

A multi-country study of dengue vaccination strategies with Dengvaxia and a future vaccine candidate in three dengue-endemic countries: Vietnam, Thailand, and Colombia

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Abstract

Background: The dengue vaccination era began when Dengvaxia (CYD-TDV) became available in 2016. In addition, several second-generation vaccine candidates are currently in phase 3 trials, suggesting that a broader availability of dengue vaccines may be possible in the near future. Advancing on the recent WHO-SAGE recommendations for the safe and effective use of CYD-TDV at the regional level on average, this study investigates the vaccination impacts and cost-effectiveness of CYD-TDV and of a hypothetical new vaccine candidate (NVC) in a country-specific manner for three endemic countries: Vietnam, Thailand, and Colombia.

Methods: The vaccination impacts of CYD-TDV and NVC were derived by fitting the empirical seroprevalence rates of 9 year olds into an individual-based meta-population transmission model, previously used for the WHO-SAGE working group. The disability-adjusted life years were estimated by applying country-specific parametric values. The cost-effectiveness analyses of four intervention strategies in combination with routine and catch-up campaigns were compared for both vaccines to inform decision makers regarding the most suitable immunization program in each of the three countries.

Results and conclusion: Both CYD-TDV and NVC could be cost-effective at the DALY threshold cost of \$2,000 depending upon vaccination costs. With CYD-TDV, targeting 9 year olds in routine vaccination programs and 10-29 year olds as a one-off catch-up campaign was the most cost-effective strategy in all three countries. With NVC, while the most cost-effective strategy was to vaccinate 9-29 and 9-18 year olds in Vietnam and Thailand respectively, vaccinating younger age cohorts between 1 and 5 years old in Colombia was more cost-effective than other strategies. Given that three countries will soon face decisions regarding whether and how to incorporate CYD-TDV or future dengue vaccines into their budget-constrained national immunization programs, the current study outcomes can be used to help decision makers understand the expected impacts and cost-effectiveness of such vaccines.

Keywords: dengue; dengue vaccine; vaccination strategies; cost-effectiveness of dengue vaccines

Introduction

Dengue fever is a major public health concern in many parts of the tropics and subtropics. The global burden of dengue has increased substantially in recent years. A recent study shows that there are approximately 96 million apparent and 294 million inapparent dengue infections occurring annually[1]. The majority of dengue-endemic regions of the world, and therefore the burden of dengue, are in developing countries. Nevertheless dengue control activities are not often considered a priority for public health interventions, partly due to the absence of specific treatment, and the costly nature of vector control activities in a developing-country setting[2, 3].

Due to the complexity of the disease which is caused by four related but antigenitically distinct viruses (serotypes), it has been challenging not only to have a full understanding of dengue ecology and immunology[4], but also to develop effective vaccines against it[5]. For example, it is known that infection with one dengue serotype provides life-long immunity only to that specific serotype and temporary cross-protection to other serotypes, but sequential infection with two different serotypes can bring favorable (short-term heterologous protection) or detrimental outcomes due to a high degree of antigenic cross-reactivity[5-8]. In particular, while a patient with a primary dengue infection normally experiences mild symptoms, a heterologous secondary infection tends to lead to more severe illness, partly due to the antibody dependent enhancement (ADE) caused by non-protective heterotypic antibodies arising from the primary infection[6, 7, 9]. Humans who have experienced a secondary, heterologous infection and recovered are believed to be protected against further infections[4].

A first live, attenuated tetravalent vaccine (Dengvaxia, CYD-TDV) became commercially available in 2016 and has already been licensed in some dengue-endemic countries (e.g. Brazil, Mexico, Philippines, and Thailand). There have been several debates regarding the safety signal of CYD-TDV where the main issue is the increased risk of developing severe illness on vaccinated seronegative individuals[10-13]. The Strategic Advisory Group of Experts (SAGE), WHO's independent expert advisory committee, organized a consortium of eight modeling groups to produce WHO/SAGE reports and position papers on the safe and effective use of CYD-TDV[14, 15]. The researchers recently published the estimated long-term safety, public health impact, and cost-effectiveness of CYD-TDV based on the outcomes from the modeling groups[16]. The WHO's main aim was to inform general recommendations on the optimal use of CYD-TDV. Critically, these reports raise the importance of having country-specific inputs when considering the introduction of CYD-TDV, given that the use of CYD-TDV is not recommended for populations with low seroprevalence due to potential longer-term risks of severe dengue in vaccinated seronegative individuals[14]. In particular, the authors reported that the cost-effectiveness results should be interpreted as the regional cost-effectiveness of vaccination on average, and not as the cost-effectiveness in a country-specific context. More recently (2017), Sanofi Pasteur officially confirmed that while CYD-TDV provides protective benefit against dengue fever in those who are seropositive, more severe illness could occur following vaccination upon a subsequent dengue infection in those who are seronegative[17]. Based on the preliminary results from the recent analysis of vaccine safety of CYD-TDV, WHO also updated its position that CYD-TDV should be administered only to individuals who have been infected with dengue prior to vaccination, such that why are seropositive prior to vaccination[18].

The main interests of the current study lie in understanding the cost-effectiveness of dengue vaccines in three endemic countries: Vietnam, Thailand, and Colombia. Dengue has been highly prevalent in these countries, causing substantial economic burden[3]. Nonetheless, CYD-TDV has not been introduced into a nationwide vaccination program in any of the countries at the time of this research. The vaccine is licensed in Thailand but is currently being used only in the private sector, and neither Vietnam nor Colombia has licensed the vaccine yet. In addition to CYD-TDV, there are several second-generation vaccine candidates in phase 3 trials, and it is therefore expected that these three countries will soon face decisions on incorporating the current and future vaccine candidates into their budget-constrained national vaccination programs[3, 19]. Therefore, having robust estimates of the cost-effectiveness of existing and future dengue vaccines would help facilitate the process of vaccine introduction into national immunization programs. This study presents vaccination impacts and cost-

effectiveness analyses (CEA) of dengue vaccines with various vaccination strategies for two different vaccine types: Dengvaxia (CYD-TDV) and a new vaccine candidate (NVC). In the case of NVC, the current study proposes hypothetical vaccine profiles and measures impact outcomes compared with CYD-TDV. Vaccination impacts were derived via a transmission model previously used in the WHO study, and this is the first time that country-specific CEA has been conducted by applying such a model to current and future vaccines.

Methods

Transmission model

Vaccination impact was estimated using a spatially explicit, individual-based meta-population transmission model[9, 20] developed by the Oxford/Exeter group for the WHO SAGE working group exercise; the details on model parameters can be found in Flasche et al.[16]. Briefly, human individuals were categorized into susceptible, incubating, infectious or recovered with respect to each serotype, allowing for up to four sequential infections. The human population was arranged in a regular grid of subpopulations with size kept constant, and death rates for both humans and mosquitos were age-dependent. For the current multi-country study, the model was fitted against empirical seroprevalence rates of children at 9 years old by adjusting the human-to-vector and vector-to-human transmission probabilities, as done previously by the Oxford/Exeter group [16]. The seroprevalence rates of 9 year olds in Colombia and 9-12 year olds in Vietnam and Thailand were obtained from two published results and used as the baseline seroprevalence rates in these countries[21, 22].

Table 1 summarizes key parameter values and vaccination strategies considered in this study. Vaccine efficacy for CYD-TDV was that reported from the two phase 3 trials (CYD14 and CYD15), and thus vaccine efficacy varied by serotype[23]. Vaccine efficacy for NVC was assumed to be 80% against all four serotypes. In order to understand the long-term safety of CYD-TDV, long-term follow-up analysis has been carried out[23]. One of the findings in the follow-up study was the decrease in the protective effect of CYD-TDV against hospitalization among virologically-confirmed dengue (VCD) cases during the last three years of follow-up compared to the first two years[24]. Due to data limitations, it is unclear how to identify the exact cause of increased risk among vaccinated children age 2-5 years during year 3 and children age 9-11 years during year 4, but one of the possible explanations is waning vaccine-induced immunity followed by risk of natural infection[24]. In the previous WHO SAGE modeling group exercises, the half-life of the CYD-TDV efficacy was assumed to be between 1-1.5 years or less than 1 year for both seronegative and seropositive recipients by the majority of the groups, except three groups who assumed a longer duration of efficacy for seropositive recipients[16]. It should be noted that there is no clear evidence on the half-life of the CYD-TDV efficacy at the time of this research. Thus, the current study followed the assumptions used for the previous WHO SAGE exercise with the half-life for seropositives being slightly longer, given lower relative risk against hospitalization observed for vaccinated young adults compared to controls at year 5 during the long-term follow-up study[24]. In comparison, the half-life of NVC efficacy was assumed to be 8 years regardless of serostatus of vaccine recipients in order to see how the longer half-life would effectively control disease transmission. In addition, CYD-DTV vaccination was presumed to act like a silent natural infection, consistent with the WHO modeling exercise[16], whereas no silent infection was assumed for NVC vaccination.

As a default policy, 9 year olds were targeted for routine vaccination (RT9) with and without a one-off catch-up campaign targeting age cohorts between 10 and 18 years old (CU1018). Unlike the notion of targeting an appropriate age cohort for routine vaccination with CYD-DTV, which was extensively discussed previously[16, 25, 26], no clear guideline has been provided with regard to catch-up campaign strategies. Thus, the age group of 10-29 year olds was selected for an additional catch-up campaign scenario (CU1029). CYD-TDV is not recommended for children under 9 years old due to the increased risk of hospitalized and severe illness in the age group of 2-5 year olds[14, 24]. This is believed to be due to CYD-TDV causing a silent infection, and therefore breakthrough infections that are secondary-like. However, as NVC was assumed not to cause a silent infection, a vaccination strategy for younger age cohorts, that is 1 year olds routine (RT1) and 2-5 year olds catch-up campaign (CU0205), was also simulated with NVC. For both vaccines, the vaccination impacts were

projected for a 30-year period, to be comparable with the previous WHO SAGE working group exercise.

Table 1. Parameter values for transmission model and vaccination strategies

	CYD-TDV	NVC
Vaccine efficacy ^a	58.4% (serotype1), 47.1% (serotype2), 73.6% (serotype3), 83.2%(serotype4)	80% for all serotypes
Efficacy half-life (exponential decay)	3 years for seropositives; 1 year for seronegatives	8 years for all serostatus
Coverage rate	80% (alternatively 50%)	80% (alternatively 50%)
Vaccine doses	3 doses	2 doses
Vaccination strategies	9yo routine 9yo routine & 10-18 catch-up 9yo routine & 10-29 catch-up	9yo routine 9yo routine & 10-18yo catch-up 9yo routine & 10-29yo catch-up 1yo routine & 2-5yo catch-up
Seropositivity rate at 9yo ^b	62.1 (Vietnam), 79.5 (Thailand), 20.5 (Colombia)	
Transmission probabilities (human to vector)	0.5 (Vietnam), 0.425 (Thailand), 0.2951 (Colombia)	
Transmission probabilities (vector to human)	0.51 (Vietnam), 0.43 (Thailand), 0.2953 (Colombia)	

^a Source for CYD-TDV: [23]

^b Sources: [21, 22]

Health economic model

Disability-adjusted life years (DALYs) were used to estimate the cost-effectiveness of CYD-TDV and NVC with various vaccination strategies for comparison. Table 2 shows health economic parameter values used for the DALY estimation. Based upon the changes made in the 2010 estimates of the global burden of disease[27], age weighting and time discounting were dropped in the YLL and YLD estimations. The age of death by age group was estimated using the ICD10 mortality data from the WHO, which provides age of death by various causes[28]. Any deaths that occurred in the A90-91 categories of the dataset were included to estimate the age of death due to dengue infection. Due to the absence of the mortality data for the ICD10 A90-91 categories in Vietnam, it was assumed that the age of death in Vietnam would be similar to that in Thailand. The WHO life table was used to estimate life expectancy from the age at death for each of the three countries[29]. Future costs were discounted at the rate of 3%.

It has been challenging to estimate accurate disease burden at the country level, given that a majority of the surveillance data is focused on a specific location within a country. The concept of expansion factors (EF) has been useful to correct case-underreporting[30]. However, the use of unreliable EF estimates may result in biased answers when calculating cost-effectiveness of a vaccine introduction because a small change in an EF can be highly sensitive to the total number of cases at the country-level. For example, applying a site-specific EF estimate to the country-level may cause significant overestimation (or underestimation) of actual cases. In the three countries included in this study, the number of dengue cases is regularly reported to the upper-level health management unit (i.e. Ministry of Health) from health facilities at the municipality-level. Given the difficulty in calculating accurate EF estimates by the geographical or administrative unit in each country, two scenario analyses were conducted for comparison. First, the number of dengue cases reported to the national-level health authority (i.e. Ministry of Health) was considered to be the lower bound of the overall dengue burden, presuming that case-underreporting exists in all three countries[31-33]. Second, a recent study reported dengue epidemiologic trends in multiple countries where two phase 3 trials (CYD14, CYD15) were conducted[22]. As the two trials targeted age cohorts and locations where dengue burden was supposed to be highly prevalent in each country, the upper bound of the overall dengue burden was set by using the incidence rates estimated in the control groups of these two trials to derive the total number of cases. For both scenarios, the observed age patterns of dengue infections in the three countries were used to distribute the cases by age group[3]. A recent study reported the economic burden of dengue fever in Vietnam, Thailand, and Colombia based on a standardized survey tool and methodology[3]. The societal perspective of the findings from this study was used to calculate the economic burden of dengue infection by patient type (outpatient vs. inpatient), as well as by age

group. As described in [3], the costs were adjusted by the ratio of cost-to-charge and expressed in 2014 USD.

Both vaccine procurement and delivery costs are unknown since NVC is a hypothetical dengue vaccine and CYD-TDV has not been introduced in a national immunization program in the three countries at the time of this research. Thus, instead of assuming one single price for each vaccine, the current study outcomes are presented to show the incremental cost-effectiveness ratios (ICERs) over the range (\$0-\$150) of the total costs to fully vaccinate a person in each country. In other words, the maximum cost per fully vaccinated person to be cost-effective is determined for all intervention strategies. Conventionally, 1 to 3 times GDP per capita has often been used as a threshold cost per DALY averted, but this approach has been criticized and discouraged by WHO[34, 35]. The recent studies recommended that for the low-middle income country setting, 0.5 GDP per capita would be a reasonable threshold when taking into account health opportunity costs[36, 37]. In addition, the WHO SAGE working group study identified other similar interventions including new vaccines and dengue interventions which may be comparable with investments in dengue vaccination. Thus, the cost-effectiveness of the current study outcomes is presented under different threshold assumptions which include not only the GDP-per-capita-related measure, but also the ICERs of other similar interventions ranging from \$2,000 to \$10,000 as reported by the WHO SAGE working group[16].

Sensitivity and uncertainty analyses

In order to assess the uncertainty of the current study, the following sensitivity and scenario analyses were conducted: (1) because the disability weight chosen was identified as one of the most influential parameters in calculating DALY estimates in existing studies[38-43], sensitivity analyses were conducted with varying assumptions of the disability weights used in previous dengue burden studies, as summarized in Table 2; (2) in addition, given the uncertainty with regard to the dengue burden level by country, two scenario analyses were conducted as described above; (3) due to the absence of clear guidance on the eligible age group for a one-off catch-up campaign, the vaccination impact was additionally estimated for the age group of 10-29 and compared with the age group of 10-18; (4) all results were simulated under 80% and 50% coverage scenarios, and the outcomes with the latter scenario are presented in Supplementary 1.

Table 2. Health economic parameters

Parameter	Vietnam	Thailand	Colombia	Source
Disability weight (base)	0.55; 0.21	0.55; 0.21	0.55; 0.21	[39, 41]
Disability weight (sensitivity analysis 1)	0.85; 0.81	0.85; 0.81	0.85; 0.81	[40, 43]
Disability weight (sensitivity analysis 2)	0.13; 0.05	0.13; 0.05	0.13; 0.05	[42]
Disease burden (high scenario, /100,000)	3,182	5,934	2,614	[22]
Disease burden (low scenario, /100,000)	112	217	106	[26, 31-33]
Duration of illness (days, inpatient; outpatient)	7.4; 6.2	7.8; 6.1	10.4; 8.7	[3]
Age of death by age group	Same as Thailand	5.3; 14.1; 37.1	3.4; 14.4; 53.1	[28]
Life expectation at age of death by age group	72.6; 67.8; 44.1	70.9; 66; 42.2	74.8; 66.1; 29.95	[29]
Economic burden of dengue (age < 9yo)	\$282.6; \$81.3	\$126.2; \$49.8	\$109.3; \$151.3	[3]
Economic burden of dengue (9 ≤ age < 19yo)	\$178.9; \$57.3	\$196.2; \$44.7	\$250.4; \$112.7	[3]
Economic burden of dengue (age ≥ 19yo)	\$205.4; \$64.5	\$188.3; \$24.7	\$319.7; \$164.0	[3]
Wastage factor during vaccination campaigns	10%	10%	10%	Assumed
0.5 GDP per capita	\$1,026.2	\$2,970.9	\$3,956.7	World bank

Results

Figure 1 demonstrates disease reduction in percentage induced by vaccination. The first row shows the disease

reduction by the routine vaccination scenario (RT9) across the three countries. In Vietnam and Thailand where the seropositivity rates in 9 year olds are greater than 60%, relying solely on routine vaccination with CYD-TDV would not appear to be effective in the long-run in reducing the number of infected cases over the 30-year period. Due to the higher efficacy and the longer half-life assumed for NVC, a larger disease reduction is observed for NVC compared with CYD-TDV. For both vaccines, the highest impact is observed in the short-term, with NVC not only reaching larger reductions but also for a longer period of time. Two factors related to vaccine-induced protection dictate the temporary nature of the positive impact: (1) waning of vaccine-induced protection which is longer for NVC and (2) protection offered by both vaccines that is only partial and therefore weaker than protection conferred by natural infection. On the other hand, in Colombia where the seropositivity rate at 9 years old is lower than in the other two countries, routine vaccination with NVC achieves a high level of disease reduction (approximately 80%) after the 10th year of introduction, and this protection level is maintained even after the early vaccinated cohorts start experiencing the waning of protection. CYD-TDV results in a longer period of positive impact when compared to the Thai and Vietnamese scenarios, but still with little impact in the long-term.

In addition to routine vaccination, the age groups of 10-18 years old (RT9CU1018) and 10-29 years old (RT9CU1029) are considered for a one-off catch-up campaign, and the results are shown in the second and third rows of Figure 1. Compared to the routine-only scenario, the reduction in infection reaches its highest level quickly in the 2nd year following introduction, due to the massive uptake of the catch-up campaigns. However, the positive impact of the vaccines continuously decreases for both CYD-TDV and NVC, given vaccine waning effects and partial vaccine-induced protection. Similar to routine vaccination, a faster decline is observed for CYD-TDV than for NVC because of the longer half-life and partial protection assumed for NVC. In some scenarios, negative reductions (infection rebounds) at some time points are projected in all three countries with CYD-TDV, and in Vietnam and Thailand with NVC (a common consequence of catch-up campaigns). With the use of NVC, this negative reduction is not observed in Colombia where transmission intensity is relatively low. In addition, the rebounds are reduced with the 10-18 catch-up scenario, compared to the 10-29 catch-up scenario, in Vietnam and Thailand. This is mainly because, in the very short-term, the 10-18 catch-up campaign reduces transmission less than does the 10-29 catch-up campaign, which allows for fewer susceptible individuals to build up in the population.

Figure 1. Overall disease reduction by vaccination with CYD-TDV and NVC

The percentage reduction in the number of hospitalized cases due to vaccination is shown in Figure 2. CYD-TDV and NVC behave differently depending upon the baseline seropositivity rate. In Vietnam and Thailand where the seropositivity rate is high, the reduction in hospitalization is greater with NVC than with CYD-TDV for the first 10-15 years since vaccination. However, after this period, more hospitalized cases are saved by CYD-TDV than by NVC in Vietnam and Thailand. This is because CYD-TDV was assumed to cause a clinically silent infection. That is, in the high seroprevalence settings in Thailand and Vietnam, the majority of children would have had exposure to dengue prior to vaccination (seropositives), such that vaccination with CYD-TDV avoids a natural secondary infection which is known to be associated with more severe illness (thus, more hospitalized cases). On the other hand, this assumption was not taken for NVC, meaning that seropositives (with one infection) receiving the vaccine could still develop a breakthrough, secondary-like infection with higher risk of severe illness. In Colombia where the seropositivity rate is low, vaccination with CYD-TDV triggers more hospitalized cases: because most children aged 9 years old and young adults targeted for vaccination are dengue naïve in this lower-endemic setting, those vaccinated with CYD-TDV would be primed to have a secondary-like infection which is related to the high risk of hospitalization. On the other hand, vaccination with NVC is highly effective in preventing hospitalized cases in Colombia over the predicted period because the massive initial reduction in transmission results in a negligible population-level risk of acquiring two infections. Together with the results of Figure 1, these simulations suggest that in a scenario similar to the one used here for Colombia, dengue infection and disease could be controlled with a NVC-like vaccine.

Figure 2. The proportion of reduction in hospitalization with CYD-TDV and NVC

The target age groups for the three vaccination strategies discussed so far are 9 years old and above. While CYD-TDV is not recommended for children under 9 years old, it is worthwhile to simulate the vaccination impacts on younger age cohorts with NVC: 1 year old routine and 2-5 years old catch-up campaign (RT1CU0205). As the vaccinated age cohorts are smaller than the previous two catch-up strategies, the peak of the disease and infection reduction is lower by around 10% to 20% compared to the other catch-up strategies, as shown in Figure 3. However, the detrimental impact of vaccination – that is, negative disease reduction for a short / medium period – is virtually eliminated under this strategy compared to the other two catch-up strategies. In Colombia, the proportion of disease and infection reduction reaches approximately 80% (close to individual vaccine efficacy) which is kept throughout the predicted period, suggesting that targeting the small number of younger age cohorts would be still cost-effective without increasing the risk of hospitalization.

Figure 3. The proportion of reduction by 1yo routine and 2-5yo catch-up with NVC

The total number of DALY saved over the 30-year period is shown in Supplementary 2. The total DALYs saved are highest in Thailand and lowest in Colombia. Due to the higher vaccine efficacy and duration assumed for NVC than for CYD-TDV, a greater number of DALYs averted are observed with NVC compared to CYD-TDV. However, regardless of the disease burden level, both CYD-TDV and NVC provide positive returns to all countries in terms of the total DALYs saved over the prediction period (30 years).

The incremental cost-effectiveness ratios (ICERs) of various vaccination strategies under the high burden scenario are shown in Figure 4. In Vietnam, the vaccination costs range from \$12 (RT9) to \$60 (RT9CU1029) with CYD-TDV, and all costs range up to \$150 with NVC, to be cost-effective at the threshold cost of \$2,000 per DALY averted. In Thailand, both vaccines appear to be highly cost-effective at the same threshold cost (\$2,000) of averting a DALY, except for the 9 years old routine vaccination strategy with CYD-TDV where vaccination would be cost-effective if the total cost were below \$80. In Colombia, with NVC, all four vaccination strategies are highly cost-effective, and with CYD-TDV, the vaccination costs range from \$41 (RT9) to \$55 (RT9CU1029) to be cost-effective at the threshold cost of \$2,000 per DALY averted. It should be noted that targeting younger age cohorts (RT1CU0205) with NVC appears to be the most cost-effective strategy in Colombia where the seroprevalence rate is relatively low.

Overall, while vaccine interventions with NVC are more cost-effective than with CYD-TDV, most vaccination strategies with CYD-TDV are also cost-effective if vaccination costs are below the threshold cost line as indicated in Figure 4. Furthermore, cost-savings - whereby saved economic burden exceeds the total costs of vaccine interventions - could be achieved for both vaccines if vaccination costs were set properly. For example, cost-savings could be observed if vaccination costs were lower than the following thresholds for the RT9 strategy as an example: \$3.6 (CYD-TDV) and \$52 (NVC) in Vietnam, \$20.8 (CYD-TDV) and \$138.4 (NVC) in Thailand, and \$22.3 (CYD-TDV) and \$156.9 (NVC) in Colombia. However, vaccine interventions become much less cost-effective in all three countries under the low-burden scenario for both vaccines. For example, the RT9CU1029 strategy with CYD-TDV becomes cost-effective only when vaccination costs are set below \$2.1, \$6.4, and \$2.2 at the threshold cost of \$2,000 per DALY in Vietnam, Thailand, and Colombia respectively. Likewise, the vaccination costs with NVC are also lowered compared to the high-burden scenario, ranging from \$6.3 to \$26.2, with the RT9 strategy in Vietnam being the least cost-effective and the RT9CU1018 strategy in Thailand being the most cost-effective (see Supplementary Figure 1(f)). Additional threshold costs for averting a DALY are also shown in Figure 4, and vaccination costs to be cost-effective can be identified in the same manner.

Figure 4. Incremental cost-effectiveness ratios (ICERs) under the high burden scenario (coverage 80%)

In addition to the scenario analyses by disease burden and coverage rate, sensitivity analyses were conducted

with two sets of disability weights in comparison with the baseline disability weight assumption. As shown in Figure 5, vaccination costs at the threshold cost of \$2,000 per DALY averted decrease by 2% to 3% compared to the baseline disability weight across vaccination strategies in all countries if the lower estimates of the disability weight are assumed. Using the higher disability weight assumption, the vaccination costs at the same DALY threshold increase by 0.4% to 10%. Overall, the intervention strategies become more cost-effective with the higher disability weight and less cost-effective with the lower disability weight.

Figure 5. Sensitivity analyses with varying disability weights (coverage 80%)

* See Supplementary Table 3 for the range of total DALY saved by disability weights

In addition, Figure 6 demonstrates a one-way sensitivity analysis for the RT9 strategy at the threshold cost of \$2,000 for averting a DALY (see Supplementary 1 for other strategies). The parameter changes in coverage rates and discount rates are highly influential on the changes in the cost-effective vaccination cost. As expected, more cost-effectiveness results can be obtained when the economic burden is higher, and vaccine wastage rate is lower.

Figure 6. One-way sensitivity analysis for the RT9 strategy

Discussion

The current study estimates the cost-effectiveness of various vaccination strategies in Vietnam, Thailand, and Colombia. In conjunction with one of the transmission models previously considered by the WHO SAGE working group, the study outcomes were generated by running stochastic numerical simulations applying country-specific inputs as much as possible, and as recommended by Flasche et al.[16]. With this consideration, our study aimed at identifying effective vaccination strategies by comparing the current and hypothetical vaccines.

Given the higher efficacy and the longer duration of NVC compared to CYD-TDV, vaccination with NVC was more cost-effective than with CYD-TDV. However, in high-transmission settings, mass vaccination (routine plus catch-up) with CYD-TDV resulted in averting hospitalized cases even after the waning of vaccine efficacy for some of the early routine and catch-up vaccine recipients. On the other hand, in Colombia where the seropositivity rate is low, vaccination with CYD-TDV caused more hospitalized cases, and this finding is consistent with WHO/SAGE reports[14, 15] and respective scientific publication[16]. NVC performed much better than CYD-TDV in terms of overall and hospitalized cases averted in Colombia. It should be noted that in this lower transmission setting, a vaccine with 80% efficacy against all four serotypes and a half-life of 8 years would be highly effective at controlling disease without observing disease rebounds during the 30-year projection period. In some scenarios, future disease rebounds, which were also in line with the findings from previous studies, were observed for some vaccination strategies with both CYD-TDV and NVC due to the following reasons [20, 25]: (1) as time went by, the small proportion of the population (i.e. new-born babies) not vaccinated remained fully susceptible due to the general reduction in transmission associated with vaccination of the rest of the population; (2) owing to the waning effect of vaccine efficacy, susceptibility also slowly accumulated in the vaccinated group leading to a larger pool of susceptible hosts to be infected later; (3) people who had been vaccinated were being given vaccine-induced immunity which is partial and weaker than naturally-induced immunity, hence, as coverage accumulates, a larger proportion of the population was partially-susceptible when compared to the pre-vaccination era in which complete, natural immunity ruled.

Overall, the study results suggest that both CYD-TDV and NVC can be cost-effective at the DALY threshold cost of \$2,000 per DALY averted by setting proper vaccination costs. Among the four vaccination strategies considered in this study, the most cost-effective strategy varies by country and by vaccine type. In the case of CYD-TDV, targeting 9 year olds as a routine vaccination with a one-off catch-up campaign for 10-29 year olds appeared to be the most cost-effective strategy in all three countries. With NVC, the most cost-effective strategy

varied by country: RT9CU1029 in Vietnam, RT9CU1018 in Thailand, and RT1CU0205 in Colombia. In particular, vaccinating younger age cohorts was more cost-effective and suggestive of effective disease control than any other simulated strategies in Colombia. Apart from vaccine effectiveness, the 2-dose scheme assumed for NVC would likely increase logistical efficiency and save indirect costs compared to the 3-dose scheme of CYD-TDV by eliminating an additional visit to achieve the full compliance of vaccination. It should be noted that there are other existing CEA studies based on different modeling approaches[39, 44-49], and vaccination costs for being cost-effective appear to vary due to different country-specific contexts (i.e. disease burden, economic burden, etc.) and parametric assumptions. In particular, while the recent studies with CYD-TDV used more or less similar efficacy rates published from the two large trials (CYD14 and CYD15) [45-49], the assumption for the waning effects on seronegatives and seropositives differs, which affects the cost-effectiveness of the same vaccine (the shorter the duration of efficacy, the lower the cost-effectiveness).

Some areas of uncertainty deserve attention. Seroprevalence will vary within a country. For example, there was a discrepancy between the seroprevalence rate of 9 year olds used for this study and the L'Azou et al. estimate for the age group of 9-12 year olds[21, 22]. The two studies were conducted in different provinces, indicating that seroprevalence does indeed vary in Colombia. Previous studies showed the geographical difference of dengue risk factors, partly due to the densely populated areas at high elevation in Colombia, and suggested alternative ways to identify populations at high risk for further serological surveys or diagnostic tests to screen them out prior to vaccination[5, 26]. This is particularly important given that the manufacturer of CYD-TDV officially announced that more cases of severe disease could occur when vaccinating seronegatives[17], and that WHO updated its recommendation that CYD-TDV only be administered to seropositive individuals[18]. These recent announcements highlight that it is critical to identify serostatus of vaccine recipients prior to vaccination with CYD-TDV. Apart from the soundness of a model structure in general, vaccine efficacy and duration play a critical role in determining cost-effectiveness of a vaccine intervention. Similar to previous studies, the current study relied on limited information regarding CYD-TDV (i.e. the duration of efficacy), and this should be further investigated in the future as more data on CYD-TDV become available. Vaccine efficacy may vary not only by serotype, but also by serostatus. However, given that the efficacy of CYD-TDV was only available either by serotype or by serostatus, and not by both, the former was used, and the results might differ if such information were available[23]. Similarly, given the absence of efficacy and half-life data for any of the second-generation vaccine candidates, it was assumed that NVC is 80% efficacious with a half-life of 8 years.

Starting with CYD-TDV, the dengue vaccination era began in 2016, and other second-generation vaccine candidates are currently in the pipeline. Many dengue-endemic countries, including the three in this study, are resource-constrained and will soon face decisions on if, when, and how to introduce the current or future dengue vaccines into their national immunization programs. Taking into account their limited health budgets and their need to prioritize among competing health problems, it is critical to start considering the effective use of a safe dengue vaccine at the population level in order to maximize positive societal returns and minimize any detrimental impacts. The current study outcomes can be used as a tool for understanding the impacts of dengue vaccination and the cost-effectiveness of different intervention strategies in the country-specific context. With the vaccination costs for cost-effectiveness demonstrated in this study, the final outcomes can help decision makers incorporate dengue vaccination into their national immunization programs in Vietnam, Thailand, and Colombia.

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Conflicts of interests

The authors do not have any affiliations with or involvement in any entity with any financial interest or non-

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Authors' contributions

JSL designed the study, conducted the analyses, and wrote the manuscript; JL was involved in the transmission model construction and data interpretation; AF and SG contributed to data interpretation and overall inputs on the study outcomes.

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NA

Appendix A. Supplementary materials

Accepted Manuscript Version

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