A multi-country study of dengue vaccination modelling using econometric and GIS approaches in three dengue-endemic countries: Vietnam, Thailand, and Colombia



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Abstract

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The overall theme of this thesis is to generate innovative health-economic outcomes which are needed prior to the introduction of population-level dengue immunization programs in three dengue-endemic countries: Vietnam, Thailand, and Colombia. This thesis consists of six chapters which are distinctive but inter-related. Following the introductory chapter, where the existing literature search is carried out, in Chapter 2 I begin by conducting a multi-country study of the economic burden of dengue fever based on standardized field studies in the three dengue-endemic countries.

In Chapter 3, an Early Warning Signal (EWS) model is developed based upon climate and non-climate factors. In particular, this chapter adopts a theory of elasticity, which is not common in the field of health economics but which is a key notion in economics, to predict geographically-dispersed dengue outbreaks in Colombia.

The econometric technique used in the third chapter is further extended to the mixed-effects modeling work in Chapter 4 where high-risk areas for dengue fever are identified at the 5 km by 5 km geographical unit, and the number of dengue vaccine doses is estimated at the population-level in Vietnam, Thailand, and Colombia. The concepts and methodologies applied in both Chapter 3 and 4 are unconventional but clearly underscore the needs for innovative approaches in order to respond to existing public health problems.

Based on the findings from Chapter 1 to Chapter 4, the vaccination impacts and cost-effectiveness of dengue vaccination strategies are estimated in the three dengue-endemic countries in Chapter 5. Vaccination impact is derived from a spatially explicit, individual-based meta-population transmission model developed by the Oxford/Exeter group for the WHO Strategic Advisory Group Experts (SAGE) working group exercise. In addition, country-specific health economic parameters are taken from the economic burden field studies in the second chapter of the thesis. In particular, Chapter 5 is designed to reflect the most up-to-date information on the dengue vaccine development: including controversial debates over CYD-TDV, introducing a new vaccine candidate (NVC) with no safety concern identified in CYD-TDV.

Lastly, Chapter 6 summarizes the roles of the four core chapters as a country-specific investment case, and underscores the importance of an evidence-based decision-making process prior to implementing vaccination campaigns at the population-level.

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Chapter 1. Introduction

1.1 Introduction

1.1.1 Dengue's population biology

Dengue fever is a major public health concern in many parts of the tropics and sub-tropics. Dengue virus is transmitted to humans by infective female *Aedes* mosquitoes, of which the two most common species are *Aedes aegypti* and *Aedes albopictus*. *Aedes aegypti* is often found in human habitats and uses water containers as breeding sites. A previous study indicated that human blood is strongly preferred by female adult mosquitoes for egg production (Scott et al., 2000). Clinical presentations of dengue are usually mild symptoms including fever, headache, rash, and joint pains, but dengue infection occasionally develops into potentially lethal complications called dengue shock syndrome and dengue hemorrhagic fever, which are leading causes of hospitalization and death in dengue-endemic countries (WHO, 2016, Lee et al., 2017c). A recent study calculated that there are 96 million apparent and 294 million inapparent dengue infections occurring annually (Bhatt et al., 2013). The total annual global cost of dengue fever was estimated to be US$8.9 billion in 2013 (Shepard et al., 2016).

Dengue's immunity and population biology are complex. Dengue virus is a single strand of RNA (Lourenco et al., 2018). There are four antigenically distinct serotypes (DENV 1-4) interacting with each other. It is known that each of the four serotypes was introduced into the human population at different points in time, and the earliest introduction, of DENV 2, was approximately 1,000 years ago (Lourenco et al., 2018, Twiddy et al., 2003, Weaver and Vasilakis, 2009). Infection with one serotype provides life-long immunity to that specific

serotype but does not offer prolonged protection against the other three serotypes (Lee et al., 2017a). Given a high degree of antigenic cross-reactivity—whereby an antibody against one antigen binds with another antigen—a sequential infection of two different serotypes may bring positive outcomes such as short-term cross-protection, whereby a primary infection confers temporary protection against a subsequent infection with different dengue serotypes. However, this type of subsequent heterologous infection may also cause severe illness due to the antibody dependent enhancement (ADE) during the second infection mediated by non-protective heterotypic antibodies arising from the primary infection (Rodriguez-Roche and Gould, 2013, Bhoomiboonchoo et al., 2015, Reiner et al., 2014, Lourenco and Recker, 2013). In other words, preexisting antibodies induced by a primary infection do not neutralize the virus from a subsequent heterotypic infection but, instead, help the virus infect more efficiently, resulting in the increase of the overall replication of the virus (Whitehead et al., 2007).

1.1.2 Dengue vaccines

In the context of dengue, a first live attenuated, tetravalent dengue vaccine (Dengvaxia, CYD-TDV) became available in 2016, and several dengue-endemic countries have already licensed this vaccine. More importantly, there are second-generation vaccine candidates that are currently in phase 3 trials. In fact, care must be taken when considering vaccination with CYD-TDV. While CYD-TDV provides protective benefits against dengue fever for those who have had prior infection, it is possible for vaccinated seronegative individuals to develop more severe illness following a subsequent dengue infection (Sanofi Pasteur, 2017). The exact cause

of the elevated risk of developing more severe illness is not clear yet. A potential explanation is that vaccination mimics a silent natural infection in providing short-lived heterologous protection followed by the waning effect of vaccine-induced immunity, and a first natural infection after vaccination with CYD-TDV then acts as a secondary-like breakthrough infection among seronegative vaccine recipients (Flasche et al., 2016b, Lee et al., 2018). This safety signal of CYD-TDV has important implications when estimating the population-level impact of vaccination (i.e. positive vs. negative impacts of the intervention depending upon the seroprevalence rates of target age cohorts).

1.1.3 Health economics of dengue

There are relatively few studies from a health-economic perspective of dengue. This is partly because dengue vaccines have not been available until recent times. Considering the potentially broader availability of dengue vaccines in the near future, health-economic research is essential for understanding the current societal economic burden of the disease (i.e. cost-of-illness) and to measure the potential impacts of public health interventions at the population level (i.e. cost-effectiveness analysis). In addition to the conventional health-economic outcomes, the use of applied econometrics and Geographic Information System (GIS) techniques create new ways to identify high-risk areas at the smaller scale geographical unit and to predict dengue outbreaks, and these unconventional approaches can produce effective measures when designing public-health intervention programs. For example, a vaccine supply shortage is expected in many dengue-endemic countries at least during the initial phase of the vaccine introduction. Even if the vaccine supply becomes sufficient for

both vaccine manufacturers and vaccine-demanding countries several years after the introductory phase, many dengue-endemic countries would likely face financial burden for population-level vaccine interventions. Thus, identifying high-risk areas at the smaller geographical scale can help facilitate a more efficient allocation of limited vaccines by targeting the right populations. Furthermore, predicting dengue epidemics can provide opportunities for public health officials to prepare for vector control activities and healthcare interventions including reactive vaccinations. In sum, combining all evidence generated from health economic research is useful not only to understand the overall societal gains of public interventions, but also to facilitate the efficient allocation of limited resources (i.e. safe and effective dengue vaccines).

The main interest of this chapter lies in identifying existing literature on the health economic evidence of dengue fever. In particular, there was the relatively larger number of previous studies on economic burden compared to cost-effectiveness analyses due in part to the long-term absence of dengue vaccines. Therefore, a systematic literature review was carried out for economic burden of dengue fever. In addition, previous studies were searched regarding early warning system models of the disease, as well as the cost-effectiveness analyses of dengue vaccine interventions. Before introducing the detailed methodological approaches of the health economic research work in the following chapters, the current chapter provides a critical overview of existing evidence and summarizes motivating reasons for more detailed health-economic analyses as a part of the country-specific investment case.

1.2 Methods

1.2.1 Economic burden of dengue fever

A systematic literature review was conducted by searching the PubMed electronic database. The key words used were ("dengue" OR ("dengue" AND "fever") OR "dengue fever") AND ("cost of illness" OR ("cost" AND "illness") OR "economic cost" OR ("economic" AND "cost") OR "economic impact" OR ("economic" AND "impact") OR "economic burden" OR ("economic" AND "burden"). Any papers published between January 1970 and September 2015 were included, and the search was limited to papers written in English. Among the papers searched from the PubMed database, the first screening was conducted by going through all abstracts, and the papers which reported the economic burden of dengue fever were shortlisted. For the selected papers, a more comprehensive (full-length) review was carried out.

One of the major concerns regarding the economic burden of dengue fever was that methodologies among the existing studies were not often standardized, making it difficult to conduct an accurate comparison. The estimation of the economic burden of dengue fever may vary due to many different reasons:

- First, the accuracy and level of the economic burden may differ depending on whether a study is conducted during an endemic or an epidemic period, given that there are more difficulties in resource allocation (i.e. the number of available beds, doctors, and nurses) at some local health facilities during an epidemic period.

- Second, many local health facilities in developing countries identify dengue patients based on clinical symptoms, rather than on serology or viral isolations (laboratory confirmation). Because lab-confirmation is also complicated by issues of sensitivity (true positive rate) and specificity (true negative rate), diagnostic methods for dengue patients may play a critical role in determining the number of dengue-confirmed patients and the average cost of dengue fever.

- Third, dengue infection causes not only mild symptoms (fever, headache, etc.), but also a potentially lethal complication in the shape of severe dengue, which is a leading cause of hospitalization and death in many South-/Southeast-Asian and Latin American countries (WHO, 2016, Lee et al., 2017c). Thus, to have a full understanding of the economic burden of dengue fever, it is desirable to include both inpatients and outpatients of dengue fever.

- Fourth, as dengue fever has been observed in both children and adults, it would be ideal to have a broader target age group for a study.

- Fifth, since the duration of dengue illness ranges from 6 to 20 days or longer (Suaya et al., 2009, Tiga et al., 2016), it is important to capture all costs spent during the entire period of illness, rather than only costs spent at one specific point in time during the illness.

- Sixth, because dengue patients may need to spend resources on not only medical services but also on non-medical services (i.e. transportation, food, and lodging) or

substitute laborers, the total economic burden may vary depending on the inclusion of these different cost components.

- Seventh, some of the economic burden studies were conducted based on primary datasets, but some other studies estimated the economic burden of dengue fever by using secondary information or by extrapolating from existing data. While both study types contribute to filling the existing knowledge gap, it is desirable to distinguish between them to allow more proper comparisons across studies.

Given the diverse types of methodologies and inclusion criteria which were previously used to estimate the economic burden of dengue fever, a standardized set of criteria would be useful to make systematic assessments among the papers identified at the final stage of the literature review. The following standardized categories were examined for each of the identified studies: (1) study circumstance (epidemic, endemic), (2) dengue confirmation (clinical symptoms, laboratory-confirmed, etc.), (3) patient type (inpatient, outpatient, etc.), (4) target age group, (5) cost-collection period (i.e. inclusion of medical costs for additional visits other than a study enrollment visit), (6) direct medical costs, (7) direct non-medical costs, (8) indirect costs, (9) study type (direct estimation, extrapolation, secondary data, etc.). It should be noted that the estimates were directly taken from the papers and not adjusted for inflation.

The Dengue Vaccine Initiative (DVI) has conducted extensive multi-disciplinary cost-of-illness (COI) studies in Vietnam, Thailand, and Colombia, using a standardized methodology (Lee et al., 2017c). The rational for the study is to fill the existing knowledge gap and to inform decision makers about the economic burden of dengue fever and to assess the

economic efficiency of vaccine introduction strategies (Lee et al., 2017c). One of the strengths is that the studies are executed in a standardized design in multiple sites. The studies look not only at adults but also at children, and all patients are included based on lab-confirmation for both inpatients and outpatients. The systematic data collected from multiple sites makes it possible to set up more effective vaccination strategies for controlling the disease (see Chapter 2). Based on the 9 categories identified above, each of the literature studies was thoroughly reviewed to see whether each study has sufficient information. Some of the existing studies also reported an estimate of disability-adjusted life years (DALYs), and these studies were separately identified and utilized in cost-effectiveness analyses (see Chapter 5).

1.2.2 Early warning systems of dengue fever and cost-effectiveness analyses of vaccine interventions

Unlike the economic burden analysis, which is one of the more popular measures in the field of health-economics, existing literature on both early warning systems (EWS) and cost-effective analyses (CEA) is rare for various reasons. The scarcity of information on EWS is largely due to the unconventional nature of the statistical framework to develop a model. There is no standard way of constructing such models; methodological frameworks could vary depending on types of disease, risk factors, and biological assumptions included in transmission models. Sometimes, predicting an outbreak may not be feasible for some disease categories, and further, this type of modeling work has not been a major subject in the area of health economics (see Chapter 3 and 4). On the other hand, the CEA has been widely used to evaluate the societal benefits and costs of public-health interventions. Nonetheless, in the

context of dengue fever, the number of existing studies is limited because dengue vaccines have not been available until recent times. Prior to 2016, when a first dengue vaccine (Dengvaxia, CYD-TDV) became commercially available, a limited number of studies had been conducted based on broad assumptions of a hypothetical dengue vaccine. Thus, existing papers for both EWS and CEA were identified by manually tracking the references of dengue outbreak-related studies, as well as of dengue economic-evaluation studies.

1.3 Results

1.3.1 Economic burden of dengue fever

The initial search using the key words, identified 173 papers from the database, as shown in Figure 1. After going through the abstracts and titles, 138 papers were omitted, resulting in 35 papers for a more comprehensive review. The full-text versions of these papers were assessed, and 23 papers were selected at the final stage of the current literature review search. These final papers were assessed based upon the 9 criteria described above, and further divided into sub-categories: primary data (n = 18), secondary data (n = 5), and DALY estimation (n = 9).

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA)

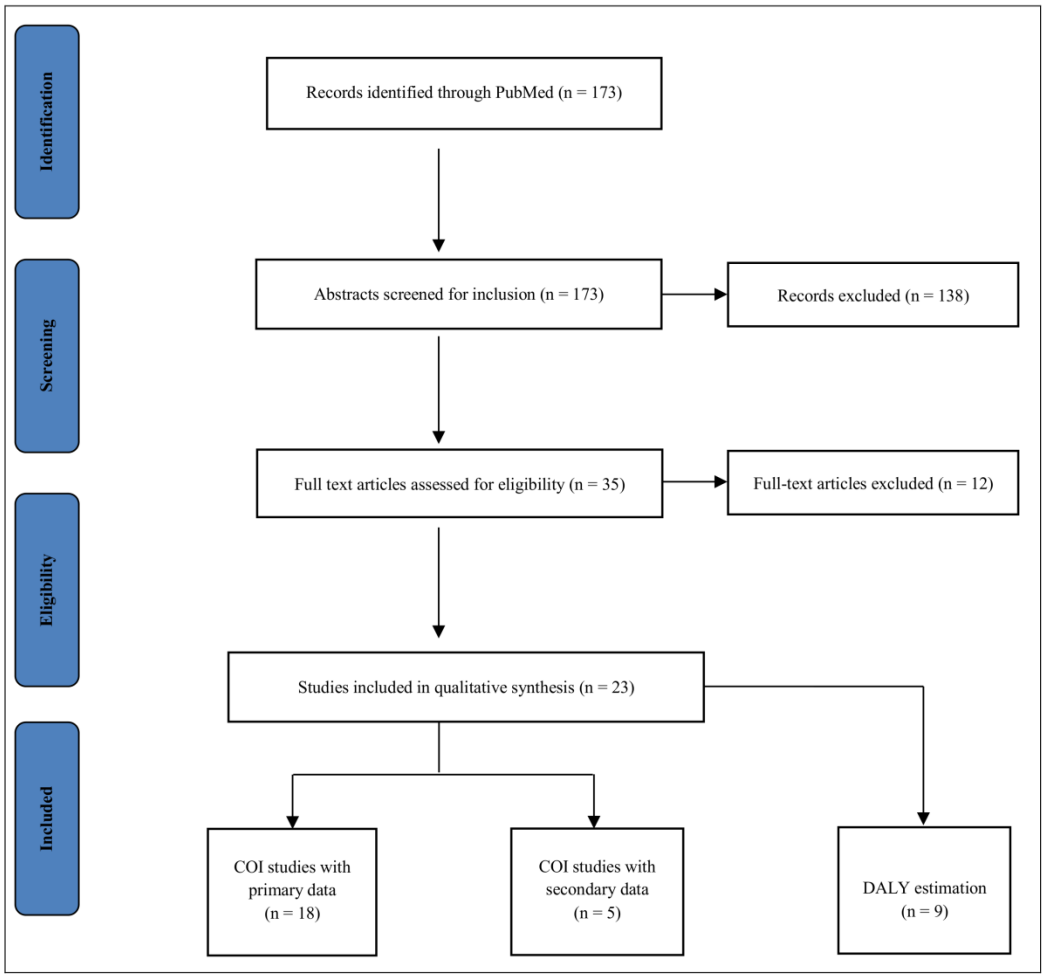

Table 1 summarizes the final 23 papers identified by the systematic literature review. Economic burden studies were found in various countries reflecting the fact that the disease had been prevalent in many parts of the tropics and subtropics. However, no study was identified in Africa. Four studies were carried out in a multi-country setting, and 3 of 23 studies were conducted during dengue outbreaks. 48% of the existing studies used laboratory

confirmation to enroll dengue patients, and 26% of the studies relied on clinical symptoms or both clinical symptoms and laboratory-testing. The rest of the studies did not clearly indicate how they identified dengue patients. Seven studies only reported the COI estimates for inpatients or patients with dengue hemorrhagic fever, whereas the other studies reported economic burden for both inpatients and outpatients.

Because dengue illness can sometimes last longer than 20 days, outpatients may need to visit health facilities several times, and inpatients may seek additional treatments before and after hospitalization. Thus, it is critical to capture all costs spent during the entire period of illness. Of the 23 studies, 11 considered multiple time points of health facility visits during the study periods, in order to estimate the total cost of dengue illness. While all studies took into account direct medical costs, some studies did not include either direct non-medical costs or indirect costs when estimating the total costs. Of the 23 studies, 22% estimated the economic burden of dengue fever using secondary data sources. In other words, the estimates from these studies were not directly derived from primary data collection but from extrapolating from existing literature.

Among the 18 papers of the 23 studies, including multi-country studies, which estimated the economic burden of dengue fever using primary data, 11 were from Asia, and 9 were conducted in South America. The estimates and methods used for the economic burden are summarized in Table 2. Given that there were variations in terms of the reported cost components across the studies, the following criteria were applied to summarize the costs in Table 2: (1) if several cost components were reported in a study (i.e. total cost, direct medical

cost, direct non-medical cost, etc.), the more aggregated level of the cost component (i.e. total cost) was chosen, (2) the total cost per episode was preferred to the total cost at the population-level, (3) given the first two criteria, the estimates by patient type (i.e. inpatient, outpatient) were preferred to the combined estimates. The majority of the 18 studies were implemented after 2010, except Okanurak et al., Anderson et al., and Wettstein et al. There were five studies that focused on a specific age cohort rather than on all age cohorts. It is interesting to observe that the costs were widely variable among several studies from the same country, reflecting differences in methodology, health systems, cost collection perspectives, and target patient groups in each study. For example, of the four studies identified for Thailand, Anderson et al. and Clark et al. reported $32 in 2002 and $44 in 2001 respectively as the economic burden of dengue fever, but Okanurak et al. reported $141-216 in 1994. This large difference cannot be explained by the study periods chosen because Okanurak et al.'s study was conducted prior to the other studies. In fact, there were important methodological differences between these studies. Okanurak et al. reported the economic burden for patients with dengue-hemorrhagic-fever who generally went through more severe illness with a longer duration. On the other hand, the estimates from the studies of Anderson et al. and Clark et al. were for general inpatients and outpatients with dengue fever. Moreover, these latter two studies only considered patients' out-of-pocket costs, which made their estimates relatively lower than the estimate of Okanurak et al.

It should be noted that it is possible that some additional studies may have been available since the finalization of the formal systematic literature review and analysis. Thus, a further search was carried out using the same key words for the extended period until May 2018 and

this identified nine additional studies. The same details shown in Table 1 and 2 were extracted for the additional studies and presented in Table 3 and 4.

Table 1. Summary of the final 23 papers

Paper	Country	Circumstance	Dengue confirmation	Patient type	Cost collection period	Direct medical cost[k]	Direct non-medical cost[l]	Indirect cost[m]	Data source	Reference
Beaute et al.	Cambodia	Endemic	NA	NA	1 time point	Yes	Yes	Yes	Secondary	(Beaute and Vong, 2010)
Stahl et al.	Multiple countries[a]	Epidemic	CS[e] (Peru); NA (others)	OP[g], IP[h], ICU[i]	NA	Yes	No	Yes	Primary	(Stahl et al., 2013)
Edillo et al.	The Philippines	Endemic	CS	OP, IP	NA	Yes	Yes	No	Primary	(Edillo et al., 2015)
Anderson et al.	Thailand	Endemic	LC[f]	OP, IP	Previous pharmacy visit assumed	Yes	Yes	Yes	Primary	(Anderson et al., 2007)
Shepard et al.	Multiple countries[b]	Endemic	NA	OP, IP	NA	Yes	Yes	Yes	Secondary	(Shepard et al., 2013)
Rafique et al.	Pakistan	Endemic	LC	IP	3 time points	Yes	Yes	Not clear	Primary	(Rafique et al., 2015)
Vieira Machado et al.	Brazil	Epidemic	LC	IP	NA	Yes	No	No	Primary	(Vieira Machado et al., 2014)
Huy et al.	Cambodia	Endemic	LC	OP, IP	2 time points	Yes	Yes	Yes	Primary	(Huy et al., 2009)
Clark et al.	Thailand	Endemic	LC	IP	3 time points	Yes	Yes	Yes	Primary	(Clark et al., 2005)

Shepard et al.	Multiple countries[c]	Endemic	NA	OP, IP	NA	Yes	Yes	Yes	Secondary	(Shepard et al., 2011)
Suaya et al.	Multiple countries[d]	Endemic	LC (Panama, Venezuela); CS (others)	OP, IP	2 time points	Yes	Yes	Yes	Primary	(Suaya et al., 2009)
Okanurak et al.	Thailand	Endemic	CS	DHF[j]	2 time points	Yes	Yes	Yes	Primary	(Okanurak et al., 1997)
Harving et al.	Vietnam	Endemic	LC	IP DHF	2 time points	Yes	Yes	Yes	Primary	(Harving and Ronsholt, 2007)
Castro Rodriguez et al.	Colombia	Endemic	LC & CS	OP, IP	NA	Yes	Yes	Yes	Primary	(Castro Rodriguez et al., 2015)
Tam et al.	Vietnam	Endemic	LC	IP DHF	3 time points	Yes	Yes	Yes	Primary	(Tam et al., 2012)
Carrasco et al.	Singapore	Endemic	NA	OP, IP	NA	Yes	Yes	Yes	Secondary	(Carrasco et al., 2011)
Wettstein et al.	Nicaragua	Endemic	LC & CS	OP, IP	NA	Yes	No	Yes	Primary	(Wettstein et al., 2012)
Armien et al.	Panama	Endemic	LC	OP, IP	NA	Yes	Yes	Yes	Primary	(Armien et al., 2008)
Shepard et al.	India	Endemic	LC	OP, IP	2 time points for IP	Yes	No	No	Primary	(Shepard et al., 2014)
Halasa et al.	Puerto	Endemic	LC	OP, IP	2 time points for IP	Yes	Yes	Yes	Primary	(Halasa et

	Rico									al., 2012)
Tarragona et al.	Argentina	Epidemic	Not clear	OP, IP	NA	Yes	No	Yes	Primary	(Tarragona et al., 2012)
Shepard et al.	Malaysia	Endemic	Not clear	OP, IP	NA	Yes	Yes	Yes	Secondary	(Shepard et al., 2012)
Undurraga et al.	Mexico	Endemic	LC	OP, IP	2 time points	Yes	Yes	Yes	Primary	(Undurraga et al., 2015)

[a] Peru, Dominican Republic, Vietnam, and Indonesia

[b] Bhutan, Brunei, Cambodia, East Timor, Indonesia, Laos, Malaysia, Myanmar, Philippines, Singapore, Thailand, and Vietnam

[c] Andean sub-region, Central America, North America, Southern cone, and The Caribbean

[d] Brazil, El Salvador, Guatemala, Panama, Venezuela, Cambodia, Malaysia, and Thailand

[e] Clinical symptoms

[f] Laboratory-confirmation

[g] Outpatient

[h] Inpatient

[i] Intensive care unit

[j] Dengue Hemorrhagic Fever

[k] Direct medical costs consist of any fees related to consultation, medication, and laboratory test.

[l] Direct non-medical costs include any payments related to transportation, lodging, or food incurred while seeking medical treatment.

[l] Indirect costs includes productivity loss (wage loss) and additional costs for hiring substitute laborers or caregivers.

Table 2. Details on existing studies with primary data

Paper	Country	Study year	Age group	Cost type	Cost of illness	Method
Stahl et al.	Vietnam	2011	Children, Adults	TC[a]	$13,000,000	Based on interviews with 5-10 patients, dengue clinicians for typical treatment and required resources for a dengue patient, lab staff for complementing the information of the clinical, pharmacy staff for the cost of each item, chief entomologist or vector control manager and staff in the communication department, and document analysis (clinical histories of patients)
	Indonesia	2011	Children, Adults	TC	$6,750,427	
	Peru	2011	Children, Adults	TC	$4,500,000	
	Dominican Republic	2011	Children, Adults	TC	$2,800,000	
Edillo et al.	The Philippines	2008-2012	All	DMC[b] per episode	$565.04 (IP), $120.38(OP)	Based on the medical bills of hospitalized dengue patients using macro-costing approach
Anderson et al.	Thailand	1998-2002	5-15 yo	TC per episode	$31.79 (DF), $39.09 (DHF)	Based on out-of-pocket costs; 200 baht per private clinic visit, 30 baht public insurance system for public facilities, 50 baht per day of hospitalization for the cost of food for an attendant family member, assumed that all patients made a previous pharmaceutical visit at costs of 50 baht
Rafique et al.	Pakistan	2011	All	DC[c] per episode	$358.23 (IP)	Based on interviews with 250 dengue-confirmed patients; out-of-pocket costs
Machado et al.	Brazil	2010	All	DMC per episode	$740.1 (IP)	Based on medical records
Huy et al.	Cambodia	2006	≤ 15 yo	TC per episode	$40.1 (IP), $14.3 (OP)	Based on interviews with 30 dengue cases (lab-confirmed) and 30 non-dengue cases (control); out-of-pocket costs
Clark et al.	Thailand	2001	All (but mostly	TC per episode	$44 (IP)	Based on 204 surveys; out-of-pocket costs

			children)			
	Brazil	2004-2007	All	TC per episode	$681.93 (IP), $294.12 (OP)	
	El Salvador	2004-2007	< 15 yo	TC per episode	$459.33 (IP), $88.04 (OP)	
	Guatemala	2004-2007	All	TC per episode	$409.24 (IP), $85.87 (OP)	
	Panama	2004-2007	All	TC per episode	$1,078.48 (IP), $336.08 (OP)	Based on surveys; the numbers presented in the article were
Suaya et al.	Venezuela	2004-2007	All	TC per episode	$607.46 (IP), $162.69 (OP)	expressed in international $, thus converted using the official
	Cambodia	2004-2007	All	TC per episode	$115.42 (IP)	exchange rates
	Malaysia	2004-2007	All	TC per episode	$955.77 (IP), $320.19 (OP)	
	Thailand	2004-2007	All (but mostly ≤ 15 yo)	TC per episode	$572.96 (IP)	
	Thailand (Bangkok)	1994	< 15 yo	TC per episode	$172.89 (DHF child), $216.09 (DHF adult)	
Okanurak et al.						Based on interviews, hospital records, and prevention and vector
	Thailand (Suphan Buri)	1994	All	TC per episode	$141.47 (DHF child), $176.67 (DHF adult)	control program
Harving et al.	Vietnam	2005	≤ 15 yo	TC per episode	$61.36 (DHF)	Based on interviews with 175 children
Rodriguez et al.	Colombia	2010-2012	All	TC per episode	In 2012, $202.3 (OP DF), $497.9 (IP DF), $2306.7 (DHF)	Based on household surveys, and healthcare system access
Tam et al.	Vietnam	2006-2007	All	TC per episode	$167.78 (IPD DHF)	Based on interviews with 144 lab-confirmed cases; out-of-pocket costs
Wettstein et al.	Nicaragua	1996-2010	All	TC per episode	$125-$273 (1996-2010)	Based on data from the Nicaraguan Ministry of Health (MINSA) and SILAIS
Armien et al.	Panama	2005	All	TC per episode	$1,065 (IP), $332 (OP)	Based on surveys, several assumptions for direct medical costs
Shepard et al.	India	2010-2013	All	DMC per episode	$197.03 (IP public), $248.11	Based on data from 10 hospitals using macro-costing approach

					(IP private), $23.49 (OP public), $26.09 (OP private)	
Halasa et al.	Puerto Rico	2008-2010	All	TC per episode	$5,497 (IP), $1,279 (OP)	Based on interviews with 100 patients; high indirect costs
	Argentina (Central region)	2009	All	TC	$425,375 (scenario1) $522,284 (scenario2) $739,942 (scenario3)	
Tarragona et al.	Argentina (Northwest and Cuyo region)	2009	All	TC	$2,966,877 (scenario1) $3,567,048 (scenario2) $3,922,295 (scenario3)	Based on unit prices of services and ad-hoc surveys (n = 201)
	Argentina (Northeast region)	2009	All	TC	$2,423,391 (scenario1) $2,949,888 (scenario2) $4,075,838 (scenario3)	
Undurraga et al.	Mexico	2010-2011	All	TC per episode	$1,327 (IP), $451 (OP)	Based on data from two public hospitals using macro-costing approach, WHO-CHOICE, and the cohort survey and previous studies

[a] Total Cost

[b] Direct Medical Cost

[c] Direct Cost

Table 3. Summary of additional 9 papers

Paper	Country	Circumstance	Dengue confirmation	Patient type	Cost collection period	Direct medical cost	Direct non-medical cost	Indirect cost	Data source	Reference
Zubieta-Zavala et al.	Mexico	Endemic	LC	OP, IP, ICU	1 time point	Yes[a]	Yes	Yes	Primary	(Zubieta-Zavala et al., 2016)
Luh et al.	Taiwan	Endemic, Epidemic	NA	OP, IP	NA	Yes	No	Yes	Primary	(Luh et al., 2018)
Fezzazu et al.	Multiple countries[b]	Endemic	LC	OP, IP	NA	Yes	Yes	Yes	Secondary	(El Fezzazi et al., 2017)
Legorreta-Soberanis et al.	Mexico	Endemic	NA	OP, IP	NA	Yes	Yes	Yes	Primary	(Legorreta-Soberanis et al., 2017)
Pham et al.	Vietnam	Endemic	CS	IP	2 time points	Yes	Yes	Yes	Primary	(Pham et al., 2017)
Uhart et al.	3 French territories of the Americas[c]	Endemic	CS	IP	NA	Yes	No	No	Primary	(Uhart et al., 2016)
Vo et al.	Vietnam	Endemic	LC[d]	IP	NA	Yes	No	No	Primary	(Vo et al., 2017)
Tozan et al.	Thailand	Endemic	CS	IP	1 time point	Yes	Yes	Yes	Primary	(Tozan et al., 2017)
Lee et al.	Multiple countries[e]	Endemic	LC	OP, IP	3 time points	Yes	Yes	Yes	Primary	(Lee et al., 2017c)

[a] TC may not be calculated by summing DMC, DNMC, and IC because the source data for DMC is not exactly the same as selected patients interviewed for DNMC and IC.

[b] CYD-TDV trial sites (CYD14 and CYD15)

[c] French Guiana, Martinique, and Guadeloupe

[d] The authors included costs for diagnostic tests but did not specify the details.

[e] Vietnam, Thailand, and Colombia

Table 4. Details on the additional studies with primary data

Paper	Country	Study year	Age group	Cost type	Cost of illness	Method
Zubieta-Zavala et al.	Mexico	2012	All	DMC per episode	$490.93 (IP SS[a]), $1644.69 (IP IMSS[b]), $32.60 (OP SS), $92.03 (OP IMSS)	Based on chart reviews of two healthcare systems (SS, IMSS), interviews with selected patients
Luh et al.	Taiwan	1998-2014	All	TC	$8,851,224 (epidemic), $717.86 (endemic)	Based on the resource-based relative value scale (RBRVS) system
Legorreta-Soberanis et al.	Mexico	2010	All	TC per episode	$514 (IP), $50.87 (OP)	Based on the Camino Verde trial (surveys)
Pham et al.	Vietnam	2015-2016	All	TC per episode	$139.3 (IP)	Based on interviews with patients and the Cu Chi general hospital electronic database
Uhart et al.	3 French territories of the Americas	2007-2011	All	TC per episode	€2,758 (IP)	Based on the French national hospital administrative database (payer perspective)
Vo et al.	Vietnam	2013-2015	All	TC per episode	$48.1 (IP)	Based on the Cu Chi general hospital electronic database (payer perspective; neither DNMC nor IC)
Tozan et al.	Thailand	2015	All	TC per episode	$171.2 (DF), $226.1 (DHF)	Based on interviews with patients (no public expenditure)
	Vietnam	2012	All	TC per episode	$213 (IP), $64 (OP)	
Lee et al.	Thailand	2016	All	TC per episode	$181 (IP), $43 (OP)	Based on interviews with patients and hospital records
	Colombia	2015	All	TC per episode	$278 (IP), $144 (OP)	

[a] Secretariat of Health (Mexican healthcare system)

[b] The Mexicam Social Security Institute (Mexican healthcare system)

1.3.2 Early Warning Systems of dengue fever and Cost-effectiveness analysis of dengue vaccine interventions

Several efforts have been made to understand the main drivers of dengue epidemics. Juffrie and Focks used sea-surface temperature anomalies to identify the occurrence of dengue epidemics in Yogyakarta, Indonesia, and Bangkok, Thailand (Juffrie and Focks, 2009). Lowe et al. developed an early warning system for dengue outbreaks in Southeast Brazil using several climate and non-climate datasets (Lowe et al., 2013). More recently, Huang et al. found that El Nino-Southern Oscillation climate cycles and temperature were important factors affecting the weekly occurrence of the four dengue serotypes in Cairns, Australia (Huang et al., 2015). Adde et al. also identified summer Equatorial Pacific Ocean sea-surface temperature and Azore high sea-level pressure as significant indicators in predicting dengue epidemics in French Guiana (Adde et al., 2016). All of these models were geographically specific, and the model frameworks were variable. Nonetheless, the existing studies showed that dengue epidemics are strongly related to meteorological data. Given the nature of dengue as a vector-borne disease, some of the climate data affecting the spread of vectors more commonly were consistently observed in these previous studies (i.e. temperature).

While CEA has been widely used to evaluate the societal costs and benefits of vaccine interventions, not many studies are available in the context of dengue fever, due to the long-term absence of a vaccine. Shepard et al. estimated cost-effectiveness of a pediatric dengue vaccine in Southeast Asia using a societal perspective and determined the cost per disability-adjusted life year (DALY) to be $50 (Shepard et al., 2004). Lee et al. conducted the cost-effectiveness analysis to understand better the potential economic value of a

dengue vaccine with varying scenarios in Thailand, and showed that vaccination would be highly cost-effective for a total vaccination cost less than $60 and vaccine efficacy greater than 50% (Lee et al., 2011). Carrasco et al. reported that in Singapore, vaccine programs would not be cost-effective if the price per dose were greater than $100 for a 3-dose regimen with duration of 10 years of immunity (Carrasco et al., 2011). Durham et al. carried out a cost-effectiveness analysis based on Phase 2b dengue vaccine trials taking into account both an optimistic efficacy scenario and a lower-efficacy scenario in Brazil (Durham et al., 2013). The study showed that vaccination might be cost-effective for vaccination costs up to $534 with the optimistic efficacy scenario and up to $237 with the lower-efficacy scenario (Durham et al., 2013). However, all of the aforementioned studies had to rely on broad assumptions because there were no vaccines available at the times when these studies were conducted. Since the two large phase-3 trials for CYD-TDV were completed in South Asia (CYD 14) in 2014 and Latin America (CYD 15) in 2015 (Capeding et al., 2014, Villar et al., 2015a, Hadinegoro et al., 2015), more recent studies have utilized the trial outcomes to understand the cost-effectiveness of the first dengue vaccine called Dengvaxia (CYD-TDV) developed by Sanofi Pasteur (Shafie et al., 2017, Shim, 2016, Shim, 2017b, Shim, 2017a, Zeng et al., 2018, Flasche et al., 2016b). Among the recent studies, Flasche et al. conducted a comprehensive cost-effectiveness analysis based on eight transmission modeling groups (Flasche et al., 2016b), and the study outcomes formed the basis for the first WHO SAGE recommendation on the safe use of Dengvaxia (CYD-TDV) (World Health, 2017). Nonetheless, it should be noted that vaccination costs appear to vary even among the recent studies due to different country-specific contexts and parametric assumptions. In particular, vaccine efficacy for CYD-

TDV is available either by serostatus or by serotype, but not by both. More importantly, the waning effects of CYD-TDV on those of its recipients who are seronegative and those who are seropositive are not yet clear, which may significantly affect the cost-effectiveness of CYD-TDV.

1.4 Discussion

This chapter focused on the systematic literature review of the economic burden for dengue fever, as well as on additional reference searches regarding early warning system models for dengue outbreaks, and cost-effectiveness analyses for dengue vaccine interventions. The existing literature on all three subjects was identified in various parts of Asian and Latin American countries, reflecting the importance and awareness of the disease in those regions. The economic burden of dengue fever appeared to be significant according to the available evidence (Table 2). However, because many of the existing studies estimated the cost of illness using different methodologies and study designs, it was difficult to make proper comparisons among the studies. The previous studies indicated that it would be possible to predict dengue epidemics, but the model construction and outcomes might be geographically focused. Regarding the cost-effectiveness analyses of dengue vaccine interventions, existing studies showed that vaccination may be cost-effective with variable vaccination costs, and that the CEA outcomes are highly dependent upon country-specific parameters and assumptions on vaccine profiles (i.e. efficacy, waning effects).

A comprehensive economic burden study is costly and labor-intensive, requiring timely

data collection and efforts to reduce data errors such as recall bias. Nonetheless, this type of economic burden study provides a basis for more advanced health-economic models which are critical for an evidence-based policy-making process. Thus, updated economic burden estimates based on consistent methods are necessary in order to generate reliable cost-effectiveness outcomes of dengue vaccine interventions. In the context of dengue fever, cost-effectiveness analyses of various vaccination strategies are rare, especially at the population-level. One of the main reasons for this is that dengue vaccines had been absent for a long time due to the complicated nature of the disease. However, a recombinant tetravalent vaccine candidate (CYD-TDV) that had completed Phase 3 clinical trials in Southeast Asia and South America became commercially available in 2016. In addition, there are several second-generation vaccine candidates which are currently in Phase-3 trial at the time of this research. As the dengue-vaccination era recently began, and a broader availability of dengue vaccines seems to be promising in the near future, it is critical to start considering safe and effective ways of vaccine distribution at the population-level, and to examine the cost-effectiveness of such interventions.

1.5 Thesis outline

This thesis consists of six chapters which are distinctive but inter-related. Following this introductory chapter, where the existing literature search is carried out, Chapter 2 investigates a multi-country study of the economic burden of dengue fever based on standardized field studies in Vietnam, Thailand, and Colombia. The first dengue vaccine has already been licensed in several dengue-endemic countries. Given the growing

interests in the effective use of the vaccine, it is critical to understand the economic burden of dengue fever to guide decision-makers in setting health-policy priorities. The study findings can be used to consider accelerated introduction of vaccines into the public and private sector programs and to prioritize alternative health interventions among competing health problems.

In Chapter 3, I develop an Early Warning Signal (EWS) model for dengue outbreaks. Dengue has been prevalent in Colombia, with high risk of outbreaks in various locations. While the prediction of dengue epidemics will bring significant benefits to society, accurate forecasts have been a challenge. The Climate Risk Factor (CRF) index is constructed based upon temperature, precipitation, and humidity. Considering the conditions necessary for vector survival and transmission behavior, elevation and population density are taken into account. An Early Warning Signal (EWS) model is developed by estimating the elasticity of the climate risk factor function to detect dengue epidemics. The study outcomes can be used to minimize potential societal losses by prioritizing limited healthcare services and resources, as well as by conducting vector control activities prior to experiencing epidemics.

In Chapter 4, dengue vaccine supply strategies are developed under endemic and epidemic conditions. Given that the first dengue vaccine (CYD-TDV) became available in 2016 and several second-generation dengue vaccines are currently in the pipeline, it is critical to understand the efficient allocation of dengue vaccines considering the geographical variation of the disease. Based on the findings in Chapter 3, the CRF index is further estimated for Thailand and Vietnam. A non-linear mixed effects model is chosen to validate the relationship between the CRF index and dengue incidence proxy. Given the

statistical significance of the CRF index, high-risk areas for dengue fever are identified at the 5 km by 5 km resolution. The findings of this study can guide the decision makers in the three countries regarding the efficient distribution of vaccines by identifying populations at high risk at 5 km by 5 km resolution.

Taking into account the recent WHO SAGE recommendations on the effective and safe use of Dengvaxia at the regional level on average (World Health Organization, 2017a, World Health Organization, 2017b), Chapter 5 investigates the vaccination impacts and cost-effectiveness of CYD-TDV and a hypothetical new vaccine candidate (NVC) in a country-specific manner for the three dengue endemic countries: Vietnam, Thailand, and Colombia. The vaccination impacts of CYD-TDV and NVC are derived by fitting the empirical seroprevalence rates of 9 year olds into a spatially explicit, individual-based, meta-population transmission model which was previously constructed by an Oxford/Exeter group for the WHO SAGE exercise. The disability adjusted life years (DALYs) are estimated by applying country-specific parametric values. The cost-effectiveness of four intervention strategies in combination with routine and catch-up campaigns is compared for both vaccine types to inform the most suitable immunization program in each of the three countries.

Finally, in Chapter 6 I summarize all findings and evidence produced throughout this DPhil research project and conclude with recommendations for dengue vaccine introduction at the population-level in Vietnam, Thailand, and Colombia.

Chapter 2. A multi-country study of the economic burden of dengue fever: Vietnam, Thailand, and Colombia

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Author contributions:

JSL took the lead on field surveys, monitored the data collection, conducted formal analysis, created all figures, and wrote the manuscript. VM, JKL, MC, KSL, and BAM participated in the study investigation and acquisition of funding. CS, DAD, DCPF, THAN, AR, PC, and LV were involved in the data collection in each of the three countries. AF provided overall supervision.

2.1 Abstract

Dengue fever is a major public health concern in many parts of the tropics and subtropics. The first dengue vaccine has already been licensed in six countries. Given the growing interests in the effective use of the vaccine, it is critical to understand the economic burden of dengue fever to guide decision-makers in setting health policy priorities.

A standardized cost-of-illness study was conducted in three dengue endemic countries: Vietnam, Thailand, and Colombia. In order to capture all costs during the entire period of illness, patients were tested with rapid diagnostic tests on the first day of their clinical visits, and multiple interviews were scheduled until the patients recovered from the current illness. Various cost items were collected such as direct medical and non-medical costs, indirect costs, and non-out-of-pocket costs. In addition, socio-economic factors affecting disease severity were also identified by adopting a logit model. We found that total cost per episode ranges from $141 to $385 for inpatient and from $40 to $158 outpatient, with Colombia having the highest and Thailand having the lowest. The percentage of the private economic burden of dengue fever was highest in the low-income group and lowest in the high-income group. The logit analyses showed that early treatment, higher education, and better knowledge of dengue disease would reduce the probability of developing more severe illness.

The cost of dengue fever is substantial in the three dengue endemic countries. Our study findings can be used to consider accelerated introduction of vaccines into the public and private sector programs and prioritize alternative health interventions among competing health problems. In addition, a community would be better off by propagating the socio-

economic factors identified in this study, which may prevent its members from developing severe illness in the long run.

2.1 Introduction

Dengue fever is a major public health concern in many parts of the tropics and subtropics. Dengue is a vector-borne viral illness and transmitted to humans by two mosquito vectors: *Aedes aegypti* and *Aedes albopictus*. There are four serotypes that cause dengue, with a wide clinical spectrum of symptoms. A previous study estimates there are 96 million apparent and 294 million inapparent dengue infections occurring yearly (Bhatt et al., 2013).

While many countries in the tropics and subtropics recognize dengue as a public health concern, dengue control efforts were not often considered as a priority due to the absence of specific treatment and costly vector control interventions in developing countries (Beaute and Vong, 2010). Having reviewed publicly available literature on the economic burden of dengue, there were a relatively small number of empirical studies. While Suaya et al. covered eight countries with a common method, many of the other existing studies were not standardized in terms of their methodologies, with varying assumptions making them difficult to compare (Stahl et al., 2013, Vieira Machado et al., 2014, Suaya et al., 2009).

Given that there continues to be a lack of economic assessment of dengue, evidence on the economic burden of dengue fever is urgently needed to guide decision-makers on the expected returns on their investments and to set health policy priorities (Stahl et al., 2013).

The Dengue Vaccine Initiative (DVI) has conducted extensive multidisciplinary dengue-fever studies for decision-makers in three countries: Vietnam, Thailand, and Colombia (Lim et al., 2016). The rationale for these studies is to contribute data to inform policymakers about the economic burden of dengue fever and to assess the economic efficiency of vaccine introduction strategies.

In Vietnam, dengue is highly prevalent, and the incidence rate is reported to be 145/100,000 population according to the national surveillance system data from 2010 (World Health Organization, Lee et al., 2015). All four dengue serotypes circulate (Tien et al., 2010). Vietnam seems to follow similar trends to Thailand where dengue epidemiology has been studied extensively. Despite mosquito control efforts, dengue fever/dengue hemorrhagic fever (DF/DHF) has steadily increased in both incidence and range of distribution in Thailand, and the incidence rate in 2010 was reported to be 177/100,000 population (Lee et al., 2015, World Health Organization, 2012). Dengue has now spread to all provinces, districts, sub-districts and communities, and is seen every year (Burke et al., 1988).

Meanwhile dengue has been prevalent for the past 20 years in Colombia. In 2010, Colombia experienced a nationwide epidemic with a dengue incidence rate of 685/100,000 population (Zeng et al., 2018, Lee et al., 2015). Further, outbreaks have been observed in many parts of the country since 2011. Dengue epidemiology in Colombia is characterized by the circulation of all four dengue serotypes. The country has a well-established national dengue surveillance system.

A recombinant tetravalent vaccine candidate (CYD-TDV) has completed Phase 3 clinical

trials in Southeast Asia and South America, and has been already licensed in some dengue-endemic countries. Understanding the benefits of vaccination is necessary in order to facilitate accelerated development and introduction of safe and effective dengue vaccines into public-sector programs of dengue-endemic countries.

These three endemic countries will soon face decisions on whether, and how, to incorporate current and future vaccine candidates within their highly budget-constrained national vaccination programs (Lee et al., 2015). As population-wide vaccination campaigns must be carefully determined considering the allocation of scarce resources among competing health problems (Carrasco et al., 2011), the updated economic burden estimates of dengue from this study can be used to develop cost-effective vaccination strategies and sustainable financing plans for dengue vaccine introduction in Vietnam, Thailand, and Colombia. Furthermore, taking advantage of the standardized study design in a multi-country setting, this study attempts to explore and understand socio-economic factors affecting the level of disease severity that results in different levels of economic burden.

2.3 Methods

2.3.1 Study design

Table 1 summarizes the study areas for three countries. The economic burden survey was conducted in locations where DVI's epidemiologic studies were being carried out at the same time. The health facilities were chosen because they were main hospitals and centers

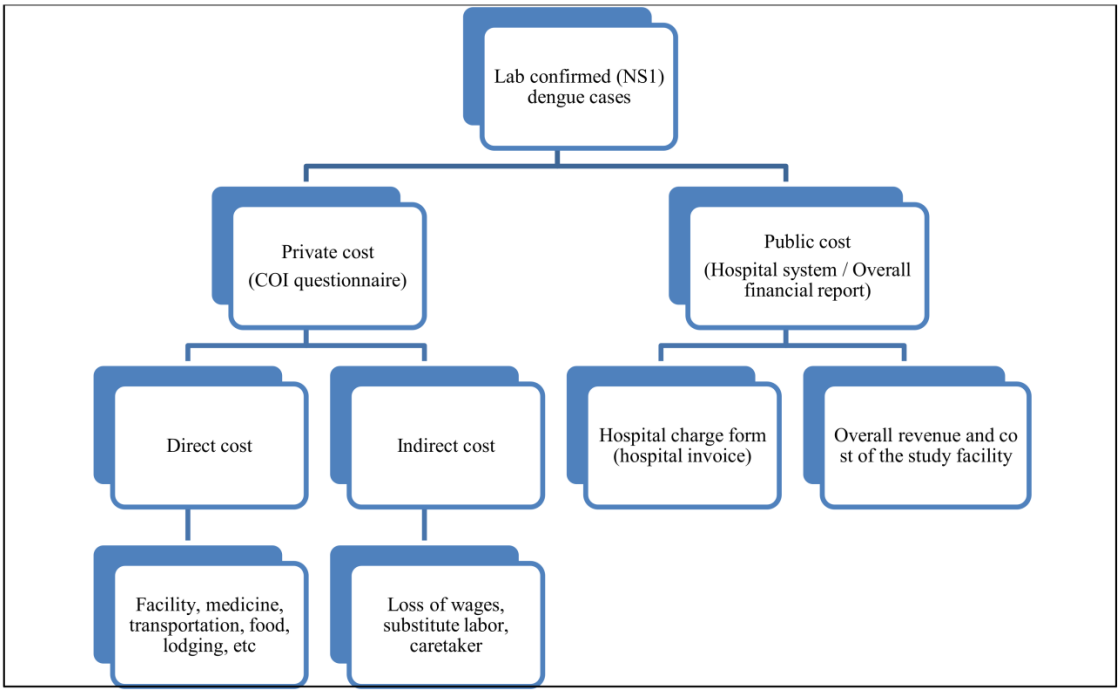
providing care for the defined catchment area population. In Vietnam, Khanh Hoa General Hospital is a tertiary care facility with 1,000 beds and the largest hospital in the province. The hospital is staffed with 195 doctors, 59 assistant doctors, 5 pharmacists, and 336 nurses. Bang Phae Community Hospital (BPCH) is a primary healthcare provider in Bang Phae district in Thailand. The facility is a 48-bed medium-sized tertiary care facility which conducts up to 400 outpatient consultations per day. Two health facilities were chosen in Colombia. Clinic of Piedecuesta is a secondary and tertiary care facility with a total of 42 beds. The clinic has 19 general practitioners, 36 specialists and assistants, and 39 nurses. Hospital de Piedecuesta is a 27-bed medium sized primary care facility that conducts up to 76.9% of its consultations for outpatients, with the rest being for the emergency service. Among patients who came to one of the study facilities listed in Table 1, febrile patients experiencing fever for less than 7 days were recruited for rapid tests. The economic burden survey was administered for those who were positive on the test result and who consented to participate in the survey. There were three sections in the cost-of-illness (COI) survey: day 1, day 10~14, and day 28. As part of the study procedure, the febrile patients were tested on the first day of their clinic visit, and COI surveys were administered to patients throughout the duration of their illness. On day 1, dengue-confirmed patients were asked whether they had visited any health facilities prior to the current visit (visit 1). If they had made any visits, interviewers asked how much money they had paid for direct medical and direct non-medical costs such as facility fees, medications, food, lodgings, and transportation, etc. Patients were reminded to come back to the hospital in 10 to 14 days, and, so as to prevent recall bias, they were provided with a diary card to record costs for further treatments, and other indirect cost information, such as substitute labor or

caregivers. On the second visit (day 10 to 14), direct medical and non-medical costs spent during the first visit and any additional visits before the second interview were collected. In addition, patients were asked if any indirect costs had occurred such as wage loss, costs for substitute labor and/or caregivers. Once direct and indirect cost information was obtained, interviewers asked patients about socio-economic questions such as patients' household income, education, general perceptions towards dengue fever, and routine vector control activities, etc. If there were any patients who were still feeling sick at the end of their second visit, a third interview was scheduled for day 28. The third questionnaire covered the period between day 10-14 and day 28. The day 28 survey could be conducted via telephone rather than in-person if necessary. The project-related tests were omitted from the analyses, as these may not have been incurred under routine clinical practice.

Table 1. Study areas

Country	Province	City (or district)	Study period	Health facility for study
Vietnam	Khanh Hoa	Nha Trang	Oct, 2011 - Oct, 2012	Khanh Hoa General Hospital
Thailand	Ratchaburi	Bang Phae	Oct, 2011 - Dec, 2016	Bang Phae Community Hospital
Colombia	Santander	Piedecuesta	Aug, 2014 - Jul, 2015	Hospital de Piedecuesta, Clinica Piedecuesta

Fig 1. Overall study design



2.3.2 Direct cost

Direct cost can be divided into two categories: (1) direct medical costs; and (2) direct non-medical costs. Direct medical costs include consultation, medication, and laboratory test costs. Patients' out-of-pocket costs for these categories were first assessed through a questionnaire. Respondents were asked whether total treatment cost was covered by the patient (or his/her family members), insurance (private, public), or both. Because payments made by patients may not always cover the entire costs of medical treatments, hospital bill records for patients who were enrolled in the study were accessed to identify treatment costs that were not captured by patients' out-of-pocket costs. In Colombia and Thailand, the hospital records were computerized and showed different sources of payments such as

from private / public insurance, etc. However, no such system was available in Vietnam, thus medical service utilization forms, which recorded the type of services provided and hospital charges for each service, were employed for enrolled dengue fever patients in Vietnam. The data from the private surveys was then linked to the treatment records of patients (hospital charges) to better understand the full spectrum of the costs of dengue and how the economic burden is distributed among the public and private sectors.

Ratio of cost-to-charge. While some studies report patients' out-of-pocket costs – which are part or all of hospital charges – as direct medical costs of dengue fever (Anderson et al., 2007, Huy et al., 2009), adjusting hospital charges by the cost-to-charge ratio is another way to understand the overall societal cost of a disease. The cost-to-charge ratio is estimated by dividing the total annual hospital costs by the total annual revenue of the hospital (Anh et al., 2010). The rationale behind the use of the cost-to-charge ratio is that in many circumstances, for various reasons, costs may not be the same as charges (Finkler, 1982). Charges can be higher than costs because charges may include a component to cover replacement and expansion of facilities or the need to cover losses from those who cannot afford services. In some contexts, hospital charges are lower than costs because health facilities are subsidized by governments or non-governmental organizations (NGOs) in rural areas of less-developed countries where not many people can afford health services. While the overall societal cost of a disease can be estimated by multiplying hospital charges by the cost-to-charge ratio, the direct economic impact on patients to be treated for that disease can be better assessed by the overall hospital charge information (Finkler, 1982). In this study, the ratios of cost-to-charge (RCC) were separately estimated for all three sites. In Vietnam and Thailand, one of the study team members was assigned to

access the financial information of the study facilities. One of the study facilities in Colombia produces a comprehensive financial report every year which consists of hospital revenue from various sources and all costs including staff salary and capital assets, etc. However, such information was not obtained for the other health facility in Colombia due to logistical issues. While the financial structure of health facilities could vary, the study team ensured it included the following components: (1) the costs covered labor (i.e. staff salary, welfare), material and capital costs occurring from all sources. Capital costs include equipment, vehicle, building, and all other construction after taking into account depreciation. (2) the charges included hospital revenue from all services provided and external funding. Both overall charges and societal costs are presented.

Direct non-medical cost covers the expenses related to transportation, food, and lodgings incurred by a patient when seeking treatment, as well as by individuals accompanying a patient. The respondents were asked to provide direct medical and non-medical cost information for all visits that a patient made during their illness.

2.3.3 Indirect cost

Indirect cost consists of three components: patient wage loss due to illness; substitute labor cost; and caregiver's cost.

Patient productivity loss. A patient or his/her guardian was asked what the patient would have been doing if the patient had not been sick and how much the patient normally gets paid for one day's work if the patient earns wages. These questions were followed by determining the total number of days the patient lost wages due to illness. For patients who make any income, their productivity loss was calculated by multiplying the self-reported

daily wage by the total number of wage-loss days. In addition, a series of questions was asked to determine the number of days that the patient was completely unable to perform, partially unable to perform, and completely able to perform his/her usual activities. For those who do not earn any income, a full-day loss was considered for the days that they were completely unable to perform, and a half-day loss was assigned for the days that they were partially unable to perform their usual activities. In order to estimate a student's loss in monetary value, the number of the student-loss days was multiplied by the government expenditure per primary student expressed in USD (Statistics, 2015). The government expenditure per primary student includes general government expenditure such as current, capital, and transfers for a given level of education. While this indicator is useful for comparing average spending on one student between countries, the estimates would be conservative because the indicator does not reflect total spending per student, including household contributions. For patients who normally perform housework and did not earn any wage, their productivity loss was converted into monetary value using the minimum wage for that country (VND 87,500 per day in Vietnam, THB 300 per day in Thailand, and COP 25,667 per day in Colombia) (Briefing, 2013, Economics, 2015, Wageindicator.org, 2015).

Substitute labor costs. Some patients need to hire substitute labor in order to carry out his/her work as the patient is unable to perform usual activities due to illness. Substitute labor might be a member of the household or someone who is hired externally. After identifying the number of substitute laborers and the relationship of the substitute laborer to the patient, respondents were asked whether they were paid or not. If paid, the daily payment for hiring a substitute laborer was recorded. Opportunity costs were also assessed.

The opportunity cost of a choice is the loss of potential gain from other alternatives by choosing that specific activity. The number of days that a substitute laborer had to cut back on his/her usual activity was collected and multiplied by a daily payment for substitute laborer's original activity to calculate the total opportunity cost. If the substitute laborer was compensated in lieu of his/her usual activities, only the amount of money that was paid for the entire duration of the service was counted. If the substitute laborer was not paid for doing the patient's work and had to cut back on his/her usual activity, then the opportunity cost was added to the substitute labor cost. Care should be taken when considering patient wage loss and substitute labor costs because one may think that a patient's work-day loss would be compensated by substitute labor. However, the way that the questionnaire was designed was such that respondents were first asked whether patients lost any wages due to illness and then they were asked questions about the substitute labor cost section. In other words, patients who did not lose any wages by hiring substitute laborer(s) would not report any wage loss in the first part. If patients reported some wage loss even if they had a substitute laborer, this should be interpreted as wage loss that the substitute laborer was not able to cover.

Caregiver's costs. Some patients need to have a caregiver while they convalesce during a severe illness period. Opportunity cost plays an important role here because most caregivers tend to be family members who do not get paid for taking care of the patient but may need to cut back on their usual activities. For these patients, the same types of questions for substitute labor were asked, and total costs for caregivers were derived in the similar way taking into account the opportunity costs.

The total indirect costs were estimated by summing all three components: patient wage

loss; substitute labor costs; and caregivers' costs. All local currency units were converted using the official exchange rate from World Bank and expressed in 2014 USD, and the cost outcomes were also expressed in purchasing power parity (PPP) rates in the supplementary section. The official exchange rate is the rate determined in the legally sanctioned exchange market, and the PPP exchange rate reflects that the currency of one country would be converted into another currency to buy the same amount of goods and services. The PPP rates would be useful for the international comparison of non-tradable goods. Confidence intervals were estimated using the bootstrap approach, a common non-parametric technique which deals with skewed cost data (Chaudhary and Stearns, 1996, Gray et al., 2010, Nixon et al., 2010). Bootstrapping treats the observed sample as an empirical distribution, and draws a sample repeatedly with replacement (STATA, 2013)(STATA, 2013). From these data, the standard error (SE) can be calculated as follows:

$$\widehat{se} = \left\{\frac{1}{k-1}\sum(\hat{y} - \bar{y})^2\right\}^{\frac{1}{2}}$$

where $\hat{y}$ is the statistic for the ith bootstrap sample, $\bar{y}$ is the value of the statistic calculated using the original observations, and k is the number of replications (STATA, 2013)(STATA, 2013). The percentile method (2.5^{th} and 97.5^{th} percentiles of the distribution) was used to produce a 95% confidence interval (STATA, 2013, Gray et al., 2010).

2.3.4 Disease severity

While dengue infection usually causes flu-like illness with mild symptoms, the infection occasionally develops into a potentially lethal complication called severe dengue (WHO, 2016). Severe dengue has become a leading cause of hospitalization and death in some Asian and Latin American countries.

The DVI's cost-of-illness (COI) surveys include questions not only on direct and indirect cost information of dengue fever, but also on general socio-economic information such as education, routine vector control activities, and general perceptions towards dengue fever. Questions were identically administered at all three sites, and these variables can be compared by disease severity. In this study, severe illness was defined if a patient was either hospitalized or confirmed as having dengue hemorrhagic fever (DHF) based on clinical symptoms. Whether a patient goes through severe illness or not is a dichotomy, and a dichotomous dependent variable can be considered as a function of healthcare-seeking behavior, education, and household perceptions on dengue fever and likelihood, etc. A logit model is suitable for this analysis because such models handle categorical dependent variables using maximum likelihood estimation. The binomial logistic regression estimates the log odds that individuals will be in each of two categories of a dichotomous dependent variable.

$$\ln\left(\frac{\pi}{1-\pi}\right) = \sum_{k=0}^{K} x_k \beta_k$$

where K is the number of independent variables, x_{ik}, β are the coefficients, and the dependent variable is the log of the expected probabilities of being in each of the two categories, conditional on the values of the independent variables. Given that the surveys were standardized across the three sites, all samples were combined to achieve a larger sample size for robust model outcomes.

2.3.5 Ethics Statement

The cost-of-illness survey questionnaires were approved by the ethical review committees in three countries (National Institute of Hygiene and Epidemiology in Vietnam, Faculty of Tropical Medicine, Mahidol University in Thailand, Universidad de Santander in Colombia), as well as Ministry of Health in three countries and Institutional Review Board of the International Vaccine Institute. Written informed consent was obtained prior to conducting interviews, and respondents were informed that they could terminate interviews at any time. If any study participants were minors, their parents or guardians provided consent on behalf of all child participants under the age of 18 years old.

2.4 Results

Table 2 shows patient characteristics for each study site by patient type (see S1 Table for additional information). The average number of total sick days ranges from 7 to 10 for inpatients and 6 to 9 for outpatients. While a majority of the patients sought treatment prior to the study enrollment in Vietnam, less than half of the patients did so in Thailand and Colombia. More patients tended to have caregivers than substitute labor in all three

countries. In Vietnam, more than 80% of the patients responded that they had caregivers. On average, patients older than 5 years were not completely able to perform their usual activities for 5 to 7 days as inpatients, and 3 to 5 days as outpatients. The average age of the patients was 20 - 23 years in Vietnam and Colombia, and 15 years in Thailand. The self-reported mean household income per month was $423, $548, and $665 in Vietnam, Thailand, and Colombia, respectively.

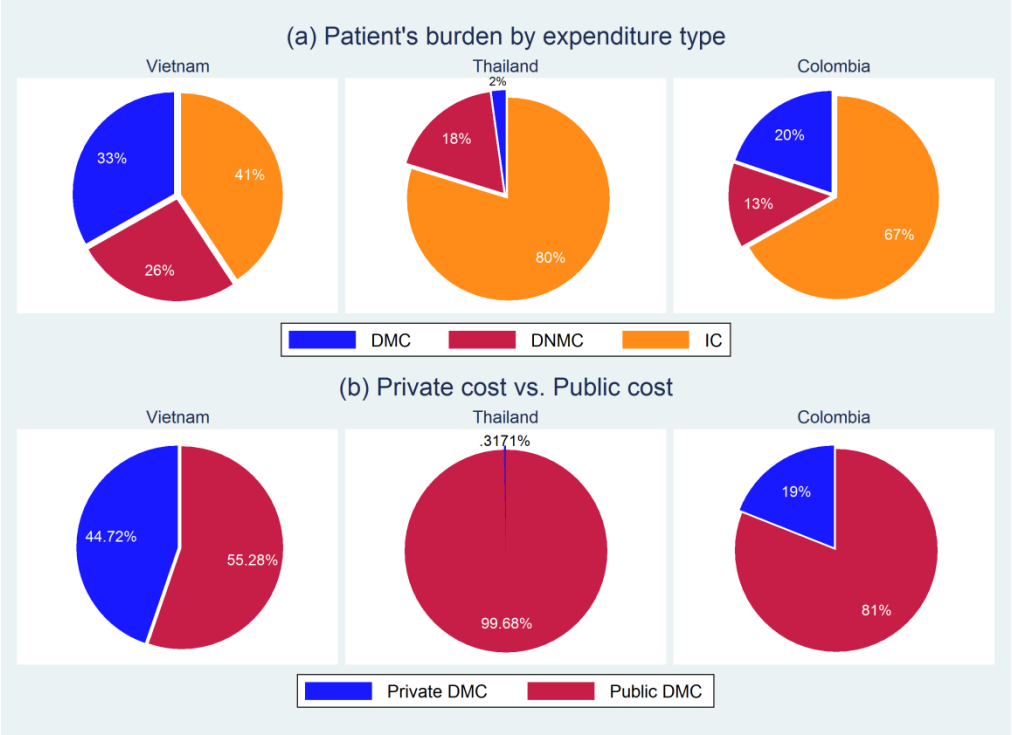
Table 2. Descriptive statistics

	Vietnam (SD)		Thailand (SD)		Colombia (SD)	
	Inpatient	**Outpatient**	**Inpatient**	**Outpatient**	**Inpatient**	**Outpatient**
N	59	92	45	40	70	160
Sick days prior to enrollment	3.7 (1.8)	2.8 (1.4)	2.7 (1.3)	2.2 (1.2)	5.1 (1.5)	4.3 (1.6)
Total sick days	7.4 (2.9)	6.2 (1.7)	7.8 (2.1)	6.1 (1.4)	10.4 (2.9)	8.7 (2.4)
% seeking treatment prior to enrollment	96.6% (0.2)	95.7% (0.2)	17.8% (0.4)	20.0% (0.4)	32.9% (0.5)	43.1% (0.5)
% patients with substitute labor	50% (0.5)	11.1% (0.3)	0.0% (0.0)	0.0% (0.0)	7.0% (0.3)	17.8% (0.4)
% patients with caregivers	98.3% (0.1)	85.9% (0.4)	46.7% (0.5)	12.5% (0.3)	40.0% (0.5)	48.8% (0.5)
No. of full days lost due to illness	6.7 (2.9)	5.4 (2.0)	4.7 (2.6)	2.5 (2.1)	5.8 (2.2)	4.7 (2.0)
No. of partial days lost due to illness	0.4 (1.1)	0.7 (1.6)	2.8 (1.7)	3.0 (2.0)	3.1 (1.5)	2.8 (1.9)
Average patient age (years)	21.5 (12.8)	20.2 (9.3)	16.3 (9.3)	14.6 (9.7)	23.2 (12.7)	20.6 (13.1)
Average monthly household income	$453 (304.2)	$404 (315.9)	$470 (227.1)	$635 (373.6)	$618 (456.1)	$686 (385.7)

Fig 2 summarizes the proportions of patient burden by expenditure, as well as the percentage share of patient's out-of-pocket (OOP) costs versus non-OOP costs, such as government subsidy or payments from other insurance schemes. For all three countries, indirect cost accounts for the highest proportion of patient's OOP among the three

expenditure types in Fig 2(a): direct medical cost (DMC), direct non-medical cost (DNMC), and indirect cost (IC). While DMC is the second highest burden for patients in Vietnam and Colombia, DMC is only 2% in Thailand. This is mainly because people in Thailand are covered by its universal healthcare system so patients do not have to pay for most of the OOP costs related to direct medical services. This is more apparent in Fig 2(b). About 99% of DMC are covered by the public sector, which is the universal healthcare system in Thailand. The proportion of the non-OOP costs is also high in Colombia, at 81%. In Vietnam, public DMC coverage is less than that of the other two countries, meaning that more patients tend to pay directly for the medical services that they receive.

Fig 2. The percentage share of the economic burden for dengue fever[a]



[a] DMC – Direct Medical Costs; DNMC – Direct Non-Medical Cost; IC – Indirect Cost

The economic burden of dengue fever is shown in Table 3. DMC is highest among the three expenditure types, after taking into account both private and public spending. Total cost per inpatient episode is $200, $141, and $385 in Vietnam, Thailand, and Colombia, respectively. In the case of outpatients, total cost per episode ranges from $40 to $158, with Colombia having the highest and Thailand having the lowest. It is interesting to see that IC and DNMC are higher in Vietnam than in Thailand despite the higher average income in Thailand. This is because there was no reported substitute laborer cost in Thailand, and the duration of caregiver's work was shorter in Thailand than in Vietnam. In addition, while the meal service was included for inpatients in the hospital charge in the

health facility of Thailand, all patients had to pay extra for food in Vietnam. Considering the mean duration of the disease, total cost per day was calculated. It appeared that Colombia had again the highest cost per day, followed by Vietnam and Thailand. The societal total costs were also estimated after adjusting for the ratio of cost-to-charge (RCC). While the total cost per episode went up after the adjustment in Vietnam and Thailand, it went down in Colombia. By age group, the total cost per episode is higher for the older age group than the younger age group in Thailand and Colombia, but this is the opposite in Vietnam as shown in Fig 3. This is mainly due to the high number of inpatients than outpatients in the younger age group in Vietnam. The economic burden was further disaggregated by age group, patient type, and cost type in Table 4.

The economic burden of dengue fever would have varying impacts on household equity. For those who reported their monthly income, three income groups were first generated based on percentiles of monthly income: low-income group (income≤25%), middle-income group (25%<income≤75%), and high-income group (income>75%). The list of household assets in the survey was designed to include various items from essentials to luxury goods reflecting the local context of each country. Given this, the level of the household assets in each income group was identified, and the respondents who did not report their monthly income were categorized into the three income groups based upon their levels of household assets. The mean income value of the group to which these households belonged was assigned. The total OOP for the economic burden of dengue fever was then estimated as a proportion of the self-reported household monthly income by income group. As shown in Fig 4, the percentage of the economic burden of dengue for the low-income group was 36%, 17%, and 45% in Vietnam, Thailand, and Colombia,

respectively. The percentage of the economic burden of dengue fever decreased moving towards the higher income groups. Due to the universal healthcare system, the percentage of the DMC burden was less than 1% for all three income groups in Thailand, which reduces the overall OOP burden for patients.

Table 3. Average economic burden of dengue fever per episode[a]

	Vietnam[b]						Thailand						Colombia					
	Inpatient (n = 59)			Outpatient (n = 92)			Inpatient (n = 45)			Outpatient (n = 40)			Inpatient (n = 70)			Outpatient (n = 160)		
	USD[c]	BT CI[c] (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)	
Direct Medical Cost (DMC)	$83	$62	$108	$26	$22	$30	$81	$67	$95	$7	$6	$8	$245	$199	$297	$33	$30	$36
Direct Non-Medical Cost (DNMC)	$51	$44	$58	$9	$7	$13	$13	$7	$21	$5	$4	$6	$27	$20	$34	$17	$15	$21
Indirect Cost (IC)[d]	$67	$48	$89	$27	$20	$36	$47	$36	$59	$28	$23	$33	$113	$85	$144	$107	$76	$145
Total Cost	$200	$165	$239	$62	$52	$74	$141	$119	$164	$40	$34	$45	$385	$331	$443	$158	$124	$197
Total Cost per Day	$29	$24	$34	$10	$8	$12	$19	$16	$22	$7	$6	$7	$38	$32	$44	$18	$14	$22
Total Cost (RCC adjustment)	$213	$175	$256	$64	$54	$76	$181	$153	$210	$43	$37	$48	$278	$239	$318	$144	$111	$183

[a] All local currency values were converted using the official exchange rates from World Bank. See S2 Table for values converted using the Purchasing Power Parity (PPP) conversion factor

[b] Because data collection was done in 2012 in Vietnam, the estimates were inflated to 2014 USD.

[c] Bootstrapping with the percentile method.

[d] See S3 Table for further break-down of indirect cost

Table 4. Disaggregated average economic burden of dengue fever per episode[a]

	Vietnam						Thailand						Colombia					
	Inpatient			Outpatient			Inpatient			Outpatient			Inpatient			Outpatient		
	USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)	
Direct Medical Cost (DMC), age < 15	$106	$61	$170	$24	$17	$31	$73	$53	$93	$6	$5	$8	$212	$149	$283	$31	$26	$36
Direct Medical Cost (DMC), age ≥ 15	$72	$52	$97	$27	$22	$32	$89	$70	$106	$8	$6	$11	$262	$201	$331	$35	$30	$40
Direct Non-Medical Cost (DNMC), age < 15	$55	$45	$66	$14	$7	$22	$8	$5	$11	$5	$4	$6	$33	$21	$49	$16	$12	$21
Direct Non-Medical Cost (DNMC), age ≥ 15	$49	$40	$58	$8	$5	$11	$17	$7	$33	$5	$3	$7	$23	$16	$33	$18	$15	$23
Indirect Cost (IC), age < 15	$75	$47	$111	$30	$20	$40	$52	$35	$72	$32	$26	$37	$59	$28	$98	$87	$40	$156
Indirect Cost (IC), age ≥ 15	$63	$40	$91	$26	$17	$38	$43	$29	$58	$20	$10	$29	$140	$103	$181	$121	$84	$165

[a] All local currency values were converted using the official exchange rates from World Bank. See S2 Table for values converted using the Purchasing Power Parity (PPP) conversion factor

Fig 3. Total cost per patient by age group

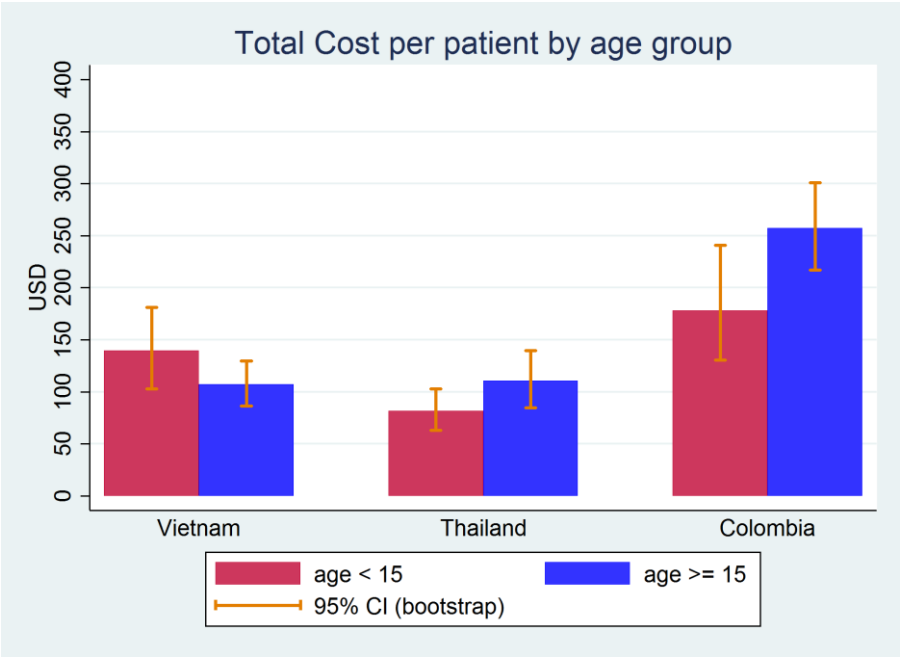


Fig 4. Proportion of the economic burden (OOP costs) by income group

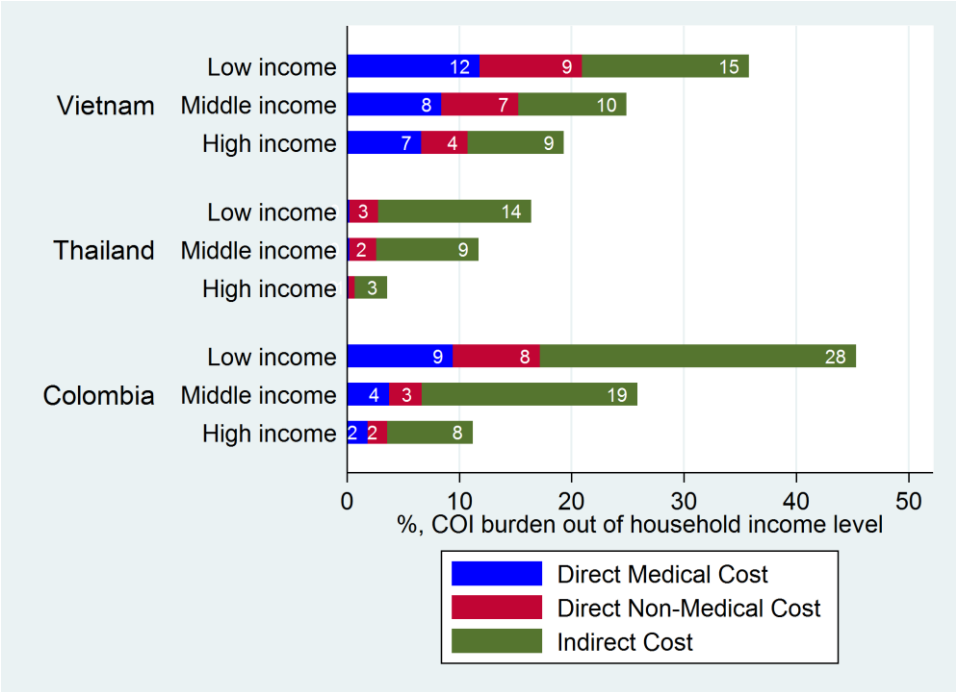


Table 5 shows the regression outputs. While the type 1 model is parsimonious and only includes the variables related to the current illness, the type 2 model was run with all possible covariates including socio-economic variables. As expected, the number of sick days before and after the study enrollment was highly significant and positively related to severe illness. The seeking-early-treatment variable is also statistically significant at the 1% level and decreased the odds of experiencing severe illness for both models. This indicates that patients who sought treatment at the early stage of illness would be less likely to develop severe illness later on. While patients with severe illness tended to have more substitute labor or caregiver(s) than patients with non-severe illness, this variable is marginally significant in type 2. Compared with patients with no education, patients with some or higher education were less likely to have severe illness for the current episode. Age, household income levels, and vector control activities were not statistically significant. In addition, the dengue perception score was developed based upon respondents' general knowledge of dengue fever, and was categorized into three levels with the lowest score indicating the poor level of knowledge on dengue fever. Having less awareness or lacking general knowledge of dengue fever was positively associated with experiencing severe illness. It was also shown that patients were less likely to develop less severe illness when there were more household members who had been previously infected and recovered. Overall, the type 2 model was preferred over the type 1 model based on the difference of the Akiake Information Criterion (AIC) values (Hilbe, 2011). It should be noted that some of the milder cases may never receive medical attention, and this may be related to income and education levels. While this would be difficult to be

statistically tested in this study given the absence of healthcare-seeking behavior indicators outside the study facilities, the distributions of non-severe and severe patients appear to be similar over income and education levels, holding other factors constant (see S4 Figure). This partly indicates that there was no serious selection bias in the dataset.

Table 5. Socio-economic factors influencing disease severity (regression outputs)

Independent variable[b]	Type 1			Type 2		
	Coeff (in OR[a])	(SE)		Coeff (in OR)	(SE)	
Age (year)	1.00	(0.01)		1.01	(0.01)	
Sick days before the study enrollment	1.26	(0.08)	***	1.35	(0.09)	***
Sick days after the study enrollment	1.21	(0.05)	***	1.20	(0.05)	***
Seeking early treatment	0.55	(0.12)	***	0.44	(0.1)	***
Substitute labor/caregiver	1.34	(0.29)		1.59	(0.37)	**
Education 2 (some education)				0.35	(0.17)	**
Education 3 (university / post graduate)				0.29	(0.15)	**
Income level (middle)				0.80	(0.19)	
Income level (high)				0.96	(0.29)	
Dengue perception (poor)				1.96	(0.75)	*
Dengue perception (medium)				2.18	(0.55)	***
Previous infections within household				0.48	(0.12)	***
Vector control activity				0.93	(0.2)	
Constant	0.10	(0.04)	***	0.16	(0.1)	***
N	466.00			466.00		
Log likelihood	-290.57			-277.80		
AIC	593.13			583.59		

[a] Odds ratio

[b] Reference categories of the categorical variables: Education 1 (no education), Income level (high), Dengue perception (high)

* Significance at the 10% level, ** at the 5% level, *** at the 1% level

2.5 Discussion

Estimates of the economic burden of dengue fever may vary depending upon a country's healthcare system and the different methodologies applied. While there were existing economic burden studies, the advantages of the current study are that it relies on the implementation of a standardized survey tool and the inclusion of various expenditure types and age groups in multiple countries. This makes it possible to make a more complete comparison across the three dengue-endemic countries. Using the standardized methodology, this study found that the total cost per dengue episode is $200, $141, $385 for inpatients and $62, $40, $158 for outpatients in Vietnam, Thailand, and Colombia, respectively. Among the various OOP expenditure components, indirect cost was the biggest private burden for patients in all three countries. Non-OOP payments, such as from insurance or nationwide healthcare system, reduce patients' burden of DMC. The patients' share of burden of DMC was the least in Thailand, followed by Colombia and Vietnam. In all three countries, the percentage of the private economic burden of dengue fever was highest in the low-income group and lowest in the high-income group.

Though many previous studies were not based on standardized methodologies, making them difficult to compare (Stahl et al., 2013, Vieira Machado et al., 2014), some existing studies that did not use secondary data sources or extrapolation were compared with the current study outcomes (see S5 Table for summary). Tam et al. reported $167.8 per DHF inpatient episode in 2006 in Vietnam (Tam et al., 2012). Once the estimate was inflated to 2014 USD using consumer price index, this value was higher than our estimate. However, it should be noted that this previous study only looked at DHF inpatients who were supposed to experience more severe illness. Another study by Harving et al. showed the

average total cost of $61.4 per DHF inpatient younger than 15 years in 2005 (Harving and Ronsholt, 2007). Our estimate per inpatient episode for the same age group is $125.2, which is less than Harving et al.'s estimate after inflation adjustment ($147.1), but again Harving et al. also looked only at DHF inpatients. In Thailand, while Anderson et al. and Clark et al. reported the average total cost of $31.8 to $44 per inpatient and $10.2 per outpatient (Anderson et al., 2007, Clark et al., 2005), Okanurak et al. estimated the total cost per inpatient as $172.9 and $141.5 from two different sites in Thailand (Okanurak et al., 1997). The estimates from Anderson et al. and Clark et al. were lower than our study estimates even after inflation adjustment. One of the main reasons is that the former two studies focused on patients' OOP costs, whereas our study took into account both patients' OOP payments and public payments, which would make for a large difference especially in the context of Thailand. On the other hand, Okanurak et al. looked at DHF patients, resulting in higher costs than our study estimates. Suaya et al. also estimated dengue cost of illness in Thailand and reported $573 for inpatients, which is a lot higher than the other study estimates including ours (Suaya et al., 2009). Rodriguez et al. estimated a total cost of $497.9 per inpatient and $202.3 per outpatient in Colombia. There are similarities between this previous study and our study in terms of the cost items considered and the sub-component estimates. They reported higher indirect cost estimates, making the overall costs higher than our estimates. This could be partly because the previous study included projected lost income due to death, whereas the current study did not have any deaths occurred during the study period.

In addition to the estimation of the economic burden of dengue fever, the logit model was constructed to identify factors explaining variance of disease severity. The logit analyses

showed that early treatment, higher education, and better knowledge of dengue disease would be associated with a reduction of the probability of developing more severe illness. This can be partly explained by the fact that secondary dengue infection which would likely cause more severe illness would be inversely correlated with the independent variables. As the disease ranges from flu-like mild symptoms (dengue) to potentially lethal complications (severe dengue), resulting in different levels of economic burden, a community would be better off expanding the factors identified in this study, which may prevent its members from developing severe illness in the long run.

Some areas of uncertainty deserve attention. While the study captured all patients' OOP costs spent during the entire period of illness by conducting multiple interviews, public DMC payments and RCCs were limited to our study's health facilities. Because a majority of the costs were incurred during the enrollment visit at the study's facilities rather than at referral facilities or pharmacies across the study sites, the estimates would not be greatly influenced. However, our estimates are conservative. In Colombia, where two health facilities were involved, the RCC was only obtained from one of the facilities due to logistical issues. Because these study facilities were in the same district, a single RCC was used for all patients. While various cost and charge items were taken into account for the estimation of the RCC, the detailed list of financial information was confidential for some of the health facilities, limiting the way that the estimates were presented. Ideally, our study samples should be more heterogeneous and representative of the entire countries. Given that this study was carried out in locations where epidemiologic studies were being conducted at the same time, care must be taken when generalizing the estimates beyond the study's communities. Nonetheless, hospital charges may vary in different locations of a

country, but within the same country the unit prices for service items may not be as variable as the charges. Assuming the duration of illness is similar within a country, factors which may influence the total cost adjusted by the ratio of cost-to-charge in the same country are patient's out-of-pocket expenditures for direct non-medical costs and indirect costs. Because these are directly related to the income level in a community, it would be possible to understand the representativeness of our estimates by comparing the average income of the study communities with Gross National Income (GNI) per capita. The study refusal rates among eligible patients were 2.3% and 1.4% in Thailand and Colombia respectively. Due to logistical issues, the refusal rate could not be estimated in Vietnam. While there were no patients who felt sick after the 2nd interview of the current study, Tiga et al. reported that some dengue patients experience persistent symptoms such as asthenia, fatigue, and trouble working (Tiga et al., 2016). It should be noted that there may be patients who do not generally come to the professional health sector such as our study facilities (Shepard et al., 2016). While the current study captured any non-medical sector visits such as traditional healers or others before and after the study enrollment, there may have been non-enrolled dengue patients who did not come to any of our study facilities during the study period, and this may have been partially related to patient's education and income levels.

The burden of dengue has been rising partly due to the absence of population-wide vaccination campaigns and the limited impacts of vector control activities. A previous study assumed that vector control would not be able to achieve permanent reduction of dengue based on the experience of Singapore (Carrasco et al., 2011). The first live attenuated, tetravalent dengue vaccine (CYD-TDV) has been already licensed in some

dengue-endemic countries. To maximize the effective use of a dengue vaccine, vaccination strategies should be carefully considered after taking into account various competing health problems at the country level. Identifying effective vaccination strategies requires various sources of information such as accurate incidence rates, the long-term behavior of the vaccine (i.e., waning rates of efficacy, the rate of any adverse effects, etc.) and the price of the vaccine. Along with more details, this study's estimates of the economic burden of dengue fever can play a critical role in determining cost-effective vaccination strategies, and so facilitate the process of dengue vaccine introduction by guiding decision-makers on the expected societal health benefits through vaccination.

Chapter 3. Early Warning Signal for Dengue Outbreaks and Identification of High Risk Areas for Dengue Fever in Colombia using climate and non-climate datasets

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Author contributions:

JSL conceptualized the study, collected data, conducted the analyses, created all figures, and wrote the manuscript. MC and IYP participated in the data collection and interpretation. JKL, MH, and LV contributed to data interpretation and study design. AF contributed to data interpretation and overall inputs on the study outcomes.

3.1 Abstract

Dengue has been prevalent in Colombia with high risk of outbreaks in various locations. While the prediction of dengue epidemics will bring significant benefits to the society, accurate forecasts have been a challenge. Given competing health demands in Colombia, it is critical to consider the effective use of the limited healthcare resources by identifying high risk areas for dengue fever.

The Climate Risk Factor (CRF) index was constructed based upon temperature, precipitation, and humidity. Considering the conditions necessary for vector survival and transmission behavior, elevation and population density were taken into account. An Early Warning Signal (EWS) model was developed by estimating the elasticity of the climate risk factor function to detect dengue epidemics. The climate risk factor index was further estimated at the smaller geographical unit (5km by 5km resolution) to identify populations at high risk.

From January 2007 to December 2015, the Early Warning Signal model successfully detected 75% of the total number of outbreaks 1~5 months ahead of time, 12.5% in the same month, and missed 12.5% of all outbreaks. The climate risk factors showed that populations at high risk are concentrated in the Western part of Colombia where more suitable climate conditions for vector mosquitoes and the high population level were observed compared to the East.

This study concludes that it is possible to detect dengue outbreaks ahead of time and identify populations at high risk for various disease prevention activities based upon observed climate and non-climate information. The study outcomes can be used to

minimize potential societal losses by prioritizing limited healthcare services and resources, as well as by conducting vector control activities prior to experiencing epidemics.

3.2 Introduction

Dengue is complicated. There are four serotypes of the dengue virus, and dengue infection occurs in almost all age groups (WHO, 2015, Rodriguez-Roche and Gould, 2013). Dengue is endemic in many parts of the tropics and subtropics, and dengue endemic countries are also exposed to the risk of periodic outbreaks (Division of Vector-Borne Diseases (DVBD), 2014, WHO, 2015). In Colombia, dengue has been prevalent over the last 20 years with different degrees of incidence rates and epidemics in various geographical locations (Instituto Nacional de Salud (INS), 2014, Villar et al., 2015b). Due to the complexity of the disease, there are still large knowledge gaps regarding the causes of dengue epidemics (Murray et al., 2013, Imai et al., 2015, Barmak et al., 2011, Lowe et al., 2013). Infection with one serotype provides life-long immunity to that specific serotype. Therefore, subsequent introduction of the same serotype in a community would be less likely to cause the occurrence of a dengue epidemic if there were a small population of dengue-susceptible individuals (Imai et al., 2015, Runge-Ranzinger et al., 2008, Barmak et al., 2011). However, due to a high degree of antigenic cross-reactivity, sequential infection of two different serotypes can bring favorable or detrimental outcomes depending upon known and unknown factors including timing of infection (Bhoomiboonchoo et al., 2015, Halsey et al., 2012, Rodriguez-Roche and Gould, 2013). For example, a primary infection may help slow the spread of secondary heterologous infection when some degrees of

cross-protection are conferred (Sabin, 1952, Rodriguez-Roche and Gould, 2013, Reiner et al., 2014, Halsey et al., 2012). On the other hand, many studies have shown that subsequent heterologous infection would likely increase the probability of experiencing severe dengue fever (Halstead and Simasthien, 1970, Russell et al., 1968, Guzman et al., 2000, Graham et al., 1999). One of the known mechanisms is the antibody dependent enhancement (ADE) during the second infection mediated by non-protective heterotypic antibodies arising from the primary infection (Bhoomiboonchoo et al., 2015, Lourenco and Recker, 2013, Rodriguez-Roche and Gould, 2013, Reiner et al., 2014). In dengue endemic countries such as Colombia, the number of dengue cases is periodically reported to the upper-level health management unit (i.e. provincial or Ministry of Health) from various health facilities at the municipality level (Instituto Nacional de Salud (INS), 2014, Carabalí and Hendrickx, 2012). In the case of dengue fever, like any other diseases, severe cases are detected more easily than mild symptoms, which in turn, leads to a higher volume of reported caseload (Sarti et al.). Thus, having more severe cases is also related to the high likelihood of observing dengue epidemics when an epidemic is determined based on official statistics of reported cases.

While it is undeniable that all of these aspects would affect the occurrence of dengue epidemics directly and indirectly, it does not appear to be practical in proving the impacts of these factors on the occurrence of dengue epidemics due to the following reasons: (1) despite various efforts to disentangle the complexity of the disease (Bhoomiboonchoo et al., 2015), it is still uncertain to generalize how one serotype reacts with another in terms of cross-protection or ADE for all possible scenarios among four serotypes, as well as the duration of the interactions (Lourenço and Recker, 2016, Huang et al., 2015); (2) even if

this uncertainty is going to be uncovered in the near future, it would be very difficult to obtain the details of sero-prevalence history over a long period of time for each cohort in all specific locations. These limitations make it difficult to understand how much of each factor would contribute to the actual probability of a dengue epidemic occurrence (Imai et al., 2015, Louis et al., 2014, Lowe et al., 2013).

A more practical way is to focus on the basic principle of the occurrence of a dengue epidemic. Simply put, a dengue epidemic occurs when a large number of people become infected within a short period of time (Rodriguez-Roche and Gould, 2013, Imai et al., 2015). It requires a large number of vector mosquitoes (*Aedes aegypti*), as well as high transmission probability, and frequent contact between people and the vectors (biting rate) to sustain transmission (Division of Vector-Borne Diseases (DVBD), 2014, Imai et al., 2015, Rodriguez-Roche and Gould, 2013). In other words, a dengue epidemic would more likely occur when vector mosquitoes increase within a short time period in a location where dengue viruses are currently circulating and population density with no immunity to one of the four serotypes is high during the same period (Barmak et al., 2011, Louis et al., 2014, Lowe et al., 2013). Further, the importation of infected cases into a community where there is no immunity to that specific serotype would cause an epidemic as well.

Following this principle, the main concept of this study lies in the increase of vector mosquitoes as a primary factor of a dengue epidemic taking into account population density at different elevation levels. As a vector-borne viral disease, there is a wide range of factors that influence the spatial and temporal dynamics of mosquito populations: temperature, rainfall, and humidity, etc. (Louis et al., 2014, Hii et al., 2012, Lowe et al., 2013). There have been several efforts to understand the relationship between dengue

epidemics and climate change. Juffrie and Focks used sea surface temperature anomalies to identify the occurrence of dengue epidemics in Yogyakarta, Indonesia and Bangkok, Thailand (Juffrie and Focks, 2009). Lowe et al. developed an epidemic early warning system for Southeast Brazil using several climate and non-climate datasets (Lowe et al., 2013). More recently, Huang et al. found that El Nino-Southern Oscillation climate cycles and temperature were important factors affecting the weekly occurrence of the four dengue serotypes in Cairns, Australia (Huang et al., 2015). Adde et al. also identified summer Equatorial Pacific Ocean sea surface temperatures and Azore high sea-level pressure as significant indicators in predicting dengue epidemics in French Guiana (Adde et al., 2016). While some of the climate factors were more commonly used due to the nature of a vector-borne disease, their applications varied and were geographically focused. These findings from previous literature showed that climate factors play a significant role in the occurrence of dengue epidemics.

This study first attempts to predict a dengue epidemic by developing an Early Warning Signal (EWS) model based upon the temporal relationship between the occurrence of dengue epidemics and climate variability which affects mosquito populations in Colombia. Furthermore, using climate data and topographical information, the study identifies population at high risk for dengue fever for efficient disease prevention activities.

3.3 Methods

Dengue Incidence Proxy (DIP) was created to observe the trend of the dengue incidence in Colombia. The number of dengue fever cases and population data were obtained from

SIVIGILA and Departamento Administrativo Nacional de Estadistica (DANE) which are both official governmental programs in Colombia (Instituto Nacional de Salud (INS), 2014, Departamento Nacional de Estadistica de Colombia). Dividing the dengue fever cases reported by population can be used as a good proxy to observe the overall trend of dengue fever. SIVIGILA also provides a weekly report on epidemiological events (Boletin Epidemiologico) which discloses the proportions of municipalities that were not responsive for each department (Sivigila). Thus, the number of cases was adjusted by the proportions for underreporting by assuming that a non-responsive municipality would have the average number of cases per responsive municipality of that department: the reported cases by department was divided by the number of the responsive municipalities in that department, applied to non-responsive municipalities, and added to the reported cases by department. DIP was estimated by dividing the adjusted cases by population. While Boletin Epidemiologico was available over the study period, a more consistent pattern of the underreporting system was observed in the reports since 2011 after the large outbreak in 2010. Because a robust case reporting system is critical for determining the relationships between DIP and climate data, some departments out of 31 departments were excluded if over 20% of underreporting based on Boletin Epidemiologico occurred more than twice since 2011. An outbreak was defined as a relative term in this study. In other words, as long as an unusual peak in DIP was observed in a department, it was considered as an outbreak even if the DIP value in that department was relatively low compared to other departments where dengue is more prevalent. An unusual peak was marked by department if the slope of DIP over every six months fell into the highest 10% of the observations.

Table 1 summarized the datasets used in this study. Considering the spatial and temporal

dynamics of mosquito populations, three climate datasets and two non-climate datasets were selected as factors which can explain variation in DIP. The climate raster datasets include air temperature, precipitation, and specific humidity (PSD, Schneider, 2015, PSD). The monthly climate datasets were obtained from 2006 to 2015, and all the raster files were resampled into 0.008 by 0.008 degree resolution by taking the nearest neighbor assignments. It should be noted that the study presumed that it is critical to consider how long favorable conditions for vector mosquitoes persist (Lowe et al., 2013, Huang et al., 2015). In other words, a current epidemic is a result of the climate conditions consistently observed during the past months, rather than single temporal (monthly or daily) values at present. For example, if warm temperature and high humidity were observed only for a short time period of each year, these conditions would less likely affect the larval development or virus replication to cause an epidemic (Hii et al., 2012). Thus, after checking cross-correlograms to define a proper period, the 12-month moving average of the mean values of each climate data was estimated by department (Supplementary 1).

In addition to the climate factors, night light data and elevation raster files were included(National Geophysical Data Center, GLOBE Task Team and others (Hastings). Night lights data which is available by year was used to understand population density instead of conventional population statistics. The use of the night-lights data provides more flexibility to estimate population density at various levels of geographical units over time than the projected population data (Lee et al., 2016). Prior to applying the night-lights data, correlations between night-lights data and population data were tested to ensure that the night-lights data can be used as an appropriate proxy ($\rho = 0.94$). The most recent night-lights data was for 2013 at the time of the research. As the population level does not

change dramatically during a short period of time, the population level in 2013 was assumed to be consistent in 2014 and 2015. High population density would have two opposite effects in terms of transmission intensity depending upon the level of a reproduction number: (1) dilution of infectious individuals by having a large pool of host populations, (2) a large number of susceptible hosts to be infected, leading to the surge of infected cases. For the latter case, while transmission would be more intensive in a place where population density is high, holding other climate factors constant, it does not have to be necessarily true in areas at high elevations (Lowe et al., 2013). A previous study found that it is difficult for *Aedes aegypti* mosquitoes to survive at an elevation of 6,000 – 8,000 feet or even at lower elevations in temperate latitudes (Christophers, 1960). Because many people in Colombia live at high elevations (i.e. Bogota), the mean value of the night lights was used to estimate population density separately for people living under 1,500 meters and those living over 1,500 meters by department (Heller, 2010).

Table 1. Data description

Type	Degree resolution	Resampled resolution[a]	Temporal resolution	Period	Period (12MA)[b]
Air temperature	0.5 by 0.5	0.008 by 0.008	Monthly	Jan 2006 - Dec 2015	Jan 2007 - Dec 2015
Precipitation	1 by 1	0.008 by 0.008	Monthly	Jan 2006 - Dec 2015	Jan 2007 - Dec 2015
Specific humidity	2.5 by 2.5	0.008 by 0.008	Monthly	Jan 2006 - Dec 2015	Jan 2007 - Dec 2015
Night lights	0.008 by 0.008	0.008 by 0.008	Yearly	2006 - 2013	2007 - 2013
Elevation	0.008 by 0.008	0.008 by 0.008	NA	NA	NA

[a] Climate datasets were resampled by using the nearest option in ArcGIS

[b] 12-month moving average

The three climate datasets are partially correlated but also have their own distinctive characteristics. In order to preserve all the information contained in each of the climate datasets, the Climate Risk Factor (CRF) index was created. The advantage of using a composite index is that it prevents multicollinearity when running regressions against independent variables with some level of the correlations among the variables. The three climate variables and population density under 1,500 meters were used by department. The precipitation variable, which has a negative relationship with DIP, was reversed, so all variables go towards the same underlying concept (the increase in DIP). The variables were first standardized individually by subtracting the mean and dividing by the standard deviation. The standardized values were then averaged across the variables (Treiman, 2014, Lee et al., 2016). The final values were converted into a range from zero (low risk) to one (high risk) and multiplied by 100 for an easier interpretation. It should be noted that the temperature and specific humidity data used in this study are measures at the surface level. More precisely, air temperature is at 2 meters above the ground surface, and specific humidity is measured near surface at sea level with pressure level 1,000 millibars. Thus, it would be desirable to adjust the CRF index by the risk proportion at low and high elevation. The proportion at risk was estimated by dividing the sum of the night lights observed under 1,500 meters elevation by the sum of the total night lights in each department. The final CRF index was the product of the raw CRF index and the proportion at risk.

There were two dominant patterns observed during past dengue epidemics in Colombia: (1) rapid increase of the CRF index, (2) relatively steady increase of the CRF index at

different levels of the CRF and DIP values. In other words, the slope of the CRF index curve at various levels of the CRF index and DIP values appeared to be critical in predicting the occurrence of dengue epidemics. In order to assess this combined relationship, the elasticity of the CRF index curve was estimated. This is defined as the percentage change in DIP in response to a one percent change in the CRF index (Bratt et al., 2002, Huang and Lin, 2000). The stationarity of the dataset was tested to ensure that there were no trend and periodic seasonal effects. The augmented Dickey-Fuller (ADF) unit-root test was used to test whether the dataset is stationary by department (StataCorp, 2015, Dickey and Fuller, 1979). DIP is non-negative integer values, and count models were used to fit DIP as a function of the CRF index (Supplementary 2). The DIP dataset consists of two parts: (1) model dataset, (2) validation dataset. The model was constructed based on monthly DIP and the CRF index by department from January 2007 to December 2015. The validation dataset which was separated from the model dataset was established from January 2016 to April 2016 and used to validate the model performance. Overdispersion—where the variance is greater than the mean—was tested using the Z-score test at the 5% significant level (Piza, 2012, Gardner et al., 1995, Hilbe, 2011). In addition, the Akaike Information Criterion (AIC) fit test was used to compare the model fits between Poisson and negative binomial models. Being a non-linear model, the elasticity of the CRF function can be given as(Hilbe, 2011):

$$Elasticity = \frac{\partial E(y_i|x_i)}{\partial x_i} \cdot \frac{x}{y} = \exp(x_i'\beta_k)\beta_k \cdot \frac{x}{y}$$

where $\exp(x_i'\beta)$ is the expected DIP values, β_k is the coefficient of CRF, x is the explanatory, and y is the response.

As shown above, the main interest of the study lay in estimating elasticities, and count models were used as an intermediary step in calculating elasticities. Given the geographical variations of dengue outbreaks, it is critical to estimate the elasticities separately by department with varying coefficient values of CRF. In this context, the current model was preferred to non-linear mixed models with a fixed coefficient and random effects since the use of coefficients and the measure of marginal effects and elasticities were more straightforward, reducing any possibility of potential overspecification (i.e. multiple adjustments) (Hilbe, 2011, Atkins et al., 2013). Because the model was run separately for each department allowing variation in the CRF index by department, there is no concern about creating the effect of spatial autocorrelation. The elasticities were derived for every six months from January 2007 to December 2015. Early Warning Signal (EWS) was modeled such that dengue epidemics in Colombia can likely occur when the elasticity of the CRF index is maximized given the instantaneous slopes of DIP and the CRF index over time are positive minimizing the squared residuals.

Maximize:

$$Elasticity, E$$

Subject to:

$$(1)\ \beta_{DIP} = \frac{\sum_{i=t}^{t+5}(DIP_i - \overline{DIP})}{\sum_{i=t}^{t+5}(T_i - \bar{T})} > 0$$

and

$$(2)\ \beta_{CRF} = \frac{\sum_{i=t}^{t+5}(CRF_i - \overline{CRF})}{\sum_{i=t}^{t+5}(T_i - \bar{T})} > 0$$

where $\overline{DIP}$ *and* $\overline{CRF}$ are the means of DIP *and* CRF, T is time (month). The elasticities were then categorized into three percentiles: low level warning (0-50%), medium level warning (50-75%), and high level warning (75-100%). As expressed by Adde et al., the hit rate (HR) and false alarm rate (FAR) were defined as below(Adde et al., 2016):

$$HR\ (or\ sensitivity) = \frac{(Detections \mid Outbreak)}{(Detections + Misses \mid Outbreak)}$$

$$FAR\ (or\ 1 - specificity) = \frac{(False\ signals \mid No\ outbreak)}{(No\ signals + False\ signals \mid No\ outbreak)}$$

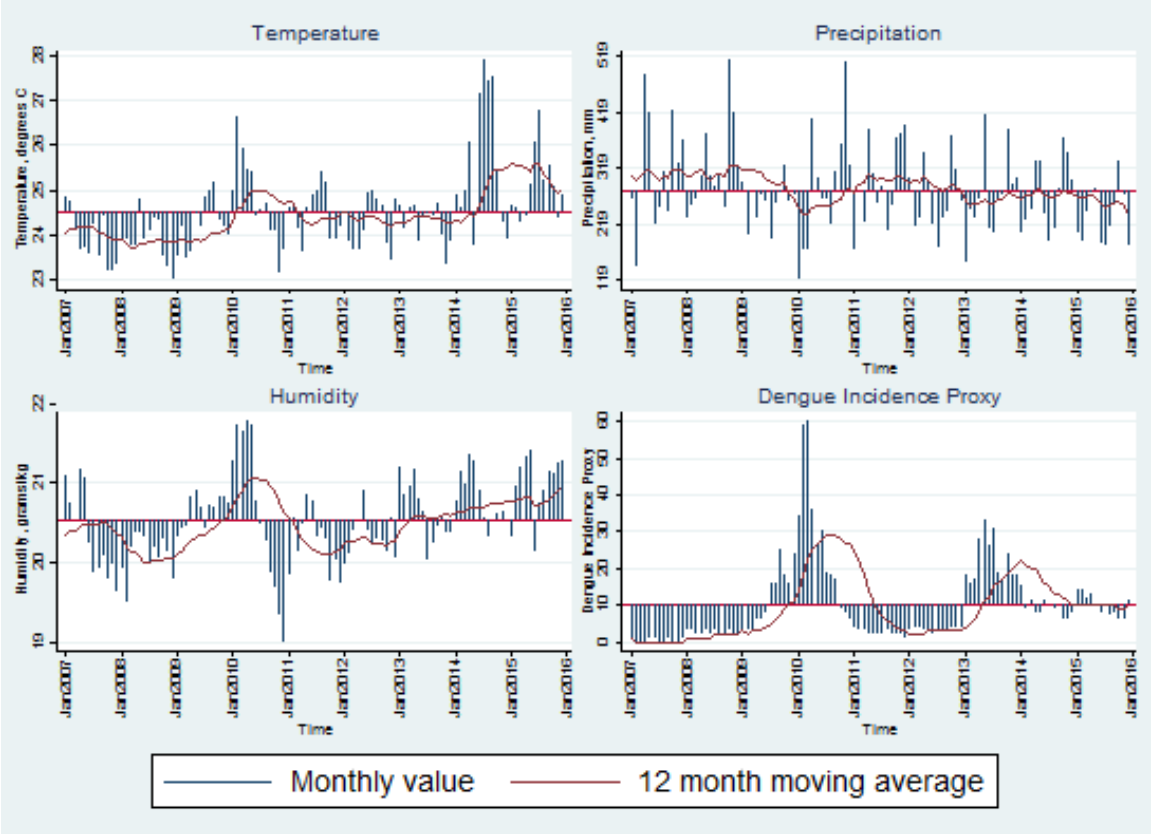
In addition, a sensitivity analysis was conducted with various moving average scenarios to make sure that the 12-month moving average is the most suitable period for the performance of the EWS model.

Given that the CRF index is statistically significant to explain variance of DIP for the departments where significant underreporting was not observed, the CRF index was further estimated at the smaller geographical level (5km by 5km resolution) for the entire country and used to identify high risk areas.

3.4 Results

During the period from January 2007 to December 2015, two major outbreaks were observed in many parts of Colombia. Figure 1 presents the overall trends of the three climate factors, as well as the DIP from 2007 to 2015 in Valle del Cauca, one of the departments where dengue fever is highly prevalent (see Supplementary 3 for other departments). Looking at the bottom right panel in Figure 1, there were two major outbreaks in 2010 and 2013 in the department. Comparing the trend of DIP with the climate factors, DIP appears to be positively correlated with temperature and humidity, but has a negative relationship with precipitation.

Figure 1. Climate factors and DIP over time in Valle del Cauca*



* See Supplementary 3 for other departments

13 of 31 departments in Colombia were chosen after checking the robustness of the case reporting system. The ADF test showed that we reject the null hypothesis, which means that the dataset is stationary. As shown in table 2, the CRF index is highly significant for all departments except Guaviare and Magdalena, thus 11 departments were selected for further analysis.

Table 2. Regression outputs of the CRF index on DIP

Department	N	Selected model	P-value for Z-score test (overdispersion)	Constant (α)		CRF (β)		AIC[b]	AIC (comparison)[c]
Antioquia	108	Poisson	0.47	-2.89	***	0.31	***	3.84	4.26
Arauca	108	NB[a]	0.00	2.00	***	0.06	***	8.46	30.37
Boyaca	108	NB	0.05	-0.59		0.51	***	4.26	4.19
Cauca	108	Poisson	0.19	-0.45	*	0.08	***	3.53	3.58
Cundinamarca	108	NB	0.03	-5.35	***	0.52	***	2.55	2.26
Guaviare	108	NB	0.02	3.23	***	-0.01		7.69	16.72
Huila	108	NB	0.00	0.49		0.05	***	7.87	14.33
Magdalena	108	NB	0.00	0.92		0.02		5.44	7.05
Norte de Santander	108	NB	0.00	1.61	***	0.05	**	7.68	10.54
Quindio	108	NB	0.02	-3.01	***	0.11	***	7.41	21.83
Risaralda	108	Poisson	0.11	-0.62	*	0.07	***	4.56	4.69
Santander	108	NB	0.00	1.07	*	0.06	**	7.12	9.89
Valle del Cauca	108	NB	0.00	-2.75	***	0.12	***	6.20	8.68

[a] Negative Binomial

[b] Akiake Information Criterion

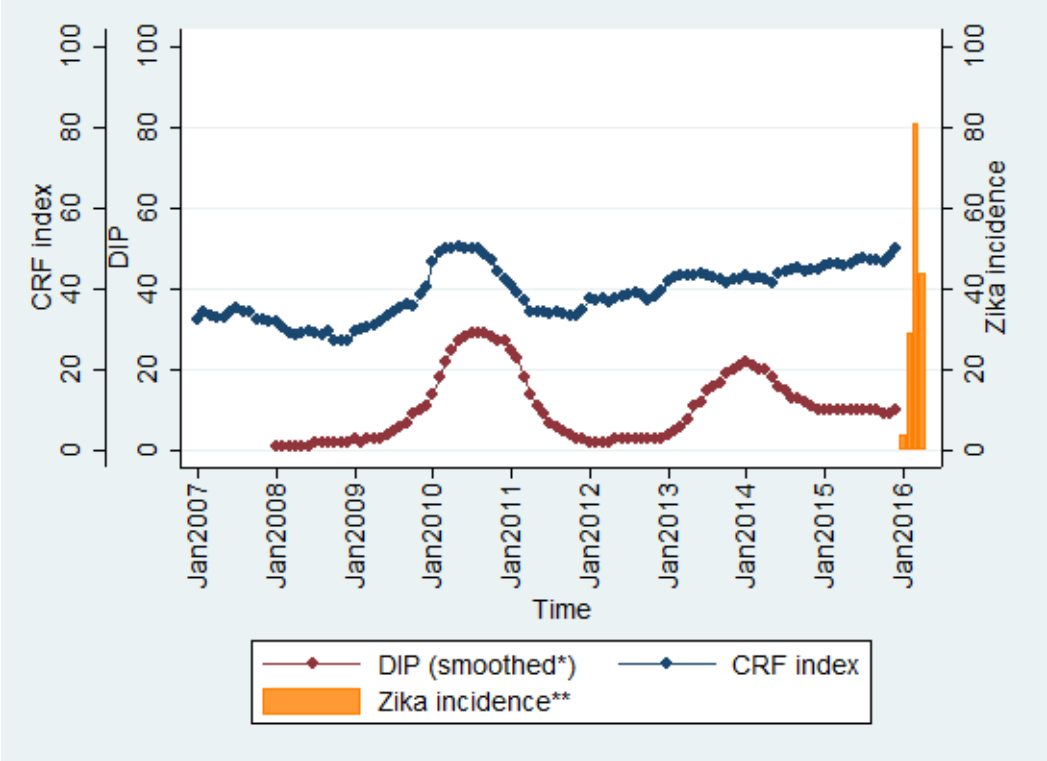
[c] AICs for non-selected count models were presented for comparison. The AIC fit test was consistent with the Z-score test in terms of choosing a better model fit except Boyaca and Cundinamarca. Since the AIC differences were trivial for the two departments, the Bayesian Information Criterion (BIC) was further assessed, and NB was preferred over Poisson.

* Significance at the 10% level, ** at the 5% level, *** at the 1% level

The CRF index and DIP were plotted over time to show the overall trend in Figure 2 (see supplementary 4 for other departments). It is clear that the epidemic that occurred in 2010 was picked up by the steep increase of the CRF index. In 2013, another epidemic was observed. While there was no rapid change in terms of the CRF index during a short period in 2013, the CRF index reached its high level following the steady increase of the index

since 2012. These provide an important point where an occurrence of future dengue epidemic can be related not only to the rapid increase of the CRF index, but also to the various levels of the CRF index and DIP. These combined relationships can be further explained by the elasticity of the CRF index which was used to develop an Early Warning Signal (EWS) model.

Figure 2. The CRF index and DIP over time in Valle del Cauca***



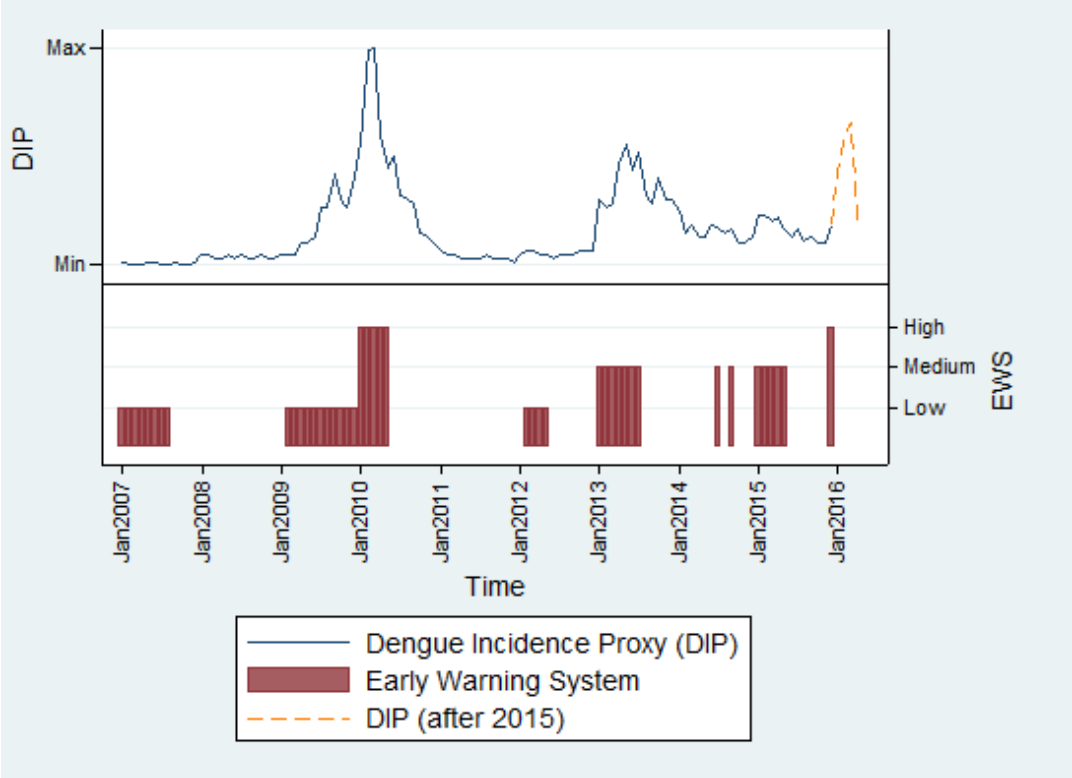
* DIP was smoothed out to reduce short-term fluctuations and highlight longer term trends for demonstration

**Zika cases were reported in 2015 as well, but zika incidence rates (/100,000) were not clearly shown for year 2015 due to the low number of reported cases

*** See Supplementary 4 for other departments

In Figure 3, the EWS based on the elasticity of the function was demonstrated for Valle del Cauca. In the department, the peak DIP was observed in March 2010, and the EWS signaled the high level warning sign two months before the peak (January 2010). Similarly, the second peak occurred in May 2013, and the EWS level went up from low to medium in January 2013 and remained at the same level until the end of the peak. It should be noted that there was no major outbreak observed throughout 2015 despite the continuous increase of the CRF index. Instead, Zika, another viral disease caused by *Aedes aegypti* emerged in 2015 and continued to increase in 2016. Overall, all 11 departments experienced dengue epidemics in 2010, and nine of them had additional minor outbreaks since 2011. Among the total of 24 observed outbreaks, EWS successfully detected 18 (75%) 1~5 months ahead of time and, three (12.5%) in the same month, and missed three (12.5%) (Supplementary 6).

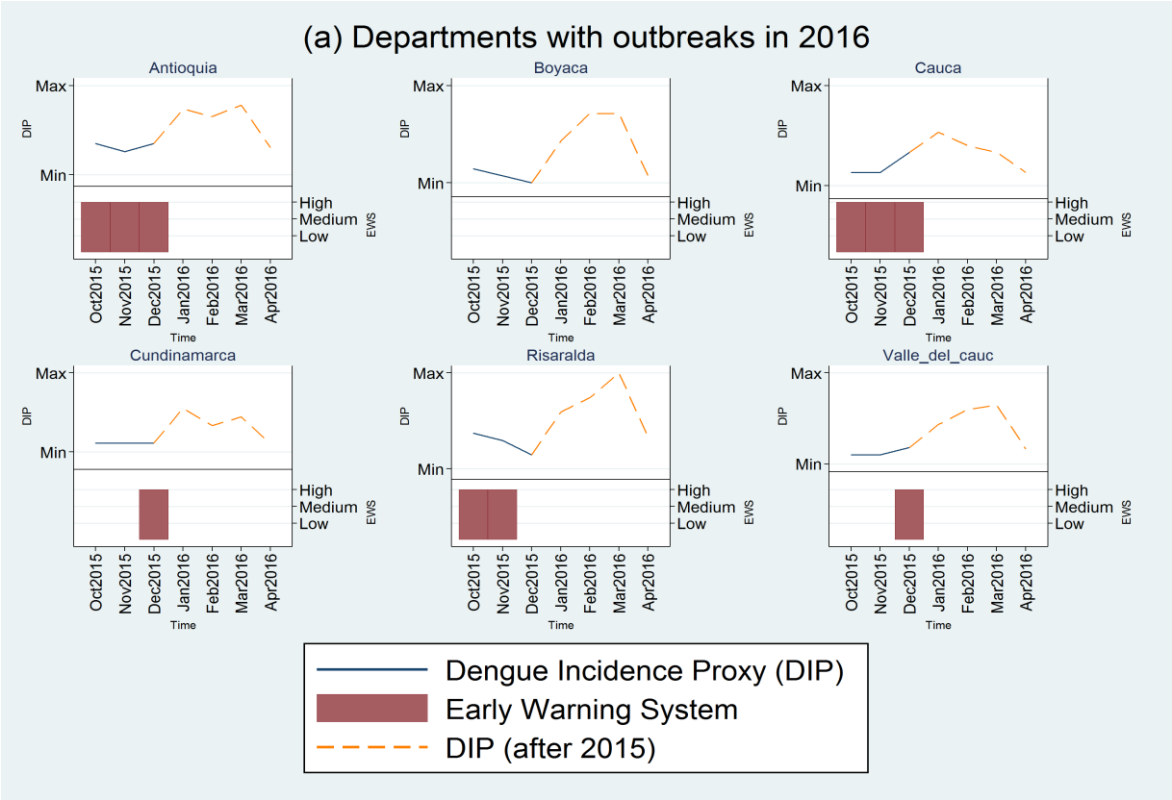
Figure 3. Early Warning Signal in Valle del Cauca

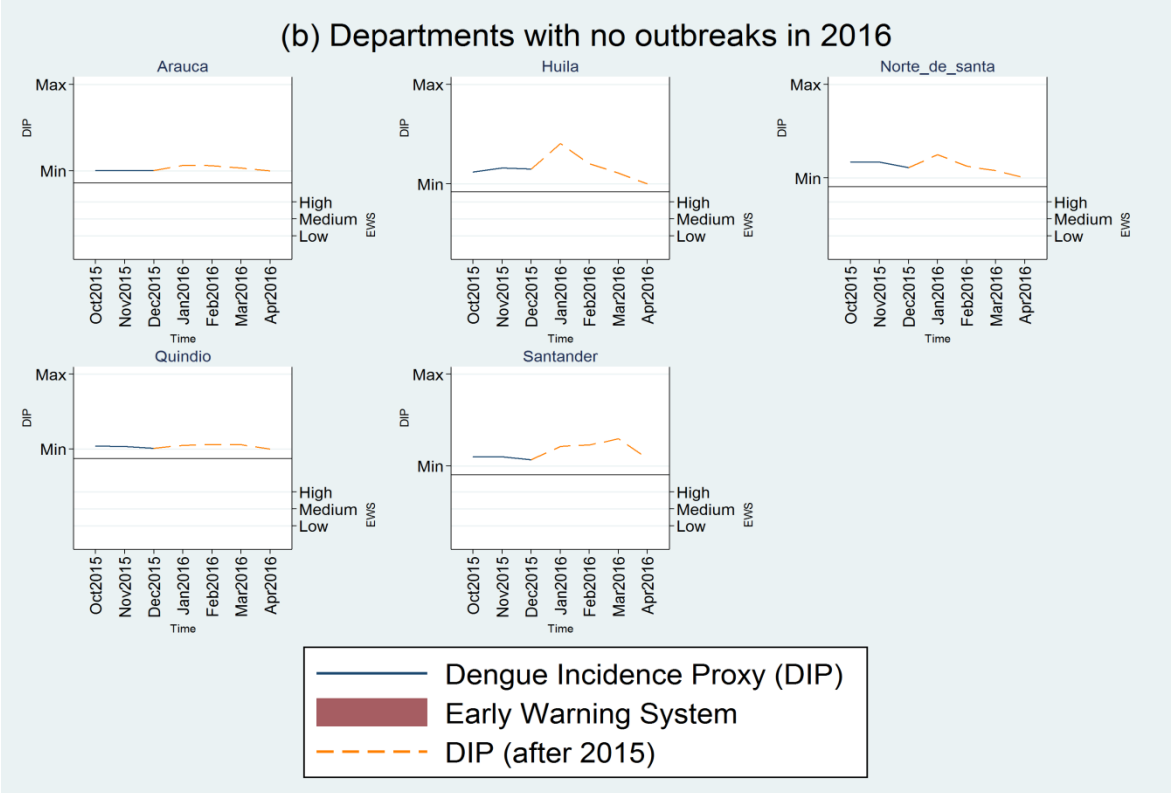


The EWS model predictability was examined with the validation data in 2016 which was separated from the model. It is interesting to see that the EWS already signaled the high level warning sign at the end of 2015, which accurately predicted another outbreak in two months (February 2016) that is out of the study period. Figure 4 further demonstrates the EWS model performance with the validation data for all 11 departments. 6 of 11 departments experienced outbreaks between January 2016 and April 2016. The EWS model successfully predicted these outbreaks 1~5 months ahead of time for all departments except Boyaca (HR = 83.3%). In addition, the EWS model did not send out any false alarms for the other 5 departments where no outbreak occurred during the out-of-

sample period (FAR = 0%). In other words, sensitivity (HR), specificity, positive predictive value, and negative predictive value of the validation data were as follows: 83.3%, 100%, 100%, and 83.3%.

Figure 4. EWS accuracy with the validation data in 2016



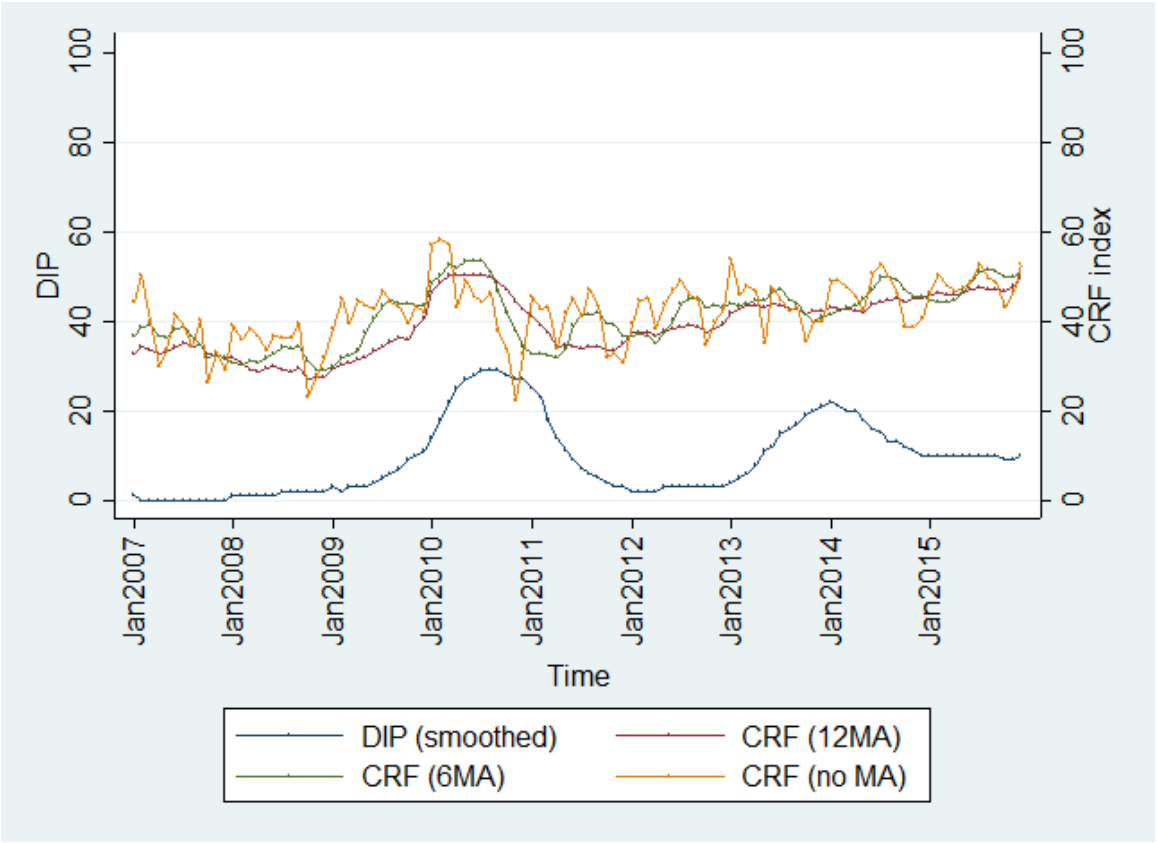


The sensitivity analysis was performed with different moving average scenarios (12 months, 6 months, current value). As shown in Table 3, the hit rate was the highest with the 12-month moving average scenario, meaning that the current model produced the most accurate prediction compared to the 6-month and no-moving-average scenarios. The false alarm rate increased as the moving average period was shortened. This is mainly because the index becomes too sensitive and changes quickly due to the short duration of the moving averages of the climate datasets. As a result, it does not distinguish between minor fluctuations and major outbreaks (Figure 5). This sensitive behavior of the CRF index with the shorter term scenarios proves our presumption that a current dengue epidemic is a result of the consistent long-term patterns of the climate conditions.

Table 3. Sensitivity analysis with additional moving average scenarios

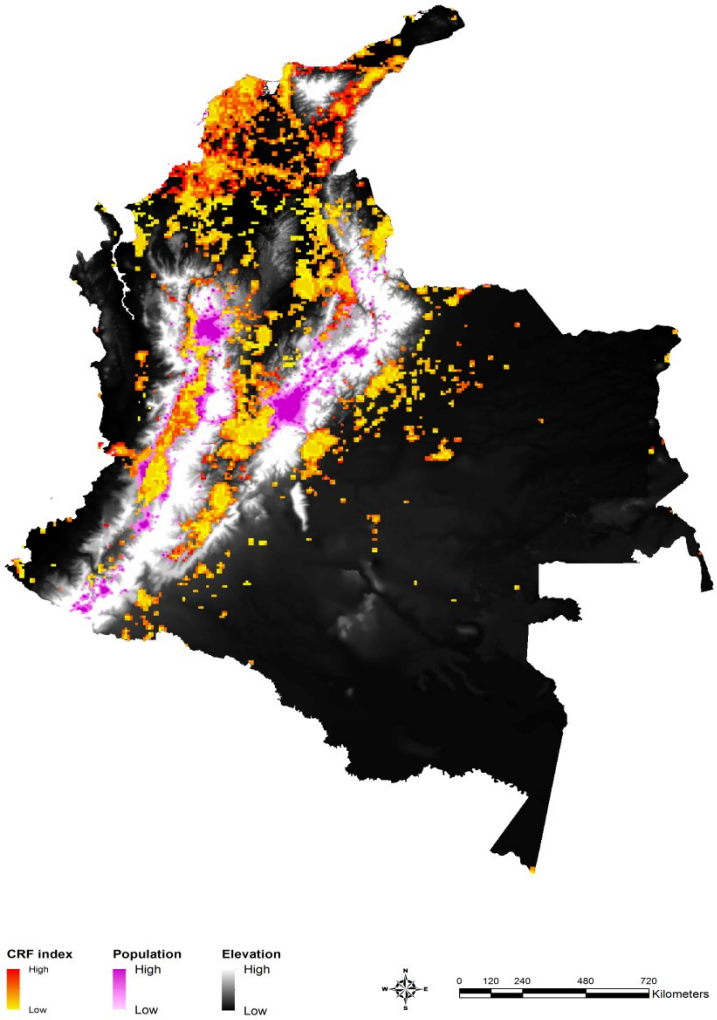
Scenario	HR (sensitivity)	FAR	Specificity	Positive Predictive Value	Negative Predictive Value
12 month MA	87.5%	3.1%	96.9%	91.3%	95.4%
6 month MA	75.0%	4.7%	95.3%	85.7%	91.0%
Current value (no MA)	83.3%	6.3%	93.8%	83.3%	93.8%

Figure 5. The CRF index with different moving average scenarios in Valle del Cauca



Given that the CRF index explains variation in DIP reasonably well, the CRF index was estimated at 5km by 5km resolution, and the most recent time of the index (December 2015) was presented in Figure 6 (see supplementary 5 for more details). As expected, populations at high risk are concentrated in the Western part of the country due to more suitable climate conditions for vector mosquitoes and the high population level compared to the East. Using the geo-coordinates of the high risk areas at 5km by 5km resolution, it is possible to identify the locations for people at high risk more accurately for efficient disease prevention activities.

Figure 6. Identification of high risk areas in Dec, 2015*



Source: Authors' analysis of data from National Oceanic and Atmospheric Administration (NOAA)

* See supplementary 5 for more details

3.5 Discussion

This study confirms that dengue fever transmission is strongly related to climate factors as well as population density at different topographical conditions. One of the advantages of

the CRF index is to prevent multicollinearity by combining all relevant climate indicators which may have some degrees of correlations with each other but have distinctive characteristics at the same time. During the study period from January 2007 to December 2015, the nationwide dengue epidemic occurred in 2010 was well explained by the rapid changes of the CRF index. Even if the CRF index increased steadily, the study found that it was still possible to detect an epidemic by adopting the elasticity of the function which takes into account not only the slopes but also the various levels of CRF and DIP.

In 2015, some inconsistent patterns between CRF and DIP were observed for some departments (Supplementary 7). This inconsistency may be related to the unexpected emergence of Zika, which started being reported in 2015. As shown in Figure 2, the number of Zika cases has continuously increased since 2015. However, it is still premature to make any firm statements regarding the impact of Zika on dengue fever due to uncertainty of the diseases. Given that reported cases are mainly based on clinical symptoms, there may have been a chance of misdiagnosis between the two diseases. In addition, due to the surge of an unfamiliar disease (Zika) imposing more difficulties on resource allocation at the local health facility level, it would be difficult to keep a consistent pattern in the case-reporting system from municipality-level heath facilities. Excluding 2015, a number of false alarms where EWS sends out the medium or high level signals but DIP remains low were only observed twice in Cauca (April and December 2014) during the study period.

Some areas of uncertainty deserve attention. While the CRF index performed well for 11 of 13 departments, the index was not statistically significant in Magdalena and Guaviare. This may have been caused partly by the inconsistent patterns of reported cases over time.

Because the EWS was estimated based upon the most recent observed climate datasets, the EWS in this study is limited to issuing alerts with short-time intervals (1~5 months ahead). Given that, at present there are 1~2 month delays until the climate data become available, EWS with the short intervals (i.e. less than two months) may not, for now, be practical in operational modes. However, this limitation can be improved based upon the availability of the climate datasets in real-time in the future, and the 1~5 month intervals would provide enough room for public health officials to prepare for selected vector control activities and healthcare interventions (i.e. increase the number of beds at high risk areas) in the dengue-endemic setting (Lowe et al., 2013, Juffrie and Focks, 2009). It should be noted that the study did not attempt to produce any longer-term predictions due to chaos and uncertainty in climate forecasts in the long run. Considering that long-term climate forecasts could be variable depending upon assumptions (i.e. future CO_2 omission level), the method proposed in this study could minimize potential bias which may be caused by uncertainty in input datasets. The climate datasets have coarse resolutions. While the datasets were resampled using the nearest option in this study, the model outcomes can be further improved with finer scale resolutions. It is worth noting that the cycling of El Niño and La Niña, called El Niño Southern Oscillation (ENSO), may have indirect impacts on the occurrence of dengue epidemics in South America by changing the patterns of climate variables such as temperature, precipitation, and humidity (Adde et al., 2016). While any unusual changes of the climate variables affected by such events were captured by using the 12-month moving averages, further investigation would be needed to identify accurate impacts of El Niño on climate factors including its timing.

Nonetheless, our model provided accurate forecasts for the validation period for 5 of 6

departments that experienced outbreaks in 2016. In addition, this study identified populations at high risk for dengue at 5km by 5km resolution. The study findings can be used to accelerate introduction of dengue prevention activities and prioritize alternative health interventions among competing health demands in Colombia.

The CRF index summarized multiple climate and non-climate risk factors into a single indicator which helps decision makers to understand easily (Lee et al., 2016). While some of the climate factors were more commonly used in the existing literature due to the nature of a vector-borne disease, the applications of the climate data in these studies appeared to vary. The proposed EWS model in this study used the concept of elasticity to understand how DIP changes to varying levels of the CRF index and successfully detected dengue outbreaks in Colombia. In addition, the CRF index was further estimated at 5km by 5km resolution. The areas where the CRF index values have been continuously high over time can be prioritized for appropriate healthcare interventions. Furthermore, this can guide decision makers to find relevant locations where future surveillance studies can be conducted.

Chapter 4. Dengue vaccine supplies under endemic and epidemic conditions in three dengue-endemic countries: Colombia, Thailand, and Vietnam

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Author contributions:

JSL designed the study, conducted the analyses, created all figures, and wrote the manuscript. JKL, DAD, and THAN were involved in data collection and data interpretation. AF contributed to data interpretation and overall inputs on the study outcomes.

4.1 Abstract

Dengue fever has been a major public health concern in Colombia, Thailand, and Vietnam. Unlike other infectious diseases, dengue vaccines had not been available for a long time, causing difficulties to control the disease. However, the first live attenuated, tetravalent dengue vaccine (CYD-TDV) became available in 2016 and has been already licensed in some dengue-endemic countries. Because several second-generation dengue vaccines are also in the pipeline, it is critical to understand the efficient allocation of dengue vaccines considering the geographical variation of the disease.

The Climate Risk Factor (CRF) index was created using the climate and non-climate factors in the three countries. A random-coefficient negative binomial model was chosen to validate the relationship between the CRF index and dengue incidence proxy. Given the statistical significance of the CRF index, high risk areas for dengue fever were identified at the 5km by 5km resolution and used to estimate vaccination coverage rates and the number of doses required for various types of vaccination scenarios by country.

Based upon a three-dose scheme, the estimated number of vaccines required for routine vaccination targeting 9 years old ranged from 1 to 2.6 million doses across the countries during the first year of introduction. A one-off catch-up campaign targeting the age group of 10-17 year olds would require 8 to 18 million additional doses. Routine vaccination (with or without a catch-up campaign) covered 63%, 90%, and 91% of the targeted age group populations in Colombia, Thailand, and Vietnam respectively. Given that many dengue-endemic countries face limited resources and that the costs for mass vaccination campaigns may not be trivial, the findings of this study can guide the decision makers in

the three countries regarding the efficient distribution of vaccines by identifying populations at high risk at 5km by 5km resolution.

4.2 Introduction

Dengue fever has been a major public health concern in many parts of tropical and subtropical regions around the world as the global burden of dengue has increased dramatically in recent years. A study finds an estimated 96 million apparent and 294 million inapparent dengue infections occurring annually (Bhatt et al., 2013). Many dengue-endemic countries are also exposed to the risk of periodic outbreaks. Due to the complexity of the disease—with four related but antigenically distinct dengue viruses—it has been challenging not only to have a full understanding of the disease, but also to develop effective vaccines against the disease.

After a long period without dengue vaccines, the dengue vaccination era began in 2016 as the first live, attenuated tetravalent dengue vaccine (Dengvaxia, CYD-TDV) became commercially available. Several second-generation dengue vaccine candidates are in the pipeline. There is no doubt that safe dengue vaccines can be used as an effective tool to control dengue fever in dengue-endemic countries that have solely relied on vector control activities till now. However, it is also true that many dengue-endemic countries face a problem of limited resources (i.e. allocation of limited budget among competing health demands) (Carrasco et al., 2011). Because dengue-endemic countries facing constraints on funding sources may need to place priority on vaccinating populations at high risk rather than all of their populations, vaccination strategies should be carefully examined in order

to target the right populations who are most urgently in need of vaccines.

This study projects the potential demands for dengue vaccines in three dengue-endemic countries: Colombia, Thailand, and Vietnam. While CYD-TDV has already been approved in several dengue-endemic countries, discussions are still ongoing regarding where and how to use the vaccine in order to maximize the protection induced from the vaccine while minimizing any potential detrimental effects (Azman and Lessler, 2015, Capeding et al., 2014, Ferguson et al., 2016, Flasche et al., 2016a). In addition, some of the second-generation dengue vaccine candidates are currently conducting phase 3 trials at the time of our research. As such, while some elements of the vaccine profile for CYD-TDV were taken into account throughout this study (i.e. 3-dose scheme), the study was designed to be more generally applicable to other second-generation vaccines and so not strictly restricted to the vaccine profile and safety matters of CYD-TDV (World Health Organization, 2017b).

The primary goal of the current study lies in the identification of populations at high risk for dengue fever and the estimation of vaccination coverage rates, as well as the estimation of the number of vaccine doses required in Colombia, Thailand, and Vietnam. Since vaccine supplies may be limited during the early stage of vaccine introduction, it is critical to predict the number of vaccines required and identify high-risk areas where vaccination campaigns should be prioritized. Furthermore, dengue-endemic countries are exposed to the risk of periodic outbreaks. During an emergency such as an epidemic, different vaccination strategies need to be considered because the impacts of vaccination may not be maximized if implemented late or if the right places are not targeted due to supply limitations or delays in the short-run (Azman and Lessler, 2015). Thus, in this study both

pre-emptive and reactive vaccination strategies are considered, taking into account the supply shortage during the initial phase of the vaccine introduction. In particular, the geographically dispersed risk levels of dengue fever-that is disease hotspots and non-hotspots-were identified based on various climate and non-climate risk factors in an effort to prioritize vaccination campaigns and improve the efficiency of vaccine allocation (Lee et al., 2017a).

4.3 Methods

All three countries were assumed to prioritize dengue vaccination for high-risk areas when vaccine supply may be limited during the early stage of the vaccine introduction, and to target broader populations in medium-to-low risk areas as the introduction stage phases out. In order to identify geographically dispersed risk levels for dengue fever, the Climate Risk Factor (CRF) index was adopted. The CRF index was previously formulated based on the 12-month moving averages of temperature, precipitation, and humidity, adjusted by non-climate factors which are population density and elevation (Lee et al., 2017a). The CRF index was then validated with Dengue Incidence Proxy (DIP) which was calculated by dividing the number of monthly dengue fever cases by population in Colombia from January 2007 to December 2015. The final DIP values were expressed per 100,000 and rounded up to obtain integer values. Similar procedures were applied to prepare the datasets and construct the CRF index for Thailand and Vietnam in the current study. Briefly, the monthly climate datasets were resampled into 0.008 by 0.008 degree resolution by taking the nearest neighbor assignments. Given that a current epidemic is a result of the

climate conditions observed during the past months, rather than single temporal values at present, cross-correlations between various periods (current, 6, 12 months) of the moving averages of the climate datasets and Dengue Incidence Proxy (DIP) with time lags were tested. The 12-month moving average was selected as the most appropriate period which explains the level of the current DIP. In addition to the climate datasets, non-climate factors were considered in constructing the CRF index: night light data (for population density); and elevation raster files. The three climate datasets and population density were used by province in each country. The variables were standardized, and the values were averaged across the variables. The final values were converted into a range from zero (low risk) to one (high risk) and adjusted by the risk proportion which was estimated by dividing the sum of the night lights observed under 1,500 meters elevation by the sum of the total night lights in each province. The full description on the mathematical formulation of the CRF index can be found at (Lee et al., 2017a). Supplementary 1 summarizes how the CRF index was constructed for selected provinces in the three countries where dengue has been prevalent. For the current study, the CRF index and DIP were further estimated for each province in Thailand and Vietnam during the same study period. In Thailand, the number of monthly dengue fever cases and population information by province were obtained from the Ministry of Public Health (Bureau of Epidemiology (Department of Disease Control), 2016). In Vietnam, the number of dengue fever cases by province was provided by the National Institute of Hygiene and Epidemiology (NIHE), and the population data was acquired from the General Statistics Office of Vietnam (General Statistics Office of Vietnam, 2016, National Institute of Hygiene and Epidemiology, 2016).

Since DIP can be considered as non-negative integer values, count models were previously used taking into account overdispersion. The positive relationships between DIP and the CRF index were validated during the study period from January 2007 to December 2015 in Colombia (Lee et al., 2017a). However, as the current study focused on validating the relationships between DIP and the CRF index, non-linear mixed models were adopted to identify global maximums in all three countries. As pointed out by Mohebbi et al., overdispersion may occur because of misspecification of the mean function or the probability model, and (or) spatial autocorrelation (Mohebbi et al., 2014). While the former is more common in general count models, the latter occurs when counts of events are observed in small geographical areas when overdispersion and residual spatial autocorrelation are present (Mohebbi et al., 2014). The full specification of the modeling procedure is described in Supplementary 2. The final model selected throughout the procedure is a random-coefficients negative binomial model where the conditional distribution of the function can be written as (Rabe-Hesketh and Skrondal, 2008, StataCorp, 2013):

$$f(y_i|v_i,\alpha) = exp\left[\sum_{t=1}^{n_i}\left\{ln\Gamma\left(y_{it}+\frac{1}{\alpha}\right) - ln\Gamma(y_{it}+1) - ln\Gamma\left(\frac{1}{\alpha}\right) - \frac{1}{\alpha}ln(1+\alpha\mu_{it}) + y_{it}ln\left(\frac{\alpha\mu_{it}}{1+\alpha\mu_{it}}\right)\right\}\right]$$

where y_{it} is the observed value, μ_{it} is the expected value of the outcome ($\mu_{it} = exp(x_{it}\beta + z_{it}v_i)$), x_{it} is the vector of the fixed effects covariates, β is the coefficient,

v_i is the random effects, z_{it} is the vector of the random effects covariates, and α is the conditional overdispersion parameter in a mean-overdispersion parameterization (Hilbe, 2011, Hilbe et al., 2003, Rabe-Hesketh and Skrondal, 2008, StataCorp, 2013).

Given the statistical significance of the CRF index in explaining the variance of DIP, the CRF index was further estimated at the refined geographical unit (5km by 5km resolution) from January 2007 to December 2015. The CRF index was then categorized into 10 risk-levels based upon every 10th percentile by province, with the highest score indicating the greatest risk for dengue fever. This information was used to target populations at high risk and to estimate vaccine uptake rates to achieve efficient allocation of the limited healthcare resources. Supplementary 3 compares the actual distributions of reported dengue cases with the CRF index by country and shows that there is a great consistency between the two distributions.

4.3.1 Spatial coverage for pre-emptive vaccination

Based on the validation models provided in the previous and current studies, all three countries would remain dengue-endemic and less likely experience dengue outbreaks when the level of the CRF index is very low (Lee et al., 2017a). Thus, the low level of the CRF index was assumed to represent the dengue-endemic condition. While some provinces in a dengue-endemic country experience dengue epidemics, others in the same country do not experience outbreaks during the same period due to the geographically diverse behavior of dengue outbreaks. In order to identify high-risk areas for all provinces during the dengue-endemic setting, the time points where the CRF index values were the lowest during the study period were identified by province in each country. The CRF index

values estimated at 5km by 5km resolution responding to these specific time points were used to understand the variation of the geographical risk levels of dengue fever for the endemic periods. As vaccine supply may be limited during the early stage of introduction, vaccine uptake rates, for both routine and catch-up vaccination, were also taken into account for the first three years following introduction. It was presumed that vaccination was prioritized for populations in high-risk areas where the CRF index values were above the 75th percentiles at year 1, expanded to the second high-risk areas (50-75th percentiles) at year 2 and the third high-risk areas (25-50th percentiles) at year 3. After year 3, all provinces were expected to cover all expanded risk areas where the CRF index values were over the 25th percentiles.

4.3.2 Spatial coverage for reactive vaccination

While a dengue outbreak can occur throughout a country at a given time (i.e. nationwide outbreak), some outbreaks are more geographically focused. Furthermore, the magnitudes of outbreaks can differ by geographical location even during a nationwide outbreak. For example, Colombia experienced a nationwide dengue outbreak in 2010 but the outbreaks in 2013 were only observed in selected provinces. In this study, an outbreak was defined in the same way as the previous study: as long as an unusual peak in DIP was observed in a province, it was considered as an outbreak even if the DIP value in that province was relatively low compared to other provinces where dengue is more prevalent (Lee et al., 2017a). Given the positive relationship between the CRF index and DIP validated in the model, the time points where the CRF index values were the highest by province were assumed to be the dengue-epidemic periods. In addition to the validation model outcomes specified in Supplementary 2, the association between the high level of the CRF index and

a dengue epidemic is further demonstrated in Supplementary figure 1(e) where the high levels of the CRF index values correspond to dengue outbreaks. Similar to the case of pre-emptive vaccination, the CRF index values at 5km by 5km resolution corresponding to these specific time points were obtained to identify populations at high risk during the epidemic situation. For reactive vaccination, two scenarios were assumed: (1) target hotspots only (areas with CRF index values greater than the 75th percentiles), (2) target both hotspots and non-hotspots (areas with CRF index values greater than the 25th percentiles).

4.3.3 Vaccine demand forecast

As a default policy, 9 year olds were targeted for routine vaccination and 10-17 year olds for a one-off catch-up campaign. While recent studies discuss extensively the notion of targeting an appropriate age group for routine vaccination with CYD-DTV depending upon dengue transmission intensity, there is no clear consensus as to which age group to target with a catch-up campaign with this vaccine (Ferguson et al., 2016, Flasche et al., 2016a, Flasche et al., 2016b). In this study, the age group of 10-17 year olds was chosen for a catch-up campaign based upon the comparative modeling exercise by WHO (Flasche et al., 2016a), and, as an alternative, the vaccine demand for the age group of 10-29 year olds was also presented (Lourenço and Recker, 2016) [see Supplementary 2]. A 3-dose scheme was assumed for pre-emptive vaccination, and all three doses were given to recipients within a year. During an emergency situation such as an outbreak, it would not be realistic to administer all three doses in a short period of time. Hence, in the absence of nationwide routine and catch-up vaccinations, as a reactive response a single-dose was assumed to be administered to the population of 9-29 year olds at risk. It is debatable

whether this single-dose strategy would be effective in the case of CYD-DTV. A previous modeling outcome showed that a single-dose of CYD-DTV might be enough to achieve protective immunity in seropositive individuals (Ferguson et al., 2016). However, this would still require more time to determine given the absence of direct findings from any clinical data, and single-dose protective immunity may be improved upon in future dengue vaccines.

Obtaining long-term population projections at the sub-national boundary level is a challenge. In order to obtain population projections by grid-cell of 5km by 5km resolution, the country-level population projections by age group were first obtained from 2017 to 2040 for three countries (The World Bank, 2016). The population data were then adjusted by the satellite night lights data which are available at 30 arc-second grid spacing (approximately $1km^2$) (National Geophysical Data Center): the projected populations were multiplied by the ratio of the sum of the night lights in a pixel and the sum of the total night lights of the corresponding province. Prior to the adjustment, correlations between night-lights data and provincial-level population data were examined to ensure that this adjustment reasonably approximated populations at the grid-cell level (Lee et al., 2016). The variables and assumptions used in the demand forecasting model are summarized in Table 1. The demand forecast was projected from 2017 to 2040 for the pre-emptive vaccination strategy. Due to sporadic occurrences of dengue epidemics, the year 2020 was selected as an example of the demand forecast during an outbreak situation, but the estimation can be done for other years.

4.3.4 Sensitivity analyses

In this study, vaccination coverage rates were estimated by taking into account vaccine uptake levels for pre-emptive vaccination and hotspots for reactive vaccination strategies. As these factors were constructed based upon the geographically dispersed risk levels of dengue fever using the CRF index, sensitivity analyses were conducted to reflect uncertainty levels of the estimates by applying various threshold levels of the CRF index as shown in Table 1.

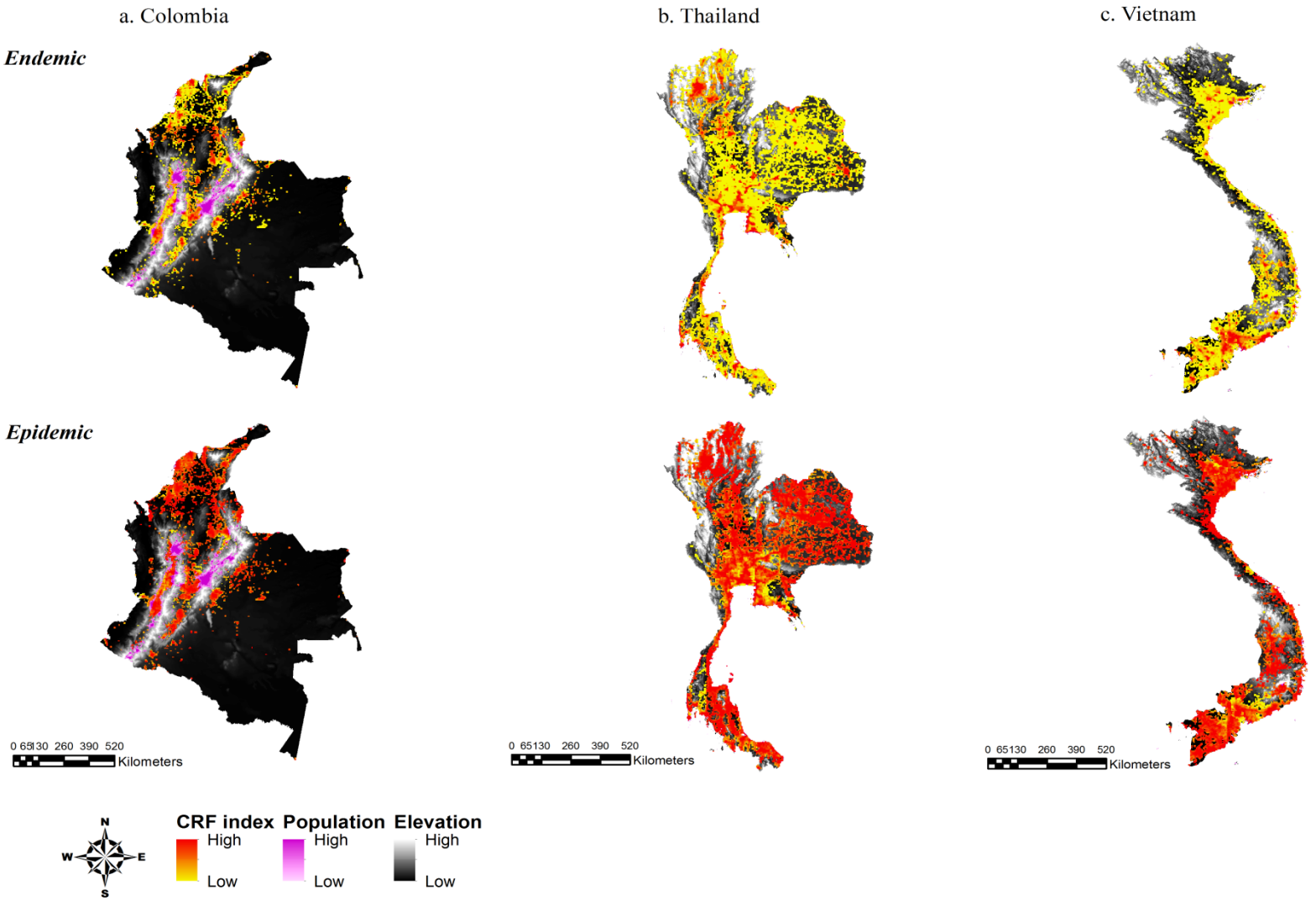
Table 1. Model assumptions

	Pre-emptive vaccination	**Reactive vaccination**
Number of doses	3 doses	1 dose
Wastage rate	10%	10%
Geographical unit	5km by 5km resolution	5km by 5km resolution
Coverage	Populations at risk (the CRF index during an endemic period > 25th percentiles)	Populations at risk (the CRF index during an epidemic period > 25th percentiles)
Uptake rate	First three years	N/A
Vaccination strategies	9yo routine w/ and w/o 10-17yo catch-up campaign (alternatively, 10-30yo catch-up campaign)	9-29yo in hotspots only, 9-29yo in hotspots & non-hotspots
Projection period	2017 - 2040	2020
Sensitivty analysis 1	1st high-risk areas (> 90th percentiles) 2nd high-risk areas (75th - 90th percentiles) 3rd high-risk areas (50th - 75th percentiles)	Hotspots (> 90th percentiles) Hotspots & non-hotspots (> 50th percentiles)
Sensitivty analysis 2	1st high-risk areas (> 50th percentiles) 2nd high-risk areas (25th - 50th percentiles) 3rd high-risk areas (1st - 25th percentiles)	Hotspots (> 50th percentiles) Hotspots & non-hotspots (> 1st percentiles)

4.4 Results

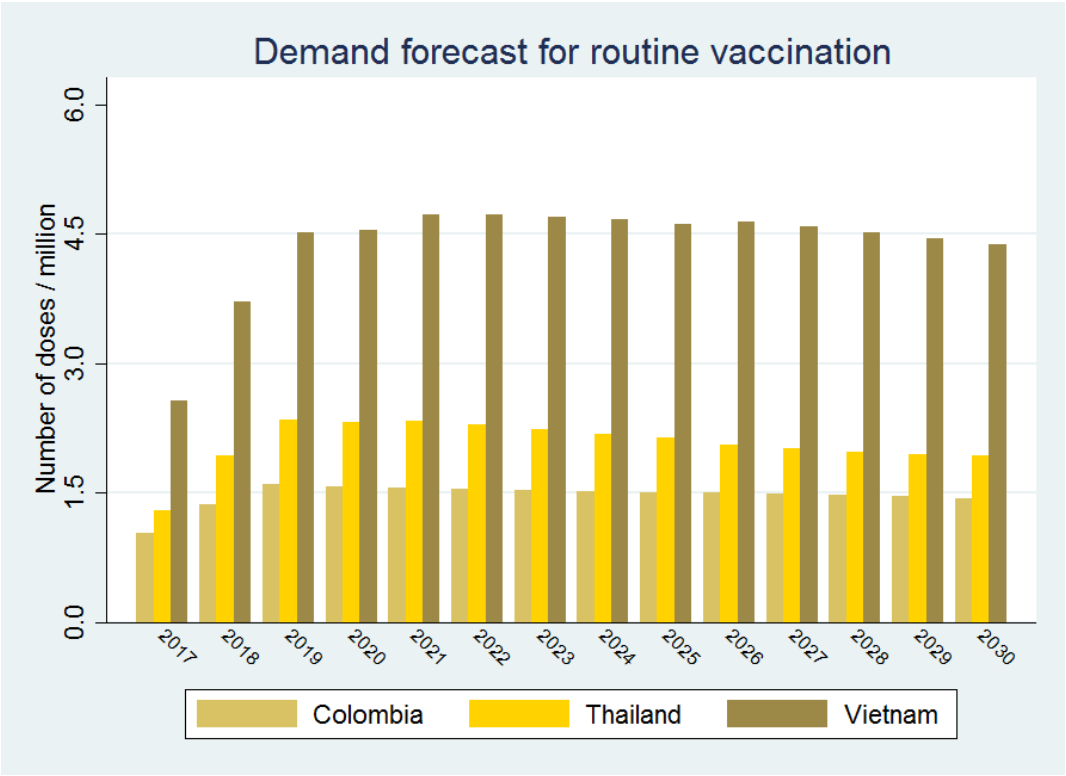
The risk level for dengue fever is not only variable over time but also geographically dispersed. The CRF index was validated against DIP by using a random-coefficients negative binomial model and proved to be statistically significant at explaining the variance of DIP. The full model specifications and outcomes are presented in Supplementary 2. Various risk levels of dengue fever based on the CRF index are demonstrated in Figure 1. The upper panel shows the risk levels during endemic periods in (a) Colombia, (b) Thailand, and (c) Vietnam. While the majority of the areas were at low risk, some locations where population density is high (i.e. Bangkok in Thailand, Ho Chi Minh City in Vietnam) appeared to be at high risk. In the lower panel, the CRF index levels at the time when each province experienced a dengue epidemic between 2007 and 2015 were used to simulate risk levels for the dengue epidemic setting. It was shown that populations residing at high elevation were not at high risk even during the epidemic periods (i.e. Bogota in Colombia).

Figure 1. Risk levels for endemic and epidemic situations based on the CRF index



Children at 9 years old were targeted for routine vaccination. A 3-dose scheme was assumed to start in 2017. The estimated number of vaccines required for routine vaccination is shown in Figure 2. For all three countries, vaccines were distributed to the highest-risk areas first, and gradually to the second and third highest-risk areas during the first 3 years given the scenario that vaccine supply would be limited right after the vaccine introduction. In 2017, in Colombia, Thailand, and Vietnam respectively, approximately 1, 1.2, and 2.6 million doses would be required to vaccinate populations at high risk, and the numbers peak at 1.6, 2.3, and 4.7 million doses in 4 to 6 years after the introduction. Overall, the number of doses required for the routine vaccination is the highest in Vietnam and the lowest in Colombia. Population size in risk areas played a major role in determining the number of doses in each country. It was also observed that the total number of doses decreases slightly as time goes by because of the decline in projected population on account of the ongoing drop in the birth rate in these countries (The World Bank, 2016, United Nations, 2015).

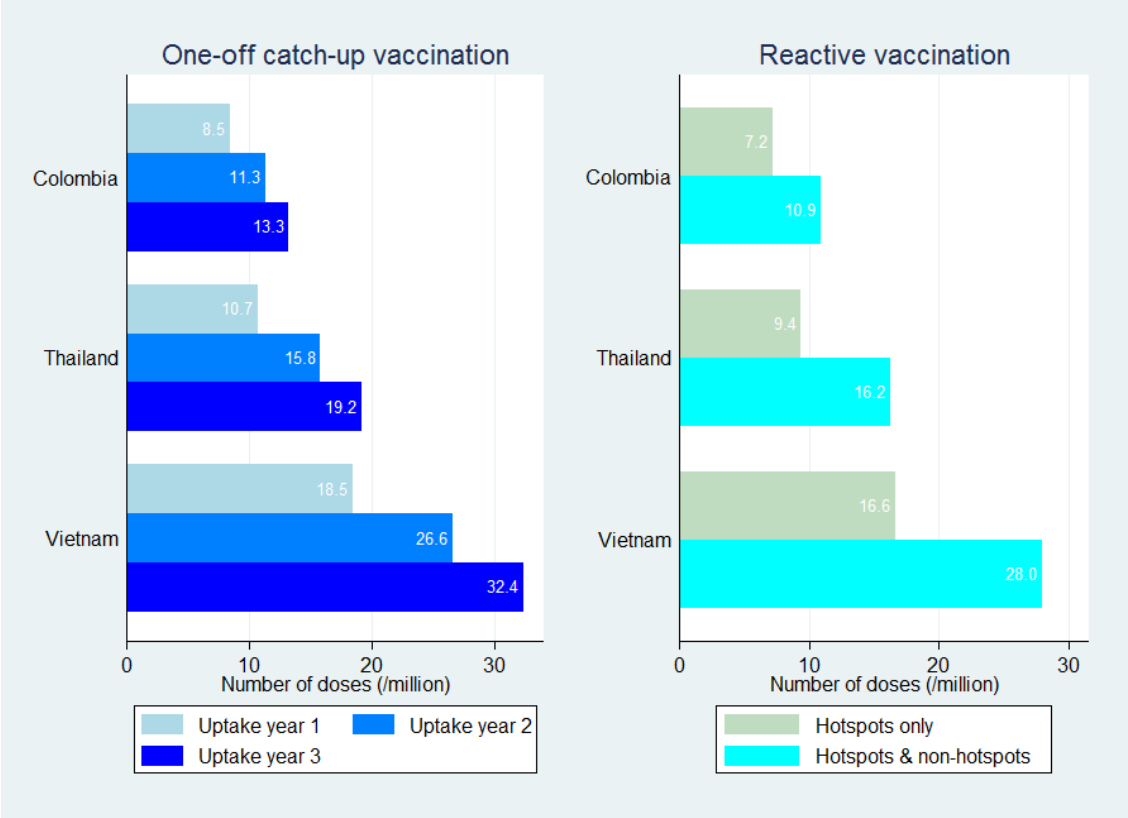
Figure 2. Number of vaccine doses required for routine vaccination



In addition to routine vaccination, a one-off catch-up campaign was considered for the age group of 10-17 year olds taking into account the same uptake scenarios as for routine vaccination (Figure 3). At year 1, the number of vaccine doses required for the catch-up campaign ranged from 8 million to 18 million with Vietnam having the highest and Colombia the lowest. At year 3, the required number of doses went up to 13 million doses in Colombia and 32 million doses in Vietnam. As an emergency response, reactive vaccination was planned to target (1) hotspots only, as well as (2) both hotspots and non-hotspots. Targeting only hotspots would require 7, 9, and 17 million doses in Colombia, Thailand, and Vietnam respectively. About 3.5 to11 million doses would be additionally

needed to cover non-hotspots during an epidemic situation as shown in Figure 3.

Figure 3. Number of vaccine doses estimated for a one-off catch-up campaign and reactive vaccination

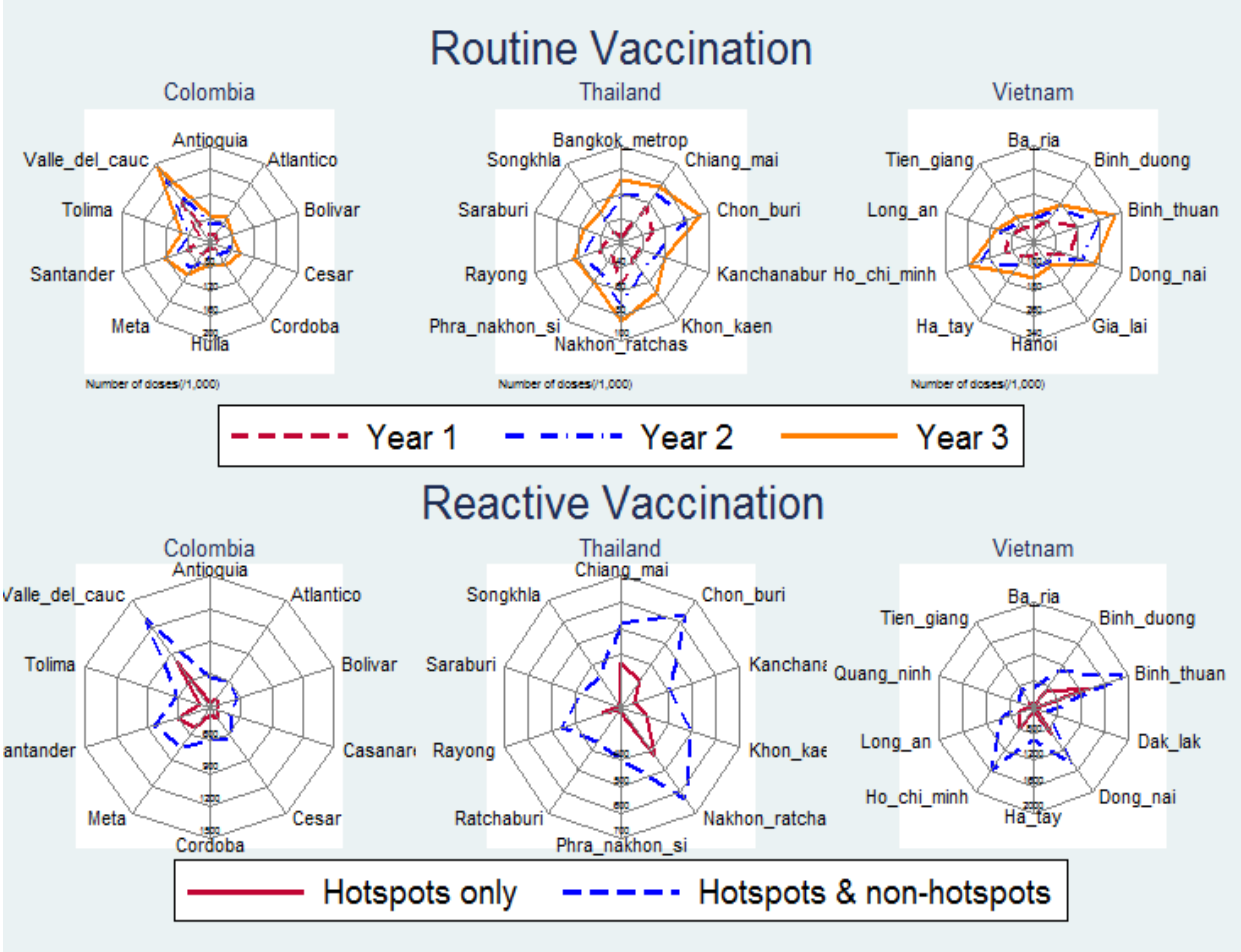


* See Supplementary 2 for an alternative catch-up campaign scenario targeting the age group of 10-29 year olds

The 10 provinces in each country which were expected to consume the most doses of vaccines are presented in Figure 4. In Colombia, Valle del Cauca followed by Santander and Meta appeared to be the most vaccine demanding provinces in terms of routine and reactive vaccinations. In Thailand, Chon Buri province would require the highest number

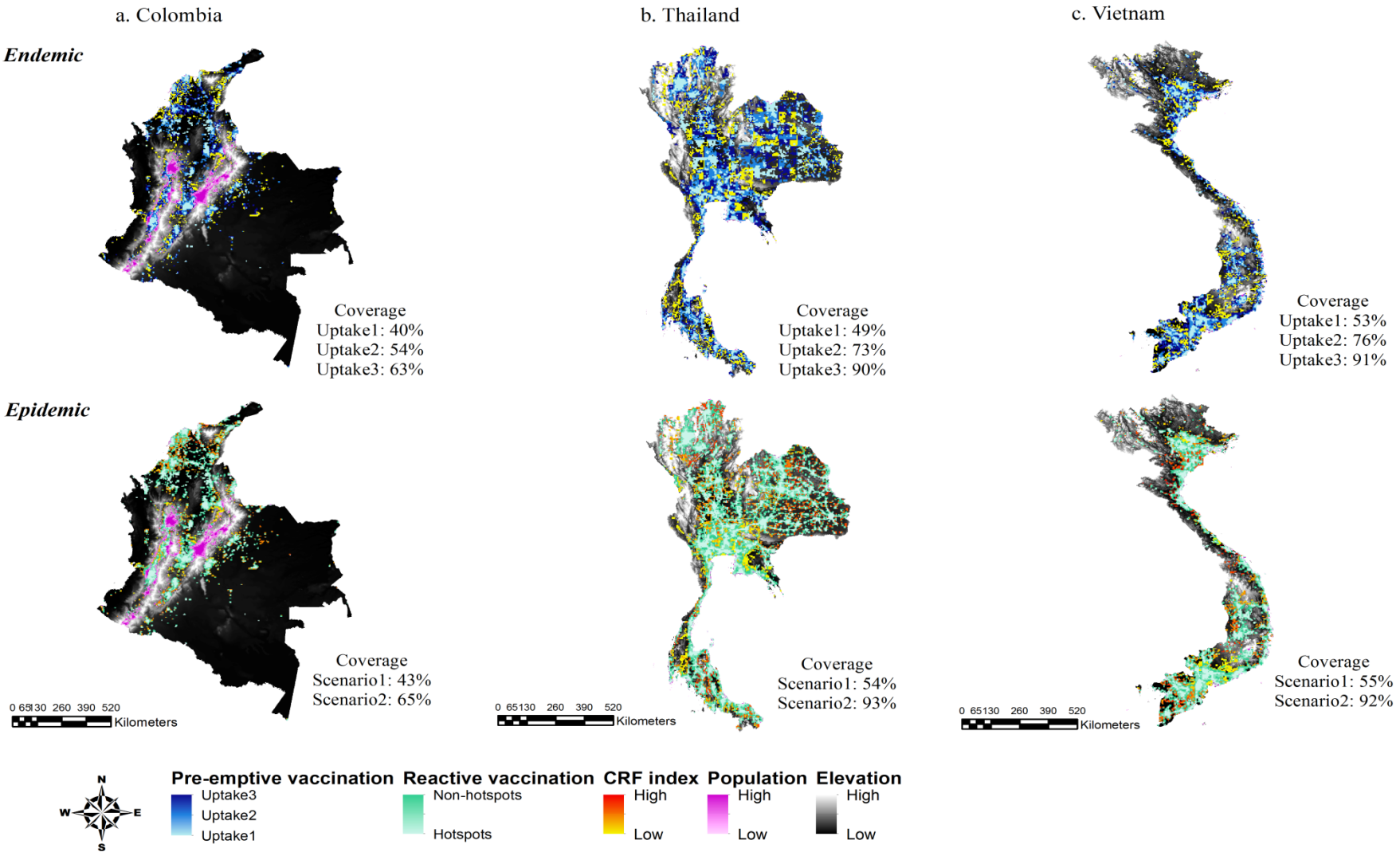
of vaccines at year 3 of the routine vaccination. On the other hand, Nachon Rachas was predicted to overtake Chon Buri in terms of the required vaccine stockpiles when targeting hotspots during an outbreak situation. In Vietnam, Binh Thuan was anticipated to require the largest number of vaccines for both routine and reactive vaccinations.

Figure 4. Top 10 provinces in terms of the number of vaccines demand by vaccination scenario



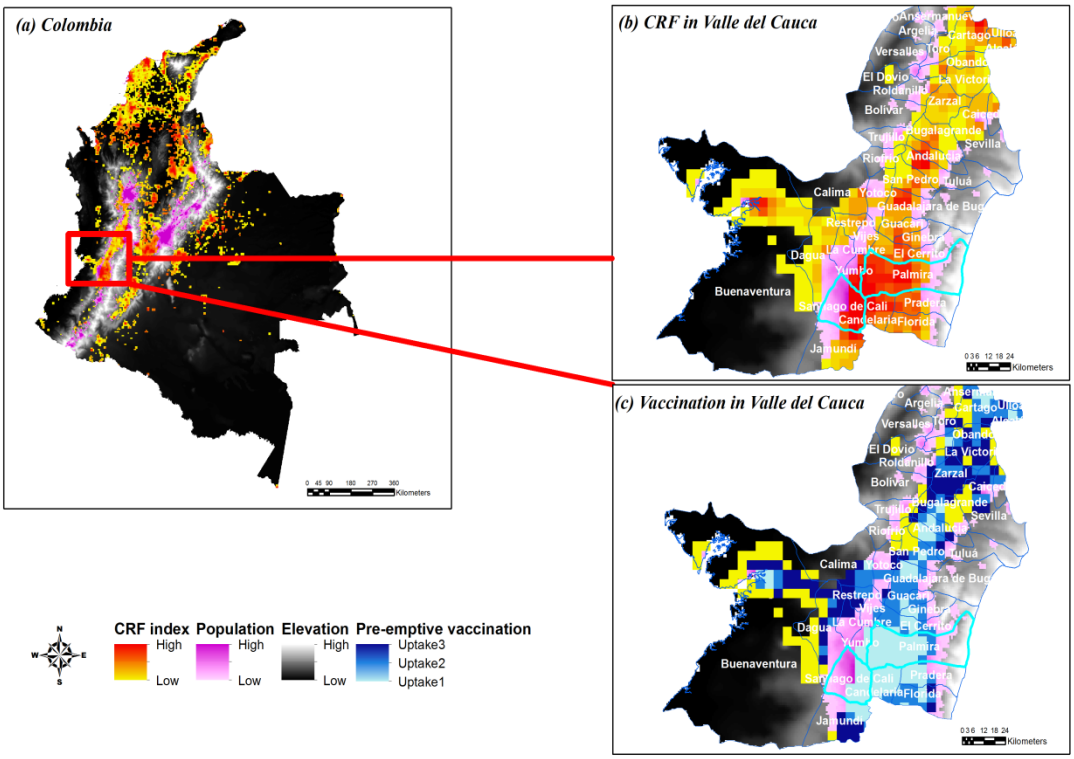
During endemic periods, routine vaccination (with or without a catch-up campaign) covered 63%, 90%, and 91% of the targeted age group populations in Colombia, Thailand, and Vietnam respectively (Figure 5). When the focus is on disease hotspots during an outbreak (scenario 1), about half of the targeted age group are expected to get vaccinated. The coverage rates became over 90% in Thailand and Vietnam, and 65% in Colombia as the reactive vaccination strategy expands target areas into non-hotspots (scenario 2). The vaccination coverage rates in Colombia were lower than the other countries because some densely populated areas were geographically located at high elevation (i.e. Bogota), which in turn put less priority on vaccinating populations residing in these areas.

Figure 5. Vaccination coverage rates for pre-emptive and reactive approaches



In addition to the overall coverage rates estimated for the selected vaccination strategies, the CRF index estimated at the 5km by 5km resolution can be used to explain the intra-province heterogeneity of high risk areas and to pin down the locations for efficient vaccine distributions, minimizing the misallocation of limited resources. For example, Valle del Cauca was mentioned as one of the most vaccine-demanding provinces in Colombia. In fact, SIVIGILA, an official governmental program of the epidemiological surveillance system in Colombia, reported that dengue fever had been highly prevalent in Valle del Cauca and that 60% of the reported dengue cases in the province between 1999 and 2010 were harbored in two municipalities (Cali and Palmira) (Sivigila). As shown in Figure 6(b), the high-risk areas of dengue fever are heterogeneous even within a province, and the intra-province heterogeneity of the CRF index is highly consistent with what had been reported by SIVIGILA. The high-risk areas are indeed concentrated in the Eastern part of Cali and the Western part of Palmira in Valle del Cauca. Considering the uptake levels based upon the CRF index in the current study, these high risk areas were prioritized for vaccination as highlighted in light blue in Figure 6(c), and target areas were expanded to the second and third risk areas at year 2 and year 3 after the introduction.

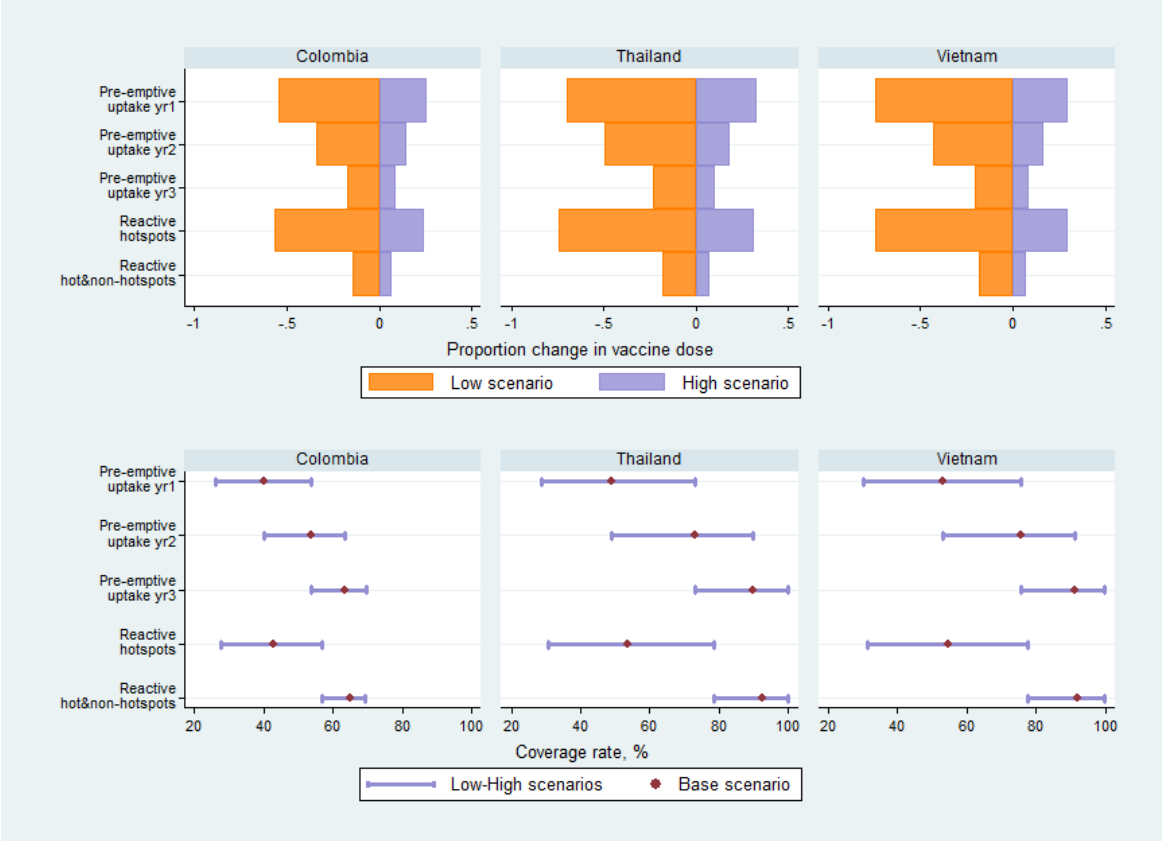
Figure 6. Intra-province heterogeneity of high risk areas in Valle del Cauca



Depending upon the CRF threshold levels, the number of vaccine doses required and vaccine coverage rates vary as shown in Figure 7. In the lower-bound scenario compared to the baseline threshold, the number of doses decreased by 14-57%, 18-74%, 18-75% in Colombia, Thailand, and Vietnam respectively. The large rates of decrease were observed for the first uptake year of the pre-emptive vaccination and for the hotspot only strategy of the reactive vaccination because the target areas for these strategies were significantly reduced under the lower-bound scenario. With the upper-bound scenario, the changing rates in the number of doses were less than 30% compared to the baseline threshold across the countries. Vaccination coverage rates ranged from 26% to 54% in Colombia, 29%-73%

in Thailand, and 30%-76% in Vietnam for the first year of introduction, and gradually increased.

Figure 7. Sensitivity analyses



* Low scenario based on sensitivity analysis 1; high scenario based on sensitivity analysis 2

4.5 Discussion

This study identified populations at high risk for dengue fever based on the CRF index which was statistically significant in explaining the variance of DIP in three dengue-

endemic countries (Colombia, Thailand, and Vietnam). Given that a dengue vaccine has not yet been widely used for nationwide vaccination campaigns, the current study estimates coverage rates by taking into account the geographically dispersed risk levels of dengue fever using the CRF index, and calculates the expected number of vaccine doses for various types of vaccination strategies.

As pre-emptive vaccination strategies, 9 year olds were targeted for routine vaccination, and 10-17 year olds (alternatively 10-29) were considered for a one-off catch-up campaign. Given that vaccine supply would be limited during the early stage of the vaccine introduction, gradual uptake rates were taken into account for the first three years since introduction. This study not only estimated the number of vaccine doses required for selected vaccination strategies, but also identified areas for vaccination at 5km by 5km resolution, thus minimizing the misallocation of vaccines. In particular, each risk-level cell as shown in Figure 5 is small enough to be utilized within various levels of administrative boundaries such as municipality or province. Thus, three countries can determine their target strategies by relatively large admin-boundary (i.e. province), small admin-boundary (i.e. municipality), or even smaller level (5km by 5km).

In addition to pre-emptive vaccination strategies, reactive vaccination was considered. Vaccine stockpiles are needed in order to ensure rapid access to vaccines for countries experiencing epidemics (Costa, 2009). In fact, all three countries are exposed to nationwide dengue outbreaks. For example, dengue serotype 4 has not been common for the past decade in Colombia, and many people would likely be susceptible for this serotype. If serotype 4 were introduced to Colombia, there would be a high chance of experiencing a nationwide outbreak similar to the one in 2010. It may be premature to

discuss vaccination strategies during a dengue outbreak situation given the lack of information on dengue vaccine profiles at the present time. However, in the case of other infectious diseases such as cholera and yellow fever, previous studies showed that the biggest hurdles to reactive vaccination were the clear identification of geographical areas to be targeted and the timing of vaccination (Chaignat and Monti, 2007, World Health Organization, 2010, Levin et al., 2012, Azman and Lessler, 2015). With the currently available dengue vaccine (CYD-TDV), there is a possibility to complement the single dose administered during an outbreak with a second and third dose administered later on.

The CRF index can be considered as a useful tool in understanding the overall risk level of dengue fever at the smaller geographical unit (Lee et al., 2017a). While there is no doubt that serological studies would provide more accurate information on the disease in a specific location or site within a country, it would be difficult to obtain the details of seroprevalence history over a long-period of time for each cohort in all specific locations of dengue-endemic countries. Thus, accompanying existing and future serological studies, the CRF index can be used to identify geographical areas at high risk for dengue fever, and to facilitate public health-policy interventions in the governmental (or macro)-perspective (i.e. nationwide vaccination campaigns). For example, a WHO position paper indicated that the introduction of CYD-TDV is recommended in geographic settings where seroprevalence is greater than 50% (World Health Organization, 2017b). As it would be logistically difficult to conduct seroprevalence studies in all specific locations of a country, the CRF index can be used to identify high risk areas where further serological studies can be conducted for vaccination. In addition, the current study outcomes can be used to spot areas where serological testing of individuals can be conducted prior to vaccination in

order to screen potential vaccine recipients, thus facilitating a more efficient allocation of limited resources (Ferguson et al., 2016). As many dengue-endemic countries may not have enough resources to support mass vaccination programs for the current and future vaccines, decision makers may need to identify well-defined geographical locations to prioritize vaccinating populations at high risk (Dewan et al., 2013, Lee et al., 2016). The current study outcomes can help resource-constrained countries plan more effective vaccination strategies at the local level by prioritizing areas at high risk since vaccine supply may be limited during the early phase of a new vaccine introduction (Lee et al., 2016).

One of the important findings was that while the timing and locations of dengue outbreaks were variable, there was a general consensus that many provinces in the three countries experienced dengue epidemics in 2010 and 2013, and many of these epidemics were clearly captured by the rapid increase of the CRF index and the high level of the CRF index (see Supplementary figure 1(e)). This indicates that the use of the CRF index would potentially be an informative tool even in other dengue-endemic countries where there is no sophisticated national surveillance system. Furthermore, there were existing studies which shed light on early warning systems of dengue outbreaks (Huang et al., 2015, Lowe et al., 2013, Lee et al., 2017a). The findings from these studies can be used to aid the timing of reactive vaccination, and such models can be further expanded to other dengue-endemic countries considering the use of vaccines for controlling dengue outbreaks. The reactive vaccination strategies presented in this study need to be further updated as more guidelines on the use of the current and future dengue vaccines become available. Nonetheless, the results from this study provide a good starting point for decision makers

to design vaccination strategies in response to dengue outbreaks and to approximate the required number of doses (i.e. stockpiles) for emergency situations.

Some areas of uncertainty need attention. Care must be taken when applying the study outcomes to the use of CYD-TDV as the aforementioned WHO position paper indicated 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 (World Health Organization, 2017b); this study was designed to be more generally applicable for decision-makers when considering other second-generation dengue vaccines. Unlike Colombia, the number of monthly dengue fever cases was not adjusted for potential case-underreporting in Thailand and Vietnam due to the lack of data sources. Thus, the estimated DIP values in Thailand and Vietnam might not be as robust as the one in Colombia. Considering the nature of the validation models, the performance of the model would not be significantly affected as long as the patterns of case-underreporting or overreporting would be consistent by province over time. However, it may be possible to observe inconsistent patterns of case-reporting during outbreak periods when there are more difficulties for some municipalities on resource allocation (Lee et al., 2017a). Vaccine uptake rates and coverage rates were determined based upon the CRF index, but the study did not take into account local specific contexts such as logistics, and the local-level interests that may play an important role in achieving the estimated coverage rates. As previously described, the climate raster datasets were at relatively coarse resolutions (Lee et al., 2017a). While the datasets were resampled in this study, future research work with finer scale resolutions will further strengthen the precision of the current model outcomes. The level of dengue vaccine compliance rate could vary by country and vaccine

type. Given that none of the three countries has introduced the current dengue vaccine at the time of this research, it was assumed that all three doses were given to recipients within a year, but the actual probability of achieving full compliance may be lower than assumed in this study.

Given that many dengue-endemic countries face limited resources and that the costs for mass vaccination campaigns may not be trivial, it is critical for decision makers to consider the efficient allocation strategy of dengue vaccines by targeting the right populations in high-risk areas. In addition to the current CYD-TDV, several second-generation dengue vaccines are expected to be available in the near future. The findings of this study can guide the decision makers in the three countries regarding the efficient distribution of vaccines during both endemic and epidemic situations, minimizing the waste of limited resources.

4.6 Acknowledgements

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Chapter 5. 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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Author contributions:

JSL designed the study, conducted the analyses, created all figures, and wrote the manuscript. JL supervised the application of the transmission modeling work. AF and SG contributed to data interpretation and overall inputs on the study outcomes.

5.1 Abstract

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.

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.

Both CYD-TDV and NVC could be cost-effective at the threshold of $2,000 per DALY averted 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.

5.2 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 (Bhatt et al., 2013). 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 (Beaute and Vong, 2010, Lee et al., 2017c).

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 (Lourenco et al., 2018), but also to develop effective vaccines against it (Lee et al., 2017a). 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 (Rodriguez-Roche and Gould, 2013, Bhoomiboonchoo et al., 2015, Halsey et al., 2012, Lee et al., 2017a). 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 (Rodriguez-Roche and Gould, 2013, Bhoomiboonchoo et al., 2015, Lourenco and Recker, 2013). Humans who have experienced a secondary, heterologous infection and recovered are believed to be protected against further infections (Lourenco et al., 2018).

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 (Halstead and Russell, 2016, Hadinegoro et al., 2016, Dans et al., 2017, Dans et al., 2018). 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 (World Health Organization, 2017a, World Health Organization, 2016). 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 (Flasche et al., 2016b). 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 (World Health Organization, 2017a). 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, it is possible to develop more severe illness following vaccination upon a subsequent dengue infection in those who are seronegative (Sanofi Pasteur, 2017). 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 (seropositives) (World Health Organization, 2017b).

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 (Lee et al., 2017c). 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 (Lee et al., 2015,

Lee et al., 2017c). 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.

5.3 Methods

5.3.1 Transmission model

Vaccination impact was estimated using a spatially explicit, individual-based meta-population transmission model (Lourenco and Recker, 2013, Lourenço and Recker, 2016) 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. (Flasche et al., 2016b). 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 (Flasche et al., 2016b). 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 (Carabali et al., 2017, L'Azou et al., 2016).

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 (Hadinegoro et al., 2015). 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 (Hadinegoro et al., 2015). 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 (Gessner and Halsey, 2017). 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 (Gessner and Halsey, 2017). 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 (Flasche et al., 2016b). 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 (Gessner and Halsey, 2017). 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 (Flasche et al., 2016b), 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 (Ferguson et al., 2016, Flasche et al., 2016b, Lee et al., 2017b), 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 (World Health Organization, 2017a, Gessner and Halsey, 2017). 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: (Hadinegoro et al., 2015)

[b] Sources: (L'Azou et al., 2016, Carabali et al., 2017)

5.3.2 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 (Murray et al., 2012), 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 (systems, 2017). 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 (WHO Global Health Observatory (GHO) data, 2017). 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 (Coudeville et al., 2016). 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 (Sivigila, 2016, Bureau of Epidemiology (Department of Disease Control), 2016, National Institute of Hygiene and

Epidemiology, 2016). Second, a recent study reported dengue epidemiologic trends in multiple countries where two phase 3 trials (CYD14, CYD15) were conducted (L'Azou et al., 2016). 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 (Lee et al., 2017c). A recent study reported the economic burden of dengue fever in Vietnam, Thailand, and Colombia based on a standardized survey tool and methodology (Lee et al., 2017c). 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 (Lee et al., 2017c), 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 (Marseille et al., 2015, Newall et al., 2014). 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 (Woods et al., 2016, Russell et al., 2017). 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 (Flasche et al., 2016b).

5.3.3 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 (Anderson et al., 2007, Carrasco et al., 2011, Meltzer et al., 1998, Mathers, 2008, IHME, 2017, Gubler and Meltzer, 1999), 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, inpatient; outpatient)	0.55; 0.21	0.55; 0.21	0.55; 0.21	(Mathers, 2008, Carrasco et al., 2011)
Disability weight (sensitivity analysis 1, inpatient; outpatient)	0.85; 0.81	0.85; 0.81	0.85; 0.81	(Meltzer et al., 1998, Gubler and Meltzer, 1999)
Disability weight (sensitivity analysis 2, inpatient; outpatient)	0.13; 0.05	0.13; 0.05	0.13; 0.05	(IHME, 2017)
Disease burden (high scenario, /100,000)	3,182	5,934	2,614	(L'Azou et al., 2016)
Disease burden (low scenario, /100,000)	112	217	106	(Sivigila, 2016, National Institute of Hygiene and Epidemiology, 2016, Bureau of Epidemiology (Department of Disease Control), 2016, Lee et al., 2017b)
Duration of illness (days, inpatient; outpatient)	7.4; 6.2	7.8; 6.1	10.4; 8.7	(Lee et al., 2017c)
Age of death by age group (years)	Same as Thailand	5.3; 14.1; 37.1	3.4; 14.4; 53.1	(systems, 2017)
Life expectation at age of death by age group (years)	72.6; 67.8; 44.1	70.9; 66; 42.2	74.8; 66.1; 29.95	(WHO Global Health Observatory (GHO) data, 2017)
Economic burden of dengue (age < 9yo, inpatient; outpatient)	$282.6; $81.3	$126.2; $49.8	$109.3; $151.3	(Lee et al., 2017c)
Economic burden of dengue (9 ≤ age < 19yo, inpatient; outpatient)	$178.9; $57.3	$196.2; $44.7	$250.4; $112.7	(Lee et al., 2017c)
Economic burden of dengue (age ≥ 19yo, inpatient; outpatient)	$205.4; $64.5	$188.3; $24.7	$319.7; $164.0	(Lee et al., 2017c)
Wastage factor during vaccination campaigns	10%	10%	10%	Assumed

0.5 GDP per capita	$1,026.2	$2,970.9	$3,956.7	(The World Bank, 2014)

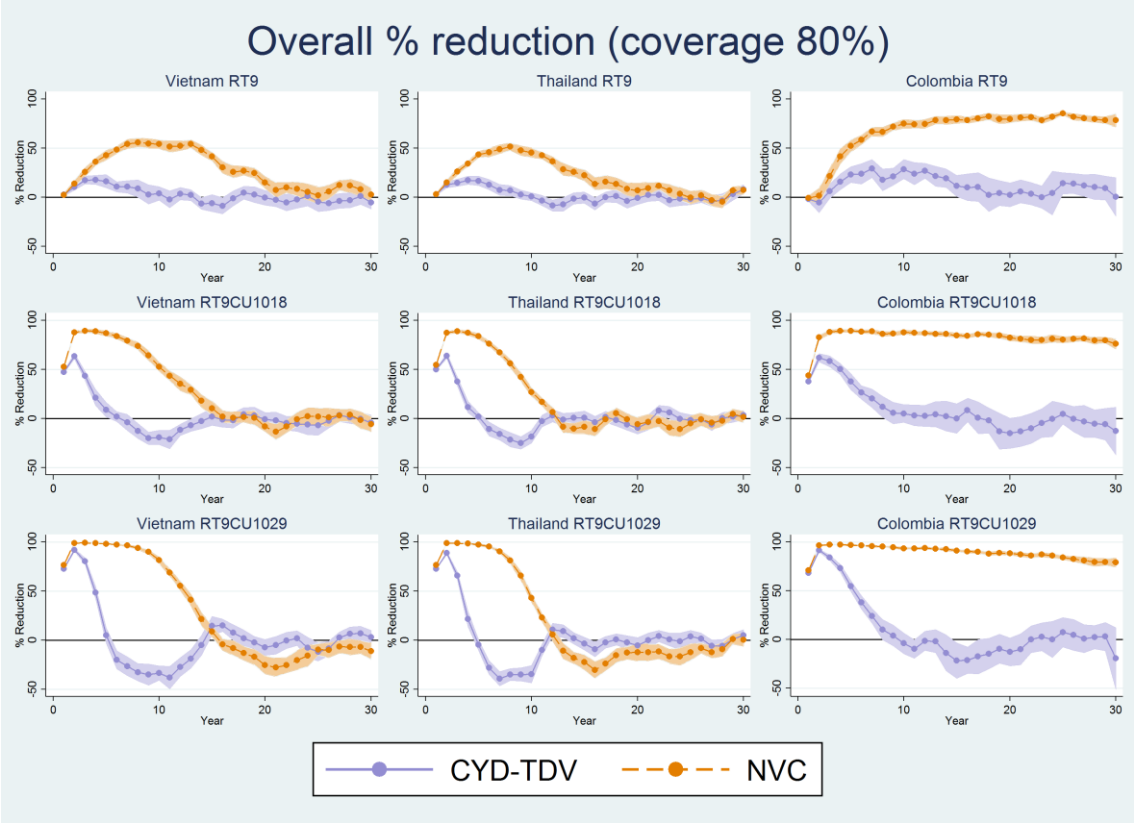
5.4 Results

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.

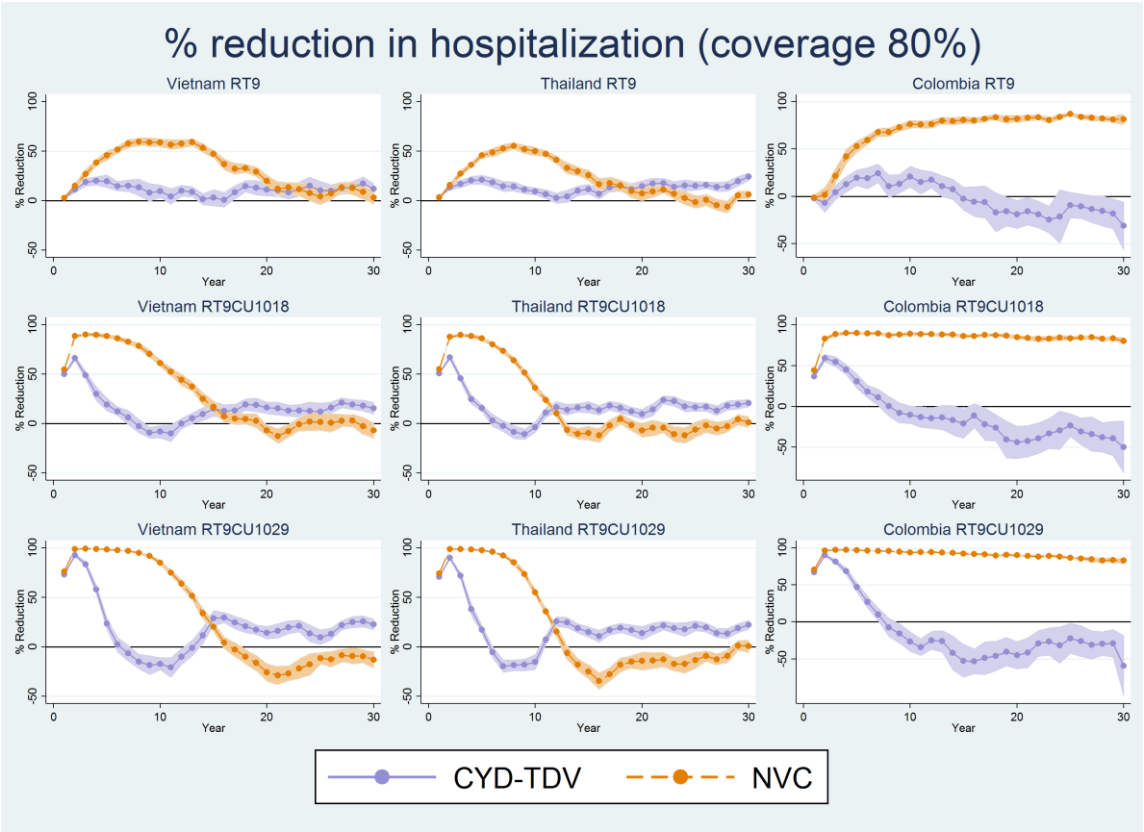
Figure 1. Overall disease reduction by vaccination with CYD-TDV and NVC



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.

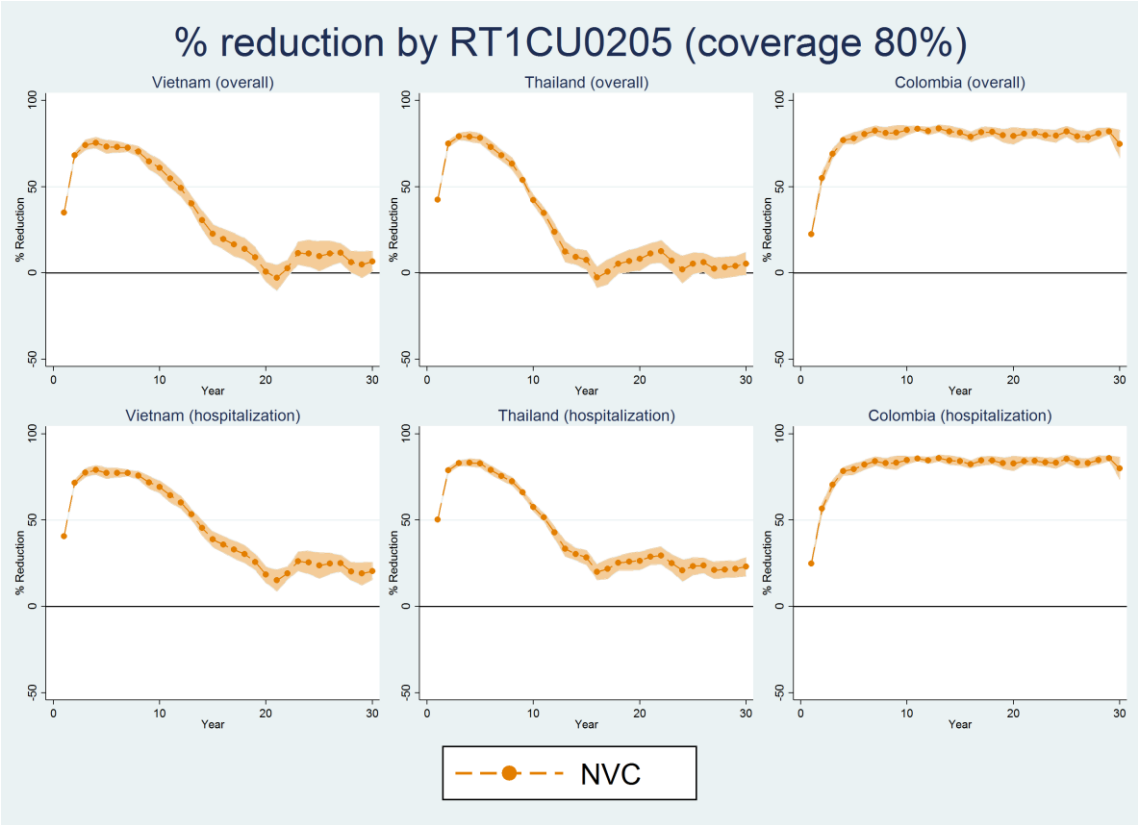
Figure 2. The proportion of reduction in hospitalization with CYD-TDV and NVC



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

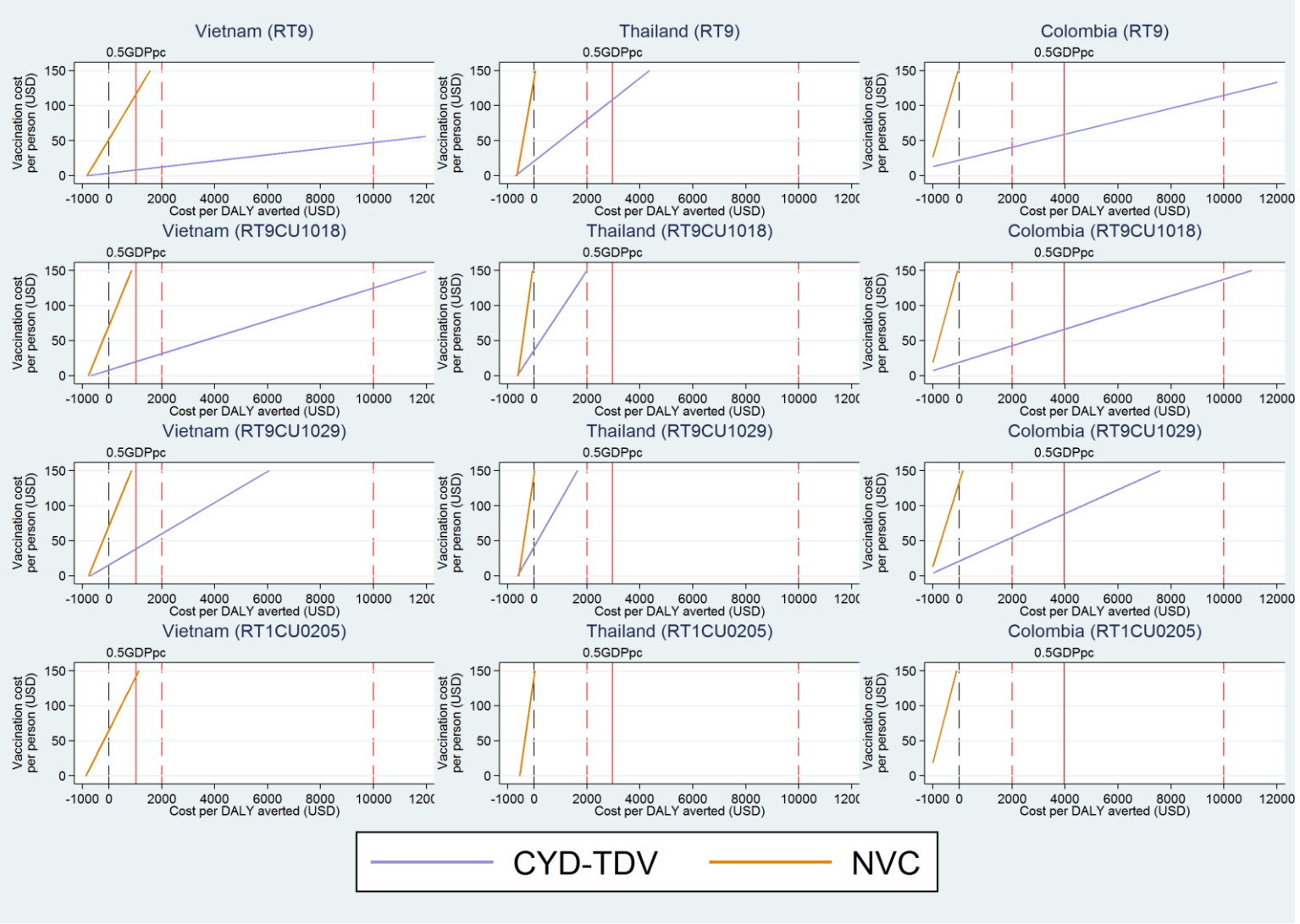
DALYs averted are observed with NVC compared to CYD-TDV. However, regardless of the disease burden level, both CYD-TDV and NVC provide positive returns to all countries in terms of the total DALYs saved over the prediction period (30 years).

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

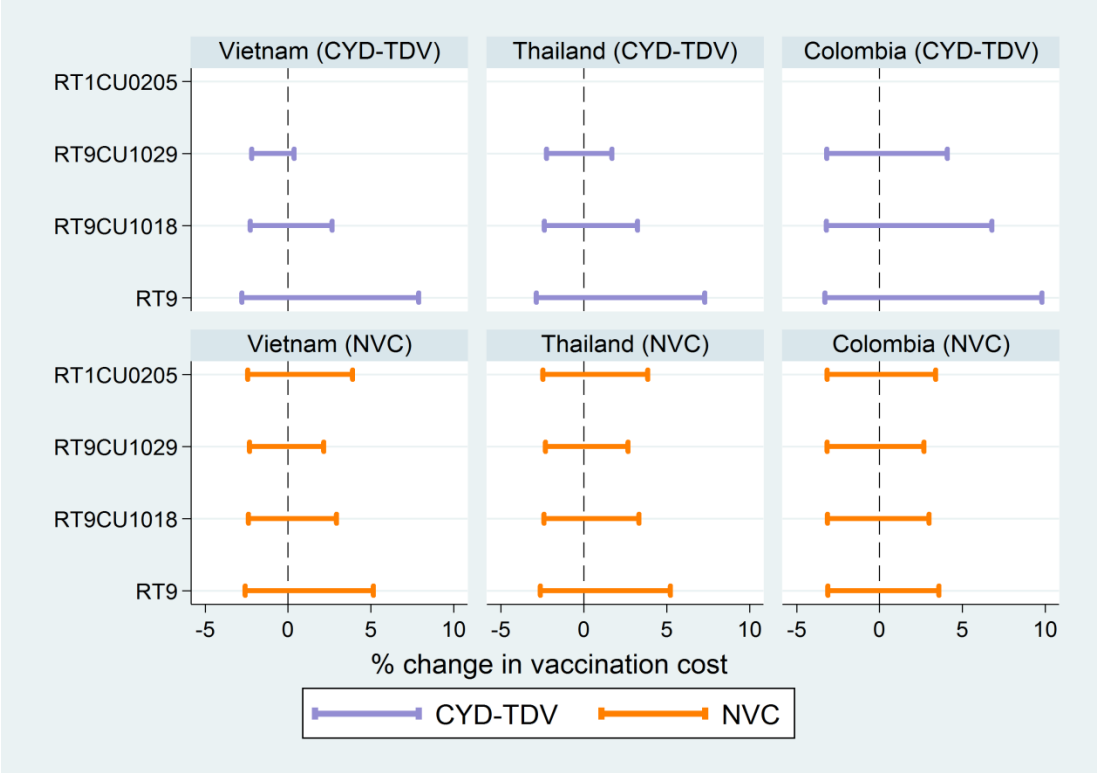
Colombia. However, vaccine interventions become much less cost-effective in all three countries under the low-burden scenario for both vaccines. For example, the RT9CU1029 strategy with CYD-TDV becomes cost-effective only when vaccination costs are set below $2.1, $6.4, and $2.2 at the threshold cost 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.

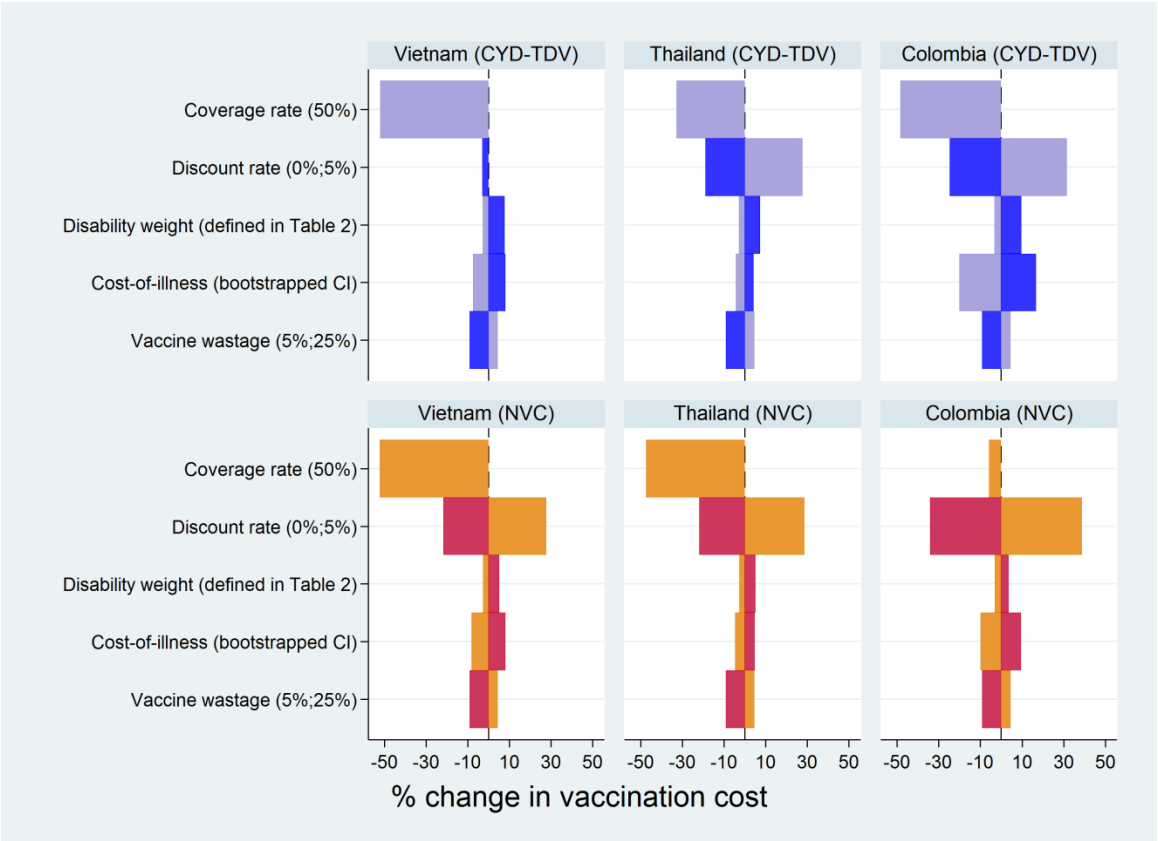
Figure 5. Sensitivity analyses with varying disability weights (coverage 80%)



* 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



5.5 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., 2016b). 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 (World Health Organization, 2017a, World Health Organization, 2016) and respective scientific publication (Flasche et al., 2016b). 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 (Ferguson et al., 2016,

Lourenço and Recker, 2016): (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 (Carrasco et al., 2011, Lee et al., 2011,

Shafie et al., 2017, Shim, 2016, Shim, 2017b, Shim, 2017a, Zeng et al., 2018), 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) (Shim, 2016, Shim, 2017b, Shim, 2017a, Shafie et al., 2017, Zeng et al., 2018), 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 (Carabali et al., 2017, L'Azou et al., 2016). 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 (Lee et al., 2017a, Lee et al., 2017b). This is particularly important given that the manufacturer of CYD-TDV officially announced that more cases of severe disease could occur when vaccinating seronegatives (Sanofi Pasteur, 2017), and that WHO updated its recommendation that CYD-TDV only be administered to seropositive individuals (World Health Organization, 2017b). These recent announcements highlight that it is critical to identify serostatus of vaccine recipients prior to vaccination with CYD-TDV, which will likely increase the cost. 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 (Hadinegoro et al., 2015). 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.

Chapter 6. Conclusion

6.1 The problem

Dengue fever is a vector-borne disease, mainly transmitted by *Aedes aegypti* and *Aedes albopictus* mosquitoes. The epidemiology of the disease is very complicated. There are four antigenically distinctive serotypes interacting with each other. It is known that a primary infection provides life-long immunity to that specific serotype, but that a sequential heterologous infection may cause more severe illness after a short-term cross protection (Rodriguez-Roche and Gould, 2013, Halsey et al., 2012, Reiner et al., 2014). Many studies have indicated that the increasing probability of experiencing severe illness may be related to antibody-dependent enhancement (ADE) during the second infection mediated by non-protective heterotypic antibodies arising from the primary infection (Rodriguez-Roche and Gould, 2013, Reiner et al., 2014, Bhoomiboonchoo et al., 2015, Lourenco and Recker, 2013). Due in part to ADE, while dengue infection generally causes mild symptoms including fever, headache, rash, and joint pains, a heterologous secondary infection may develop into lethal complications which are the main causes of hospitalization and death in many parts of the tropics and sub-tropics where dengue is prevalent (WHO, 2016, Lee et al., 2017c). A recent study estimated that there are 96 million apparent and 294 million inapparent dengue infections occurring annually (Bhatt et al., 2013).

6.2 The challenge

One of the main challenges for controlling dengue fever had been the long-term absence of effective and safe dengue vaccines due to the complicated nature of the disease. In 2016, a

first live-attenuated, tetravalent dengue vaccine called Dengvaxia (CYD-TDV) by Sanofi Pasteur became commercially available. However, the introduction of CYD-TDV has created a wide range of controversial debates (Halstead and Russell, 2016, Hadinegoro et al., 2016, Dans et al., 2017, Dans et al., 2018). Briefly, the major concern lies in vaccinating seronegative individuals with CYD-TDV. The vaccine provides low to intermediate levels of protection against dengue (varying efficacy rates by serotype) when vaccinating seropositive individuals. However, for seronegative individuals who have never been infected with dengue fever at the time of vaccination, their first natural infection after vaccination with CYD-TDV may act as a secondary-like breakthrough infection which develops into more severe illness (World Health Organization, 2017a, Flasche et al., 2016b). This safety concern was raised when two large clinical trials (CYD14, CYD15) had been completed although the issue was less clear at that time. In the WHO's following first position paper based on the limited available data (World Health Organization, 2017a), this risk was clearly mentioned, but at the same time, the position paper indicated that CYD-TDV can be used for target age groups with seroprevalence rates greater than 50% (≥70% for optimal benefits). Even if the elevated risk of vaccinating seronegatives was discussed, the recommendation based on seroprevalence (proportion of people who have been already infected) includes seronegative individuals for vaccination unless the seroprevalence rate of target population is 100%. In November 2017, Sanofi Pasteur officially announced that while CYD-TDV provides protective benefits 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 (Sanofi Pasteur, 2017). Shortly after, WHO also updated its position on the use of CYD-TDV,

stating that the vaccine should be only administered to seropositive individuals (World Health Organization, 2017b). This safety signal of CYD-TDV leads to the following challenge: how do public health officials identify seropositives when considering vaccination at the population-level in a country? Without a doubt, a comprehensive seroprevalence survey targeting all of potential vaccine recipients could answer this question. However, not many dengue-endemic countries are capable of conducting such surveys for all age cohorts covering broad geographical areas within a country. Alternatively, pre-screening tests prior to vaccination with CYD-TDV may be considered, but no rapid-diagnostic test which detects past infections is currently available, and even if it becomes available, this will create additional costs at the population-level. Above all, none of these points helps protect seronegative individuals from dengue viruses. There are second-generation vaccine candidates that are currently going through phase 3 trials at the time of this research, and it is evident that many dengue-endemic countries are expecting to see an improved version of dengue vaccine in the near future.

6.3 Importance of a country-investment case

Considering the complexities of dengue fever, as well as of the currently available vaccine, it is particularly important for country-level decision makers to set up detailed plans on when and how to conduct vaccination in a way to maximize positive benefits and minimize any detrimental impacts. The major objectives of investments in dengue vaccination are to achieve the following:

- Understand the current economic burden of dengue fever

- Identify geographical distribution of the disease within a country
- Prioritize high-risk areas for efficient resource allocations
- Understand the need for both pre-emptive and reactive vaccination programs
- Estimate the costs and the benefits of vaccine interventions at the population-level
- Motivate industry to expedite on-going and future development work of dengue vaccines to meet the potential demand at an affordable price

The following sub-sections summarize the previous chapters of this thesis and provide the specific roadmap of a country-investment case in three dengue-endemic countries: Vietnam, Thailand, and Colombia.

6.3.1 Economic burden of dengue fever

The cost-of-illness (COI) study of a disease provides not only the financial burden of contracting the disease, but also baseline information that feeds into a more detailed health-economic evaluation model such as a cost-effectiveness analysis. COI estimates are the costs which could be saved by implementing public-health interventions including nationwide immunization programs. In the context of dengue, previous economic burden studies were conducted in different parts of dengue-endemic regions (Constenla et al., 2015). While there is no doubt that previous studies have contributed to filling the knowledge gap, it is also true that the majority of the study outcomes are difficult to compare because the studies, except for a few multi-country studies, applied different inclusion criteria and methodologies.

In Chapter 2, the economic burden of dengue fever was estimated by implementing a

standardized survey design and methodology across three dengue-endemic countries: Vietnam, Thailand, and Colombia (Lee et al., 2017c). In this study, it was desirable to include the following criteria in order to make more comprehensive comparisons among current and future economic burden studies: (1) cost components (direct medical cost; direct non-medical cost; indirect cost), (2) cost type (out of pocket payment; public expenditure), (3) patient type (inpatient; outpatient), (4) dengue confirmation (laboratory confirmation), (5) age (all age group), (6) period (entire duration of illness). As shown in Table 1, the study indicated that indirect costs, which include productivity loss and hiring substitute laborers (or caretakers), account for the highest burden for patients in all three countries. The proportion of patient's out-of-pocket payments on direct medical costs was significantly lower in Thailand compared to Vietnam and Colombia due to the universal healthcare system implemented in Thailand. The total burden of out-of-pocket payments was the highest among the low-income groups across all three countries, and the proportion of the burden decreased when moving towards the higher-income groups. The average societal cost of dengue per episode in 2014 USD was $213 for inpatients and $64 for outpatients in Vietnam, $181 for inpatients and $43 for outpatients in Thailand, and $278 for inpatients and $144 for outpatients in Colombia.

Table 1. Economic burden of dengue fever

USD in 2014	Vietnam		Thailand		Colombia	
	Inpatient	Outpatient	Inpatient	Outpatient	Inpatient	Outpatient
Direct Medical Cost (DMC)	$83	$26	$81	$7	$245	$33
Direct Non-Medical Cost (DNMC)	$51	$9	$13	$5	$27	$17
Indirect Cost (IC)	$67	$27	$47	$28	$113	$107
Total Cost	$200	$62	$141	$40	$385	$158
Total Cost (RCC adjustment)	$213	$64	$181	$43	$278	$144
Patient's burden by expenditure type (DMC, DNMC, IC)	33%; 26%; 41%		2%; 18%; 80%		20%; 13%; 67%	
Proportion of private vs. public cost	44.7%; 55.3%		0.3%; 99.7%		19%; 81%	

6.3.2 Identification of high-risk areas and vaccine demand forecast

This investment case proposes identifying high-risk areas for vaccination and prioritizing geographical locations for vaccine distributions, taking into account the dengue-specific context as listed below:

- Spatial (geographical) variation of dengue occurrences (high-risk areas, non-risk areas)
- Temporal variation of dengue occurrences (pre-emptive, reactive strategies)
- Potential vaccine supply limitation during the initial phase of introduction at the population-level
- Safety concern of CYD-TDV (potential use of pre-screening tests focusing on high-risk areas)

- Financial burden for launching a nationwide immunization program at the population level

In Chapter 3 and Chapter 4, the Climate Risk Factor (CRF) index was developed based on three climate data (temperature, precipitation, and humidity) and two non-climate datasets (elevation, population density) (Lee et al., 2017a, Lee et al., 2017b). The CRF index was validated against empirical dengue incidence proxies, and the geographically dispersed risk levels of dengue fever were identified at the 5 km by 5 km resolution in Vietnam, Thailand, and Colombia (Lee et al., 2017b). The risk levels were categorized into 10 numerical scales which were then used to target populations at high risk, to identify disease hotspots and non-hotspots, and to estimate the required number of vaccine doses and uptake rates for the efficient allocation of vaccines. Given that vaccine supply might be limited during the early stage of the vaccine introduction, gradual uptake rates were taken into account for the first three years after introduction. Table 2 shows the estimated number of vaccine doses and coverage rates. Assuming a 3-dose scheme, approximately 2.6, 1.2, and 1 million doses were estimated to vaccinate populations at high risk when conducting routine vaccination of 9 years old at year 1 (uptake level 1). Then, the numbers went up to 4.5, 2.3, and 1.6 million doses three years after the introduction, as vaccination was expanded to broader areas in Vietnam, Thailand, and Colombia respectively. Adding a one-off catch-up campaign of 10-17 year olds to the routine immunization would require an additional 13 to 32 million doses, with Vietnam having the highest number of doses and Colombia having the lowest number of doses at year 3 when the full uptake level was achieved. The number of populations residing in high-risk areas was a major driver in determining the number of vaccine doses. The provinces demanding most vaccines were

Binh Thuan in Vietnam, Chon Buri in Thailand, and Valle del Cauca in Colombia. During an endemic period, coverage rates for vaccinating populations-at-risk were estimated to be 91%, 90%, and 63% of targeted age-group populations in Vietnam, Thailand, and Colombia respectively. In the case of an epidemic period, and if only focusing on disease hotspots for all three countries, approximately 50% of the targeted age group would be required to get vaccinated. If the reactive vaccination strategy expanded target areas into non-hotspots as well, coverage rates of target populations would go up to 65% in Colombia and over 90% in Vietnam and Thailand. In the case of reactive vaccination, one of the key factors was timing of interventions. In Chapter 3, an early warning signal model was developed to detect dengue outbreaks in order to facilitate reactive vaccinations (Lee et al., 2017a). More detailed geographical locations of risk areas at the finer resolution were fully described in (Lee et al., 2017b).

Table 2. Vaccine demand forecasts and coverage rates

	Vietnam	**Thailand**	**Colombia**
No. of doses for routine vaccination (at year 1; at year 3 in million)	2.6; 4.5	1.3; 2.3	1; 1.6
No. of doses for catch-up vaccination (at year 1; at year 3 in million)	18.5; 32.4	10.7; 19.2	8.5; 13.3
No. of doses for reactive vaccination (hotspots only; hotspots & non-hotspots in million)	16.6; 28	9.4; 16.2	7.2; 10.9
Coverage rates (endemic, uptake level 1-3)	53%; 76%; 91%	49%; 73%; 90%	40%; 54%; 63%
Coverage rates (epidemic, hotspots only; hotspots & non-hotspots)	55%; 92%	54%; 93%	43%; 65%

6.3.3 Expected public health impacts of the investment

Given the safety concern of CYD-TDV which was recently announced by Sanofi Pasteur

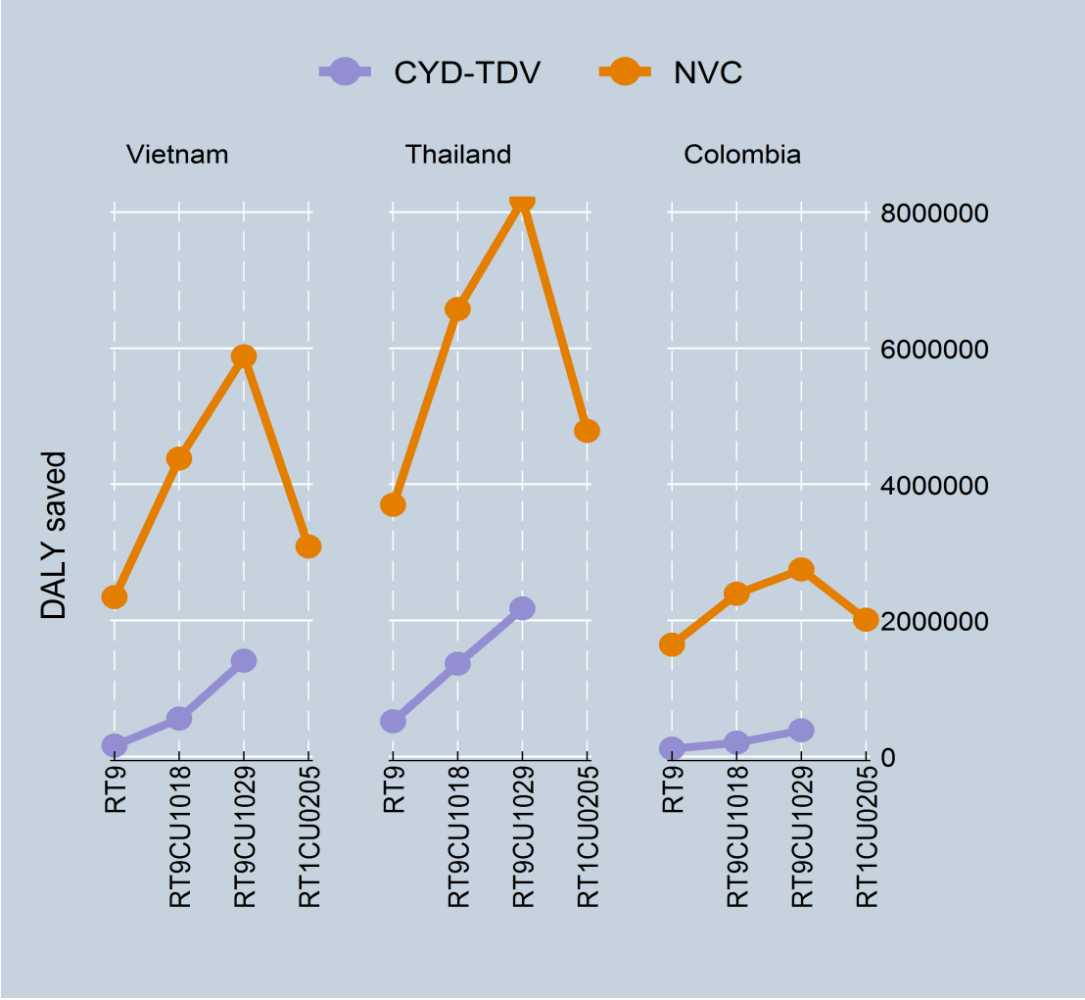
and WHO (Sanofi Pasteur, 2017, World Health Organization, 2017b), Chapter 5 aims to understand the impacts of vaccine interventions using two different vaccine profiles: (1) CYD-TDV, (2) a new vaccine candidate (NVC). The vaccination impacts of both vaccines were estimated using an individual-based meta-population transmission model that was previously developed by Oxford/Exeter group and used for the WHO-Strategic Advisory Group of Experts (SAGE) working group exercise. The efficacy rates of CYD-TDV were obtained from the actual clinical trial outcomes (Hadinegoro et al., 2015), but vaccine efficacy for NVC was assumed to be 80% against all four serotypes given that there were no efficacy data available for any of the second-generation vaccine candidates at the time of this research (Lee et al., 2018). Since the two large clinical trials of CYD-TDV in Asia (CYD14) and Latin America (CYD15), the hospital-based follow-up study of CYD-TDV has been conducted in order to understand the long-term safety of the vaccine (Hadinegoro et al., 2015). One of the findings in the hospital-based phase study was the increased risk of developing more severe illness among vaccinated seronegative individuals (Hadinegoro et al., 2015). The exact cause of the elevated risk of hospitalization is unclear. A potential explanation is that vaccination mimics a silent natural infection in providing short-lived heterologous protection followed by the waning effect of vaccine-induced immunity. A first natural infection after vaccination with CYD-TDV then acts as a secondary-like breakthrough infection among seronegative vaccine recipients (Flasche et al., 2016b, Lee et al., 2018). Considering this safety concern of CYD-TDV, a key distinction between CYD-TDV and NVC (apart from varying efficacy rates and vaccine half-life) was presumed to be that vaccination with NVC does not act as a silent infection, whereas vaccination with CYD-TDV does. The following seroprevalence rates of 9 year olds were

used from published data: 62.1% in Vietnam, 79.5% in Thailand, and 20.5% in Colombia (Carabali et al., 2017, L'Azou et al., 2016). Four vaccination strategies were considered: routine vaccination of 9 year olds (RT9), RT9 with a one-off catch-up campaign of 10-18 year olds (RT9CU1018), RT9CU1029, and RT1CU0205 (only for NVC). Disability-adjusted life years (DALYs) were estimated using country-specific parameters obtained from existing literature. The full details on model construction and parameters can be found in Chapter 5 (Lourenco and Recker, 2013, Lourenço and Recker, 2016, Flasche et al., 2016b, Lee et al., 2018).

In general, due to the higher efficacy and the longer half-life assumed for NVC, vaccination with NVC appeared to be more effective than vaccination with CYD-TDV. As expected, vaccination with CYD-TDV in the low seroprevalence setting (i.e. Colombia) caused more hospitalized cases, because the majority of vaccine recipients were seronegative individuals who would then be primed to have a secondary-like infection which is associated with more severe illness. While both vaccines demonstrated the positive impacts of vaccination (disease reduction), the level of the positive impacts decreased as time went by, given vaccine waning effects. In particular, some of the vaccination strategies which involve the mass uptake of vaccination (i.e. catch-up campaigns) resulted in disease rebounds owing to the waning effects of vaccine efficacy. Nonetheless, both CYD-TDV and NVC averted a positive number of DALYs for all four strategies during the 30-year period across the three countries. As shown in Figure 1, a higher number of DALYs was saved by vaccination with NVC than by vaccination with CYD-TDV. Even if some of the mass catch-up campaigns caused disease rebounds due to the waning effects of the vaccines, the overall aggregated number of averted DALYs was

positive for the predicted period. Considering the range of total vaccination costs per person from $0 to $150, any vaccination costs within the range would be cost-effective with NVC at the threshold cost of $2,000 per DALY averted across the countries. On the other hand, in order to be cost-effective at the same threshold per DALY averted when using CYD-TDV, vaccination costs varied. The detailed outcomes with diverse scenarios are available in (Lee et al., 2018).

Figure 1. Total number of DALYs saved



6.4 Constraints

There are several potential impediments of this proposed investment case First, the safety signal of CYD-TDV on seronegative individuals indicates that vaccination with CYD-TDV at the population-level should be carefully determined. Second, it is uncertain when any second-generation vaccines (i.e. NVC-like vaccines) will become available and whether actual second-generation vaccines will remedy the shortcomings of CYD-TDV. Third, seroprevalence rates are geographically dispersed, and this may cause the variability of vaccination impacts and cost-effectiveness for vaccine interventions within a country. Fourth, it is important to meet the potential demand for new and safe dengue vaccines which are dependent upon the production capacity of vaccine manufacturers. Fifth, increasing awareness of dengue fever among donor communities is critical to launch dengue vaccination campaigns, because all three countries will face the financial burden of a new population-level vaccine intervention given many other competing health problems.

6.5 Recommendations

Considering that CYD-TDV is currently available and that new second-generation vaccine candidates (NVC) arein phase 3 trials, the findings from Chapter 2 to Chapter 5 of the thesis provides vaccine-specific recommendations separately for CYD-TDV and NVC assuming that NVC will not be subject to the safety concern raised by CYD-TDV.

Recommendations with CYD-TDV

- With CYD-TDV, targeting 9 year olds for routine vaccination and 10-29 year olds

for a one off catch-up campaign (RT9CU1029) is the most cost-effective strategy among the three vaccination strategies considered in Vietnam, Thailand, and Colombia. However, care must be taken that this outcome should be interpreted as the overall impact of the intervention at the population-level. As previously indicated (Flasche et al., 2016b, Lee et al., 2018), vaccinating seronegative individuals who have not had any previous dengue infection at the time of vaccination may cause more severe illness at the individual-level.

- More precisely, Sanofi Pasteur, the manufacturer of CYD-TDV, recently announced that while CYD-TDV provides protective benefits against dengue fever for those who had prior infection, it is possible that vaccinated seronegative individuals might develop more severe illness following a subsequent dengue infection (Sanofi Pasteur, 2017). WHO also updated its position reflecting that CYD-TDV should be only administered to those who are seropositives at the time of vaccination (World Health Organization, 2017b).

- Considering the safety signal of CYD-TDV and the recent announcements, it is inevitable that it will be necessary to identify seropositive individuals of target age groups in order to conduct vaccination with CYD-TDV. One way to do this is to test target individuals prior to vaccination, so as to screen them out. However, rapid diagnostic tests are currently not available to determine serostatus in vaccination sites, and testing broad target populations would make vaccination campaigns highly costly. Thus, it is recommended that it will be desirable to identify disease hotspots within a country for the screening test. While existing surveillance study outcomes are helpful to determine high-risk areas, the

surveillance data is limited in number, and such studies often do not cover wide geographical areas in countries. Alternatively, the Climate Risk Factor (CRF) index which is available at the finer resolution (5 km by 5 km), with coverage of the whole country, can be used to detect potential high-risk areas for dengue fever (Lee et al., 2017b).

Recommendations with NVC

- With NVC, the most cost-effective strategy by country is RT9CU1029 in Vietnam, RT9CU1018 in Thailand, and RT1CU0205 in Colombia. The target age group of the most cost-effective strategy in Colombia is the younger age cohorts where vaccination with CYD-TDV was not suggested by the previous WHO-SAGE recommendation. In particular, for a NVC-like vaccine which has efficacy of 80% against all four serotypes with the coverage rate of 80%, it was shown that the proportion of disease reduction reaches approximately 80%, and this level of protection is kept throughout the predicted period in Colombia (Lee et al., 2018).

- A NVC-like vaccine eliminates the increasing risk of hospitalization for vaccinated seronegative individuals due to the absence of the role of silent infection. This certainly provides additional benefits to dengue-endemic countries in low-seroprevalence settings compared to the use of CYD-TDV. However, in the longer term, NVC with the absence of silent infection may increase more severe cases compared to CYD-TDV in a high-seroprevalence setting if NVC does not provide prolonged protection. In other words, those who had primary natural infections at the time of vaccination would likely experience their natural secondary infections

in this high-seroprevalence setting once the efficacy of NVC wanes.

- Even if NVC is assumed to be free from the existing safety signal of CYD-TDV, it is still recommended that it will be desirable to identify populations in high-risk areas based on the CRF index and surveillance data in order to prioritize areas for vaccination due to the following reasons: (1) upon the development of NVC, there may be a vaccine supply shortage at least during the early phase of vaccine introduction; (2) given that there are many other competing health problems in the three countries, vaccinating high-risk areas during the initial stage of the introduction and expanding vaccination areas in the following years would reduce the financial burden of the governments, (3) considering that none of the three countries has introduced a population-level vaccination campaign for dengue fever, prioritizing high risk areas would facilitate controlling the disease in the short-run.

6.6 Summary

The development of a safe and effective dengue vaccine poses a number of challenges due in part to the complicated nature of dengue fever. However, the first dengue vaccine (Dengvaxia, CYD-TDV) became available in 2016, and with several second-generation vaccine candidates currently in development, it appears that a broader range of dengue vaccines may be possible in the future. The current thesis summarizes the comprehensive economic evaluation outcomes for the current and future dengue vaccines in three dengue-endemic countries and underscores the role of a country-specific investment case prior to the introduction of vaccination at the population-level.

In Chapter 2, a standardized set of field surveys were implemented in order to understand the economic burden of dengue fever in Vietnam, Thailand, and Colombia. In addition, the logit model was constructed to identify factors explaining variance of disease severity. Compared to previous economic burden studies shown in Chapter 1, Chapter 2 presented costs items in a standardized manner to make more accurate comparisons among the countries. Given that this study was carried out in locations where epidemiologic studies were being conducted at the same time, care must be taken when generalizing the estimates beyond the study sites. Nonetheless, considering that the cost is not supposed to be as variable as the charge, we applied the ratio of cost-to-charge (RCC) to convert the value of charge into the value of cost.

In Chapter 3 and 4, an early warning signal (EWS) model was developed for dengue outbreaks, and high risk areas for dengue fever were identified at the 5 km by 5 km resolution. Apart from pre-emptive vaccination strategies, which are extensively discussed in the current investment case, it would be worthwhile to start considering reactive vaccination strategies because all three countries are also exposed to the risk of periodic outbreaks. Previous studies indicated that the most challenging issues for reactive vaccination are to capture the right timing of an outbreak and to make a clear identification of geographical areas to be targeted (Azman and Lessler, 2015, Chaignat and Monti, 2007, Lee et al., 2017b). The existing models on early warning systems can be used to find the right timing of intervention (Lee et al., 2017a, Huang et al., 2015, Lowe et al., 2013), and the CRF index at the refined resolution can also serve as a useful tool to predict potential disease hotspots during an outbreak (Lee et al., 2017b, Lee et al., 2017a). The concepts and methodologies applied in both Chapter 3 and 4 are unconventional but clearly underscore

the need for innovative approaches in order to respond to existing public health problems. Nonetheless, some of the climate datasets have coarse resolution, thus the datasets were resampled using the nearest option. For future research, this should be further improved based on climate datasets with finer scale resolutions.

Lastly, in Chapter 5 the vaccination impacts and cost-effectiveness were estimated for CYD-TDV and a new vaccine candidate (NVC). The study outcomes were derived by applying country-specific parameters, as well as by reflecting the most up-to-date information on the dengue vaccine development. The findings from Chapter 5 are meaningful to understand the safety signal of CYD-TDV at the population-level and to highlight the desirable features of new and improved dengue vaccines. Given the limited use of CYD-TDV, it will be particularly important to keep an eye on the detailed characteristics of future vaccines and to understand their potential impacts at the population-level.

As the dengue vaccination era finally began, I hope that my DPhil research work contributes to filling the existing knowledge gaps in the three dengue-endemic countries, and, furthermore, provides valuable lessons to other dengue-endemic countries.

7. Appendix: Supplementary information

7.1 Chapter 2

Supplementary Table 1. The number of days lost due to illness

	Vietnam (SD, range)		Thailand (SD, range)		Colombia (SD, range)	
	Inpatient	**Outpatient**	**Inpatient**	**Outpatient**	**Inpatient**	**Outpatient**
No. of days lost (patients)[a]	6.9 (2.9, 0-16)	5.7 (1.7, 3-10)	6.1 (2.3, 2-14.5)	4.0 (1.6, 1-8)	7.4 (2.3, 3-14.5)	6.1 (1.9, 2-13)
No. of days lost (substitute laborers)[b]	7.0 (10.1, 0-44)	2.1 (4.0, 0-10)	0.0	0.0	3.8 (4.3, 0-8)	3.3 (3.7, 0-11)
No. of days lost (caregivers)[c]	8.1 (7.6, 0-44)	2.0 (3.2, 0-14)	2.1 (2.2, 0-6)	2 (2.8, 0-6)	5.4 (3.7, 0-11)	4.9 (4.3, 0-20)

[a] The average number of days lost due to illness for all enrolled patients older than 5 years old.

[b] The average number of days lost for all substitute laborers per patient among those who had at least 1 substitute laborer.

[c] The average number of days lost for all caregivers per patient among those who had at least 1 caretaker.

Supplementary Table 2. Average economic burden in PPP

(a) Average economic burden of dengue fever per episode in PPP

	Vietnam[a]						Thailand						Colombia					
	Inpatient (n = 59)			Outpatient (n = 92)			Inpatient (n = 45)			Outpatient (n = 40)			Inpatient (n = 70)			Outpatient (n = 160)		
	I$[c]	BT CI[b] (lower, upper)		I$	BT CI (lower, upper)		I$	BT CI (lower, upper)		I$	BT CI (lower, upper)		I$	BT CI (lower, upper)		I$	BT CI (lower, upper)	
Direct Medical Cost (DMC)	$235	$176	$307	$74	$62	$87	$214	$178	$250	$18	$15	$21	$415	$335	$501	$56	$50	$62
Direct Non-Medical Cost (DNMC)	$144	$126	$165	$27	$19	$36	$33	$18	$56	$12	$10	$15	$45	$34	$58	$30	$25	$35
Indirect Cost (IC)	$191	$137	$253	$76	$56	$102	$125	$96	$157	$75	$62	$88	$192	$144	$243	$181	$128	$245
Total Cost	$571	$471	$682	$177	$147	$212	$371	$313	$433	$105	$90	$120	$651	$559	$748	$266	$210	$333
Total Cost per Day	$82	$67	$98	$28	$24	$33	$49	$41	$59	$17	$15	$19	$64	$55	$74	$30	$24	$37
Total Cost (RCC adjustment)	$609	$500	$729	$182	$153	$217	$479	$405	$555	$113	$98	$128	$470	$404	$537	$243	$187	$309

[a] Because data collection was done in 2012 in Vietnam, the estimates were inflated to 2014 USD.

[b] Bootstrapping with the percentile method.

[c] All local currency values were converted using the Purchasing Power Parity (PPP) conversion factor from World Bank.

(b) Disaggregated average economic burden of dengue fever per episode in PPP

	Vietnam						Thailand						Colombia					
	Inpatient			Outpatient			Inpatient			Outpatient			Inpatient			Outpatient		
	USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)	
Direct Medical Cost (DMC), age < 15	$301	$174	$485	$67	$48	$89	$192	$139	$246	$17	$14	$20	$358	$252	$477	$52	$44	$61
Direct Medical Cost (DMC), age ≥ 15	$207	$149	$276	$76	$62	$91	$234	$186	$281	$21	$15	$29	$442	$340	$560	$58	$51	$67
Direct Non-Medical Cost (DNMC), age < 15	$158	$130	$187	$40	$21	$63	$21	$14	$29	$12	$10	$15	$56	$35	$82	$27	$21	$35
Direct Non-Medical Cost (DNMC), age ≥ 15	$138	$115	$164	$22	$14	$32	$44	$17	$86	$12	$8	$17	$40	$27	$56	$31	$25	$38
Indirect Cost (IC), age < 15	$214	$135	$316	$84	$58	$115	$137	$94	$189	$84	$70	$98	$100	$47	$165	$146	$67	$264
Indirect Cost (IC), age ≥ 15	$181	$113	$260	$74	$49	$108	$113	$77	$153	$52	$26	$76	$236	$174	$306	$205	$142	$279

Supplementary Table 3. Indirect cost break-down

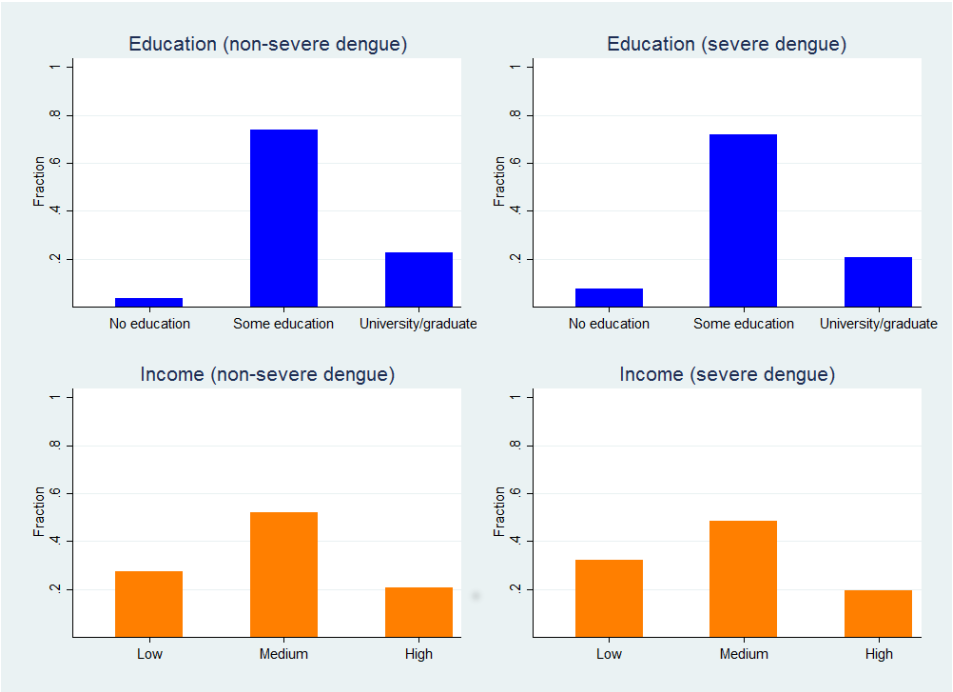
	Vietnam						Thailand						Colombia					
	Inpatient (n = 59)			Outpatient (n = 92)			Inpatient (n = 45)			Outpatient (n = 40)			Inpatient (n = 70)			Outpatient (n = 160)		
	USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)	
Patient's wage loss	$15	$9	$22	$18	$13	$24	$36	$28	$44	$27	$23	$32	$91	$66	$119	$47	$37	$59
Substitute labor cost	$10	$4	$18	$2	$0	$4	$0	$0	$0	$0	$0	$0	$6	$1	$14	$22	$6	$44
Caregiver cost	$41	$27	$59	$7	$4	$11	$11	$4	$21	$1	$0	$3	$16	$6	$28	$37	$16	$69

* The costs were converted by the official exchange rates

	Vietnam						Thailand						Colombia					
	Inpatient (n = 59)			Outpatient (n = 92)			Inpatient (n = 45)			Outpatient (n = 40)			Inpatient (n = 70)			Outpatient (n = 160)		
	USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)	
Patient's wage loss	$44	$27	$64	$51	$37	$70	$95	$74	$116	$72	$61	$84	$154	$112	$201	$80	$63	$100
Substitute labor cost	$29	$11	$52	$5	$0	$11	$0	$0	$0	$0	$0	$0	$10	$1	$23	$37	$10	$74
Caregiver cost	$118	$76	$169	$21	$11	$31	$30	$11	$56	$3	$0	$8	$27	$10	$48	$63	$27	$117

* The costs were converted by the PPP rates

Supplementary Figure 4. Distribution of education and income

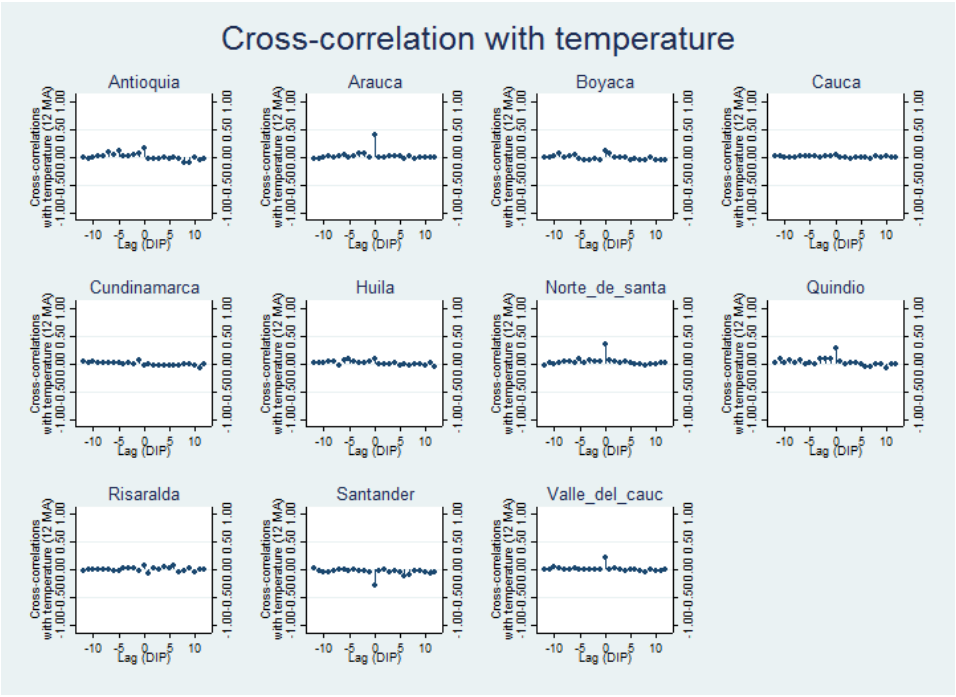


7.2 Chapter 3

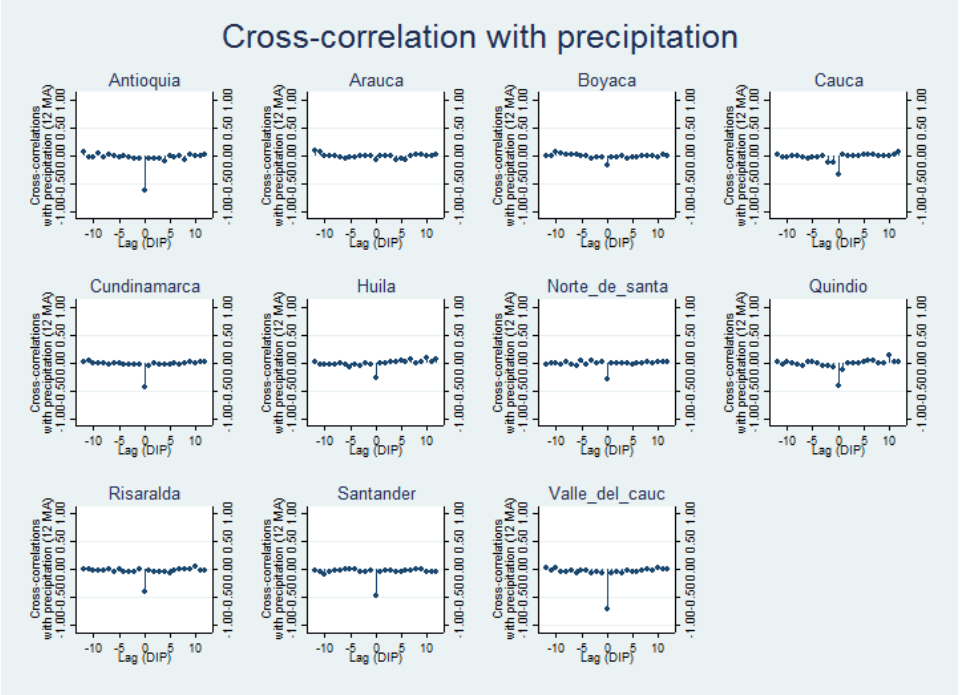
Supplementary 1. Cross-correlograms of climate datasets and DIP

A cross-correlogram is useful to check correlations between one variable and another variable with time lags. This study presumed that a current epidemic is a result of the climate conditions observed during the past months, rather than single temporal values at present. In this regard, cross-correlations between various periods (current, 6, 12 months) of the moving averages of the climate datasets and observed Dengue Incidence Proxy (DIP) with time lags were examined. The 12-month moving average was selected as the most appropriate period which explains the current status (lag 0) of DIP. In the figure below, the 12-month moving averages were plotted against DIP with time lags. Overall, while temperature and humidity are positively related to DIP at lag 0, precipitation shows negative relationships with the current status of DIP. It should be noted that more consistent and stronger correlations were observed for precipitation and humidity than temperature across departments.

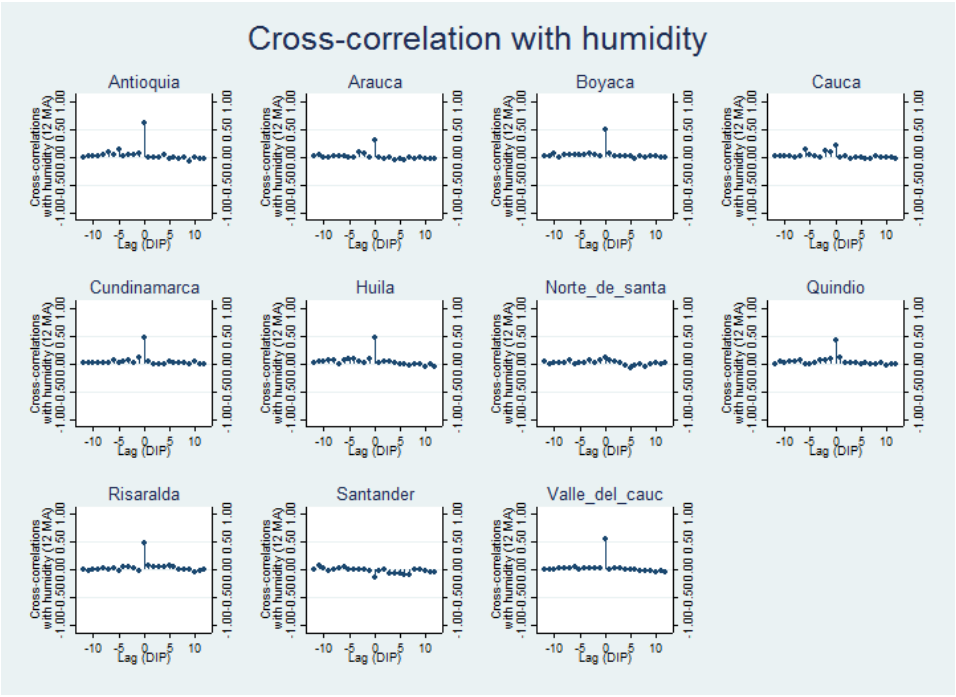
Supplementary Figure 1(a). Cross-correlation with temperature



Supplementary Figure 1(b). Cross-correlation with precipitation



Supplementary Figure 1(c). Cross-correlation with humidity



Supplementary 2. Model specifications (Hilbe 2011, Haab and McConnel 2002)

The Poisson probability density function can be written as:

$$\Pr(y_i = n) = \frac{e^{-\lambda_i}\lambda_i^n}{n!}, \quad n = 0, 1, 2 \ldots$$

where *n* is observed count, and λ_i is the mean, $\lambda_i = \exp(x_i\beta)$. For the Poisson model, the mean is equal to the variance of the distribution. However, the variance tends to be greater than the mean in many situations, and this is called overdispersion. When overdispersion exists, the standard errors estimated in the Poisson mode are underestimated, causing the rejection of null hypotheses of no association.

The negative binomial technique relaxes the assumption of equality of the mean and variance by adding a gamma distributed error term. A common version of the negative binomial model is as follows:

$$E(y_i|x_i\beta) = \lambda_i = \exp(x_i\beta)$$

$$\log\big(E(y_i)\big) = x_i\beta + \theta_i$$

where θ_i represents unobserved individual differences (or unobserved heterogeneity).

$$Pr(y) = \frac{\Gamma(y_i + \frac{1}{\alpha})}{\Gamma\left(y_i + \frac{1}{\alpha}\right)\Gamma(\frac{1}{\alpha})}\left(\frac{\frac{1}{\alpha}}{\frac{1}{\alpha} + \lambda_i}\right)^{\frac{1}{\alpha}}\left(\frac{\lambda_i}{\frac{1}{\alpha} + \lambda_i}\right)^{y_i}$$

where $\lambda_i = \exp(x_i\beta)$. The mean of the negative binomial distribution is $E(y_i) = \lambda_i = \exp(x_i\beta)$. However, now the variance of the dependent variable is $V(y_i) = \lambda_i(1 + \alpha\lambda_i)$. The parameter α is considered to be the overdispersion parameter.

In order to check overdispersion, Z-tests score was used. Z-tests score examines the hypothesis that the Poisson model is overdispersed.

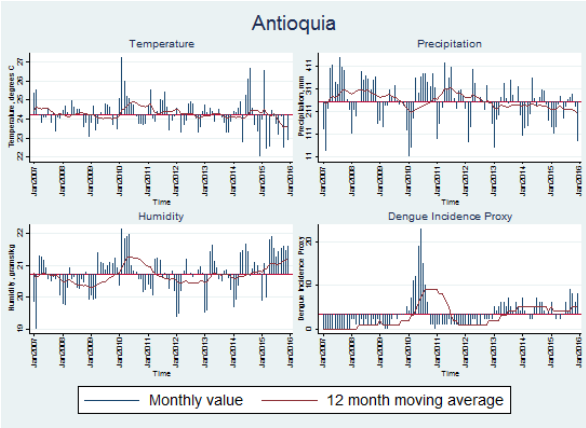
$$Z_i = \frac{(y_i - \mu_i)^2 - y_i}{\mu_i\sqrt{2}}$$

where y_i = observation i, μ_i = predicted value of i.

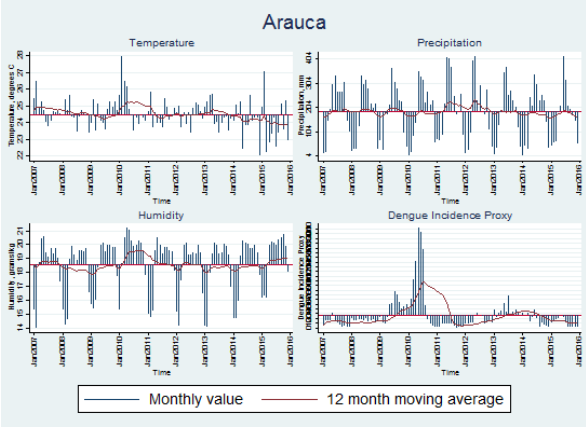
After regressing Z, if Z coefficient is significant, the hypothesis of no overdispersion is rejected.

Supplementary 3. Climate factors and DIP over time by department

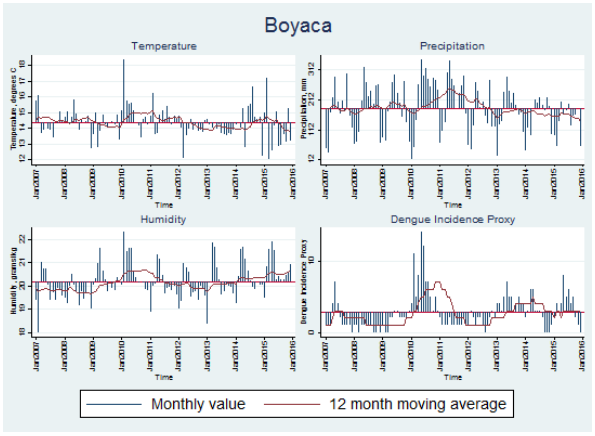
Supplementary Figure 3(a). Antioquia



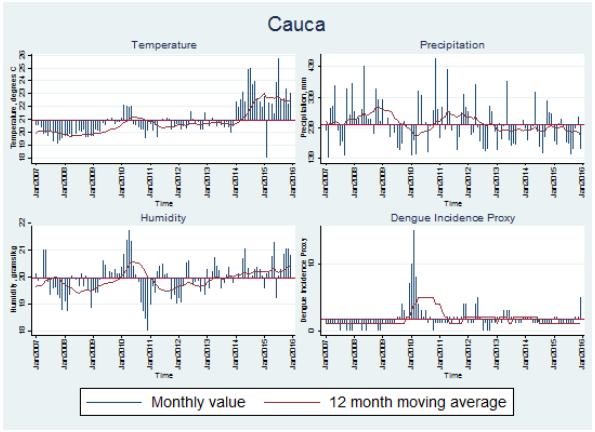
Supplementary Figure 3(b). Arauca



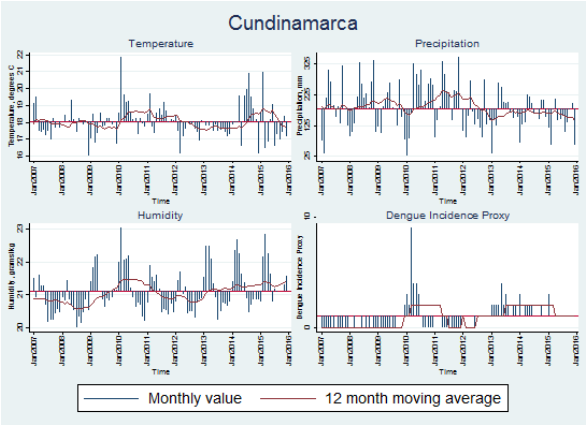
Supplementary Figure 3(c). Boyaca



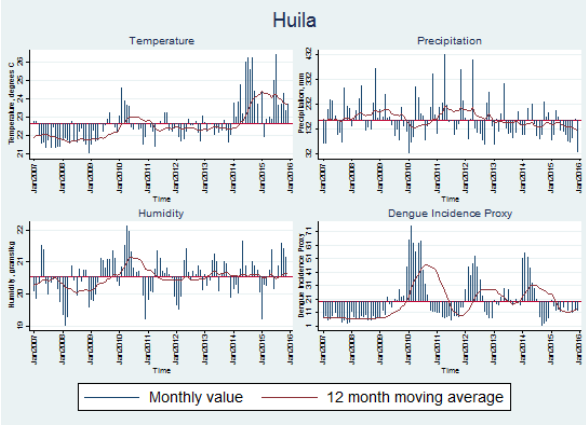
Supplementary Figure 3(d). Cauca



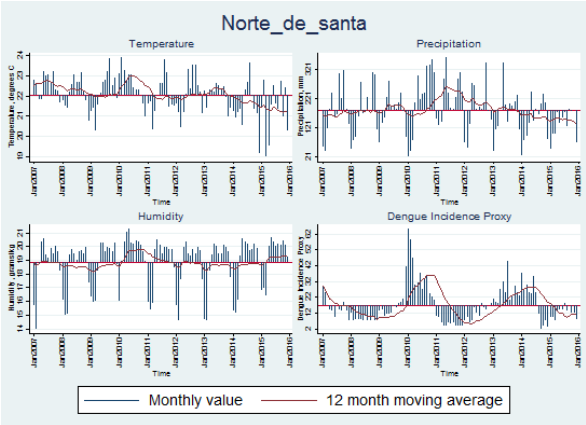
Supplementary Figure 3(e). Cundinamarca



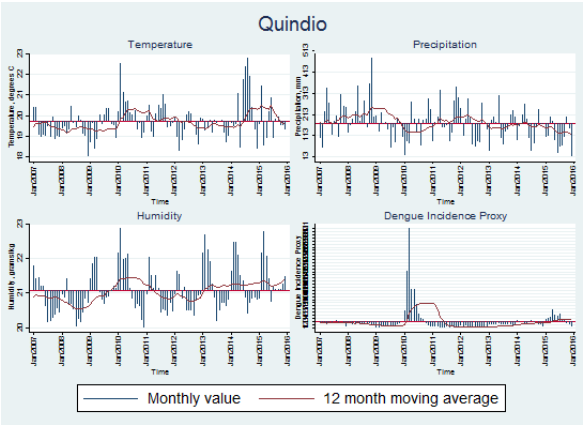
Supplementary Figure 3(f). Huila



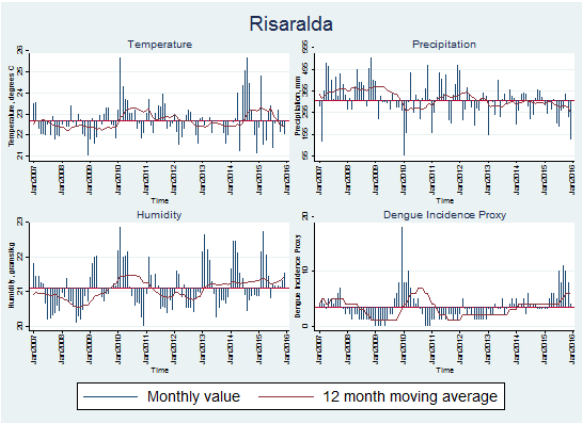
Supplementary Figure 3(g). Norte de Santa



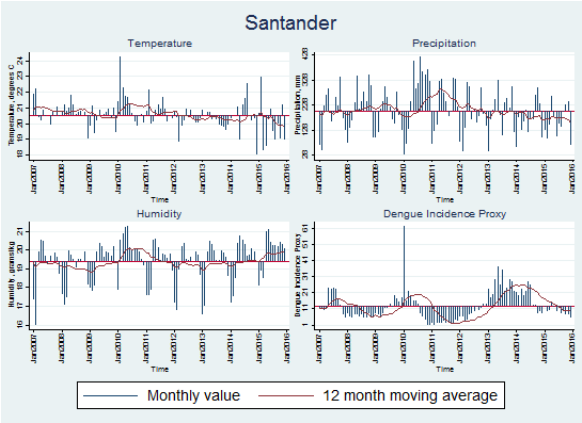
Supplementary Figure 3(h). Quindio



Supplementary Figure 3(i). Risaralda



Supplementary Figure 3(j). Santander



Supplementary 4. The CRF index and DIP over time by department

Supplementary Figure 4



* DIP was smoothed out to reduce short-term fluctuations and highlight longer term trends for demonstration

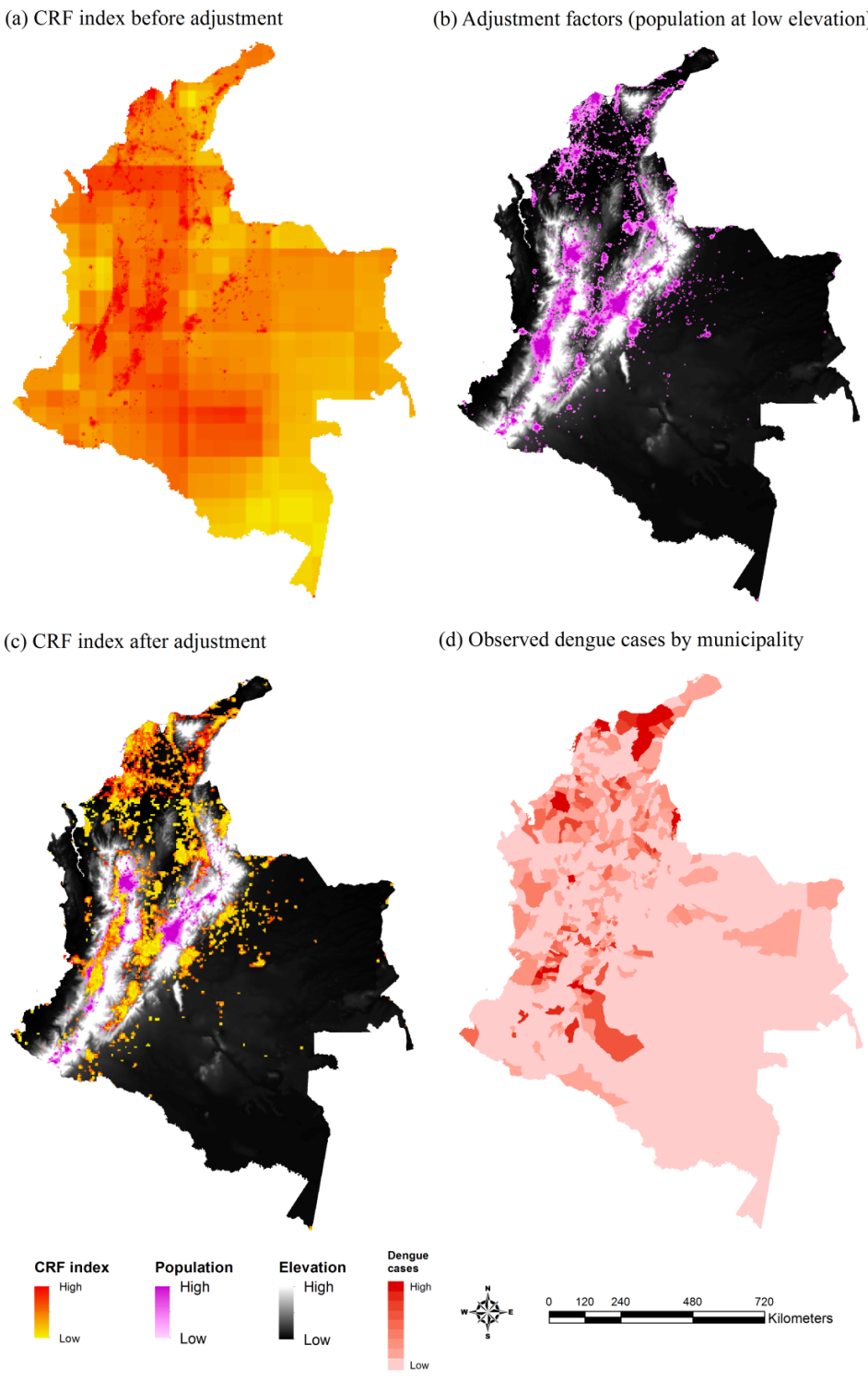
**Zika cases were reported in 2015 as well, but zika incidence rates (/100,000) were not clearly shown for year 2015 due to the low number of reported cases

Supplementary 5. Identification of high risk areas for dengue fever

Given that the CRF index explains variation in DIP reasonably well, the CRF index was estimated at 5km by 5km resolution, and the most recent time of the index (December 2015) was presented in Supplementary figure 5. Figure 5(a) depicts the CRF index without taking into account the population at different elevation levels. Overall, the Western part of Colombia is at higher risk than the Eastern part of the country. Apart from the impact of

the climate factors, this is also partly due to population density. Looking at Figure 5(b), population density appeared to be a lot higher in the North-Western areas of Colombia compared to the South-Eastern. The CRF index was then adjusted by the risk proportion and shown in Figure 5(c). As expected, populations at high risk are concentrated in the Western part of the country due to more suitable climate conditions for vector mosquitoes and the high population level compared to the East. In fact, the total number of cases reported from four departments in the East side of the country (Amazonas, Guainia, Vaupes, and Vichada) was only 2.5% of the total cases (5,524) reported from Valle del Cauca alone throughout 2015. There are areas where high population level was observed (purple in Figure 5(c)) but not identified as high-risk areas. This is the population living at high elevation. Bogota would be a good example where dengue has not been prevalent despite the high level of population density in the city. Lastly, Figure 5(d) shows the reported dengue cases in December 2015 by municipality. It is clear to see that the high risk areas identified by the model (Figure 5(c)) are consistent with the municipalities with the actual high caseloads shown in Figure 5(d). Using the geo-coordinates of the high risk areas at 5km by 5km resolution, it is possible to identify the locations for people at high risk more accurately for the disease prevention activities.

Supplementary Figure 5. CRF index before and after the adjustment of population at low elevation in Dec, 2015



Source: Authors' analysis of data from National Oceanic and Atmospheric Administration (NOAA)

Supplementary 6. EWS for 11 departments during the study period

The table below shows Early Warning Signals (EWS) during the study period for 11 departments. 23 outbreaks were detected using the slope of DIP, and one unusual peak was manually added after qualitative adjustment. Correct warning signals 1~5 months ahead of time, correct warning signals in the same month, and missed warning signals were marked as a, b, and c, respectively. In addition, sensitivity (SE), specificity (SP), positive predictive value (PPV), and negative predictive value (NPV) were summarized in Table S6(b).

Table S6(a)

Department	Time	DIP[d]	Outbreak peak	EWS[e]
Antioquia	Nov-09	3		Low
Antioquia	Dec-09	5		Low
Antioquia[a]	Jan-10	4		High
Antioquia	Feb-10	7		High
Antioquia	Mar-10	11		High
Antioquia	Apr-10	12		High
Antioquia	May-10	19		High
Antioquia	Jun-10	23	V	High
Antioquia	Jul-10	15		.
Antioquia	Aug-10	10		.
…	…	…		…
Antioquia	May-15	2		.
Antioquia	Jun-15	3		.
Antioquia[a]	Jul-15	6		High
Antioquia	Aug-15	4		High
Antioquia	Sep-15	9	V	High
Antioquia	Oct-15	8		High
Antioquia	Nov-15	6		High
Antioquia	Dec-15	8		High

Department	Time	DIP	Outbreak peak	EWS
Arauca	Apr-09	21		.
Arauca[a]	May-09	50		Low
Arauca	Jun-09	52		Low
Arauca	Jul-09	77	V	Low
Arauca	Aug-09	70		Low
Arauca	Sep-09	55		Low
Arauca	Oct-09	41		.
…	…	…		…
Arauca	Jan-10	43		.
Arauca[a]	Feb-10	61		High
Arauca	Mar-10	102		High
Arauca	Apr-10	141		High
Arauca	May-10	212	V	High
Arauca	Jun-10	203		High
Arauca	Jul-10	167		High
Arauca	Aug-10	47		.
Arauca	Sep-10	18		.
…	…	…		…
Arauca	Mar-13	30		.
Arauca	Apr-13	35		.

Arauca[a]	May-13	51		Low
Arauca	Jun-13	34		Low
Arauca	Jul-13	67	V*	Low
Arauca	Aug-13	27		Low
Arauca	Sep-13	33		.
Arauca	Oct-13	39		.

Department	Time	DIP	Outbreak peak	EWS
Boyaca	Nov-09	2		.
Boyaca	Dec-09	3		Low
Boyaca[a]	Jan-10	4		Medium
Boyaca	Feb-10	11		Medium
Boyaca	Mar-10	5		Medium
Boyaca	Apr-10	8		Medium
Boyaca	May-10	14	V	Medium
Boyaca	Jun-10	12		Medium
Boyaca	Jul-10	7		.
Boyaca	Aug-10	7		.

Department	Time	DIP	Outbreak peak	EWS
Cauca	Nov-09	2		Low
Cauca	Dec-09	7		Low
Cauca[a]	Jan-10	10		Medium
Cauca	Feb-10	15	V	Medium
Cauca	Mar-10	8		Medium
Cauca	Apr-10	4		Medium
Cauca	May-10	3		.
Cauca	Jun-10	2		.
…	…	…		…
Cauca	Jul-15	1		.
Cauca	Aug-15	1		.
Cauca[a]	Sep-15	1		High
Cauca	Oct-15	2		High
Cauca	Nov-15	2		High
Cauca	Dec-15	5	V	High

Department	Time	DIP	Outbreak peak	EWS
Cundinamarca	Nov-09	1		Low
Cundinamarca	Dec-09	2		Low
Cundinamarca[a]	Jan-10	3		High
Cundinamarca	Feb-10	2		High
Cundinamarca	Mar-10	9	V	High
Cundinamarca	Apr-10	4		High
Cundinamarca	May-10	4		High
Cundinamarca	Jun-10	3		.
Cundinamarca	Jul-10	1		.
…	…	…		…
Cundinamarca	Nov-12	1		Low
Cundinamarca	Dec-12	1		Low
Cundinamarca[a]	Jan-13	2		Medium
Cundinamarca	Feb-13	2		Medium
Cundinamarca	Mar-13	2		Medium
Cundinamarca	Apr-13	2		Medium
Cundinamarca	May-13	4	V	Medium
Cundinamarca	Jun-13	2		Medium
Cundinamarca	Jul-13	3		.
Cundinamarca	Aug-13	2		.

Department	Time	DIP	Outbreak peak	EWS
Huila	Nov-09	23		Low
Huila	Dec-09	45		Low
Huila[a]	Jan-10	65		High
Huila	Feb-10	75	V	High
Huila	Mar-10	62		High

Huila	Apr-10	56		High
Huila	May-10	62		High
Huila	Jun-10	64		.
Huila	Jul-10	42		.
…	…	…		…
Huila	Nov-11	14		.
Huila	Dec-11	14		.
Huila	Jan-12	28		Low
Huila	Feb-12	45		Low
Huila	Mar-12	38		Low
Huila	Apr-12	47		Low
Huila[c]	May-12	53	V	Low
Huila	Jun-12	45		Low
Huila	Jul-12	35		.
Huila	Aug-12	23		.
…	…	…		…
Huila	Nov-13	18		.
Huila	Dec-13	16		.
Huila[a]	Jan-14	51		Medium
Huila	Feb-14	55	V	Medium
Huila	Mar-14	52		Medium
Huila	Apr-14	44		.
Huila	May-14	33		.

Department	Time	DIP	Outbreak peak	EWS
Norte de Santander	Nov-09	21		Low
Norte de Santander	Dec-09	41		Low
Norte de Santander[b]	Jan-10	65	V	High
Norte de Santander	Feb-10	58		High
Norte de Santander	Mar-10	47		High
Norte de Santander	Apr-10	30		High
Norte de Santander	May-10	31		.
Norte de Santander	Jun-10	37		.
…	…	…		…
Norte de Santander	Feb-13	19		.
Norte de Santander	Mar-13	18		.
Norte de Santander	Apr-13	27		Low
Norte de Santander	May-13	32		Low
Norte de Santander	Jun-13	25		Low
Norte de Santander[c]	Jul-13	45	V	Low
Norte de Santander	Aug-13	20		Low
Norte de Santander	Sep-13	23		.
Norte de Santander	Oct-13	29		.

Department	Time	DIP	Outbreak peak	EWS
Quindio	Nov-09	12		Low
Quindio	Dec-09	20		Low
Quindio[a]	Jan-10	54		High
Quindio	Feb-10	184		High
Quindio	Mar-10	321	V	High
Quindio	Apr-10	123		High
Quindio	May-10	125		High
Quindio	Jun-10	77		.
Quindio	Jul-10	43		.
…	…	…		…
Quindio	Nov-14	9		.
Quindio	Dec-14	2		.
Quindio[a]	Jan-15	28		Medium
Quindio	Feb-15	30		Medium
Quindio	Mar-15	33		Medium
Quindio	Apr-15	59	V	Medium
Quindio	May-15	42		Medium
Quindio	Jun-15	38		Medium
Quindio	Jul-15	46		High
Quindio	Aug-15	22		.
Quindio	Sep-15	26		.

Department	Time	DIP	Outbreak peak	EWS
Risaralda	Nov-09	8		Low
Risaralda[c]	Dec-09	18	V	Low
Risaralda	Jan-10	8		High
Risaralda	Feb-10	8		High
Risaralda	Mar-10	10		High
Risaralda	Apr-10	7		.
Risaralda	May-10	5		.
…	…	…		…
Risaralda	May-15	6		Medium
Risaralda	Jun-15	5		Medium
Risaralda[a]	Jul-15	10		High
Risaralda	Aug-15	8		High
Risaralda	Sep-15	11	V	High
Risaralda	Oct-15	10		High
Risaralda	Nov-15	8		High
Risaralda	Dec-15	4		.

Department	Time	DIP	Outbreak peak	EWS
Santander	Jun-07	23		.
Santander[b]	Jul-07	24	V	Low
Santander	Aug-07	23		Low
Santander	Sep-07	17		.
Santander	Oct-07	13		.
…	…	…		…
Santander	Nov-09	15		Low
Santander	Dec-09	18		Low
Santander[b]	Jan-10	62	V	High
Santander	Feb-10	16		High
Santander	Mar-10	22		High
Santander	Apr-10	19		.
Santander	May-10	16		.
…	…	…		…
Santander	Nov-12	14		Low
Santander	Dec-12	14		Low
Santander[a]	Jan-13	23		Medium
Santander	Feb-13	18		Medium
Santander	Mar-13	20		Medium
Santander	Apr-13	29		Medium
Santander	May-13	37	V	Medium
Santander	Jun-13	26		Medium
Santander	Jul-13	35		Medium
Santander	Aug-13	22		Medium
Santander	Sep-13	24		.
Santander	Oct-13	29		.

Department	Time	DIP	Outbreak peak	EWS
Valle del Cauca	Nov-09	16		Low
Valle del Cauca	Dec-09	24		Low
Valle del Cauca[a]	Jan-10	34		High
Valle del Cauca	Feb-10	59		High
Valle del Cauca	Mar-10	60	V	High
Valle del Cauca	Apr-10	36		High
Valle del Cauca	May-10	27		High
Valle del Cauca	Jun-10	30		.
Valle del Cauca	Jul-10	19		.
…	…	…		…
Valle del Cauca	Nov-12	4		.
Valle del Cauca	Dec-12	4		.
Valle del Cauca[a]	Jan-13	18		Medium
Valle del Cauca	Feb-13	16		Medium
Valle del Cauca	Mar-13	17		Medium
Valle del Cauca	Apr-13	28		Medium
Valle del Cauca	May-13	33	V	Medium
Valle del Cauca	Jun-13	26		Medium
Valle del Cauca	Jul-13	31		Medium

Valle del Cauca	Aug-13	19	.
Valle del Cauca	Sep-13	17	.

[a] Correct warning signals 1~5 months ahead of time

[b] Correct warning signals in the same month

[c] Missed warning signals

[d] Observed DIP

[e] Based on three categorization of the elasticities: low level warning (0-50%), medium level warning (50-75%), and high level warning (75-100%).

[*] This peak was manually added after checking the DIP trend

Table S6(b)

Department	SE	SP	PPV	NPV
Antioquia	100%	100%	100%	100%
Arauca	100%	100%	100%	100%
Boyaca	100%	100%	100%	100%
Cauca	100%	67%	50%	100%
Cundinamarca	100%	100%	100%	100%
Huila	67%	100%	100%	83%
Norte de Santander	50%	100%	100%	86%
Quindio	100%	100%	100%	100%
Risaralda	50%	100%	100%	86%
Santander	100%	100%	100%	100%
Valle del Cauca	100%	100%	100%	100%

Supplementary 7. EWS for 11 departments in 2015

There were some inconsistent patterns observed between CRF and DIP due to the unexpected emergence of Zika which started being reported in 2015. The estimated FAR went up to 25% during 2015. As Zika is another viral disease caused by *Aedes aegypti,* the increased FAR might be explained by the growing number of reported Zika cases.

Department	Time	DIP	EWS
Antioquia	Jan-15	6	.
Antioquia	Feb-15	3	.
Antioquia	Mar-15	2	.
Antioquia	Apr-15	3	.
Antioquia	May-15	2	.
Antioquia	Jun-15	3	.
Antioquia	Jul-15	6	High
Antioquia	Aug-15	4	High
Antioquia	Sep-15	9	High
Antioquia	Oct-15	8	High
Antioquia	Nov-15	6	High
Antioquia	Dec-15	8	High

Department	Time	DIP	EWS
Arauca	Jan-15	11	.
Arauca	Feb-15	12	.
Arauca	Mar-15	17	Medium
Arauca	Apr-15	20	Medium
Arauca	May-15	26	Medium
Arauca	Jun-15	22	Medium

Arauca	Jul-15	12	High
Arauca	Aug-15	2	.
Arauca	Sep-15	2	.
Arauca	Oct-15	1	.
Arauca	Nov-15	1	.
Arauca	Dec-15	1	.

Department	Time	DIP	EWS
Boyaca	Jan-15	2	High
Boyaca	Feb-15	4	High
Boyaca	Mar-15	3	High
Boyaca	Apr-15	4	High
Boyaca	May-15	8	High
Boyaca	Jun-15	5	.
Boyaca	Jul-15	6	.
Boyaca	Aug-15	4	.
Boyaca	Sep-15	5	.
Boyaca	Oct-15	2	.
Boyaca	Nov-15	1	.
Boyaca	Dec-15	0	.

Department	Time	DIP	EWS
Cauca	Jan-15	2	.
Cauca	Feb-15	2	High
Cauca	Mar-15	1	High
Cauca	Apr-15	1	High
Cauca	May-15	1	.
Cauca	Jun-15	1	.
Cauca	Jul-15	1	.
Cauca	Aug-15	1	.
Cauca	Sep-15	1	High
Cauca	Oct-15	2	High
Cauca	Nov-15	2	High
Cauca	Dec-15	5	High

Department	Time	DIP	EWS
Cundinamarca	Jan-15	3	High
Cundinamarca	Feb-15	1	High
Cundinamarca	Mar-15	1	.
Cundinamarca	Apr-15	1	.
Cundinamarca	May-15	1	.
Cundinamarca	Jun-15	1	.
Cundinamarca	Jul-15	1	.
Cundinamarca	Aug-15	1	.
Cundinamarca	Sep-15	1	.
Cundinamarca	Oct-15	1	.
Cundinamarca	Nov-15	1	.
Cundinamarca	Dec-15	1	High

Department	Time	DIP	EWS
Huila	Jan-15	20	.
Huila	Feb-15	15	.
Huila	Mar-15	12	.
Huila	Apr-15	13	.
Huila	May-15	11	High
Huila	Jun-15	14	.
Huila	Jul-15	19	High
Huila	Aug-15	12	High
Huila	Sep-15	19	High
Huila	Oct-15	10	.
Huila	Nov-15	13	.
Huila	Dec-15	12	.

Department	Time	DIP	EWS
Norte de Santander	Jan-15	9	.
Norte de Santander	Feb-15	9	Medium
Norte de Santander	Mar-15	7	Medium
Norte de Santander	Apr-15	13	Medium

Norte de Santander	May-15	14	Medium
Norte de Santander	Jun-15	14	Medium
Norte de Santander	Jul-15	18	High
Norte de Santander	Aug-15	13	High
Norte de Santander	Sep-15	17	High
Norte de Santander	Oct-15	12	.
Norte de Santander	Nov-15	12	.
Norte de Santander	Dec-15	8	.

Department	Time	DIP	EWS
Quindio	Jan-15	28	Medium
Quindio	Feb-15	30	Medium
Quindio	Mar-15	33	Medium
Quindio	Apr-15	59	Medium
Quindio	May-15	42	Medium
Quindio	Jun-15	38	Medium
Quindio	Jul-15	46	High
Quindio	Aug-15	22	.
Quindio	Sep-15	26	.
Quindio	Oct-15	14	.
Quindio	Nov-15	11	.
Quindio	Dec-15	4	.

Department	Time	DIP	EWS
Risaralda	Jan-15	3	.
Risaralda	Feb-15	3	.
Risaralda	Mar-15	5	Medium
Risaralda	Apr-15	6	Medium
Risaralda	May-15	6	Medium
Risaralda	Jun-15	5	Medium
Risaralda	Jul-15	10	High
Risaralda	Aug-15	8	High
Risaralda	Sep-15	11	High
Risaralda	Oct-15	10	High
Risaralda	Nov-15	8	High
Risaralda	Dec-15	4	.

Department	Time	DIP	EWS
Santander	Jan-15	12	.
Santander	Feb-15	9	.
Santander	Mar-15	10	High
Santander	Apr-15	15	High
Santander	May-15	12	High
Santander	Jun-15	9	High
Santander	Jul-15	12	High
Santander	Aug-15	8	.
Santander	Sep-15	9	.
Santander	Oct-15	7	.
Santander	Nov-15	7	.
Santander	Dec-15	5	.

Department	Time	DIP	EWS
Valle del Cauca	Jan-15	14	Medium
Valle del Cauca	Feb-15	14	Medium
Valle del Cauca	Mar-15	12	Medium
Valle del Cauca	Apr-15	13	Medium
Valle del Cauca	May-15	10	Medium
Valle del Cauca	Jun-15	8	.
Valle del Cauca	Jul-15	10	.
Valle del Cauca	Aug-15	7	.
Valle del Cauca	Sep-15	8	.
Valle del Cauca	Oct-15	6	.
Valle del Cauca	Nov-15	6	.
Valle del Cauca	Dec-15	11	High

Supplementary 8. Adjustment for case-underreporting

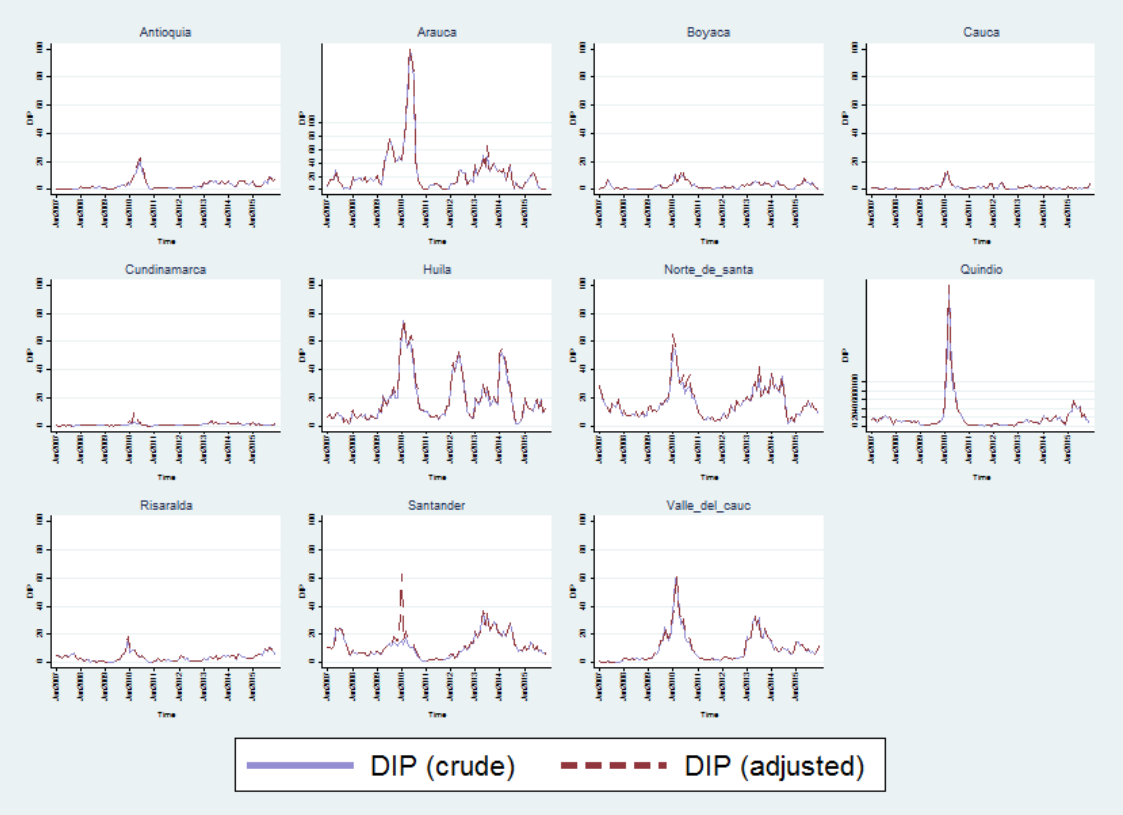
Our study attempted to adjust the crude cases reported by SIVIGILA by the proportions of municipalities who were not responsive for each department. The assumption used in this study, "a non-responsive municipality would have the average number of cases per responsive municipality of that department", may not be perfect, but this is a sensible assumption based on the following reason:

Considering the nature of the EWS model using count models and the elasticity of the function, what is important is a consistent pattern of case-reporting by department over time. In other words, a consistent underreporting or consistent overreporting would not affect the performance of the EWS model because this would merely shift the entire DIP curve either downwards (underreporting) or upwards (overreporting). Thus, what we wanted to be cautious was any lack of consistency over time in terms of case-reporting. Supplementary Figure 8 depicts the trend of the crude DIP and the adjusted DIP over time. As described in the main text, Colombia experienced a nationwide dengue outbreak in 2010. For example, in Santander, while there was no big difference between the crude and adjusted DIPs during non-epidemic periods, a substantial difference between the two was observed in 2010. This clearly indicates a lack of consistency in terms of case-reporting during the outbreak period. Likewise, the crude and adjusted DIPs appeared to be similar during non-epidemic seasons in Norte de Santander, but again discrepancies were observed during the two outbreak periods (2010 and 2013).

Given that case-reporting patterns among all municipalities were reasonably consistent (no significant discrepancy between crude and adjusted DIPs) during non-epidemic periods and discrepancies only occur during outbreak periods, it is reasonable to assume that there

were more difficulties for some municipalities on resource allocation at the local health facility level during the epidemic periods, impeding a consistent pattern in the case-reporting system from municipality-level heath facilities, even if non-responsive municipalities were experiencing the similar emergency situations with other responsive municipalities.

Supplementary Figure 8. Adjustment for case-underreporting



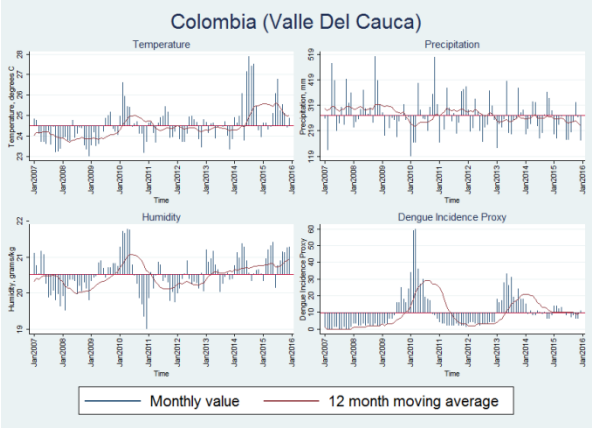
7.3 Chapter 4

Supplementary 1. The construction of the Climate Risk Factor (CRF) index

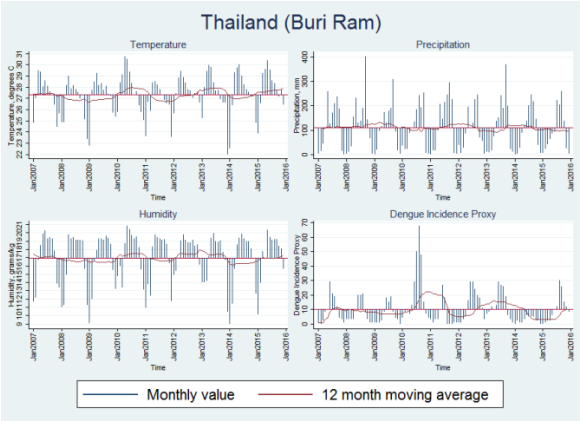
Supplementary figures 1 (a) - (c) show the trends of temperature, precipitation, humidity, and Dengue Incidence Proxy (DIP) during the study period from 2007 to 2015. As previously identified by Lee et al., temperature and humidity are positively associated with DIP, but precipitation has a negative relationship with DIP (Lee et al., 2017a).

Supplementary figure 1 (d) demonstrates cross-correlograms between the 12-month moving averages of the three climate datasets and DIP with time lags. As observed in supplementary figures 1 (a) – (c), the cross-correlograms confirmed that the 12-month moving averages of temperature and humidity are positively related to DIP at lag 0, while that of precipitation shows negative relationships with the current status of DIP.

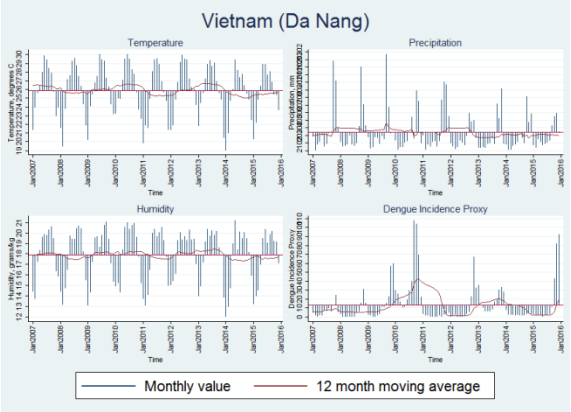
Supplementary Figure 1(a)



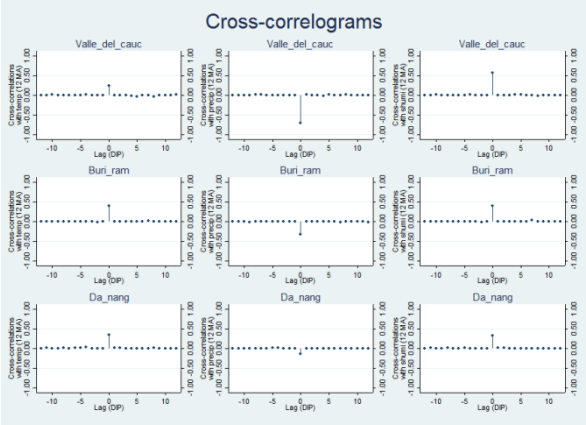
Supplementary Figure 1(b)



Supplementary Figure 1(c)

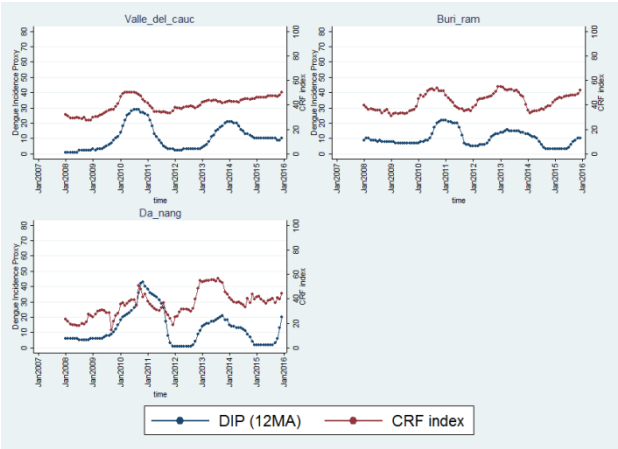


Supplementary Figure 1(d)



The CRF index and DIP over time were plotted in supplementary figure 1 (e). Strong associations between the CRF index and DIP were observed in all three provinces. It is interesting to see that all provinces across the countries experienced epidemics in 2010 and 2013. In addition, the epidemics in 2010 were clearly captured by the rapid increase of the CRF index in the three provinces. While in 2013 the epidemics observed were also associated with the steep increase of the CRF index in Buri Ram and Da Nang, the epidemic in Valle del Cauca corresponded to the high level of the CRF index. More details on Valle del Cauca can be found at (Lee et al., 2017a).

Supplementary Figure 1(e)



Supplementary 2. Model specifications

As Dengue Incidence Proxy (DIP) can be considered as non-negative integer values, count models were suitable to fit DIP as a function of the Climate Risk Factor (CRF) index. The model selection procedures are described in full detail as below.

As a baseline count model, the Poisson probability density function (PDF) can be written as:

$$f(\mathrm{y};\lambda \text{ or } \mu) = \frac{\lambda_i^{y_i} e^{-\lambda_i}}{y_i!} \quad or \quad \frac{\mu_i^{y_i} e^{-\mu_i}}{y_i!}$$

where y_i is the observed count, and λ_i is the predicted mean of count response, $\lambda_i = \exp(x_i\beta)$. Given the Poisson PDF, the likelihood function and its log-likelihood form can be derived as:

$$L(\beta; y) = \prod_{i=1}^{n} \frac{exp(-exp(x_i\beta))\left(exp(x_i\beta)\right)^{y_i}}{y_i!}$$

$$lnL(\beta; y) = \sum_{i=1}^{n} [y_i(x_i\beta) - exp(x_i\beta) - ln\Gamma(y_i + 1)]$$

where β is the coefficient for the predictor x. For a Poisson model, it is assumed that the mean is equal to the variance of the distribution. When the response variance is greater than the mean, the model is misspecified due to overdispersion. Such extra dispersion in the model results from excessive correlation in the data. When dealing with spatial patterns of (un)correlated count data, such as disease incidence or mortality, it is critical to choose an appropriate statistical approach for estimating the variance and mean in order to prevent overdispersion of the model. As pointed out by Mohebbi et al., overdispersion may occur

because of (1) misspecification of the mean function or the probability model, or (2) spatial autocorrelation (Mohebbi et al., 2014). While the former is more common in general count models, the latter occurs when counts of events are observed in small geographical areas when overdispersion and residual spatial autocorrelation are present (Mohebbi et al., 2014). Overdispersion may not significantly affect the coefficient estimates but may cause standard errors of the model to be underestimated (Hilbe, 2011, Lee et al., 2016). The Pearson dispersion statistic shows the level of overdispersion, indicating extra dispersion with a value of the Pearson statistic greater than 1.0:

$$\frac{\sum_i (y_i - \mu_i)^2}{V(\mu_i)}$$

where y_i is the observed count, and μ_i is the predicted values.

In addition, the Z-score test can be used to examine if the amount of overdispersion is sufficient to violate the basic assumptions of the model (Lee et al., 2016, Hilbe, 2011):

$$\mathrm{Z_i} = \frac{(\mathrm{y_i} - \mu_\mathrm{i})^2 - \mathrm{y_i}}{\mu_\mathrm{i}\sqrt{2}}$$

where y_i is observed values, μ_i is predicted values. A Poisson regression was first run by country, and the Z-statistics were calculated to test for Poisson overdispersion. As shown in Table S1, t-probabilities are less than 0.0005, and the null hypothesis that there is no overdispersion in the model is rejected for all three countries. Thus, a negative binomial model, which relaxes the assumption of equality of the mean and variance by adding a gamma distributed error term, was preferred to a Poisson model in three countries.

Table S1. Z-score test

Country	Z-statistic					
	Coeff	Std. Err.	T	P>|t|	95% Conf. Interval	
Colombia	17.15	2.37	7.23	0.00	12.50	21.80
Thailand	14.47	1.41	10.27	0.00	11.71	17.23
Vietnam	19.51	1.49	13.10	0.00	16.59	22.43

The negative binomial probability mass function and its log-likelihood can be written as(Hilbe, 2011):

$$f(y;\mu,\alpha) = \frac{\Gamma\left(y_i + \frac{1}{\alpha}\right)}{\Gamma(y_i+1)\Gamma\left(\frac{1}{\alpha}\right)}\left(\frac{1}{(1+\alpha\mu_i)}\right)^{\frac{1}{\alpha}}\left(\frac{\alpha\mu_i}{(1+\alpha\mu_i)}\right)^{y_i}$$

$$L(\beta;y,\alpha) = \sum_{i=1}^{n} y_i ln\left(\frac{\alpha exp(x_i'\beta)}{1+\alpha exp(x_i'\beta)}\right) - \frac{1}{\alpha} ln\left(1+\alpha exp(x_i'\beta)\right) + ln\Gamma\left(y_i + \frac{1}{\alpha}\right) - \Gamma(y_i+1) - \Gamma\left(\frac{1}{\alpha}\right)$$

where α is the negative binomial heterogeneity or overdispersion parameter. The mean of the negative binomial distribution is $E(x_i) = \lambda_i = exp(x_i\beta)$. However, now the variance of the dependent variable is $V(x_i) = \lambda_i(1+\alpha\lambda_i)$ (Hilbe, 2011).

Table S2 presents the regression outputs for Poisson and negative binomial models. The CRF index was statistically significant at the 1% level for both models in all three countries. However, similar to the Z-score test results above, the Pearson dispersion

statistics were greater than 20 in the Poisson models across the countries, indicating excess dispersion in the models. A negative binomial model was used to account for the overdispersion. The Akaike Information Criterion (AIC) values of the negative binomial models were substantially less than those of corresponding Poisson models, indicating that the data were better modeled by negative binomial than by Poisson. In addition, the negative binomial models shown in Table S2 accommodate much of the overdispersion, with the Pearson dispersion statistics ranging from 1.86 to 3.83. However, extra correlation was still left in the data. This extra overdispersion might be caused by the panel-specific effect of individual provinces in a country, which was further investigated below.

Table S2. Regression outputs

	Colombia						Thailand						Vietnam					
`	Poisson			NB			Poisson			NB			Poisson			NB		
	Coef	SE		Coef	SE		Coef	SE		Coef	SE		Coef	SE		Coef	SE	
Constant	1.698	0.013	***	1.547	0.039	***	1.976	0.009	***	1.971	0.032	***	0.649	0.015	***	-0.107	0.048	**
CRF	0.017	0.000	***	0.022	0.001	***	0.010	0.000	***	0.010	0.001	***	0.031	0.000	***	0.046	0.001	***
N	3348			3348			8316			8316			5832			5832		
Log likelihood	-28047			-10897			-68474			-28777			-55019			-17915		
Pearson dispersion	25.260			2.584			21.463			1.860			28.562			3.830		
AIC	16.756			6.511			16.469			6.921			18.869			6.144		

Apart from the misspecification of the mean function or the probability model, spatial autocorrelation is another cause of overdispersion when dealing with counts of events observed in geographically adjacent areas (Mohebbi et al., 2014). In particular, the level of dengue incidence may be correlated between neighboring provinces due to the similar climate and non-climate environments affecting the number of vector populations. Moran's I is a popular measure to test spatial autocorrelation and is defined as:

$$\mathrm{I} = \frac{\sum_{i=1}^{N}\sum_{j=1}^{N} w_{ij}\rho_{ij}}{\frac{1}{N}\sum_{i=1}^{N}(y_i - \bar{y})^2 \sum_{i=1}^{N}\sum_{j=1}^{N} w_{ij}}$$

where y_i is the value in region r_i, y_j is the value in region r_j, $\bar{y}$ is the average value of Y, ρ_{ij} is $(y_i - \bar{y})(y_j - \bar{y})$, the degree of similarity between provinces r_i and r_j, and w_{ij} is the degree of proximity (weight) between regions r_i and r_j (Pisati, 2012). Each off-diagonal point in the inverse distance weights matrix is:

$$w_{ij} = \frac{1}{distance\ between\ r_i\ and\ r_j}$$

Thus, the weight matrix entries are higher for two points which are closer than for those which are further apart (UCLA). Moran's I was computed by country and shown in Table S3. Given the test results, we reject the null hypothesis that there is no global spatial correlation. In other words, there are positive spatial autocorrelations among adjacent provinces in all three countries exhibiting similar values.

Table S3. Moran's I

Country	Variable	I	E(I)	SD	Z	P
Colombia	DIP	0.076	-0.033	0.028	3.884	0.000
	CRF	0.021	-0.033	0.030	1.806	0.035
Thailand	DIP	0.128	-0.013	0.019	7.529	0.000
	CRF	0.259	-0.013	0.020	13.909	0.000
Vietnam	DIP	0.112	-0.019	0.023	5.760	0.000
	CRF	0.199	-0.019	0.028	7.685	0.000

In a dataset where there are multiple observations from different provinces, it is sensible to account for the correlation in the data within a given panel (i.e. province) (Hilbe et al., 2003). In longitudinal data, random effects are often considered as a way to model intra-cluster correlation. While the fixed effects quantify the overall effects of the CRF index across all panels, the random effects take into account the variation across the panels. In other words, the fixed effects are the specific effects of each level, and the random effects are the standard deviations of variation at each level among panels.

Mixed-Effects Poisson

Following the Poisson PDF defined above, the probability for a specific outcome in a panel-level Poisson model is:

$$P(Y_{it} = y_{it}) = \frac{e^{-\mu_{it}}\mu_{it}^{y_{it}}}{y_{it}!}$$

where μ_{it} is the expected value of the outcome, and subscript t indexes the observations associated with panel i. Taking into account random-effects, μ_{it} is defined as:

$$\mu_{it} = exp(x_{it}\beta + z_{it}\nu_i)$$

where x_{it} is the vector of the fixed effects covariates, ν_i is the random effects, and z_{it} is the vector of the random effects covariates. Random effects models do not directly estimate random effects but estimate the parameters that describe the distribution of the random effects. The probability for a two-level Poisson can be written as (Hilbe et al., 2003):

$$P(Y_{it} = y_{it}) = \frac{e^{-exp(x_{it}\beta + z_{it}\nu_i)} exp(x_{it}\beta + z_{it}\nu_i)^{y_{it}}}{y_{it}!}$$

Since observations within a panel are independent, the conditional distribution of y_i in a two-level Poisson model, given a set of cluster-level random effects ν_i, is (StataCorp, 2013):

$$f(y_i|\nu_i) = \prod_{t=1}^{n_i} \frac{exp\{-exp(x_{it}\beta + z_{it}\nu_i)\}\{exp(x_{it}\beta + z_{it}\nu_i)\}^{y_{it}}}{y_{it}!}$$

$$= exp\left[\sum_{t=1}^{n_i}\{y_{it}(x_{it}\beta + z_{it}\nu_i) - exp(x_{it}\beta + z_{it}\nu_i) - ln(y_{it}!)\}\right]$$

As shown in Table S4, the random-intercept Poisson (RiPS) model produced a better fit compared to the original Poisson but was not as good as the standard negative binomial model in terms of the AIC statistics. This is partly due to the presence of the overdispersion in the RiPS models. The negative binomial model can be considered as a random-effects model since it is a Poisson model with a gamma-distributed random effect (StataCorp, 2013). On the other hand, as described by Rabe-Hesketh and Skrondal, having a random-intercept in a mixed-effects Poisson model causes overdispersion if the variance

component is greater than 0 ($\psi_{11} > 0$) given the marginal variance defined as (Rabe-Hesketh and Skrondal, 2008):

$$Var(y_{it}|x_{it}) = \mu_{it}^{M} + (\mu_{it}^{M})^2\{exp(\psi_{11}) - 1\}$$

where μ_{it}^{M} is the marginal expectation of the count, and ψ_{11} is the variance of the random-intercept component. In Table S4, the random-intercept variance components were greater than 0 in all three countries, and the likelihood-ratio tests confirmed that there was enough variability among panels.

Mixed-Effects Negative Binomial

The probability of a two-level negative binomial model can be written as:

$$P(y_{it}|\nu_i, \alpha) = \frac{\Gamma\left(y_{it} + \frac{1}{\alpha}\right)}{\Gamma(y_{it} + 1)\Gamma\left(\frac{1}{\alpha}\right)}\left(\frac{1}{(1 + \alpha\mu_{it})}\right)^{\frac{1}{\alpha}}\left(\frac{\alpha\mu_{it}}{(1 + \alpha\mu_{it})}\right)^{y_{it}}$$

Since observations within a panel are independent, the conditional distribution of y_i in a two-level negative binomial model, given a set of panel-level random effects ν_i and the conditional overdispersion parameter α in a mean-overdispersion parameterization is (StataCorp, 2013, Hilbe, 2011):

$$f(y_i|v_i,\alpha) = \prod_{t=1}^{n_i} \frac{\Gamma\left(y_{it}+\frac{1}{\alpha}\right)}{\Gamma(y_{it}+1)\Gamma\left(\frac{1}{\alpha}\right)} \left(\frac{1}{(1+\alpha\mu_{it})}\right)^{\frac{1}{\alpha}} \left(\frac{\alpha\mu_{it}}{(1+\alpha\mu_{it})}\right)^{y_{it}}$$

$$= exp\left[\sum_{t=1}^{n_i}\left\{ln\Gamma\left(y_{it}+\frac{1}{\alpha}\right) - ln\Gamma(y_{it}+1) - ln\Gamma\left(\frac{1}{\alpha}\right) - \frac{1}{\alpha}ln(1+\alpha\mu_{it})\right.\right.$$

$$\left.\left. + \; y_{it}ln\left(\frac{\alpha\mu_{it}}{1+\alpha\mu_{it}}\right)\right\}\right]$$

where $\mu_{it} = exp(x_{it}\beta + z_{it}v_i)$. The marginal variance is:

$$Var(y_{it}|x_{it}) = \mu_{it}^{M} + (\mu_{it}^{M})^2\{exp(\psi_{11})(1+\alpha) - 1\}$$

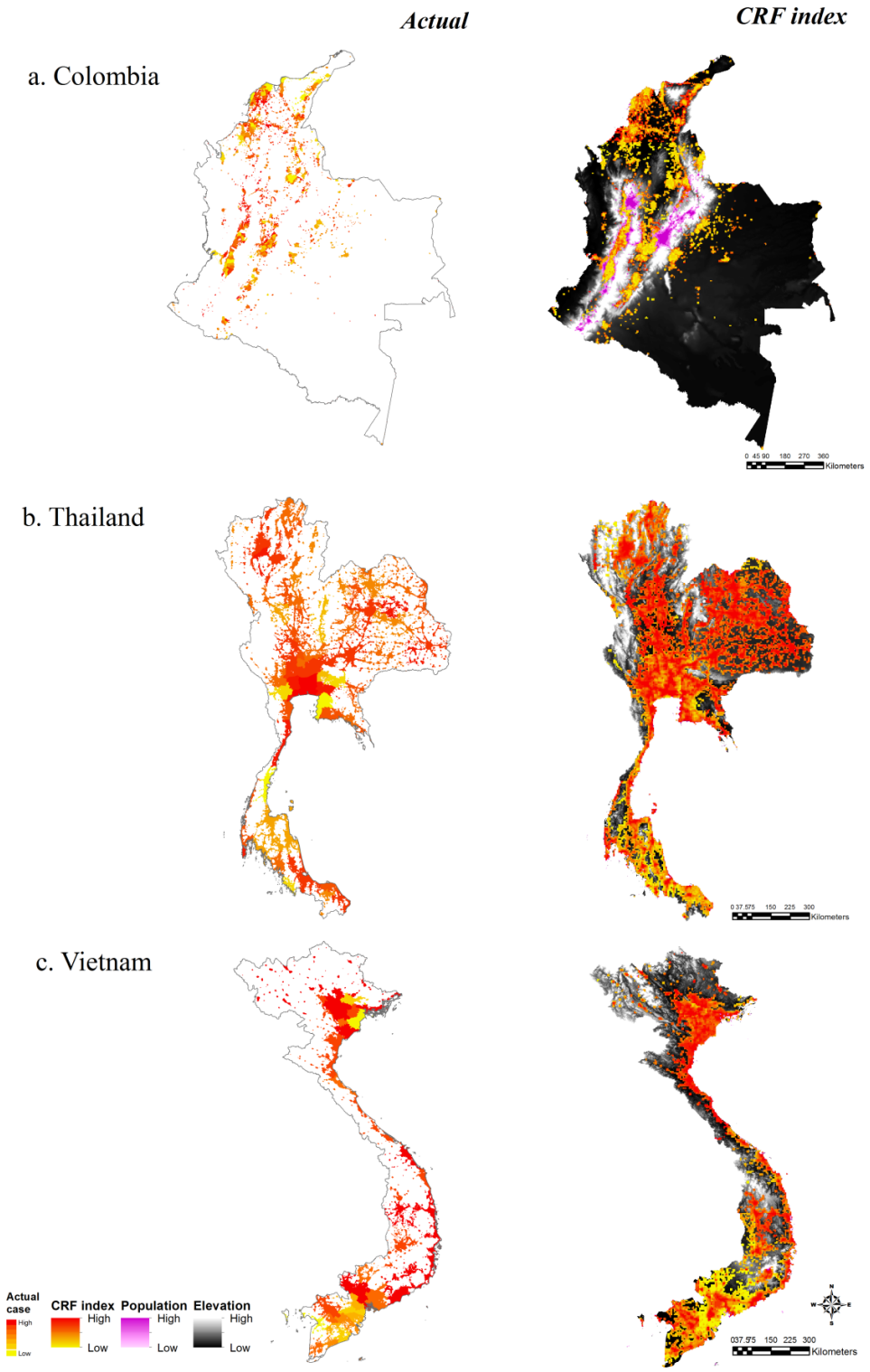
where ψ_{11} is the variance component of the random intercept. When $\psi_{11} = 0$, the variance function becomes that of a standard negative binomial model. When $\alpha = 0$, the variance function is the same as that of a two-level random-intercept Poisson model (StataCorp, 2013).

In Table S4, the CRF index is statistically significant in all three countries. The AIC statistics for the mixed negative binomial models, which are random-intercept negative binomial (RiNB) and random-coefficient negative binomial (RcNB), are lower than any of the previous models for all three countries. Comparing the RiNB models with the RcNB models, the conditional overdispersion $\alpha\left(= exp(ln\alpha)\right)$ values and the AIC statistics are lower for the RcNB models than for the RiNB models indicating that the RcNB models provide better fits for the current data.

Table S4

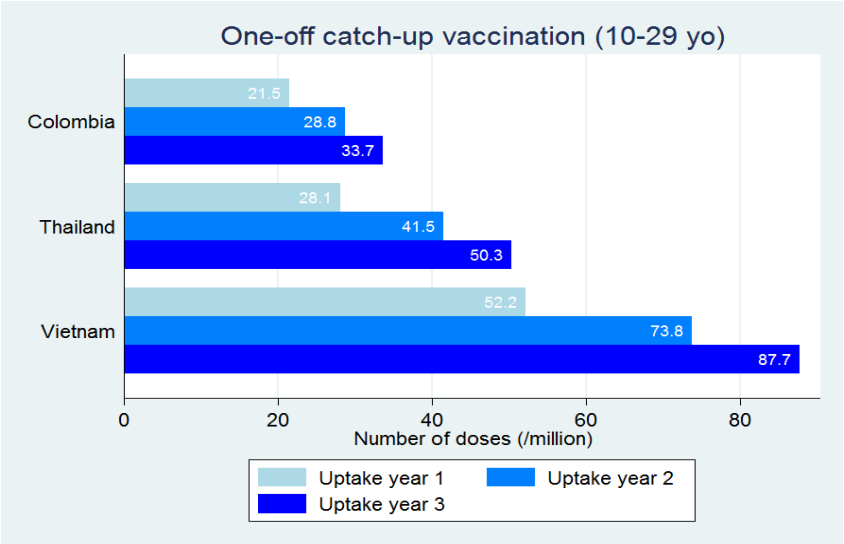
`	Colombia								Thailand								Vietnam							
`	RiPS			RiNB			RcNB		RiPS			RiNB			RcNB			RiPS			RiNB			RcNB	
	Coef	SE		Coef	SE		Coef	SE	Coef	SE		Coef	SE		Coef	SE		Coef	SE		Coef	SE		Coef	SE	
Constant	0.504	0.154	***	0.149	0.199		0.158	0.399	-0.134	0.107		0.046	0.119		0.107	0.155		0.337	0.297		-0.460	0.313		0.047	0.481	
CRF	0.046	0.001	***	0.057	0.004	***	0.082	0.017	***	0.055	0.001	***	0.051	0.002	***	0.055	0.004	***	0.013	0.001	***	0.031	0.003	***	0.025	0.008	***
RE constant	0.694	0.177		0.820	0.217		4.439	1.284	0.827	0.134		0.668	0.114		1.443	0.302		4.809	0.963		4.488	0.910		12.096	2.672	
RE CRF							0.008	0.003							0.001	0.000								0.003	0.001	
N	3348			3348			3348		8316			8316			8316			5832			5832			5832		
Log likelihood	-20098			-10027			-9961		-56871			-27881			-27739			-35453			-14623			-14448		
Ln(alpha)				-0.214			-0.301					-0.184			-0.252						0.197			0.064		
AIC	12.008			5.992			5.953		13.678			6.706			6.672			12.159			5.016			4.957		

Supplementary 3. Distributions of actual dengue cases and the CRF index in Dec, 2015



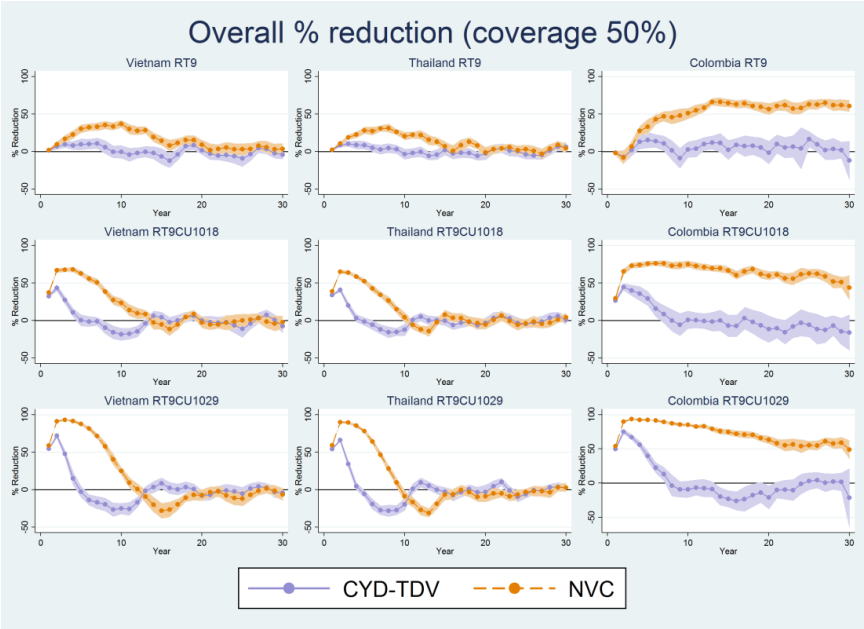
As shown in the figure above, there is a great consistency between the distributions of actual cases and the CRF index. While the actual dengue cases were available at the provincial level in Thailand and Vietnam, SIVIGILA provided dengue cases by province, as well as by municipality in Colombia. Thus, for the latter, cases at the municipality level were used since this level showed the distribution of cases at the smaller geographical unit than at the provincial level. Because the actual number of reported dengue cases were only available at the broad administrative level in all three countries, the distribution of the actual cases were shown after filtering by the population (night lights) and elevation levels for the following reason: even if one province shows a high level of dengue cases (as cases are only available at the provincial level), this does not mean that the number of cases was observed in all of smaller geographical locations in the province. For example, there would be no cases in the areas where there is no population residing in that province. Thus, this is a more sensible way to present cases only available at the broad administrative boundary, reducing the misrepresentation of the actual case distribution within a province.

Supplementary 4. Alternative catch-up campaign scenario

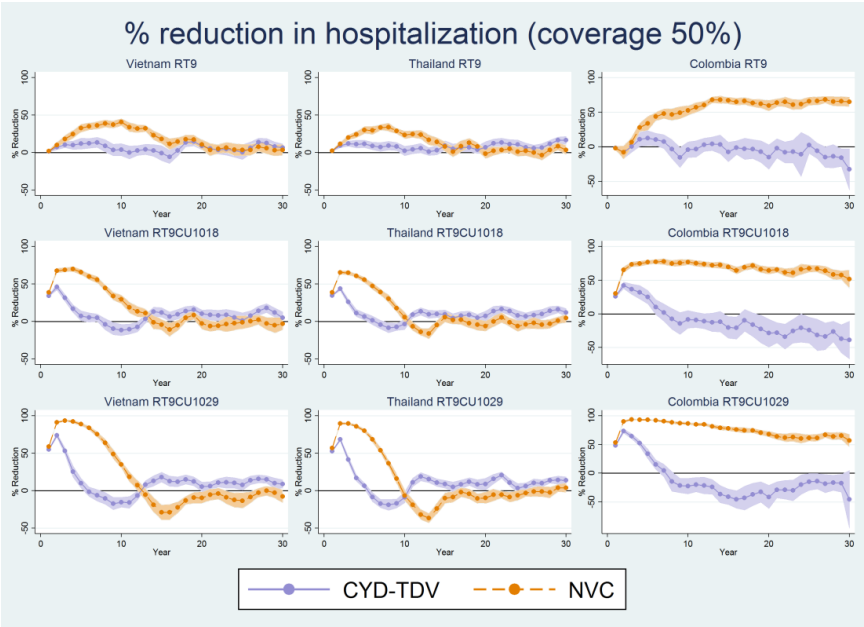


7.4 Chapter 5

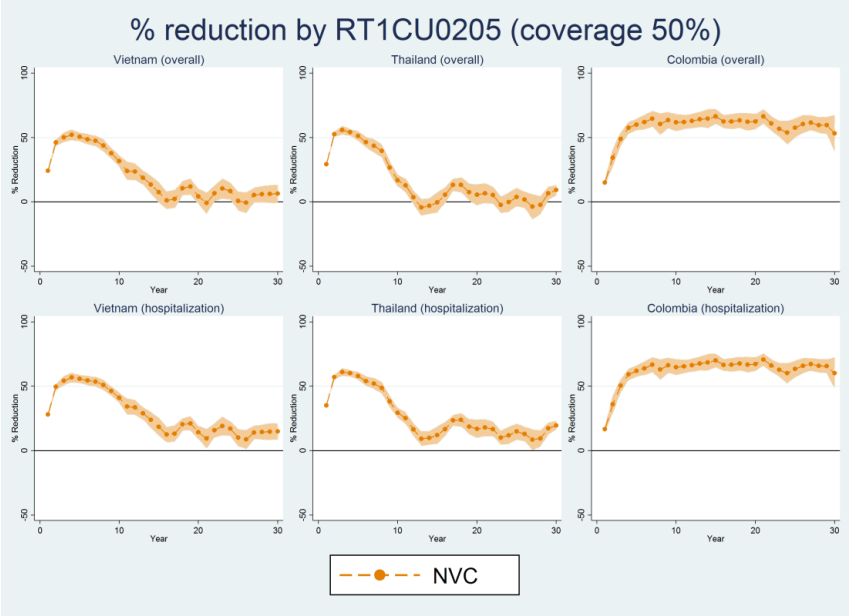
Supplementary Figure 1(a). The proportion of overall disease reduction with CYD-TDV and NVC (coverage 50%)



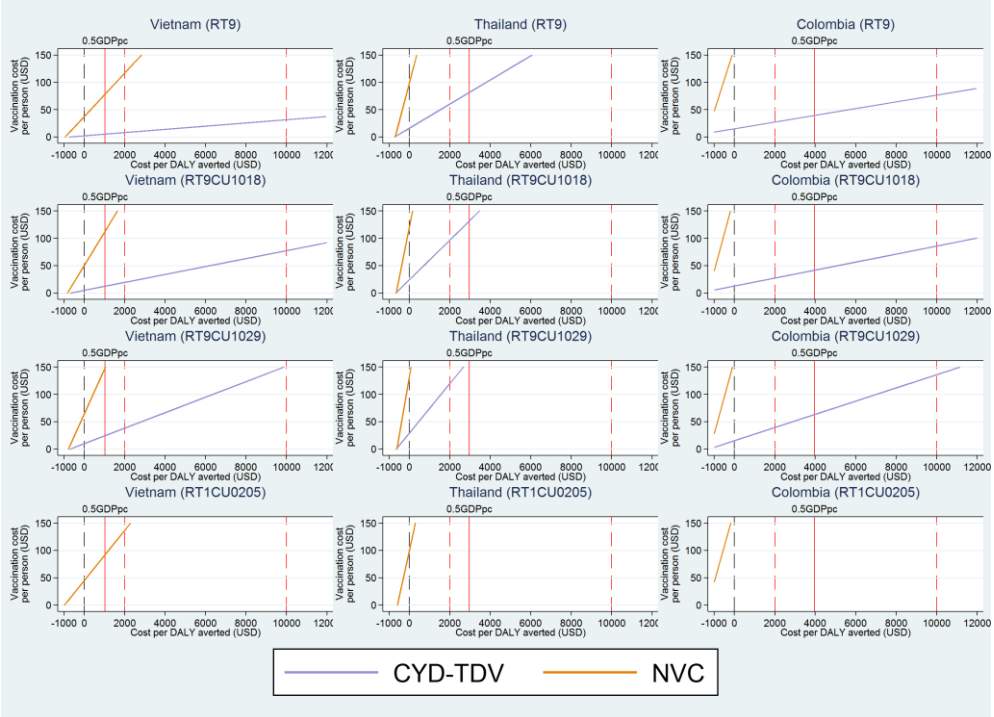
Supplementary Figure 1(b). The proportion of reduction in hospitalization with CYD-TDV and NVC (coverage 50%)



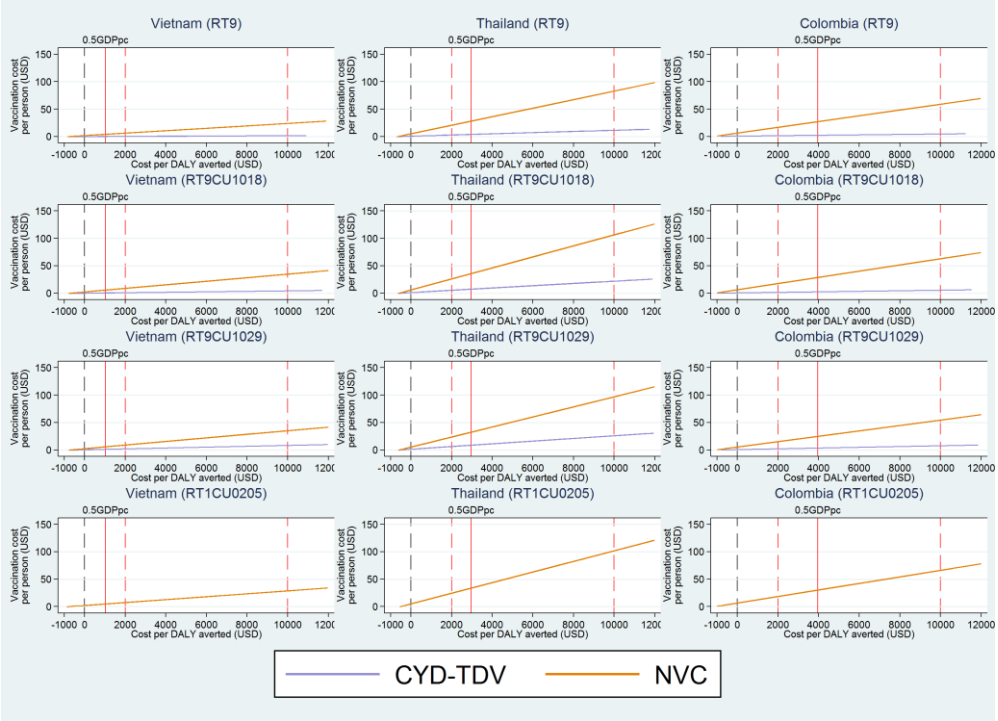
Supplementary Figure 1(c). The proportion of reduction by 1yo routine and 2-5yo catch-up with NVC (coverage 50%)



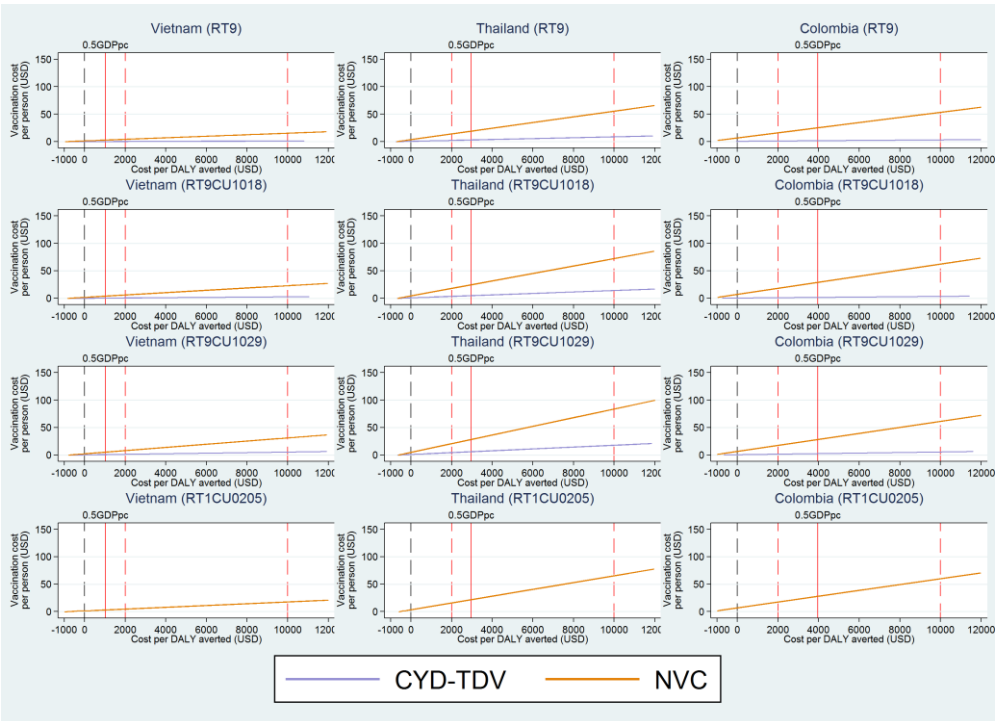
Supplementary Figure 1(d). Incremental cost-effectiveness ratios (ICERs) under the high burden scenario (coverage 50%)



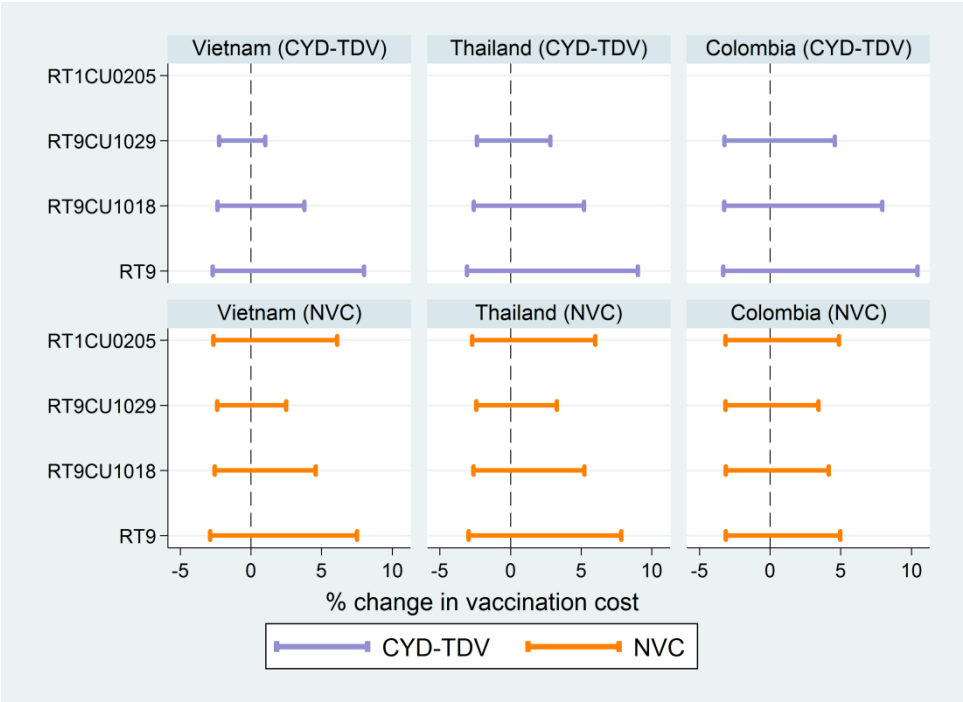
Supplementary Figure 1(e). Incremental cost-effectiveness ratios (ICERs) under the low burden scenario (coverage 80%)



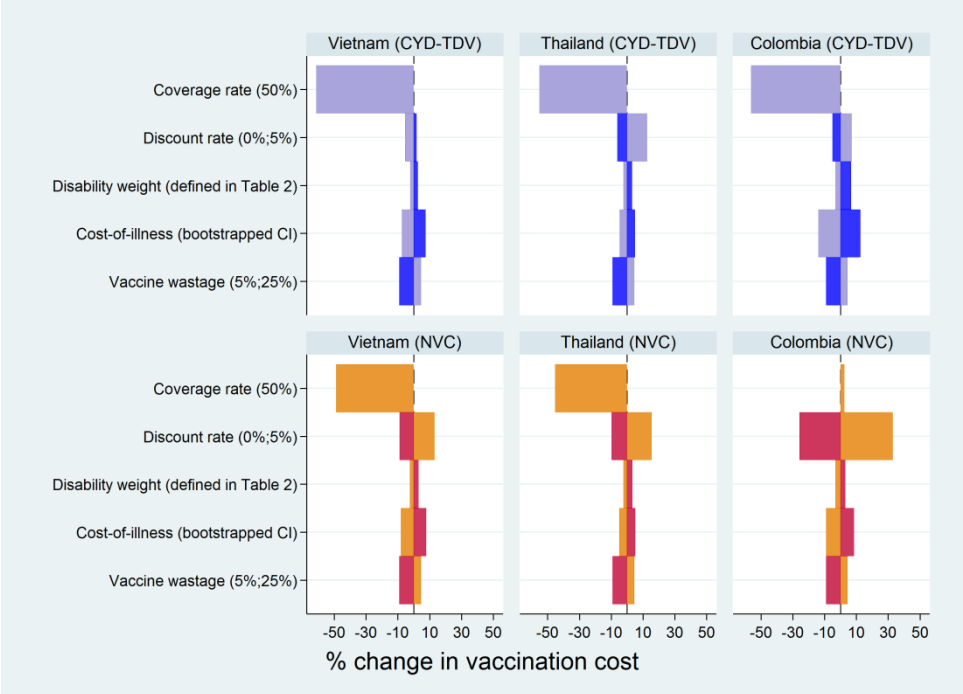
Supplementary Figure 1(f). Incremental cost-effectiveness ratios (ICERs) under the low burden scenario (coverage 50%)



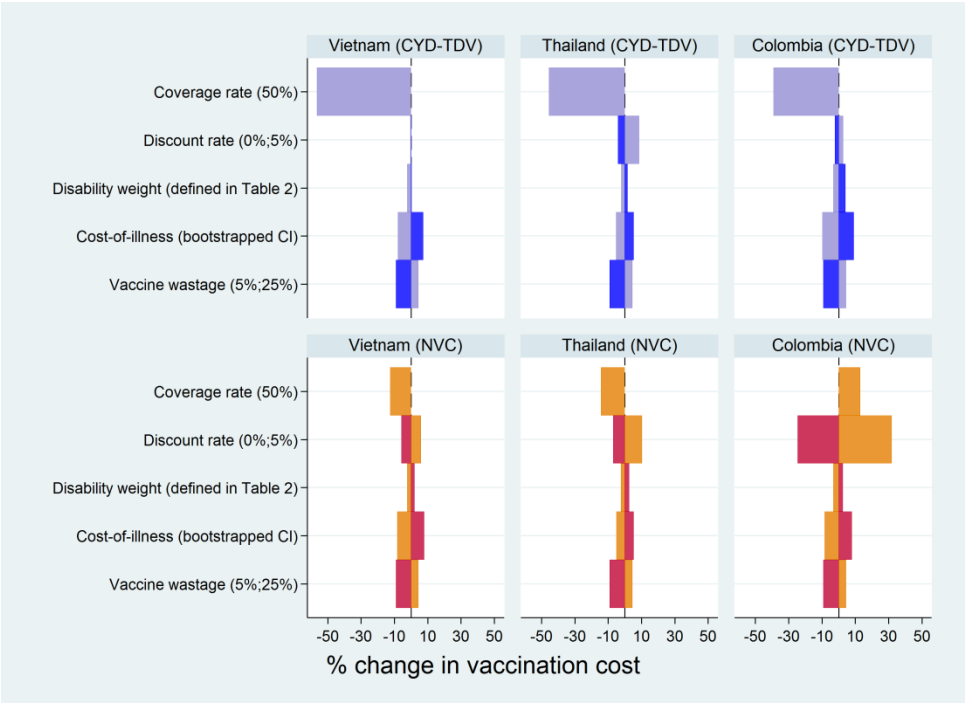
Supplementary Figure 1(g). Sensitivity analyses with varying disability weights (coverage 50%)



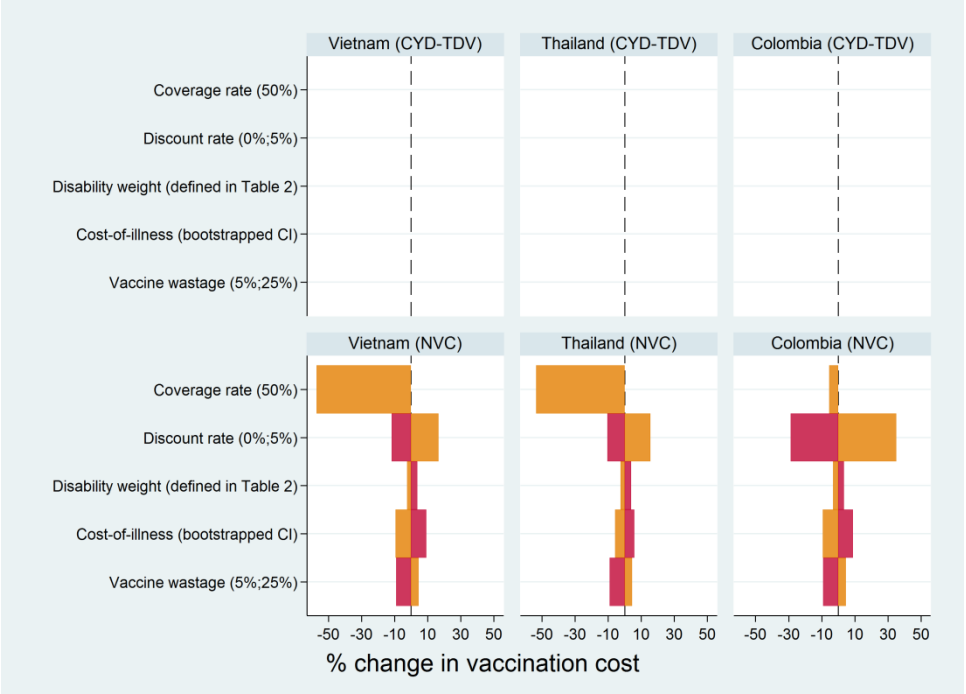
Supplementary Figure 1(h). One-way sensitivity analysis for the RT9CU1018 strategy at the threshold cost of $2,000 per DALY averted



Supplementary Figure 1(i). One-way sensitivity analysis for the RT9CU1029 strategy at the threshold cost of $2,000 per DALY averted



Supplementary Figure 1(j). One-way sensitivity analysis for the RT1CU0205 strategy at the threshold cost of $2,000 per DALY averted



Supplementary 2. Total DALY saved during the 30 year period by burden level and vaccination strategy

Burden scenario	Strategy	Vietnam		Thailand		Colombia	
		CYD-TDV	NVC	CYD-TDV	NVC	CYD-TDV	NVC
High burden	RT9	162,030	2,343,085	516,110	3,698,247	116,856	1,643,072
	RT9CU1018	557,067	4,378,932	1,366,253	6,576,188	202,694	2,389,952
	RT9CU1029	1,406,484	5,879,466	2,174,720	8,176,024	385,751	2,747,339
	RT1CU0205	NA	3,088,941	NA	4,786,754	NA	2,012,108
Low burden	RT9	5,700	82,433	18,902	135,443	4,733	66,545
	RT9CU1018	19,598	154,057	50,037	240,844	8,209	96,794
	RT9CU1029	49,482	206,848	79,646	299,435	15,623	111,269
	RT1CU0205	NA	108,673	NA	175,308	NA	81,491

Supplementary 3. The range of total DALY saved during the 30 year period by disability weight[a]

Burden scenario	Strategy	Vietnam				Thailand				Colombia			
		CYD-TDV		NVC		CYD-TDV		NVC		CYD-TDV		NVC	
		Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper	Lower	Upper
High burden	RT9	155,835	181,594	2,259,504	2,522,326	496,713	571,067	3,573,330	3,968,731	108,640	144,838	1,563,309	1,740,763
	RT9CU1018	540,305	577,568	4,236,577	4,561,968	1,324,398	1,426,654	6,375,546	6,871,769	191,329	229,361	2,275,827	2,505,191
	RT9CU1029	1,365,776	1,413,543	5,694,119	6,058,861	2,111,964	2,224,124	7,937,520	8,465,750	366,447	412,344	2,616,357	2,864,444
	RT1CU0205	NA	NA	2,984,031	3,268,404	NA	NA	4,640,473	5,030,716	NA	NA	1,915,757	2,122,526
Low burden	RT9	5,483	6,389	79,493	88,739	18,191	20,915	130,868	145,349	4,400	5,866	63,315	70,502
	RT9CU1018	19,009	20,320	149,049	160,497	48,504	52,249	233,495	251,669	7,749	9,289	92,172	101,462
	RT9CU1029	48,050	49,730	200,327	213,159	77,348	81,455	290,701	310,046	14,841	16,700	105,964	116,011
	RT1CU0205	NA	NA	104,983	114,987	NA	NA	169,951	184,243	NA	NA	77,589	85,963

[a] The lower and upper bounds correspond to two sets of disability weights used for the sensitivity analysis in the main text

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Published papers

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RESEARCH ARTICLE

A multi-country study of the economic burden of dengue fever: Vietnam, Thailand, and Colombia

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Abstract

Background

Dengue fever is a major public health concern in many parts of the tropics and subtropics. The first dengue vaccine has already been licensed in six countries. Given the growing interests in the effective use of the vaccine, it is critical to understand the economic burden of dengue fever to guide decision-makers in setting health policy priorities.

Methods/Principal findings

A standardized cost-of-illness study was conducted in three dengue endemic countries: Vietnam, Thailand, and Colombia. In order to capture all costs during the entire period of illness, patients were tested with rapid diagnostic tests on the first day of their clinical visits, and multiple interviews were scheduled until the patients recovered from the current illness. Various cost items were collected such as direct medical and non-medical costs, indirect costs, and non-out-of-pocket costs. In addition, socio-economic factors affecting disease severity were also identified by adopting a logit model. We found that total cost per episode ranges from $141 to $385 for inpatient and from $40 to $158 outpatient, with Colombia having the highest and Thailand having the lowest. The percentage of the private economic burden of dengue fever was highest in the low-income group and lowest in the high-income group. The logit analyses showed that early treatment, higher education, and better knowledge of dengue disease would reduce the probability of developing more severe illness.

Conclusions/Significance

The cost of dengue fever is substantial in the three dengue endemic countries. Our study findings can be used to consider accelerated introduction of vaccines into the public and

private sector programs and prioritize alternative health interventions among competing health problems. In addition, a community would be better off by propagating the socio-economic factors identified in this study, which may prevent its members from developing severe illness in the long run.

Author summary

Dengue fever has been prevalent in South-East Asia and South America. Despite the increase of dengue fever cases, there continues to be a lack of economic assessment partly due to the absence of vaccines until recent times. Many of the previous economic burden studies for dengue fever were not standardized, making them difficult to compare. We implemented the standardized economic burden survey for dengue fever in a multi-country setting: Vietnam, Thailand, and Colombia. We found that the economic burden of dengue fever is substantial in all three dengue endemic countries. Our study also identified socio-economic factors which are related to the probability of experiencing severe illness. The first live attenuated, tetravalent dengue vaccine (CYD-TDV) has been already licensed in some dengue-endemic countries. As three countries will soon face decisions on whether and how to incorporate current and future vaccine candidates within their budget constraints, the updated economic burden estimates can be used to develop sustainable financing plans.

Introduction

Dengue fever is a major public health concern in many parts of the tropics and subtropics. Dengue is a vector-borne viral illness and transmitted to humans by two mosquito vectors: *Aedes aegypti* and *Aedes albopictus*. There are four serotypes that cause dengue, with a wide clinical spectrum of symptoms. A previous study estimates there are 96 million apparent and 294 million inapparent dengue infections occurring yearly [1].

While many countries in the tropics and subtropics recognize dengue as a public health concern, dengue control efforts were not often considered as a priority due to the absence of specific treatment and costly vector control interventions in developing countries [2]. Having reviewed publicly available literature on the economic burden of dengue, there were a relatively small number of empirical studies. While Suaya et al. covered eight countries with a common method, many of the other existing studies were not standardized in terms of their methodologies, with varying assumptions making them difficult to compare [3–5].

Given that there continues to be a lack of economic assessment of dengue, evidence on the economic burden of dengue fever is urgently needed to guide decision-makers on the expected returns on their investments and to set health policy priorities [3]. The Dengue Vaccine Initiative (DVI) has conducted extensive multidisciplinary dengue-fever studies for decision-makers in three countries: Vietnam, Thailand, and Colombia [6]. The rationale for these studies is to contribute data to inform policymakers about the economic burden of dengue fever and to assess the economic efficiency of vaccine introduction strategies.

In Vietnam, dengue is highly prevalent, and the incidence rate is reported to be 145/100,000 population according to the national surveillance system data from 2010 [7,8]. All four dengue serotypes circulate [9]. Vietnam seems to follow similar trends to Thailand where dengue epidemiology has been studied extensively. Despite mosquito control efforts, dengue

fever/dengue hemorrhagic fever (DF/DHF) has steadily increased in both incidence and range of distribution in Thailand, and the incidence rate in 2010 was reported to be 177/100,000 population [8,10]. Dengue has now spread to all provinces, districts, sub-districts and communities, and is seen every year [11].

Meanwhile dengue has been prevalent for the past 20 years in Colombia. In 2010, Colombia experienced a nationwide epidemic with a dengue incidence rate of 685/100,000 population [8,12]. Further, outbreaks have been observed in many parts of the country since 2011. Dengue epidemiology in Colombia is characterized by the circulation of all four dengue serotypes. The country has a well-established national dengue surveillance system.

A recombinant tetravalent vaccine candidate (CYD-TDV) has completed Phase 3 clinical trials in Southeast Asia and South America, and has been already licensed in some dengue-endemic countries. Understanding the benefits of vaccination is necessary in order to facilitate accelerated development and introduction of safe and effective dengue vaccines into public-sector programs of dengue-endemic countries.

These three endemic countries will soon face decisions on whether, and how, to incorporate current and future vaccine candidates within their highly budget-constrained national vaccination programs [8]. As population-wide vaccination campaigns must be carefully determined considering the allocation of scarce resources among competing health problems [13], the updated economic burden estimates of dengue from this study can be used to develop cost-effective vaccination strategies and sustainable financing plans for dengue vaccine introduction in Vietnam, Thailand, and Colombia. Furthermore, taking advantage of the standardized study design in a multi-country setting, this study attempts to explore and understand socio-economic factors affecting the level of disease severity that results in different levels of economic burden.

Methods

Study design

Table 1 summarizes the study areas for three countries, and the overall study design is shown in Fig 1. The economic burden survey was conducted in locations where DVI's epidemiologic studies were being carried out at the same time. The health facilities were chosen because they were main hospitals and centers providing care for the defined catchment area population. In Vietnam, Khan Hoa General Hospital is a tertiary care facility with 1,000 beds and the largest hospital in the province. The hospital is staffed with 195 doctors, 59 assistant doctors, 5 pharmacists, and 336 nurses. Bang Phae Community Hospital (BPCH) is a primary healthcare provider in Bang Phae district in Thailand. The facility is a 48-bed medium-sized tertiary care facility which conducts up to 400 outpatient consultations per day. Two health facilities were chosen in Colombia. Clinic of Piedecuesta is a secondary and tertiary care facility with a total of 42 beds. The clinic has 19 general practitioners, 36 specialists and assistants, and 39 nurses. Hospital de Piedecuesta is a 27-bed medium sized primary care facility that conducts up to 76.9% of its consultations for outpatients, with the rest being for the emergency service. Among patients who came to one of the study facilities listed in Table 1, febrile patients

Table 1. Study areas.

Country	Province	City (or district)	Study period	Health facility for study
Vietnam	Khanh Hoa	Nha Trang	Oct, 2011—Oct, 2012	Khan Hoa General Hospital
Thailand	Ratchaburi	Bang Phae	Oct, 2011—Dec, 2016	Bang Phae Community Hospital
Colombia	Santander	Piedecuesta	Aug, 2014—Jul, 2015	Hospital de Piedecuesta, Clinica Piedecuesta

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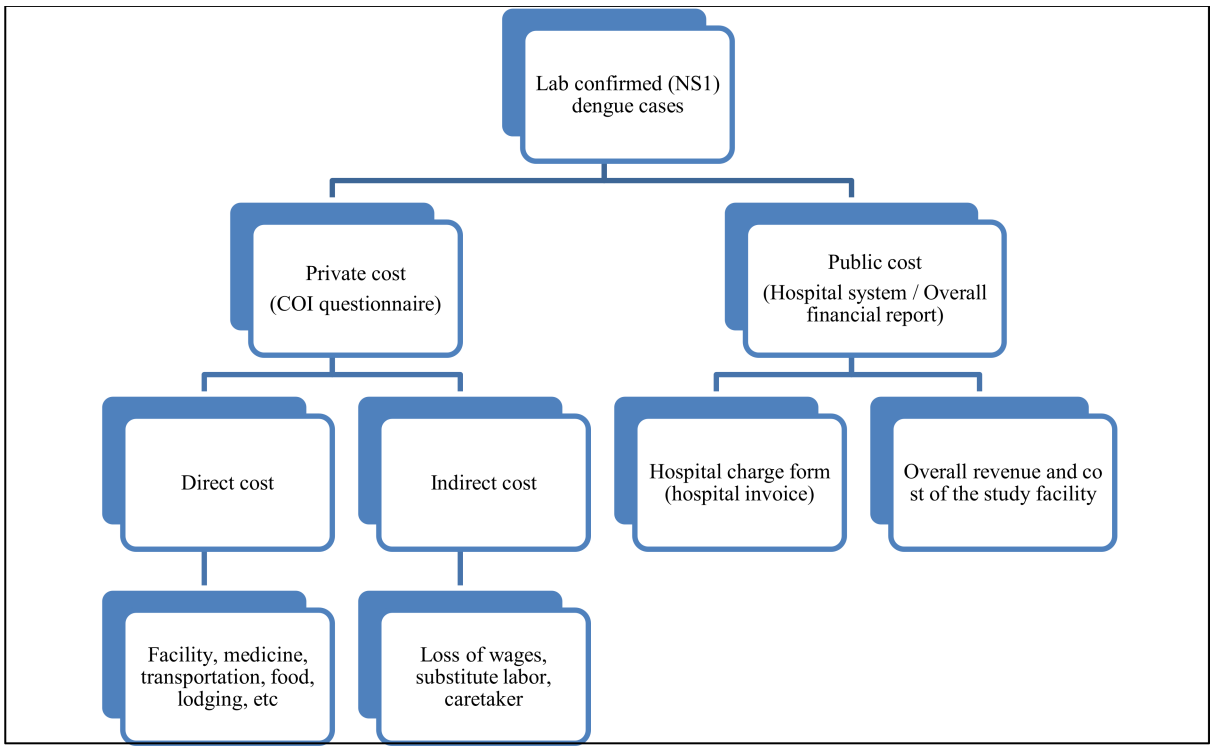

Fig 1. Overall study design.

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experiencing fever for less than 7 days were recruited for rapid tests. The economic burden survey was administered for those who were positive on the test result and who consented to participate in the survey. There were three sections in the cost-of-illness (COI) survey: day 1, day 10~14, and day 28. As part of the study procedure, the febrile patients were tested on the first day of their clinic visit, and COI surveys were administered to patients throughout the duration of their illness. On day 1, dengue-confirmed patients were asked whether they had visited any health facilities prior to the current visit (visit 1). If they had made any visits, interviewers asked how much money they had paid for direct medical and direct non-medical costs such as facility fees, medications, food, lodgings, and transportation, etc. Patients were reminded to come back to the hospital in 10 to 14 days, and, so as to prevent recall bias, they were provided with a diary card to record costs for further treatments, and other indirect cost information, such as substitute labor or caregivers. On the second visit (day 10 to 14), direct medical and non-medical costs spent during the first visit and any additional visits before the second interview were collected. In addition, patients were asked if any indirect costs had occurred such as wage loss, costs for substitute labor and/or caretakers. Once direct and indirect cost information was obtained, interviewers asked patients about socio-economic questions such as patients' household income, education, general perceptions towards dengue fever, and routine vector control activities, etc. If there were any patients who were still feeling sick at the end of their second visit, a third interview was scheduled for day 28. The third questionnaire covered the period between day 10–14 and day 28. The day 28 survey could be conducted via telephone rather than in-person if necessary. The project-related tests were omitted from the analyses, as these may not have been incurred under routine clinical practice.

Direct cost

Direct cost can be divided into two categories: (1) direct medical costs; and (2) direct non-medical costs. Direct medical costs include consultation, medication, and laboratory test costs. Patients' out-of-pocket costs for these categories were first assessed through a questionnaire. Respondents were asked whether total treatment cost was covered by the patient (or his/her family members), insurance (private, public), or both. Because payments made by patients may not always cover the entire costs of medical treatments, hospital bill records for patients who were enrolled in the study were accessed to identify treatment costs that were not captured by patients' out-of-pocket costs. In Colombia and Thailand, the hospital records were computerized and showed different sources of payments such as from private / public insurance, etc. However, no such system was available in Vietnam, thus medical service utilization forms, which recorded the type of services provided and hospital charges for each service, were employed for enrolled dengue fever patients in Vietnam. The data from the private surveys was then linked to the treatment records of patients (hospital charges) to better understand the full spectrum of the costs of dengue and how the economic burden is distributed among the public and private sectors.

Ratio of cost-to-charge. While some studies report patients' out-of-pocket costs–which are part or all of hospital charges–as direct medical costs of dengue fever [14,15], adjusting hospital charges by the cost-to-charge ratio is another way to understand the overall societal cost of a disease. The cost-to-charge ratio is estimated by dividing the total annual hospital costs by the total annual revenue of the hospital [16]. The rationale behind the use of the cost-to-charge ratio is that in many circumstances, for various reasons, costs may not be the same as charges [17]. Charges can be higher than costs because charges may include a component to cover replacement and expansion of facilities or the need to cover losses from those who cannot afford services. In some contexts, hospital charges are lower than costs because health facilities are subsidized by governments or non-governmental organizations (NGOs) in rural areas of less-developed countries where not many people can afford health services. While the overall societal cost of a disease can be estimated by multiplying hospital charges by the cost-to-charge ratio, the direct economic impact on patients to be treated for that disease can be better assessed by the overall hospital charge information [17]. In this study, the ratios of cost-to-charge (RCC) were separately estimated for all three sites. In Vietnam and Thailand, one of the study team members was assigned to access the financial information of the study facilities. One of the study facilities in Colombia produces a comprehensive financial report every year which consists of hospital revenue from various sources and all costs including staff salary and capital assets, etc. However, such information was not obtained for the other health facility in Colombia due to logistical issues. While the financial structure of health facilities could vary, the study team ensured it included the following components: (1) the costs covered labor (i.e. staff salary, welfare), material and capital costs occurring from all sources. Capital costs include equipment, vehicle, building, and all other construction after taking into account depreciation. (2) the charges included hospital revenue from all services provided and external funding. Both overall charges and societal costs are presented.

Direct non-medical cost covers the expenses related to transportation, food, and lodgings incurred by a patient when seeking treatment, as well as by individuals accompanying a patient. The respondents were asked to provide direct medical and non-medical cost information for all visits that a patient made during their illness.

Indirect cost

Indirect cost consists of three components: patient wage loss due to illness; substitute labor cost; and caretaker's cost.

Patient productivity loss. A patient or his/her guardian was asked what the patient would have been doing if the patient had not been sick and how much the patient normally gets paid for one day's work if the patient earns wages. These questions were followed by determining the total number of days the patient lost wages due to illness. For patients who make any income, their productivity loss was calculated by multiplying the self-reported daily wage by the total number of wage-loss days. In addition, a series of questions was asked to determine the number of days that the patient was completely unable to perform, partially unable to perform, and completely able to perform his/her usual activities. For those who do not earn any income, a full-day loss was considered for the days that they were completely unable to perform, and a half-day loss was assigned for the days that they were partially unable to perform their usual activities. In order to estimate a student's loss in monetary value, the number of the student-loss days was multiplied by the government expenditure per primary student expressed in USD [18]. The government expenditure per primary student includes general government expenditure such as current, capital, and transfers for a given level of education. While this indicator is useful for comparing average spending on one student between countries, the estimates would be conservative because the indicator does not reflect total spending per student, including household contributions. For patients who normally perform housework and did not earn any wage, their productivity loss was converted into monetary value using the minimum wage for that country (VND 87,500 per day in Vietnam, THB 300 per day in Thailand, and COP 25,667 per day in Colombia) [19–21].

Substitute labor costs. Some patients need to hire substitute labor in order to carry out his/her work as the patient is unable to perform usual activities due to illness. Substitute labor might be a member of the household or someone who is hired externally. After identifying the number of substitute laborers and the relationship of the substitute laborer to the patient, respondents were asked whether they were paid or not. If paid, the daily payment for hiring a substitute laborer was recorded. Opportunity costs were also assessed. The opportunity cost of a choice is the loss of potential gain from other alternatives by choosing that specific activity. The number of days that a substitute laborer had to cut back on his/her usual activity was collected and multiplied by a daily payment for substitute laborer's original activity to calculate the total opportunity cost. If the substitute laborer was compensated in lieu of his/her usual activities, only the amount of money that was paid for the entire duration of the service was counted. If the substitute laborer was not paid for doing the patient's work and had to cut back on his/her usual activity, then the opportunity cost was added to the substitute labor cost. Care should be taken when considering patient wage loss and substitute labor costs because one may think that a patient's work-day loss would be compensated by substitute labor. However, the way that the questionnaire was designed was such that respondents were first asked whether patients lost any wages due to illness and then they were asked questions about the substitute labor cost section. In other words, patients who did not lose any wages by hiring substitute laborer(s) would not report any wage loss in the first part. If patients reported some wage loss even if they had a substitute laborer, this should be interpreted as wage loss that the substitute laborer was not able to cover.

Caregiver's costs. Some patients need to have a caregiver while they convalesce during a severe illness period. Opportunity cost plays an important role here because most caregivers tend to be family members who do not get paid for taking care of the patient but may need to cut back on their usual activities. For these patients, the same types of questions for substitute

labor were asked, and total costs for caregivers were derived in the similar way taking into account the opportunity costs.

The total indirect costs were estimated by summing all three components: patient wage loss; substitute labor costs; and caretakers' costs. All local currency units were converted using the official exchange rate from World Bank and expressed in 2014 USD, and the cost outcomes were also expressed in purchasing power parity (PPP) rates in the supplementary section. The official exchange rate is the rate determined in the legally sanctioned exchange market, and the PPP exchange rate reflects that the currency of one country would be converted into another currency to buy the same amount of goods and services. The PPP rates would be useful for the international comparison of non-tradable goods. Confidence intervals were estimated using the bootstrap approach, a common non-parametric technique which deals with skewed cost data [22–24]. Bootstrapping treats the observed sample as an empirical distribution, and draws a sample repeatedly with replacement [25]. From these data, the standard error (SE) can be calculated as follows:

$$\hat{se} = \left\{ \frac{1}{k-1} \sum (\hat{y} - \bar{y})^2 \right\}^{\frac{1}{2}}$$

where $\hat{y}$ is the statistic for the ith bootstrap sample, $\bar{y}$ is the value of the statistic calculated using the original observations, and k is the number of replications [25]. The percentile method (2.5^{th} and 97.5^{th} percentiles of the distribution) was used to produce a 95% confidence interval [23,25].

Disease severity

While dengue infection usually causes flu-like illness with mild symptoms, the infection occasionally develops into a potentially lethal complication called severe dengue [26]. Severe dengue has become a leading cause of hospitalization and death in some Asian and Latin American countries.

The DVI's cost-of-illness (COI) surveys include questions not only on direct and indirect cost information of dengue fever, but also on general socio-economic information such as education, routine vector control activities, and general perceptions towards dengue fever. Questions were identically administered at all three sites, and these variables can be compared by disease severity. In this study, severe illness was defined if a patient was either hospitalized or confirmed as having dengue hemorrhagic fever (DHF) based on clinical symptoms. Whether a patient goes through severe illness or not is a dichotomy, and a dichotomous dependent variable can be considered as a function of healthcare-seeking behavior, education, and household perceptions on dengue fever and likelihood, etc. A logit model is suitable for this analysis because such models handle categorical dependent variables using maximum likelihood estimation. The binomial logistic regression estimates the log odds that individuals will be in each of two categories of a dichotomous dependent variable.

$$\ln\left(\frac{\pi}{1-\pi}\right) = \sum_{k=0}^{K} x_k \beta_k$$

where K is the number of independent variables, x_{ik}, β are the coefficients, and the dependent variable is the log of the expected probabilities of being in each of the two categories, conditional on the values of the independent variables. Given that the surveys were standardized across the three sites, all samples were combined to achieve a larger sample size for robust model outcomes.

Ethics statement

The cost-of-illness survey questionnaires were approved by the ethical review committees in three countries (National Institute of Hygiene and Epidemiology in Vietnam, Faculty of Tropical Medicine, Mahidol University in Thailand, Universidad de Santander in Colombia), as well as Ministry of Health in three countries and Institutional Review Board of the International Vaccine Institute. Written informed consent was obtained prior to conducting interviews, and respondents were informed that they could terminate interviews at any time. If any study participants were minors, their parents or guardians provided consent on behalf of all child participants under the age of 18 years old.

Results

Table 2 shows patient characteristics for each study site by patient type (see S1 Table for additional information). The average number of total sick days ranges from 7 to 10 for inpatients and 6 to 9 for outpatients. While a majority of the patients sought treatment prior to the study enrollment in Vietnam, less than half of the patients did so in Thailand and Colombia. More patients tended to have caregivers than substitute labor in all three countries. In Vietnam, more than 80% of the patients responded that they had caregivers. On average, patients older than 5 years were not completely able to perform their usual activities for 5 to 7 days as inpatients, and 3 to 5 days as outpatients. The average age of the patients was 20–23 years in Vietnam and Colombia, and 15 years in Thailand. The self-reported mean household income per month was $423, $548, and $665 in Vietnam, Thailand, and Colombia, respectively.

Fig 2 summarizes the proportions of patient burden by expenditure, as well as the percentage share of patient's out-of-pocket (OOP) costs versus non-OOP costs, such as government subsidy or payments from other insurance schemes. For all three countries, indirect cost accounts for the highest proportion of patient's OOP among the three expenditure types in Fig 2(A): direct medical cost (DMC), direct non-medical cost (DNMC), and indirect cost (IC). While DMC is the second highest burden for patients in Vietnam and Colombia, DMC is only 2% in Thailand. This is mainly because people in Thailand are covered by its universal healthcare system so patients do not have to pay for most of the OOP costs related to direct medical services. This is more apparent in Fig 2(B). About 99% of DMC are covered by the public sector, which is the universal healthcare system in Thailand. The proportion of the non-OOP costs is also high in Colombia, at 81%. In Vietnam, public DMC coverage is less than that of the other two countries, meaning that more patients tend to pay directly for the medical services that they receive.

Table 2. Descriptive statistics.

	Vietnam (SD)		Thailand (SD)		Colombia (SD)	
	Inpatient	Outpatient	Inpatient	Outpatient	Inpatient	Outpatient
N	59	92	45	40	70	160
Sick days prior to enrollment	3.7 (1.8)	2.8 (1.4)	2.7 (1.3)	2.2 (1.2)	5.1 (1.5)	4.3 (1.6)
Total sick days	7.4 (2.9)	6.2 (1.7)	7.8 (2.1)	6.1 (1.4)	10.4 (2.9)	8.7 (2.4)
% seeking treatment prior to enrollment	96.6% (0.2)	95.7% (0.2)	17.8% (0.4)	20.0% (0.4)	32.9% (0.5)	43.1% (0.5)
% patients with substitute labor	50% (0.5)	11.1% (0.3)	0.0% (0.0)	0.0% (0.0)	7.0% (0.3)	17.8% (0.4)
% patients with caretakers	98.3% (0.1)	85.9% (0.4)	46.7% (0.5)	12.5% (0.3)	40.0% (0.5)	48.8% (0.5)
No. of full days lost due to illness	6.7 (2.9)	5.4 (2.0)	4.7 (2.6)	2.5 (2.1)	5.8 (2.2)	4.7 (2.0)
No. of partial days lost due to illness	0.4 (1.1)	0.7 (1.6)	2.8 (1.7)	3.0 (2.0)	3.1 (1.5)	2.8 (1.9)
Average patient age	21.5 (12.8)	20.2 (9.3)	16.3 (9.3)	14.6 (9.7)	23.2 (12.7)	20.6 (13.1)
Average household income	$453 (304.2)	$404 (315.9)	$470 (227.1)	$635 (373.6)	$618 (456.1)	$686 (385.7)

https://doi.org/10.1371/journal.pntd.0006037.t002

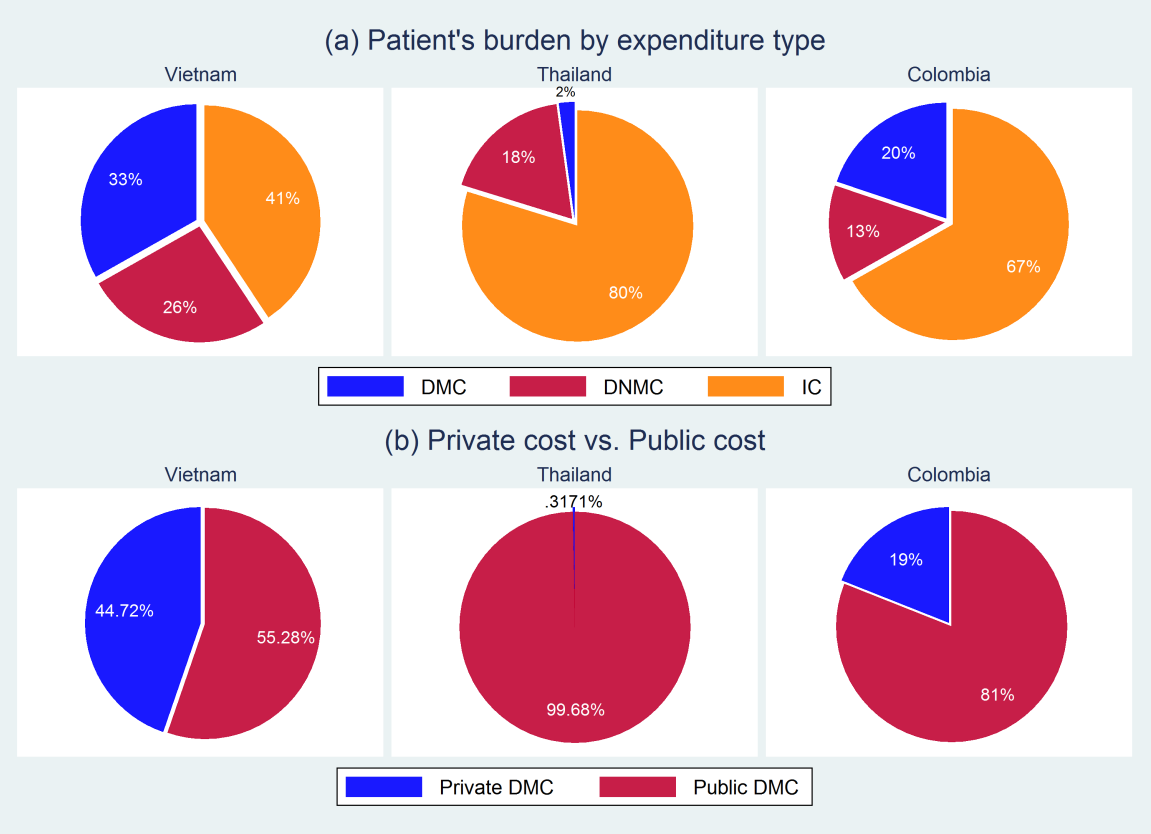

Fig 2. The percentage share of the economic burden for dengue fever by (a) expenditure type and (b) payer type.

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The economic burden of dengue fever is shown in Table 3. DMC is highest among the three expenditure types, after taking into account both private and public spending. Total cost per inpatient episode is $200, $141, and $385 in Vietnam, Thailand, and Colombia, respectively. In the case of outpatients, total cost per episode ranges from $40 to $158, with Colombia having the highest and Thailand having the lowest. It is interesting to see that IC and DNMC are higher in Vietnam than in Thailand despite the higher average income in Thailand. This is because there was no reported substitute laborer cost in Thailand, and the duration of caregiver's work was shorter in Thailand than in Vietnam. In addition, while the meal service was included for inpatients in the hospital charge in the health facility of Thailand, all patients had to pay extra for food in Vietnam. Considering the mean duration of the disease, total cost per day was calculated. It appeared that Colombia had again the highest cost per day, followed by Vietnam and Thailand. The societal total costs were also estimated after adjusting for the ratio of cost-to-charge (RCC). While the total cost per episode went up after the adjustment in Vietnam and Thailand, it went down in Colombia. By age group, the total cost per episode is higher for the older age group than the younger age group in Thailand and Colombia, but this is the opposite in Vietnam as shown in Fig 3. This is mainly due to the high number of inpatients than outpatients in the younger age group in Vietnam. The economic burden was further disaggregated by age group, patient type, and cost type in Table 4.

The economic burden of dengue fever would have varying impacts on household equity. For those who reported their monthly income, three income groups were first generated based

Table 3. Average economic burden of dengue fever per episode[a].

	Vietnam[b]						Thailand						Colombia					
	Inpatient (n = 59)			Outpatient (n = 92)			Inpatient (n = 45)			Outpatient (n = 40)			Inpatient (n = 70)			Outpatient (n = 160)		
	USD[c]	BT CI[c] (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)	
Direct Medical Cost (DMC)	$83	$62	$108	$26	$22	$30	$81	$67	$95	$7	$6	$8	$245	$199	$297	$33	$30	$36
Direct Non-Medical Cost (DNMC)	$51	$44	$58	$9	$7	$13	$13	$7	$21	$5	$4	$6	$27	$20	$34	$17	$15	$21
Indirect Cost (IC)[d]	$67	$48	$89	$27	$20	$36	$47	$36	$59	$28	$23	$33	$113	$85	$144	$107	$76	$145
Total Cost	$200	$165	$239	$62	$52	$74	$141	$119	$164	$40	$34	$45	$385	$331	$443	$158	$124	$197
Total Cost per Day	$29	$24	$34	$10	$8	$12	$19	$16	$22	$7	$6	$7	$38	$32	$44	$18	$14	$22
Total Cost (RCC adjustment)	$213	$175	$256	$64	$54	$76	$181	$153	$210	$43	$37	$48	$278	$239	$318	$144	$111	$183

[a] All local currency values were converted using the official exchange rates from World Bank. See S2 Table for values converted using the Purchasing Power Parity (PPP) conversion factor

[b] Because data collection was done in 2012 in Vietnam, the estimates were inflated to 2014 USD.

[c] Bootstrapping with the percentile method.

[d] See S3 Table for further break-down of indirect cost

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on percentiles of monthly income: low-income group (income $\leq$ 25%), middle-income group (25% $<$ income $\leq$ 75%), and high-income group (income $>$ 75%). The list of household assets in the survey was designed to include various items from essentials to luxury goods reflecting the local context of each country. Given this, the level of the household assets in each income group was identified, and the respondents who did not report their monthly income were categorized into the three income groups based upon their levels of household assets. The mean income value of the group to which these households belonged was assigned. The total OOP for the economic burden of dengue fever was then estimated as a proportion of the self-reported household monthly income by income group. As shown in Fig 4, the percentage of

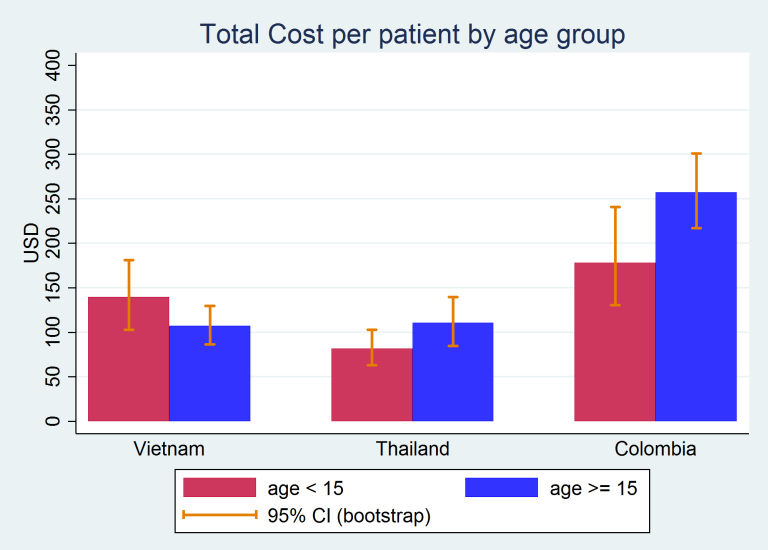

Fig 3. Total cost per patient by age group.

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Table 4. Disaggregated average economic burden of dengue fever per episode[a].

	Vietnam						Thailand						Colombia					
	Inpatient			Outpatient			Inpatient			Outpatient			Inpatient			Outpatient		
	USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)		USD	BT CI (lower, upper)	
Direct Medical Cost (DMC), age < 15	$106	$61	$170	$24	$17	$31	$73	$53	$93	$6	$5	$8	$212	$149	$283	$31	$26	$36
Direct Medical Cost (DMC), age ≥ 15	$72	$52	$97	$27	$22	$32	$89	$70	$106	$8	$6	$11	$262	$201	$331	$35	$30	$40
Direct Non-Medical Cost (DNMC), age < 15	$55	$45	$66	$14	$7	$22	$8	$5	$11	$5	$4	$6	$33	$21	$49	$16	$12	$21
Direct Non-Medical Cost (DNMC), age ≥ 15	$49	$40	$58	$8	$5	$11	$17	$7	$33	$5	$3	$7	$23	$16	$33	$18	$15	$23
Indirect Cost (IC), age < 15	$75	$47	$111	$30	$20	$40	$52	$35	$72	$32	$26	$37	$59	$28	$98	$87	$40	$156
Indirect Cost (IC), age ≥ 15	$63	$40	$91	$26	$17	$38	$43	$29	$58	$20	$10	$29	$140	$103	$181	$121	$84	$165

[a] All local currency values were converted using the official exchange rates from World Bank. See S2 Table for values converted using the Purchasing Power Parity (PPP) conversion factor

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the economic burden of dengue for the low-income group was 36%, 17%, and 45% in Vietnam, Thailand, and Colombia, respectively. The percentage of the economic burden of dengue fever decreased moving towards the higher income groups. Due to the universal healthcare system, the percentage of the DMC burden was less than 1% for all three income groups in Thailand, which reduces the overall OOP burden for patients.

Table 5 shows the regression outputs. While the type 1 model is parsimonious and only includes the variables related to the current illness, the type 2 model was run with all possible

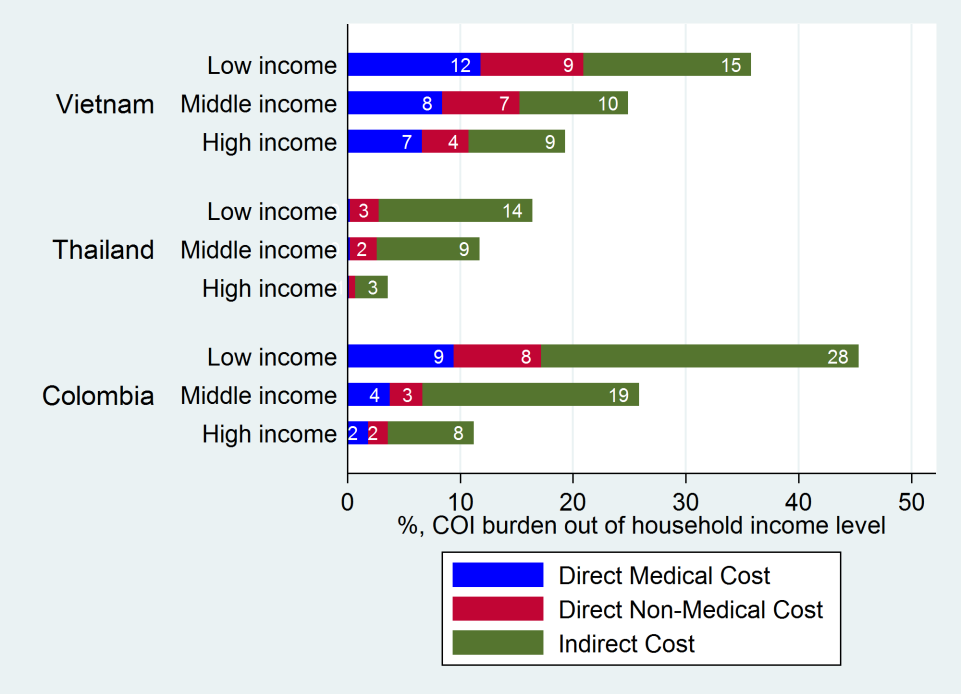

Fig 4. Proportion of the economic burden (OOP costs) by income group.

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Table 5. Socio-economic factors influencing disease severity (regression outputs).

Independent variable[b]	Type 1			Type 2		
	Coeff (in OR[a])	(SE)		Coeff (in OR)	(SE)	
Age (year)	1.00	(0.01)		1.01	(0.01)	
Sick days before the study enrollment	1.26	(0.08)	***	1.35	(0.09)	***
Sick days after the study enrollment	1.21	(0.05)	***	1.20	(0.05)	***
Seeking early treatment	0.55	(0.12)	***	0.44	(0.1)	***
Substitute labor/caretaker	1.34	(0.29)		1.59	(0.37)	**
Education 2 (some education)				0.35	(0.17)	**
Education 3 (university / post graduate)				0.29	(0.15)	**
Income level (middle)				0.80	(0.19)	
Income level (high)				0.96	(0.29)	
Dengue perception (poor)				1.96	(0.75)	*
Dengue perception (medium)				2.18	(0.55)	***
Previous infections within household				0.48	(0.12)	***
Vector control activity				0.93	(0.2)	
Constant	0.10	(0.04)	***	0.16	(0.1)	***
N	466.00			466.00		
Log likelihood	-290.57			-277.80		
AIC	593.13			583.59		

[a] Odds ratio

[b] Reference categories of the categorical variables: Education 1 (no education), Income level (high), Dengue perception (high)

* Significance at the 10% level

** at the 5% level

*** at the 1% level

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covariates including socio-economic variables. As expected, the number of sick days before and after the study enrollment was highly significant and positively related to severe illness. The seeking-early-treatment variable is also statistically significant at the 1% level and decreased the odds of experiencing severe illness for both models. This indicates that patients who sought treatment at the early stage of illness would be less likely to develop severe illness later on. While patients with severe illness tended to have more substitute labor or caretaker(s) than patients with non-severe illness, this variable is marginally significant in type 2. Compared with patients with no education, patients with some or higher education were less likely to have severe illness for the current episode. Age, household income levels, and vector control activities were not statistically significant. In addition, the dengue perception score was developed based upon respondents' general knowledge of dengue fever, and was categorized into three levels with the lowest score indicating the poor level of knowledge on dengue fever. Having less awareness or lacking general knowledge of dengue fever was positively associated with experiencing severe illness. It was also shown that patients were less likely to develop less severe illness when there were more household members who had been previously infected and recovered. Overall, the type 2 model was preferred over the type 1 model based on the difference of the Akiake Information Criterion (AIC) values [27]. It should be noted that some of the milder cases may never receive medical attention, and this may be related to income and education levels. While this would be difficult to be statistically tested in this study given the absence of healthcare-seeking behavior indicators outside the study facilities, the distributions of non-severe and severe patients appear to be similar over income and education levels, holding other factors constant (see S1 Fig). This partly indicates that there was no serious selection bias in the dataset.

Discussion

Estimates of the economic burden of dengue fever may vary depending upon a country's healthcare system and the different methodologies applied. While there were existing economic burden studies, the advantages of the current study are that it relies on the implementation of a standardized survey tool and the inclusion of various expenditure types and age groups in multiple countries. This makes it possible to make a more complete comparison across the three dengue-endemic countries. Using the standardized methodology, this study found that the total cost per dengue episode is $200, $141, $385 for inpatients and $62, $40, $158 for outpatients in Vietnam, Thailand, and Colombia, respectively. Among the various OOP expenditure components, indirect cost was the biggest private burden for patients in all three countries. Non-OOP payments, such as from insurance or nationwide healthcare system, reduce patients' burden of DMC. The patients' share of burden of DMC was the least in Thailand, followed by Colombia and Vietnam. In all three countries, the percentage of the private economic burden of dengue fever was highest in the low-income group and lowest in the high-income group.

Though many previous studies were not based on standardized methodologies, making them difficult to compare [3,4], some existing studies that did not use secondary data sources or extrapolation were compared with the current study outcomes (see S4 Table for summary). Tam et al. reported $167.8 per DHF inpatient episode in 2006 in Vietnam [28]. Once the estimate was inflated to 2014 USD using consumer price index, this value was higher than our estimate. However, it should be noted that this previous study only looked at DHF inpatients who were supposed to experience more severe illness. Another study by Harving et al. showed the average total cost of $61.4 per DHF inpatient younger than 15 years in 2005 [29]. Our estimate per inpatient episode for the same age group is $125.2, which is less than Harving et al.'s estimate after inflation adjustment ($147.1), but again Harving et al. also looked only at DHF inpatients. In Thailand, while Anderson et al. and Clark et al. reported the average total cost of $31.8 to $44 per inpatient and $10.2 per outpatient [14,30], Okanurak et al. estimated the total cost per inpatient as $172.9 and $141.5 from two different sites in Thailand [31]. The estimates from Anderson et al. and Clark et al. were lower than our study estimates even after inflation adjustment. One of the main reasons is that the former two studies focused on patients' OOP costs, whereas our study took into account both patients' OOP payments and public payments, which would make for a large difference especially in the context of Thailand. On the other hand, Okanurak et al. looked at DHF patients, resulting in higher costs than our study estimates. Suaya et al. also estimated dengue cost of illness in Thailand and reported $573 for inpatients, which is a lot higher than the other study estimates including ours [5]. Rodriguez et al. estimated a total cost of $497.9 per inpatient and $202.3 per outpatient in Colombia. There are similarities between this previous study and our study in terms of the cost items considered and the sub-component estimates. They reported higher indirect cost estimates, making the overall costs higher than our estimates. This could be partly because the previous study included projected lost income due to death, whereas the current study did not have any deaths occurred during the study period.

In addition to the estimation of the economic burden of dengue fever, the logit model was constructed to identify factors explaining variance of disease severity. The logit analyses showed that early treatment, higher education, and better knowledge of dengue disease would be associated with a reduction of the probability of developing more severe illness. This can be partly explained by the fact that secondary dengue infection which would likely cause more severe illness would be inversely correlated with the independent variables. As the disease ranges from flu-like mild symptoms (dengue) to potentially lethal complications (severe

dengue), resulting in different levels of economic burden, a community would be better off expanding the factors identified in this study, which may prevent its members from developing severe illness in the long run.

Some areas of uncertainty deserve attention. While the study captured all patients' OOP costs spent during the entire period of illness by conducting multiple interviews, public DMC payments and RCCs were limited to our study's health facilities. Because a majority of the costs were incurred during the enrollment visit at the study's facilities rather than at referral facilities or pharmacies across the study sites, the estimates would not be greatly influenced. However, our estimates are conservative. In Colombia, where two health facilities were involved, the RCC was only obtained from one of the facilities due to logistical issues. Because these study facilities were in the same district, a single RCC was used for all patients. While various cost and charge items were taken into account for the estimation of the RCC, the detailed list of financial information was confidential for some of the health facilities, limiting the way that the estimates were presented. Ideally, our study samples should be more heterogeneous and representative of the entire countries. Given that this study was carried out in locations where epidemiologic studies were being conducted at the same time, care must be taken when generalizing the estimates beyond the study's communities. Nonetheless, hospital charges may vary in different locations of a country, but within the same country the unit prices for service items may not be as variable as the charges. Assuming the duration of illness is similar within a country, factors which may influence the total cost adjusted by the ratio of cost-to-charge in the same country are patient's out-of-pocket expenditures for direct non-medical costs and indirect costs. Because these are directly related to the income level in a community, it would be possible to understand the representativeness of our estimates by comparing the average income of the study communities with Gross National Income (GNI) per capita. The study refusal rates among eligible patients were 2.3% and 1.4% in Thailand and Colombia respectively. Due to logistical issues, the refusal rate could not be estimated in Vietnam. While there were no patients who felt sick after the 2nd interview of the current study, Tiga et al. reported that some dengue patients experience persistent symptoms such as asthenia, fatigue, and trouble working [32]. It should be noted that there may be patients who do not generally come to the professional health sector such as our study facilities [33]. While the current study captured any non-medical sector visits such as traditional healers or others before and after the study enrollment, there may have been non-enrolled dengue patients who did not come to any of our study facilities during the study period, and this may have been partially related to patient's education and income levels.

The burden of dengue has been rising partly due to the absence of population-wide vaccination campaigns and the limited impacts of vector control activities. A previous study assumed that vector control would not be able to achieve permanent reduction of dengue based on the experience of Singapore [13]. The first live attenuated, tetravalent dengue vaccine (CYD-TDV) has been already licensed in some dengue-endemic countries. To maximize the effective use of a dengue vaccine, vaccination strategies should be carefully considered after taking into account various competing health problems at the country level. Identifying effective vaccination strategies requires various sources of information such as accurate incidence rates, the long-term behavior of the vaccine (i.e., waning rates of efficacy, the rate of any adverse effects, etc.) and the price of the vaccine. Along with more details, this study's estimates of the economic burden of dengue fever can play a critical role in determining cost-effective vaccination strategies, and so facilitate the process of dengue vaccine introduction by guiding decision-makers on the expected societal health benefits through vaccination.

Supporting information

S1 Table. The number of days lost due to illness.
(DOCX)

S2 Table. Average economic burden of dengue fever per episode in PPP.
(DOCX)

S3 Table. Indirect cost break-down.
(DOCX)

S4 Table. Study comparisons.
(DOCX)

S1 Fig. The distribution of patients by education and income.
(TIF)

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RESEARCH ARTICLE Open Access

Early warning signal for dengue outbreaks and identification of high risk areas for dengue fever in Colombia using climate and non-climate datasets

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Abstract

Background: Dengue has been prevalent in Colombia with high risk of outbreaks in various locations. While the prediction of dengue epidemics will bring significant benefits to the society, accurate forecasts have been a challenge. Given competing health demands in Colombia, it is critical to consider the effective use of the limited healthcare resources by identifying high risk areas for dengue fever.

Methods: The Climate Risk Factor (CRF) index was constructed based upon temperature, precipitation, and humidity. Considering the conditions necessary for vector survival and transmission behavior, elevation and population density were taken into account. An Early Warning Signal (EWS) model was developed by estimating the elasticity of the climate risk factor function to detect dengue epidemics. The climate risk factor index was further estimated at the smaller geographical unit (5 km by 5 km resolution) to identify populations at high risk.

Results: From January 2007 to December 2015, the Early Warning Signal model successfully detected 75% of the total number of outbreaks 1 ~ 5 months ahead of time, 12.5% in the same month, and missed 12.5% of all outbreaks. The climate risk factors showed that populations at high risk are concentrated in the Western part of Colombia where more suitable climate conditions for vector mosquitoes and the high population level were observed compared to the East.

Conclusions: This study concludes that it is possible to detect dengue outbreaks ahead of time and identify populations at high risk for various disease prevention activities based upon observed climate and non-climate information. The study outcomes can be used to minimize potential societal losses by prioritizing limited healthcare services and resources, as well as by conducting vector control activities prior to experiencing epidemics.

Keywords: Dengue, Early warning system, Dengue epidemic, Population at risk for dengue fever

Background

Dengue is complicated. There are four serotypes of the dengue virus, and dengue infection occurs in almost all age groups [1, 2]. Dengue is endemic in many parts of the tropics and subtropics, and dengue endemic countries are also exposed to the risk of periodic outbreaks [1, 3]. In Colombia, dengue has been prevalent over the last 20 years with different degrees of incidence rates and epidemics in various geographical locations [4, 5]. Due to the complexity of the disease, there are still large knowledge gaps regardingthe causes of dengue epidemics [6–9]. Infection with one serotype provides life-long immunity to that specific serotype. Therefore, subsequent introduction of the same serotype in a community would be less likely to cause the occurrence of a dengue epidemic if there were a small population of dengue-susceptible individuals [7, 8, 10]. However, due to a high degree of antigenic cross-reactivity, sequential infection of two different serotypes can bring

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favorable or detrimental outcomes depending upon known and unknown factors including timing of infection [2, 11, 12]. For example, a primary infection may help slow the spread of secondary heterologous infection when some degrees of cross-protection are conferred [2, 12–14]. On the other hand, many studies have shown that subsequent heterologous infection would likely increase the probability of experiencing severe dengue fever [15–18]. One of the known mechanisms is the antibody dependent enhancement (ADE) during the second infection mediated by non-protective heterotypic antibodies arising from the primary infection [2, 11, 14, 19]. In dengue endemic countries such as Colombia, the number of dengue cases is periodically reported to the upper-level health management unit (i.e. provincial or Ministry of Health) from various health facilities at the municipality level [4, 20]. In the case of dengue fever, like any other diseases, severe cases are detected more easily than mild symptoms, which in turn, leads to a higher volume of reported caseload [21]. Thus, having more severe cases is also related to the high likelihood of observing dengue epidemics when an epidemic is determined based on official statistics of reported cases.

While it is undeniable that all of these aspects would affect the occurrence of dengue epidemics directly and indirectly, it does not appear to be practical in proving the impacts of these factors on the occurrence of dengue epidemics due to the following reasons: (1) despite various efforts to disentangle the complexity of the disease [11], it is still uncertain to generalize how one serotype reacts with another in terms of cross-protection or ADE for all possible scenarios among four serotypes, as well as the duration of the interactions [22, 23]; (2) even if this uncertainty is going to be uncovered in the near future, it would be very difficult to obtain the details of sero-prevalence history over a long period of time for each cohort in all specific locations. These limitations make it difficult to understand how much of each factor would contribute to the actual probability of a dengue epidemic occurrence [7, 9, 24].

A more practical way is to focus on the basic principle of the occurrence of a dengue epidemic. Simply put, a dengue epidemic occurs when a large number of people become infected within a short period of time [2, 7]. It requires a large number of vector mosquitoes (*Aedes aegypti*), as well as high transmission probability, and frequent contact between people and the vectors (biting rate) to sustain transmission [2, 3, 7]. In other words, a dengue epidemic would more likely occur when vector mosquitoes increase within a short time period in a location where dengue viruses are currently circulating and population density with no immunity to one of the four serotypes is high during the same period [8, 9, 24]. Further, the importation of infected cases into a community where there is no immunity to that specific serotype would cause an epidemic as well.

Following this principle, the main concept of this study lies in the increase of vector mosquitoes as a primary factor of a dengue epidemic taking into account population density at different elevation levels. As a vector-borne viral disease, there is a wide range of factors that influence the spatial and temporal dynamics of mosquito populations: temperature, rainfall, and humidity, etc. [9, 24, 25]. There have been several efforts to understand the relationship between dengue epidemics and climate change. Juffrie and Focks used sea surface temperature anomalies to identify the occurrence of dengue epidemics in Yogyakarta, Indonesia and Bangkok, Thailand [26]. Lowe et al. developed an epidemic early warning system for Southeast Brazil using several climate and non-climate datasets [27]. More recently, Huang et al. found that El Nino-Southern Oscillation climate cycles and temperature were important factors affecting the weekly occurrence of the four dengue serotypes in Cairns, Australia [23]. Adde et al. also identified summer Equatorial Pacific Ocean sea surface temperatures and Azore high sea-level pressure as significant indicators in predicting dengue epidemics in French Guiana [28]. While some of the climate factors were more commonly used due to the nature of a vector-borne disease, their applications varied and were geographically focused. These findings from previous literature showed that climate factors play a significant role in the occurrence of dengue epidemics.

This study first attempts to predict a dengue epidemic by developing an Early Warning Signal (EWS) model based upon the temporal relationship between the occurrence of dengue epidemics and climate variability which affects mosquito populations in Colombia. Furthermore, using climate data and topographical information, the study identifies population at high risk for dengue fever for efficient disease prevention activities.

Methods

Dengue Incidence Proxy (DIP) was created to observe the trend of the dengue incidence in Colombia. The number of dengue fever cases and population data were obtained from SIVIGILA and Departamento Administrativo Nacional de Estadistica (DANE) which are both official governmental programs in Colombia [4, 29]. Dividing the dengue fever cases reported by population can be used as a good proxy to observe the overall trend of dengue fever. SIVIGILA also provides a weekly report on epidemiological events (Boletin Epidemiologico) which discloses the proportions of municipalities that

were not responsive for each department [30]. Thus, the number of cases was adjusted by the proportions for underreporting by assuming that a non-responsive municipality would have the average number of cases per responsive municipality of that department: the reported cases by department was divided by the number of the responsive municipalities in that department, applied to non-responsive municipalities, and added to the reported cases by department. DIP was estimated by dividing the adjusted cases by population. While Boletin Epidemiologico was available over the study period, a more consistent pattern of the underreporting system was observed in the reports since 2011 after the large outbreak in 2010. Because a robust case reporting system is critical for determining the relationships between DIP and climate data, some departments out of 31 departments were excluded if over 20% of underreporting based on Boletin Epidemiologico occurred more than twice since 2011. An outbreak was defined as a relative term in this study. In other words, as long as an unusual peak in DIP was observed in a department, it was considered as an outbreak even if the DIP value in that department was relatively low compared to other departments where dengue is more prevalent. An unusual peak was marked by department if the slope of DIP over every six months fell into the highest 10% of the observations.

Table 1 summarized the datasets used in this study. Considering the spatial and temporal dynamics of mosquito populations, three climate datasets and two non-climate datasets were selected as factors which can explain variation in DIP. The climate raster datasets include air temperature, precipitation, and specific humidity [31–33]. The monthly climate datasets were obtained from 2006 to 2015, and all the raster files were resampled into 0.008 by 0.008 degree resolution by taking the nearest neighbor assignments. It should be noted that the study presumed that it is critical to consider how long favorable conditions for vector mosquitoes persist [9, 23]. In other words, a current epidemic is a result of the climate conditions consistently observed during the past months, rather than single temporal (monthly or daily) values at present. For example, if warm temperature and high humidity were observed only for a short time period of each year, these conditions would less likely affect the larval development or virus replication to cause an epidemic [25]. Thus, after checking cross-correlograms to define a proper period, the 12-month moving average of the mean values of each climate data was estimated by department (Additional file 1).

In addition to the climate factors, night light data and elevation raster files were included [34, 35]. Night lights data which is available by year was used to understand population density instead of conventional population statistics. The use of the night-lights data provides more flexibility to estimate population density at various levels of geographical units over time than the projected population data [36]. Prior to applying the night-lights data, correlations between night-lights data and population data were tested to ensure that the night-lights data can be used as an appropriate proxy ($\rho = 0.94$). The most recent night-lights data was for 2013 at the time of the research. As the population level does not change dramatically during a short period of time, the population level in 2013 was assumed to be consistent in 2014 and 2015. High population density would have two opposite effects in terms of transmission intensity depending upon the level of a reproduction number: (1) dilution of infectious individuals by having a large pool of host populations, (2) a large number of susceptible hosts to be infected, leading to the surge of infected cases. For the latter case, while transmission would be more intensive in a place where population density is high, holding other climate factors constant, it does not have to be necessarily true in areas at high elevations [9]. A previous study found that it is difficult for *Aedes aegypti* mosquitoes to survive at an elevation of 6000–8000 ft or even at lower elevations in temperate latitudes [37]. Because many people in Colombia live at high elevations (i.e. Bogota), the mean value of the night lights was used to estimate population density separately for people living under 1500 m and those living over 1500 m by department [38].

The three climate datasets are partially correlated but also have their own distinctive characteristics. In order to preserve all the information contained in each of the

Table 1 Data description

Type	Degree resolution	Resampled resolution[a]	Temporal resolution	Period	Period (12MA)[b]
Air temperature	0.5 by 0.5	0.008 by 0.008	Monthly	Jan 2006 - Dec 2015	Jan 2007 - Dec 2015
Precipitation	1 by 1	0.008 by 0.008	Monthly	Jan 2006 - Dec 2015	Jan 2007 - Dec 2015
Specific humidity	2.5 by 2.5	0.008 by 0.008	Monthly	Jan 2006 - Dec 2015	Jan 2007 - Dec 2015
Night lights	0.5 by 0.5	0.008 by 0.008	Yearly	2006–2013	2007–2013
Elevation	0.5 by 0.5	0.008 by 0.008	NA	NA	NA

[a]Climate datasets were resampled by using the nearest option in ArcGIS
[b]12-month moving average

climate datasets, the Climate Risk Factor (CRF) index was created. The advantage of using a composite index is that it prevents multicollinearity when running regressions against independent variables with some level of the correlations among the variables. The three climate variables and population density under 1500 m were used by department. The precipitation variable, which has a negative relationship with DIP, was reversed, so all variables go towards the same underlying concept (the increase in DIP). The variables were first standardized individually by subtracting the mean and dividing by the standard deviation. The standardized values were then averaged across the variables [36, 39]. The final values were converted into a range from zero (low risk) to one (high risk) and multiplied by 100 for an easier interpretation. It should be noted that the temperature and specific humidity data used in this study are measures at the surface level. More precisely, air temperature is at 2 m above the ground surface, and specific humidity is measured near surface at sea level with pressure level 1000 millibars. Thus, it would be desirable to adjust the CRF index by the risk proportion at low and high elevation. The proportion at risk was estimated by dividing the sum of the night lights observed under 1500 m elevation by the sum of the total night lights in each department. The final CRF index was the product of the raw CRF index and the proportion at risk.

There were two dominant patterns observed during past dengue epidemics in Colombia: (1) rapid increase of the CRF index, (2) relatively steady increase of the CRF index at different levels of the CRF and DIP values. In other words, the slope of the CRF index curve at various levels of the CRF index and DIP values appeared to be critical in predicting the occurrence of dengue epidemics. In order to assess this combined relationship, the elasticity of the CRF index curve was estimated. This is defined as the percentage change in DIP in response to a 1 % change in the CRF index [40, 41]. The stationarity of the dataset was tested to ensure that there were no trend and periodic seasonal effects. The augmented Dickey-Fuller (ADF) unit-root test was used to test whether the dataset is stationary by department [42, 43]. DIP is non-negative integer values, and count models were used to fit DIP as a function of the CRF index (Additional file 1: Supplementary 2). The DIP dataset consists of two parts: (1) model dataset, (2) validation dataset. The model was constructed based on monthly DIP and the CRF index by department from January 2007 to December 2015. The validation dataset which was separated from the model dataset was established from January 2016 to April 2016 and used to validate the model performance. Overdispersion—where the variance is greater than the mean—was tested using the Z-score test at the 5% significant level [44–46]. In addition, the Akaike Information Criterion (AIC) fit test was used to compare the model fits between Poisson and negative binomial models. Being a non-linear model, the elasticity of the CRF function can be given as [46]:

$$Elasticity = \frac{\partial E(y_i, |x_i)}{\partial x_i} \cdot \frac{x}{y} = \exp\left(x_i' \beta_k\right)\beta_k \cdot \frac{x}{y}$$

where $\exp\left(x_i^{'}\beta\right)$ is the expected DIP values, β_k is the coefficient of CRF, x is the explanatory, and y is the response.

As shown above, the main interest of the study lay in estimating elasticities, and count models were used as an intermediary step in calculating elasticities. Given the geographical variations of dengue outbreaks, it is critical to estimate the elasticities separately by department with varying coefficient values of CRF. In this context, the current model was preferred to non-linear mixed models with a fixed coefficient and random effects since the use of coefficients and the measure of marginal effects and elasticities were more straightforward, reducing any possibility of potential overspecification (i.e. multiple adjustments) [46, 47]. Because the model was run separately for each department allowing variation in the CRF index by department, there is no concern about creating the effect of spatial autocorrelation. The elasticities were derived for every six months from January 2007 to December 2015. Early Warning Signal (EWS) was modeled such that dengue epidemics in Colombia can likely occur when the elasticity of the CRF index is maximized given the instantaneous slopes of DIP and the CRF index over time are positive minimizing the squared residuals.

Maximize:

$$Elasticity, E$$

Subject to:

$$(1)\ \beta_{DIP} = \frac{\sum_{i=t}^{t+5}\left(DIP_i - \overline{DIP}\right)}{\sum_{i=t}^{t+5}\left(T_i - \overline{T}\right)} > 0$$

and

$$(2)\ \beta_{CRF} = \frac{\sum_{i=t}^{t+5}\left(CRF_i - \overline{CRF}\right)}{\sum_{i=t}^{t+5}\left(T_i - \overline{T}\right)} > 0$$

where $\overline{DIP}$ *and* $\overline{CRF}$ are the means of *DIP and CRF*, T is time (month). The elasticities were then categorized into three percentiles: low level warning (0–50%), medium level warning (50–75%), and high level warning (75–100%). As expressed by Adde et al., the hit rate (HR) and false alarm rate (FAR) were defined as below [28]:

$$HR\ (or\ sensitivity) = \frac{(Detections \mid Outbreak)}{(Detections + Misses \mid Outbreak)}$$

$$FAR\ (or\ 1\text{–}specificity) = \frac{(False\ signals \mid No\ outbreak)}{(No\ signals + False\ signals \mid No\ outbreak)}$$

In addition, a sensitivity analysis was conducted with various moving average scenarios to make sure that the 12-month moving average is the most suitable period for the performance of the EWS model.

Given that the CRF index is statistically significant to explain variance of DIP for the departments where significant underreporting was not observed, the CRF index was further estimated at the smaller geographical level (5 km by 5 km resolution) for the entire country and used to identify high risk areas.

Results

During the period from January 2007 to December 2015, two major outbreaks were observed in many parts of Colombia. Figure 1 presents the overall trends of the three climate factors, as well as the DIP from 2007 to 2015 in Valle del Cauca, one of the departments where dengue fever is highly prevalent (see Additional file 1: Supplementary 3 for other departments). Looking at the bottom right panel in Fig. 1, there were two major outbreaks in 2010 and 2013 in the department. Comparing the trend of DIP with the climate factors, DIP appears to be positively correlated with temperature and humidity, but has a negative relationship with precipitation.

13 of 31 departments in Colombia were chosen after checking the robustness of the case reporting system. The ADF test showed that we reject the null hypothesis, which means that the dataset is stationary. As shown in Table 2, the CRF index is highly significant for all departments except Guaviare and Magdalena, thus 11 departments were selected for further analysis.

The CRF index and DIP were plotted over time to show the overall trend in Fig. 2 (see Additional file 1: Supplementary 4 for other departments). It is clear that the epidemic that occurred in 2010 was picked up by the steep increase of the CRF index. In 2013, another epidemic was observed. While there was no rapid change in terms of the CRF index during a short period in 2013, the CRF index reached its high level following the steady increase of the index since 2012. These provide an important point where an occurrence of future dengue epidemic can be related not only to the rapid increase of the CRF index, but also to the various levels of the CRF index and DIP. These combined relationships can be further explained by the elasticity of the CRF index which was used to develop an Early Warning Signal (EWS) model. In Fig. 3, the EWS based on the elasticity of the function was demonstrated for Valle del Cauca. In the department, the peak DIP was observed in March 2010, and the EWS signaled the high level warning sign two months before the peak (January 2010). Similarly, the second peak occurred in May 2013, and the EWS level went up from low to medium in January 2013 and remained at the same level until the end of the peak. It

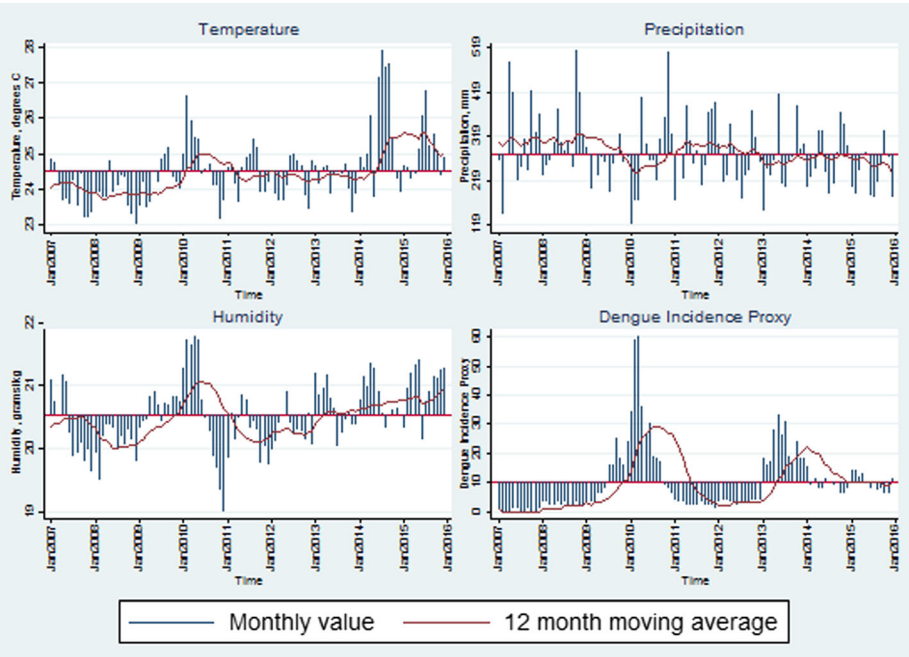

Fig. 1 Climate factors and DIP over time in Valle del Cauca*. * See Additional file 1: Supplementary 3 for other departments

Table 2 Regression outputs of the CRF index on DIP

Department	Number	Selected model	*P*-value for Z-score test (overdispersion)	Constant (α)		CRF (β)		AIC[b]	AIC (comparison)[c]
Antioquia	108	Poisson	0.47	−2.89	***	0.31	***	3.84	4.26
Arauca	108	NB[a]	0.00	2.00	***	0.06	***	8.46	30.37
Boyaca	108	NB	0.05	−0.59		0.51	***	4.26	4.19
Cauca	108	Poisson	0.19	−0.45	*	0.08	***	3.53	3.58
Cundinamarca	108	NB	0.03	−5.35	***	0.52	***	2.55	2.26
Guaviare	108	NB	0.02	3.23	***	−0.01		7.69	16.72
Huila	108	NB	0.00	0.49		0.05	***	7.87	14.33
Magdalena	108	NB	0.00	0.92		0.02		5.44	7.05
Norte de Santander	108	NB	0.00	1.61	***	0.05	**	7.68	10.54
Quindio	108	NB	0.02	−3.01	***	0.11	***	7.41	21.83
Risaralda	108	Poisson	0.11	−0.62	*	0.07	***	4.56	4.69
Santander	108	NB	0.00	1.07	*	0.06	**	7.12	9.89
Valle del Cauca	108	NB	0.00	−2.75	***	0.12	***	6.20	8.68

[a]Negative Binomial
[b]Akiake Information Criterion
[c]AICs for non-selected count models were presented for comparison. The AIC fit test was consistent with the Z-score test in terms of choosing a better model fit except Boyaca and Cundinamarca. Since the AIC differences were trivial for the two departments, the Bayesian Information Criterion (BIC) was further assessed, and NB was preferred over Poisson
* Significance at the 10% level, ** at the 5% level, *** at the 1% level

should be noted that there was no major outbreak observed throughout 2015 despite the continuous increase of the CRF index. Instead, Zika, another viral disease caused by *Aedes aegypti* emerged in 2015 and continued to increase in 2016. Overall, all 11 departments experienced dengue epidemics in 2010, and nine of them had additional minor outbreaks since 2011. Among the total of 24 observed outbreaks, EWS successfully detected 18 (75%) 1 ~ 5 months ahead of time and, three (12.5%) in the same month, and missed three (12.5%) (Additional file 1: Supplementary 6).

The EWS model predictability was examined with the validation data in 2016 which was separated from the model. It is interesting to see that the EWS already signaled the high level warning sign at the end of 2015, which accurately predicted another outbreak in two months (February 2016) that is out of the study period. Figure 4 further demonstrates the EWS model performance with the validation data for all 11 departments. 6 of 11 departments experienced outbreaks between January 2016 and April 2016. The EWS model successfully predicted these outbreaks 1 ~ 5 months ahead of

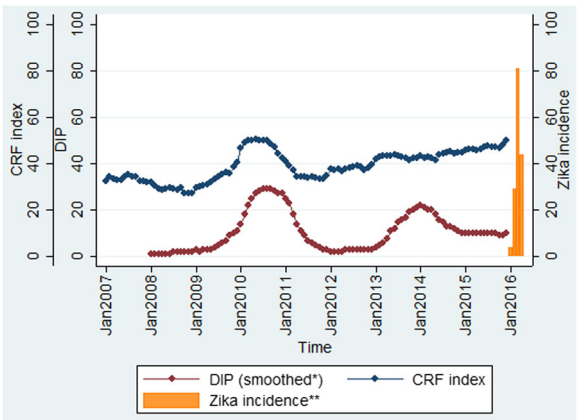

Fig. 2 The CRF index and DIP over time in Valle del Cauca***. * DIP was smoothed out to reduce short-term fluctuations and highlight longer term trends for demonstration. **Zika cases were reported in 2015 as well, but zika incidence rates (/100,000) were not clearly shown for year 2015 due to the low number of reported cases. *** See Additional file 1: Supplementary 4 for other departments

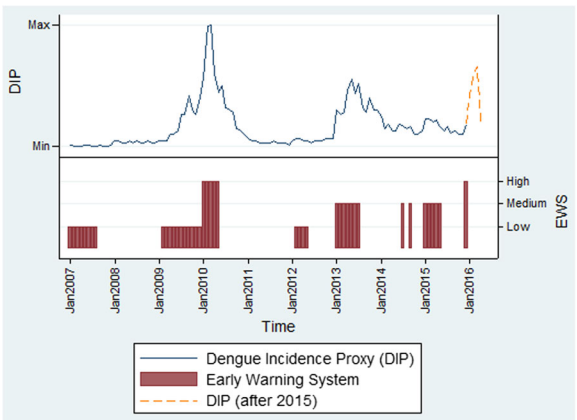

Fig. 3 Early Warning Signal in Valle del Cauca

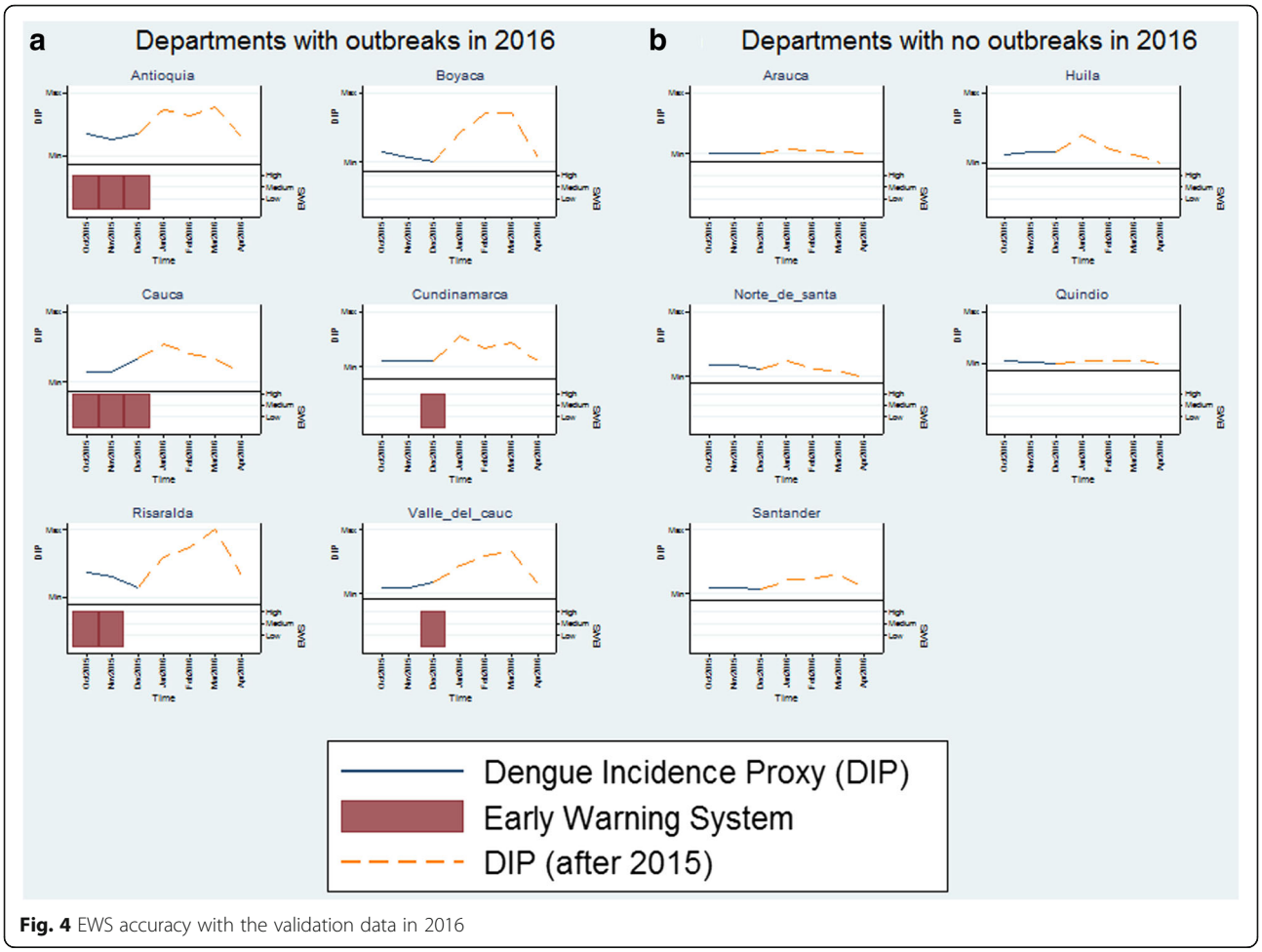

Fig. 4 EWS accuracy with the validation data in 2016

time for all departments except Boyaca (HR = 83.3%). In addition, the EWS model did not send out any false alarms for the other 5 departments where no outbreak occurred during the out-of-sample period (FAR = 0%). In other words, sensitivity (HR), specificity, positive predictive value, and negative predictive value of the validation data were as follows: 83.3%, 100%, 100%, and 83.3%.

The sensitivity analysis was performed with different moving average scenarios (12 months, 6 months, current value). As shown in Table 3, the hit rate was the highest with the 12-month moving average scenario, meaning that the current model produced the most accurate prediction compared to the 6-month and no-moving-average scenarios. The false alarm rate increased as the moving average period was shortened. This is mainly because the index becomes too sensitive and changes quickly due to the short duration of the moving averages of the climate datasets. As a result, it does not distinguish between minor fluctuations and major outbreaks (Fig. 5). This sensitive behavior of the CRF index with the shorter term scenarios proves our presumption that a current dengue epidemic is a result of the consistent long-term patterns of the climate conditions.

Given that the CRF index explains variation in DIP reasonably well, the CRF index was estimated at 5 km by 5 km resolution, and the most recent time of the index (December 2015) was presented in Fig. 6 (see Additional file 1: Supplementary 5 for more details). As expected, populations at high risk are concentrated in the Western

Table 3 Sensitivity analysis with additional moving average scenarios

Scenario	HR (sensitivity)	FAR	Specificity	Positive Predictive Value	Negative Predictive Value
12 month MA	87.5%	3.1%	96.9%	91.3%	95.4%
6 month MA	75.0%	4.7%	95.3%	85.7%	91.0%
Current value (no MA)	83.3%	6.3%	93.8%	83.3%	93.8%

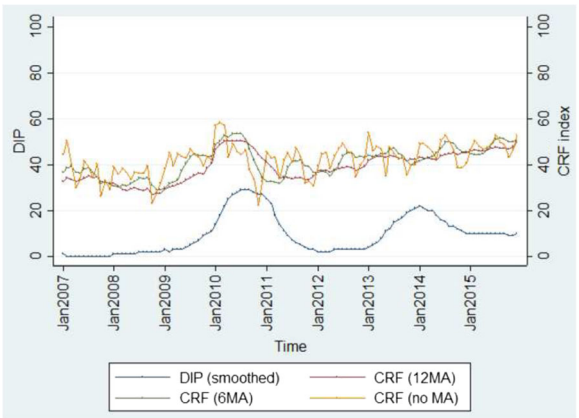

Fig. 5 The CRF index with different moving average scenarios in Valle del Cauca

part of the country due to more suitable climate conditions for vector mosquitoes and the high population level compared to the East. Using the geo-coordinates of the high risk areas at 5 km by 5 km resolution, it is possible to identify the locations for people at high risk more accurately for efficient disease prevention activities.

Discussion

This study confirms that dengue fever transmission is strongly related to climate factors as well as population density at different topographical conditions. One of the advantages of the CRF index is to prevent multicollinearity by combining all relevant climate indicators which may have some degrees of correlations with each other but have distinctive characteristics at the same time. During the study period from January 2007 to December 2015, the nationwide dengue epidemic occurred in 2010 was well explained by the rapid changes of the CRF index. Even if the CRF index increased steadily, the study found that it was still possible to detect an epidemic by adopting the elasticity of the function which takes into account not only the slopes but also the various levels of CRF and DIP.

In 2015, some inconsistent patterns between CRF and DIP were observed for some departments (Additional file 1: Supplementary 7). This inconsistency may be related to the unexpected emergence of Zika, which started being reported in 2015. As shown in Fig. 2, the number of Zika cases has continuously increased since 2015. However, it is still premature to make any firm statements regarding the impact of Zika on dengue fever due to uncertainty of the diseases. Given that reported cases are mainly based on clinical symptoms, there may have been a chance of misdiagnosis between the two diseases. In addition, due to the surge of an unfamiliar disease (Zika) imposing more difficulties on resource allocation at the local health facility level, it would be difficult to keep a consistent pattern in the case-reporting system from municipality-level heath facilities. Excluding 2015, a number of false alarms where EWS sends out the medium or high level signals but DIP remains low were only observed twice in Cauca (April and December 2014) during the study period.

Some areas of uncertainty deserve attention. While the CRF index performed well for 11 of 13 departments, the index was not statistically significant in Magdalena and Guaviare. This may have been caused partly by the inconsistent patterns of reported cases over time. Because the EWS was estimated based upon the most recent observed climate datasets, the EWS in this study is limited to issuing alerts with short-time intervals (1 ~ 5 months ahead). Given that, at present there are 1 ~ 2 month delays until the climate data become available, EWS with the short intervals (i.e. less than two months) may not, for now, be practical in operational modes. However, this limitation can be improved based upon the availability of the climate datasets in real-time in the future, and the 1 ~ 5 month intervals would provide enough room for public health officials to prepare for selected vector control activities and healthcare interventions (i.e. increase the number of beds at high risk areas) in the dengue-endemic setting [9, 26]. It should be noted that the study did not attempt to produce any longer-term predictions due to chaos and uncertainty in climate forecasts in the long run. Considering that long-term climate forecasts could be variable depending upon assumptions (i.e. future CO_2 omission level), the method proposed in this study could minimize potential bias which may be caused by uncertainty in input datasets. The climate datasets have coarse resolutions. While the datasets were resampled using the nearest option in this study, the model outcomes can be further improved with finer scale resolutions. It is worth noting that the cycling of El Niño and La Niña, called El Niño Southern Oscillation (ENSO), may have indirect impacts on the occurrence of dengue epidemics in South America by changing the patterns of climate variables such as temperature, precipitation, and humidity [28]. While any unusual changes of the climate variables affected by such events were captured by using the 12-month moving averages, further investigation would be needed to identify accurate impacts of El Niño on climate factors including its timing.

Nonetheless, our model provided accurate forecasts for the validation period for 5 of 6 departments that experienced outbreaks in 2016. In addition, this study identified populations at high risk for dengue at 5 km by 5 km resolution. The study findings can be used to accelerate introduction of dengue prevention activities and prioritize alternative health interventions among competing health demands in Colombia.

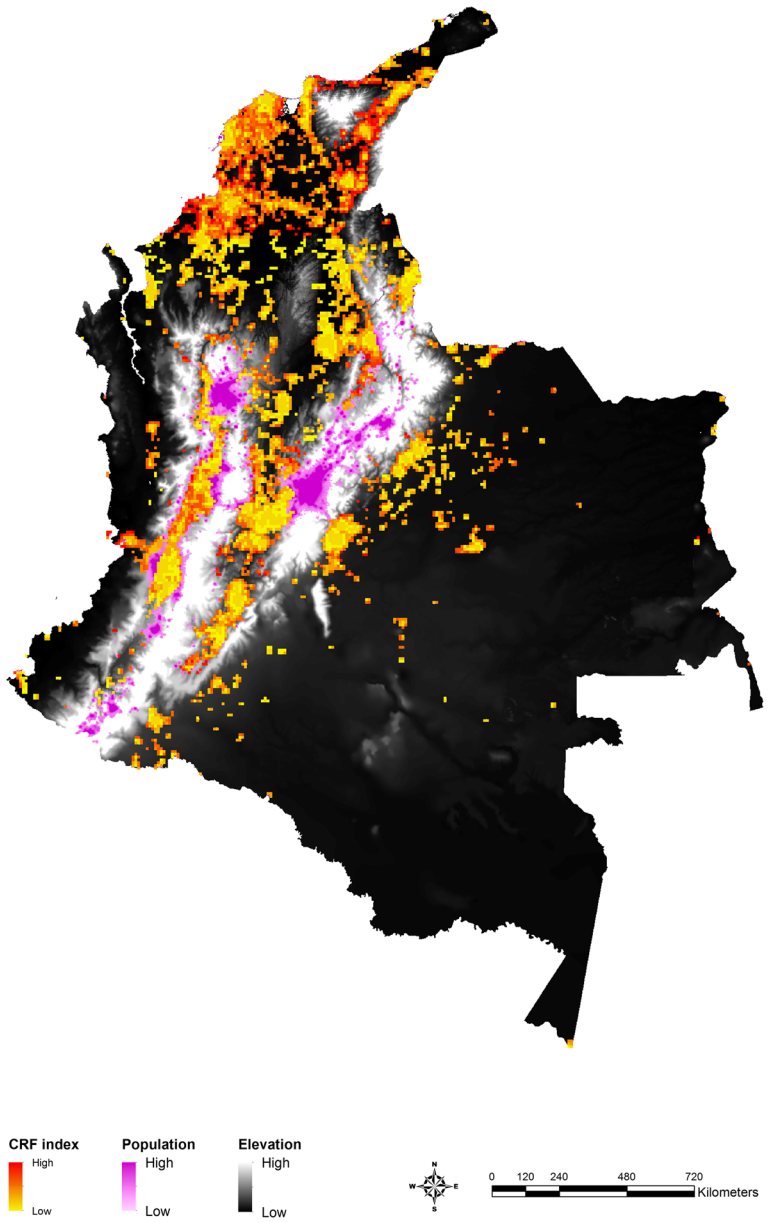

Fig. 6 Identification of high risk areas in Dec, 2015*. * See Additional file 1: Supplementary 5 for more details

Conclusions

The CRF index summarized multiple climate and non-climate risk factors into a single indicator which helps decision makers to understand easily [36]. While some of the climate factors were more commonly used in the existing literature due to the nature of a vector-borne disease, the applications of the climate data in these studies appeared to vary. The proposed EWS model in this study used the concept of elasticity to understand how DIP changes to varying levels of the CRF index and successfully detected dengue outbreaks in Colombia. In addition, the CRF index was further estimated at 5 km by 5 km resolution. The areas where the CRF index values have been continuously high over time can be prioritized for appropriate healthcare interventions. Furthermore, this can guide decision makers to find relevant locations where future surveillance studies can be conducted.

Additional files

Additional file 1: Supplementary 1.Cross-correlograms of climate datasets and DIP. Supplementary 2. Model specifications. Supplementary 3. Climate factors and DIP over time by department. Supplementary 4. The CRF index and DIP over time by department. Supplementary 5. Identification of high risk areas for dengue fever. Supplementary 6. EWS

for 11 departments during the study period. Supplementary 7. EWS for 11 departments in 2015. (ZIP 2317 kb)

Abbreviations
ADE: Antibody Dependent Enhancement; ADF: Augmented Dickey Fuller; AIC: Akaike Information Criterion; CRF: Climate Risk Factors; DIP: Dengue Incidence Proxy; EWS: Early Warning Signal

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Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Authors' contributions
JS Lee conducted the analyses and wrote the manuscript; M Carabali and IY Park carried out data collection and data interpretation; JK Lim, M Herrera, and LA Villa contributed to data interpretation and study design; A Farlow contributed to data interpretation and overall inputs on the study outcomes.

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Competing interests
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Dengue vaccine supplies under endemic and epidemic conditions in three dengue-endemic countries: Colombia, Thailand, and Vietnam

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ABSTRACT

Background: Dengue fever has been a major public health concern in Colombia, Thailand, and Vietnam. Unlike other infectious diseases, dengue vaccines had not been available for a long time, causing difficulties to control the disease. However, the first live attenuated, tetravalent dengue vaccine (CYD-TDV) became available in 2016 and has been already licensed in some dengue-endemic countries. Because several second-generation dengue vaccines are also in the pipeline, it is critical to understand the efficient allocation of dengue vaccines considering the geographical variation of the disease.

Methods: The Climate Risk Factor (CRF) index was created using the climate and non-climate factors in the three countries. A random-coefficient negative binomial model was chosen to validate the relationship between the CRF index and dengue incidence proxy. Given the statistical significance of the CRF index, high risk areas for dengue fever were identified at the 5 km by 5 km resolution and used to estimate vaccination coverage rates and the number of doses required for various types of vaccination scenarios by country.

Results and conclusions: Based upon a three-dose scheme, the estimated number of vaccines required for routine vaccination targeting 9 years old ranged from 1 to 2.6 million doses across the countries during the first year of introduction. A one-off catch-up campaign targeting the age group of 10–17 year olds would require 8 to 18 million additional doses. Routine vaccination (with or without a catch-up campaign) covered 63%, 90%, and 91% of the targeted age group populations in Colombia, Thailand, and Vietnam respectively. Given that many dengue-endemic countries face limited resources and that the costs for mass vaccination campaigns may not be trivial, the findings of this study can guide the decision makers in the three countries regarding the efficient distribution of vaccines by identifying populations at high risk at 5 km by 5 km resolution.

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1. Introduction

Dengue fever has been a major public health concern in many parts of tropical and subtropical regions around the world as the global burden of dengue has increased dramatically in recent years. A study finds an estimated 96 million apparent and 294 million inapparent dengue infections occurring annually [1]. Many dengue-endemic countries are also exposed to the risk of periodic outbreaks. Due to the complexity of the disease—with four related but antigenically distinct dengue viruses—it has been challenging not only to have a full understanding of the disease, but also to develop effective vaccines against the disease.

After a long period without dengue vaccines, the dengue vaccination era began in 2016 as the first live, attenuated tetravalent dengue vaccine (Dengvaxia, CYD-TDV) became commercially available. Several second-generation dengue vaccine candidates are in the pipeline. There is no doubt that safe dengue vaccines can be used as an effective tool to control dengue fever in dengue-endemic countries that have solely relied on vector control activities till now. However, it is also true that many dengue-endemic countries face a problem of limited resources (i.e. allocation of limited budget among competing health demands) [2]. Because dengue-endemic countries facing constraints on funding sources may need to place priority on vaccinating populations at high risk rather than all of their populations, vaccination strategies should be carefully examined in order to target the right populations who are most urgently in need of vaccines.

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This study projects the potential demands for dengue vaccines in three dengue-endemic countries: Colombia, Thailand, and Vietnam. While CYD-TDV has already been approved in several dengue-endemic countries, discussions are still ongoing regarding where and how to use the vaccine in order to maximize the protection induced from the vaccine while minimizing any potential detrimental effects [3–6]. In addition, some of the second-generation dengue vaccine candidates are currently conducting phase 3 trials at the time of our research. As such, while some elements of the vaccine profile for CYD-TDV were taken into account throughout this study (i.e. 3-dose scheme), the study was designed to be more generally applicable to other second-generation vaccines and so not strictly restricted to the vaccine profile and safety matters of CYD-TDV [7].

The primary goal of the current study lies in the identification of populations at high risk for dengue fever and the estimation of vaccination coverage rates, as well as the estimation of the number of vaccine doses required in Colombia, Thailand, and Vietnam. Since vaccine supplies may be limited during the early stage of vaccine introduction, it is critical to predict the number of vaccines required and identify high-risk areas where vaccination campaigns should be prioritized. Furthermore, dengue-endemic countries are exposed to the risk of periodic outbreaks. During an emergency such as an epidemic, different vaccination strategies need to be considered because the impacts of vaccination may not be maximized if implemented late or if the right places are not targeted due to supply limitations or delays in the short-run [3]. Thus, in this study both pre-emptive and reactive vaccination strategies are considered, taking into account the supply shortage during the initial phase of the vaccine introduction. In particular, the geographically dispersed risk levels of dengue fever-that is disease hotspots and non-hotspots-were identified based on various climate and non-climate risk factors in an effort to prioritize vaccination campaigns and improve the efficiency of vaccine allocation [8].

2. Methods

All three countries were assumed to prioritize dengue vaccination for high-risk areas when vaccine supply may be limited during the early stage of the vaccine introduction, and to target broader populations in medium-to-low risk areas as the introduction stage phases out. In order to identify geographically dispersed risk levels for dengue fever, the Climate Risk Factor (CRF) index was adopted. The CRF index was previously formulated based on the 12-month moving averages of temperature, precipitation, and humidity, adjusted by non-climate factors which are population density and elevation [8]. The CRF index was then validated with Dengue Incidence Proxy (DIP) which was calculated by dividing the number of monthly dengue fever cases by population in Colombia from January 2007 to December 2015. The final DIP values were expressed per 100,000 and rounded up to obtain integer values. Similar procedures were applied to prepare the datasets and construct the CRF index for Thailand and Vietnam in the current study. Briefly, the monthly climate datasets were resampled into 0.008 by 0.008 degree resolution by taking the nearest neighbor assignments. Given that a current epidemic is a result of the climate conditions observed during the past months, rather than single temporal values at present, cross-correlations between various periods (current, 6, 12 months) of the moving averages of the climate datasets and Dengue Incidence Proxy (DIP) with time lags were tested. The 12-month moving average was selected as the most appropriate period which explains the level of the current DIP. In addition to the climate datasets, non-climate factors were considered in constructing the CRF index: night light data (for population density); and elevation raster files. The three climate datasets and population density were used by province in each country. The variables were standardized, and the values were averaged across the variables. The final values were converted into a range from zero (low risk) to one (high risk) and adjusted by the risk proportion which was estimated by dividing the sum of the night lights observed under 1500 m elevation by the sum of the total night lights in each province. The full description on the mathematical formulation of the CRF index can be found at [8]. Supplementary 1 summarizes how the CRF index was constructed for selected provinces in the three countries where dengue has been prevalent. For the current study, the CRF index and DIP were further estimated for each province in Thailand and Vietnam during the same study period. In Thailand, the number of monthly dengue fever cases and population information by province were obtained from the Ministry of Public Health [9]. In Vietnam, the number of dengue fever cases by province was provided by the National Institute of Hygiene and Epidemiology (NIHE), and the population data was acquired from the General Statistics Office of Vietnam [10,11].

Since DIP can be considered as non-negative integer values, count models were previously used taking into account overdispersion. The positive relationships between DIP and the CRF index were validated during the study period from January 2007 to December 2015 in Colombia [8]. However, as the current study focused on validating the relationships between DIP and the CRF index, non-linear mixed models were adopted to identify global maximums in all three countries. As pointed out by Mohebbi et al., overdispersion may occur because of misspecification of the mean function or the probability model, and (or) spatial autocorrelation [12]. While the former is more common in general count models, the latter occurs when counts of events are observed in small geographical areas when overdispersion and residual spatial autocorrelation are present [12]. The full specification of the modeling procedure is described in Supplementary 2. The final model selected throughout the procedure is a random-coefficients negative binomial model where the conditional distribution of the function can be written as [13,14]:

$$f(y_i|v_i,\alpha) = exp\left[\sum_{t=1}^{n_i}\left\{ln\Gamma\left(y_{it}+\frac{1}{\alpha}\right) - ln\Gamma(y_{it}+1) - ln\Gamma\left(\frac{1}{\alpha}\right) - \frac{1}{\alpha}ln(1+\alpha\mu_{it}) + y_{it}ln\left(\frac{\alpha\mu_{it}}{1+\alpha\mu_{it}}\right)\right\}\right]$$

where y_{it} is the observed value, μ_{it} is the expected value of the outcome ($\mu_{it} = exp(x_{it}\beta + z_{it}v_i)$), x_{it} is the vector of the fixed effects covariates, β is the coefficient, v_i is the random effects, z_{it} is the vector of the random effects covariates, and α is the conditional overdispersion parameter in a mean-overdispersion parameterization [13–16].

Given the statistical significance of the CRF index in explaining the variance of DIP, the CRF index was further estimated at the refined geographical unit (5km by 5 km resolution) from January 2007 to December 2015. The CRF index was then categorized into 10 risk-levels based upon every 10th percentile by province, with the highest score indicating the greatest risk for dengue fever. This information was used to target populations at high risk and to estimate vaccine uptake rates to achieve efficient allocation of the limited healthcare resources. Supplementary 3 compares the actual distributions of reported dengue cases with the CRF index by country and shows that there is a great consistency between the two distributions.

2.1. Spatial coverage for pre-emptive vaccination

Based on the validation models provided in the previous and current studies, all three countries would remain dengue-endemic and less likely experience dengue outbreaks when the level of the CRF

index is very low [8]. Thus, the low level of the CRF index was assumed to represent the dengue-endemic condition. While some provinces in a dengue-endemic country experience dengue epidemics, others in the same country do not experience outbreaks during the same period due to the geographically diverse behavior of dengue outbreaks. In order to identify high-risk areas for all provinces during the dengue-endemic setting, the time points where the CRF index values were the lowest during the study period were identified by province in each country. The CRF index values estimated at 5 km by 5 km resolution responding to these specific time points were used to understand the variation of the geographical risk levels of dengue fever for the endemic periods. As vaccine supply may be limited during the early stage of introduction, vaccine uptake rates, for both routine and catch-up vaccination, were also taken into account for the first three years following introduction. It was presumed that vaccination was prioritized for populations in high-risk areas where the CRF index values were above the 75th percentiles at year 1, expanded to the second high-risk areas (50–75th percentiles) at year 2 and the third high-risk areas (25–50th percentiles) at year 3. After year 3, all provinces were expected to cover all expanded risk areas where the CRF index values were over the 25th percentiles.

2.2. Spatial coverage for reactive vaccination

While a dengue outbreak can occur throughout a country at a given time (i.e. nationwide outbreak), some outbreaks are more geographically focused. Furthermore, the magnitudes of outbreaks can differ by geographical location even during a nationwide outbreak. For example, Colombia experienced a nationwide dengue outbreak in 2010 but the outbreaks in 2013 were only observed in selected provinces. In this study, an outbreak was defined in the same way as the previous study: as long as an unusual peak in DIP was observed in a province, it was considered as an outbreak even if the DIP value in that province was relatively low compared to other provinces where dengue is more prevalent [8]. Given the positive relationship between the CRF index and DIP validated in the model, the time points where the CRF index values were the highest by province were assumed to be the dengue-epidemic periods. In addition to the validation model outcomes specified in Supplementary 2, the association between the high level of the CRF index and a dengue epidemic is further demonstrated in Supplementary Fig. 1(d) where the high levels of the CRF index values correspond to dengue outbreaks. Similar to the case of pre-emptive vaccination, the CRF index values at 5 km by 5 km resolution corresponding to these specific time points were obtained to identify populations at high risk during the epidemic situation. For reactive vaccination, two scenarios were assumed: (1) target hotspots only (areas with CRF index values greater than the 75th percentiles), (2) target both hotspots and non-hotspots (areas with CRF index values greater than the 25th percentiles).

2.3. Vaccine demand forecast

As a default policy, 9 year olds were targeted for routine vaccination and 10–17 year olds for a one-off catch-up campaign. While recent studies discuss extensively the notion of targeting an appropriate age group for routine vaccination with CYD-DTV depending upon dengue transmission intensity, there is no clear consensus as to which age group to target with a catch-up campaign with this vaccine [5,6,17]. In this study, the age group of 10–17 year olds was chosen for a catch-up campaign based upon the comparative modeling exercise by WHO [6], and, as an alternative, the vaccine demand for the age group of 10–29 year olds was also presented [18] [see Supplementary 2]. A 3-dose scheme was assumed for pre-emptive vaccination, and all three doses were given to recipients within a year. During an emergency situation such as an outbreak, it would not be realistic to administer all three doses in a short period of time. Hence, in the absence of nationwide routine and catch-up vaccinations, as a reactive response a single-dose was assumed to be administered to the population of 9–29 year olds at risk. It is debatable whether this single-dose strategy would be effective in the case of CYD-DTV. A previous modeling outcome showed that a single-dose of CYD-DTV might be enough to achieve protective immunity in seropositive individuals. [5]. However, this would still require more time to determine given the absence of direct findings from any clinical data, and single-dose protective immunity may be improved upon in future dengue vaccines.

Obtaining long-term population projections at the sub-national boundary level is a challenge. In order to obtain population projections by grid-cell of 5 km by 5 km resolution, the country-level population projections by age group were first obtained from 2017 to 2040 for three countries [19]. The population data were then adjusted by the satellite night lights data which are available at 30 arc-second grid spacing (approximately 1 km^2) [20]: the projected populations were multiplied by the ratio of the sum of the night lights in a pixel and the sum of the total night lights of the corresponding province. Prior to the adjustment, correlations between night-lights data and provincial-level population data were examined to ensure that this adjustment reasonably approximated populations at the grid-cell level [21]. The variables and assumptions used in the demand forecasting model are summarized in Table 1. The demand forecast was projected from 2017 to 2040 for the pre-emptive vaccination strategy. Due to sporadic

Table 1
Model assumptions.

Type	Pre-emptive vaccination	Reactive vaccination
Number of doses	3 doses	1 dose
Wastage rate	10%	10%
Geographical unit	5 km by 5 km resolution	5 km by 5 km resolution
Coverage	Populations at risk (the CRF index during an endemic period >25th percentiles)	Populations at risk (the CRF index during an epidemic period >25th percentiles)
Uptake rate	First three years	N/A
Vaccination strategies	9yo routine w/ and w/o 10-17yo catch-up campaign (alternatively, 10-30yo catch-up campaign)	9-29yo in hotspots only, 9-29yo in hotspots & non-hotspots
Projection period	2017–2040	2020
Sensitivty analysis 1	1 st high-risk areas (>90th percentiles) 2nd high-risk areas (75th–90th percentiles) 3rd high-risk areas (50th–75th percentiles)	Hotspots (>90th percentiles) Hotspots & non-hotspots (>50th percentiles)
Sensitivty analysis 2	1 st high-risk areas (>50th percentiles) 2nd high-risk areas (25th–50th percentiles) 3rd high-risk areas (1st–25th percentiles)	Hotspots (>50th percentiles) Hotspots & non-hotspots (>1 st percentiles) □

occurrences of dengue epidemics, the year 2020 was selected as an example of the demand forecast during an outbreak situation, but the estimation can be done for other years.

2.4. Sensitivity analyses

In this study, vaccination coverage rates were estimated by taking into account vaccine uptake levels for pre-emptive vaccination and hotspots for reactive vaccination strategies. As these factors were constructed based upon the geographically dispersed risk levels of dengue fever using the CRF index, sensitivity analyses were conducted to reflect uncertainty levels of the estimates by applying various threshold levels of the CRF index as shown in Table 1.

3. Results

The risk level for dengue fever is not only variable over time but also geographically dispersed. The CRF index was validated against DIP by using a random-coefficients negative binomial model and proved to be statistically significant at explaining the variance of DIP. The full model specifications and outcomes are presented in Supplementary 2. Various risk levels of dengue fever based on the CRF index are demonstrated in Fig. 1. The upper panel shows the risk levels during endemic periods in (a) Colombia, (b) Thailand, and (c) Vietnam. While the majority of the areas were at low risk, some locations where population density is high (i.e. Bangkok in Thailand, Ho Chi Minh City in Vietnam) appeared to be at high risk. In the lower panel, the CRF index levels at the time when each province experienced a dengue epidemic between 2007 and 2015 were used to simulate risk levels for the dengue epidemic setting. It was shown that populations residing at high elevation were not at high risk even during the epidemic periods (i.e. Bogota in Colombia).

Children at 9 years old were targeted for routine vaccination. A 3-dose scheme was assumed to start in 2017. The estimated number of vaccines required for routine vaccination is shown in Fig. 2. For all three countries, vaccines were distributed to the highest-risk areas first, and gradually to the second and third highest-risk areas during the first 3 years given the scenario that vaccine supply would be limited right after the vaccine introduction. In 2017, in

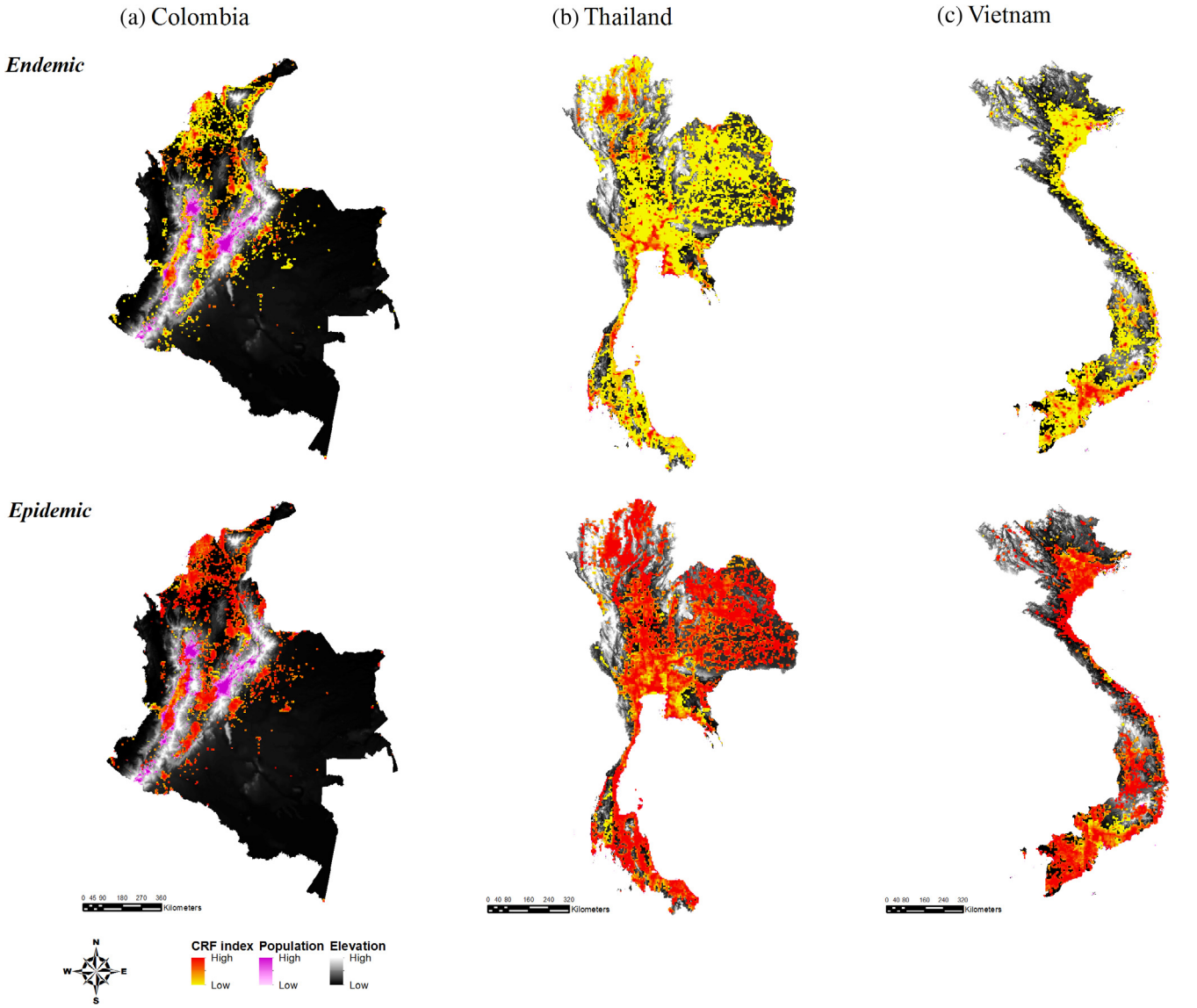

Fig. 1. Risk levels for endemic and epidemic situations based on the CRF index.

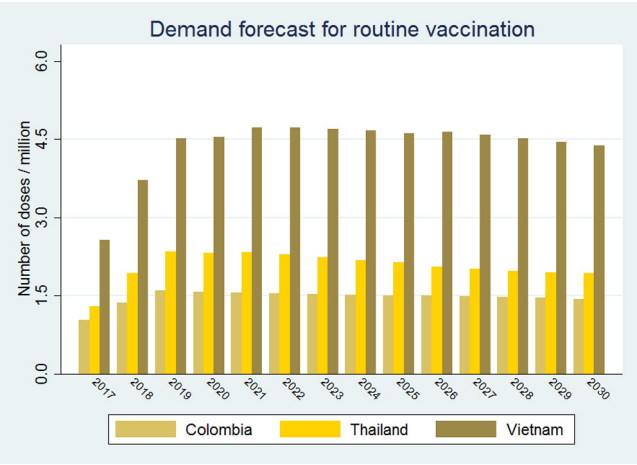

Fig. 2. Number of vaccine doses required for routine vaccination.

Colombia, Thailand, and Vietnam respectively, approximately 1, 1.2, and 2.6 million doses would be required to vaccinate populations at high risk, and the numbers peak at 1.6, 2.3, and 4.7 million doses in 4 to 6 years after the introduction. Overall, the number of doses required for the routine vaccination is the highest in Vietnam and the lowest in Colombia. Population size in risk areas played a major role in determining the number of doses in each country. It was also observed that the total number of doses decreases slightly as time goes by because of the decline in projected population on account of the ongoing drop in the birth rate in these countries [19,22].

In addition to routine vaccination, a one-off catch-up campaign was considered for the age group of 10–17 year olds taking into account the same uptake scenarios as for routine vaccination (Fig. 3). At year 1, the number of vaccine doses required for the catch-up campaign ranged from 8 million to 18 million with Vietnam having the highest and Colombia the lowest. At year 3, the required number of doses went up to 13 million doses in Colombia and 32 million doses in Vietnam. As an emergency response, reactive vaccination was planned to target (1) hotspots only, as well as (2) both hotspots and non-hotspots. Targeting only hotspots would require 7, 9, and 17 million doses in Colombia, Thailand, and Vietnam respectively. About 3.5 to11 million doses would be additionally needed to cover non-hotspots during an epidemic situation as shown in Fig. 3.

The 10 provinces in each country which were expected to consume the most doses of vaccines are presented in Fig. 4. In Colombia, Valle del Cauca followed by Santander and Meta appeared to be the most vaccine demanding provinces in terms of routine and reactive vaccinations. In Thailand, Chon Buri province would require the highest number of vaccines at year 3 of the routine vaccination. On the other hand, Nachon Rachas was predicted to overtake Chon Buri in terms of the required vaccine stockpiles when targeting hotspots during an outbreak situation. In Vietnam, Binh Thuan was anticipated to require the largest number of vaccines for both routine and reactive vaccinations.

During endemic periods, routine vaccination (with or without a catch-up campaign) covered 63%, 90%, and 91% of the targeted age group populations in Colombia, Thailand, and Vietnam respectively (Fig. 5). When the focus is on disease hotspots during an outbreak (scenario 1), about half of the targeted age group are expected to get vaccinated. The coverage rates became over 90% in Thailand and Vietnam, and 65% in Colombia as the reactive vaccination strategy expands target areas into non-hotspots (scenario 2). The vaccination coverage rates in Colombia were lower than the other countries because some densely populated areas were geographically located at high elevation (i.e. Bogota), which in turn put less priority on vaccinating populations residing in these areas.

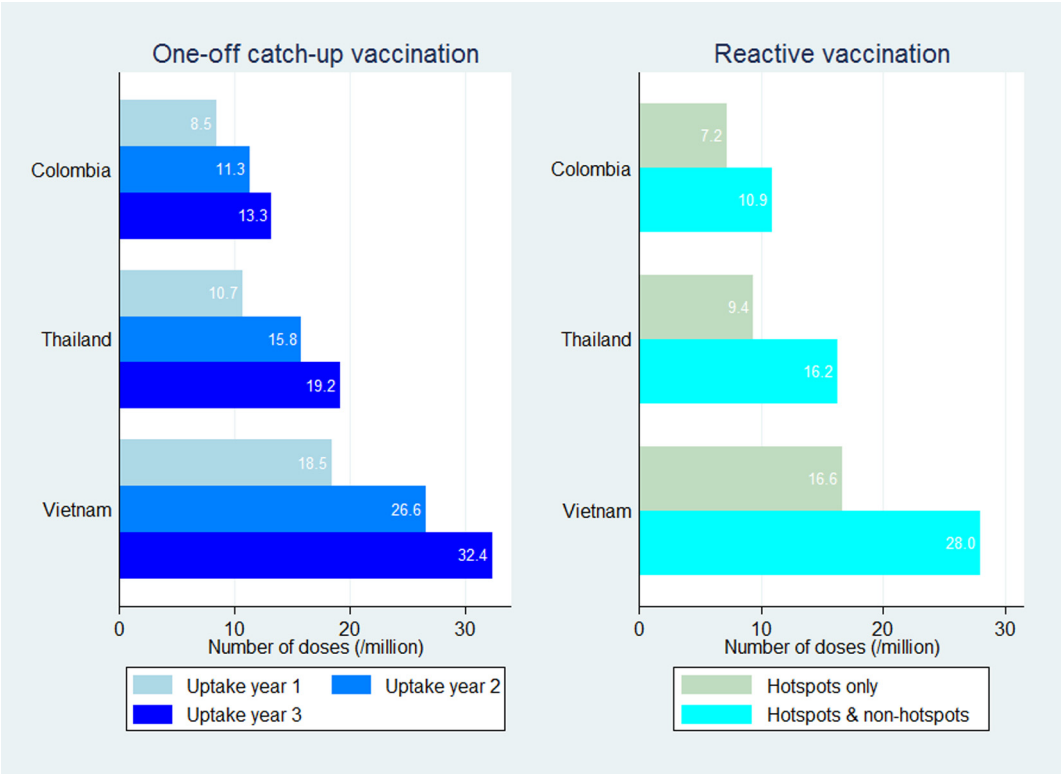

Fig. 3. Number of vaccine doses estimated for a one-off catch-up campaign and reactive vaccination. *See Supplementary 2 for an alternative catch-up campaign scenario targeting the age group of 10–29 year olds.

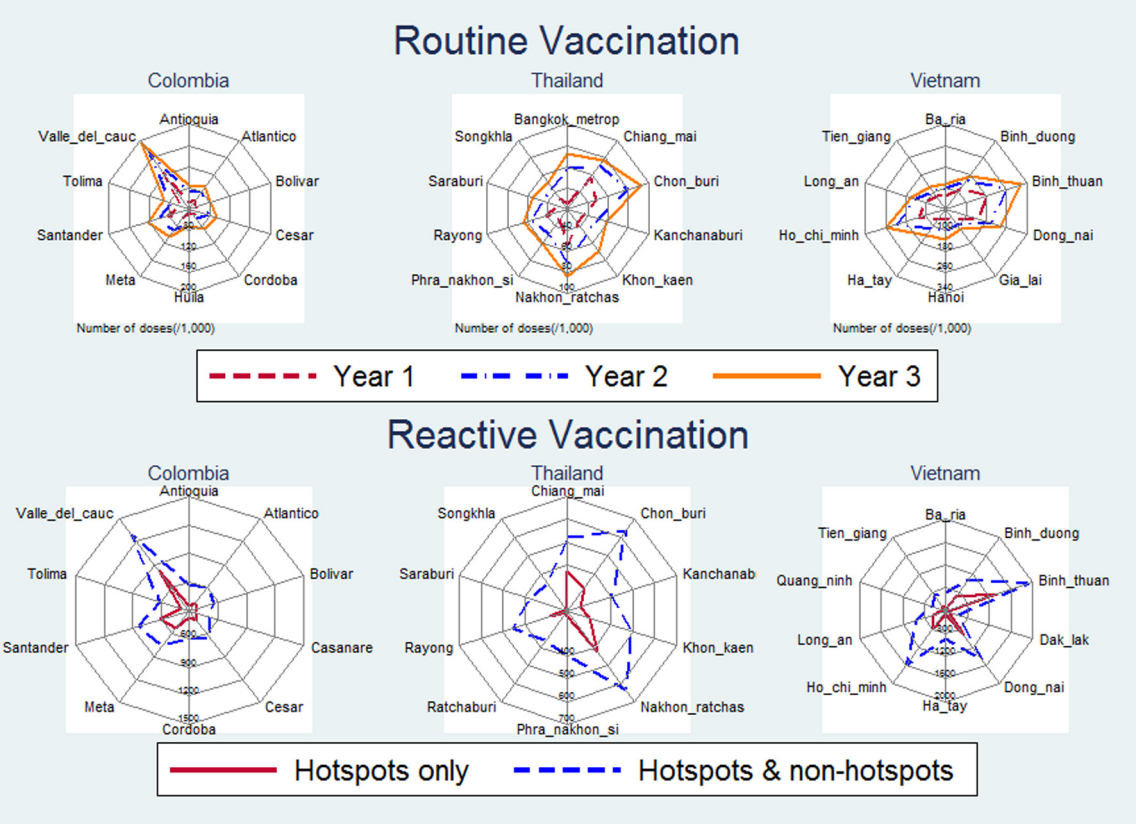

Fig. 4. Top 10 provinces in terms of the number of vaccines demand by vaccination scenario.

In addition to the overall coverage rates estimated for the selected vaccination strategies, the CRF index estimated at the 5 km by 5 km resolution can be used to explain the intra-province heterogeneity of high risk areas and to pin down the locations for efficient vaccine distributions, minimizing the misallocation of limited resources. For example, Valle del Cauca was mentioned as one of the most vaccine-demanding provinces in Colombia. In fact, SIVIGILA, an official governmental program of the epidemiological surveillance system in Colombia, reported that dengue fever had been highly prevalent in Valle del Cauca and that 60% of the reported dengue cases in the province between 1999 and 2010 were harbored in two municipalities (Cali and Palmira) [23]. As shown in Fig. 6(b), the high-risk areas of dengue fever are heterogeneous even within a province, and the intra-province heterogeneity of the CRF index is highly consistent with what had been reported by SIVIGILA. The high-risk areas are indeed concentrated in the Eastern part of Cali and the Western part of Palmira in Valle del Cauca. Considering the uptake levels based upon the CRF index in the current study, these high risk areas were prioritized for vaccination as highlighted in light blue in Fig. 6(c), and target areas were expanded to the second and third risk areas at year 2 and year 3 after the introduction.

Depending upon the CRF threshold levels, the number of vaccine doses required and vaccine coverage rates vary as shown in Fig. 7. In the lower-bound scenario compared to the baseline threshold, the number of doses decreased by 14–57%, 18–74%, 18–75% in Colombia Thailand, and Vietnam respectively. The large rates of decrease were observed for the first uptake year of the pre-emptive vaccination and for the hotspot only strategy of the reactive vaccination because the target areas for these strategies were significantly reduced under the lower-bound scenario. With the upper-bound scenario, the changing rates in the number of doses were less than 30% compared to the baseline threshold across the countries. Vaccination coverage rates ranged from 26% to 54% in Colombia, 29% to 73% in Thailand, and 30% to 76% in Vietnam for the first year of introduction, and gradually increased.

4. Discussions

This study identified populations at high risk for dengue fever based on the CRF index which was statistically significant in explaining the variance of DIP in three dengue-endemic countries (Colombia, Thailand, and Vietnam). Given that a dengue vaccine has not yet been widely used for nationwide vaccination campaigns, the current study estimates coverage rates by taking into account the geographically dispersed risk levels of dengue fever using the CRF index, and calculates the expected number of vaccine doses for various types of vaccination strategies.

As pre-emptive vaccination strategies, 9 year olds were targeted for routine vaccination, and 10–17 year olds (alternatively 10–29) were considered for a one-off catch-up campaign. Given that vaccine supply would be limited during the early stage of the vaccine introduction, gradual uptake rates were taken into account for the first three years since introduction. This study not only estimated the number of vaccine doses required for selected vaccination strategies, but also identified areas for vaccination at 5 km by 5 km resolution, thus minimizing the misallocation of vaccines. In particular, each risk-level cell as shown in Fig. 5 is small enough to be utilized within various levels of administrative boundaries such as municipality or province. Thus, three countries can determine their target strategies by relatively large admin-boundary (i.e. province), small admin-boundary (i.e. municipality), or even smaller level (5 km by 5 km).

In addition to pre-emptive vaccination strategies, reactive vaccination was considered. Vaccine stockpiles are needed in order

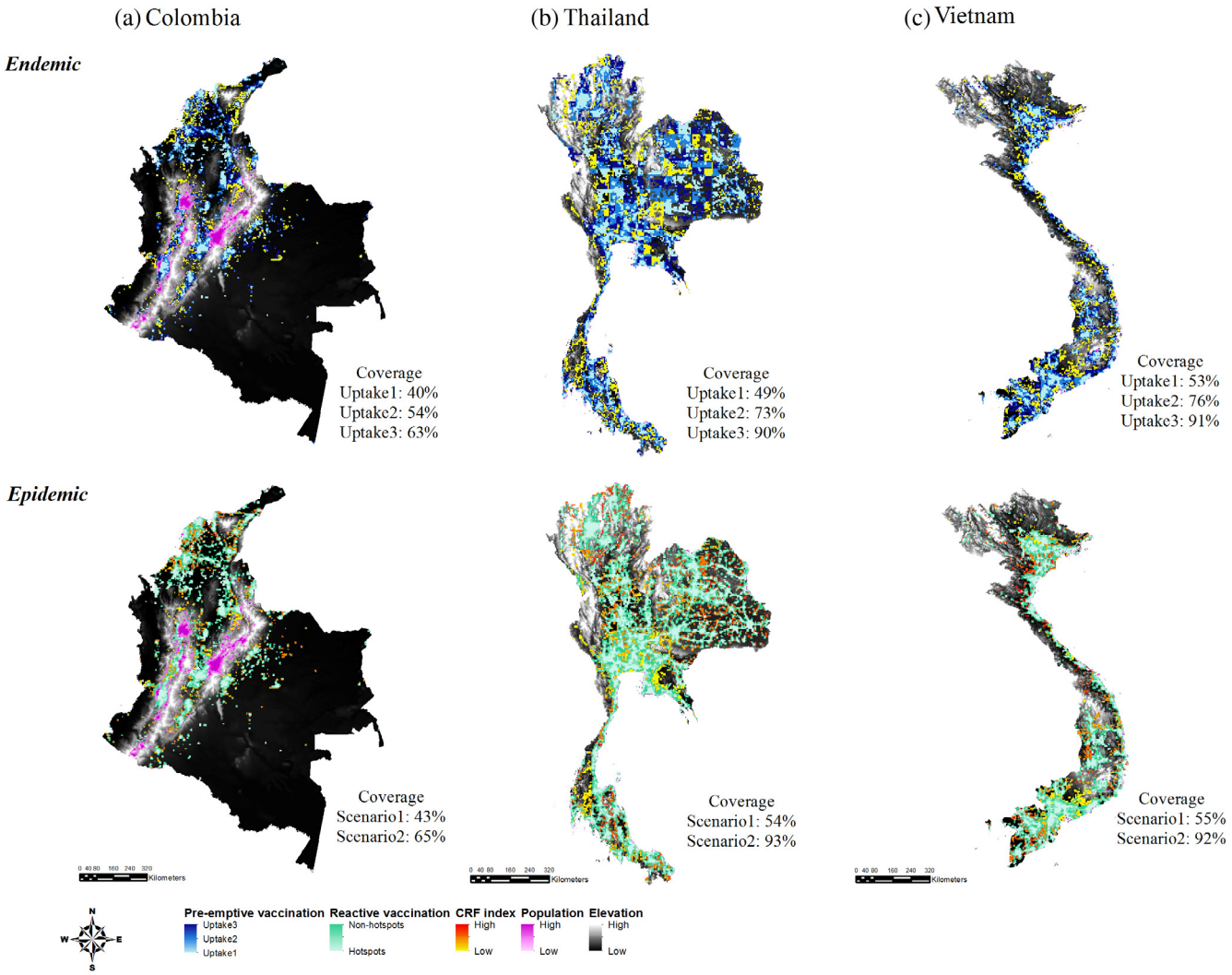

Fig. 5. Vaccination coverage rates for pre-emptive and reactive approaches.

to ensure rapid access to vaccines for countries experiencing epidemics [24]. In fact, all three countries are exposed to nationwide dengue outbreaks. For example, dengue serotype 4 has not been common for the past decade in Colombia, and many people would likely be susceptible for this serotype. If serotype 4 were introduced to Colombia, there would be a high chance of experiencing a nationwide outbreak similar to the one in 2010. It may be premature to discuss vaccination strategies during a dengue outbreak situation given the lack of information on dengue vaccine profiles at the present time. However, in the case of other infectious diseases such as cholera and yellow fever, previous studies showed that the biggest hurdles to reactive vaccination were the clear identification of geographical areas to be targeted and the timing of vaccination [3,25–27]. With the currently available dengue vaccine (CYD-TDV), there is a possibility to complement the single dose administered during an outbreak with a second and third dose administered later on.

The CRF index can be considered as a useful tool in understanding the overall risk level of dengue fever at the smaller geographical unit [8]. While there is no doubt that serological studies would provide more accurate information on the disease in a specific location or site within a country, it would be difficult to obtain the details of seroprevalence history over a long-period of time for each cohort in all specific locations of dengue-endemic countries. Thus, accompanying existing and future serological studies, the CRF index can be used to identify geographical areas at high risk for dengue fever, and to facilitate public health-policy interventions in the governmental (or macro)-perspective (i.e. nationwide vaccination campaigns). For example, a WHO position paper indicated that the introduction of CYD-TDV is recommended in geographic settings where seroprevalence is greater than 50% [7]. As it would be logistically difficult to conduct seroprevalence studies in all specific locations of a country, the CRF index can be used to identify high risk areas where further serological studies can be conducted for vaccination. In addition, the current study outcomes can be used to spot areas where serological testing of individuals can be conducted prior to vaccination in order to screen potential vaccine recipients, thus facilitating a more efficient allocation of limited resources [5]. As many dengue-endemic countries may not have enough resources to support mass vaccination programs for the current and future vaccines, decision makers may need to identify well-defined geographical locations to prioritize vaccinating populations at high risk [21,28]. The current study outcomes can help resource-constrained countries plan more effective vaccination strategies at the local level by prioritizing areas at high risk since vaccine supply may be limited during the early phase of a new vaccine introduction [21].

One of the important findings was that while the timing and locations of dengue outbreaks were variable, there was a general consensus that many provinces in the three countries experienced

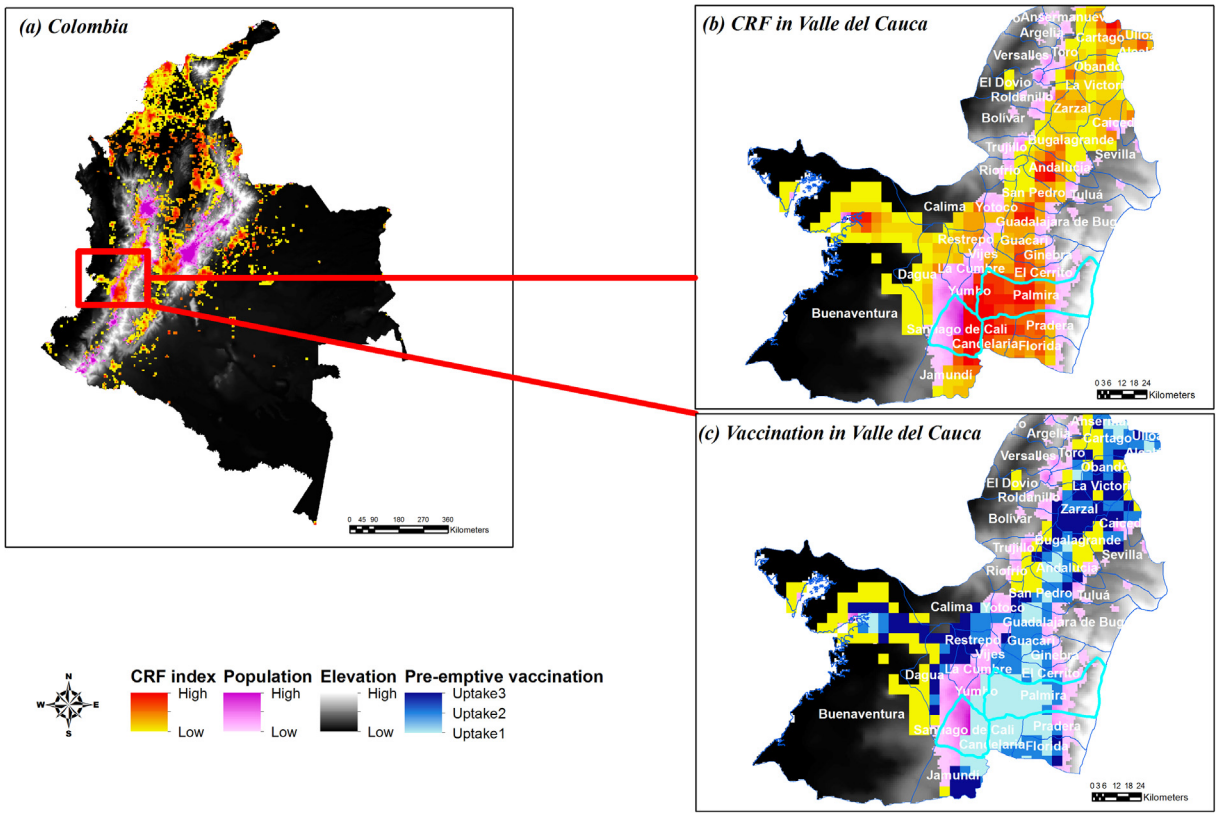

Fig. 6. Intra-province heterogeneity of high risk areas in Valle del Cauca.

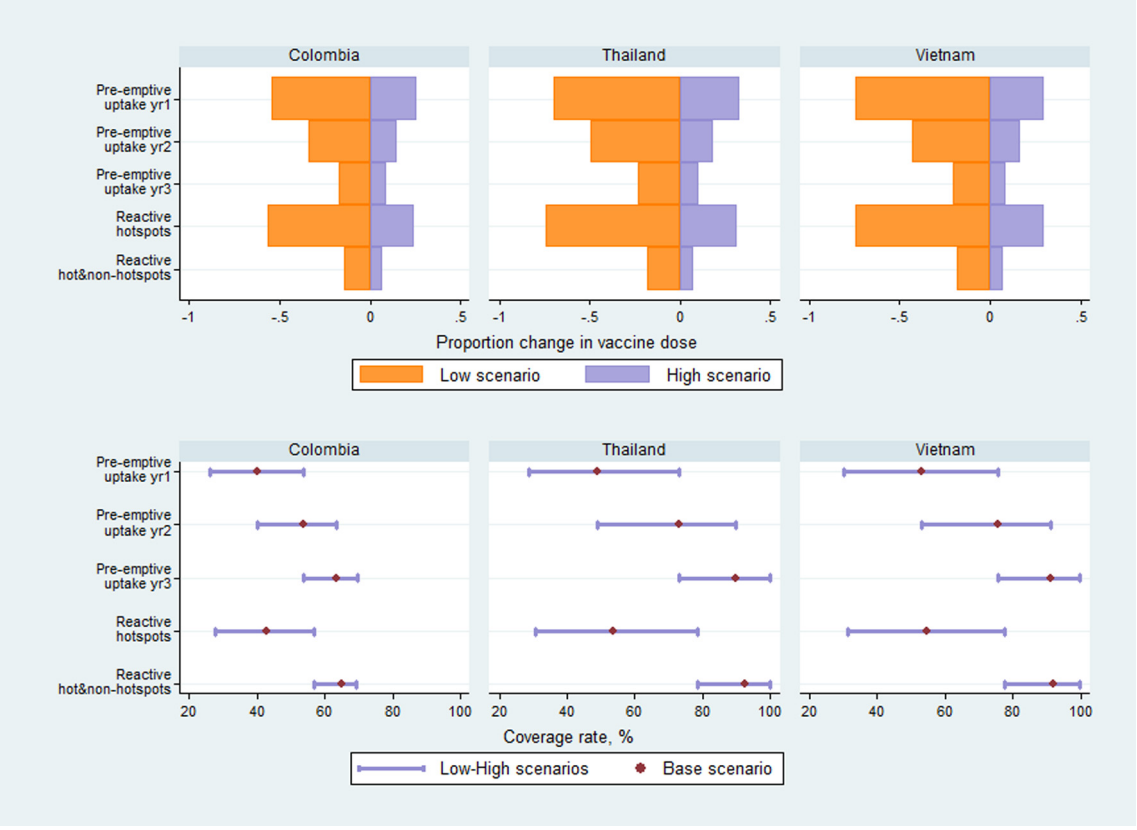

Fig. 7. Sensitivity analyses. *Low scenario based on sensitivity analysis 1; high scenario based on sensitivity analysis 2.

dengue epidemics in 2010 and 2013, and many of these epidemics were clearly captured by the rapid increase of the CRF index and the high level of the CRF index (see Supplementary Fig. 1(e)). This indicates that the use of the CRF index would potentially be an informative tool even in other dengue-endemic countries where there is no sophisticated national surveillance system. Furthermore, there were existing studies which shed light on early warning systems of dengue outbreaks [8,29,30]. The findings from these studies can be used to aid the timing of reactive vaccination, and such models can be further expanded to other dengue-endemic countries considering the use of vaccines for controlling dengue outbreaks. The reactive vaccination strategies presented in this study need to be further updated as more guidelines on the use of the current and future dengue vaccines become available. Nonetheless, the results from this study provide a good starting point for decision makers to design vaccination strategies in response to dengue outbreaks and to approximate the required number of doses (i.e. stockpiles) for emergency situations.

Some areas of uncertainty need attention. Care must be taken when applying the study outcomes to the use of CYD-TDV as the aforementioned WHO position paper indicated 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 [7]; this study was designed to be more generally applicable for decision-makers when considering other second-generation dengue vaccines. Unlike Colombia, the number of monthly dengue fever cases was not adjusted for potential case-underreporting in Thailand and Vietnam due to the lack of data sources. Thus, the estimated DIP values in Thailand and Vietnam might not be as robust as the one in Colombia. Considering the nature of the validation models, the performance of the model would not be significantly affected as long as the patterns of case-underreporting or overreporting would be consistent by province over time. However, it may be possible to observe inconsistent patterns of case-reporting during outbreak periods when there are more difficulties for some municipalities on resource allocation [8]. Vaccine uptake rates and coverage rates were determined based upon the CRF index, but the study did not take into account local specific contexts such as logistics, and the local-level interests that may play an important role in achieving the estimated coverage rates. As previously described, the climate raster datasets were at relatively coarse resolutions [8]. While the datasets were resampled in this study, future research work with finer scale resolutions will further strengthen the precision of the current model outcomes. The level of dengue vaccine compliance rate could vary by country and vaccine type. Given that none of the three countries has introduced the current dengue vaccine at the time of this research, it was assumed that all three doses were given to recipients within a year, but the actual probability of achieving full compliance may be lower than assumed in this study.

Given that many dengue-endemic countries face limited resources and that the costs for mass vaccination campaigns may not be trivial, it is critical for decision makers to consider the efficient allocation strategy of dengue vaccines by targeting the right populations in high-risk areas. In addition to the current CYD-TDV, several second-generation dengue vaccines are expected to be available in the near future. The findings of this study can guide the decision makers in the three countries regarding the efficient distribution of vaccines during both endemic and epidemic situations, minimizing the waste of limited resources.

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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-financial interest in the subject matter discussed in the manuscript.

Authors' contributions

JL designed the study, conducted the analyses, and wrote the manuscript; JKL, DAD, and THAN were involved in data collection and data interpretation; AF contributed to data interpretation and overall inputs on the study outcomes.

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Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2017.10.070.

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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 $2000 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.

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1. 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 nor-

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mally 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.

2. Methods

2.1. 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

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].

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 and 1.5 years or <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.

2.2. 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.

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)	3182	5934	2614	[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

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 $2000 to $10,000 as reported by the WHO SAGE working group [16].

2.3. 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.

3. Results

Fig. 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 Fig. 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.

The percentage reduction in the number of hospitalized cases due to vaccination is shown in Fig. 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 Fig. 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.

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 Fig. 3. However, the detri-

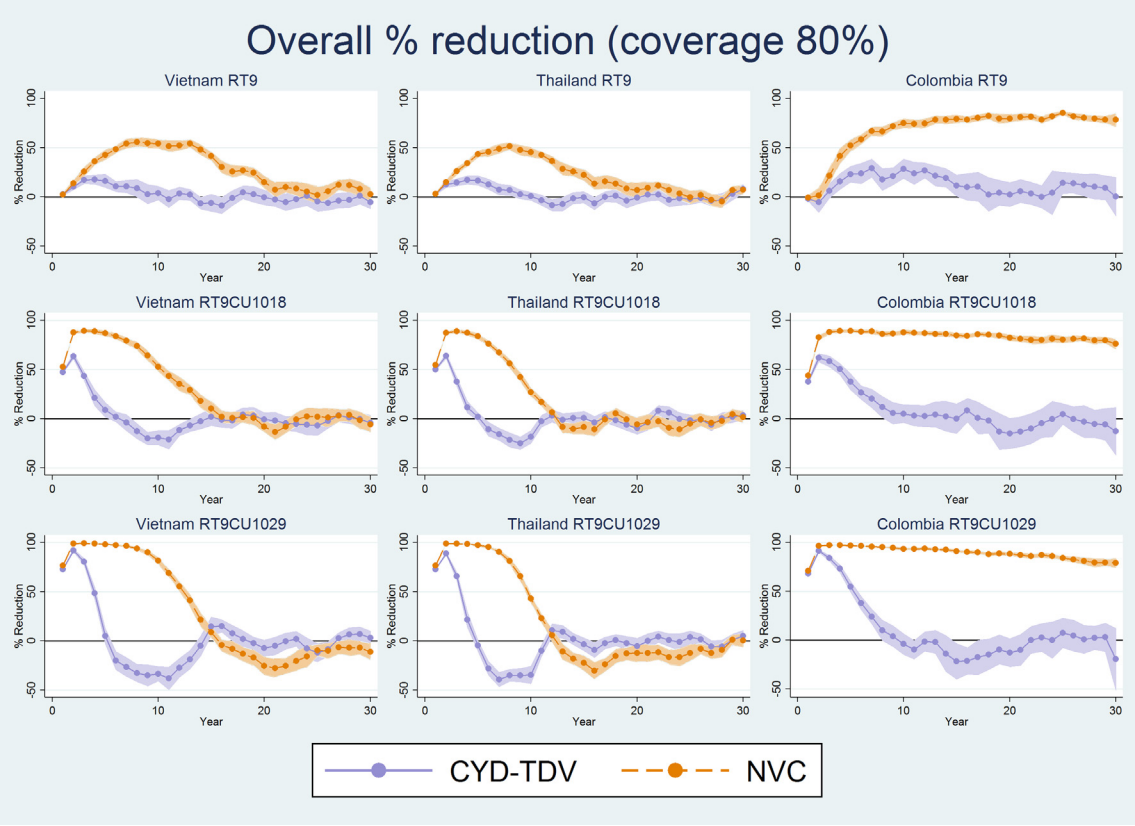

Fig. 1. Overall disease reduction by vaccination with CYD-TDV and NVC.

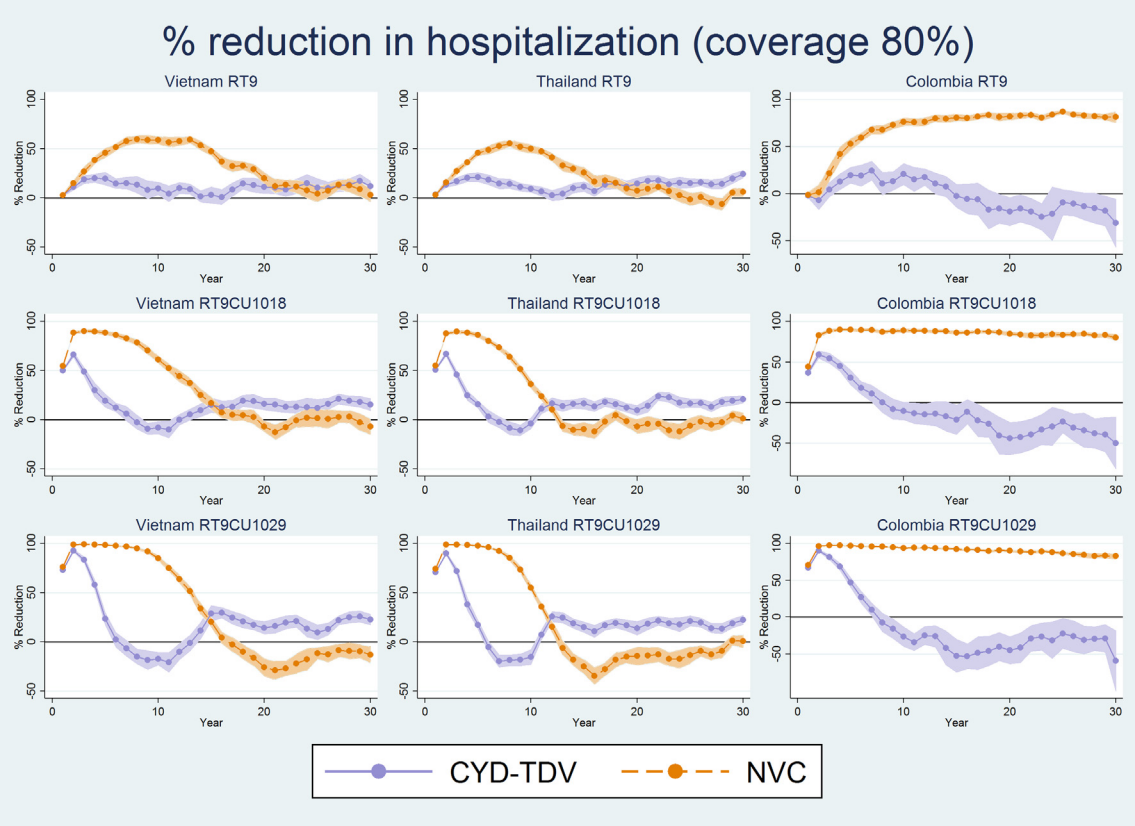

Fig. 2. The proportion of reduction in hospitalization with CYD-TDV and NVC.

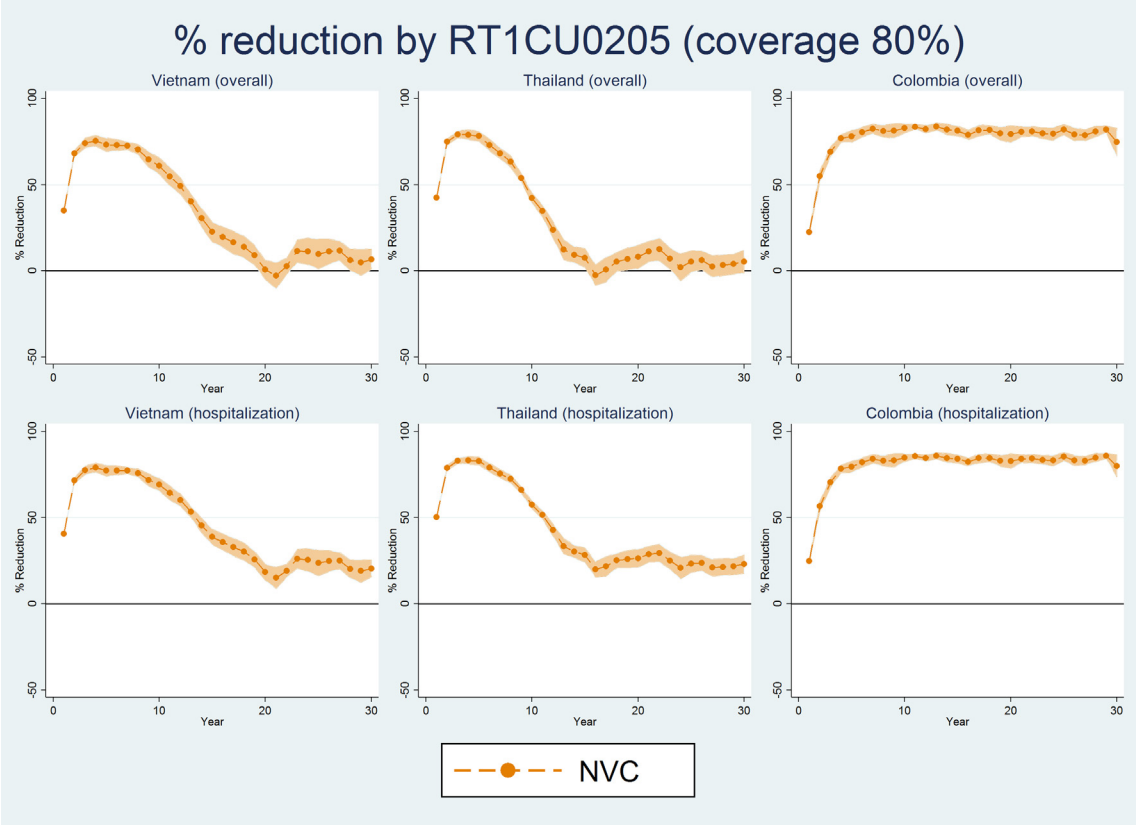

Fig. 3. The proportion of reduction by 1yo routine and 2–5yo catch-up with NVC.

mental 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.

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 Fig. 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 $2000 per DALY averted. In Thailand, both vaccines appear to be highly cost-effective at the same threshold cost ($2000) 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 $2000 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 Fig. 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 $2000 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 Fig. 1(f)). Additional threshold costs for averting a DALY are also shown in Fig. 4, and vaccination costs to be cost-effective can be identified in the same manner.

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 Fig. 5, vaccination costs at the threshold cost of $2000 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

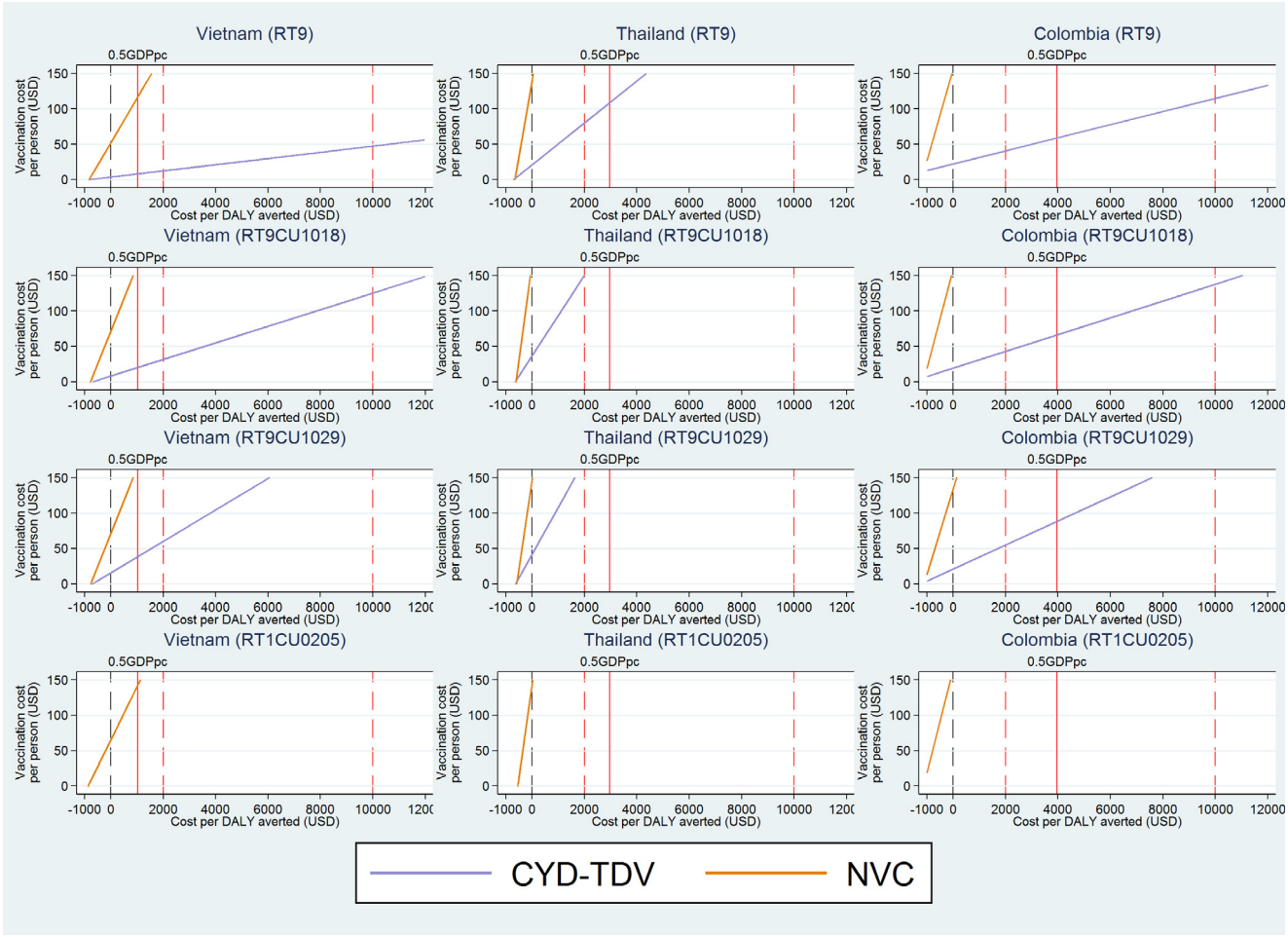

Fig. 4. Incremental cost-effectiveness ratios (ICERs) under the high burden scenario (coverage 80%).

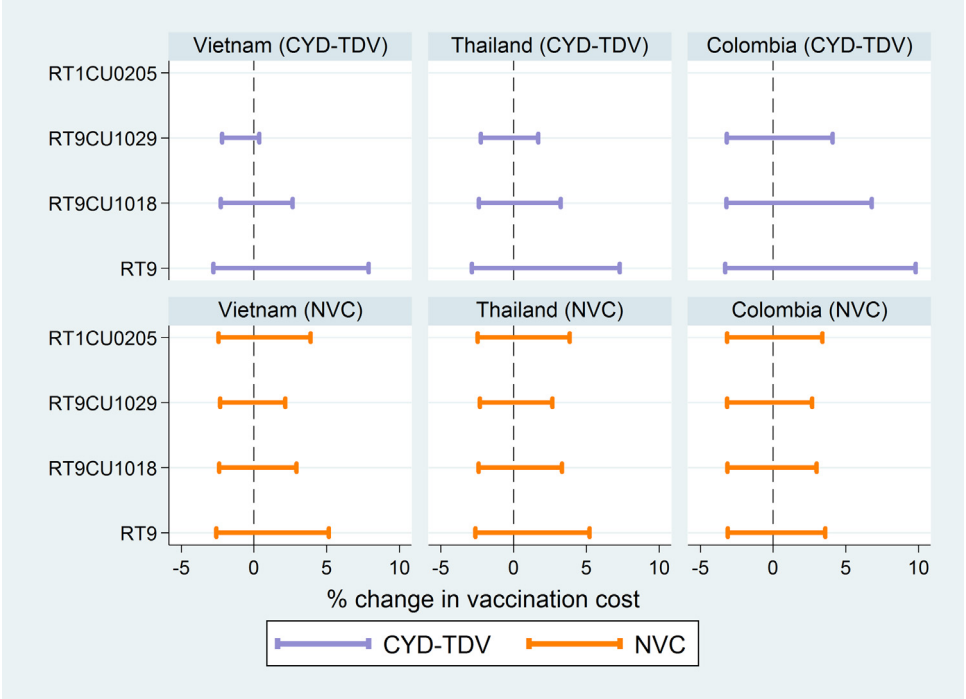

Fig. 5. Sensitivity analyses with varying disability weights (coverage 80%). (see Supplementary Table 3 for the range of total DALY saved by disability weights)

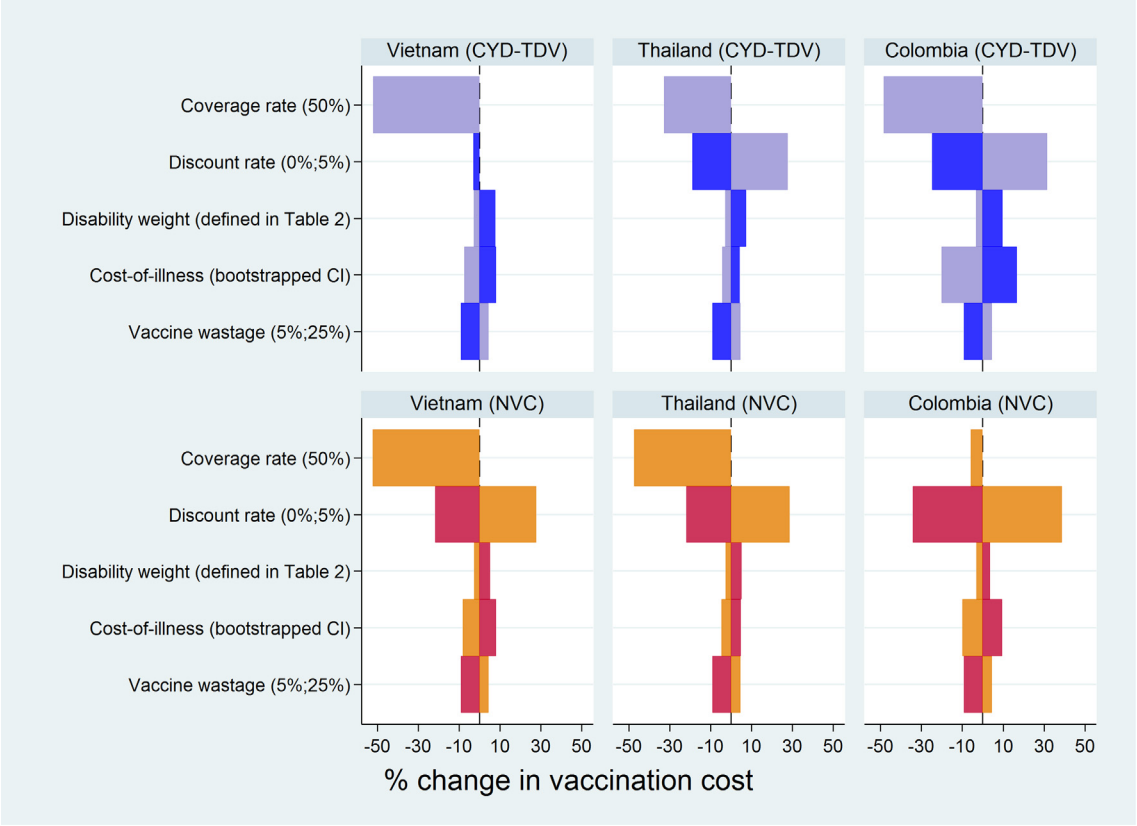

Fig. 6. One-way sensitivity analysis for the RT9 strategy.

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.

In addition, Fig. 6 demonstrates a one-way sensitivity analysis for the RT9 strategy at the threshold cost of $2000 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.

4. 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 $2000 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-financial interest in the subject matter discussed in the manuscript.

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.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.vaccine.2018.03.002.

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