Cost-effectiveness of Dengvaxia in Puerto Rico

Guido España, Alex Perkins

The latest results of the CYD-TDV vaccine show an increased risk of severe dengue upon infection among vaccinees without previous exposure to dengue virus (DENV) [1]. The World Health Organization (WHO) recommends a pre-vaccination screening to ensure that only those with previous exposure to DENV are vaccinated [2]. However, rapid diagnostic tests with high sensitivity and specificity are not currently available. We have previously discussed the benefits and cost-effectiveness of pre-screening vaccination for economic scenarios of the Philippines and Brazil [3]. Here, we discuss the implications of this strategy for Puerto Rico in terms of epidemiological benefits and cost-effectiveness.

# DESCRIPTION OF METHODS SPECIFIC FOR PUERTO RICO

## Agent-Based Model

As described in the manuscript with our main analyses [3], our agent-based model was previously used to make projections of vaccination impact with CYD-TDV in the absence of serological screening [4]. Although our model has been parameterized to data from Iquitos, Peru, we performed generic simulations that could represent scenarios of transmission from low to high intensity. These simulations showed agreement to the other seven models in the consortium. To estimate the impact of the pre-screening vaccination strategy with CYD-TDV for Puerto Rico, we modified our assumptions on costs, and focused our analyses on transmission scenarios with similar prevalence on 9-year-olds (PE). We assumed a coverage of 80% and simulated the sensitivity and specificity of serological screening from 0 - 1.

## Cost-effectiveness analysis

We updated our assumptions of treatment of dengue for ambulatory cases and hospitalizations, based on estimates from 2002 to 2010 [5]. Using the consumer price index for Puerto Rico, we projected these costs to 2019 USD. Similarly, we took the GDP per-capita for Puerto Rico in 2016 [6] and projected its value to 2019.

**Table 1. Dengue costs.**

|  |  |  |
| --- | --- | --- |
|  | Cost (USD) | Cost Projected (2019 USD) |
| Ambulatory | 239 (2010) | 311 |
| Hospitalization | 1615 (2010) | 2107 |
| GDP per-Capita | 30,833 (2016) | 30,833 |

We estimated the quality-adjusted life-years (QALY) gained with the pre-vaccination screening using disability weights and the time of disability from previous studies **(**[**SHIM**](SHIM) **or someoneelse)**. We assumed a weight of 1 to estimate the QALYs gained from deaths averted. Similar to other studies (REFs), we used a discounting weight of 3% per year for future cases, and we adjusted for life-expectancy using a discounting rate of 3% as well.

**Table 2. Disability weights.**

|  |  |  |
| --- | --- | --- |
| Event | Disability weight | Time of disability |
| Dengue fever | 0.0158 | 4 days |
| Hospitalization | 0.545 | 14 days |
| Deaths | 1 | Life-expectancy - age of death |

We then calculated the Incremental Cost-Effectiveness Ratio (ICER) as

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As others have, we deemed the intervention cost-effective if the ICER was below 3 GDP per-Capita, and very cost-effective if the ICER fell below 1 GDP per-Capita. We assumed a baseline scenario of costs. To evaluate the ICER of the pre-vaccination screening scenarios in Puerto Rico, we assumed a baseline scenario of the costs of the intervention. The cost per fully vaccinated child was set to 70 USD based on pricing information from the Philippines [REF], the cost to screen an individual for previous exposure to DENV as 10 USD, based on a study in Thailand [REF]. We assumed a baseline scenario of specificity (0.95) and sensitivity (0.8) of screening based on the available rapid diagnostic tests [7]. Given the uncertainty in these values, we assessed the sensitivity of ICER estimates to variation in these parameters.

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## Estimates of the intensity of transmission in Puerto Rico (PE9)

Estimates of seroprevalence in Puerto Rico indicate that prevalence in 9-year-olds is at most 50%. Coudeville et al. estimated 50% of prevalence in 9-year-olds [8] in the clinical trial sites. According to Argüello, 49.8% of participants between 10-18 years of age had a positive IgG anti-DENV antibodies [9]. Hence, we assume that the seroprevalence in 9-year-olds is around 40-50%.

# RESULTS

## Epidemiological benefits from vaccination

Using an agent-based model, we found that the benefits of pre-vaccination screening depend on the sensitivity, specificity, and transmission intensity. For the specific case of Puerto Rico, we assume a moderate intensity of transmission with a prevalence in nine-year olds around 50% () [8,9]. In this scenario, our results suggest a linear relationship between the proportion of hospitalizations, and the sensitivity and specificity of screening. Hence, positive outcomes could be obtained with at least high sensitivity or high specificity of screening (Fig. [1](#fig:org096c66c)). However, the largest benefits were found in scenarios of high sensitivity and specificity. From the perspective of an individual screened for previous DENV and possibly vaccinated, the relative risk showed a similar trend than from the public health perspective (Fig. [2](#fig:org29cefb3)). These results depend on our baseline assumption on the transmission intensity in Puerto Rico. If the transmission intensity of Puerto Rico resembles more a lower transmission setting (), tests with high specificity would be required to obtain public health benefits. In contrast, if Puerto Rico has a higher transmission intensity () than our assumptions, then public health benefits would be found in wider ranges of specificity and sensitivity, and these benefits would depend mostly on the sensitivity.

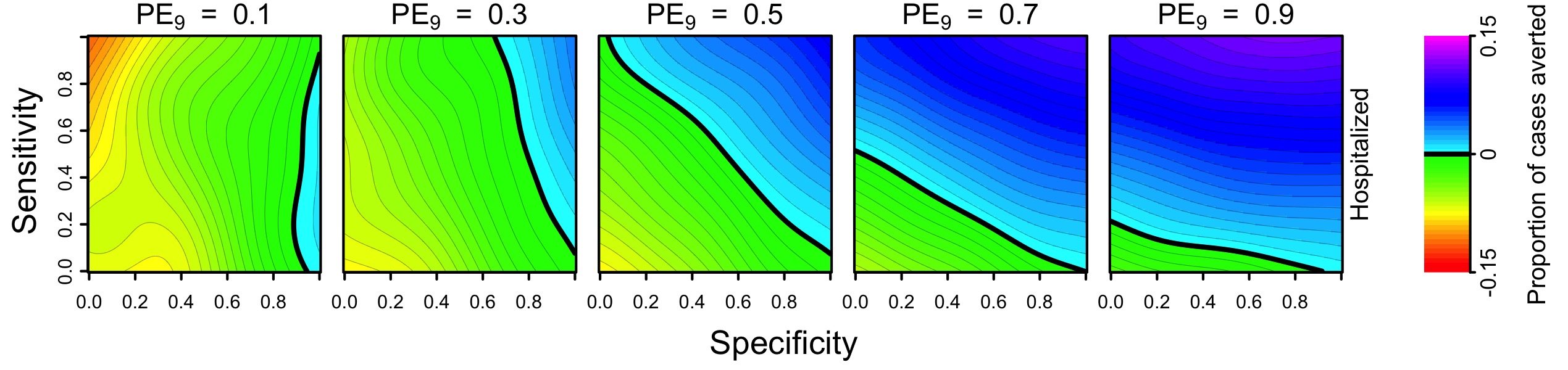


Figure 1. Proportion of cases averted with pre-vaccination screening strategy with CYD-TDV over 10 years

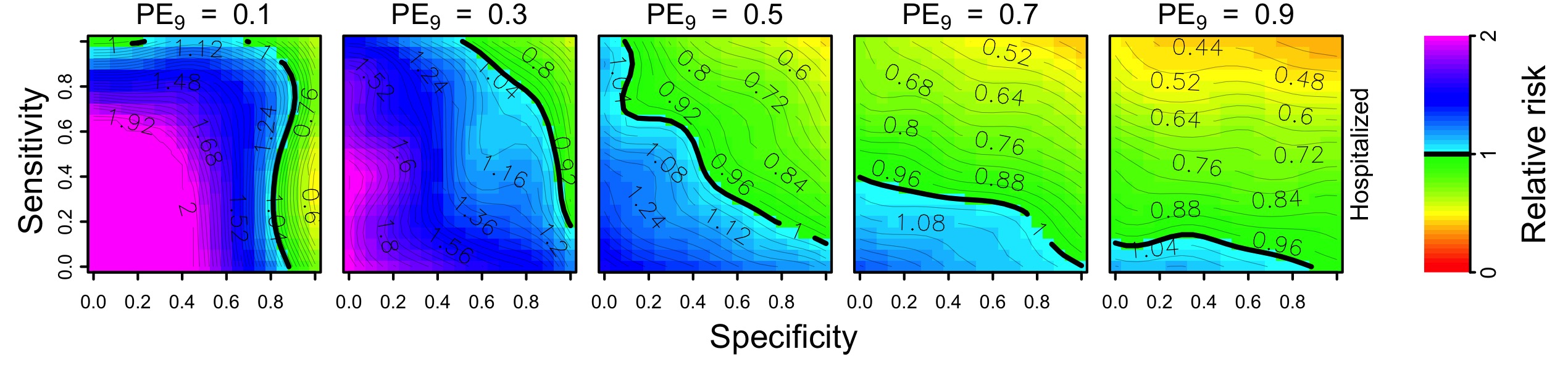


Figure 2. Relative risk of individuals screened and possibly vaccinated in a pre-vaccination screening strategy with CYD-TDV over 10 years

Table 3. Outcomes.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| PE | Spec. | Sens. | Costs (Vax) | Costs (Screen) | Costs averted | QALYs gained |
|  |  |  |  |  |  |  |
|  |  |  |  |  |  |  |

## Cost-effectiveness of pre-vaccination screening strategies

Out cost-effectiveness analysis suggests that the intervention would be cost-effective in Puerto Rico at the assumed price of the vaccine (70 USD) (Fig. [3](#fig-ICER)). Below 200 USD per fully vaccinated person, pre-vaccination screening would be cost-effective from a public payer perspective (ICER < 3 GDP per Capita). Very cost-effective scenarios could be achieved with a vaccine price below 95 USD per vaccinated individual. Also, at 18 USD per vaccinated individual, the costs of the intervention are equal to the costs without intervention (ICER = 0). Nonetheless, these cost-effectiveness thresholds depend on our assumptions of specificity and sensitivity of screening.

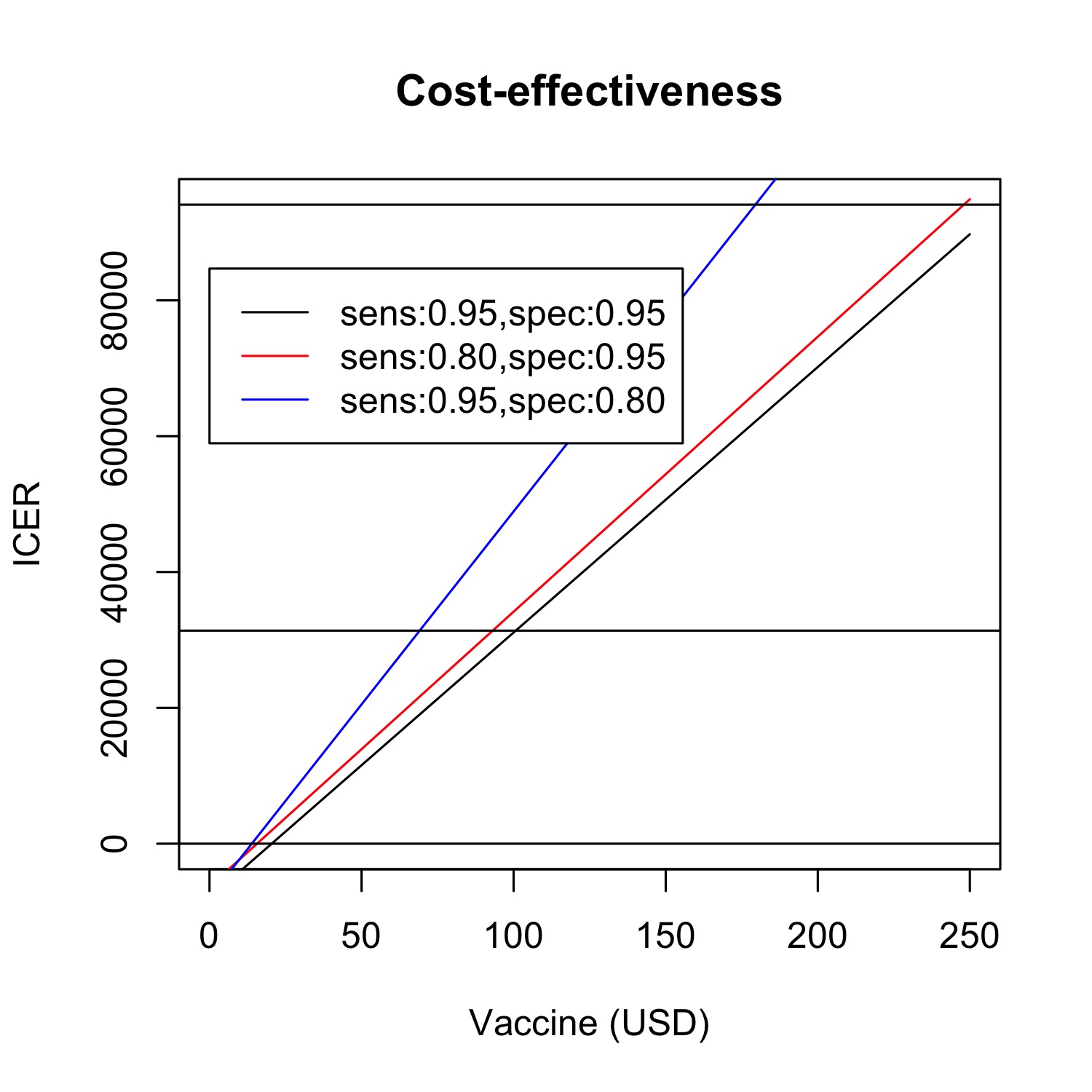


Figure 3. ICER for different values of a fully vaccinated individual. The baseline cost of serological screening was fixed to 10 USD.

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## Tornado diagram and sensitivity analysis

We varied the baseline value of five parameters of the cost-effectiveness analysis: sensitivity, specificity, PE9, vaccine cost for a fully vaccinated individual, and screening unit cost. The ranges of the parameter values are summarized in table 4. Compared to the sensitivity of screening, the specificity showed a larger impact in the cost-effectiveness of the intervention (Fig. 4). The lowest assumption of this parameter (0.5) resulted in an ICER above four time the GDP per Capita of Puerto Rico. In contrast, the same value for the sensitivity of screening yielded an ICER slightly above one GDP per Capita. We also found that a lower transmission intensity (50% below baseline) than what we have assumed would affect the cost-effectiveness of the intervention more than a higher transmission intensity (50% above baseline). Finally, a higher cost of the screening test (50 USD) would still result in ICER values below three GDP per Capita, and the vaccine cost could be up to 250 USD for ICER values below three GDP per Capita.

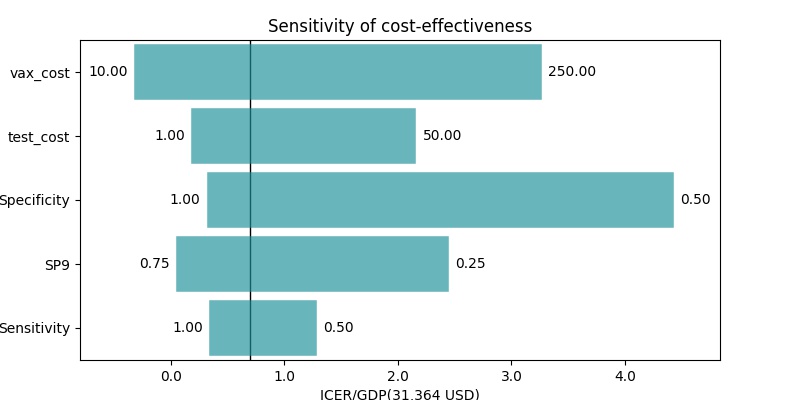
 Figure 4. Sensitivity analysis of cost-effectiveness.

Table 4. Sensitivity analysis

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| parameter | min | max | ICER\_min | ICER\_max | ICER\_default | GDP |
| Sensitivity | 0.50 | 1.00 | 32622.40 | 18452.13 | 22012.70 | 31364.60 |
| SP9 | 0.25 | 0.75 | 69042.20 | 9161.02 | 22012.70 | 31364.60 |
| Specificity | 0.50 | 1.00 | 131214.40 | 17682.60 | 22012.70 | 31364.60 |
| test\_cost | 1.00 | 50.00 | 13438.97 | 60118.17 | 22012.70 | 31364.60 |
| vax\_cost | 10.00 | 250.00 | -2279.54 | 94889.41 | 22012.70 | 31364.60 |

# Discussion

Using an agent-based model of dengue transmission, we simulated the impact of a pre-vaccination screening strategy for 10 years of routine vaccination at different levels of transmission. Our model has been previously calibrated to represent longitudinal data of dengue transmission in Peru. This model has also been used in assessments of vaccination impact with CYD-TDV [4]. Assuming a moderate transmission intensity (PE = 0.5) in Puerto Rico, we found that this intervention could be beneficial from the public health and individual perspective, conditioned to moderate values of sensitivity and high values of specificity.

The cost-effectiveness analysis showed that this intervention could also be cost-effective assuming high specificity, moderate sensitivity, and moderate transmission intensity. Our sensitivity analysis shows that changes ensuring high specificity would be more relevant than high sensitivity to achieve cost-effective interventions. This could be a result of our main assumption of moderate transmission intensity in Puerto Rico. Assuming this is the case, it would be important to ensure highly specific screening tests for pre-vaccination screening interventions to minimize the number of seronegative individuals and to improve cost-effectiveness by reducing the cost per QALY gained.

Compared to our previous simulation analysis for the Philippines and Brazil [3], the main differences of this analysis are the costs of treatment of dengue fever and severe dengue cases, which are based on studies from 2010. More recent estimates of this type of costs would refine the estimates of cost-effectiveness of pre-vaccination screening with CYD-TDV in Puerto Rico.

**References**

1. Sridhar S, Luedtke A, Langevin E, Zhu M, Bonaparte M, Machabert T, et al. Effect of Dengue Serostatus on Dengue Vaccine Safety and Efficacy. New England Journal of Medicine. 2018;379: 327–340. doi:[10.1056/NEJMoa1800820](https://doi.org/10.1056/NEJMoa1800820)

2. World Health Organization. Revised SAGE recommendation on use of dengue vaccine. 2018;

3. España G, Yao Y, Anderson KB, Fitzpatrick MC, Smith DL, Morrison AC, et al. Model-based assessment of public health impact and cost-effectiveness of dengue vaccination following screening for prior exposure. bioRxiv. Cold Spring Harbor Laboratory; 2019; doi:[10.1101/367060](https://doi.org/10.1101/367060)

4. Flasche S, Jit M, Rodŕiguez-Barraquer I, Coudeville L, Recker M, Koelle K, et al. The Long-Term Safety, Public Health Impact, and Cost-Effectiveness of Routine Vaccination with a Recombinant, Live-Attenuated Dengue Vaccine (Dengvaxia): A Model Comparison Study. von Seidlein L, editor. PLOS Medicine. Public Library of Science; 2016;13: 1–19. doi:[10.1371/journal.pmed.1002181](https://doi.org/10.1371/journal.pmed.1002181)

5. Halasa YA, Shepard DS, Zeng W. Economic cost of dengue in Puerto Rico. The American journal of tropical medicine and hygiene. ASTMH; 2012;86: 745–752.

6. World Bank. GDP per capita. 2016;

7. Luo R, Fongwen N, Kelly-Cirino C, Harris E, Wilder-Smith A, Peeling R. Rapid diagnostic tests for determining dengue serostatus: A systematic review and key informant interviews. Clinical Microbiology and Infection. Elsevier; 2019; doi:[10.1016/j.cmi.2019.01.002](https://doi.org/10.1016/j.cmi.2019.01.002)

8. Coudeville L, Baurin N, Vergu E. Estimation of parameters related to vaccine efficacy and dengue transmission from two large phase III studies. Vaccine. 2016;34: 6417–6425. doi:[10.1016/j.vaccine.2015.11.023](https://doi.org/10.1016/j.vaccine.2015.11.023)

9. Argüello DF, Tomashek KM, Quiñones L, Beltran M, Acosta L, Santiago LM, et al. Incidence of dengue virus infection in school-aged children in Puerto Rico: A prospective seroepidemiologic study. The American journal of tropical medicine and hygiene. ASTMH; 2015;92: 486–491.