	Monthly estimations	Honorio NA, et al. Spatial evaluation and modeling of Dengue seroprevalence and vector density in Rio de Janeiro, Brazil. PLoS Negl Trop Dis. 2009;3(11):e545. ISSN 1935-2727, http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0000545 (Honorio et al., 2009)
Transmission probability upon bite	Host to Vector: 0.9 Vector to Host: 0.9	De Castro Medeiros LC, et al. Modeling the dynamic transmission of dengue fever: investigating disease persistence. PLoS Negl Trop Dis. 2011;5(1):e942. ISSN 1935-2727. Model: 4.5 days (68% CI 3–6) (de Castro Medeiros et al., 2011). Data: model, 0.90 used for both probability (from Focks 1995 and Watson 1999)
Force of the infection from an external reservoir	0.00005	Coudeville L, Garnett GP. Transmission dynamics of the four dengue serotypes in southern Vietnam and the potential impact of vaccination. PLoS One. 2012;7(12):e51244. ISSN 1932-6203 (Coudeville & Garnett, 2012)
Parameters related to vaccination		
Vaccine efficacy	• Estimated from Phase 3 efficacy studies with the consideration of the following characteristics of the vaccine profile: • differences in efficacy between serotypes • difference in efficacy according to serostatus at baseline • increase in efficacy with doses for subjects vaccinated when seropositive • increase efficacy against hospitalized cases • accelerated exposure to secondary and post-secondary infection in case of vaccination • reduced efficacy against asymptomatic infection compared to against symptomatic infection (50% relative efficacy)	CYD14&15 results (Phase III clinical trials) and long-term follow up of hospitalized cases. Sources: Hadinegoro SR, et al. Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease. N Engl J Med. 2015;373(13):1195-206. ISSN 0028-4793 (Hadinegoro et al., 2015) Villar L, et al. Efficacy of a Tetravalent Dengue Vaccine in Children in Latin America. N Engl J Med. 2015;372(2):113-23. ISSN 0028-4793 (Villar et al., 2015) Capeding MR, et al. Clinical efficacy and safety of a novel tetravalent dengue vaccine in healthy children in Asia: a phase 3, randomised, observer-masked, placebo-controlled trial. Lancet. 2014;384(9951):1358-65. ISSN 0140-6736 (Capeding et al., 2014) Coudeville L, et al. Estimation of parameters related to vaccine efficacy and dengue transmission from two large phase III studies. Vaccine 2015. ISSN 0264-410X (Coudeville et al., 2015)

Duration of vaccine protection	On average: d1: 2.5 years d2: 5 years d3: 10 years		Assumptions: This assumed duration of protection (ie, 10 years on average for 3 doses) is conservative: when considering the live-attenuated yellow fever vaccine for which a duration of protection above 20 years has been reported. (Gotuzzo et al., 2013 http://www.ncbi.nlm.nih.gov/pubmed/24006295) (Gotuzzo et al., 2013) when considering the waning rate and duration of protection estimated from long-term follow-up of phase III trials for pre-exposed people (Coudeville et al., 2015) Follow-up of phase II and III studies, in addition to the extensive phase IV plan, will help to refine the duration of protection.
Coverage rate	d1: 90% d2: 67.5% d3: 45%		Assumptions based on country experience Brazilian Health Ministry. Vaccine coverage. Available at: http://tabnet.datasus.gov.br/tabdata/livroidb/Com2007/Com_F13.pdf (Brazilian Health Ministry, 2007)
Wastage rate	10% for routine 5% for catch up (mass immunization campaign)		PROVAC guidelines (Vaccine Introduction Guidelines. PAHO: adding a vaccine to a national immunization program: decision and implementation)
Duration of mass immunization campaign	End of catch-up: 4 years		Assumption based on feasibility. We consider that at least all targeted population receive the first dose in the 3 first years, the 4th year is the finalization of the catch up (2nd and 3rd missing dose)
Vaccination program strategy	Geographic area: National Scenarios: Routine at 9 years + 7 Catch up cohorts campaign Routine at 9 years + 16 Catch up cohorts campaign		Araujo et al. 2016: "A program with routine vaccination at 9 years old and 7-16 catch-up cohorts were shown to be the most efficient in Brazil over a 10-year period" (Araujo et al., 2016)
Year of start public vaccination	2016		Assumption
Economic parameters			
Currency	BRL Jan 2016		All costs have been updated to Jan 2016 using IPCA inflation rates (Instituto Brasileiro de Geografia e Estatística [IBGE], Diretoria de Pesquisas, Coordenação de Índices de Preços, Sistema Nacional de Índices de Preços ao Consumidor. 2016. Available at: http://www.ibge.gov.br/home/estatistica/indicadores/precos/inpc_ipca/ipca-inpc_201602_1.shtm (Instituto Brasileiro de Geografia e Estatística (IBGE), 2016)
Perspectives	Public Payer	Societal	
Direct cost per ambulatory case	143 (BRL2013) → 171 (BRL2016)	206 (BRL2013) → 243 (BRL2016)	Martelli CM, et al. Economic Impact of Dengue: Multicenter Study across Four Brazilian Regions. PLoS Negl Trop Dis. 2015;9(9):e0004042. ISSN 1935-2727 (Martelli et al., 2015) Data given in BRL 2013 were updated to 2016 inflation rates
Indirect cost per ambulatory case	0	187 (BRL2013) → 221 (BRL2016)	
Direct cost per hospitalized case	538 (BRL2013) → 633 (BRL2016)	816 (BRL2013) → 961 (BRL2016)	
Indirect cost per hospitalized case	0	201 (BRL2013) → 237 (BRL2016)	
GDP/per capita	28,876		IBGE, Banco Central do Brasil estimates, 2015. http://www.bcb.gov.br/?INDICATORS Use to estimate the costs of premature deaths – loss of productivity (human capital approach) (Instituto Brasileiro de Geografia e Estatística (IBGE), 2015)
Cost-effective threshold	86,629		3x GDP per capita (WHO guidelines)

Vaccination costs / dose (other than vaccine price)	7.3	Based on (Goldie, Kim et al. 2007) (Goldie et al., 2007) and (Novaes, Almeida et al. 2015) (Novaes et al., 2015) for HPV. Include freight, supplies, administration, monitoring, cold chain, injection safety, operational, programmatic services, social mobilization and outreach for new adolescent vaccine
Others parameters		
Time horizon	10 years (2016–2025)	Time horizon long enough to measure the whole benefits of vaccination (Ultsh et al. 2015) (Ultsch et al., 2016)
Discount rate	Health outcomes: 5% Economic outcomes: 5%	Brazilian HE guidelines

Table S2. Vaccination costs (other than vaccine price) per dose available i n the literature and considered in the present analysis to estimate the cost of introducing a dengue vaccination program.

Vaccine	Vaccination cost (other than vaccine price) per dose	Sources	In $R2016 using IPCA inflation rates
Dengue	Not considered in the analysis	Durham et al., 2013 (Durham *et al.*, 2013)	NA
Meningococcal C	2.098 (in BRL 2006)	De Soarez et al., 2011 (de Soarez *et al.*, 2011)	3.6
PCV10	1US$ Year of the costs not available	Sartori et al., 2012 (Sartori *et al.*, 2012)	NA
PPV23	Vaccine public payer price + door to door transportation cost = US$15 (in US$ 2008). No medical visit costs considered (opportunistic) Administration costs not separated from vaccine price	Neto et al., 2011 (Neto *et al.*, 2011)	NA
Pneumoccocal	**1.90 US$ = 3.57R$** In US$ december 2011, exchange rate of US$1 = BRL1.88	De Soarez et al., 2015 (de Soarez *et al.*, 2015)	4.7
HPV	Minimum cost per vaccinated individual (I$2000): - Vaccine dose (three doses × unit cost) 15.00 (6.00–390.00) - Vaccine wastage 15% = I$ 2.25 (5–20) - Freight, supplies, supply wastage and administration 2.81 - Incremental immunization support (monitoring, cold chain, injection safety, operational and programmatic services) 2.94 - Incremental cost of social mobilization and outreach for new adolescent vaccine 2.00 (0–3.00) **-> 2.81 + 2.94 + 2.00 = 7.75/vaccinated = 2.58I$/dose** (without wastage rate since already included in our present analysis separatly)	Goldie et al 2007 (Goldie *et al.*, 2007)	Difficult to update because from I$2000. Used in following HPV analysis anyway (CONITEC and Novaes et al., 2015 (Novaes *et al.*, 2015))
HPV	**R$8.33** for administration, investment in logistic in 2008. **+ inclusion of an investment for the 1st year of launch**	CONITEC file 2008	Suggestion to use peer-reviewed publication developed after the CONITEC file: see Novaes et al 2015 (Novaes *et al.*, 2015)
HPV	Costs in US$ 2008, at the exchange rate of US$ 1.00 = R$1.83. Administration costs estimated at **US$ 10 per vaccinated girl (US$ 3.33 per dose),** based on previous studies relating to Brazil (Goldie *et al.*, 2007), including wastage rate. Confusion between I$ from Goldie et al., 2007(Goldie *et al.*, 2007) and US$ (I$ higher than US$). Moreover, no inflation rate applied between value in I$ 2000 from Goldie et al., 2007 and the Novaes 2015 study in US$ 2008 An estimate produced by the NIP for **infrastructure coordination and logistics investments needed to introduce this new vaccine was also considered (US$ 15 million)** For present analysis, consider a cost of US$7.75 per vaccinated = 2.58 per dose excluding wastage rate = BRL4.72	Novaes et al., 2015 (Novaes *et al.*, 2015)	7.3

Rotavirus	Since the rotavirus vaccine can be administered at the same time as the current recommended tetravalent DTPw-Hib and OPV vaccines, incremental administration costs were assumed to be low. Both **administration costs (US$1, in BRL2004, exchange rate: US$1 = BRL2.65, Brazilian Central Bank)** and expected losses from waste (10% of vaccine doses) were taken from the literature, as no local data were available (Podewils et al., 2005;192 (suppl 1):S133-45.) (Podewils *et al.*, 2005)	De Soárez et al 2008 (de Soarez *et al.*, 2008)	4.96

Table S3. Studies available in the literature which estimate or consider the impact of dengue in term of disability

Subjects/patients	Average duration of symptoms in days/Duration of impaired QoL in days	Health status index during dengue episode	Disability weight	Methodology	DALY lost per non-fatal dengue case
Martelli et al 2011 (Martelli *et al.*, 2011)				EuroQOL thermometer-like scale during the dengue episode, Brazil 372 laboratory-confirmed dengue patients >12 years old	
Ambulatory	10.9 (supported by Suaya et al., 2009 (Suaya et al., 2009) values for Brazil: 12.3 ± 5.2)	0.2	0.8 (1-health status)		0.024
Hospitalized	11.2 (supported by Suaya et al., 2009 (Suaya et al., 2009) values for Brazil: 13.3 ± 5.0)	0.1	0.9 (1-health status)		0.028
Lum et al 2008 (Lum *et al.*, 2008)				EuroQol visual thermometer scale 207 participants, 40% were ambulatory and 60% were hospitalized	
Ambulatory	9	~0.45	0.55 (1-health status)		0.014
Hospitalized	13	~0.39	0.61 (1-health status)		0.022
Shepard et al 2011 (Shepard *et al.*, 2011), Luz et al 2009 (Luz *et al.*, 2009)				Use Meltzer 1998 Puerto Rico: Disabilities were assumed to be the same for each level of severity, with a base rate of 0.81, which is class 5 in the world bank classification	
Dengue fever	Shepard: 4.5 (2–7) Luz: Uniform distribution (2–7)		0.81		0.010
Dengue hemorrhagic fever	Shepard: 14 (10–18) Luz: Uniform distribution (10–18)		0.81		0.031
Carrasco et al 2011 (Carrasco *et al.*, 2011)				3 sets of disability weights considered: 1. based on recent literature estimates, reflects that all symptomatic cases are incapable of carrying out normal daily activities during illness; 2. based on WHO disability weights; 3. weights obtained in an empirical study that measured daily the losses in quality of life through the course of the infection using the visual thermometer-like scale technique.	
Dengue fever	NA		0.211 (WHO) 0.81 (Literature)		NA
Dengue haemorrhagic fever/ dengue shock syndrome	NA		0.5 (WHO) 0.85 (Literature)		NA

Durham et al 2013 (Durham et al., 2013)				Use WHO | Global Burden of Disease 2004: disability for infectious disease in general reported in the GBD 1990	
Dengue fever	0.019 years *365 days = 6.9		0.197		0.004
Dengue haemorrhagic fever/ dengue shock syndrome	0.0325 years *365 days = 11.9		0.545		0.018
Lee et al 2011 (Lee *et al*., 2011)				Use WHO | Global Burden of Disease 2004: disability for infectious disease in general reported in the GBD 1990	
Dengue fever	NA		0.197		NA
Dengue haemorrhagic fever	NA		0.545		NA
Global Burden of Disease study (Murray *et al*., 2015)				The disability weights are the one associated to "health states" and are not specific to dengue	
Acute dengue fever, equivalent to the health state: "infectious disease, acute episode, moderate"	6 days	94.50%	0.051 (0.032–0.074)		0.001
Severe acute dengue, equivalent to the health state: "infectious disease, acute episode, severe"	14 days	5.50%	0.133 (0.088–0.190)		0.005
Post-dengue chronic fatigue, equivalent to the health state: "Infectious disease, post-acute consequences"	6 months	8.50%	0.219 (0.148–0.308)		0.108

NA: Not available; QoL: Quality of Life.; DALY: Disability Adjusted Life Year.
DALY lost per non-fatal dengue case = (number of days with dengue symptoms/365 days) x disability.

Table S4. Parameters and variation included in the univariate sensitivity analysis

Parameters	Min	Base case	Max	Rational / Comments
Vaccine coverage rate of the 1st dose (routine & catch up)	80%	90%	100%	Assumption based on implementation feasibility
Vaccine administration cost/dose	5.9	7.3	8.8	Assumption ±20%
Catch-up duration	2 years	3 years	4 years	Assumption based on implementation feasibility
Drop in compliance	20%	25%	30%	Assumption based on implementation feasibility
Wastage routine/Catch up	5%/0%	10%/5%	15%/10%	Assumption
Cost of dengue disease	–20%	See inputs	+20%	Assumption ±20%
DALYs ambulatory – hospitalized	0.019–0.022	0.024–0.028	0.029–0.034	Assumption ±20%
Under-reporting factor ambulatory/hospitalized	2.6–1.1	3.2–1.6	3.8–1.7	Assumption ±20%
Discount rate on health and costs	0%	5%	10%	BZ HE guidelines
Vaccine protection duration for the 3-dose schedule	5 years	10 years	30 years	Assumption based on Coudeville et al. 2016 (Coudeville et al., 2016)

Table S5. Parameters and variation included in the probabilistic sensitivity analysis

Probabilistic sensitivity analysis					
Parameters	**Distribution type**	**Min**	**Max**	**Mode**	**Comments**
Vaccine Wastage for the Routine Program	Triangular	5%	15%	10%	–
Vaccine Wastage for the Catch up Program	Triangular	0%	10%	5%	–
Drop in compliance	Triangular	0.8	1.2	1	Mode at 100% and variation of ±20%
Cost per dengue case	Triangular	0.8	1.2	1	Mode at 100% and variation of ±20%
Vaccines administration costs	Triangular	0.5	1.5	1	Mode at 100% and variation of ±50% (i.e. 3.24 mode, min 2.2, max 4.3)
Average duration of protection (years)	Triangular	0.5	3	1	Meaning: Dose 1: 1.25–7.5 years Dose 2: 2.5–15 years Dose 3: 5–30 years
Relative efficacy against asymptomatic infection	Triangular	0	1	0.5	Meaning from 0% (no efficacy against asymptomatic infection) to 100%
Vaccine efficacy	Discrete Uniform	1	100	na	Level of uncertainty seen in Phase 3 (Naïve bootstrap based on estimated efficacy)
Annual endemicity	Discrete Uniform	0	1000	na	10% range of uncertainty considered and applied on base case endemicity

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