Estimating the Burden of Dengue in the Philippines Using a Dynamic Transmission Model

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ABSTRACT

Objective. This study aimed to describe dengue burden in the Philippines. Specifically, health and economic costs of the disease were estimated.

Methods. A published serotype-specific and age-stratified dengue dynamic transmission model was populated with Philippine-specific dengue epidemiology and cost data. Data were gathered from literature and record reviews. Dengue experts were consulted to validate the model parameters. Sensitivity analyses were performed to test the uncertainty of input parameters on model outcomes.

Results. By 2016 to 2020, it is estimated that annually, average hospitalized cases will amount to 401,191 and ambulatory cases will amount to 239,497; resulting to USD 139 million (PhP 5.9 billion) and USD 19 million (PhP 827 million) worth of aggregate costs shouldered by the public payer for hospitalized and ambulatory cases, respectively. Average annual productivity losses may amount to USD 19 million (PhP 821 million) and DALY lost is expected to be 50,622.

Conclusion. The cost of dengue is high especially since the Philippines is an endemic country. Thus, there is a need to optimize government interventions such as vector control and vaccination that aim to prevent dengue infections.

Key Words: dengue, dengue cost estimation, dynamic transmission model, epidemiology, Philippines

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INTRODUCTION

Dengue is considered the most important mosquito-borne viral disease; latest estimates reveal that dengue infects 390 million people each year, and 96 million of cases manifest with varying severity.[1,2] Dengue is transmitted mainly by *Aedes aegypti* mosquito.[3] Dengue has four known serotypes called DENV-1, DENV-2, DENV-3, DENV-4. More than 125 countries are dengue endemic and 50% of the world's population live in dengue endemic areas.[2,4-8]

This study aimed to describe the burden of dengue in the Philippines. The Philippines is a tropical and highly dengue-endemic country.[9] One recent report shows that the Philippines ranks fourth in Southeast Asia based on annual average reported dengue episodes between 2001 and 2010; and upon applying underreporting expansion factors to government surveillance data, it demonstrated that there is an estimated average of 315,892 hospitalized and ambulatory dengue cases per year, with 1,218 cases resulting to death.[10] Computations from the 2010-2014 Department of Health (DOH) Disease Surveillance Reports (DSR) show that dengue has an annual case fatality rate of 0.32% and dengue is more fatal to infants and the elderly – with case fatality rates of 0.56% in ages 0 to 5, 0.50% in ages 5 to 9, and 0.46% in ages 65 and up. Estimates of annual direct medical costs of dengue ranges from USD 229 million to USD 353 million to USD 642 million (or PhP 5.4 billion, PhP 8.3 billion, PhP 15.0 billion, respectively).[10-13] These high annual direct medical costs show that dengue incurs significant socioeconomic costs to the Philippines. Therefore, the objective of the study was to estimate the health and cost impact of dengue fever in the absence of public health intervention, e.g. vaccination.

MATERIALS AND METHODS

The model

To describe dengue burden in the Philippines, a web-based interface called DENMOD of the dengue dynamic transmission model developed by Coudeville and Garnett was used.[14] The model includes the interaction of four dengue serotypes, the interaction of human hosts and vectors, age-specific levels of transmission, and seasonality of the disease. Some important assumptions of the model include: a constant age structure, a constant annual growth rate of human and vector population, the absence of maternal antibodies, the lifetime dengue infection of female mosquitoes upon first infection, and the infectiousness of symptomatic cases being four times more than asymptomatic ones due to higher viremia in patients with symptomatic dengue compared with asymptomatic individuals.[15,16] Data on cross-protection duration were based from the dengue vaccine clinical trial data while cross-enhancement was not considered in this analysis.[17] Figure 1 shows a diagrammatic illustration of the model.

Outcomes considered

Aside from dengue cases and aggregated costs of dengue, the model can estimate dengue's disability-adjusted life years (DALYs). DALYs reflect the debilitating impact of disease on an individual's life, which may also persist beyond the duration of the disease itself. The DALY is a function of age, sex, life expectancy, and a disability weight which is used for computing the years lost due to disability (YLD) caused by a disease. For dengue, Shepard, et al. reported that ambulatory-managed dengue has a disability weight of 0.010 while hospitalized dengue has 0.031.[17] Disability weights range from 0 to 1; the higher the weight, the more severe the disease is, and a weight of 1 is equal to death.

Collection of the model parameters

Literature search on dengue epidemiology, vector biology, and dengue costs for the Philippines were done using two databases: US National Library of Medicine and the National Institutes of Health Medical (PubMed) and the Philippines-based Health Research and Development Information Network (HERDIN). Review of government records such as the DOH DSR and Philippine Health Insurance Corporation (PhilHealth) claims data were conducted. Data gathered were subject to validation through a focus group discussion (FGD) or key informant interviews (KIIs) with experts in the fields of entomology, immunology, virology, and epidemiology and healthcare providers specialized in family medicine, infectious diseases, and pediatrics.

Calibration Parameters

Table 1 summarizes the calibration parameters used. Only key calibration parameters are described in this subsection.

Data on hospitalized dengue cases from 2009 to 2014 were sourced from the DOH DSR. The DSR is a passive surveillance system that only captures hospitalized cases, thus, to get the ambulatory cases, we estimated that 5% of the reported cases from the DSR were ambulatory and 95% were hospitalized as observed in Shepard et al.'s study.[10] Then, DSR hospitalized and ambulatory cases were adjusted using published expansion factors since evidence from an active surveillance in Palawan suggests that underreporting of the DSR prevails.[12] DSR hospitalized cases and ambulatory cases were multiplied with 4.9 and 11.7 expansion factors, respectively.[12,18] Adjusted cases therefore arrive at a hospitalized-to-ambulatory case ratio of 62.6-to-37.4. The resulting ratio closely resembles estimates from Borja and Lorenzo and Edillo et al.[12,19]

Natural infection is assumed to confer lifelong protection to the infecting serotype, with cross-protection against non-infecting serotypes lasting for approximately 16.16 months as estimated from the pooled Asia and Latin America Phase III dengue vaccine clinical trial.[20] The existence of antibody-dependent enhancement (ADE) which is assumed to cause cross-enhancement has not been considered in this analysis.

RESULTS AND DISCUSSION

The model's estimated monthly dengue incidence per 100,000 closely reflected the DSR data (Figure 2). Specifically, the ratio of observed versus predicted incidence was 0.97 for 2009, 1.03 for 2010, 0.84 for 2011, 1.10 for 2012, 1.01 for 2013, and 1.09 for 2014; these results show that the model fits the actual incidence well, with the difference between estimated and actual incidences never being higher than 10%. Figure 3 shows the trend of dengue incidence as projected by the model and Table 2 shows the costs of each type of dengue.

Burden of Dengue

Figure 3 illustrates the observed and projected dengue cases. Adjusted DSR data showed that from 2009 to 2014, there were an average of 547,426 hospitalized dengue and 326,780 ambulatory dengue cases per year. The model estimated that from 2016 to 2020, annual hospitalized cases could reach 401,191 while ambulatory cases could amount

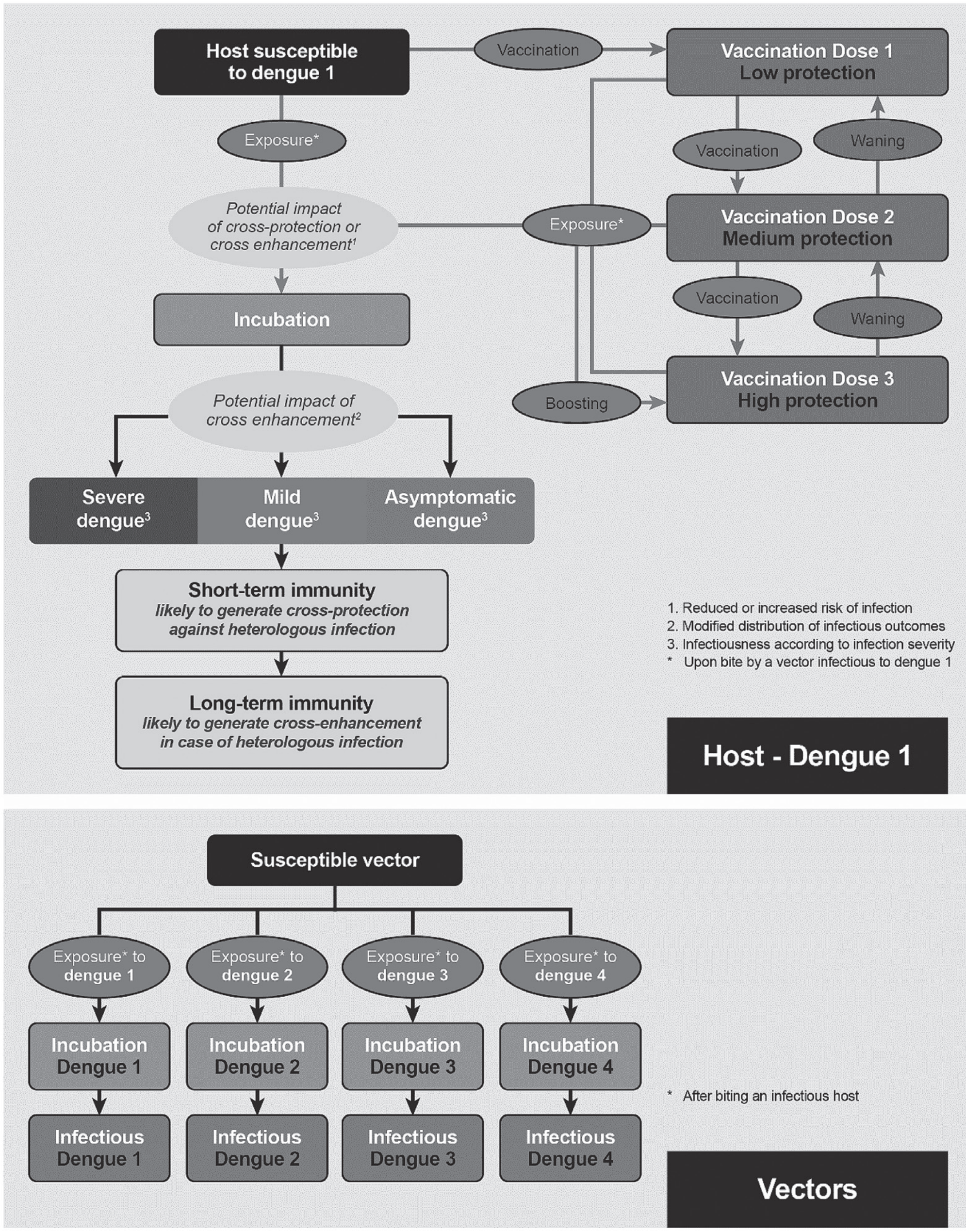

Figure 1. The flow diagram of the infection and vaccination process, from Coudeville and Garnett (2012).

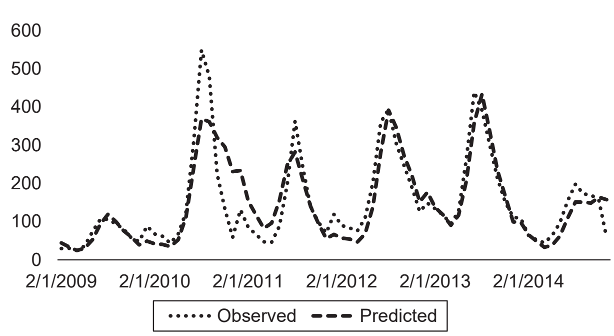

Figure 2. Historical (from DSR) and predicted weekly incidence per 100,000.

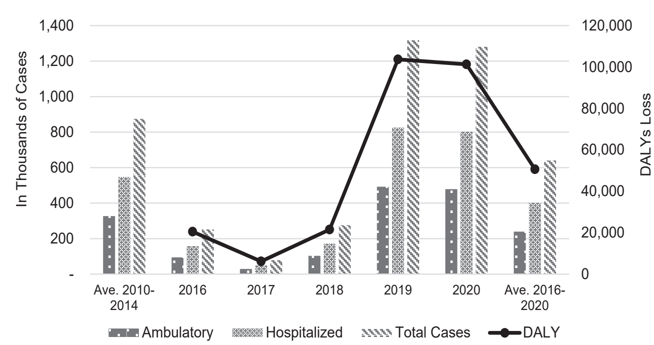

Figure 3. Estimated dengue cases and DALYs loss.

Table 1. Selected calibration parameters

Selected Calibration Parameters	Figure					
Demographic data						
Population age strata[27] (2010)						
0 - <5 y.o.	11.11%					
5 - 9 y.o.	11.20%					
10 - 14 y.o.	11.04%					
15 - 19 y.o.	10.51%					
20 - 34 y.o.	24.44%					
35 - 49 y.o.	17.49%					
50 - 64 y.o.	9.87%					
≥ 65 y.o.	4.35%					
Total	94,013,200					
Expected Annual Growth Rate	1.90%					
Epidemiological data[11]						
Population age strata	Incidence (per 100,000)	CFR				
0 - <5 y.o.	102	0.56%				
5 - 9 y.o.	225	0.50%				
10 - 14 y.o.	181	0.22%				
15 - 19 y.o.	202	0.17%				
20 - 34 y.o.	92	0.15%				
35 - 49 y.o.	30	0.32%				
50 - 64 y.o.	24	0.39%				
≥ 65 y.o.	28	0.46%				
Total	885	0.32%				
Seroprevalence[28]	2009	2010	2011	2012	2013	2014
DENV-1	8%	22%	45%	43%	46%	23%
DENV-2	26%	13%	12%	7%	0%	42%
DENV-3	65%	49%	42%	43%	25%	25%
DENV-4	1%	12%	1%	7%	29%	10%
Vector Data[29]						
Population						
January	75.16					
February	37.55					
March	12.45					
April	19.83					
May	41.04					
June	188.82					
July	248.85					
August	164.67					
September	165.46					
October	133.71					
November	68.67					
December	43.78					
Average life span[30]	14.49 days					
Daily biting rate[31]	0.76					
Transmission Rate[32]						
From Vector to Host	0.75					
From Host to Vector	0.75					
Immunity and Infection[20]						
Duration of cross-protection against non-infecting serotypes	16.16 months					

to 239,497; these estimates are lower by 26.71% from the observed average annual cases. Projected cases seem to exhibit a decline during 2016 to 2018 which is preceded by a peak during observed 2013 and 2014, and then succeeded by peaks in 2019 to 2020. DALYs lost per year amount to 50,622.

Economic Costs of Dengue

Costs of the disease are differentiated according to societal and the government's perspective. Since the cost estimates were cited from multiple sources with different time periods, costs were converted using 2013 USD exchange rates from World Bank and inflation rates from the International Monetary Fund (IMF).[21,22]

The societal direct medical cost estimated by Edillo et al. using the macro-costing approach and the indirect cost estimated by Shepard et al. through regression analysis were applied.[10,12] On the other hand, the government only pays for a capitation rate for dengue hospitalized cases through PhilHealth. PhilHealth has a different case rate between dengue fever (DF) and dengue hemorrhagic fever (DHF) but the model being used does not differentiate between DF and DHF.[23] Therefore, to arrive at a case rate for general dengue cases, the weighted average was calculated whereby the proportion of total DF and DHF to total surveillance-reported dengue cases served as weights. PhilHealth does not reimburse ambulatory dengue so to obtain the public payer's ambulatory cost, a costing exercise was done during the FGD with experts. The estimate during the FGD was then adjusted to account for facility costs by adding WHO-CHOICE estimates of facility costs for outpatient settings.[24]

Table 2 provides projection of the cost of dengue for 2016 to 2020. Only the average (not the cumulated) of 2016 to 2020 are discussed for ease of interpretation. The average cases from 2016 to 2020 were estimated to cost USD 139 million (PhP 5.9 billion) for PhilHealth per year. Aside from PhilHealth reimbursements, direct medical cost of ambulatory cases cost the government USD 19 million (PhP 827 million) annually. On the other hand, direct medical cost to the society for hospitalized cases cost USD 239 million (PhP 10 billion) while ambulatory cases cost USD 30 million (PhP 1.3 billion). Productivity losses were projected to amount to USD 15 million (PhP 641 million) for hospitalized cases, USD 4 million (PhP 179 million) for ambulatory dengue, and USD 112 million (PhP 4.7 billion) for death – making the societal cost for hospitalized cases USD 254 million (PhP 11 billion) and societal cost for ambulatory cases USD 34 million (PhP 1.4 billion). Thus, the annual average total cost to society amounts to USD 399 million (PhP 16.9 million).

Sensitivity Analyses

To address the uncertainty in the point estimates used for the model, a one-way sensitivity analysis and a probabilistic sensitivity analysis (PSA) as recommended by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) were employed (Table 3).[25] Figure 4 shows the results of the one-way sensitivity analysis wherein the difference in the 5-year societal cost (3% annual discount rate) of a chosen parameter's minimum and maximum are compared to the base case. The following parameters and their ranges and their percentages away from the base case were considered: direct hospitalization cost to the society (min: USD 208.06 or PhP 8,832 or -65%; max: USD 832.27 or PhP 35,330 or +41%), direct ambulatory cost to the society (min: USD 43.57 or PhP 1,850 or -65%; max: USD 174.30 or PhP 7,399 or +40%), indirect hospitalization cost to the society (min: USD 52.77 or PhP 2,240 or -65%; max: USD 13.19 or PhP 560 or +40%), hospitalization rate (min: 50% or -20%, max: 90% or +44%), case fatality rate (min: 0.20% or -38%, max: 1.00% or +212%), and total expansion factor (min: 5.9x or -21%, max: 7.6x or +2%). Results showed that the model estimated total societal cost from 2016 to 2020 is especially sensitive to

Table 2. Costs of dengue (2016 to 2020)

Types of Cases	[A] Cases	[B] Direct medical cost (Total public payer cost)	[C] Direct medical cost (societal)	[D] Indirect cost (productivity losses)	[E] Death-related productivity losses	[F] Total societal cost ([C] + [D] + [E])
Average of 2016 to 2020*						
Hospitalized	401,191	USD 139,480,358 PHP 5,920,941,189	USD 238,500,327 PHP 10,124,338,864	USD 15,122,196 PHP 641,937,229		USD 253,622,523 PHP 10,766,276,093
Ambulatory	239,497	USD 19,479,747 PHP 826,915,243	USD 29,816,777 PHP 1,265,722,175	USD 4,220,653 PHP 179,166,728		USD 34,037,430 PHP 1,444,888,904
Deaths	1,524				USD 111,580,012 PHP 4,736,571,526	USD 111,580,012 PHP 4,736,571,526
Total Cases	640,688	USD 158,960,104 PHP 6,747,856,432	USD 268,317,103 PHP 11,390,061,039	USD 19,342,849 PHP 821,103,957	USD 111,580,012 PHP 4,736,571,526	USD 399,239,965 PHP 16,947,736,523
Cumulated 2016 to 2020 | 3% Discount Rate						
Hospitalized	2,005,953	USD 627,714,172 PHP 26,646,466,601	USD 1,073,341,346 PHP 45,563,340,138	USD 68,055,582 PHP 2,888,959,456		USD 1,141,396,928 PHP 48,452,299,594
Ambulatory	1,197,485	USD 87,666,197 PHP 3,721,430,063	USD 134,186,728 PHP 5,696,226,604	USD 18,994,529 PHP 806,317,756		USD 153,181,257 PHP 6,502,544,360
Deaths	7,622				USD 502,260,980 PHP 21,320,978,601	USD 502,260,980 PHP 21,320,978,601
Total Cases	3,203,438	USD 715,380,369 PHP 30,367,896,664	USD 1,207,528,074 PHP 51,259,566,741	USD 87,050,111 PHP 3,695,277,212	USD 502,260,980 PHP 21,320,978,601	USD 1,796,839,165 PHP 76,275,822,554

**Simple averages of undiscounted annual figures.*

Table 3. Parameters for sensitivity analysis

Parameters	Min	Max	Source	Probability Distribution Assigned
Annual endemicity (seed for Sensitivity Analysis)	1	1000	Model Default	Discrete Uniform
Direct and indirect costs (societal perspective)	35% of base case values	140% of base case values	[4]	Triangular
Direct costs (public payer's perspective)	70% of base case	130% of base case	[18]	Triangular

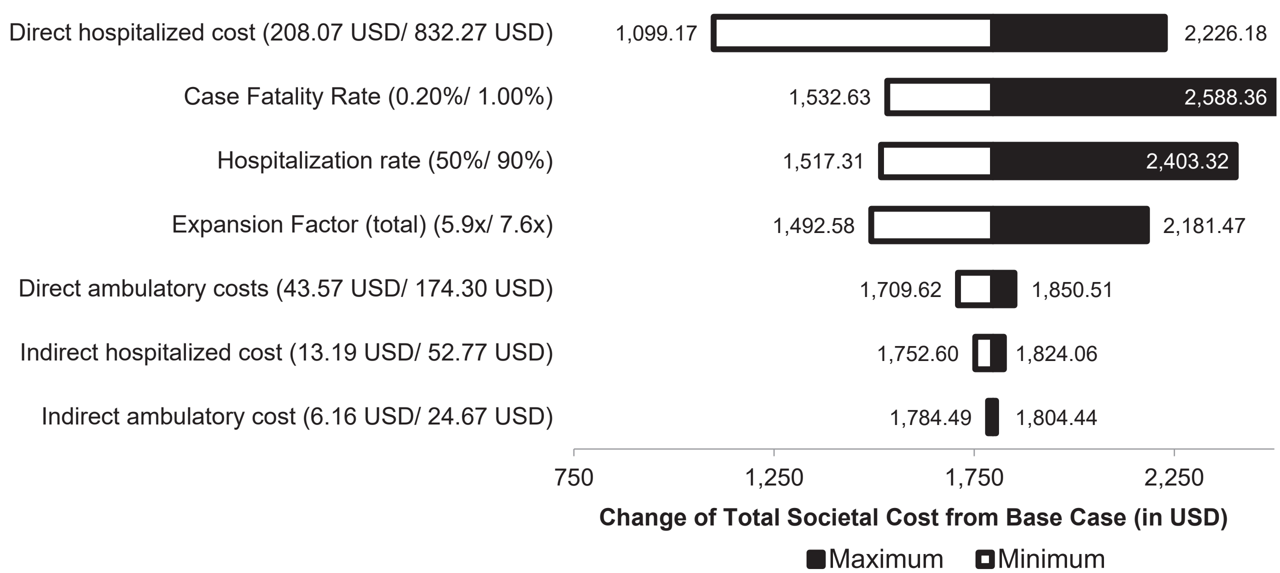

Figure 4. One-way sensitivity analysis on total societal cost (in millions).

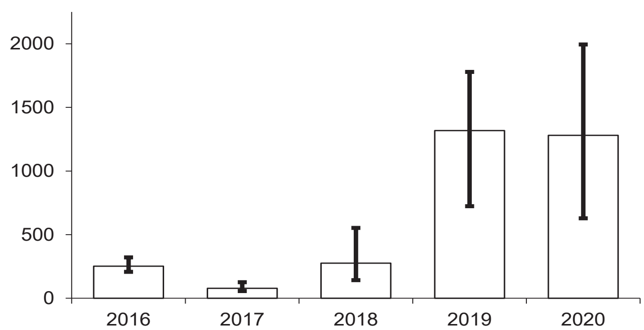

Figure 5. Projected dengue cases with error bars (95% confidence interval).

direct hospitalized cost, case fatality rate, and hospitalization rate. On the other hand, Figure 5 shows some PSA results wherein projected dengue cases and their 95% confidence intervals are displayed.

Limitations of the Study

The most important limitations in the model were the epidemiology data inputs. Serotype data in the Philippines were estimated via sero-confirmatory studies. Several country-specific dengue epidemiology data are not necessarily generalizable to the entire country due to non-representative and limited, small sample sizes.

Additionally, expansion factors were generated from only one study site and it may not be correct to assume the same level of under-reporting at the national level. However, the expansion factors used in this current study are close to newer estimates.[26]

Cost per dengue cases, one of the most important variables in this study, were based on data from Edillo et al. and Shepard et al.[10,12] It should be noted that these studies relied on a small number of hospitals and logistic regression analysis, respectively.

To address these data issues, peer-reviewed literature were evaluated and known dengue experts were consulted for the validation of model inputs as recommended by ISPOR.[25] Expansion factors based on studies in the Philippines were used to address the high likelihood of underreporting. Another limitation to the model was the unavailability of vector data in the Philippines. Most of the vector studies were conducted only in a small number of study sites within one part of the country (Metro Manila). Despite these limitations, the model is able to fit quite well with the actual historical surveillance data.

CONCLUSION

This study populated a dengue dynamic transmission model with local parameters to show that burden of dengue in the Philippines is expected to be substantial in the years to come in the absence of intervention. The model estimated an average annual hospitalized cases of 401,191 and ambulatory cases of 239,497 for 2016 to 2020. Aggregate costs shouldered by the public payer is estimated to be USD 131 million (PhP 6.5 billion) and USD 18 million (PhP 893 million) for hospitalized and ambulatory cases, respectively. Average annual productivity losses may amount to USD 18 million (PhP 893 million) and DALY lost is expected to be 50,622 life years. The results show that dengue's economic burden in the Philippines is expected to remain high, thus, government intervention like the traditional vector control or vaccination should be undertaken to curb dengue. However, a study in Singapore has shown that vaccination can be more cost-effective than vector control.[33] But in the Philippines, a modelling exercise shows that dengue vaccination can be cost-effective in certain scenarios.[34]

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Statement of Authorship

All authors approved the final version submitted.

Author Disclosure

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