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Cost-effectiveness of dengue vaccination in ten endemic countries

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ABSTRACT

Following publication of results from two phase-3 clinical trials in 10 countries or territories, endemic countries began licensing the first dengue vaccine in 2015. Using a published mathematical model, we evaluated the cost-effectiveness of dengue vaccination in populations similar to those at the trial sites in those same Latin American and Asian countries. Our main scenarios (30-year horizon, 80% coverage) entailed 3-dose routine vaccinations costing US$20/dose beginning at age 9, potentially supplemented by catch-up programs of 4- or 8-year cohorts. We obtained illness costs per case, dengue mortality, vaccine wastage, and vaccine administration costs from the literature. We estimated that routine vaccination would reduce yearly direct and indirect illness cost per capita by 22% (from US$10.51 to US$8.17) in the Latin American countries and by 23% (from US$5.78 to US$4.44) in the Asian countries. Using a health system perspective, the incremental cost-effectiveness ratio (ICER) averaged US$4,216/disability-adjusted life year (DALY) averted in the five Latin American countries (range: US$666/DALY in Puerto Rico to US$5,865/DALY in Mexico). In the five Asian countries, the ICER averaged US$3,751/DALY (range: US$1,935/DALY in Malaysia to US$5,101/DALY in the Philippines). From a health system perspective, the vaccine proved to be highly cost effective (ICER under one times the per capita GDP) in seven countries and cost effective (ICER 1–3 times the per capita GDP) in the remaining three countries. From a societal perspective, routine vaccination proved cost-saving in three countries. Including catch-up campaigns gave similar ICERs. Thus, this vaccine could have a favorable economic value in sites similar to those in the trials.

1. Introduction

Dengue, one of the world's most health threatening vector-borne viral diseases, is rapidly spreading to latitudes with little previous transmission and now places half the world's population at risk [1,2]. The 3.2 million cases reported globally to the World Health Organization (WHO) in 2015, the latest data available, are 45% above those reported in 2010 [3]. Including unreported cases, the estimated number of symptomatic dengue cases ranged from 58,400,000 [4] to 96,000,000 [1]. A dengue vaccine has engaged policy makers since 1993 as a potentially cost-effective strategy for dengue control [5]. The WHO's Commission on Macroeconomics and Health suggested that the cost-effectiveness of a health intervention could be judged by comparing its incremental cost-effectiveness ratio (ICER) per disability-adjusted life year (DALY) averted to the per capita gross domestic product (GDP) of the country or region considering its use. Under the Commission's widely used guideline [6,7], if an ICER is under one times the per capita GDP, then the intervention is highly cost-effective; an ICER between 1 and 3 times the per capita GDP makes the intervention cost effective.

A literature review identified 32 publications with economic analyses of a dengue vaccine (see Appendix, p1). Seven studies from 2013 through 2017, based on assumed or phase-2B efficacy data of a recombinant, live attenuated tetravalent dengue vaccine indicated that such a dengue vaccine would likely be cost effective [5,8–13]. A 2015 pooled analysis of results of randomized trials of the vaccine across 10 countries in the Americas and Asia reported that the efficacy against virologically-confirmed dengue illness in the 25 months post-dose 1 was 60.3% (95% confidence interval [CI]: 55.7–64.5%) for all participants (aged 2 through 16 years) and 65.6% (95% CI: 60.7–69.9%) for subjects aged 9 and above [14]. The five-year follow-up for subjects aged 9 and above (the age group

Abbreviations: CI, confidence interval; CMDVI, comparative modeling of dengue vaccine impact; DALY, disability-adjusted life year; GBD, global burden of disease; ICER, incremental cost-effectiveness ratio; WHO, World Health Organization.

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for which the vaccine was subsequently licensed) showed the vaccine efficacy remained high against hospitalized dengue in both Asia (55%, CI: 33–70%) and Latin America (68%, CI: 52–78%) [15].

Projections for Brazil, the Philippines and Mexico suggested that dengue vaccination would be cost-effective from a societal perspective provided the cost per vaccine dose in these countries remained below US$77, US$262, and US$214, respectively [11,12,16,17]. In 2015, WHO organized the Comparative Modeling of Dengue Vaccine Impact (CMDVI) exercise comparing eight mathematical models, including the one used in this study [18]. Based on the findings, WHO suggested that the vaccine would generally be cost-effective and endorsed its use in locations with a dengue seroprevalence rate of 70% or higher at the proposed age of vaccination. WHO added that the vaccine could also be used for populations with seroprevalence between 50% and 70%, with final decisions based on site-specific data [19]. Following licensure, both Brazil and the Philippines initiated sub-national public sector programs [20]. As of October 13, 2017, 19 countries had registered the Sanofi Pasteur (France) vaccine: Argentina, Bolivia, Brazil, El Salvador, Costa Rica, Guatemala, Honduras, Mexico, Paraguay, Peru, and Venezuela in Latin America, and Australia, Bangladesh, Cambodia, Indonesia, Malaysia, Philippines, Singapore, Thailand in Asia [21].

This paper develops empirical cost-effectiveness analyses to inform decision making in the 10 endemic phase-3 "countries." Hereafter, we treat Puerto Rico as a "country" for convenience. This study uses detailed three-year trial results from the countries [14], a model of dengue transmission and vaccination [22], and estimates of economic burden by country [23].

2. Methods

2.1. Overview

This cost-effectiveness analysis of dengue vaccination was conducted from both health system and societal perspectives for sites in the 10 countries where clinical trials for the licensed dengue vaccine were conducted [24,25]. Five countries are in Southeast Asia (Indonesia, Malaysia, Philippines, Thailand, and Vietnam) and five in Latin America (Brazil, Colombia, Honduras, Mexico, and Puerto Rico). The vaccination schedule consists of three injections administered at six-month intervals used in the phase-3 trials [24,25]. All vaccination strategies include routine vaccination for children aged 9 years (i.e., one age cohort vaccinated annually, termed R9). Two optional catch-up campaigns were also examined, consisting of 4 or 8 age cohorts, and reaching the target coverage over 2 years, termed R9C4 and R9C8.

The main analysis covered a 30-year span to assess the vaccine's long-term benefit against dengue's four serotypes with 80% coverage for the first dose and low drop-out (respectively 75% and 70% coverage for the second and third dose), consistent with many routine vaccination programs. Alternative scenarios explored lower (i.e. 50%) coverage and a shorter (10-year) time horizon. In each case we compared the vaccination strategies against the status quo (no vaccine) using a standard cost-effectiveness framework [26,27]. The modeling used DenMod, a web-interface for a mathematical transmission model [22] calibrated from the two large-scale phase-3 clinical trials [24,25].

2.2. Costs

All costs are expressed in 2015 US dollars. We estimated costs from both health system and societal perspectives. The health system perspective incorporated costs of vaccine purchase, vaccine delivery, and treatment of dengue cases. Our base estimate assumed a sales price of $20 per dose, close to that of the Philippines program. We derived the vaccine delivery cost from literature covering the cost of vaccine delivery in non-campaign settings (i.e., health facility-based approach, outreach, and school-based approach) and adjusted to countries' GDP per capita using a regression model. Based on our literature review, we estimated the rate of vaccine wastage at 10% for the routine program and 5% for the catch-up program. We obtained the direct treatment cost of dengue cases and associated indirect costs by setting (e.g. hospital cases and ambulatory cases) from the literature.

The societal perspective added the indirect costs of illness and premature death, and opportunity costs of time required to obtain each dengue dose [28]. We estimated the indirect cost of premature death using a human capital approach [29]. To reflect the diverse ages of dengue fatalities, we estimated this indirect cost as the product of GDP per capita times the number of discounted life years lost due to a dengue death. We estimated the time required to obtain each dengue dose to be one hour. This value reflects the breadth of potential delivery strategies with varying time requirements. The shortest would be a few minutes for an extra service at an existing clinical visit or school-based program, the initial strategy in Manila, the Philippines. The longest would entail a separate trip for a clinical visit exclusively for dengue vaccination, consistent with the community-based strategy in Brazil's Parana state. Table 1 provides vaccine delivery, treatment, and indirect costs, as well as GDP per capita and dengue case fatality rates. For more details, see Appendix, p2.

2.3. Effectiveness

We expressed effectiveness in DALYs, which account both for years of life lost due to disability and years of life lost due to premature death [30]. We calculated DALYs averted due to vaccination using three steps.

The first step was to estimate dengue cases and deaths averted due to dengue based on the vaccine's effectiveness, using results of the two large-scale phase-3 efficacy trials. These were conducted in five Latin American countries on children aged at the start of follow-up between 9 and 16 years, and five Asian countries on children aged between 2 and 14 years. These trial data were used to estimate the main parameters of a transmission model: efficacy and duration of protection by age and serostatus at vaccination, transmission intensity, and interactions among serotypes. The mathematical model used in this analysis is an age-structured, host-vector, serotype-specific compartmental model that includes seasonality and accounts for the transmission dynamics of the four dengue serotypes in humans and mosquitoes at the population level. It incorporates multiple 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.

The second step was to obtain the DALYs lost per dengue episode. Although DALYs for dengue were reported in the Global Burden of Diseases (GBD) study, GBD estimates used a generic infectious disease, not specifically dengue. Here we used results of a 2016 systematic review of DALYs for a dengue episode, which considered DALYs lost during the onset, recovery and persistent-symptom phases of a dengue episode, and estimated DALYs lost at 0.032 per ambulatory case and 0.036 per hospitalized case [31].

The third step was to combine the estimates from the previous steps and deaths due to dengue to generate DALYs averted from vaccination. The mathematical model, with equations and input data described elsewhere [32], projected the impact of various vaccination strategies in the areas where the trials were conducted.