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Model-based assessment of public health impact and cost-effectiveness of dengue vaccination following screening for prior exposure

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ABSTRACT

The tetravalent dengue vaccine CYD-TDV **(**Dengvaxia®) is the first licensed vaccine against dengue, but recent findings indicate an elevated risk of severe disease among vaccinees without prior dengue virus (DENV) exposure. The World Health Organization currently recommends CYD-TDV only for individuals with serological confirmation of past DENV exposure. Our objective was to evaluate the potential impact and cost-effectiveness of vaccination following serological screening. We used an agent-based model to simulate DENV transmission over a 30-year timeframe, with and without vaccination. We considered a range of values for the proportion of vaccinees with prior DENV exposure. We projected the proportion of symptomatic and hospitalized cases averted as a function of the sensitivity and specificity of serological screening. We evaluated the cost-effectiveness of screening and vaccination under economic scenarios representative of Brazil and the Philippines. We found that public health impact depended primarily on the sensitivity of serological screening in high-transmission settings and on a combination of sensitivity and specificity in low-transmission settings. Reducing risk from an individual perspective required high specificity, no less than 0.8. Cost-effectiveness could be achievable from the perspective of a public payer provided that screening sensitivity for prior DENV exposure and the value of a disability-adjusted life-year were both high. Cost-effectiveness was also achievable from an individual perspective, particularly with high screening specificity and low coverage. Whereas the results of this analysis offer general guidelines about CYD-TDV vaccination, decisions in specific contexts would benefit from additional, more context-specific modeling analyses. Vaccination with CYD-TDV following serological screening could have a positive impact in certain epidemiological settings, provided that screening is highly specific, at least moderately sensitive, and inexpensive.

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INTRODUCTION

A safe and effective dengue vaccine could have a major public health impact, as dengue causes approximately 9,000 deaths and between 50-100 million clinically apparent cases worldwide every year [1,2], with increasing geographic distribution [3]. The first licensed dengue vaccine, CYD-TDV (Dengvaxia®), is a tetravalent, live-attenuated vaccine that was licensed in multiple countries after demonstrating efficacy against symptomatic disease in phase-III trials [4,5]. Protection has been hypothesized to derive primarily from the vaccine functioning as a "silent infection" [6]. Following their first natural infection subsequent to vaccination, this mechanism would result in vaccinees with prior dengue virus (DENV) exposure bypassing the elevated risk of severe disease typically associated with secondary infections. Modeling analyses [6,7] indicated that vaccination with CYD-TDV could be cost-effective in populations in which the majority of vaccinees have prior DENV exposure.

The downside of this mode of protection is an elevated risk of severe disease in vaccinees with no prior DENV exposure at the time of their first natural DENV infection [8]. Recent findings [9] confirmed this hypothesis, leading to an abrupt end to CYD-TDV use in the Philippines [10] and a revision of the World Health Organization's (WHO) Strategic Advisory Group of Experts on Immunization recommendations in April 2018 on the use of the vaccine [11]. Vaccination with CYD-TDV is now recommended only for individuals with known prior DENV exposure [12]. Because DENV infection often results in asymptomatic infection or presents with mild, non-specific symptoms [13], an individual's clinical history is a poor indicator of prior exposure. Thus, serological screening must play a role in any path forward for CYD-TDV or any other future dengue vaccines with similar characteristics. Reliable inference of prior DENV exposure based on serological data can be extremely challenging, however, due to cross-reactivity among DENV serotypes and among DENV and other flaviviruses [14].

To avoid elevating the risk of severe dengue by vaccinating a DENV-naïve individual, serological screening used to inform vaccination must have high specificity (i.e., probability that a DENV-naïve individual tests seronegative). At the same time, high sensitivity (i.e., probability that an individual with prior DENV exposure tests seropositive) is important for ensuring that people who could benefit from the vaccine will receive it. The balance of benefits and harms caused by vaccination with CYD-TDV following serological screening with a given sensitivity and specificity must also be weighed against the economic benefits and costs of such a strategy. Although a strategy of CYD-TDV vaccination following serological screening has been examined with mathematical modeling before [15,16], those analyses were restricted to a scenario in which the screening assay had perfect sensitivity and specificity. In practice, imperfect sensitivity and specificity [17], tradeoffs between sensitivity and specificity [18], and cost [19] all merit consideration in analyses of serological screening in CYD-TDV vaccination programs.

We applied an agent-based model of DENV transmission to identify the conditions under which a strategy of vaccination with CYD-TDV following serological screening (hereafter, referred to together as "the intervention") would have positive impacts on health and be cost-effective. As with a previous study [7] involving this model and seven others, we focused our analysis on a strategy of routine intervention applied to a single age of nine years old. From both an individual and population perspective, we identified minimum requirements to achieve positive health impact and cost-effectiveness as a function of sensitivity, specificity, and cost, as well as vaccine cost and prior DENV exposure among nine-year olds (PE_9). We focused on cost

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scenarios representative of Brazil and the Philippines, which have both licensed CYD-TDV but differ in terms of economic conditions.

METHODS

Model description

Our agent-based model of DENV transmission was previously described elsewhere [20], where it was used to make projections of CYD-TDV impact in the absence of serological screening [7]. In this model, humans and mosquitoes are represented by individual agents who interact with each other through mosquito blood feeding at the household scale. The model assumes that transmission of any of the four DENV serotypes can occur whenever an infected mosquito blood-feeds on a susceptible human or a susceptible mosquito blood-feeds on an infected human. Infected humans acquire life-long immunity to the infecting serotype and temporary immunity to other serotypes to which they have not been previously exposed. Several model features are parameterized based on extensive data collection from Iquitos, Peru, including fine-scale patterns of human mobility [21], the demographic composition of households [22], and the geographic arrangement of residential, commercial, and other buildings [23]. Other model features were less well known a priori: the rate at which DENV was seeded into the population, the probability of an infectious mosquito infecting a susceptible human during blood-feeding, and the emergence rate of adult female mosquitoes. For a given simulation, we parameterized these features of the model by selecting a combination of parameter values that achieved a target value of the proportion of nine-year olds with prior DENV exposure after 40 years of simulation, or PE_9, as described in Appendix S1.

Vaccination following serological screening

The vaccine implemented in our simulations acted as a silent DENV infection in the recipient, as has been assumed in previous CYD-TDV modeling assessments [6,7]. This results in elevated risk of severe disease among DENV-naïve vaccinees experiencing their first natural DENV infection, because secondary infections are associated with the highest probabilities of symptomatic disease conditional on infection (1°: 0.3; 2°: 0.6; post-2°: 0.1) and hospitalization conditional on symptomatic disease (1°: 0.111; 2°: 0.209; post-2°: 0.052). Death was assumed to occur among a small proportion (0.0078) of cases of symptomatic disease. Because estimates of these quantities are highly variable across study settings [24], we adopted default values from Flasche et al. [7].

Consistent with recently revised WHO recommendations [12], we simulated serological screening immediately prior to vaccination with CYD-TDV. We focused on a strategy of routine vaccination in which a proportion of children underwent serological screening, and possibly vaccination, on their ninth birthday. One consequence of this strategy was that intervention coverage (i.e., the proportion of children screened) represents an upper limit on vaccination coverage (i.e., positive serological screening result and subsequent vaccination), with the two related by

$$\text{coverage}_{\text{vaccination}} = \text{coverage}_{\text{intervention}} \times \text{SP}_9, \quad (1)$$

where SP_9 is seropositivity among nine-year olds and is defined as

$$\text{SP}_9 = \text{PE}_9 \times \text{sensitivity} + (1 - \text{PE}_9) \times (1 - \text{specificity}). \quad (2)$$

Except where stated otherwise, our default assumption was 100% compliance with the three-dose schedule for CYD-TDV.

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Simulations of intervention impact

We performed 10^3 sets of simulations of intervention impact, with each simulation set involving one simulation with the intervention and one without. These simulation sets used the sobol function in the pomp library [25] in R [26] to evenly span a range of values of intervention coverage (10-80%), PE_9 (0.1-0.9), and sensitivity (0-1) and specificity (0-1) of serological screening. Each simulation lasted for 70 years, with the intervention being introduced after the first 40 years. Every year thereafter, a proportion of nine-year olds underwent serological screening for prior DENV exposure and were vaccinated if screening returned a positive result. Both simulations in each set were initiated with the same random number seeds, which allowed us to isolate the impact of the intervention to the greatest extent possible under a stochastic, agent-based model. With each set of parameter values, we calculated the proportion of cases averted over a 30-year period as

$$\text{proportion of cases averted} = \frac{\text{cumulative cases w/o intervention} - \text{cumulative cases w/ intervention}}{\text{cumulative cases w/o intervention}} \quad (3)$$

for both symptomatic and hospitalized cases. We summarized the simulation outputs of the proportion of cases averted with a statistical emulator, as described in Appendix S2. Results corresponding to parameter sets beyond those shown in the Results can be explored interactively online at http://denguevaccine.crc.nd.edu.

Identifying conditions for positive impact

Our first goal was to quantify the public health impact of vaccination with CYD-TDV following serological screening under different conditions. At the population level, we made projections of the proportion of cases averted over a 30-year period, separately for symptomatic and severe cases, under a range of values of intervention coverage, PE_9, sensitivity, and specificity. From the perspective of an individual who underwent serological screening and possibly vaccination, we made projections of the relative risk of experiencing a symptomatic or hospitalized case as compared to someone who forewent this intervention completely. We examined this individual risk in aggregate and stratified by prior DENV exposure.

Identifying conditions for cost-effectiveness

Our second goal was to understand the conditions under which vaccination with CYD-TDV following serological screening might be cost-effective. The intervention was deemed cost-effective if

$$\begin{aligned} \text{cost}_{\text{intervention}} < {} & \text{DALYs averted} \times \text{cost}_{\text{DALY}} + \text{symptomatic cases averted} \times \text{cost}_{\text{symp}} \\ & + \text{hospitalizations averted} \times \text{cost}_{\text{hospitalized}} + \text{deaths averted} \times \text{cost}_{\text{death}}, \end{aligned} \quad (5)$$

where $\text{cost}_{\text{symp}}$ and $\text{cost}_{\text{hospitalized}}$ reflect costs of ambulatory care and inpatient hospital care for symptomatic and hospitalized cases, respectively, and $\text{cost}_{\text{death}}$ refers to the direct cost of death, such as burial expenses and disruption to family income. DALYs refer to disability-adjusted life years, which are years of healthy life lost to disease. We based calculations of DALYs averted on three components: symptomatic cases averted and the DALYs associated with a symptomatic case, hospitalized cases averted and the DALYs associated with a hospitalized case, and deaths averted and the average number of years of life lost for an individual in our model with a dengue-associated death. The cost of a DALY, $\text{cost}_{\text{DALY}}$, was based on a country's gross domestic product (GDP) per capita, in line with WHO guidance [27]. An intervention with $\text{cost}_{\text{intervention}}$ satisfying eqn. 5 was deemed "cost-effective" when $\text{cost}_{\text{DALY}}$ = 3 x per capita GDP and "very cost-effective" when $\text{cost}_{\text{DALY}}$ = 1 x per capita GDP. Our assumptions about the

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numerical values of costs in Brazil and the Philippines are detailed in Table 1. We applied a 3% annual discounting rate to both costs and DALYs for the 30-year horizon of our projections.

We took two approaches from the perspective of the cost of the intervention, which is defined as

$$\text{cost}_{\text{intervention}} = \text{coverage}_{\text{intervention}} \times \text{cost}_{\text{screen}} + \text{coverage}_{\text{vaccination}} \times \text{cost}_{\text{vac}}, \quad (6)$$

where $\text{cost}_{\text{screen}}$ is the unit cost of serological screening and cost_{vac} is the cost of fully vaccinating a single person. Our first approach involved seeking the threshold cost of serological screening at which costs below that threshold would be cost-effective when combined with a cost_{vac} of 70 USD, which we based on pricing information from the Philippines as explained in Appendix S3. Our second approach involved determining whether a fixed $\text{cost}_{\text{screen}}$ of 10 USD (similar to a recent estimate of 9.25 USD in Vietnam [19]) would result in cost-effectiveness under three different assumptions about cost_{vac} corresponding to three, two, or one doses (70, 46, or 23 USD), assuming that any number of doses confers the same degree of protection. The possibility that fewer than three doses may confer protection against DENV infection has been suggested as a possibility but requires further investigation [28]. Under both approaches, we examined how cost-effectiveness varied as a function of intervention coverage, PE_9, and the sensitivity and specificity of serological screening.

Aspects of our cost-effectiveness analysis also differed depending on the perspective of who was paying for the intervention: either a public payer (e.g., government or healthcare provider) or an individual. Also, health benefits in terms of cases and deaths averted differ from the population and individual perspectives, with the former being of interest to a public payer. For instance, the elevated risk of severe disease among DENV-naïve vaccinees could lead to a disparity in the health risks associated with intervention from these two different perspectives. In addition, costs associated with dengue disease depended on perspective. First, we monetized the direct cost of death, $\text{cost}_{\text{death}}$, from the individual perspective as one year of productivity lost, as previously assumed by Flasche et al. [7], but we assumed no additional direct costs of fatal cases from the public payer perspective. Both perspectives considered the cost of death associated with DALYs due to premature death. Second, we assumed that ambulatory care and hospitalization costs were different for the individual and the public payer. Specific assumptions about costs from these perspectives are provided in Table 1.

Table 1. Assumed costs and DALYs associated with dengue illness.

Parameter	Brazil		Philippines	
	Public payer	Individual	Public Payer	Individual
$\text{cost}_{\text{symp}}$	\$60 [29]	\$140 [5,30]	\$20 [4,31]	\$20 [4,30]
$\text{cost}_{\text{hospitalized}}$	\$200 [29,30]	\$300 [5,30]	\$400 [5,31]	\$100 [5,30]
$\text{cost}_{\text{death}}$	-	\$11,000 [7]	-	\$3,000 [7]
Per capita GDP	\$8,649.95 [32]		\$2,951 [32]	
DALYs of symptomatic cases	0.006 [33]			
DALYs of hospitalized cases	0.02 [33]			
DALYs of fatal cases	1 x years of life lost			

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RESULTS

Conditions for positive impact from a population perspective

The proportion of cases averted depended on the sensitivity and specificity of serological screening in different ways for different values of PE_9. In terms of symptomatic cases, sensitivity was the dominant driver for values of $PE_9 \geq 0.5$ but was modulated somewhat by specificity at lower values of PE_9 (Fig. 1, top). A similar pattern held for hospitalized cases, albeit with an overall greater influence of specificity (Fig. 1, bottom). A primary driver of this relationship in the highest PE_9 setting (0.9) is that vaccination coverage depended almost exclusively on sensitivity and very little on specificity (Fig. S1). From a population perspective, achieving high coverage in a high-PE_9 setting appeared ideal, although it also appeared that high specificity had benefits in high-transmission settings by increasing the proportion of hospitalized cases averted beyond levels achievable by high vaccination coverage alone (Fig. 1, bottom right). At low PE_9, coverage was highest when specificity was low (Fig. S1), but that resulted in an increased number of DENV-naïve vaccinees who then went on to experience symptomatic disease and possibly hospitalization upon natural infection (Fig. 1, bottom left). Thus, public health impact was maximized at low PE_9 when specificity was relatively high (which reduced negative impacts) and sensitivity was relatively high (which increased coverage among the few who should have been vaccinated).

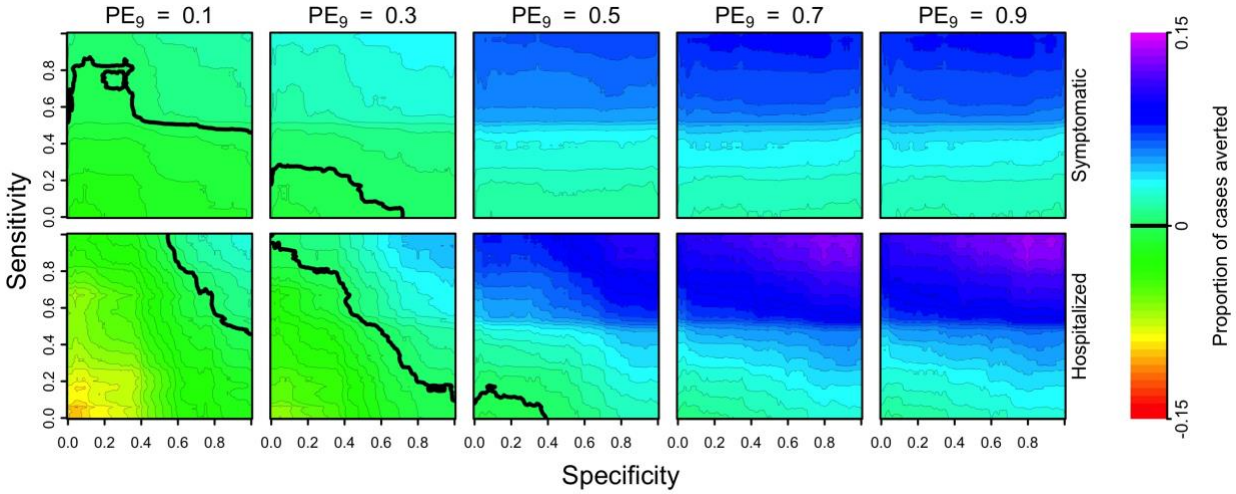

Figure 1. Cumulative proportion of cases averted (colors) over a 30-year period (top: symptomatic, bottom: hospitalized) as a function of the sensitivity (y-axis) and specificity (x-axis) of serological screening. Each column shows results for a given transmission setting, defined by the proportion of nine-year olds with previous DENV exposure, PE_9.

Conditions for positive impact from an individual perspective

From the perspective of a seropositive nine-year old who underwent serological screening and possible vaccination, the risk of symptomatic disease was generally reduced by this intervention as long as either sensitivity exceeded 0.2 or specificity exceeded 0.9 (Fig. 2, top). The greatest benefits occurred in high-transmission settings ($PE_9 \geq 0.5$) and with high specificity (>0.8), in which case relative risk was as low as 50%. In low-transmission settings ($PE_9 < 0.3$), relative risk was elevated unless specificity was nearly 1.0. In terms of hospitalization, risk was always higher in low-PE_9 settings, regardless of the sensitivity or specificity of serological screening (Fig. 2, bottom). The greatest reductions in risk of hospitalization were found in high-

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transmission settings with highly specific tests, in which case relative risk was as low as 40% (Fig. 2, bottom right). At the same time, any imperfection in specificity resulted in some children without previous exposure to DENV being vaccinated, which always resulted in an elevated risk of hospitalization (Fig. S3, top).

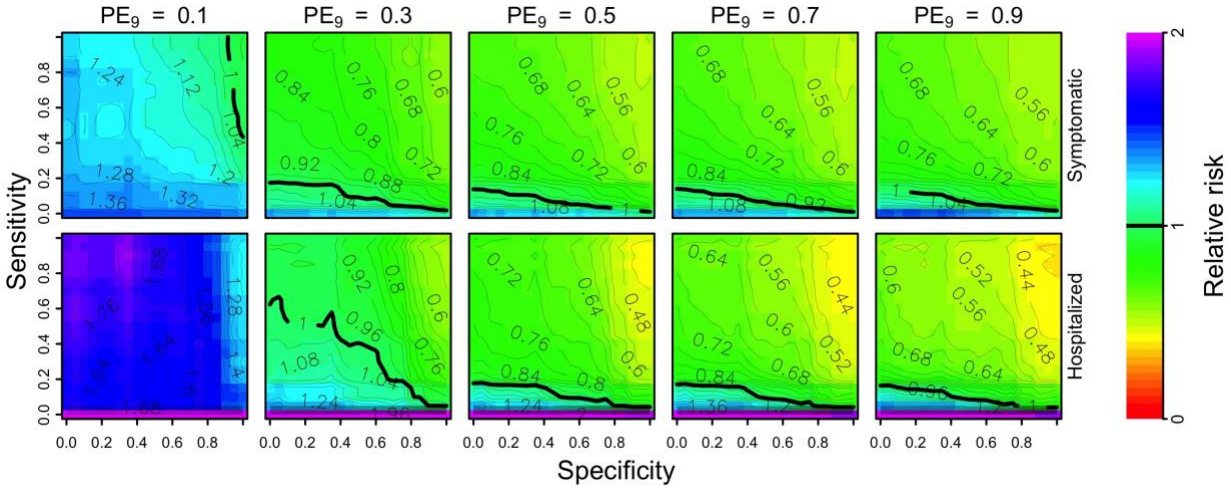

Figure 2. Per capita relative risk (colors) of symptomatic (top) and hospitalized (bottom) disease over a 30-year horizon in the first cohort to undergo serological screening and possible vaccination, as a function of the sensitivity (y-axis) and specificity (x-axis) of serological screening. Each column shows these results in a given transmission setting, defined by the proportion of nine-year olds with previous DENV exposure, PE_9.

Conditions for cost-effectiveness from a public payer perspective

From a public payer perspective, and assuming a cost for a full three doses of vaccine of 70 USD, our results suggest that a strategy of vaccinating seropositive nine-year olds would be cost-effective only under limited circumstances. In simulations of high-transmission settings ($PE_9 \geq 0.7$) and with a Brazil-like scenario about costs, vaccinating seropositive nine-year olds was cost-effective when sensitivity exceeded 0.5 (Fig. 3, bottom right). In this scenario, we found that the threshold cost for serological screening (i.e., the maximum cost at which the intervention could still be cost-effective) was approximately 30 USD. Under a Philippines-like scenario about costs, vaccinating seropositive nine-year olds was not cost-effective under any of the scenarios considered (Fig. S4).

Our results showed that cost-effectiveness was possible under a broader range of parameters when we considered lower costs of the vaccine and a fixed cost of serological screening (10 USD). We found that reducing the cost to 46 USD (equivalent to two doses, assuming that they provide the same protection as three) had little impact on which parameter combinations (PE_9, sensitivity, specificity) resulted in cost-effectiveness (Figs. S5 & S6). In contrast, reducing the cost to 23 USD (equivalent to one dose, assuming that it provides the same protection as three) resulted in cost-effectiveness in high-transmission settings ($PE_9 \geq 0.7$) under both the Brazil and Philippines scenarios about costs (Fig. 4, Fig. S7).

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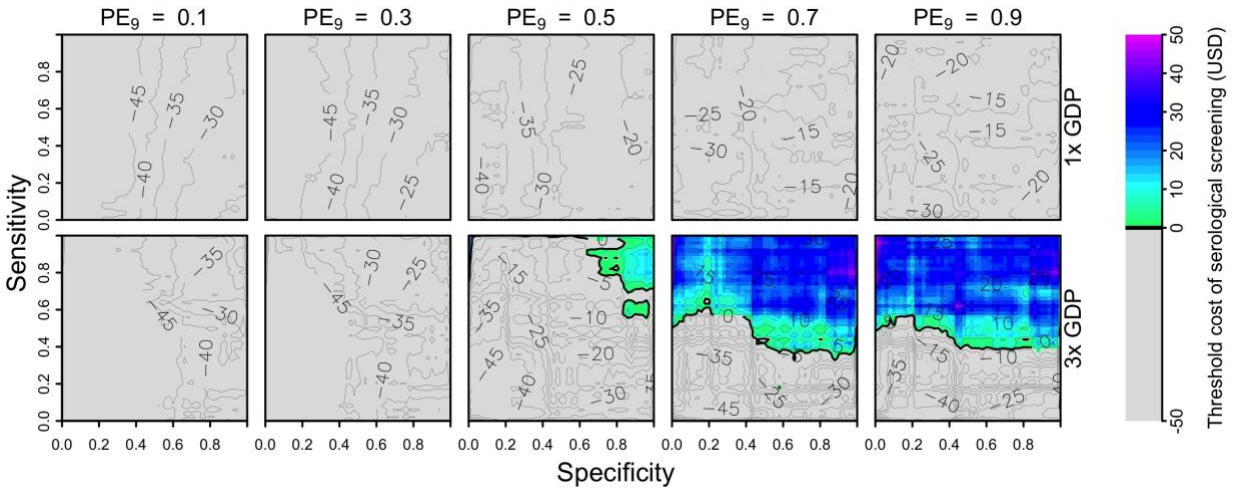

Figure 3. Threshold cost of serological screening from a public payer perspective, assuming a vaccination cost of 70 USD and economic assumptions from Brazil. Threshold costs are indicated by color as a function of sensitivity (y-axis), specificity (x-axis), and PE_9 value (columns). The value of $cost_{DALY}$ is equal to per capita GDP (8,650 USD) in the top row and three times per capita GDP in the bottom row.

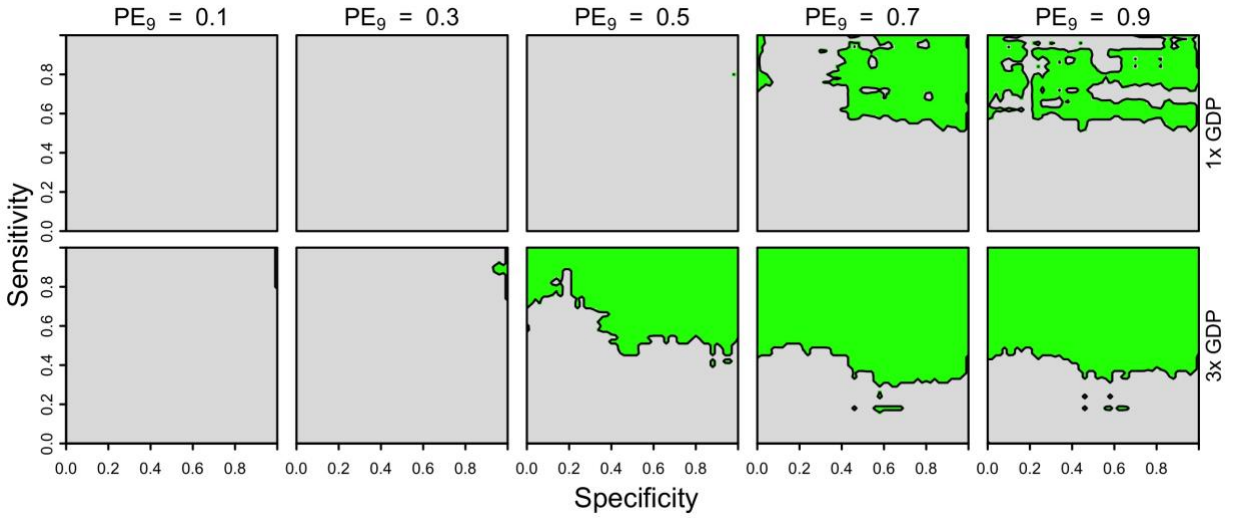

Figure 4. Cost-effectiveness of the intervention from a public payer perspective, assuming one dose of vaccine (23 USD) and a fixed cost of serological screening (10 USD) under Brazil-like cost assumptions. Cost-effectiveness according to eqn. 5 is shown in green as a function of sensitivity (y-axis), specificity (x-axis), and PE_9 value (columns). The value of $cost_{DALY}$ is equal to per capita GDP (8,650 USD) in the top row and three times per capita GDP in the bottom row.

Conditions for cost-effectiveness from an individual perspective

From an individual perspective, our results suggest that a strategy of vaccinating seropositive nine-year olds could be cost-effective under cost assumptions representative of Brazil, but not the Philippines. In contrast with the public payer perspective, cost-effectiveness from the individual perspective depended more strongly on specificity than sensitivity. Under a Brazil-like cost scenario, the intervention was cost-effective even in medium-transmission settings, provided

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that screening was highly specific (≥0.9), at least somewhat sensitive (≥0.2), and the cost of serological screening was less than 30 USD (Fig. 5, bottom row). Under a Philippines-like cost scenario, the intervention was not cost-effective from an individual perspective (Fig. S8). In both countries, low coverage (10%) had the effect of increasing the threshold cost of serological screening, but not enough to achieve cost-effectiveness under any parameters we considered for the Philippines (Figs. S9 & S10). This is a result of there being more to gain by an individual opting for the intervention when coverage is lower, due to lower indirect protection from others who are vaccinated. Lowering the number of doses also improved cost-effectiveness, assuming equivalent protection with one or two as three doses. Two doses at 46 USD at a serological screening cost of 10 USD slightly broadened the range of settings in Brazil where cost-effectiveness could be achieved (Fig. S11), and one dose at 23 USD allowed for "very cost-effective" status in settings with PE_9 as low as 0.3, provided that specificity was high (≥0.9) (Fig. 6). None of the scenarios considered resulted in cost-effectiveness under the Philippines-like scenario (Figs. S12 & S13).

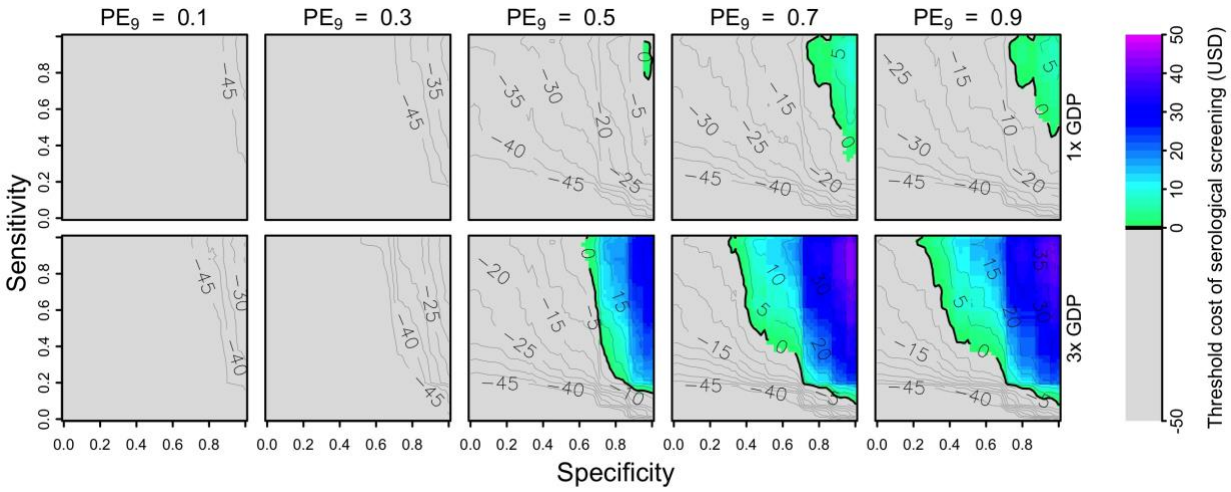

Figure 5. Threshold cost of serological screening from an individual perspective, assuming a vaccination cost of 70 USD and economic assumptions from Brazil. Threshold costs are indicated by color as a function of sensitivity (y-axis), specificity (x-axis), and PE_9 value (columns). The value of $cost_{DALY}$ is equal to per capita GDP (8,650 USD) in the top row and three times per capita GDP in the bottom row.

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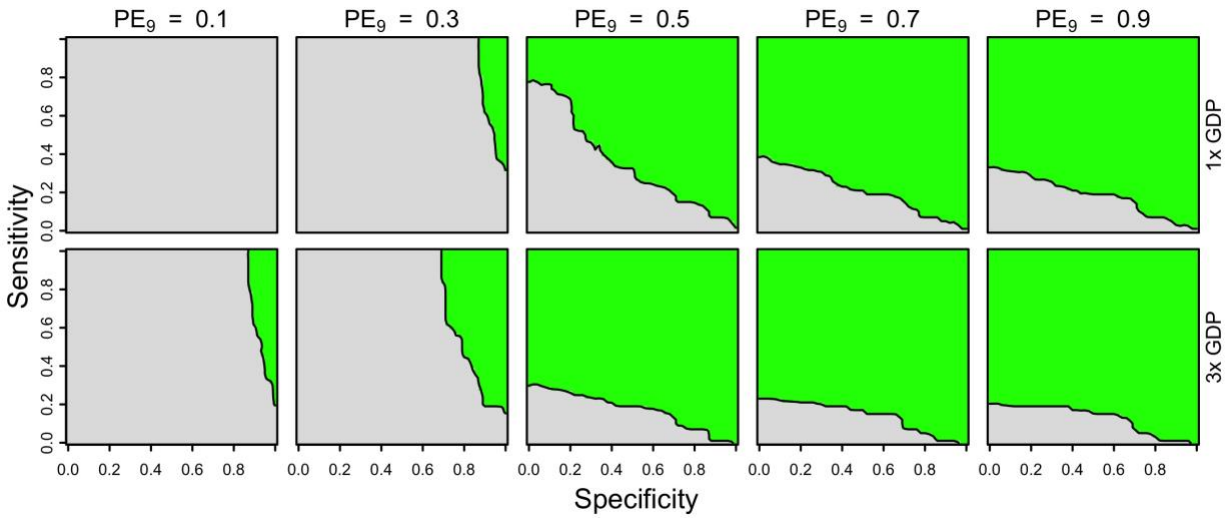

Figure 6. Cost-effectiveness of the intervention from an individual perspective, assuming one dose of vaccine (23 USD) and a fixed cost of serological screening (10 USD) under Brazil-like cost assumptions. Cost-effectiveness according to eqn. 5 is shown in green as a function of sensitivity (y-axis), specificity (x-axis), and PE_9 value (columns). The value of $cost_{DALY}$ is equal to per capita GDP (8,650 USD) in the top row and three times per capita GDP in the bottom row.

DISCUSSION

Using a model consistent with seven others that informed the WHO's initial position on CYD-TDV [7,34], we assessed the potential health impact and cost-effectiveness of the recent WHO recommendation [12] for vaccination with CYD-TDV following serological screening. In some respects, our projections were similar to previous results about vaccination without serological screening; namely, positive population-level impact in areas with high previous exposure [6,7]. In other respects, our results provide new insights on issues unique to the context of the WHO's pre-vaccination screening recommendation. First, our results suggest that population-level impacts depend mostly on sensitivity in high-transmission settings due to implications for population coverage, whereas individual-level impacts also depend strongly on specificity due to implications for individual risk of severe disease. Second, from a public payer perspective, we conclude that vaccination following serological screening is unlikely to be cost-effective except in countries with relatively high GDP and assuming a low cost of serological screening. Third, from an individual perspective, we predict that vaccination following serological screening would be potentially cost-effective under a range of scenarios at a slightly higher threshold cost, contingent on high specificity.

Similar to other modeling assessments of interventions under consideration for implementation [35–38], our study focused on offering general insights. This generality comes with the limitation of only being able to explore a relatively limited range of scenarios about vaccine roll-out. Because CYD-TDV is licensed for use in individuals ranging in age from nine to 45 years and could be deployed in a top-down manner by governments, purchased by individuals, or some combination thereof, there is an extremely wide range of scenarios that may be possible beyond that of routine application in nine-year old children that we considered. Nevertheless, certain aspects of our analysis may offer insights about a broader range of scenarios. For example, some of our results about routine vaccination in nine-year olds may

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apply under alternative scenarios if our parameter for prior exposure among nine-year olds, PE_9, is interpreted more broadly as prior exposure among vaccine recipients on the whole, at whatever age that might be. Such an extrapolation would appropriately mimic the level of prior exposure among vaccinees, but it may not accurately reflect transmission intensity in a population in which that level of prior exposure is achieved by a different age. Thus, extrapolation of our results to alternative scenarios about vaccine roll-out could be viewed as a first approximation but would require more careful follow-up analysis.

With respect to economic considerations, our results indicate that CYD-TDV vaccination following serological screening can be cost-effective from an individual perspective, but less so from a public payer perspective. Assuming as others have [39–41] that decisions about cost-effectiveness are made in reference to a multiplier between per capita GDP and $cost_{DALY}$, our results predict that cost-effectiveness will be achieved from a public payer perspective only in high-transmission areas of dengue-endemic countries with a relatively high per capita GDP, such as Panamá (13,680 USD), Brazil (8,649 USD), México (8,201 USD), and Thailand (5,807 USD) [32]. Cost-effectiveness from an individual perspective similarly appears possible in these settings, especially if coverage is low. In the event that CYD-TDV vaccination is recommended in a country but remains unfunded, it is likely that coverage and impact will be low, similar to varicella vaccines in Australia and Canada [42–44]. To the extent that access to CYD-TDV becomes associated with the economic means to pay for serological screening and vaccination, this could exacerbate socioeconomic disparities in dengue's burden. It is also important to note that our analysis of cost-effectiveness does not imply affordability. Multiple studies have shown that interventions that have been deemed "very cost-effective" have nonetheless not been implemented in low- and middle-income countries due to a variety of factors, such as implications for spending on competing public health priorities [45–47].

Although our analysis provides an indication of desirable characteristics of assays for serological screening, there is not yet an assay available that is simultaneously rapid, point of care, low cost, and both highly sensitive and specific [48]. Neutralization assays, for example, are reasonably accurate but expensive and time-consuming, whereas assays such as IgG ELISAs are faster and relatively inexpensive, but often far less accurate [17]. Given the tradeoffs between the sensitivity and specificity of any assay, our results suggest that priority should be placed on maximizing specificity to ensure maximal positive benefits for individuals who undergo serological screening. Such an approach would also minimize the potential risks associated with vaccination of DENV-naïve individuals misclassified by an imperfectly-specific assay as having been previously exposed. Achieving high specificity in determining DENV serostatus is complicated by numerous sources of cross-reactivity, including prior exposure to or vaccination against Japanese encephalitis, West Nile, yellow fever, or Zika viruses [14]. Because these factors affecting cross-reactivity are population-specific, any assay used to inform vaccination with CYD-TDV should be calibrated to results from a highly specific assay (e.g., plaque-reduction neutralization tests) in a given population to maximize specificity [49]. Inevitably though, maximizing specificity will come at the cost of decreased sensitivity [18] and reduced population-level benefits.

In theory, a highly effective, tetravalent dengue vaccine could have a substantial impact on reducing dengue's considerable burden, but that goal remains elusive for numerous reasons [50]. In the absence of a single intervention that is highly effective across a wide range of contexts, interest continues to grow in determining how to best combine multiple interventions in ways that are appropriate for a given local context [51]. Making that determination has become

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increasingly challenging due to nuanced, yet highly consequential, issues associated with use of CYD-TDV. Mathematical modeling analyses offer important capabilities for addressing this challenge due to their ability to weigh complex tradeoffs among intervention properties, as demonstrated here with respect to the sensitivity and specificity of serological screening, prior DENV exposure among vaccinees, and intervention coverage and cost. In addition, by considering both individual and population perspectives, our analysis provides information that could be informative for discourse about difficult ethical considerations surrounding the use of CYD-TDV [52].

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COMPETING INTERESTS

GE and TAP have received research support from GlaxoSmithKline for unrelated work on dengue vaccines. AWS is a consultant on vaccines for arboviral diseases for the World Health Organization (WHO). The author alone is responsible for the views expressed in this publication and they do not necessarily represent the decisions or policies of WHO. The authors declare no conflicts of interest.

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SUPPORTING INFORMATION

Appendix S1. Process for achieving a desired value of PE_9 in model simulations.

To afford the model the flexibility to achieve a range of transmission intensities, as defined by PE_9, we developed a statistical emulator of PE_9 as a function of three unknown model parameters (rate at which DENV is seeded into the population, mosquito infectiousness, adult female mosquito emergence rate). To do so, we generated 10^3 combinations of these three parameters using the sobol function in the pomp library [25] in R [26]. This function generates points that maximize distance between them within a prescribed range of values for each parameter (DENV seeding rate: $8x10^{-6}$-$2x10^{-4}$; mosquito infectiousness: 0-1; adult female mosquito emergence rate: 0-3). After simulating 40 years of transmission with a given set of those three parameters, we retrieved PE_9 from all such simulations and fitted a generalized additive model of PE_9 with independent smooth terms for each of the three parameters ($R^2 = 0.98$). In subsequent simulations focused on vaccination impact, we obtained a set of the three unknown model parameters consistent with a target value of PE_9 by repeatedly drawing sets of the three parameters until we obtained one that was associated with a value of PE_9 within one percent of the target PE_9 value.

Appendix S2. Statistical emulator of vaccination impact projections.

Despite efforts to minimize stochastic differences between paired simulations under a given parameter set, the proportions of cases averted resulting from our simulations were relatively noisy. This is due to the dynamics of the model, which are characterized by large epidemics in some years separated by low levels of incidence during inter-epidemic periods [20]. Thus, even small differences in the sequence of random number draws (due to differences in infection outcomes associated with protective effects of vaccination) can lead otherwise similar pairs of simulations to diverge in their behavior over time. Even so, there were clear patterns in the central tendency of the proportion of cases averted as a function of the parameters varied across the 10^3 parameter sets that we examined. To extract pattern from noise, we developed a statistical emulator of the proportion of cases averted as a function of four parameters described in the previous paragraph using the randomForest function from the randomForest library [49] in R. Values of the proportion of cases averted from this emulator were likewise used in calculations of cost-effectiveness.

Appendix S3. Estimate of the price of Dengvaxia® in the Philippines.

In 2016, the Philippines government paid a total of P3.5 billion targeted to vaccinate a total of 1,077,623 9-year-old public school students [50]. We assumed that this cost included three doses of vaccine plus the cost of administrating it. Hence, the unit price of a fully vaccinated price was around P3,247. This corresponded to 69.3 USD in 2016, which we rounded to 70 USD. This cost can be recalculated and updated in our analyses using the web application available online.

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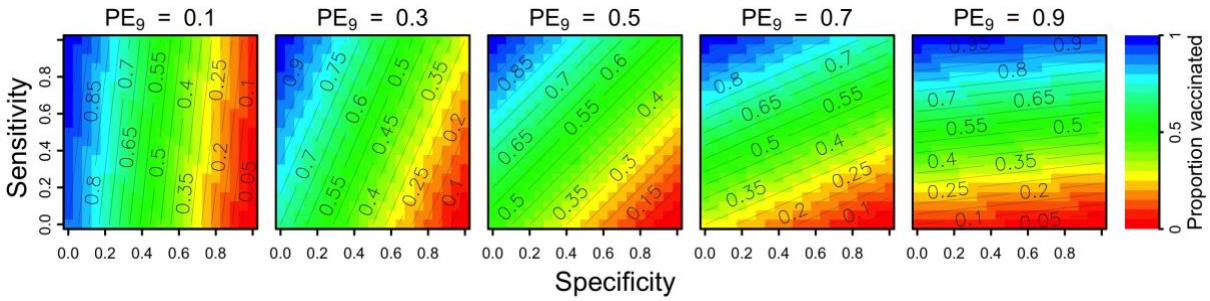

Figure S1. Relationship between the proportion of nine-year olds with previous DENV exposure (columns) and the proportion who screen positive and receive vaccination (colors). This relationship depends on the sensitivity (y-axis) and specificity (x-axis) of serological screening.

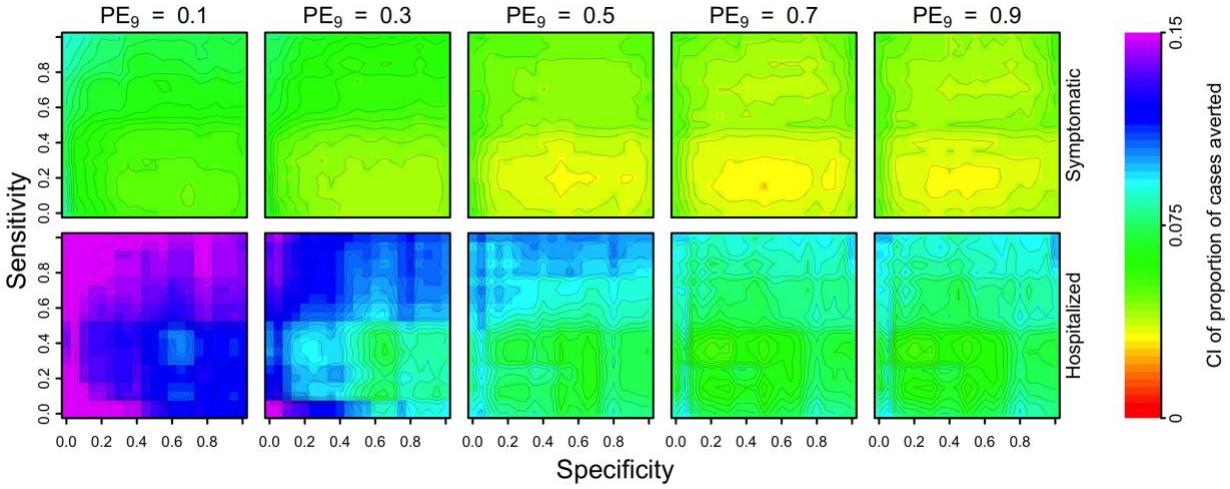

Figure S2. Width of the confidence interval of the cumulative proportion of cases averted over a 30-year period (top row: symptomatic, bottom row: hospitalized) as a function of the sensitivity (y-axis) and specificity (x-axis) of serological screening. Each column shows these results in a given transmission setting, defined by PE_9.

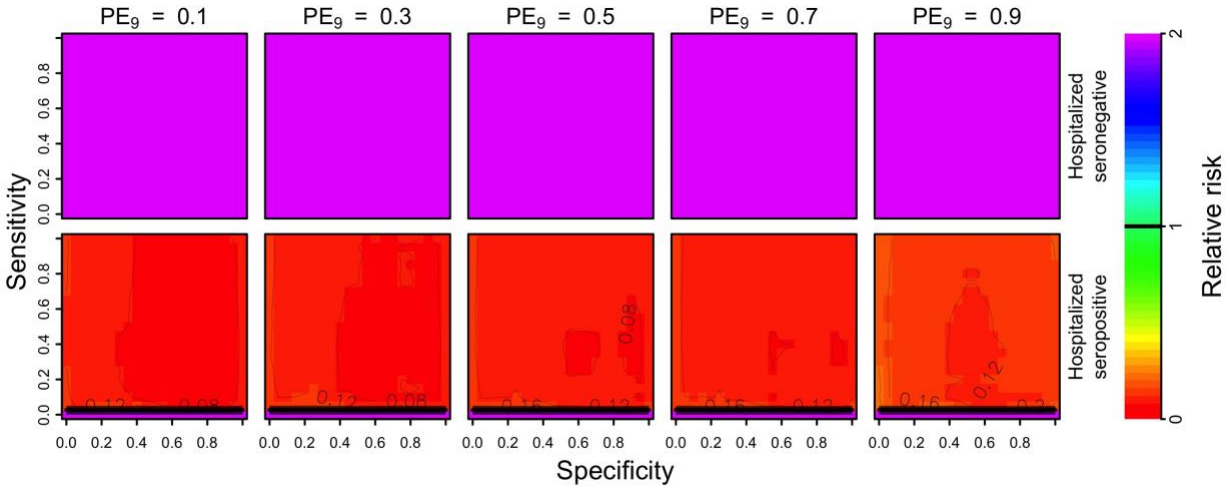

Figure S3. Per capita relative risk (colors) of hospitalizations for individuals seronegative (top) and seropositive (bottom) over a 30-year horizon in the first cohort to undergo

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serological screening and possible vaccination, as a function of the sensitivity (y-axis) and specificity (x-axis) of serological screening. Each column shows these results in a given transmission setting, defined by the proportion of nine-year olds with previous DENV exposure, PE_9.

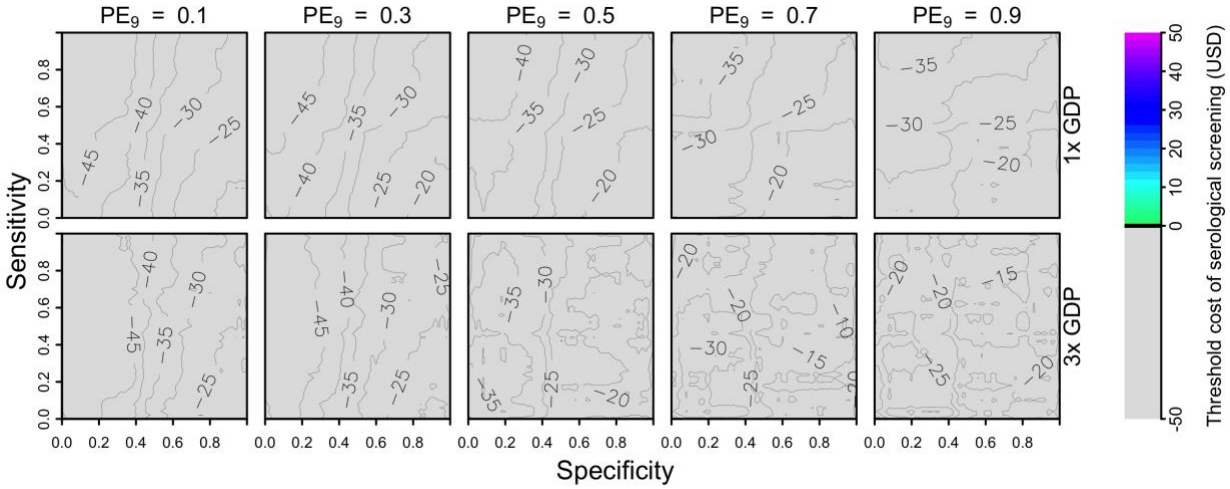

Figure S4. Threshold cost of serological screening from a public payer perspective, assuming a vaccination cost of 70 USD and economic assumptions from the Philippines. Threshold costs are indicated by color as a function of sensitivity (y-axis), specificity (x-axis), and PE_9 value (columns). The value of $cost_{DALY}$ is equal to per capita GDP (2,951 USD) in the top row and three times per capita GDP in the bottom row.

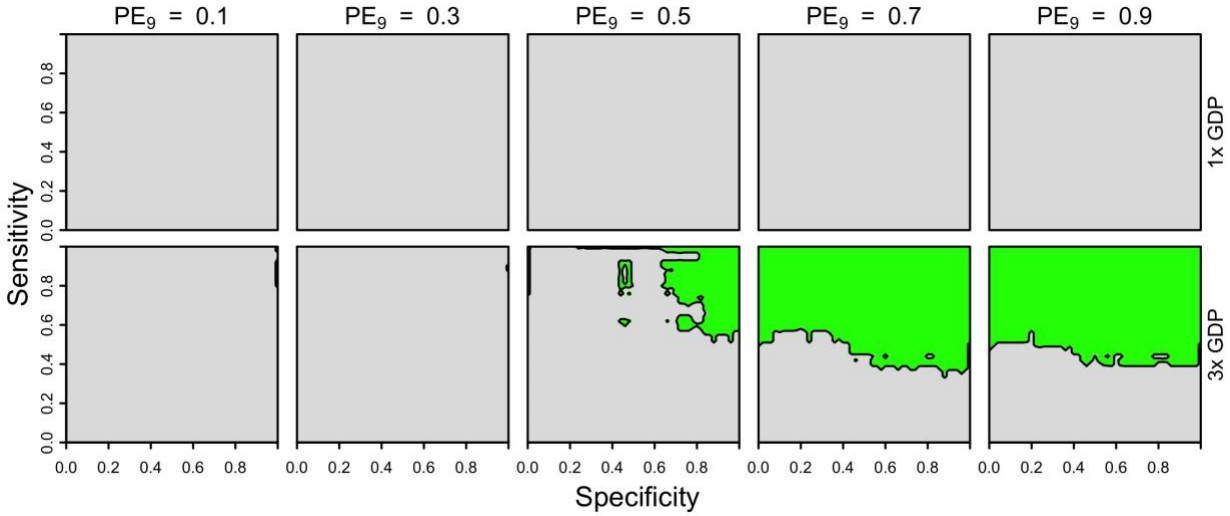

Figure S5. Cost-effectiveness of the intervention from a public payer perspective, assuming two doses of vaccine (46 USD) and a fixed cost of serological screening (10 USD) under Brazil-like cost assumptions. Cost-effectiveness according to eqn. 5 is shown in green as a function of sensitivity (y-axis), specificity (x-axis), and PE_9 value (columns). The value of $cost_{DALY}$ is equal to per capita GDP (8,650 USD) in the top row and three times per capita GDP in the bottom row.

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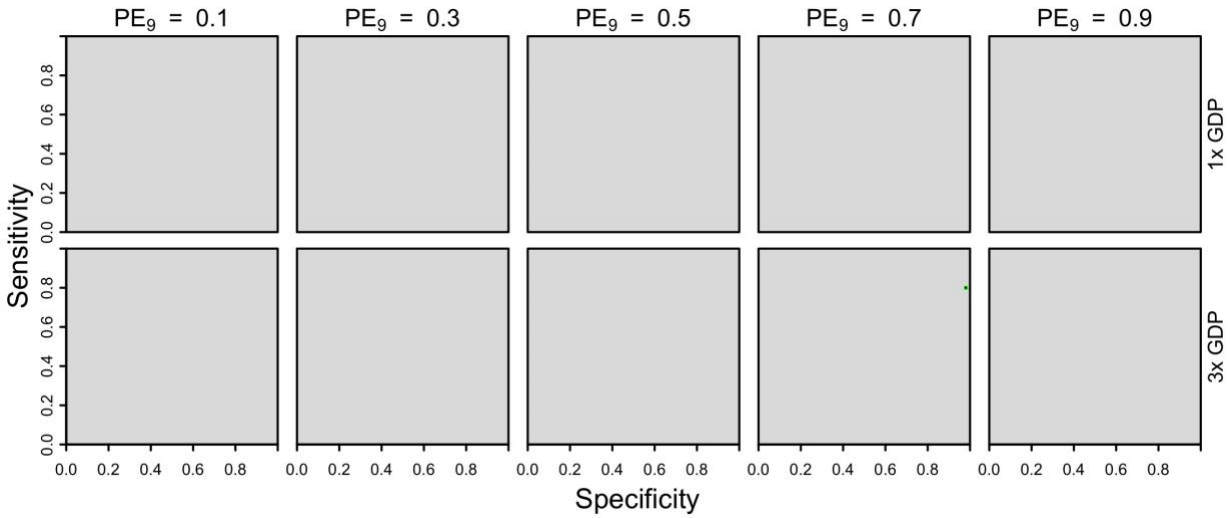

Figure S6. Cost-effectiveness of the intervention from a public payer perspective, assuming two doses of vaccine (46 USD) and a fixed cost of serological screening (10 USD) under Philippines-like cost assumptions. Cost-effectiveness according to eqn. 5 is shown in green as a function of sensitivity (y-axis), specificity (x-axis), and PE_9 value (columns). The value of $cost_{DALY}$ is equal to per capita GDP (2,951 USD) in the top row and three times per capita GDP in the bottom row.

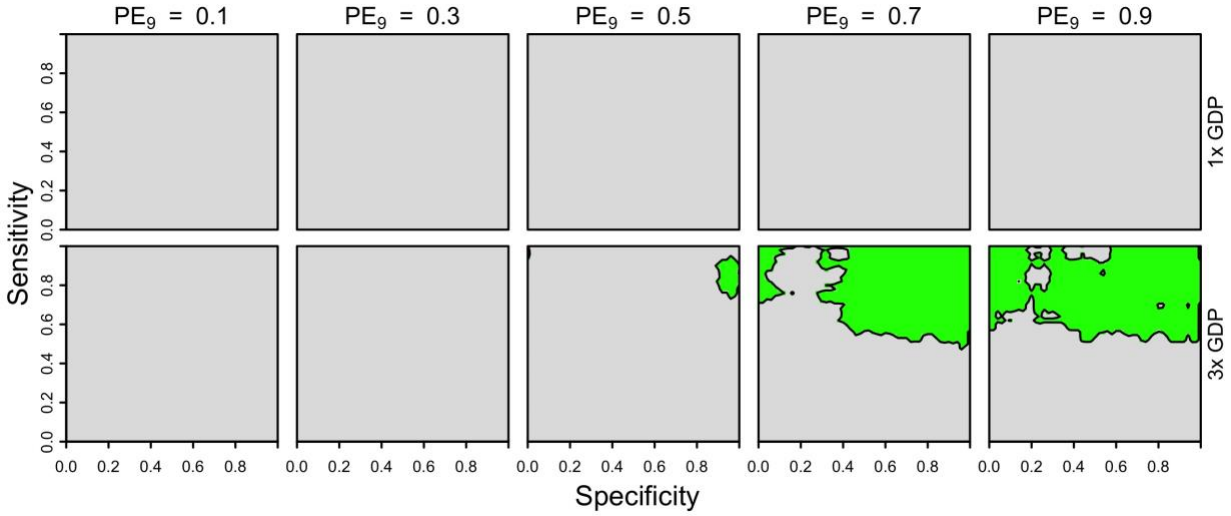

Figure S7. Cost-effectiveness of the intervention from a public payer perspective, assuming one dose of vaccine (23 USD) and a fixed cost of serological screening (10 USD) under Philippines-like cost assumptions. Cost-effectiveness according to eqn. 5 is shown in green as a function of sensitivity (y-axis), specificity (x-axis), and PE_9 value (columns). The value of $cost_{DALY}$ is equal to per capita GDP (2,951 USD) in the top row and three times per capita GDP in the bottom row.

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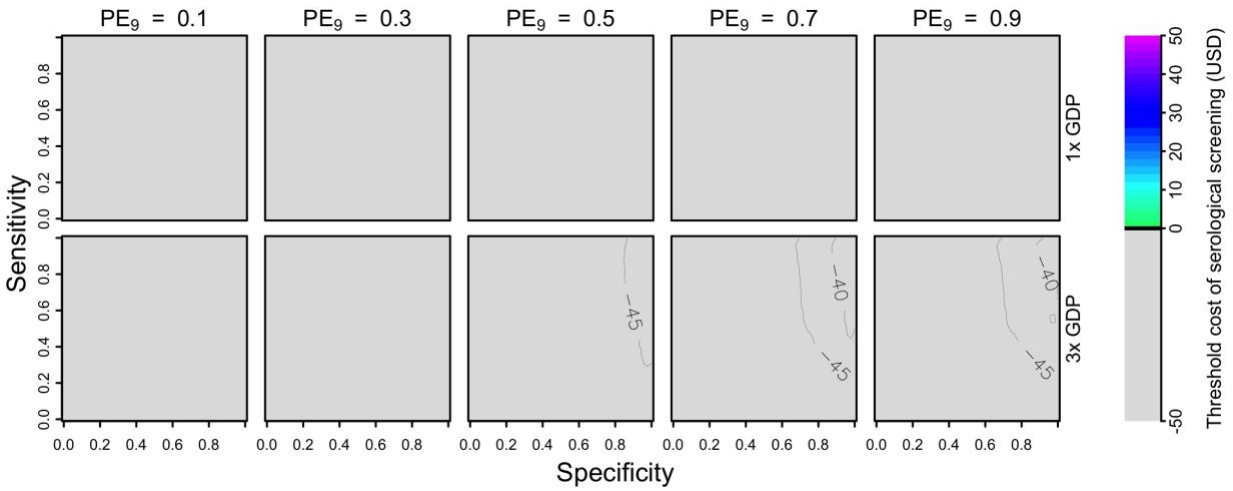

Figure S8. Threshold cost of serological screening from an individual perspective, assuming a vaccination cost of 70 USD and economic assumptions from the Philippines. Threshold costs are indicated by color as a function of sensitivity (y-axis), specificity (x-axis), and PE_9 value (columns). The value of $cost_{DALY}$ is equal to per capita GDP (2,951 USD) in the top row and three times per capita GDP in the bottom row.

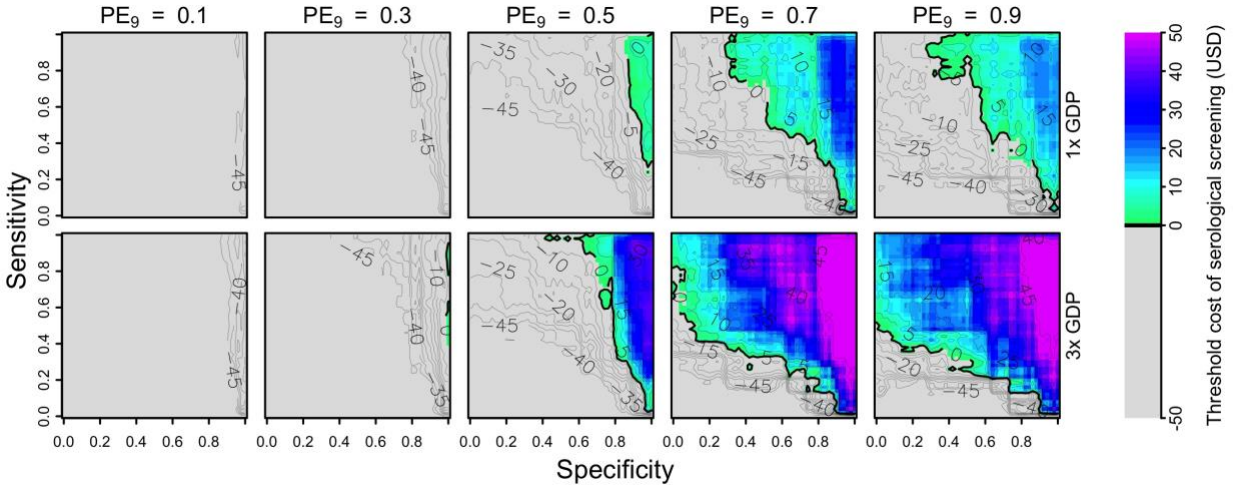

Figure S9. Threshold cost of serological screening from an individual perspective at 10% coverage, assuming a vaccination cost of 70 USD and economic assumptions from Brazil. Threshold costs are indicated by color as a function of sensitivity (y-axis), specificity (x-axis), and PE_9 value (columns). The value of $cost_{DALY}$ is equal to per capita GDP (8,650 USD) in the top row and three times per capita GDP in the bottom row.

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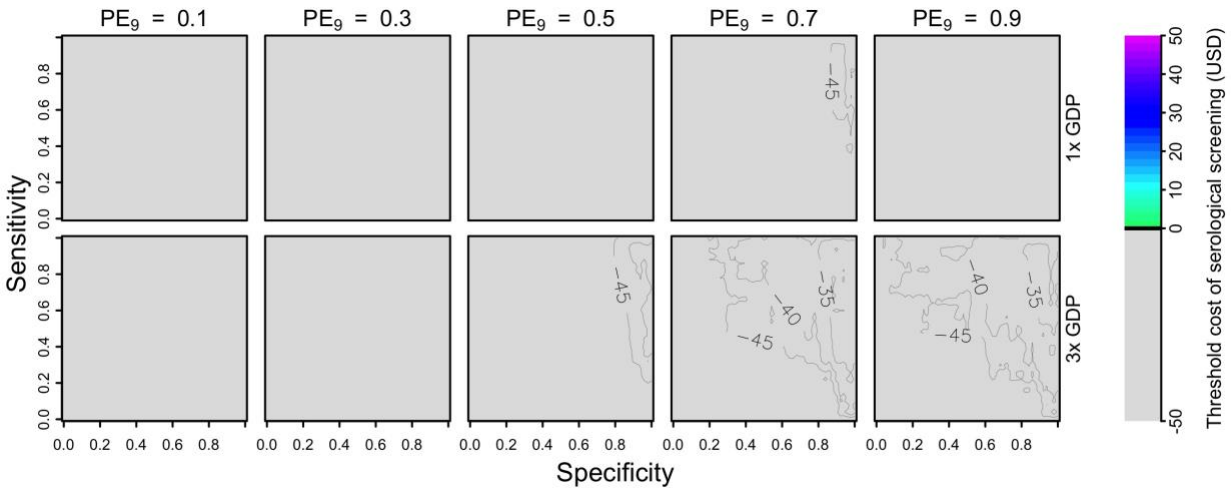

Figure S10. Threshold cost of serological screening from an individual perspective at 10% coverage, assuming a vaccination cost of 70 USD and economic assumptions from the Philippines. Threshold costs are indicated by color as a function of sensitivity (y-axis), specificity (x-axis), and PE_9 value (columns). The value of $cost_{DALY}$ is equal to per capita GDP (2,951 USD) in the top row and three times per capita GDP in the bottom row.

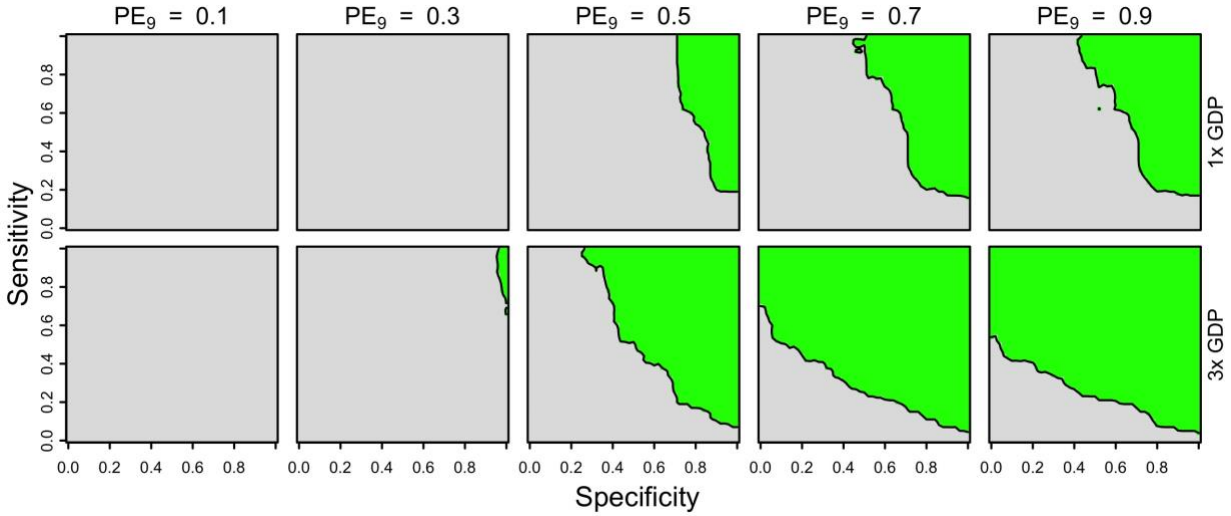

Figure S11. Cost-effectiveness of the intervention from an individual perspective, assuming two doses of vaccine (46 USD) and a fixed cost of serological screening (10 USD) under Brazil-like cost assumptions. Cost-effectiveness according to eqn. 5 is shown in green as a function of sensitivity (y-axis), specificity (x-axis), and PE_9 value (columns). The value of $cost_{DALY}$ is equal to per capita GDP (8,650 USD) in the top row and three times per capita GDP in the bottom row.

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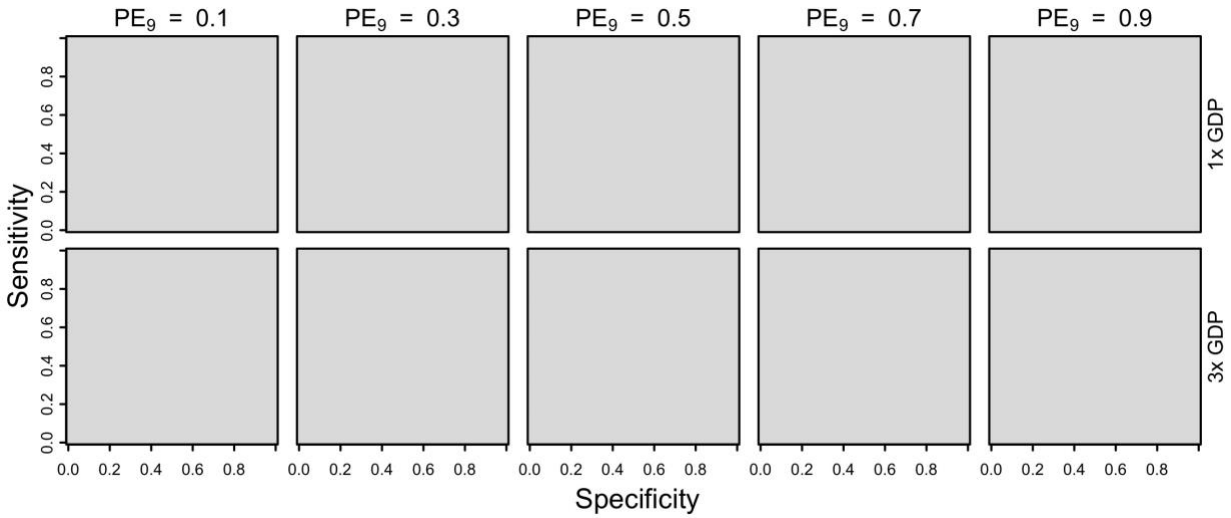

Figure 12. Cost-effectiveness of the intervention from an individual perspective, assuming two doses of vaccine (46 USD) and a fixed cost of serological screening (10 USD) under Philippines-like cost assumptions. Cost-effectiveness according to eqn. 5 is shown in green as a function of sensitivity (y-axis), specificity (x-axis), and PE_9 value (columns). The value of $cost_{DALY}$ is equal to per capita GDP (2,951 USD) in the top row and three times per capita GDP in the bottom row.

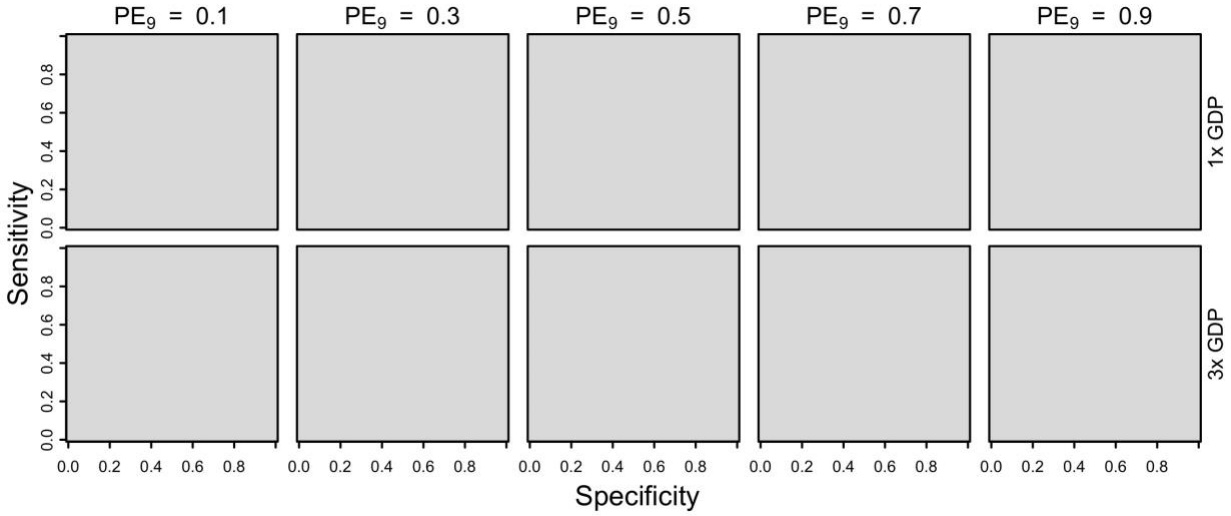

Figure S13. Cost-effectiveness of the intervention from an individual perspective, assuming one dose of vaccine (23 USD) and a fixed cost of serological screening (10 USD) under Philippines-like cost assumptions. Cost-effectiveness according to eqn. 5 is shown in green as a function of sensitivity (y-axis), specificity (x-axis), and PE_9 value (columns). The value of $cost_{DALY}$ is equal to per capita GDP (2,951 USD) in the top row and three times per capita GDP in the bottom row.