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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