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Estimation of the potential impact of dengue vaccination on clinical outcomes in Brazil

Estimativa do impacto potencial com a vacinação contra dengue nos desfechos clínicos no Brasil

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Keywords:
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ABSTRACT

Objective: The aim of the current analysis was to measure the public health impact of dengue vaccination in Brazil using a published transmission dynamics model. **Methods:** We adapted a mathematical model that represented the transmission dynamics of the four dengue fever serotypes in humans and in the mosquito. This compartmental model represents the known characteristics of dengue transmission dynamics: host-vector interactions, immunological interactions between all four dengue serotypes, age structure of the population, levels of specific transmission by age, seasonality of the disease, and growth of the human and vector population. **Results:** Our mathematical model showed a 22% (CI95%: 9-37) reduction of all cases of dengue fever for a smaller scenario (routine vaccination at 9 years old and catch-up campaign to 10 years of age) and 81% (CI95%: 67-89) in the largest scenario (routine vaccination at 9 years old and catch-up campaign to 40 years of age) over a 5-year period. For the 10-year impact, we estimated a 22% (CI95%: 12-39) reduction in the smaller scenario, and a 92% (CI95%: 80-95) reduction in the larger scenario. This reduction in the number of cases would lead to significant decrease in the number of hospitalizations. Up to 233,509 (CI95%: 148,534 - 331,849) and 739,378 (CI95%: 604,386 – 894,072) hospitalizations would be prevented over a 5-year and 10-year period, respectively, with the larger vaccination program. **Conclusion:** This analysis indicates that, within expected variations, a national dengue vaccination program in Brazil would lead to significant public health benefits by reducing dengue infections and hospitalizations.

Palavras-chave:
dengue, modelagem, vacinação

RESUMO

Objetivo: O objetivo da análise é medir o impacto na saúde pública com vacinação da dengue no Brasil, utilizando um modelo dinâmico de transmissão publicado. **Método:** Adaptamos modelo matemático que representa a dinâmica de transmissão dos quatro sorotipos da dengue em humanos e no mosquito. O modelo é determinístico, compartimental, para representar as características conhecidas da dinâmica de transmissão da dengue: interações hospedeiro-vetor; interações imunológicas entre os quatro sorotipos de dengue; estrutura etária da população; níveis de transmissão específicas por idade; sazonalidade da doença e o crescimento da população de humanos e vetores. **Resultado:** Nosso modelo matemático estimou em 22% (IC95%: 9-37) de redução dos casos de dengue para o cenário mais conservador (rotina aos 9 anos e campanha de vacinação até 10 anos) e 81% (IC95%: 67-89) no cenário mais liberal (rotina aos 9 anos e campanha de vacinação até 40 anos) ao longo de 5 anos. Para o impacto de 10 anos, estimou-se 22% (IC95%: 12-39) de redução no cenário de mais conservador e 92% (IC95%: 80-95) de redução no cenário mais liberal. Esta redução dos casos leva a redução significativa do número de hospitalizações. Até 233,509 (CI95%: 148,534 - 331,849) e 739,378 (CI95%: 604,386 – 894,072) internações poderiam ser salvas em 5 e 10 anos, respectivamente para período com o programa mais liberal de vacinação. **Conclusão:** A análise indica que, dentro de variações esperadas, um programa de vacinação nacional contra dengue no Brasil teria um benefício significativo para saúde pública, reduzindo infecções e internações de dengue.

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Introduction

The World Health Organization (WHO) estimates that approximately 390 million people per year are infected with dengue viruses ([284–528] million), and 96 million of these people ([67–136] million) show clinical manifestations of the disease (Bhatt *et al*., 2013). The Americas contribute with 14% (13 [9-18] million infections) of apparent infections worldwide, with half of this infections occurring in Brazil and Mexico (Bhatt *et al*., 2013).

In Brazil, analysis of historical series and temporal evolution of dengue reveals dissemination and internalization of the infection with periodic outbreaks, increase in the severity of cases, and reduction in the age of highest risk in some regions (Siqueira *et al*., 2005) (Teixeira *et al*., 2010).

In addition to the important medical burden, dengue causes a substantial economic impact in developing countries. Individuals, families, and governments are affected by medical care and treatment costs, wage loss, absence from school, and prolonged recovery periods (Potts, 2010). A multicenter cost of illness study for dengue was recently conducted in Brazil with primary data collection. It was estimated that outpatient cost per case was US$ 173 (95% CI: 129-218) and hospital cost per case was US$ 448 (95% CI: 333-562), from a societal perspective; and US$64 (95% CI: 48-80) and US$237 (95% CI: 177–297) per case, respectively, from the perspective of Brazil's National Health System (SUS) (Martelli *et al*., 2015).

Despite years of research, there are no specific treatments available for dengue (Wilder-Smith *et al*., 2012). Current dengue prevention and control measures, which rely mainly on vector control and appropriate case management, are costly and have not stopped the spread of the disease. Prevention measures related to dengue include vector control, population awareness, epidemiological surveillance, and at-risk population vaccination. In this context, WHO has set up objectives to reduce dengue mortality by 50% and the morbidity by 25% by 2020 (WHO, 2012).

The tetravalent candidate vaccine against dengue from Sanofi Pasteur, which demonstrated an efficacy of 60.8% in the per-protocol population for the primary outcome (virologically confirmed dengue) in Latin America and even a higher efficacy in severe and hospitalization cases, seems to be a relevant candidate for the prevention of dengue in Brazil and to achieve the goals set by the WHO (Villar *et al*., 2015). After the successful completion of phase III clinical studies, policymakers need evidence on the public health impact of vaccination to make decisions on vaccine introduction. Aligned with WHO recommendations (WHO, 2005) (WHO, 2011) (WHO-VMI Dengue Vaccine Modeling Group, 2012), models of dengue transmission can be used to address these important questions by assessing the benefits expected from various vaccination strategies. The aim of the current analysis was to measure the public health impact of dengue vaccination in Brazil, using a published transmission dynamics model.

Methods

General description of the model

Coudeville and Garnett developed a mathematical model representing the transmission dynamics of the four serotypes of dengue fever in humans and in the mosquito, and the potential impact of vaccination in the population of Southern Vietnam (Coudeville & Garnett, 2012).

The model is a compartmental one that represents the known characteristics of dengue transmission dynamics: host-vector interactions, immunological interactions between all four dengue serotypes, age structure of the population, levels of specific transmission by age, seasonality of the disease, and growth of the human and vector population. This model was extended from another model previously developed by Bartley *et al.* (2002).

In the absence of vaccination, individuals become infected after a bite from an infected mosquito. After the incubation period, which follows an exponential distribution, there are three possible outcomes of infection: asymptomatic, mild, or severe. Each infection outcome is serotype-specific and provides lifelong serotype-specific immunity, i.e., each individual can develop up to four dengue infections during his or her lifetime. The level of infectiousness (severe, mild, or asymptomatic infections) depends on the viral load and intrinsic characteristics of the host. This model considers different types of serotype interactions, temporary cross-protection (i.e., no risk of developing a heterotypic infection for a limited time after an infection), cross-enhancement (i.e., differential risk of developing symptomatic cases upon primary, secondary, tertiary, and quaternary infection), or a combination of cross-protection and cross-enhancement. Using the results of an estimation based on data collected during phase 3 studies (Coudeville & Baurin, 2015), we considered a scenario involving both cross-protection and cross-enhancement. The average duration of cross-protection was estimated to be 15.6 months. Values corresponding to relative risk of developing a symptomatic case for secondary and secondary infection compared with primary infection are shown in the appendix section.

Representation of the vector population is limited to adult female mosquitoes. The seasonal variation in mosquito density was determined by the variation in monthly growth rate for the vector population, based on an annual average (Honório *et al*., 2009). Mosquitoes were initially susceptible to dengue and had a probability of being infected after biting an infected human. After a minimum period of 8 days of incu-

bation (12 on average) (Bartley *et al*., 2002), mosquitoes became infected for their entire remaining life cycle. The authors assumed that a mosquito cannot be co-infected with more than one serotype. In addition to variation of mosquito density throughout the year, seasonality in the occurrence of dengue cases was accounted for using monthly variations in biting rates as a proxy for all factors likely to play a role in this seasonality (e.g., the variation in life expectancy of the vector, and rate of development of a viral infection).

Adaptation of the model to the Brazilian situation

Demographic model parameters

IBGE data (Instituto Brasileiro de Geografia e Estatística, 2013) were used for population characteristics: population size, population growth, age distribution, and number of survivors per age group.

Epidemiology of dengue in Brazil and model inputs

In 2014, 12,064 samples were examined for viral isolation, and 3,807 were positive (31.6%). The proportions of viral serotypes identified were DENV1 (81.7%), followed by DENV4 (16.3%), DENV2 (1.5%), and DENV3 (0.5%). Data are available regarding viral isolation from 23 federated states (UFs) (85.2%).

The distribution of notified cases in Brazilian patients with dengue during the 2010 epidemic was different from that of the 2002 and 2008 epidemics (Siqueira *et al*., 2010). Young adults were the most affected by dengue fever and dengue hemorrhagic fever during 2000–2007 and 2000–2005, respectively. However, since 2006, the incidence of dengue hemorrhagic fever among children <5 years old increased (0.47 × 100,000 in 2006), and was higher than among those aged 10–19 years and 20–29 years (0.36 × 100,000 and 0.46 × 100,000, respectively in 2006). In 2007, >53% of the cases of dengue hemorrhagic fever occurred in children <15 years old (Teixeira *et al*., 2008). Consequently, in 2007, a large proportion of hospital admissions for dengue (40.8%) occurred among those aged <10 years. Children aged 5–9 years and 10–14 years also showed an increase in hospitalization rates (68.2 and 60.6 × 100,000 inhabitants, respectively) during the 2008 epidemic in comparison with the 2002 epidemic (15.9 and 23.1 × 100,000 inhabitants, respectively). These hospitalization data are in agreement with the distribution of admissions for dengue by age for the period 2002–2011, which suggests a change in the age pattern in 2007–2008 (reduction in the first age quartile).

Data obtained from a systematic review of the literature (Teixeira *et al*., 2013) shows that the incidence of hospitalization for dengue was 31.6 per 100,000 inhabitants during the 2002 epidemic, approximately 40.8 per 100,000 inhabitants during the 2008 epidemic, and 49.7 per 100,000 inhabitants during the 2010 epidemic, indicating an increase in the dengue hospitalization rate until 2010. The hospitalization rate did not increase since 2010, and some hypothesis may explain this finding, such as the reorganization of the assistance network in the health care system, and greater population awareness about disease symptoms, making people look for assistance earlier.

In 2010, 13,909 cases were classified as dengue with complications, and 3,807 were classified as dengue hemorrhagic fever, 370 and 308 cases were fatal, respectively. Mean age of death due to dengue was approximately 38 years old in 2002, and fell to 30 years old between 2007 and 2009 (Teixeira *et al*., 2013). Figure 1A summarizes the historical series of dengue outbreaks and the number of probable cases and hospitalizations in Brazil.

For the present analysis, historical data (from 2000 to 2010) were collected mainly from a comprehensive national epidemiological literature review, published in 2013. More recent data were directly collected from SINAN database, which gathers data from the whole country. Seroprevalence data by age group came from phase III clinical trials conducted in

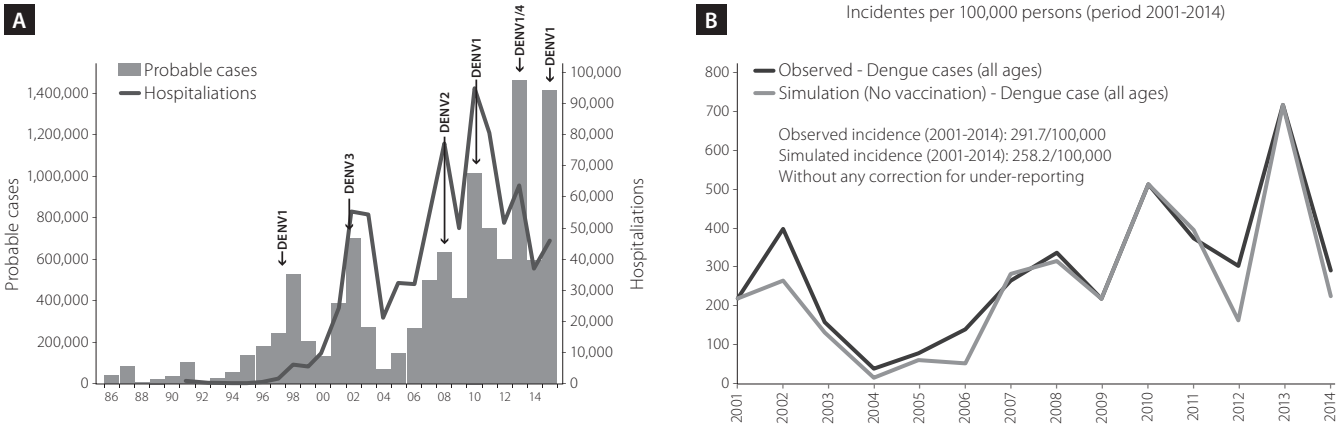

Figure 1. Incidence of dengue and number of hospitalizations from 1990 to 2015 in Brazil (A) (SINAN database), and results of the model calibration representing the observed incidence (/100,000) in dark grey, from national surveillance system, and the simulated incidence (/100,000) in light grey, from the model without any correction for under-reporting (B).

Brazil (Villar *et al*., 2015). In order to reflect the real number of cases, under-reporting of ambulatory (3.2) and hospitalized cases (1.6) were also considered based on the recent publication from Martelli *et al*. 2015. All epidemiological inputs used in the model are described in the appendix section.

Specific adjustments for calibration

The calibration of the model to Brazil requires not only Brazilian inputs but also an adjustment of the model parameters to reflect these observed inputs. This calibration adjustment consists in two main steps and was based on minimization with the method of the least squares. The first step is based on the endemic equilibrium that can be defined for the model, aiming at ensuring that the model adequately reproduces both observed age-specific seroprevalence data (by adjusting transmission parameters) and age-distribution of ambulatory and hospitalized dengue cases (by adjusting age-specific risk to develop disease upon infection). The second step aims at adjusting the monthly variation of dengue incidence over time (by adjusting month-specific biting rates) and the annual variation of circulating serotypes (by adjusting annual serotype-specific differences in the propensity of mosquitoes transmitting the disease to humans). The quality of the calibration is assessed by comparing observed and simulated data (Figure 1B).

Vaccination-related parameters

Published results of a phase 3 clinical trial that tested the vaccine in Latin America and the Caribbean demonstrated an efficacy of 60.8% in the per-protocol analysis for the primary outcome (virologically confirmed dengue) (Villar *et al*., 2015). After the third dose, the efficacy in the reduction of severe dengue was 95.5% and 80.3% against hospitalization. More recently, Sanofi Pasteur published pooled vaccine efficacy results in subjects 9-16 years of age, combining the results from Latin America, the Caribbean, and the Asia-Pacific region, consequently increasing the power of the analysis (Hadinegoro *et al*., 2015). Pooled efficacy data demonstrated 65.6% reduction in symptomatic dengue due to any serotype (per protocol: 58.4%, 47.1%, 73.6%, and 83.2% reductions due to DENV-1, DENV-2, DENV-3, and DENV-4, respectively), 81.9% reduction in subjects who were seropositive at baseline and 52.5% reduction in subjects who were seronegative at baseline, 93.2% reduction in severe disease, and 80.8% reduction in hospitalized dengue patients. Based on these results, it is assumed that a susceptible individual requires three doses to achieve a high level of protection against all four serotypes included in the vaccine. Using the pooled analysis of phase III clinical trials (Hadinegoro *et al*., 2015), parameters related to vaccine efficacy and dengue transmission were estimated for the model. The appendix section details the main criteria and sources used in the model (transmission and vaccination table).

Vaccination coverage rates for each dose were based on experience (Brazilian Health Ministry, 2007) and wastage rate on the Pan American Health Organization PROVAC guidelines (Pan American Health Organization, 2010). Many national vaccination strategies were tested considering a routine vaccination at 9 years old (considering pooled vaccine efficacy given for 9 to 16 years of age; Hadinegoro *et al*. 2015) and different numbers of catch-up cohorts in a mass immunization campaign (from 1 cohort to 31 cohorts; i.e., a vaccination of people aged from 10 to 40 years) from a prospective point of view. The end of the mass immunization campaign was assumed to occur after 4 years.

Two time horizons were used for each analysis: 5 years (2016-2020), to comply with the WHO goals for 2020, and a larger time horizon of 10 years (2016-2025) allowing us to consider the full benefits of dengue vaccination according to the conservative hypotheses on the duration of vaccine protection (Ultsch *et al*., 2015).

Sensitivity analysis

Parameter uncertainties were addressed in the current analysis using Monte Carlo simulations with 1,000 samples. The parameters considered in this probabilistic sensitivity analysis are described in the appendix section. They involved mainly dengue endemicity, vaccination efficacy, vaccination wastage, and coverage rate. We defined probability distributions for each parameter and randomly sampled values from these distributions to generate 1,000 independent model outcomes.

Results

The first step in the model was its calibration. A comparison between the historical series of the Brazilian Ministry of Health and the simulation of the number of probable cases of dengue in Brazil for each of the four serotypes, from 2001 to 2014, shows that the calibration was consistent (Figure 1B).

Table 1 gives the median number of people vaccinated per vaccination strategy, the proportion of people vaccinated compared with the total current population and the corresponding number of vaccine doses. Each vaccination strategy is indicated by the age of routine vaccination and range of cohorts in the catch-up campaign. For example, Vaccination R9&10-25 refers to R9 (Routine vaccination at 9 years) and a catch-up campaign of 16 cohorts (from 10 years old to 25 years old). In the smaller strategy (1 cohort) to the larger one (31 cohorts), 8% to 55% of the total population would be vaccinated over 5 years, and 15% to 61% over 10 years.

Figure 2 presents the 5 (2016-2020) and 10-year impact (2016-2025) of each vaccination scenario in terms of percent reduction of all dengue cases. The reduction in dengue cases would be from 22% (CI95%: 9-37) with a routine vaccination at 9 and 1 catch-up cohort, to 81% (CI95%: 67-89) with

Table 1. Number of vaccinated people and doses administered over a 5-year period and a 10-year period for each vaccination strategy

	5-year period			10-year period		
	Number of people vaccinated	**% of the total population***	**Number of doses**	**Number of people vaccinated**	**% of the total population***	**Number of doses**
R9&10 (1 cohort)	17,304,845	8%	40,222,457	30,351,541	15%	73,081,598
R9&10-12 (3 cohorts)	23,605,883	12%	55,181,471	36,652,579	18%	88,009,423
R9&10-14 (5 cohorts)	30,000,650	15%	70,423,340	43,047,346	21%	103,266,283
R9&10-16 (7 cohorts)	36,456,974	18%	85,827,134	49,503,670	24%	118,567,019
R9&10-19 (10 cohorts)	46,111,912	23%	108,803,235	59,158,608	29%	141,608,190
R9&10-21 (12 cohorts)	52,461,590	26%	123,919,129	65,508,286	32%	156,759,093
R9&10-25 (16 cohorts)	64,781,125	32%	153,191,870	77,827,821	38%	186,108,925
R9&10-30 (21 cohorts)	79,768,814	39%	188,744,948	92,815,510	45%	221,783,090
R9&10-40 (31 cohorts)	111,998,441	55%	265,398,976	125,045,137	61%	298,421,359

*Considering the 2015 population: 204,450,649 from IBGE data.

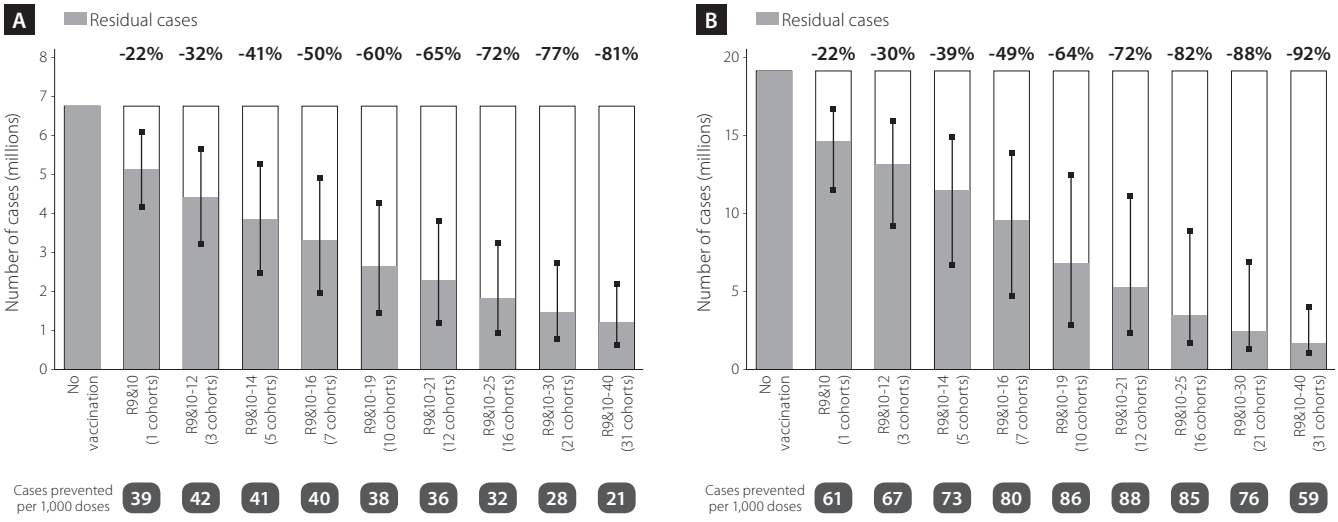

Figure 2. Prevented dengue cases over a 5-year period (A) (2016-2020) and a 10-year period (B) (2016-2025) for the different vaccination strategies (from routine vaccination at 9 years old with 1 catch-up cohort to routine vaccination at 9 years old plus 31 catch-up cohorts) compared with the situation without the vaccination program. The grey bars reflect the residual dengue cases, and the lines, the 95% confidence interval. Percentage values refer to the median percentage reduction in dengue cases.

a routine vaccination at 9 and 31 catch-up cohorts over a 5-year period, and from 22% (CI95%: 12-39) to 92% (CI95%: 80-95), respectively, over a 10-year period. This means that the number of dengue cases prevented over a 5-year compared with the situation without vaccination would range from 1,421,173 (CI95%: 639,030 – 2,669,957) with 1 catch-up cohort vaccinated, to 5,452,844 (CI95%: 3,470,772 – 7,755,088) with 31 catch-up cohorts vaccinated. Over the 10-year period, the estimated number of cases prevented would range from 4,198,402 (CI95%: 2,253,289 – 7,614,971), with 1 catch-up cohort vaccinated, to 17,270,703 (CI95%: 14,070,701 – 20,898,604), with 31 catch-up cohorts vaccinated.

Additionally, in order to help the decision-making process on the best vaccination strategy to be implemented, the efficiency of each strategy has also been assessed by calculating the number of cases prevented per 1,000 vaccine doses (Table 1). It appears that the efficiency of vaccination programs is almost constant between the strategy R9&10-12 (3 catch-up cohorts) and the strategy R9&10-16 (7 catch-up cohorts) in the 5-year analysis, and between R9&10–16

(7 catch-up cohorts) and R9&10–25 (16 catch-up cohorts) in the 10 -year analysis.

Considering the impact of dengue outbreaks in the health care system and specifically the hospital congestion, an analysis focusing on severe cases (hospitalizations and deaths) was carried out (Figure 3 - A, B, C and D). Compared with the situation without vaccination (with an estimated number of 290,482 hospitalizations; CI95%: 191,153 – 386,018), the larger vaccination strategy including 31 catch-up cohorts would decrease the number of dengue hospitalization to 52,093 (CI95%: 32,296 – 98,796) over 5 years; i.e., 233,509 (CI95%: 148,534 – 331,849) prevented hospitalizations. For the same vaccination strategy, a median of 739,378 (CI95%: 604,386 – 894,072) hospitalizations would be prevented over 10 years compared with a strategy without vaccination. In term of deaths, compared with the situation without vaccination, a program including 31 catch-up cohorts would decrease the number of dengue deaths from 2,353 (CI95%: 1547 – 3127) to 422 (CI95%: 186 – 333) over 5 years (1891 prevented deaths; CI95%: 1203 – 2688). For the same vaccination strategy, 5989 (CI95%: 7241 – 4895) deaths would be prevented over 10 years compared with a strategy without vaccination.

Based on the WHO goals to reduce dengue mortality by 50% and morbidity by 25% by 2020 (WHO, 2012), the probability of success of each dengue vaccination strategy in reducing mortality by 25% and morbidity by 50% over 5 and 10 years was also estimated (see Figure 4 – A, B, C and D). This analysis suggests that a good probability (~50% or more) of reducing dengue morbidity by 25% is reached with the inclusion of at least 2 catch-up cohorts in the mass immunization campaign (probability of 34-36% with 1 cohort, and 70-74% with 3 cohorts over 5 and 10 years). If we also consider the goal of reducing dengue mortality by 50%, vaccination strategies with at least 7 catch-up cohorts campaigns are appropriate to reach good (~50% or more) probability of success.

Discussion

Many health decisions are challenging once they are complex and may have important consequences in the future,

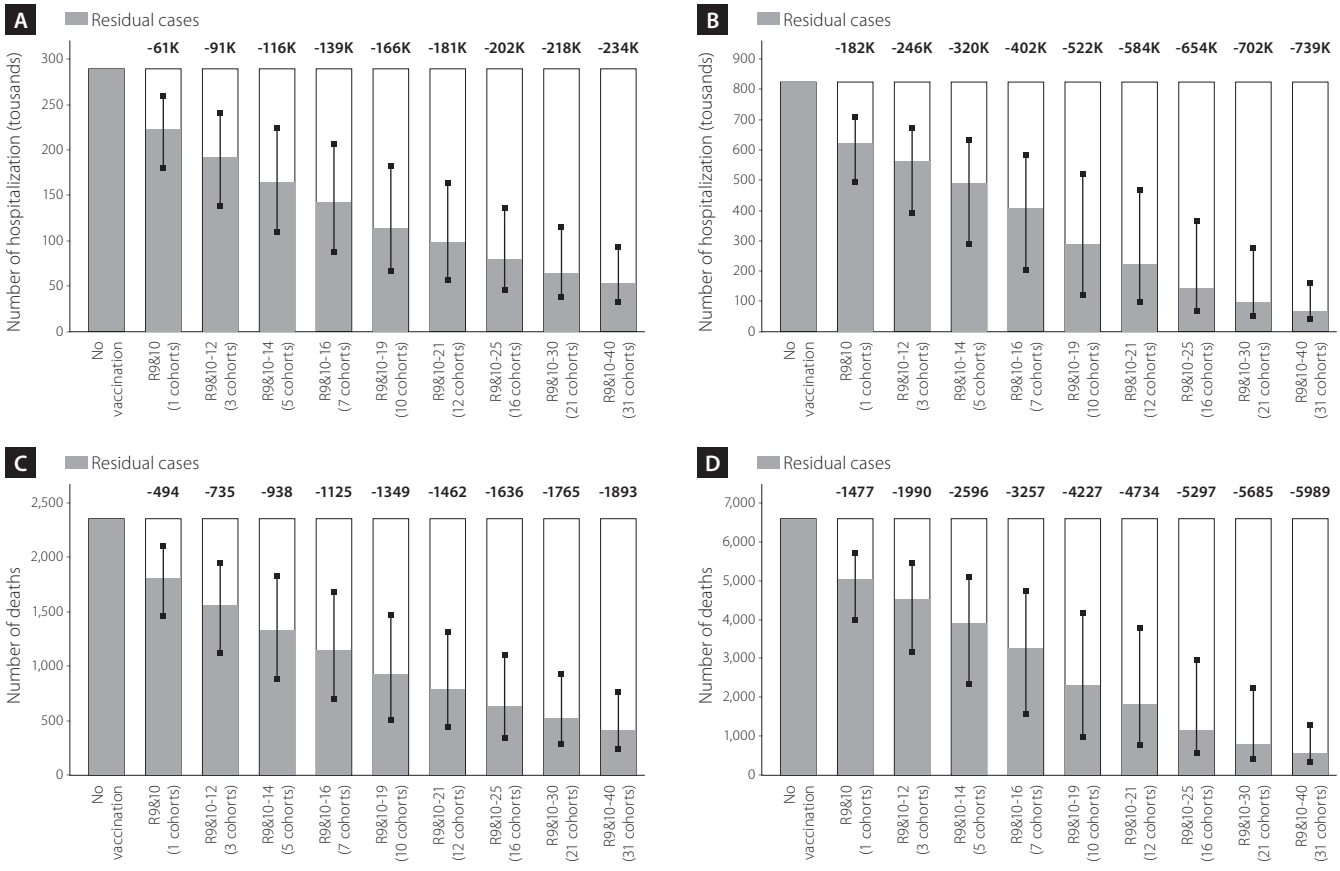

Figure 3. Prevented dengue hospitalizations and deaths over a 5-year period (A, C) (2016-2020) and a 10-year period (B, D) (2016-2025) for different vaccination strategies (from routine vaccination at 9 years old without catch-up to routine vaccination at 9 years old plus 31 catch-up cohorts) compared with the situation without the vaccination program. The grey (full or striped) bars reflect the residual dengue hospitalized cases or deaths, and the grey line, the 95% confidence interval. The grey figures on top of each bar are the median number of hospitalizations or deaths prevented.

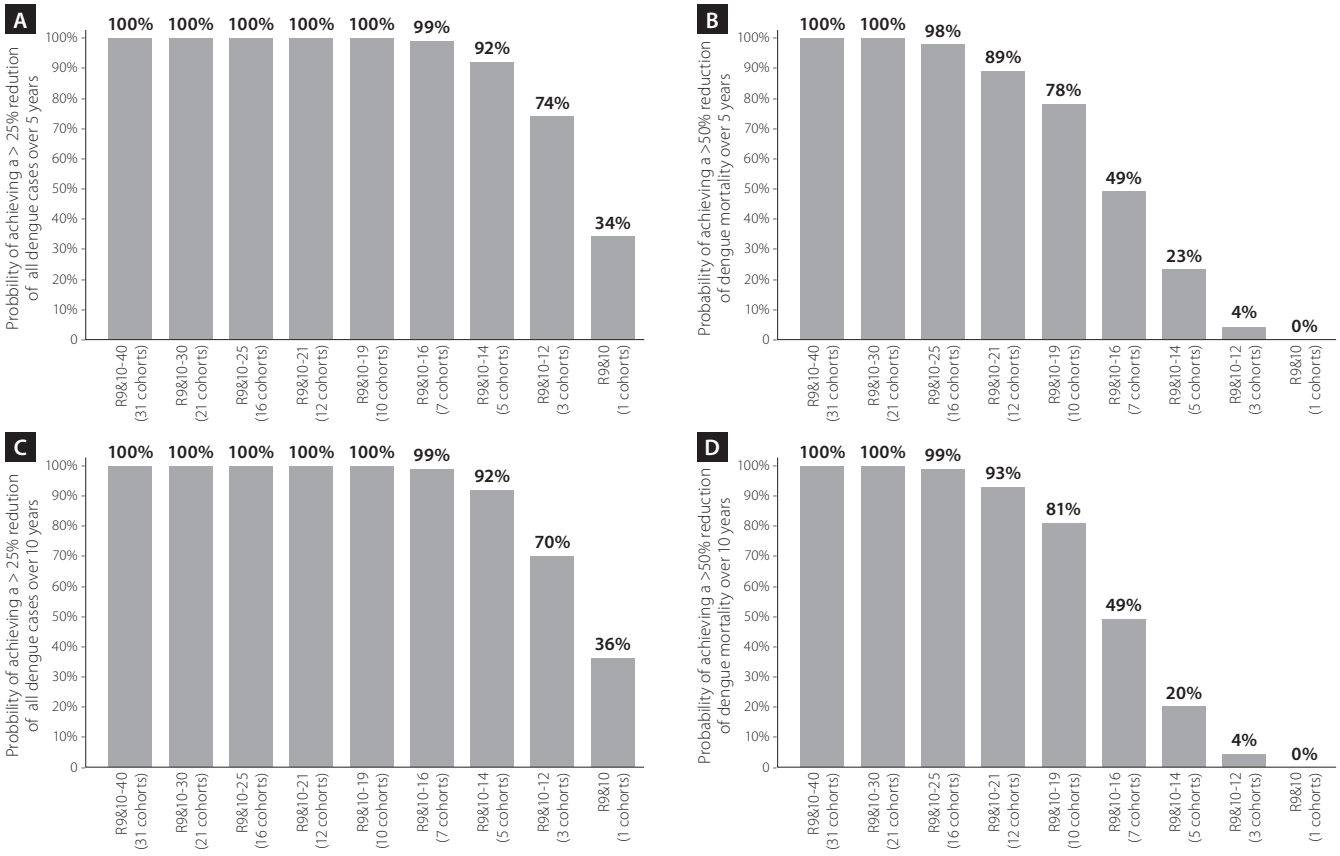

Figure 4. Probability of success of dengue vaccination in reducing morbidity by 25% (A) and mortality by 50% (B) over a 5-year period (2016-2020) as set in the WHO objectives, and probability of success of dengue vaccination in reducing morbidity by 25% (C) and mortality by 50% (D) over a 10-year period (2016-2025) considering the full benefit of dengue vaccination, according to the different vaccination programs strategies.

such as impact on morbidity, mortality, quality of life, and allocation of limited resources. Infectious disease models that reflect the dynamics of a disease, are often used to support the introduction of new vaccination programs. Indeed, transmission models can provide information about the expected health impact with different vaccination strategies on the population, and assist health policymakers in the decision to recommend and implement a new vaccination program. Models offer means to project the spread of the disease, assessing the impact of vaccination over time, and enabling the estimation of, for instance, the proportions of populations that need to be vaccinated to ensure protection.

Probabilistic health models deal with uncertainties inherent to healthcare. The point estimate of a result cannot represent the full spectrum of morbidity and mortality of a disease, so estimates that present the result by likelihood of success complement the contribution of the model to support health policymakers decisions.

Dengue modeling has been useful in helping us understand the dynamics of the virus and in generating some new hypotheses about why the dynamics exhibit certain short- and long-term irregularities. Nevertheless, when compared with diseases such as influenza or malaria, dengue modeling literature is sparse and focuses on a small number of topics, often serotype oscillations or antibody-dependent enhancement. Given the importance of mosquito populations for dengue transmission, we have a relatively poor understanding of their population dynamics. In addition, dengue models are rarely analyzed with a public health goal in mind, and few models has been determined to evaluate dengue interventions (WHO-VMI Dengue Vaccine Modeling Group, 2012).

Dengue newly developed models explore and validate the effects of weather on the mosquito life cycle (Focks *et al*., 1995), estimate serotype-specific forces of infection (Ferguson *et al*., 1999), determine the degree to which antibody-dependent enhancement (ADE) improves viral fitness (Cummings *et al*., 2005), test if ADE alone is sufficient to generate the oscillating serotype patterns seen in dengue (Wearing & Rohani 2006) (Recker *et al*., 2009), determine the impact that long-term trends in dengue transmission rates may have on dengue hemorrhagic fever incidence (Nagao & Koelle 2008), determine if long-term demographic trends are responsible for a shift in the age structure of dengue cases (Cummings *et al*., 2009), and investigate whether tertiary or quaternary dengue infections are compatible with the known epidemiology

of dengue (Wikramaratna *et al*., 2010). Few models estimate the impact of different vaccination strategies. In Brazil, only one publication analyzed the impact and cost-effectiveness of dengue vaccination (Durham *et al*., 2013), but it was based on results of a phase IIb clinical trial carried out in Thailand.

We adapted a published mathematical model for dengue vaccination to the Brazilian situation, focusing on interactions between host immune status, demography, and vector populations. Our mathematical model shows a 22% (CI95%: 9-37) reduction in all cases of dengue fever for the smaller scenario (routine vaccination at 9 years of age and a catch-up campaign to 10 years old) and 81% (CI95%: 67-89) in the larger scenario (routine vaccination at 9 years of age and a catch-up campaign to 40 years old) over a 5-year period. For the 10-year impact, we estimated a 22% (CI95%: 12-39) reduction in the smaller scenario and a 92% (CI95%: 80-95) reduction in the largest scenario. This dengue reduction may lead to significant reduction of the number of hospitalizations. Up to 233,509 (CI95%: 148,534 – 331,849) and 739,378 (CI95%: 604,386 – 894,072) hospitalizations may be prevented over a 5-year and 10-year period, respectively, with the larger vaccination program. It is worth mentioning that this reduction in cases and hospitalizations due to a dengue vaccination program would also have a positive economic impact on health care system and society that is not included in the present analysis. Broader socio-economic aspects may be also affected, such as the impact of outbreak on health care system and dengue prevention, tourism, long-term national productivity, and country attractiveness (Bärnighausen *et al*., 2013).

For the adaptation of the model to the Brazilian situation, country-specific epidemiological data were used. These data were collected from one epidemiological review and the national surveillance system (SINAN). These data were considered representative of the whole country although this representativeness may be difficult to obtain given the size of the country and the fact that data may come from developed infrastructure.

The adaptation of the model to the Brazilian situation makes use of the estimation of efficacy parameters based on data collected during phase 3 studies. More specifically, we considered a scenario accounting for both cross-protection and cross-enhancement that shows consistency with the most recent data reported for these trials regarding vaccine efficacy (Hadinegoro *et al*., 2015). We also considered a conservative assumption regarding duration of protection when the results of this estimation were compared. The current analysis is, therefore, based on the best available evidence to date regarding vaccine efficacy while keeping a conservative approach for duration of protection. As for any vaccine, additional data collected notably during long-term follow-up of Sanofi Pasteur phase III trials and phase IV trials will help to refine these parameters in the future.

Conclusion

In conclusion, the present analysis indicates that, within expected variations, a national dengue vaccination program in Brazil may lead to significant public health benefits by reducing dengue infections and hospitalizations. 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, a time-frame that enables the full benefits of vaccination to be observed. Therefore, a program with at least 7 catch-up cohorts would be recommended from a public health point of view. A program with 7 catch-up cohorts corresponds to the vaccination of 18% to 24% of the current population in 5 and 10 years, respectively, and would have an expected median impact of about 50% over 5 and 10 years, with good probability of success. The present results also suggest that the implementation of national large mass immunization programs using Sanofi Pasteur first new vaccine, in most endemic countries, may contribute to achieve the WHO goals to control dengue fever (WHO, 2012).

Competing interests

DVA, LB, MR and MA received research funding for the work described in this manuscript. DVA, LB and MR hold no financial interests in the commercial products of Sanofi Pasteur. ASP and VG are employees of Sanofi Pasteur. TMG was an employee of Sanofi Pasteur before moving to Novo Nordisk. No further conflicts of interest are declared by the authors in relation to this study.

Authors' contributions

DVA validated the model to the Brazilian scenario; and with his team (LB and MR) wrote and revised the manuscript; ASP and TMG worked on data collection, results generation and interpretation, manuscript writing and review, with the support of VGS.

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APPENDIX – **Inputs used in the Brazilian model**

Parameter	Base case	Source
Parameters related to demographics		
Total population in 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/
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
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/
Age distribution	As in the 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/
Parameters related to epidemiology		
Seroprevalence	CYD 15 Brazilian 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. doi: 10.1056/NEJMoa1411037
Serotype distribution in dengue cases (% per year)	Average 2001-14: 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, 2014, Volume 46 no. 5—2015
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 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 2010-13: 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 SIH, Update: 06/06/2014
Monthly number of deaths and 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 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

Under-reporting associated with reported incidence	Ambulatory cases: 3.2 Hospitalized cases: 1.6	Martelli et al. PLOS 2015. Cost of Illness study
Parameters related to disease transmission		
Average duration of cross-protection after natural infection	15.59 months	Estimated from CYD14 and CYD15data Coudeville L, Baurin N Potential impact of dengue vaccination in endemic areas: Insights from two large-scale efficacy trials. ASTMH 64th Annual Meeting October 25-29, 2015, Philadephia
Relative risk of developing a symptomatic case (as compared to primary infection)	Ambulatory case (2nd infection) : 1.77 Hospitalized case (2nd case) : 1.84 Symptomatic case (3rd and 4th infection : 0.39	Estimated from CYD14 and CYD15data Coudeville L, Baurin N Potential impact of dengue vaccination in endemic areas: Insights from two large-scale efficacy trials. ASTMH 64th Annual Meeting October 25-29, 2015, Philadephia
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 Yoon In-Kyu, et al. Characteristics of mild dengue virus infection in Thai children. Am J Trop Med Hyg. 2013;89(6):1081-7. 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. Carrington LB, Simmons CP. Human to mosquito transmission of dengue viruses. Front Immunol. 2014;5:290. doi: 10.3389 /fimmu.2014.00290.
Duration of dengue infection (hosts)	Average duration of the incubation period (IIP): 5.5 days	De Castro 2011: Brazilian model, 5.5 days (68% CI 4-7) 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)
	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 De Castro 2011: model, 4.5 days (68% CI 3-6)
Duration of dengue infection (vectors)	Minimum duration of the incubation period (EIP): 8 days	Bartley et al. 2002: 12 days (8-20) for duration of latent period in vector
	Average duration of the incubation period (EIP): 12 days	
Parameters related to vector data		
Vector life expectancy	14.49 days	Andraud et al (2013); French Guiana Case
Maximum lifetime	30 days	Coudeville 2012; Castanha P.M.S. et al., Force of infection of dengue serotypes in a population-based study in the northeast of Brazil. Epidemiol. Infect.(2013),141, 1080-1088
Vector/Host Ratio	2	De Castro Medeiros L. Et al., Modeling the Dynamic Transmission of Dengue Fever: Investing Disease Persistence. PLoS Negl Trop Dis 5(1):e942

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, 387-397 Other sources: 0.7 use in Durham 2013 (Scott TW, Amerasinghe PH, Morrison AC, Lorenz LH, Clark GG, Strickman D, et al. Longitudinal Studies of Aedes aegypti (Diptera: Culicidae) in Thailand and Puerto Rico: Blood Feeding Frequency. Journal of Medical Entomology. 2000 Jan;37(1):89–101. Scott TW, Morrison AC, Lorenz LH, Clark GG, Strickman D, Kittayapong P, et al. Longitudinal studies of Aedes aegypti (Diptera: Culicidae) in Thailand and Puerto Rico: population dynamics. Journal of medical entomology. 2000;37(1):77–88.)
Vector population density	Monthly estimations	Honorio 2009, http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0000545
Transmission probability upon bite	Host to Vector: 0.9	De Castro 2011: model, 0.90 used for both probability (from Focks 1995 and Watson 1999)
	Vector to Host: 0.9	
Force of the infection from an external reservoir	0.00005	Based on Coudeville 2012
Parameters related to vaccination		
Vaccine efficacy	Estimated from Phase 3 efficacy studies considering the following characteristics of the vaccine profile: - differences in efficacy between serotypes - difference in efficacy according to the serostatus at baseline - increased efficacy with doses for seropositive subjects that are vaccinated - increased efficacy against hospitalized cases - accelerated exposure to secondary and post-secondary infection in the case of vaccination - reduced efficacy against asymptomatic infection compared with symptomatic infection (50% relative efficacy)	CYD14&15 results (Phase III clinical trials) and long-term follow up of hospitalized cases (Villar, 2015, N Engl J Med.; Capeding, 2014, Lancet; Hadinegoro, 2015, N Engl J Med.) Coudeville L, Baurin N Potential impact of dengue vaccination in endemic areas : Insights from two large-scale efficacy trials. ASTMH 64th Annual Meeting October 25-29, 2015, Philadephia Coudeville L, Baurin N, Vergu E. Fitting a transmission model to data from two large phase III vaccine efficacy studies. Vaccine. 2015;Submitted.
Duration of vaccine protection	On average: d1: 2.5y d2: 5y d3: 10y	Assumptions: parameter tested in sensitivity analysis to take into account its uncertainty.
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
Wastage rate	10% for routine vaccination 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 the mass immunization campaign	End of catch-up: 4 years	Assumption based on feasibility

Vaccination program strategy	Geographic area: National Scenarios: Routine vaccination at 9yo + 1/3/5/7/10/12/16/21/31 catch-up cohorts campaign	Assumption
Year of start public vaccination	2016	Assumption

Probabilistic Sensitivity Analysis					
Parameters	**Distribution type**	**Min**	**Max**	**Mode**	**Comments**
Vaccine Wastage in Routine Vaccination Program	Triangular	5%	15%	10%	—
Vaccine Wastage in Catch-up Program	Triangular	0%	10%	5%	—
Drop-in compliance	Triangular	0.8	1.2	1	Mode at 100% and variation of +/- 20% (i.e., 25% mode, min 20%, max 30%)
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 Ph3 (Naïve bootstrap based on estimated efficacy)
Annual endemicity	Discrete Uniform	0	1000	na	10% range of uncertainty considered and applied on base case endemicity

References

Bärnighausen T, Bloom DE, Cafiero ET, O'Brien JC. Valuing the broader benefits of dengue vaccination, with a preliminary application to Brazil. Semin Immunol. 2013;25(2):104-13. doi: 10.1016/j.smim.2013.04.010. Epub 2013 Jul 22.

Bartley LM, Donnelly CA, Garnett GP. The seasonal pattern of dengue in endemic areas: mathematical intelligence models of ccms. Trans R Soc Trop Med Hyg. 2002; 96:387-97.

Bartley LM, Carabin H, Vinh Chau N, Ho V, Luxemburger C, Hien TT, *et al.* Assessment of the factors associated with flavivirus seroprevalence in a population in Southern Vietnam. Epidemiology and Infection. 2002;128(2):213-20.

Bhatt S, Gething PW, Brady J, Messina JP, Farlow AW, Moyes CL, *et al.* The global distribution and burden of dengue. Nature. 2013; 496:504-7.

Brazilian Health Ministry. Vaccine coverage. Available from: http://tabnet.datasus.gov.br/tabdata/livroidb/Com2007/Com_F13.pdf. Accessed in 15th November 2015

Coudeville L, Baurin N. Potential impact of dengue vaccination in endemic areas: Insights from two large-scale efficacy trials. ASTMH 64th Annual Meeting October 25-29, 2015, Philadephia

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. doi:10.1371/journal.pone.0051244.

Cummings DAT, Iamsirithaworn S, Lessler JT, McDermott A, Prasanthong R, Nisalak A, *et al.* (2009) The impact of the demographic transition on dengue in Thailand: insights from a statistical analysis and mathematical modeling. PLoS Med 6: e1000139. doi:10.1371/journal.pmed.1000139

Cummings DAT, Schwartz IB, Billings L, Shaw LB, Burke DS (2005) Dynamic effects of antibody-dependent enhancement on the fitness of viruses. Proc Natl Acad Sci USA 102: 15259–15264.

Durham DP, Ndeffo Mbah ML, Medlock J, Luz PM, Meyers LA, Paltiel AD, Galvani AP

Dengue dynamics and vaccine cost-effectiveness in Brazil. Vaccine. 2013.20;31(37):3957-61. doi: 10.1016/j.vaccine.2013.06.036. Epub 2013 Jun 20.

Ferguson NM, Donnelly CA, Anderson RM (1999) Transmission dynamics and epidemiology of dengue: insights from age–stratified sero–prevalence surveys. Phil Trans R Soc Lond B 354: 757–768.

Focks DA, Daniels E, Haile DG, Keesling JE (1995) A simulation model of the epidemiology of urban dengue fever: literature analysis, model development, preliminary validation, and samples of simulation results. Am J Trop Med Hyg 53: 489–506.

Hadinegoro SR, Arredondo-García JL, Capeding MR, Deseda C, Chotpitayasunondh T, Dietze R *et al.* Efficacy and Long-Term Safety of a Dengue Vaccine in Regions of Endemic Disease. N Engl J Med 2015; 373:1195-1206

Honório NA, Nogueira RMR, Codeço CT, Carvalho MS, Cruz OG, Magalhães AFM, *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. doi:10.1371/journal.pntd.0000545

Instituto Brasileiro de Geografia e Estatística – IBGE. Projeção da população do Brasil por sexo e idade para o período 2000/2060. Available at: Accessed in 15th November 2015ftp://ftp.ibge.gov.br/Projecao_da_Populacao/Projecao_da_Populacao_2013/nota_metodologica_2013.pdf

Martelli CMT, Siqueira JB Junior, Parente MPPD, Zara ALdSA, Oliveira CS, Braga C, *et al.* Economic Impact of Dengue: Multicenter Study across Four Brazilian Regions. PLoS Negl Trop Dis 2015;9(9): e0004042. doi:10.1371/journal.pntd.0004042

Nagao Y, Koelle K (2008) Decreases in dengue transmission may act to increase the incidence of dengue hemorrhagic fever. Proc Natl Acad Sci U S A 105: 2238–2243.

Pan American Health Organization. Vaccine Introduction Guidelines 2010. Available from: http://new.paho.org/hq/dmdocuments/2010/FieldGuide_NewVaccines_1stEd_e.pdf Accessed in 15th November 2015

Potts JA, Gibbons RV, Rothman AL, Srikiatkhachorn A, Thomas SJ, Supradish P, *et al.* (2010) Prediction of Dengue Disease Severity among Pediatric Thai Patients

Using Early Clinical Laboratory Indicators. PLoS Negl Trop Dis 4(8): e769. doi:10.1371/journal.pntd.0000769

Recker M, Blyuss KB, Simmons CP, Hien TT, Wills B. (2009) Immunological serotype interactions and their effect on the epidemiological pattern of dengue. Proc R Soc Lond B 276: 2541–2548.

Siqueira JB, Martelli CMT, Coelho GE, Simplício AC da R, Hatch DL. Dengue and Dengue Hemorrhagic Fever, Brazil, 1981–2002. Emerging Infectious Diseases. 2005;11(1):48-53. doi:10.3201/eid1101.031091.

Siqueira JB, Vinhal LC, Said RFC, Hoffmann JL, Martins J. Dengue no Brasil: tendências e mudanças na epidemiologia, com ênfase nas epidemias de 2008 e 2010. In: Saúde Brasil 2010: uma análise da situação de saúde e de evidências selecionadas de impacto de ações de vigilância em saúde. Ministério da Saúde, Secretaria de Vigilância em Saúde, Departamento de Análise de Situação em Saúde. Série G. Estatística e Informação em Saúde. Brasília: Ministério da Saúde, p. 372. Available at: http://portal.saude.gov.br/portal/arquivos/pdf/cap_7_saude_brasil_2010.pdf.

Teixeira LA, Lopes JS, Martins AG, Campos FA, Miranzi SS, Nascentes GA. Persistence of dengue symptoms in patients in Uberaba, Minas Gerais State, Brazil. Cad Saude Publica. 2010; 26(3): 624-30.

Teixeira MG, Costa MC, Rabbit G, Barreto ML. Recent shift in age pattern of dengue hemorrhagic fever, Brazil. Emerg Infect Dis. 2008;14:1663. doi: http://dx.doi.org/10.3201/eid1410.071164.

Teixeira MG, Siqueira, JB Jr, Ferreira GLC, Bricks L, Joint G (2013) Epidemiological Trends of Dengue Disease in Brazil (2000–2010): A Systematic Literature Search and Analysis. PLoS Negl Trop Dis 7(12): e2520. doi:10.1371/journal.pntd.0002520

Villar L, Dayan GH, Arredondo-García JL, Rivera DM, Cunha R, Deseda C *et al.* Efficacy of a tetravalent dengue vaccine in children in Latin America. N Engl J Med. 2015; 372:113-23.

Wearing HJ, Rohani P (2006) Ecological and immunological determinants of dengue epidemics. Proc Natl Acad Sci U S A 103: 11802–11807.

WHO (2005) Vaccine introduction guidelines. Adding a vaccine to national immunization programme: decision and implementation. Geneva: World Health Organization. WHO/IVB/ 05.18. Available from: http://www.who.int/immunization/hpv/plan/vaccine_introduction_guidelines_who_2005.pdf. Accessed in 15th November 2015

WHO (2011) Report of the meeting of the WHO/VMI Workshop on Dengue modeling. Geneva: World Health Organization. WHO/ IVB/11.02. Available from: http://apps.who.int/iris/bitstream/10665/70625/1/WHO_IVB_11.02_eng.pdf. Accessed in 15th November 2015

WHO (2012). Global strategy for dengue prevention and control. Available from: http://www.who.int/immunization/sage/meetings/2013/april/5_Dengue_SAGE_Apr2013_Global_Strategy.pdf. Accessed in 15th November 2015

WHO-VMI Dengue Vaccine Modeling Group. Assessing the potential of a candidate dengue vaccine with mathematical modeling. PLoS Negl Trop Dis. 2012 Mar; 6(3): e1450. Published online 2012 Mar 27. doi: 10.1371/journal.pntd.0001450

Wilder-Smith A, Renhorn KE, Tissera H. DengueTools: innovative tools and strategies for the surveillance and control of dengue. Glob Health Action. 2012;5.

Wikramaratna PS, Simmons CP, Gupta S, Recker M (2010) The effects of tertiary and quaternary infections on the epidemiology of dengue. PLoS ONE 5: e12347. doi:10.1371/ journal.pone.0012347