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Dengue dynamics and vaccine cost-effectiveness in Brazil

David P. Durham[a,*], Martial L. Ndeffo Mbah[a], Jan Medlock[b], Paula M. Luz[c], Lauren A. Meyers[d], A. David Paltiel[a], Alison P. Galvani[a]

[a] Yale School of Public Health, Yale University, New Haven, CT, United States
[b] Department of Biomedical Sciences, Oregon State University, Corvallis, OR, United States
[c] Evandro Chagas Clinical Research Institute, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil
[d] Section of Integrative Biology, University of Texas at Austin, Austin, TX, United States

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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

* Corresponding author. Tel.: +1 412 417 5732.
E-mail addresses: david.durham@yale.edu, ddurham@alumni.cmu.edu (D.P. Durham).

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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 v_i of young children are vaccinated and calculated the incidence at the endemic equilibrium while varying v_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 v_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%,

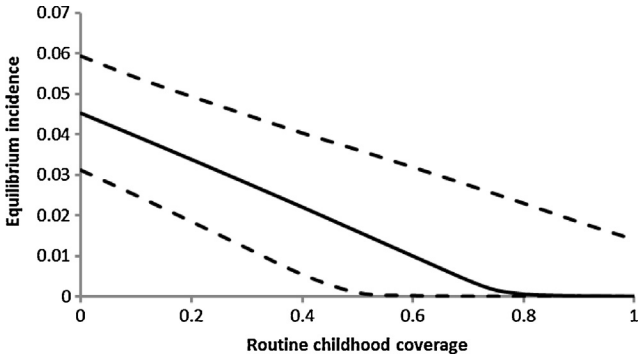

Fig. 1. Annual endemic dengue incidence (symptomatic and asymptomatic) as the routine childhood coverage at 70% vaccine efficacy increases, with 95% credible intervals (dashed).

although the upper bound of the 95% credible interval exceeded 100% (Fig. 1).

3.2. Efficient and cost-effective vaccination policies

We considered the net costs and DALYs saved across 400 unique vaccination policies. At an example cost of $250, most of those policies that are efficient, saving the most DALYs for a given outlay, and cost-effective, saving at least as many DALYs as the net cost divided by the willingness-to-pay, include between 60% and 80% routine childhood coverage, slightly below the herd-immunity level of 82% (Fig. 2c). While policies that include routine childhood coverage substantially below this level are efficient in some cases, policymakers may prefer larger programs that still fall below the willingness-to-pay but save many more DALYs (Fig. 2a and b). Conversely, policies that include routine childhood coverage in excess of herd-immunity may be efficient, but are not cost-effective at the Brazilian willingness-to-pay threshold (Fig. 2d). These results remain qualitatively similar across the full range of vaccination costs ($10–300), with the majority of efficient and cost-effective policies across this range including between 60 and 80% routine childhood coverage.

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

At a 70% vaccine efficacy, we found that the cost-effective threshold occurs at $534 (95% CI $369–1008), the very cost-effective threshold at $314 (95% CI $149–788), and the cost-saving threshold at $204 (95% CI $39–678).

3.4. Sensitivity to parameter uncertainty

We compared five vaccination policies combining 80% routine childhood coverage with varying levels of one-time mass vaccination. We calculated the vaccination cost range over which each policy would be preferred, having the highest probability of having the greatest net benefits. We found 80% routine childhood coverage with mass vaccination of 50% of the entire population to be preferred at vaccination costs up to $5 and 80% routine childhood coverage with mass vaccination of 50% of the 0–40 age group to be preferred at vaccination costs from $5 to $25. From $25 to $129, mass vaccination of the 0–15 age class was preferred, and between $129 and $285, mass vaccination of the 0–5 age class was preferred. At vaccination costs beyond $285, no vaccination at all was

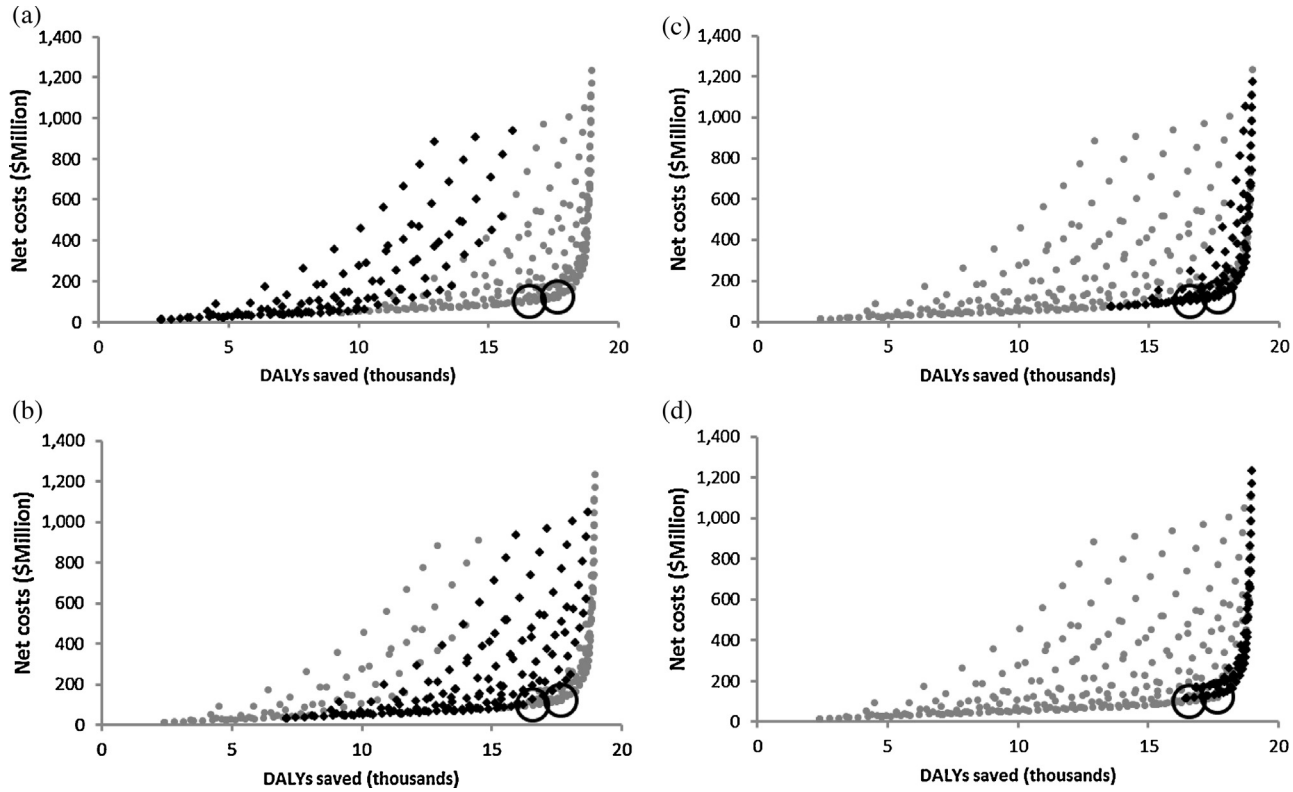

Fig. 2. Net cost and DALYs saved across 400 vaccination policies at a vaccination cost of $250. Each point represents a distinct policy combining between 0 and 90% routine childhood coverage with one-time mass vaccination of between 0 and 90% of age groups 0–5 year olds, 0–15 year olds, 0–40 year olds, or the full population. Bold diamonds indicate those policies that include (a) 0–30% routine coverage, (b) 30–60% routine coverage, (c) 60–80% routine coverage, and (d) 80–90% routine coverage. The largest policies that are very cost-effective and cost-effective are circled. Net cost and DALYs saved were discounted and summed over a 73 year period (the average life expectancy in Brazil).

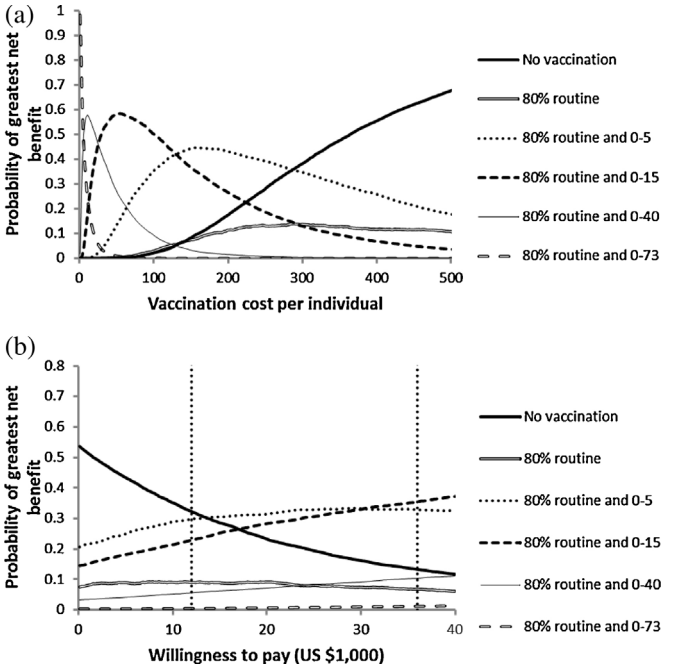

Fig. 3. Preferred policies, having the highest probability of having the greatest net benefits, at 70% vaccine efficacy. (a) Preferred policies, at a willingness-to-pay of US$ 36,000, as vaccination cost increases. (b) Preferred policies with vaccination costs sampled uniformly from the range ($10, $300), as willingness-to-pay increases. Vertical dashed lines indicate the very cost-effective threshold (US$ 12,000) and the cost-effective threshold (US$ 36,000). Evaluated policies include progressively more extensive mass vaccination: (1) No vaccination, (2) 80% routine childhood coverage with no mass vaccination, (3) 80% routine childhood coverage with mass vaccination of 50% of 0–5 year olds, (4) 80% routine childhood coverage with mass vaccination of 50% of 0–15 year olds, (5) 80% routine childhood coverage with mass vaccination of 50% of 0–40 year olds, and (6) 80% routine childhood coverage with mass vaccination of 50% of the full population.

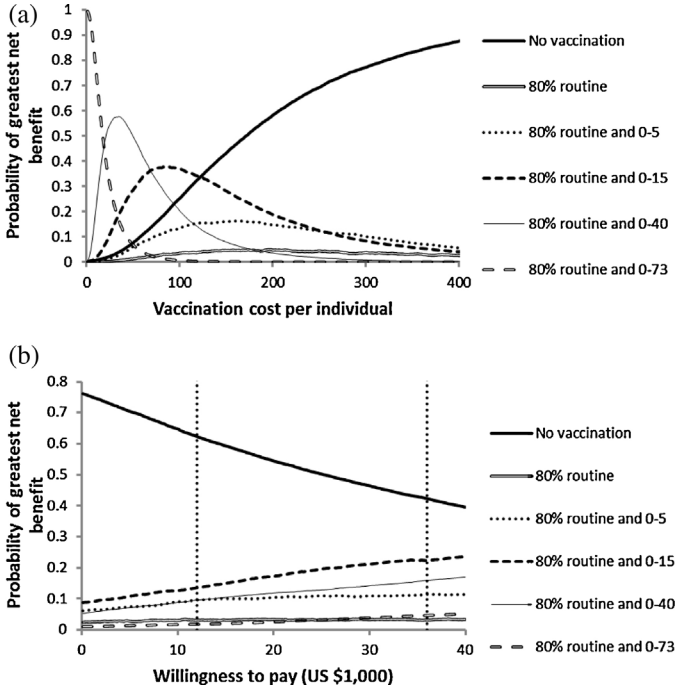

Fig. 4. Preferred policies, having the highest probability of having the greatest net benefits, at 30% vaccine efficacy. (a) Preferred policies at a willingness-to-pay of US$ 36,000, as vaccination cost increases. (b) Preferred policies with vaccination costs sampled uniformly from the range ($10, $300), as willingness-to-pay increases. Vertical dashed lines indicate the very cost-effective threshold (US$ 12,000) and the cost-effective threshold (US$ 36,000).

preferred to any of the five policies considered. 80% routine childhood coverage without mass vaccination never emerged as the preferred choice (Fig. 3a).

When we sampled vaccination cost uniformly from $10 to $300, we found that 80% routine coverage with one-time mass vaccination of the 0–5 age class was preferred for willingness-to-pay values ranging from $13,500 to $30,200, while 80% routine coverage with one-time mass vaccination of the 0–15 age class was preferred from $30,200 to beyond the cost-effective threshold. These results demonstrate that cost-effectiveness is robust to vaccination cost (Fig. 3b).

3.5. Phase 2b dengue vaccine efficacy

Using the dengue vaccine efficacy estimated in recent Phase 2b trials, we found that herd-immunity cannot be achieved even with 100% routine childhood coverage. We also found vaccination may be cost-effective up to a cost of $237 (95% CI $159–512), very cost-effective up to a cost of $141 (95% CI $63–416), and cost-saving up to a cost of $93 (95% CI $15–368).

For the Phase 2b vaccine efficacy, we found that 80% routine childhood coverage and one-time mass vaccination of 50% of the entire population was preferred at a vaccination cost up to $18, 80% routine childhood coverage and one-time mass vaccination of 50% of the 0–40 age class was preferred from $18 to $68, and 80% routine childhood coverage and one-time mass vaccination of 50% of the 0–15 age class was preferred at a vaccination cost from $68 to $121. Beyond $121, no vaccination at all was preferred to any of the five policies considered (Fig. 4a). When we treated vaccination cost as an unknown parameter in the uniform range $10–300, none of the five vaccination policies were preferred to no vaccination at all (Fig. 4b).

4. Conclusions and discussion

Our results are pertinent to decisions of policymakers regarding the design of dengue vaccination policies. We demonstrated that, at an optimistic 70% vaccine efficacy, routine vaccination of 82% of young children is sufficient to maintain herd-immunity, as well as efficient and cost-effective across a range of vaccination costs. Achieving this level of vaccination coverage should be feasible logistically given that high levels of adherence to childhood vaccination schedules are consistently maintained in Brazil [26].

The herd-immunity threshold that we calculated provides a target range for maintaining protection of the population overall. Those policies with a level of routine coverage above the herd-immunity threshold are not cost-effective, because the excess routine coverage does little to further decrease dengue burden. Conversely, those policies with substantially lower levels of routine coverage do not adequately protect the population against dengue outbreaks, reducing the cost-effectiveness. However, policies that combine routine coverage with one-time mass vaccination of young age groups have the highest probability of having the greatest net benefits, by minimizing the lag time before population immunity is established. Therefore, our results highlight the importance of combining targeted mass vaccination as soon as the vaccine becomes available with routine herd-immunity coverage for optimal control and cost-effectiveness [12,14,19].

While recent Phase 2b trials demonstrated that the dengue vaccine is safe and confers some immunity against infection, the calculated vaccine efficacy of 30% was less than expected [9]. Our results suggest that even such a vaccine with 30% efficacy may be cost-effective and possibly cost-saving provided that the total vaccination cost can be kept sufficiently low, below $237 for

cost-effectiveness and below $93 for cost-saving. However, the Phase 2b trials showed no evidence of protection against DENV-2, which has been prevalent in Brazil in recent years [9,29]. Further vaccine trials are underway to validate and refine the efficacy estimates, as well as to resolve any sampling biases in the relatively small Phase 2b trials [10]. Should these initial efficacies remain consistent following further vaccine trials, our model may be extended to incorporate serotype-specific efficacy.

Concern about antibody-dependent enhancement (ADE), whereby prior infection with a single serotype of dengue enhances an individual's risk of severe infection with other serotypes, has motivated the development of tetravalent dengue vaccines that simultaneously protect against all four serotypes [5]. The potential for a vaccine itself to generate ADE and result in more clinically severe disease has been cited by vaccine developers as a theoretical risk of vaccines currently under development, although the degree to which vaccines may generate ADE, if at all, has not yet been well established [7]. Nonetheless, there is concern that ADE may enhance the risk of more severe dengue hemorrhagic fever as vaccine immunity wanes [6]. Future expansions of our model could investigate the effect of waning vaccine immunity on population protection and, as more information becomes available about vaccine-induced ADE, quantify the tolerable range of ADE that maintains vaccination cost-effectiveness.

In this paper, we developed a host-vector model of dengue virus transmission in Brazil and used it to provide quantitative estimates of vaccine pricing, herd-immunity coverage levels, and conditions under which vaccination is likely to be cost-effective and cost-saving. Our results are in empirical agreement with observed levels of dengue prevalence [2,27,28] and previous model predictions of necessary coverage for herd-immunity [17]. While we focus on urban vaccination policies within Brazil, our model can be readily adapted to model other countries by calibrating the transmission and mosquito survival parameters to match regional endemic dengue prevalence.

Dengue continues to present a significant challenge in many regions of the world. We evaluated the cost-effectiveness of vaccination in light of recent dengue vaccine trial results. We showed that carefully targeted vaccination holds significant potential to confer excellent value and reduce the overall burden of dengue in Brazil.

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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.2013.06.036.

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