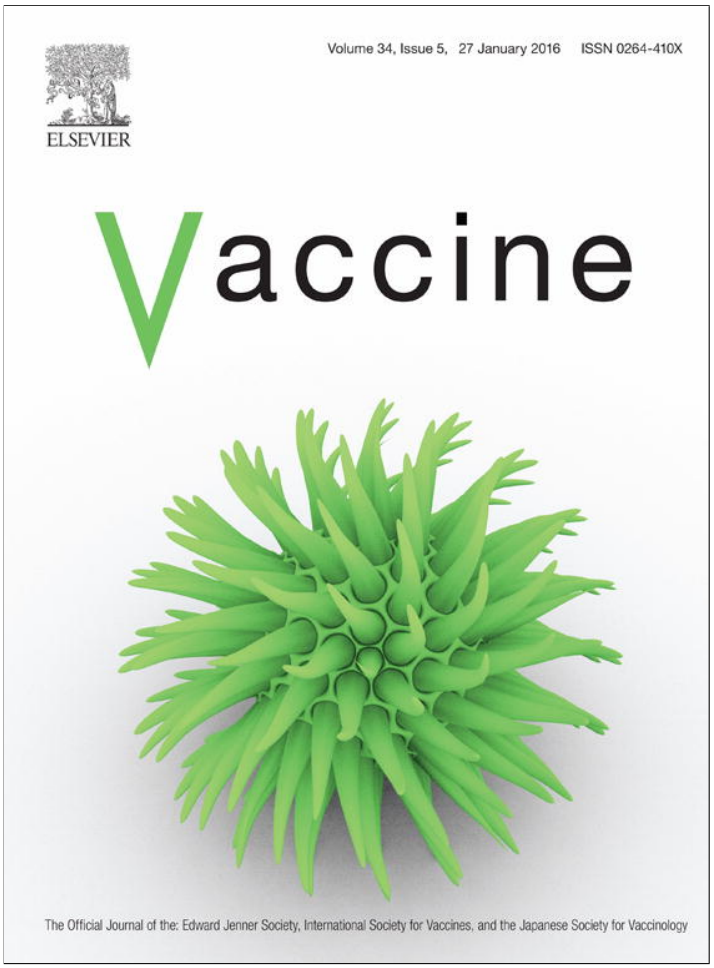

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Cost-utility analysis of dengue vaccination in a country with heterogeneous risk of dengue transmission

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ABSTRACT

Background: Dengue is one of the most important vector-borne diseases worldwide, and annually, nearly 390 million people are infected and 500,000 patients are hospitalized for severe dengue. Argentina has great variability in the risk of dengue transmission due to eco-climatic reasons. Currently no vaccines are available for dengue even though several vaccines are under development.
Objective: The aim of this study was to estimate the cost-effectiveness of a dengue vaccine in a country with heterogeneous risk of dengue transmission like Argentina.
Methods: The analysis was carried out from a societal perspective using a Markov model that included both vaccine and disease parameters. Utility was measured as disability adjusted life years (DALYs) averted, and the incremental cost-effectiveness ratio (ICER) of the vaccination was expressed in 2014 American dollars (US$) per DALY averted. One-way and probabilistic sensitivity analyses were performed to evaluate uncertainty in model outcomes, and a threshold analysis was conducted to estimate the highest possible price of the vaccine.
Results: The ICER of the vaccination program was found to be US$ 5714 per DALY averted. This value is lower than 3 times the per capita GDP of Argentina (US$ 38,619 in 2014); 54.9% of the simulations were below this value. If a vaccination program would be implemented the maximum vaccine price per dose has to be US$1.49 for a vaccination at national level or US$28.72 for a targeted vaccination in high transmission areas.
Conclusions: These results demonstrate that vaccination against dengue would be cost-effective in Argentina, especially if carried out in predetermined regions at high risk of dengue transmission. However, these results should be interpreted with caution because the probabilistic sensitivity analysis showed that there was considerable uncertainty around the ICER value. The influence of variations in vaccine efficacy, cost and other important parameters are discussed in the text.

1. Introduction

Dengue is considered to be one of the most important vector-borne diseases worldwide, and both its incidence and dispersion are rising due to environmental conditions, population growth, urbanization and globalization [1]. Annually, about 390 million people are infected and approximately 500,000 patients, including a high proportion of children, develop severe dengue and require hospitalization [2]. In Argentina, several outbreaks of dengue, occurring mainly in the northern region of the country, have been reported [3]. The largest outbreak of dengue in Argentina occurred in 2009 with over 26,000 indigenous cases and 6 deaths spread over several provinces [4]. Four dengue serotypes are circulating in the country, with reports of two or more viral serotypes being present during the same year. However, due to eco-climatic diversity among the provinces, dengue incidence shows wide variability between regions and between successive years. Some regions

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bordering the endemic areas have indigenous transmission almost every year while other regions have either the vector without the virus or have neither the virus nor the vector. These factors lead to great variability in the risk of dengue transmission throughout the country.

Currently, no vaccines or specific treatments are available for dengue and prevention depends exclusively on vector control which has demonstrated limited effectiveness in controlling disease transmission [5]. Several vaccines are under development, including three attenuated chimeric tetravalent dengue vaccines, which are the most advanced vaccines being developed [6]. Early phase III trials of one of these vaccines in Asia and America predict efficacy values greater than 50% [7,8]. According to a recent review, the pooled rates of efficacy for symptomatic dengue and severe dengue were 65.6% and 93.2% respectively for children older than 9 years [9]. A vaccine with such an efficacy profile would be of substantial benefit to public health, and would support large-scale vaccine administrations [10]. In December 2015, Mexico became the first country in the world to approve the use of this vaccine for the prevention of dengue. The tetravalent dengue vaccine will be available to children and adults who live in areas where the disease is endemic. Even though this vaccine may not completely prevent transmission, it should prevent severe disease [11]. However, it is essential to consider the costs and benefits of the dengue vaccine before it is recommended and introduced into the public market. To date, four studies on the cost-effectiveness of a hypothetical dengue vaccine have been published [12–15] and all these studies show the vaccine to be cost-effective. However, these studies were carried out in countries with a high incidence of dengue, and to the best of our knowledge, no such studies on the cost-effectiveness of the dengue vaccine have been conducted in countries with heterogeneous risk of dengue transmission like Argentina. This heterogeneity means that the virus transmission is restricted to summer months and to specific regions located in the north of the country.

The aim of this study was to estimate the cost-effectiveness of a dengue vaccine in Argentina compared to no vaccination by taking into account the current and known parameters and by performing a thorough sensitivity analysis to address potential uncertainties. This analysis was performed considering a vaccination program that might be implemented by the Argentinean Ministry of Health at national level, and an alternative scenario in which the vaccination program is targeted to high transmission areas.

2. Materials and methods

2.1. Model overview

The methods and reporting of this study are conformed to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) instrument recommended for cost-effectiveness analysis in health [16]. This study was carried out from a societal perspective and included both direct and indirect costs associated with a vaccination program at national level for children of 2 years of age [17]. In addition, two one-way sensitivity threshold analyses were performed to estimate the maximum possible price of the vaccine under two different scenarios: the vaccination program at national level and a vaccination strategy limited only to high transmission areas, as detailed later. Disability adjusted life years (DALYs) due to dengue and severe dengue was used as the index of utility. A Markov simulation model was developed with 1-year cycles that followed a hypothetical cohort of 100,000 people from birth to death, considering the life table and life expectancy of Argentina (76 years from birth). Due to the low dengue infection rates reported in Argentina, the possibility of just one reinfection with a different virus serotype was the only possibility considered. Accordingly, five possible health states were considered in the model: susceptible, immune by vaccination, immune to one serotype by natural infection, immune to two serotypes by natural infection, and dead. The vaccination branch of the Markov model is shown in Supplementary Fig. 1. As both dengue and severe dengue have a rapid onset and a short course they were incorporated in the model as transitional states. Probabilities describing the likelihood of transitions among the health states included probability of dengue virus infection, proportion of unapparent or subclinical cases, risk of severe dengue during primary and secondary infection and case-fatality rate for severe dengue. In the vaccine branch of the Markov model, the probability of being immunized was calculated as the product of the vaccination coverage and the vaccine efficacy, assuming lifetime protection. Vaccine coverage was defined as the proportion of people who receive the complete vaccination schedule in relation to the people targeted for vaccination.

2.2. Model parameters

The model parameters included transition probabilities between health states, variables for estimating costs and for estimating the DALYs associated with dengue and severe dengue (Table 1). These transition probabilities and input data for other parameters were obtained from published studies that used prospective cohort designs and reported on data from Latin America and/or Asia (see Supplementary Table 1). The annual incidence of dengue was estimated using the values of average and range for annual dengue incidence from 2009 to 2014, as reported to the Pan American Health Organization [18]. This pooled incidence was calculated considering areas showing high and low transmission rates, and other areas in which transmission was not observed, in order to account for the transmission heterogeneity. The risk of dengue was considered age-dependent, using an equation that considers the conditional risk of symptomatic dengue by age [19]. The probability of infection was calculated from the dengue incidence and the proportion of subclinical cases. Vaccination coverage data were obtained from a study that evaluated the coverage of other vaccines in Argentina, considering only those vaccines with at least 3 doses [20]. Vaccine efficacy data were obtained from a recent clinical trial in Latin America that used a vaccination schedule of 0, 6 and 12 months [8]. Model costs included direct medical costs for outpatient visits, laboratory practices, and hospital care in medical wards and in intensive care units, and were taken according to 2014 public hospital tariffs [21]. Considering the universal health coverage of Argentina, a 100% of patients were assumed to have access to medical care. Indirect costs included the absenteeism cost due to dengue illness and hospitalization, and the cost of dengue deaths as a consequence of severe dengue. These costs were estimated using the human-capital approach [22], and calculations were based on average salaries of Argentina according to statistics of the National Ministry of Labor of Argentina. The vaccination program included vaccine transport, storage and administration for a three dose scheme [7,8,23]. The price of each vaccine dose was approximated using per dose production costs and ranges estimated from a study which analyzed vaccine production costs of an attenuated chimeric tetravalent dengue vaccine produced at the Butantan Institute in Brazil [24]. Based on results from two dengue vaccine meta-analysis and two phase 3 efficacy trials, the vaccine side effects were not considered [7–9,25]. In concurrence with other studies on dengue vaccine cost-effectiveness, DALYs were used as the measure of utility with disability weights of 0.197 and 0.545 for dengue and severe dengue, respectively. These values were based on the World Health Organization disability weights for diseases and conditions [26]. DALYs per episode of dengue or severe dengue was estimated by taking into account the duration of symptoms in days. A discount rate of 0.03, with a range

Table 1
Transition probabilities, effectiveness and costs used in the model; parameter values, ranges and distributions used in the sensitivity analyses.

Model input parameter	Value (range)	Distribution for probabilistic sensitivity analysis	Source
Dengue incidence (per 100,000 persons-year)	17.66 (0.53–71.06)[a]	Beta (0.86, 4898)	Own calculation based on [18]
Age-specific risk of clinical dengue	$1 - \exp(-0.000259 \times \text{age}^{3.991})$	–	[19]
Proportion of inapparent	0.77 (0.42–0.93)[a]	Beta (6.28, 1.86)	[38]
Proportion of severe dengue (1st infection)	0.036 ()[b]		[39]
Proportion of severe dengue (2nd infection)	0.118 ()[b]		[39]
Death rate from severe dengue in children (per 1000 cases)	0.007	Point estimate	[40]
Death rate from severe dengue in adults (per 1000 cases)	0.045	Point estimate	[40]
Vaccine efficacy against dengue	0.647 (0.587–0.698)[b]	Beta (143, 78)	[8]
Vaccine efficacy against severe dengue	0.955 (0.688–0.999)[b]	Beta (5, 0.24)	[8]
Vaccine efficacy against hospitalized dengue	0.803 (0.647–0.895)[b]	Beta (24, 6)	[8]
Vaccination coverage	0.73 (0.71–0.76)[a]	Beta (690, 255)	[20]
Proportion of hospitalization (dengue cases)	0.247 (0.154–0.340)[b]	Beta (15, 48)	[41]
Proportion of hospitalization (severe dengue cases)	0.907 (0.779–0.974)[b]	Beta (24, 2)	[41]
Length of hospital stay in days (dengue cases)	3.8	Point estimate	[42]
Length of hospital stay in days (severe dengue cases)	5.0	Point estimate	[40]
Duration of illness in days (dengue cases)	4.36	Point estimate	[43]
Duration of illness in days (severe dengue cases)	8.31	Point estimate	[43]
Average number of ambulatory visits (dengue cases)	4.2	Point estimate	[42]
Cost per dengue case (US$ per ambulatory case)	141.93 (113.54–170.32)[c]	Triangular	Own calculation
Cost per dengue case (US$ per hospitalized case)	830.87 (664.70–997.04)[c]	Triangular	Own calculation
Cost per severe dengue case (US$ per ambulatory case)	225.15 (180.12–270.18)[c]	Triangular	Own calculation
Cost per severe dengue case (US$ per hospitalized case)	2139.02 (1711.02–2566.82)[c]	Triangular	Own calculation
Cost of death from severe dengue (US$ per year)	12,402.09	Point estimate	Own calculation
Vaccine price (US$ per dose)	0.58 (0.51–0.65)	Gamma (205, 355)	[24]
Vaccination cost (including vaccine transport, storage and administration for a three dose scheme) (US$ per vaccinated person)	1.89	—	Own calculation
Disability weight for dengue cases	0.197 (0.172–0.211)[a]	Beta (245, 1002)	[26]
Disability weight for severe dengue cases	0.545 (0.475–0.583)[a]	Beta (139, 116)	[26]
Vaccine price (US$ per dose)	(0–100)[a]	First and second threshold analysis	Own assumption
Dengue incidence (per 100,000 persons-year)	280.16	Second threshold analysis	Own calculation based on data from the National Ministry of Health

[a] Range: minimum–maximum.
[b] Range: 95% confidence interval.
[c] Range: value ± 20%.

from 0.00 to 0.05, was considered for both costs and utilities as it is recommended for economic evaluations [27]. The calculations used to arrive at the values for the various parameters are given in Supplementary Table 2.

2.3. Cost-utility analysis

The incremental cost-effectiveness ratio (ICER) was calculated as the ratio of the difference in vaccination and disease costs to the difference in DALYs averted and was expressed in American dollars per DALY averted (US$/DALY). Argentina does not have a defined willingness-to-pay threshold for health interventions. Thus, according to a World Health Organization report [28], the intervention was considered "cost-effective" if the cost of one DALY averted was less than three times the per capita national gross domestic product (GDP). Argentina's per capita GDP was US$ 12,873 in 2014 [29], therefore the cost-effectiveness threshold was calculated to be US$ 38,619 per DALY averted. All costs were expressed in 2014 American dollars (US$).

2.4. Sensitivity analysis

A one-way sensitivity analysis was performed for price, cost, probability and utility parameters in the Markov model to determine the impact of uncertainty on model outcomes. A probabilistic sensitivity analysis based on 10,000 Monte Carlo simulations was also performed to assess the simultaneous effect of uncertainty on model results. The gamma, beta and triangular distributions were used for the price, costs, transition probabilities and other parameters, while the outcome variables were assumed to be normally distributed [27]. A cost-effectiveness acceptability curve was plotted using probability of the vaccination being cost-effective at different threshold values of willingness-to-pay per DALY averted.

A first threshold analysis was performed to determine the maximum price per dose at which the vaccination program at national level could still be deemed cost-effective. The vaccine price per dose was varied from US$0.1 to US$100. A second threshold analysis was carried out to estimate the maximum vaccine price per dose in a scenario in which the vaccination is preceded by a risk stratification system and is limited only to high transmission areas. For this

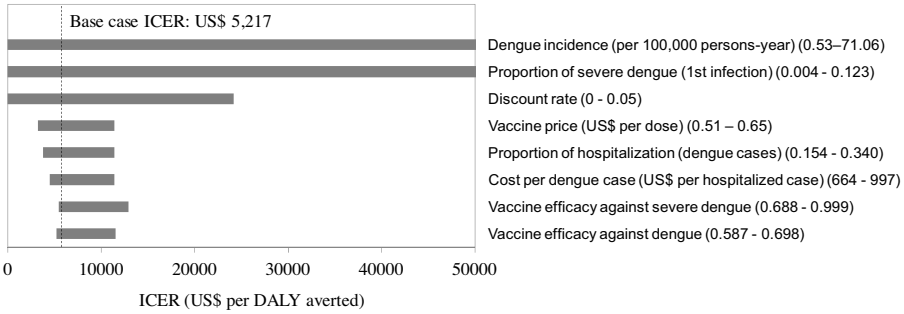

Fig. 1. Tornado diagram representing the univariate influence of key parameters in the incremental cost-effectiveness ratio (ICER). The interrupted line represents the base case ICER.

scenario, the incidence of the San Martin department was the one used. This area is located in the northern region of the country and has an average incidence of 280 cases per 100,000 people, a value greater than 10 times the pooled incidence of Argentina in the last 5 years.

3. Results

3.1. Base-case analysis

From a societal perspective, our model estimated that it would cost US$ 190,065 to treat dengue infection in the cohort of 100,000 individuals with no vaccination program, while it would cost US$ 238,815 if the vaccination program is implemented. The ICER for the vaccination program was US$ 5714 per DALY averted, implying that vaccination would be cost-effective when based on the WHO cost-effectiveness thresholds and the GDP of Argentina. When using a discount rate of 0% instead of 3%, the vaccination program was dominant compared to no vaccination.

3.2. Sensitivity analysis

A tornado diagram indicating the cost variables in descending order of influence is shown in Fig. 1. Parameters that changed the ICER by more than 10% were included in the figure. The predicted ICER values were most sensitive to changes in the rate of dengue incidence, in the proportion of severe dengue after the first infection and in the discount rate. The vaccine price was the forth parameter that had the strongest influence on the ICER. Fig. 2 shows the sensitivity of the ICER to a range of vaccine prices.

The probabilistic sensitivity analysis showed that the Median ICER was US$27,410 per DALY averted with an inter quartile range of US$555–US$140,156 per DALY averted. The cost effectiveness acceptability curve (Fig. 3) showed that the vaccination program has a 54.9% probability of being cost effective at a threshold of 3 times per capita GDP of Argentina.

The first threshold analysis estimated in US$1.49 the highest possible vaccine price per dose to still consider the vaccination program as cost-effective if the vaccination is implemented at national level. If the vaccination program is implemented in high transmission areas, as evaluated in the second threshold analysis, the highest vaccine price per dose was estimated in US$28.72.

4. Discussion

In the present study, the cost-utility of the currently most advanced tetravalent dengue vaccine was estimated using data from the largest phase III clinical trial on vaccine efficacy conducted in Latin America. Our results indicate that the dengue vaccine, which is partially effective and has a satisfactory safety profile [30], would be cost-effective, even though there is a temporally and geographically limited risk of transmission in Argentina.

Our analysis is based on data from a clinical trial of vaccine efficacy in more than 20,000 participants across Latin America. Although the initial Phase IIb study failed to reach its primary efficacy endpoint, the next two Phase III studies report efficiencies of over 50% against dengue, 80% against hospitalizations and 95% against severe forms of the disease [9,31]. It was further determined that there is no risk in administering the vaccine in dengue-endemic populations and this safety profile has been consistent across the trials [9,25,31]. Therefore, it is likely that there will be no problems in licensing this vaccine, and plans for large-scale vaccine production are already underway [11].

Regarding the vaccine price for estimating the vaccination costs of the program, production costs were considered since our model had a societal perspective and because market prices for vaccines can be highly distorted [32]. Importantly, the vaccine production

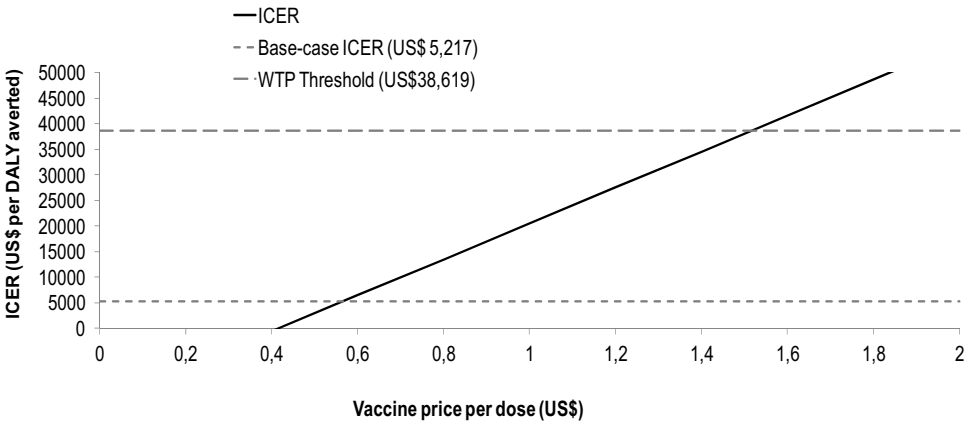

Fig. 2. Univariate analysis. Incremental cost effectiveness ratio (ICER) as a function of the vaccine price per dose (in US$).

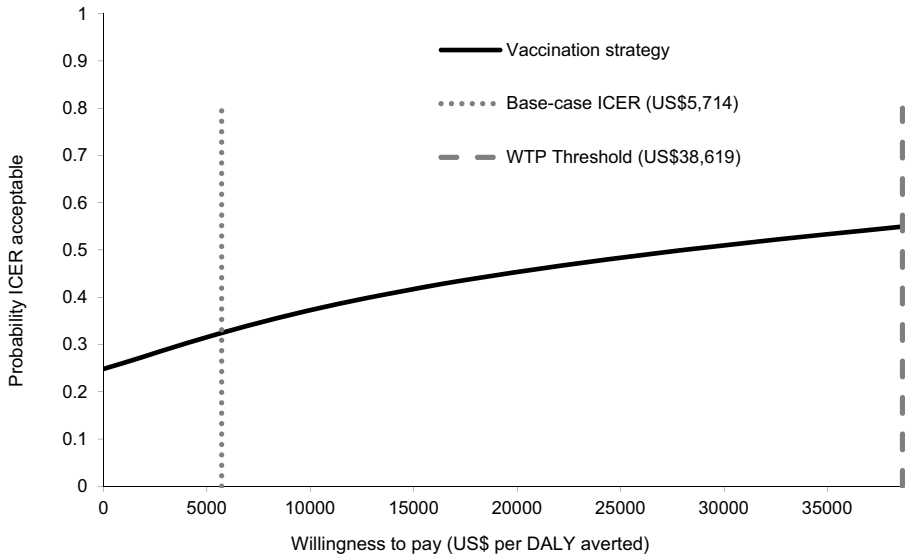

Fig. 3. Cost-effectiveness acceptability curve showing the probability that vaccination strategy is cost-effective.

costing used in our model was based on actual data derived from a study that examined vaccine production costs at the Butantan Institute in Brazil [24].

Univariate sensitivity analysis revealed that uncertainties in dengue incidence had the greatest potential impact on the ICER. Other parameters that significantly influenced the ICER were the probability of severe dengue after the first infection, the proportion of hospitalizations between dengue cases, the cost of dengue cases, the discount rate and those parameters inherent to the vaccine itself: vaccine price and efficacy. On the other hand, the probabilistic sensitivity analysis showed that there was considerable uncertainty respecting the optimum strategy, while nearly half of simulations indicated that the vaccination program at national level was not cost-effective.

The threshold analysis showed that the vaccination program at national level remained cost-effective for a vaccine price below US$1.49 per dose. However, even allowing for higher vaccine prices the vaccination strategy could be cost-effective if it is carried out conforming to a risk stratification system in predetermined high risk regions. Moreover, dengue incidence has been increasing steadily over the last two decades, and since 1998, an increase in the number of indigenous cases, the frequency of outbreaks, and the spread of the vector in areas previously unaffected by dengue have been observed [33]. Therefore, the vaccination strategy can be expected to become increasingly and steadily cost-effective over time.

A literature search revealed that there are only four published studies on the cost-effectiveness of vaccination against dengue in Asia and South America [12–15]. Further, all these studies were conducted from a societal perspective and the vaccination strategy was proven to be either cost-effective or highly cost-effective. One of these studies used estimates of the same tetravalent dengue vaccine, while the others used generic parameters of a non-specified vaccine. However, all these studies were carried out in highly endemic regions, while our analyses has been performed in the setting of limiting climatic conditions for the transmission of dengue and irregular occurrence of outbreaks.

Although we report that vaccination would be cost-effective, there are several limitations. First, dengue incidence in Argentina is both temporally and geographically highly variable and adds uncertainty to the results. Secondly and similar to other cost-effectiveness analysis based on simulation models, the results presented here are highly dependent on the probability values derived from observational studies, and the possibility of bias could not be completely avoided. Regarding to this, stringent measures were followed to ensure transparent selection of model parameters and sensitivity analyses were carried out to consider the uncertainty of these parameters. Thirdly, the present model does not factor in the effect of herd immunity. This is because according to some studies published to date, vaccine coverage required to reach herd immunity would be 82% for dengue [15,34] while we assumed a lower coverage value (73%) for base-case analysis. Consequently, and similar to other studies on vaccine cost-effectiveness, it was decided not to consider the effect of herd immunity [35,36]. However, it is also true that each vaccinated person could have an impact on the R0 and thus decrease the disease transmission independently of a vaccine coverage threshold to reach herd immunity. Accordingly, it would be worth including the effects of herd immunity in future estimations, especially when more data on indirect protection of dengue vaccine would be demonstrated. Fourthly, the use of public hospital tariffs may have masked higher dengue hospitalizations costs incurred in private settings. Fifthly, this study did not take into account the impact of dengue on international tourism [37]. This influence is difficult to measure, but its inclusion in future simulation models would probably improve the cost-effectiveness performance of dengue vaccination. Finally, the incidence of dengue, both without vaccination and after implementation of a vaccination program, was estimated assuming concurrent operation of vector control activity, and the reasons for this are twofold. First, the need to continue vector control efforts and other prevention strategies even in the presence of a vaccination program is widely recognized [10], and second, the effect of vector control activities can be separately assessed only by using a model that estimates transmission risk starting from the vector populations. Such a model would be unlike to the present model that uses the real time data on dengue incidence.

In conclusion, a dengue vaccine would be cost-effective as a prevention strategy in a country with heterogeneous risk of dengue transmission like Argentina, especially when targeting high-risk areas. However, these results should be interpreted with caution due to the high variability observed in the probabilistic sensitivity analysis. It is expected that in future the incidence of dengue would increase as a consequence of climatic changes and risks associated with globalization. If this trend continues, our results suggest that the vaccination of children will be even more cost-effective over both the medium and long term.

Conflicts of interest

The authors have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.vaccine.2015.12.040.

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