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Dengue dynamics and vaccine cost-effectiveness in Brazil

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ABSTRACT

Recent Phase 2b dengue vaccine trials have demonstrated the safety of the vaccine and estimated the vaccine efficacy with further trials underway. In anticipation of vaccine roll-out, cost-effectiveness analysis of potential vaccination policies that quantify the dynamics of disease transmission are fundamental to the optimal allocation of available doses.

We developed a dengue transmission and vaccination model and calculated, for a range of vaccination costs and willingness-to-pay thresholds, the level of vaccination coverage necessary to sustain herd-immunity, the price at which vaccination is cost-effective and is cost-saving, and the sensitivity of our results to parameter uncertainty. We compared two vaccine efficacy scenarios, one a more optimistic scenario and another based on the recent lower-than-expected efficacy from the latest clinical trials.

We found that herd-immunity may be achieved by vaccinating 82% (95% CI 58–100%) of the population at a vaccine efficacy of 70%. At this efficacy, vaccination may be cost-effective for vaccination costs up to US$ 534 (95% CI $369–1008) per vaccinated individual and cost-saving up to $204 (95% CI $39–678). At the latest clinical trial estimates of an average of 30% vaccine efficacy, vaccination may be cost-effective and cost-saving at costs of up to $237 (95% CI $159–512) and $93 (95% CI $15–368), respectively.

Our model provides an assessment of the cost-effectiveness of dengue vaccination in Brazil and incorporates the effect of herd immunity into dengue vaccination cost-effectiveness. Our results demonstrate that at the relatively low vaccine efficacy from the recent Phase 2b dengue vaccine trials, age-targeted vaccination may still be cost-effective provided the total vaccination cost is sufficiently low.

1. Introduction

Dengue poses a significant threat to both public health and economic progress in many regions of the world [1,2]. In Brazil, there are more than two million dengue fever cases annually resulting in an economic burden of over US$ 1 billion [2]. Three serotypes of the virus (DENV-1, DENV-2, DENV-3) are currently endemic in Brazil, with the fourth serotype (DENV-4) emerging [3,4].

Vaccine development has been challenging due to the necessity of eliciting long-lived protection against all four serotypes in order to avoid the elevated disease severity associated with secondary infections [5,6]. While initial studies indicated that a three dose-regime of the Sanofi Pasteur vaccine would elicit protective immunity against all four serotypes [7,8], the latest vaccine trial points to a lower overall efficacy with no evidence of serotype-specific protection against DENV-2 [9]. However, sample-size biases may have arisen in these trials [10], and further vaccine efficacy studies are underway. Recently several promising candidate tetravalent vaccines have been developed, with availability projected by 2015–2020 [11,12].

As vaccine development nears completion, country-specific studies that quantify the cost-effectiveness of the vaccine will be critical to successful public health strategies. Previous studies have estimated the cost-effectiveness of a hypothetical dengue vaccine in Southeast Asia [13–16]. However, dengue vaccine cost-effectiveness has yet to be evaluated in Brazil, where costs and epidemiological dynamics are distinct from those of Southeast Asia. Furthermore, dengue vaccine cost-effectiveness models have not addressed the secondary effects of vaccination on reducing transmission beyond the vaccine recipients [17]. We have previously shown that the effectiveness associated with vaccination campaigns can be substantially under-estimated if secondary transmission effects are not considered [18].

Here, we evaluated the cost-effectiveness of dengue vaccination, taking into account transmission dynamics, and compared the

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range of clinical estimates from the latest trials with more optimistic efficacies suggested by initial trials of the Sanofi Pasteur vaccine and by other promising vaccine candidates [6–8]. We calculated the level of routine childhood coverage required to maintain herd-immunity and evaluated a range of vaccination policies that are currently under discussion [12,14,19]. We evaluated the costs associated with, and disability-adjusted life years (DALYs) saved by, alternative vaccination policies [20], and estimated the vaccination cost at which vaccination satisfies internationally accepted standards as cost-effective, very cost-effective, and cost-saving. We evaluated the sensitivity of our results to parameter uncertainty across a range of vaccination costs and willingness-to-pay thresholds.

2. Methods

We developed a deterministic, age-structured four-serotype dengue transmission model (described in the Supplement). We evaluated 400 potential vaccination policies, each consisting of (1) between 0 and 90% routine childhood coverage, in increments of 10%, (2) a one-time mass vaccination, as the vaccine becomes available, of one of four overlapping, increasingly inclusive age groups: 0–5 year olds, 0–15 year olds, 0–40 year olds, or the full population, and (3) a level of one-time mass vaccination between 0 and 90%, in steps of 10%. We modeled the routine childhood coverage by transitioning a fraction of young children into the vaccinated class following maternal antibody waning, where represents the vaccine efficacy. We modeled the one-time mass vaccination by transitioning a fraction of all individuals in age group a into the vaccinated class at the start of the simulation. We compared a relatively optimistic vaccine efficacy of 70% (49–87%) with a lower vaccine efficacy based on the Phase 2b trial results of 30% (95% CI −13.4 to 56.6%) [9].

2.1. Population herd-immunity

To determine the degree of vaccine coverage necessary to halt transmission and sustain herd-immunity, which we numerically estimated as occurring when dengue incidence was under 1% of the pre-vaccination incidence, we assumed a constant fraction ν_i of young children are vaccinated and calculated the incidence at the endemic equilibrium while varying ν_i from 0 to 1. To calculate the 95% credible interval of herd-immunity, we defined parameter distributions for the input parameters (Table S1), and conducted 10,000 Monte Carlo iterations for each level ν_i.

2.2. Efficient and cost-effective vaccination policies

Efficient policies are defined as those which produce the greatest DALYs saved for a given outlay. To identify efficient policies, we calculated the time-discounted DALYs lost to dengue fever, dengue hemorrhagic fever/dengue shock syndrome, and dengue-related deaths, and the total costs accrued due to vaccination, medical treatment, and lost productivity over 73 years, the life expectancy in Brazil [21]. To determine the net DALYs saved, we subtracted the total DALYs lost across the population under the vaccination scenario from the total DALYs lost across the population under the no vaccination scenario. To determine the net costs accrued, we subtracted the total costs accrued under the no vaccination scenario from the total costs accrued under the vaccination scenario. We varied the vaccination cost inclusive of the full three-dose regimen and the costs of vaccine delivery and administration, drawing from estimates of the anticipated costs of dengue vaccine production, over the range $10–300 [13,15,16,19].

2.3. Cost-effective, very cost-effective, and cost-saving vaccination costs

To identify the threshold costs at which vaccination becomes cost-effective and very cost-effective, we calculated the net benefit of every policy, defined as (DALYs saved) minus (net cost divided by willingness-to-pay) [22]. Interventions that had a positive net benefit at a willingness-to-pay of three times the per capita GDP ($36,000) were deemed "cost-effective", and those that had positive net benefits at one times the per capita GDP ($12,000) were deemed "very cost-effective", in accordance with the WHO Commission on Macroeconomics and Health [21,23–25]. To derive the cost-effective and the very cost-effective vaccination costs, we identified the maximum vaccination cost at which there is at least one policy with positive net benefits at the two willingness-to-pay thresholds. To derive the threshold at which vaccination becomes cost-saving, we calculated the maximum vaccination cost at which there is at least one policy with a negative net discounted cost.

To calculate the 95% credible intervals for the cost-effective, very cost-effective, and cost-saving vaccination costs, we generated 10,000 samples from a distribution of the societal costs of dengue fever and dengue hemorrhagic fever/dengue shock syndrome in Brazil (Table S2) [1].

2.4. Sensitivity to parameter uncertainty

To evaluate the sensitivity of our results to parameter uncertainty, we compared five vaccination policies that are consistent with estimated rates of childhood vaccination schedule completion in Rio de Janeiro and contain increasingly aggressive levels of one time mass vaccination [26]: (1) 80% routine childhood coverage, (2) 80% routine childhood coverage and mass vaccination of 50% of 0–5 year olds, (3) 80% routine childhood coverage and mass vaccination of 50% of 0–15 year olds, (4) 80% routine childhood coverage and mass vaccination of 50% of 0–40 year olds, and (5) 80% routine childhood coverage and mass vaccination of 50% of the entire population. We defined probability distributions for each parameter (Tables S1 and S2) and randomly sampled values from these distributions to generate 10,000 independent model outcomes. We calculated the probability for each policy of having the greatest net benefit at the cost-effective threshold and at the very cost-effective threshold as vaccination cost was increased.

To evaluate the sensitivity of our findings to vaccination cost, we assigned to vaccination cost a uniform uncertainty distribution of $10–300 and calculated the probability for each policy of having the greatest net benefit as willingness-to-pay was increased from $0 to $36,000 (the cost-effective threshold).

2.5. Phase 2b dengue vaccine efficacy

To evaluate the vaccination policies under the lower rates of vaccine efficacy estimated during recent Phase 2b dengue vaccine trials, we repeated all simulations using a vaccine efficacy defined by a Normal distribution, with a mean of 30% and a standard deviation of 13%, constrained to the range [0%, 100%], approximating the reported vaccine efficacy of 30% (95% CI −13.4 to 56.6%) [9].

3. Results

3.1. Population herd-immunity

We calculated an equilibrium annual dengue infection incidence in the absence of vaccination of 4.56% and an annual symptomatic dengue fever incidence of 1.06%, comparable to empirical estimates [2,27,28]. We found that herd-immunity may be achieved, at 70% vaccine efficacy, by routine childhood coverage of at least 82%,