Effects of climate on dengue transmission and its economic costs for the Brazilian States

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1. Abstract

Dengue incidence has been reported to have increased globally and mostly in tropical countries over the years, influenced by the changing climatic conditions. Given the significant economic burden and human welfare impacts of the disease, most of the people and governments especially in developing countries have been adversely affected posing a development challenge. Brazil as one of the countries that has been more threatened by this important re-emerging infectious disease in Latin America has spent significant resources in the fight against dengue vector and preventive measure. This paper assesses the impacts of climate change on dengue incidence in the 27 Federal States of Brazil from 1994-2017, predicts future scenarios of the incidence according to the distribution of the vector and estimates the direct and indirect costs associated with the dengue illness for the last outbreaks in 2013-2018. Evidence of correlation between temperature and dengue was found, in past and future scenarios, although historically observed only in one quarter of the states, and the precipitation was not a determinant variable for dengue. If climate variables did not provide entirely enough explanations of the widespread transmission of dengue vector, other factors such as urbanization showed to be more determinant. Also, direct and indirect costs were higher in the most dengue-affected states, especially southeast states, and the private sector was the most economically impacted by productivity losses. However, this may change in a future scenario, when dengue will potentially continue to exist in Brazil until 2050 though on a decreasing trend especially for southern states, which will lower their costs, according to the climate-based prediction. Although, the direct and indirect costs for northern and northeast states were lower than the others, the costs for productivity loss by dengue in these states are mostly bared by individuals (non-employed) when compared to private and public sector, affecting economically the poorer population in those regions. These findings underscore the need for concerted efforts of different sectors, stakeholders and disciplines in the eradication the disease since if Brazilians continue with business as usual, there is possibility of the existence of the disease in the next 30 years.

Keywords: Climate modelling, temperature, *Aedes aegypti*, cost of illness, MaxEnt

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1. Introduction

Climate change poses significant health risks to populations and nations in a number of ways, whether directly or indirectly (UNFCCC, 2017). Population living in the tropics and subtropics are the most affected by the resulting socio-economic costs, and this presents a challenge to the achievement of Sustainable Development Goal 3 “Ensuring healthy lives and promote well-being for all at all ages” (United Nations, 2015) and economic development.

One of the viral illness climate affects is dengue fever. This disease affects all humans regardless of age and gender and can be in the form of mild dengue fever or can develop into severe dengue hemorrhagic fever (DHF) sometimes characterized by shock syndrome and mortalities in 50 to 60% of the cases (San Martin *et al*., 2010; WHO, 1997). Some of the symptoms include high fever, severe headache, muscle and joint pains, nausea, rash and fatigue (Fares *et al*., 2015). Dengue is transmitted by climate sensitive female mosquito vector *Aedes aegypti*, considered as one of the most key vector-borne diseases affecting humans in the recent past (Antonio *et al*., 2017, Horstick et al 2015). The vector *A. aegypti* is a crucial specie not only for being responsible for dengue fever but also for other viral diseases like Zika and Chikungunya (Paixão *et al*., 2018; Nogueira Reis *et al*., 2017; Carvalho, 2017). Climate affects not only the vector distribution, but also the virus development and behavior of humans, which in turn has an impact on the vector (Naish *et al*., 2014).

Dengue has presented a public health concern among nations especially in the Americas for increasing trend of reported cases in the last and current decade (San Martin *et al*., 2010). Despite the negative effects of the disease to the population and in consequence to the countries’ economy, there is no particular medicament or effective vaccine so far. Therefore, preventive measures such as vector control and early diagnosis are crucial in minimizing and managing disease incidence (Fitzpatrick *et al*., 2017). Several nations have focused their investment on those preventive measures. In Brazil alone, the budget from the Health Ministry to the states increased 83% over the last 6 years, with a total of R$ 1,7 billion in 2016 provided to vigilance of communicable diseases, which includes dengue (Fiocruz, 2017). Besides, between 2015 and 2017, R$ 465 million was invested in the development of research, vaccines and new technologies and R$395,3 million in health assistance. However, complete elimination of the vector has not been effective (Carvalho, 2017). According to World Health Organization (2018) and IPCC, increase in dengue incidence overtime is to a greater extent due to widening in geographical distribution (new habitats for the vector) and to a large transmission network. The organization calculates that annually, 390 million infections are recorded in more than 100 countries in different continents and regions. The infections number can be even bigger, and the number country affected can reach 128 (Ebi & Nealon 2016).

Brazil is one of the countries is the highest dengue fever cases in the world, with a past record of series of outbreaks, with most cases happening in the cities (Figueiredo, 2003; Carvalho, 2017). The latest outbreak occurred in 2016 where the country accounted for approximately 60% of the total cases in the Americas region (WHO, 2018). As of 2017, the country had cumulatively recorded a total number of 13.6 million cases (Salles *et al*., 2018). Among the five regions of Brazil, incidences are more prevalent in the southeast and northeast regions which are mostly urban and densely populated (Ferreira, 2012; Texeira *et al*., 2013), and where the four types of serotypes can be found. Despite the differences in magnitude of the disease in different regions and states, it is estimated that currently the vector *Aedes aegypti* exists in all the 27 federative units of Brazil and most municipalities (Viana and Ignotti, 2013; Carvalho, 2017). Further evidence by Barcellos (2013) reveal that the virus has recently arrived in some portions of the North region and since 2001 every state registered dengue cases (DATASUS). Thus, majority of people are at risk of infection because a high proportion of the Brazilian population (80%) resides in urban areas (IBGE, 2018). Throughout the year there are also seasonal variations in dengue risk and more cases has been recorded in September to May when there is rain, humid and warm temperatures conducive for more and rapid breeding (Lowe *et al*., 2011).

Due to uncertainties of the vector distribution in a climate change scenario, Caprara *et al* (2015) indicate that multi and inter-sectoral collaborations tackling demographic and socio-economic factors are necessary for minimizing the disease. For instance, investments in planned urbanization, proper sanitation, waste management, human mobility regulation (international travel and trade) are found to be some of the ways of facing incidence of dengue worldwide (Ebi and Nealon, 2018).

In summary, high dengue cases are as a result of changing climate variables and translates into both social and economic costs to households, private and public sectors. Therefore, understanding the impact of the disease in different economic sectors in a current and future climate change scenario will guide policy makers and help in planning and prioritizing resources to the relevant interventions. Against this background, the aim of the study is to investigate the climate change impacts on dengue fever incidence and the related economic implications for each state of Brazil.

Specifically, the objectives are:

2. To assess the impacts of climate variables on dengue incidence and cases in each Federal State of Brazil, historically and in future scenarios of climate change;
3. To assess the economic cost of illness (direct and indirect costs) due to dengue fever in each Federal State in Brazil.

2. Literature review

2.1. Climate variables and Dengue

Several studies have in the past investigated the relationship between climate variables, vector, virus and dengue cases. Using generalized additive model (GAM), Colón-González *et al.*, 2013 estimated the effects of weather variables on dengue incidence and future predictions of the disease occurrence in Mexico. They observed that temperatures above 18°C had an increasing effect on dengue incidence with a peak of 32°C while temperature below 5°C and above 32°C had a reduction effect on incidence. They further observed that precipitation also had a positive influence on the disease incidence as the rainfall amount rose to 550mm. Future predictions, with other factors constant indicated a 40% increase in dengue incidence by 2080 in Mexico. Similarly, Gomes *et al*., (2012)'s study in the city of Rio de Janeiro, Brazil, using the same model for the years 2001-2009, found a 45% and 6% increase in dengue incidence if minimum monthly temperatures increased by 1°C and precipitation by 10mm respectively.

Although Morin *et al*., 2013 highlighted the complexity of relationships between climate change variables favoring the spread of dengue, they noted that temperature has a key role to play in the spread of the disease especially on the ecology of both the virus and the mosquito since the two are interlinked. The whole lifecycle of the *Aedes aegypti* is dependent on temperature, and rapid replication of the virus in the vector is enabled within a shorter period. They illustrated that the mosquito development is highest at the temperature of about 27 degrees and slows down at 34 degrees. Thai and Anders (2011) demonstrated that rainfall variability between seasons and years has an influence on vector breeding sites and vector populations though the extent of the effects depends whether the breeding sites are indoors or outdoors.

Cheong *et al*., 2013 estimated the effects of weather variables on dengue incidence from 2008 to 2010 in Malaysia using Poisson generalized additive models. They found positive significant association of dengue cases, virus quantity and transmission with increases in temperature and rainfall. They argued that precipitation supports breeding sites that influences the vector life cycles in terrestrial as well as aquatic (eggs, larvae and pupae) environments. A systematic literature review conducted by Louis *et al*., 2014 indicated that several modelling and predictor tools (mathematical and statistical) from different disciplines have been used previously in dengue risk mapping. They pointed out that most studies (21/26) reviewed used population, demographic and socio-economic data for dengue risk mapping, 13 incorporated climate variables (rainfall and temperature) in their modelling with only 2 studies including relative humidity, few others included environmental data and data on entomology. MaxEnt algorithm, one of the models used for species distribution and in detecting the hotspots for dengue fever and risk analysis or mapping was also highlighted among other models. The diversity of different risk mapping models mentioned in their study shows that dengue risk mapping is relatively a rising appealing field.

2.2. Economic burden of the disease

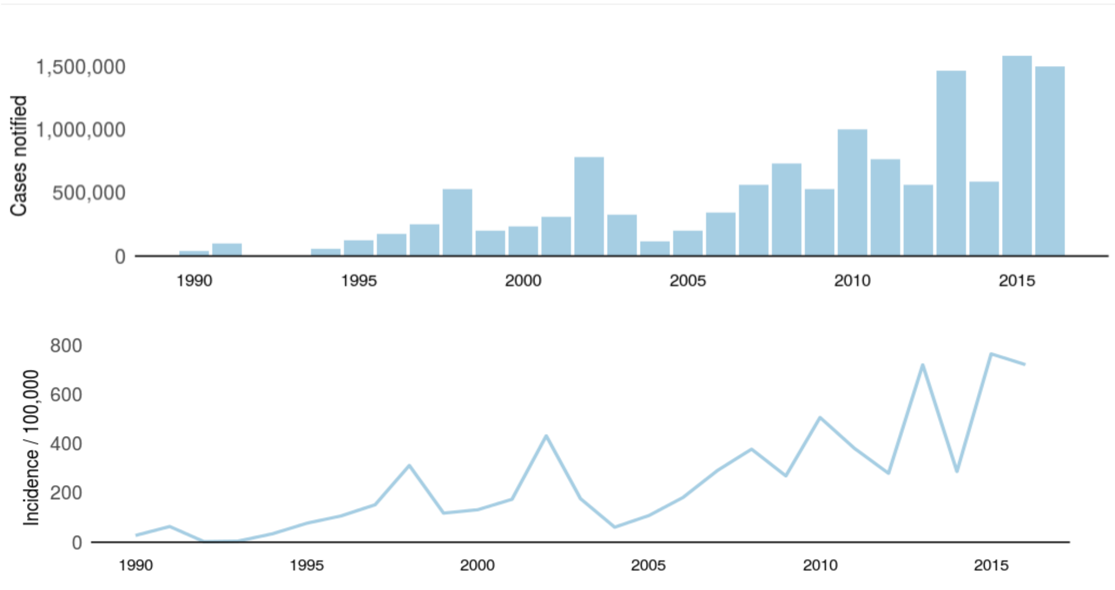
Due to increased incidences of dengue fever in the recent past, several developing countries have been exposed to huge economic burdens in the quest of preventing and controlling the disease. As much as this has been acknowledged, several previous studies have indicated very limited data availability on the costs of the dengue (Suaya *et al*, 2009; Beatty *et al*., 2011; Shepard *et al*., 2011) especially at regional and state levels. Furthermore, inability to capture all the costs of the disease from all stakeholders affected including caregivers, non-standardized assumptions and failure to account for unreported cases has led to the either under or over estimation of the costs of the disease (Beatty *et al.*, 2011). Very few previous studies used primary data in quantification of the costs, majority have undertaken systematic literature review and used secondary data sources for analysis. Vieira Machado *et al.*, 2014 using secondary data from Notifiable Diseases Information System (SINAN), medical records and interviews from a sample of 288 hospitalized patients in Dourados city (MS) in Brazil, focused only on the direct costs incurred during the 2010 outbreak for only hospitalized cases neglecting the direct medical costs for ambulatory, direct non-medical costs, indirect costs and cost related with the prevention. Yet these costs contribute a significant share to the total cost of illness especially the productivity losses. Their analysis revealed a total cost of 210,084 USD which was approximately 2.5% of GDP per capita for 2010 in the Dourados city.

Suaya *et al*., 2009 and Martelli *et al*., 2015 studies carried out a robust cost of illness analysis of dengue fever utilizing both primary and secondary data for micro-costing and extrapolation at national level. While the former focused on estimations for multicenter study (eight countries of America and Asia) on a sample of 1695 patients inclusive of 550 patients from Brazil in 2005 and extrapolation for years 2001-2005. The later study was multicenter and concentrated on four regions of Brazil on a sample of 400 patients from each region and extrapolated the total costs from 2009 to 2013. Both studies estimated direct and indirect costs of the disease in ambulatory as well as hospitalized cases and accounted for economic losses due to premature deaths as a result of dengue and school time lost by patient or caregiver for the aggregated national figures. Besides, both studies estimated cost from at least 2 perspective (household, societal, public payer) and adjusted for underreporting as recommended in health economic studies and by Duarte and Franca 2006 study. Suaya *et al.*, 2009 found a total annual cost of at least 587 million international dollars for the eight counties for actual reported cases and pointed out that the largest share of total costs in ambulatory setting was attributed to indirect costs (72%). While Martelli *et al*., 2015 total economic costs were US$ 468 million and 1,212 million at societal level - actual reported cases and after adjustment for underreporting respectively for the 2012-2013 epidemic season.

Shepard *et al*., 2011 economic study on impact of dengue focused mainly in the Americas region (six sub regions including Brazil) from a societal perspective for 2000-2007 time period. Using cost per dengue case from literature review and dengue cases from Pan American Health Organization (PAHO), direct and indirect costs of illness, inclusive of productivity losses due to death were estimated, adjusted for underreporting. Moreover, they estimated number of disability adjusted life years (DALY) lost as a non-monetary measure each year due to dengue incidence. Results indicated cumulative annual total costs ranging from US$ 0.9 – 3.1 billion for all subregions with Brazil contributing to a significant share (42%) of the total costs and indirect costs accounted for 60% of the total costs while death only 2%. However, no huge variations were observed in the number of DALYs lost per year for Brazil (36%) and other sub-regions.

Despite the high number of literature available for dengue fever, no study was found that has focused on quantifying economic costs of dengue fever at state level considering all states of Brazil from 2014 to 2017. The current study aims to fill this gap by estimating the most important aspects of cost of illness (direct and indirect costs) due to dengue fever in all the states of the five regions of Brazil.

Figure 1: Increase of dengue cases and incidence in Brazil, from 1990 to 2016.

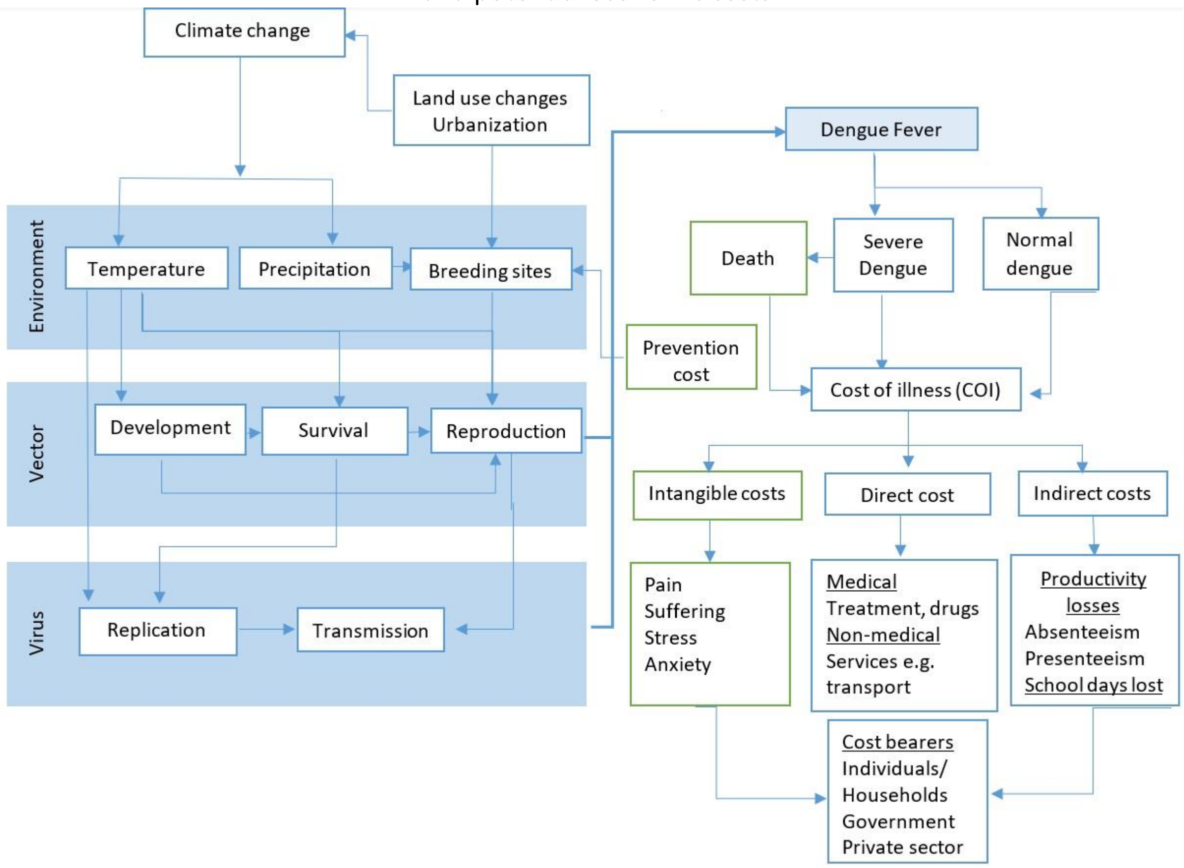


Source: World Health Organization

3. Conceptual Framework

Several complex factors are related to dengue transmission (Lowe 2011), which comprise a network of relations between environment, climate variables, the vector, the virus and social behavior. The framework (Figure 2) details the different types of dengue illness, associated social and economic costs and the different stakeholders/sectors bearing the disease burden found in the literature. Temperature is considered the most crucial climate factor affecting the development, reproduction, and survival of *Aedes aegypti* as well as the virus replication (Antonio *et al*., 2017). Rainfall on the other hand provides habitat and determines spatial distributions in affected regions. Dengue transmission is not solely influenced by environmental factors but also by human and social factors such as land use change, urbanization and population increase. These factors not only escalate the number of breeding sites but also the climate change effects, as elaborated by Ebi and Nealon (2016). Once the disease is transmitted, substantial costs are incurred for treatment and/or dealing with the illness. A proper understanding of the different costs classification and how they are measured is crucial for informed decision making. The main potential costs associated with dengue illness are showed in the framework, which focus on cost of illness approach that allows the quantification of the cost in both monetary and non-monetary direct and indirect costs of normal and severe dengue. This paper takes into account effect of temperature, rainfall and urbanization on dengue cases and incidence. It further documents the direct and indirect costs of the severe dengue and normal dengue patients only and not of the dead cases, caregivers and number of school days lost.

Figure 2: Conceptual framework on linkages and interaction of factors influencing dengue incidence and potential economic costs.



Source: Modified from Ebi and Nealon, 2016; Shepard et al., 2011.

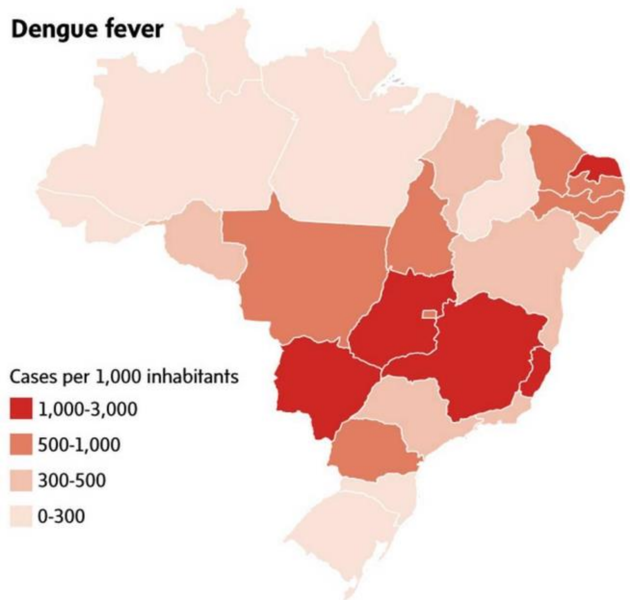
4. Methodology

4.1. Area of Study

Brazil and its states were chosen as the focus of this study. Brazil is a tropical country located in South America, with most of its 9 million km^2 area located right below the Equator Line. The country has a varied climate classification with distinct five climate regimes having different temperatures and precipitation levels - tropical, semi-arid tropical, humid equatorial, humid coastal and humid subtropical (Machado, n.d). There are 208 million inhabitants living in its 26 Federal States and one Federal District (IBGE, 2018), comprising five different geographic regions namely: North (7 states), Northeast (9 states), Central-west (4 states), Southeast (4 states) and South (3 states). Southeast and Northeast states are currently and historically where the major dengue incidence is found (DATASUS, Figure 3). However, in mid-1990s, two variations of dengue virus (DEN-1 and DEN-2) spread quickly to previously unaffected regions and from the year 2000 on all states were affected by dengue, having reported cases on their municipalities (Figure 4).

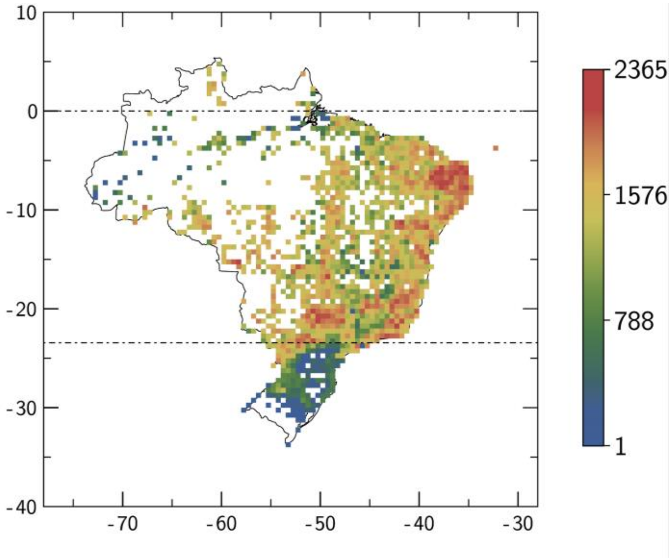
In Brazil, each level of the public sphere plays a different role in preventing dengue and applying control measures against the mosquito. The federal government, represented by the Ministry of Health, elaborates national plans, provides guidelines and consolidates the dengue-related data from the states and municipalities. Under the federal guidelines, the states give financial support and monitor the municipalities through different state bodies, to apply practical measures, such as identifying and eliminating the mosquito breeding spots. Besides, states are also the ones providing medical exams to identify the dengue diagnosis (Bernardo, 2015). Given their important role in financing prevention and treatment of dengue fever, and the fact that affected areas can switch from a region to other in a climate change future scenario (Teixeira *et al.,* 1999), this paper looks to the total 26 States and one Federal District.

Figure 3: Cases of dengue fever by state from late 2015 to mid-2016.



Source: The Globe and Mail (2017); Brazilian Ministry of Health.

Figure 4: Spatial distribution of dengue incidence between 2001 and 2012. The dashed lines correspond to the Equator and the Tropic of Capricorn.



Source: Antonio et al 2017

4.2. Historical climate scenario

In order to assess if climate has impacted the distribution of dengue cases among the States, a linear regression was made using the historical series of climate factors and dengue occurrence in each State, over 24 years (1994-2017). The climate factors selected were precipitation (mm) and temperature (°C) provided by the Database of the Meteorological Institute of Brazil (BDMET/INMET). INMET provides monthly precipitation and monthly average temperature for 265 cities in all regions of the country. In this study, meteorological stations located in the largest cities were chosen to represent the climate of the state, since dengue is predominantly a disease found in urban areas (WHO 2018, Taiul 2002).

The dengue variables selected were number of dengue cases and dengue incidence[1], obtained by the Ministry of Health, from DATASUS (until 2013) and Epidemiological boletins (from 2014). Until 2013, the classification of dengue cases in Brazil was divided into dengue hemorrhagic fever (DHF), dengue shock syndrome (DSS) and dengue with complications (CHD). In 2014, Brazil adopted the new classification of dengue cases of the World Health Organization (WHO), which classified the records as "dengue fever with warning signs" and "severe dengue fever" (Brazil 2017). In order to avoid incorrect direct comparisons, this analysis used the total cases of dengue, regardless the classification.

For climate variables, the monthly rainfall and temperature considered by state was transformed into annual data through a simple mean. The relationships between dengue (cases and incidence) and temperature and precipitation were analyzed by a linear regression using the statistical program Stata. As a complementary analysis, this study considered urban population[2] as an additional variable that could influence dengue occurrence along the time. The urban population data used is in percentage

[1] "Dengue incidence" is the number of dengue cases reported by 100 thousand inhabitants.
[2] Urban population: percentage of the total population living in urban areas, as defined by Brazil

instead of absolute numbers in order to avoid the effect of magnitude, e.g. as bigger the population of a state is, bigger is the number of cases as consequence. The data was obtained from the Brazilian Institute of Geography and Statistics (IBGE). All the data used in the study are freely available online.

4.3. Future climate scenario

Two future climate-based scenarios were built for investigating the potential distribution of dengue vector in Brazil. The premise is that the presence and the high number of the vector will increase proportionally the chances increase the number of cases reported. Given that this study focuses on species distribution for the whole Brazil, it was applied Maximum entropy (MaxEnt algorithm) model that allows mapping on a large scale and can allow incorporation of several predictors. The Maximum Entropy Model (MaxEnt) is a machine learning model which adopts the principle of maximum entropy to predict probability of species occurrence based on well-defined constraints (Phillips *et al*., 2006). It has the capability of predicting the suitability of a habitat for species based on certain environmental constraints and species-occurrence data (Freudenberger *et al*., 2016). It predicts the probability of the distribution of specie occurrence as a function of species environmental suitability above a stated limit. Therefore, the suitability of an environment for a given species depends much on its presence and environmental variables. The occurrence of species in a habitat is defined as (Convertino *et al.*, 2014):

$$P(y = 1|\mathrm{C}) = f(\mathrm{C})exp^{\eta}(\mathrm{C})\frac{P(y = 1)}{f(\mathrm{C})} \tag{1}$$

Where,
P(y) = probability of species presence
C = environmental variable/covariates
F(c) = probability of density of covariates
η(c) = constant

The predictive ability of Maxent Model is evaluated using the receiver operating characteristics (ROC) curve (Lobo *et al*., 2008). This is a plot of sensitivity versus 1- specificity. This approach evaluates model performance by measuring the area under the curve (AUC) of the receiver operating characteristics (ROC) and varies from 0 – 1 (Phillips *et al.*, 2006).

Presence data of *Aedes aegypti* recorded from 1979 – 2013 was obtained from the Global Biodiversity Information Facility (GBIF) database (Rivas *et al.*, 2017). The data was divided randomly into two sets: 70% for model training and 30% for model testing. 3176 presence records were used for model training while 1361 were used for model testing. The number of iterations for model run was set at 500 while the 'equal training sensitivity and specificity' was adopted as the threshold for evaluating model performance.

Maxent requires environmental variables, such as meteorological, soil, land use that determine species habitat. Bioclimatic variables, obtained from Worldclim Dataset (www.worldclim.org), which correspond to interpolations of observed monthly temperature and precipitation records from 1970 – 2000 at a resolution of 5 minutes (Fick and Hijmans, 2017), were used for this study. Six variables which have the most impact on *Aedes aegypti* species distribution in the study habitat were selected after initial model run using nineteen (19) bioclimatic variables (Table 1).

Table 1: Bioclimatic Parameters

Parameter	Definition	Unit
BIO3	Isothermality	-
BIO4	Temperature Seasonality (standard deviation *100)	Coefficient of variation, °C
BIO11	Mean Temperature of Coldest Quarter	°C
BIO12	Annual Precipitation	mm
BIO18	Precipitation of Warmest Quarter	mm
BIO19	Precipitation of Coldest Quarter	mm

Downscaled and bias-corrected global climate model (GCM) data for 2050 time period (2041 – 2060) was obtained from the 5th Assessment report of the Intergovernmental Panel on Climate Change ($IPCC_5$) (Hijmans et al., 2005) and used as future climate change scenarios for this study. Three GCMs and two representative concentration pathways (RCPs) at five (5) minutes spatial resolution (Table 2) were accessed through the WorldClim data archive. A representative concentration pathway (RCP) is a quantified greenhouse gas concentration adopted in the fifth Assessment Report of the Intergovernmental Panel on Climate Change ($IPCC_5$). This study considered RCP26 and RCP85 as lower and higher case scenarios of future greenhouse gas concentration in the atmosphere, respectively. Generally, six bioclimatic variables (Table 2) were used to evaluate habitat suitability for *Aedes aegypti* distributions in the future.

Table 2: Global Climate Change Models and RCPs

GCM	Code	RCP	
BCC-CSM1-1	BC	26	85
HadGEM2-AO	HE	26	85
MIROC5	MC	26	85

In this study, Maxent was used to model the current and future distributions in *Aedes aegypti* in Brazil based on current and future climate scenario (2050) respectively. All bioclimatic factors were downloaded as TIFF files and converted into ASCI files using QGIS version 2.6.1 in formats acceptable by the Maxent model. Probability of species distributions based on bioclimatic constraints were modeled using Maxent model for future climatic conditions under two scenarios (Table 2). Model result evaluation was performed using the threshold-independent method (Phillips *et al*., 2006). All the inputted bioclimatic variables were ranked in other of influence on habitat suitability for *A. aegypti* and response plots obtained to evaluate the relationship between bioclimatic factors and suitability of different regions in Brazil for the vector.

The means of the model results for the three GCMs for each of the scenarios (RCP26 and RCP85) were calculated and compared with the modeled specie distribution under current climate to obtain the expected change in the probability distribution of the specie for each of the future climate scenarios using the equation below:

$$\Delta P = P_{FUTURE} - P_{CURRENT} \quad (2)$$

Where,
ΔP= Change in the probability of Aedes aegypti distribution
P_{FUTURE}= Probability of Aedes aegypti distribution in the future for a climate scenario
$P_{CURRENT}$= Current probability of Aedes aegypti distribution

The incidence rate in Brazil was obtained by taking a six year mean for number of infected people per 100 thousand. Future changes in incidence of dengue in some locations in Brazil for both climate scenarios were estimated by assuming that it would change by the same factor as the probability of *Aedes aegypti* presence using:

$$\Delta I = I_{Current} \times \Delta P \quad (3)$$

Where,
ΔI = Change in incidence at state level
$I_{CURRENT}$ = Number of infected persons per 100 thousands
ΔP= Change in the probability of *Aedes aegypti* distribution

The input incidence data refers to states, we up-scaled the 5 km pixel outputs to the state scale by calculating the mean change of Incidence for every state, i.e. assuming an even distribution over the space of the change values to estimate the total number of persons that will be affected in the future.

4.4. Economic costs

Secondary data from DATASUS on the total number of dengue cases for each of the 27 federative units in the five regions of Brazil for a five years period (2013 - 2018) was used for the analysis. Population census data for these years were also considered on variables of interest such as working population, wage rate for different sectors in each state and proportion of people with health insurance, provided by the Brazilian Institute of Geography and Statistics (IBGE). Additionally, data from previous related studies in Brazil provided supplementary information to enable complete monetary estimation of cost of dengue illness (COI) for both direct and indirect costs. The variables derived include: (i) the proportion of adults (> 14 years) affected by dengue; (ii) the average number of work days adults were absent from work; and (iii) the average direct cost of each dengue case, differentiated by severity of disease and health system. This study considered the average number of work days lost as 5.8 and 11.5 for normal and severe dengue cases respectively. For the direct costs, were considered US$ 48 and US$ 250 cost per case for normal and severe dengue fever respectively under the public health care system, and US$ 126 and US$ 583 for normal and severe dengue fever respectively under the private health care system. These costs and day estimations were based on studies from Martelli *et al.*, (2018), Shephard *et al*., (2011) and Vieira Machado *et al.*, (2014) in Brazil. The per case direct costs were initially in US$ but translated into R$ for standardization.

It was used as an appropriate measure the human capital method that quantifies productivity loss in monetary terms with an assumption that workers outputs are measured by a proxy (gross wages) (Lensberg *et al.,* 2013; Changik Jo, 2014). It was further assumed that there was no replacement of the employed patient and each patient was only sick once for a given year. Ideally total labor productivity loss of an adult patient (TLP_i) is derived from the formula below adapted from Zander *et al*. (2015).

$$TLP_i = PLA_i + PLP_i \tag{4}$$

Where,
PLA_i = productivity loss from an absent employee for a given period of time (year)
PLP_i = reduced productivity or performance due to presenteeism

In our study only PLA_i was considered for valuation of labor productivity/income losses from absenteeism for each sick adult expressed as follows:

$$PLA_i = NA_i \times DI_i \tag{5}$$

Where,
NA_i = the number of working days each person was absent from work due to illness
DI_i = the average daily income/wage

This was then aggregated at state level accounting for the total number of dengue cases for each year under consideration. On the other hand, the direct costs for each state were calculated by multiplying the cost per dengue case with the total number of cases in each health setting, stratified according to the severity of the disease. Additionally, two case scenarios were considered – one on actual reported data and the other adjusting for underreporting using expansion factors as recommended in health economics. Expansion factors 3.2 and 1.6 for normal dengue and severe dengue fever respectively, derived from Martelli *et al*. (2015)'s sensitivity analysis, were adapted for this study. However, most of the comparisons were made based on the actual reported data provided.

The study further explored the productivity losses attributable to different sectors to understand the proportion of indirect costs borne by these sectors. In this analysis, the year 2016 was chosen since this was the year of the latest outbreak with approximately 1.5 million cases occurred then.

5. Results

5.1. Climate analysis

The analysis found that the average number of dengue cases and incidence does not have a solid and uniform dependence on climate factors - in this case, temperature and precipitation - for the states in Brazil, from 1994 to 2017. The study revealed less states correlating precipitation and dengue occurrence, in both our outcome variables: "number of cases" and "incidence", and more states with correlation between temperature and dengue incidence (Table 3, Figure *5*). Temperature was determinant especially for central-west states. In the Distrito Federal, for example, a statistically significant positive correlation was found for temperature when compared to both "number of cases" and "incidence" of dengue (Figure 6). For the northern region, correlation was found only in the state of Pará, which presented a negative correlation between temperature and dengue incidence, while the other states presented a positive correlation. Negative correlation was also found in Piauí, but between precipitation and dengue cases (Figure *7*). Piauí was the only state of Northeast to present a correlation between those two variables. On the opposite side of the country, the southern states didn't present significant correlation in this study for temperature, although Rio Grande do Sul showed positive correlation for precipitation.

From the 5 states most recently affected by dengue, there were positive correlation between temperature and dengue only in 2, which are Minas Gerais and Mato Grosso. In total, from 27 states, 7 in three regions have showed a statistically significant relationship between temperature and dengue occurrence, and 2 states between precipitation and dengue occurrence.

A complementary analysis was made comparing the percentage of urban population with dengue cases and incidence, in order to understand the relationship between urbanization and dengue. In this analysis, 9 states from the four regions indicated positive statistically significance, showing there is a relationship between percentage of people living in cities with dengue fever cases and incidence. From these 9 states, 5 were found as correlated with temperature too, which are: Alagoas (NE), Bahia (NE), Distrito Federal (DF), Mato Grosso (CW), Pará (NO) and Rio Grande do Sul (SO).

Table 3: Correlations between temperature, precipitation, urban population (%) and dengue fever cases and incidence, for the states in Brazil, from 1994 to 2017

P>|t|		Temperature	Temperature	Precipitation	Precipitation	Urban Pop (%)	Urban Pop. (%)
	States	**Cases**	**Incidence**	**Cases**	**Incidence**	**Cases**	**Incidence**
NO	Acre	0.861	0.827	0.608	0.947	0.023 (+)	0.615
	Amapá	0.503	0.487	0.55	0.648	0.784	0.95
	Amazonas	0.229	0.452	0.103	0.818	0.379	0.526
	Pará	0.161	0.049 (-)	0.899	0.329	0.268	0.012 (+)
	Rondônia	0.808	0.511	0.828	0.065	0.586	0.79
	Roraima	0.22	0.564	0.15	0.971	0.119	0.586
	Tocantins	0.555	0.915	0.36	0.751	0.282	0.641
NE	Alagoas	0.202	0.038 (+)	0.69	0.64	0.052	0.035 (+)
	Bahia	0.031 (+)	0.849	0.719	0.211	0.027 (+)	0.97
	Ceará	0.519	0.677	0.929	0.406	0.023 (-)	0.939
	Maranhão	0.317	0.473	0.116	0.249	0.449	0.892
	Paraíba	0.707	0.688	0.452	0.184	0.804	0.658
	Pernambuco	0.682	0.194	0.521	0.126	0.904	0.166
	Piauí	0.248	0.96	0.027 (-)	0.897	0.064	0.391
	Rio Grande do Norte	0.571	0.345	0.121	0.392	0.229	0.156
	Sergipe	0.59	0.67	0.481	0.625	0.937	0.866
SE	Espírito Santo	0.42	0.542	0.359	0.37	0.125	0.077
	Minas Gerais	0.734	0.044 (+)	0.799	0.803	0.843	0.803
	São Paulo	0.057	0.253	0.057	0.411	0.012 (+)	0.009 (+)
	Rio de Janeiro	0.488	0.255	0.311	0.123	0.299	0.553
CW	Distrito Federal	0.007 (+)	0.018 (+)	0.05	0.207	0.037 (+)	0.083
	Goiás	0.141	0.808	0.591	0.795	0.774	0.212
	Mato Grosso	0.094	0.007 (+)	0.784	0.076	0.036 (+)	0.256
	Mato Grosso do Sul	0.295	0.001 (+)	0.129	0.251	0.289	0.257
SO	Paraná	0.202	0.998	0.943	0.244	0.006 (+)	0.384
	Rio Grande do Sul	0.059	0.469	0.045 (+)	0.359	0.069	0.018 (+)
	Santa Catarina	0.104	0.674	0.656	0.67	0.155	0.159

*Correlations statistically significant when p < 0,05 were highlighted. Positive and negative correlations are identified as (+) and (-).

Figure 5: Federal states with statistically significant correlations when temperature, precipitation and urban population when compared to dengue incidence and cases.

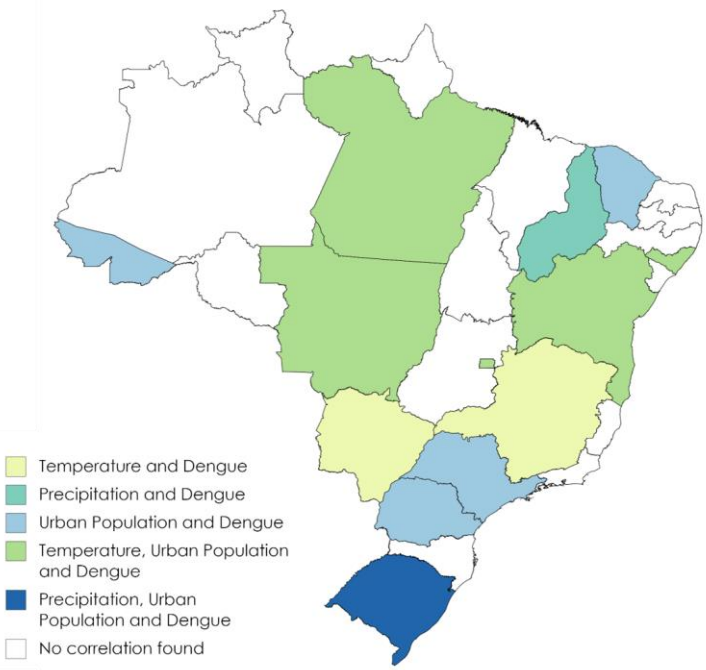


Figure 6: Positive correlation found between temperature and dengue case in Distrito Federal.

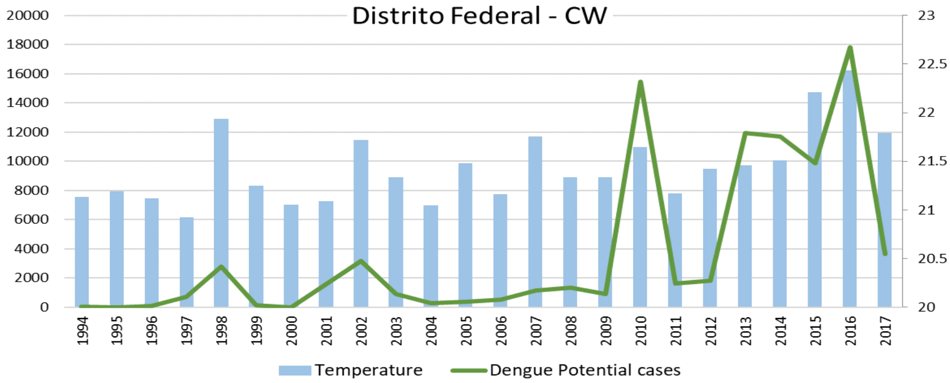
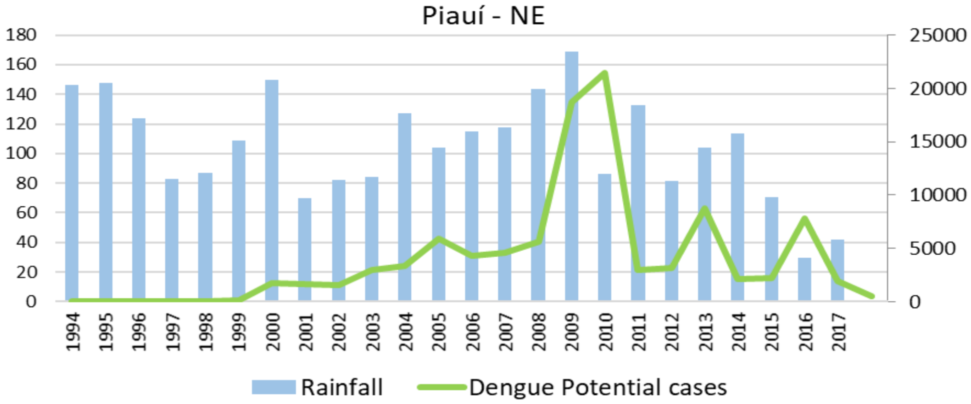


Figure 7: Negative correlation found between rainfall and dengue case in Piauí



When looking at the impact of climate factors on the dengue vector distribution in a future scenario, the results showed that Maxent performance Maxent was satisfactory with AUC = 0.74 for training data and AUC = 0.73 for test data. These results are acceptable and in line with performance criteria recommended by Phillips *et al*. (2006).

The model output indicated that bioclimatic variables such as seasonal temperature (BIO4), isothermality (BIO3) and annual precipitation (BIO12) contributed to 78.1% to the Maxent model (Table 4). Seasonal temperature contributed more than more than 50% to habitat suitability *Aedes aegypti* presence in Brazil, while precipitation only 12%, in line with the findings from the historical analysis. The GCMs result for the year 2050 shows an increase in this variable with a concurrent effect of species distribution within the study area.

Table 4: Percentage contribution of bioclimatic variables

Climatic Variable	**Name**	**Percent Contribution (%)**
BIO3	Isothermality	14
BIO4	Seasonal Temperature (°C)	52.3
BIO11	Mean temperature of coldest quarter	7
BIO12	Annual Precipitation (mm)	11.8
BIO18	Precipitation of warmest quarter	7.1
BIO19	Precipitation of coldest quarter	7.8

The different effects of these variables when used in isolation/omitted on the probability of *Aedes* aegypti distribution is also shown by the jackknife test for training, testing and AUC, respectively (Annex 1). The relationship between the bioclimatic factors and probability of *Aedes aegypti* presence is shown in Figure 8, where on the left show how habitat predicted suitability depends both on a bioclimatic factor and on its correlation with other factors, while on the right shows relationship as each factor is varied while keeping other factors at mean value. These response curves show that *Aedes aegypti* survives in regions with BIO3 of 55 – 72, BIO4 of 80 – 370 and BIO12 of 0 – 1700. Response curves for both isothermality and seasonal temperature have a Gaussian shape while annual rainfall follows a sigmoid trend.

The mean probability of *Aedes aegypti* distribution for both current, future climate scenario (RCP26) and the difference between the future and the current distribution were also calculated. The probability of *Aedes aegypti* presence in the study area for both climate change scenarios showed widespread distribution than was modeled currently. However, the RCP85 (pessimist-scenario) showed higher specie presence than the RCP26. In general, Maxent result showed a decrease in the presence of the species in some areas while some regions will record an increase in the year 2050.

Figure 8: (a) Habitat Suitability as a function of a bioclimatic factor and correlation of other factors (b) habitat Suitability as a function of a bioclimatic factor and the mean value of other variables.

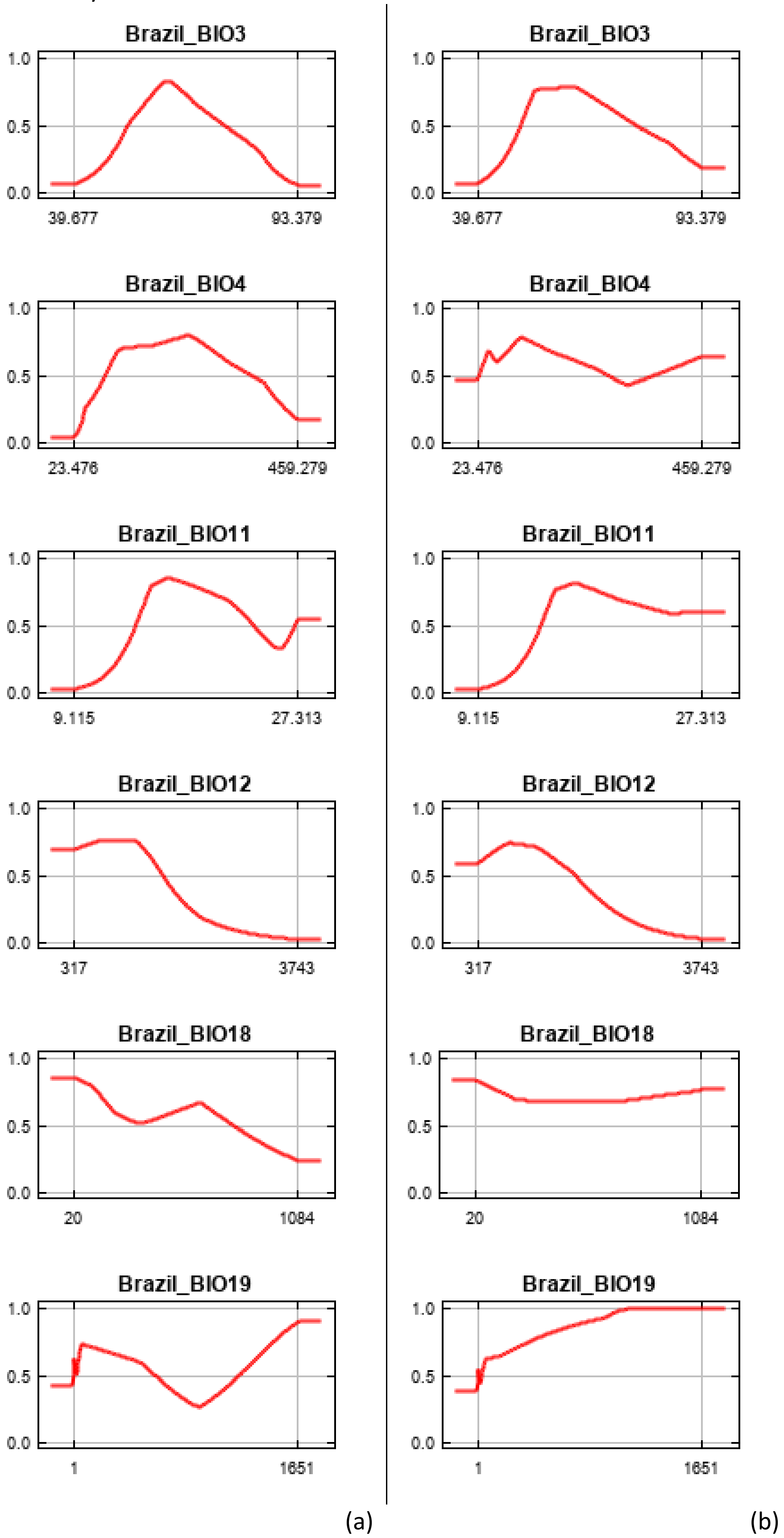
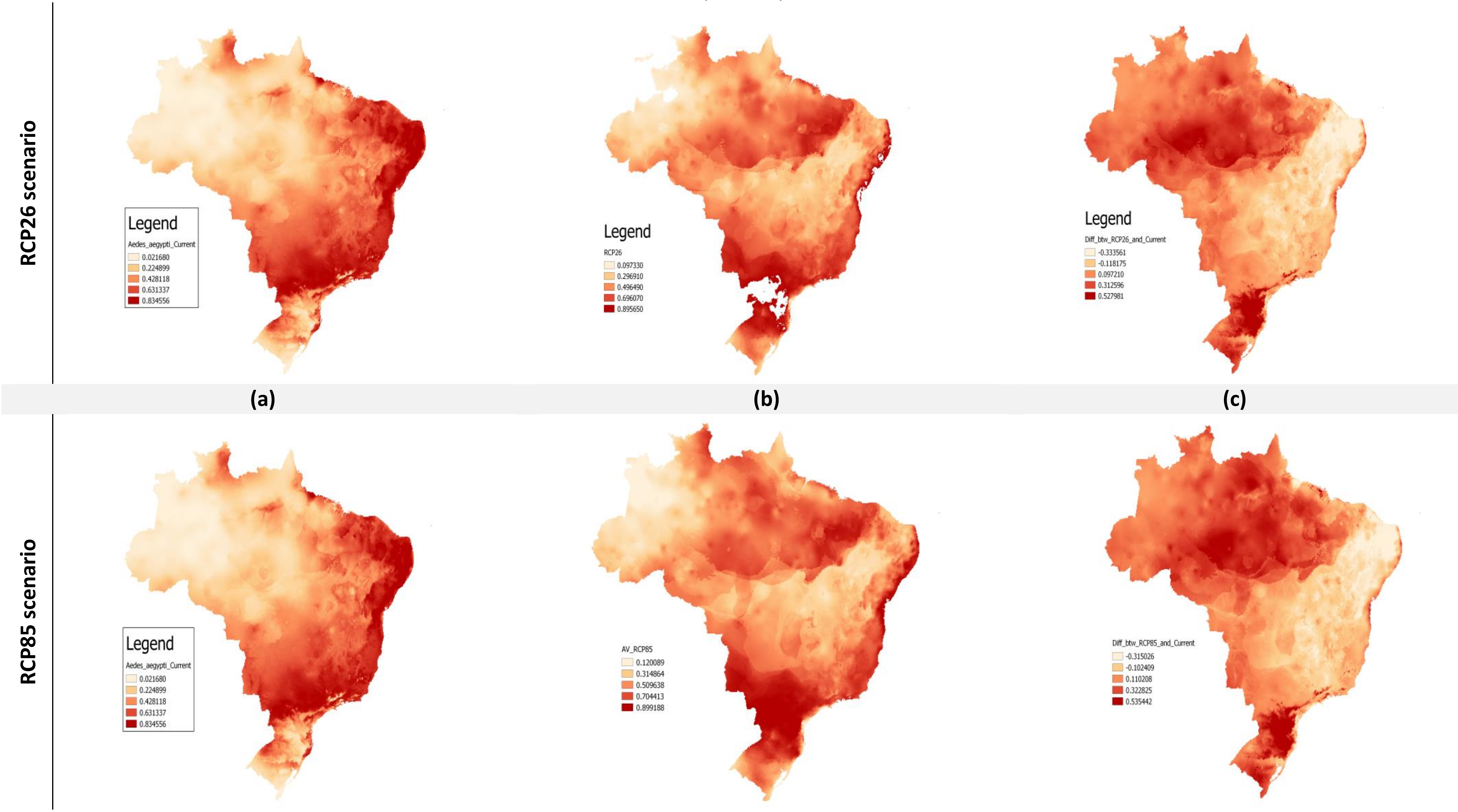
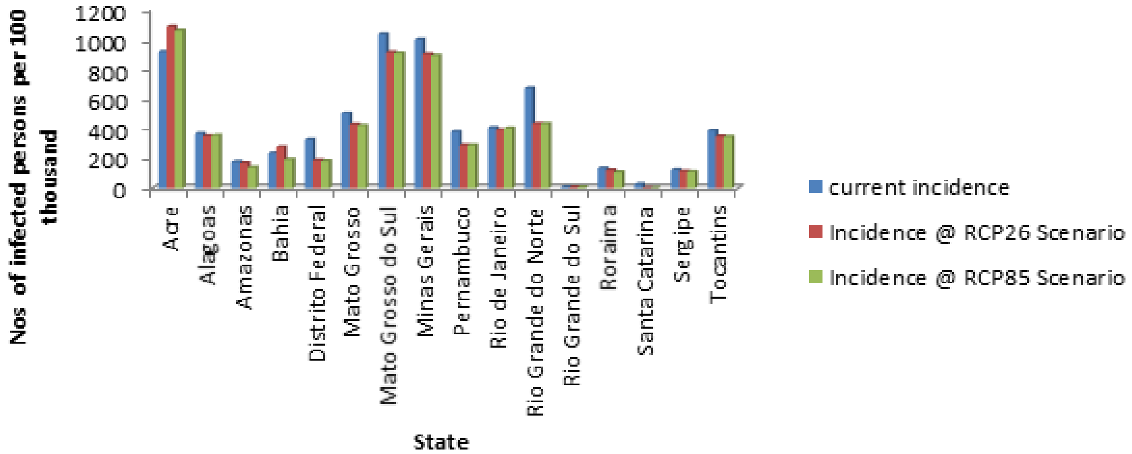


Figure 9: Probability of Aedes aegypti presence for current (a) and future climate (b), and the differences between both scenarios (c), for RCP26 and RCP85, respectively



The projected number of infected persons per 100 thousand for both climate change scenarios against the current record was calculates (Figure 10). Results of both future scenarios reveal increases in future dengue incidence in Acre state when compared to the current situation. However, future prediction of the incidence in other states indicate that the incidence will either be the same or lower than the current incidence levels.

Figure 10: Projected number of dengue incidence for both climate change scenarios versus current incidence



5.2. Economic costs

This study estimated the economic costs for the health care (direct) and productivity losses as a result of reduced labor input due to dengue illness in all states of Brazil for a five years period. It was found that normal dengue fever was the most common form of illness across the analysed years with more cases registered in 2015, 2016 and 2013, respectively. More severe dengue cases were reported in 2013 while more deaths were reported in 2015. The study found that there is a positive relationship between dengue cases and the potential economic costs (Table 5), which means the more dengue cases reported, the more the total costs for respective years. For example, costs were highest (1245 million R$) in 2015 and lowest (129 million R$) in 2017, which is proportional to the total number of cases. The costs in the year 2017 was approximately 10 and 7 times lower than 2015 and 2016 costs respectively.

Table 5: National total cost estimates based on actual reported cases

Variables		Units	2013	2014	2015	2016	2017
Normal dengue cases		Number	1,444,959	589,981	1,685,988	1,499,032	221,115
Severe dengue cases		Number	6856	689	1714	861	269
Death cases		Number	674	410	986	642	166
Direct costs	Public health	Millions R$	112.4	52.5	219.7	162.2	26.3
	Private health	Millions R$	144.8	61.2	268.8	191.8	23.8
	Total	Millions R$	257.2	113.6	488.5	354.0	50.1
Indirect costs		Millions R$	603.5	260.4	756.9	569.4	79.0
Total costs		Millions R$	860.7	374.3	1245.4	923.4	129.1
% indirect costs		Percentage	70.1	69	61	62	61

Although a smaller percentage of people (14%-37%) had a private health insurance in Brazil, the direct costs for private health system were higher than costs for public health system in all years, except for 2017. Interestingly, the proportion of indirect costs as measured by income loss due to absenteeism were observed to be higher (> 60%) than the proportion of direct costs across the years, which highlights the importance of the indirect costs to relevant sectors of the economy.

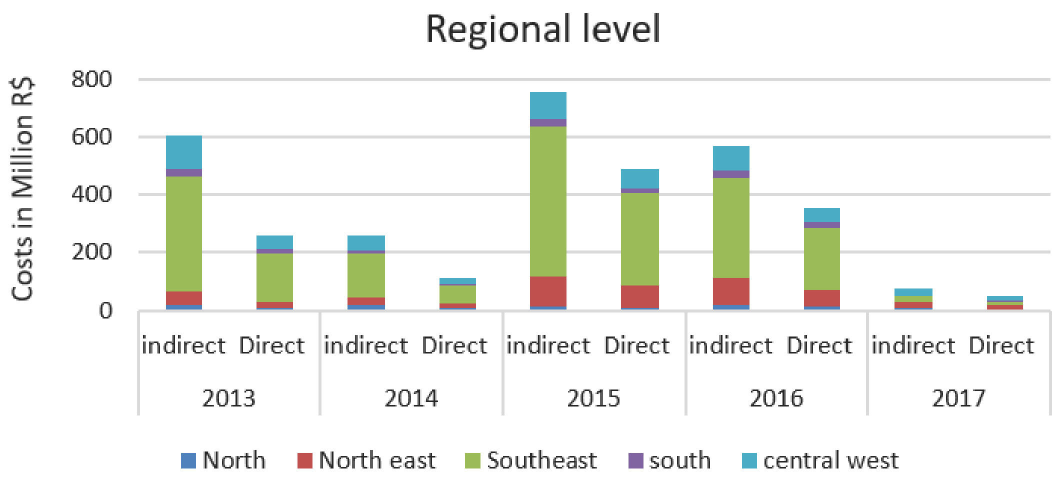
After adjusting for underreporting, the results of the economic costs at national level across years were obtained (Table 6). These results follow similar trends as previously mentioned (Table 5). The total costs were the highest on the years 2015, 2016 and 2013 respectively. Similarly, costs were higher in private health care system as compared to public health system.

Table 6: National estimates after accounting for under reporting using expansion factors

		Units	**2013**	**2014**	**2015**	**2016**	**2017**
Normal dengue cases		Number	4,623,869	1,887,939	5,395,162	4,796,902	707,568
Severe dengue cases		Number	10970	1102	2742	1378	430
Direct costs	Public health	Million R$	355.4	167.3	701.3	518.2	83.9
	private health	Million R$	458.4	195.3	858.1	613.0	75.8
	Total	Million R$	813.8	362.7	1559.3	1131.2	159.7
Indirect costs		Million R$	1922.2	832.5	2419.8	1821.1	252.5
Total costs		Million R$	2736.1	1195.1	3979.1	2952.3	412.2

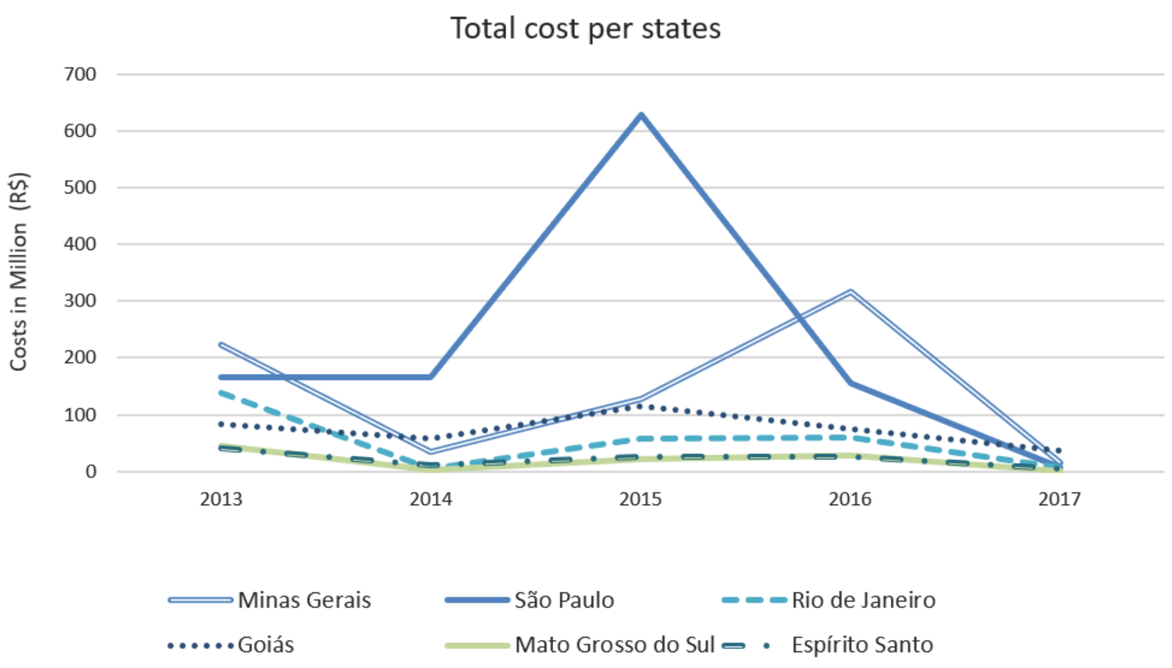
Direct and indirect costs were also calculated for the five regions in Brazil. Higher proportion of costs in relation to the total direct and indirect costs were recorded in Southeast, Northeast and Central-West, regions where most of the dengue cases were reported. For Southeast, where the highest values were found, the total productivity losses (indirect costs) were R$ 399; 153; 519; 343 and 19 Million for 2013, 2014, 2015, 2016 and 2017 years respectively while the direct costs were 170; 64; 320, 216 and 12 million R$ respectively (Figure 11).

Figure 11: Total direct and indirect costs for the five regions of Brazil



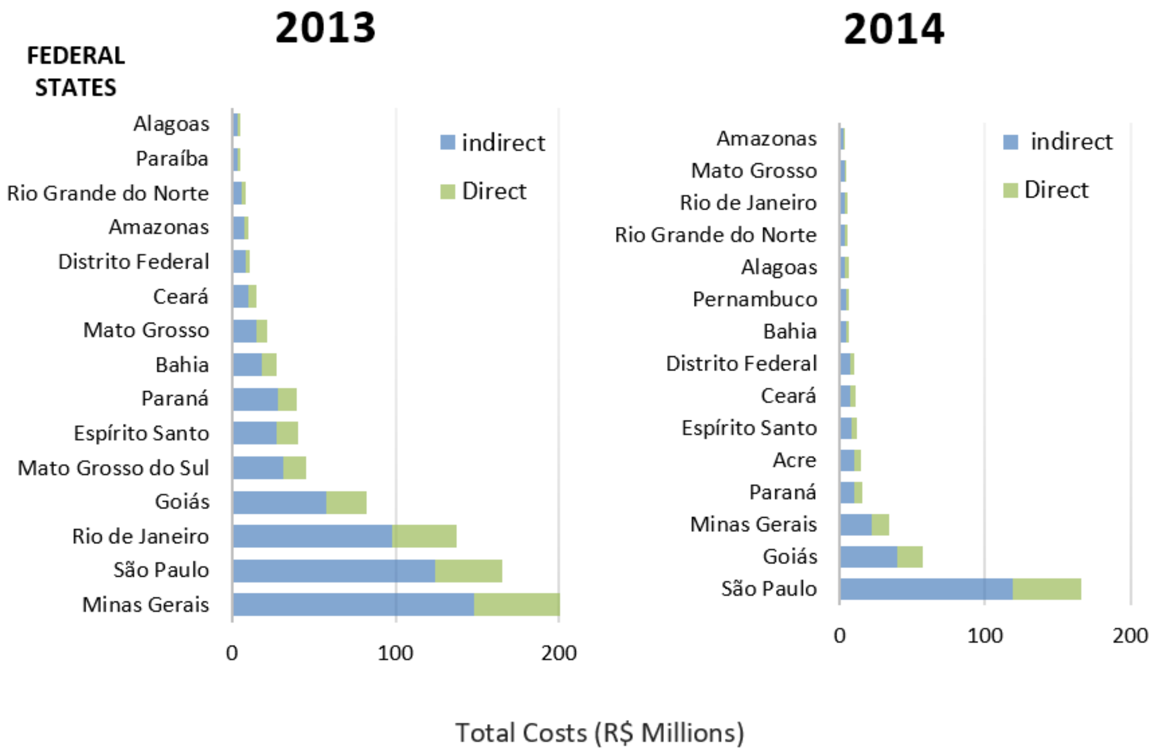
Total economic costs for the 27 federative states was computed in this study. Because of the high number of cases per state and due to large variations in the costs, only five states incurring the huge economic burden are illustrated in Figure 12. Across the five years period high total economic losses were experienced consistently in three states; São Paulo, Minas Gerais located in southeast region and Goiás in central-west region. In 2015, only one state (São Paulo) accounted for nearly half (630 million R$) of all the total national costs while total costs were almost the same for this state in 2013 and 2014 - around 165 million R$. In those years, the number of normal dengue cases were also the same at 220,392 and 225,763 and severe dengue cases 453, 191 respectively, for 2013 and 2014. The costs were slightly lower in 2016 (155 millions) as compared to 2013 and 2014. Nevertheless in 2017, the economic costs of this state were negligible. Minas Gerais state also incurred the highest costs in 2013 and 2016 at 224 and 316 million R$ respectively. There is a fluctuating pattern in the economic costs over the years clearly indicating that outbreaks of dengue occur after specific time period of the years and as much as there were lower cases in 2017, there might be more cases in the subsequent years.

Figure 12: Total costs for the top five states over five years period



Taking into consideration the economic costs of the different states for each year, results indicate that the proportion of indirect costs were consistently higher for each state over the five years period. In this paper, it is indicated the top 15 states out of the 27 incurring high total costs due to dengue fever each year. Apart from the three states aforementioned, substantial costs were evident in Rio de Janeiro, Mato Grosso do Sul, Espírito Santo, Parana and Bahia in 2013 (Figure 13). The scenario slightly changed in 2014, when states as Mato Grosso do Sul did not anymore feature among the top 15, or reduced its costs significantly as Rio de Janeiro. New states appeared in the costs rank in 2014, such as Acre (North region) in 5th place.

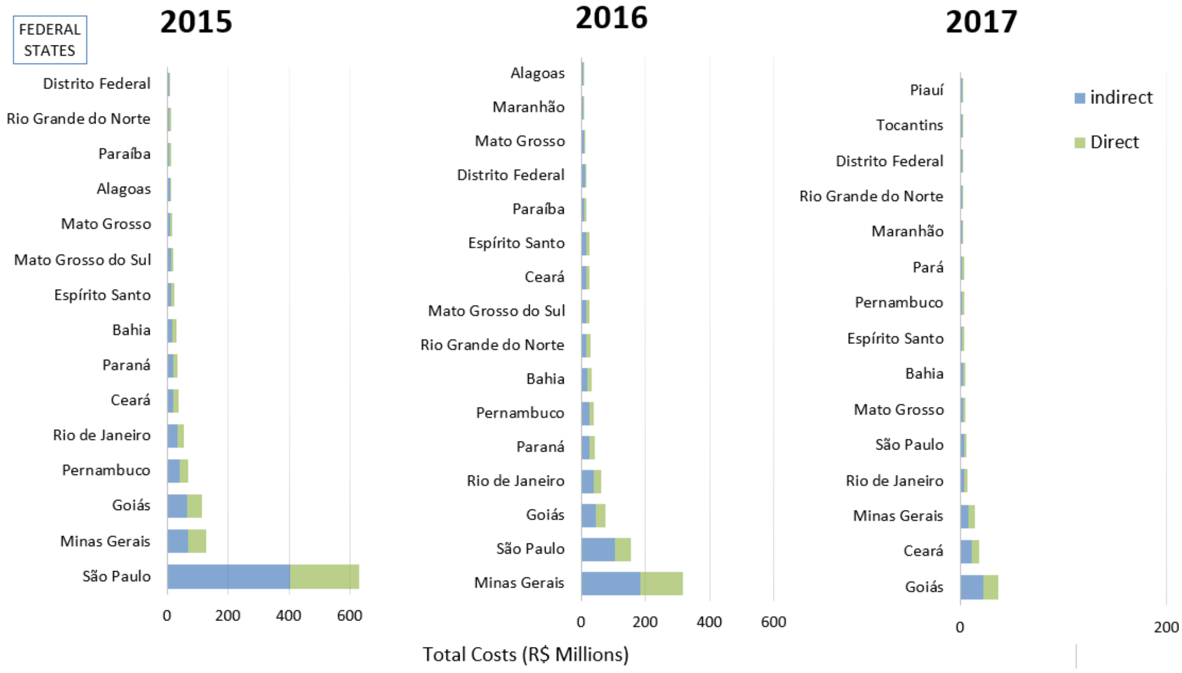
Figure 13: Total direct and indirect costs for the top 15 states for 2013 and 2014



In 2015, the huge economic burden was borne by one state - São Paulo, while the rest of the costs were distributed among the others (Figure 14). Pernambuco and Rio de Janeiro appeared among the top 5 states for both 2015 and 2016 years. The total economic cost for Rio de Janeiro remained almost the same from 2015 to 2016 while Pernambuco costs reduced by half in 2016 when compared to the previous year.

In 2017, about all the states experienced a reduction in economic costs of illness (Figure 14). Even the state of Goiás which recorded the highest economic costs in 2017, when compared with preceding years, this was just half of the costs incurred by this state in 2016, 2013 and 2014 and three times lower the costs recorded in 2015. The exception was Ceará, state which came second in 2017 and registered 18 million R$ as economic costs, higher than the costs observed in 2013 and 2014 (R$ 15 and 11 million respectively). Still, when compared to the 2015, the costs for Ceará in 2017 were half of the costs in 2015 and slightly lower than in 2016. Overall, other states such as Distrito Federal, Rio Grande do Norte and Ceará consistently appeared among the top 15 states while Tocantins, Rondônia, Piauí, Maranhão, Amapá, Roraima, Sergipe, Rio Grande do Sul and Santa Catarina were consistently at the bottom 10 over the 5 years period.

Figure 14: Total direct and indirect costs the top 15 states for 2015, 2016 and 2017

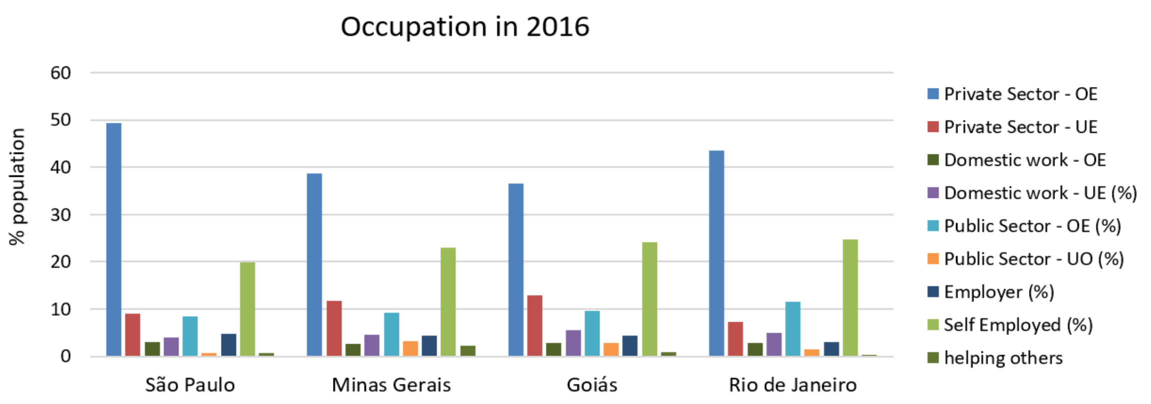


5.2.1. Productivity losses for different sectors in 2016

As previously detailed, productivity losses of adults' population due to dengue contributed to a significant share of the total economic costs of illness, for each state for the five years period. This study also explored the economic costs for different sectors in a dengue fever scenario, according to the employment status of the affected person.

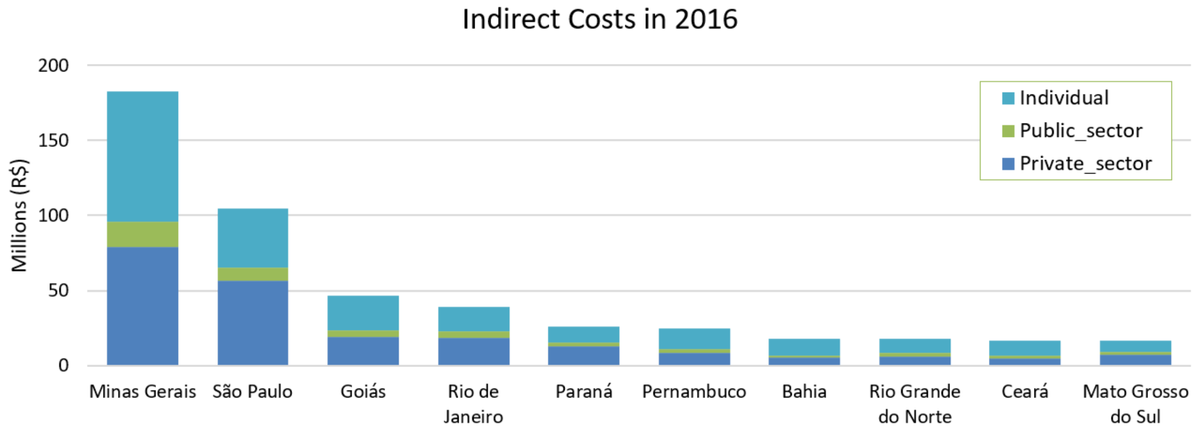
In 2016, just about half of the working population were employed by the private sector (officially and unofficially employed). The rest were working in the public sector, self-employed, employers, domestic workers or helping others. This trend is followed by the the four states that experienced highest dengue incidence in that year (Figure 15), in which 38 to 49% of people were officially employed in private sector, with the highest rates found in São Paulo (49%) and in Rio de Janeiro (44%). The proportion of people self-employed in states ranged from 20% - 25% in all four states.

Figure 15: Percentage of population employed in different sectors in the four states which presented highest indirect costs in 2016. OE: officially/formally employed; UE: unofficially/informally employed



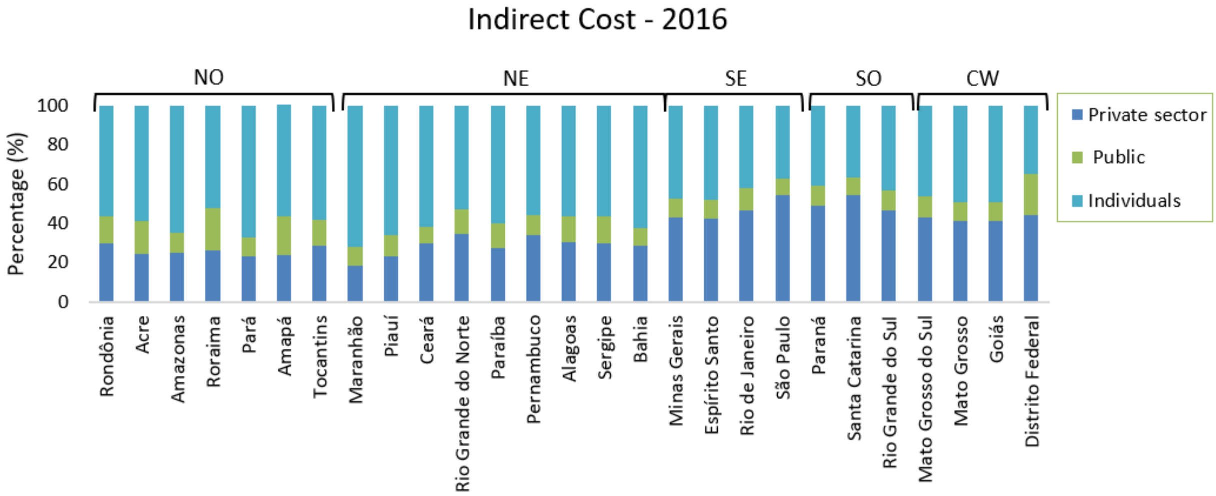
Based on the different categories of employment sectors and their respective average wages, the strata were further narrowed down to enable allocation of the economic costs to three major sectors: Private, Public and Individual. The total indirect costs for 2016 (569.4 million R$) were distributed among these three sectors based on the proportion of people in each strata and recorded dengue cases (Figure 16). Most of the indirect economic burden was borne by either individuals or private sector employers in nearly all states. The selected 10 states incurring the highest indirect costs in 2016 confirms this. For instance, in Minas Gerais the total indirect costs in million R$ for individuals cumulatively (87) was higher than that for private (79) and for public sector (17). On the other hand, private sector costs were high (57) in São Paulo as compared to the individuals and (39) and public sector (8.1).

Figure 16: Total indirect cost borne by different sectors for the 10 highest dengue occurrence states, in 2016



This can also be seen by region. For the states in North and Northeast, the individuals were the most disadvantaged for they incurred a higher proportion of the income losses when affected by dengue. In Southeast and Central-west, the percentage was shared between individuals and private sector, while in the South, most productivity losses were borne by the private sector (Figure 17). It is worth mentioning the higher percentage of costs borne by public sector in Roraima, Amapá and Distrito Federal when compared to the public sector losses in other states.

Figure 17: Proportion of indirect costs (productivity losses) borne by different sectors for the 27 states and their regions for 2016



6. Discussion

Past research has shown that climate factors can play a crucial role in the transmission dynamics of dengue by influencing vector mosquito's development and ecology (Jetten & Focks 1997). However, this study revealed that changes in temperature and precipitation each year are, in general, not entirely determinant to exacerbate the disease distribution in the state level as expected over the last 25 years in Brazil. Especially for precipitation, the results obtained indicate that rainfall variation from one year to other does not represent a determinant constraint for dengue fever occurrence, which follows the findings from Barcellos 2013 for the years 2001-2012. In fact, for the state of Piauí, even in the drier years, the dengue cases continued to increase. The mosquito needs water for its reproduction and it was expected that as more rainfall and more humid the weather is, more breeding spots would be available. However the availability of those spots appears to be more influenced by other factors such as the behaviour of the society than the quantity of rainfall itself. Actions regarding mosquito control are essential to decrease the number of mosquitos and consequently the occurrence not only of dengue fever but other associated diseases like yellow fever and zika. Potential breeding spots to be targeted are, for example, water-storage jars and drums, cemetery urns, discarded rubber tires, buckets, and other man-made containers, which are able to contain rainfall water.

It is worth noting that the average annual precipitation number (used here) may hide an important effect for dengue: the seasonality effects. As mentioned before, dengue fever is a seasonal disease which have a strong annual cycle with highest incidence in the warmest and most humid months, from January to May (Lowe 2011). The average annual precipitation do not consider differences within the year when there is, for example, a more humid summer and drier winter in the same year. The more humid summer could lead to an increase in dengue occurrence without differ from precipitation data from other years.

Beyond the precipitation findings, Barcellos (2013) indicated that warm climate cities have more risk of dengue transmission than those located in the mesothermal zone. Barcellos (2013) also pointed that Chowell et al (2011) also identified local temperature as a strong regulator of dengue transmission persistence in Peru. Similar results were found on this paper which brought up a different analysis looking at differences in temperature between the years. The result was that in warmer years, one quarter of the states presented higher dengue incidence. However, it is important to investigate impacts of seasonality in the increased transmission of the disease by state during warmer summers and the later notified cases, as found in Gomes et al 2012 study. In this paper, in both future climate change scenarios analyzed, the seasonal temperature was also the most determinant variable for the distribution of the vector, playing a crucial role on potential increase of the dengue incidence. The results also pointed that both climate change scenarios follow same trend and shows a shift from southern to northern Brazil in probability of habitat presence in the future.

Still comparing temperature and dengue relations, this study indicates no correlation between temperature and dengue occurrence in the states from South region. According to Barcellos (2013) results, "southern states have been preserved from dengue epidemics, where few dengue cases have been registered, most of them imported from endemic regions." Except for a dengue outbreak in Paraná in 2016, such statement reflects on the low economic costs bared in a dengue fever scenario by the states over the last 5 years, obtained in this paper. On the opposite of the southern states, correlation between temperature and dengue was found statistically significant for states such as Minas Gerais, Distrito Federal, Mato Grosso do Sul, which have been affected by dengue outbreaks over the last years and have been featured as top 15 on economic losses for direct and indirect costs by the disease. One of these units, the Distrito Federal, presented positive significant correlation for both dengue cases and incidence, when compared to temperature. The Distrito Federal is not considered a state itself but a federal unit with the size of larger cities of Brazil. The statistically significance and the size of the territory may not be a coincidence, but potentially confirms that narrow down the investigation of climate factors on dengue transmission to smaller units such as cities instead of regions can present more precise results. Dengue incidence was also positively correlated to temperature in Minas Gerais, state which had the highest productivity loss in 2016, being most of these costs carried by the private sector. In this case, measure to avoid a increase of temperature on a climate change scenario would prevent Minas Gerais further economic losses in a future outbreak of the disease. However, in general, this study has shown that the most affected states by temperature and/or precipitation are not the ones who are bearing the highest economic losses for dengue occurrence.

Still, even if climate was conducive for dengue, effects of temperature and precipitation in the dengue incidence in the tropics can be inhibited by other factors, such as use of air conditioning and window screening (Che-Mendoza *et al* 2015), and the different strategies mosquito uses to exploit microclimates (Reiter 2001). In this study, only bioclimatic variables were used to represent environmental factors required for species distribution modeling. Land-use, use of agrochemicals, digital elevation map (DEM), and other factors which can also influence *Aedes* habitat suitability were not considered. For the historical analysis, results have shown that urban population can be more determinant than temperature and precipitation for dengue incidence in this study. The present historical analysis indicates urban population as the factor that correlates with more states for dengue incidence, following other researches that considers human activities are more crucial to dengue transmission than climate factors. However even urban population is not a consensus for dengue transmission. Barcellos 2013 shows that "population size has a positive and statistically significant association with dengue transmission permanence". On the other hand, Antonio *et al* (2017) did not find significant correlation between population size and dengue case rates in Brazilian municipalities in the period 2001–2012. Future studies could compare states on urban population and dengue incidence among themselves along the years.

Despite the different positions, it is safe to indicate that a rapid expansion of urban population increases the risk of transmission of dengue diseases. In urban areas, there are not only "new opportunities for the reproduction of vector populations, but also for the interaction between infected and susceptible people" (Almeida et al 2009 cited Ault 1994, p.35-49). This is also agreed by Antonio et al (2017), when they suggest human mobility as the main reason for dengue outbreaks in areas where the mosquito was present, but the virus just arrived afterwards. This was probably the case of Acre and Pará, located in the Amazon region, which in this study presented correlation between urban population and dengue incidence and cases, respectively. Acre state, for instance, has never recorded a case of dengue until the year 2000. Ten years later there were 35 thousand cases, and the main reason appeared to be the land use changes, especially the construction of roads, which not only connected the state with the other regions of the country but also brought the vector and the virus, besides more hosts (Lana *et al* 2017, Beaubien 2017). The scenario for dengue incidence in Acre tends to increase in future years, as indicated by results from the future analysis showing Acre as the only state where dengue incidence will be higher than current incidence in both climate change scenarios. Therefore, the presence of the virus alone in a state does not mean that dengue cases in human will occur, as well, as the opposite: the presence of the vector does not affect human without the presence of the virus (Colón-Gonzales *et al* 2018). That is why issues such as human mobility regulation must be targeted along with vector prevention and development of researches and future vaccine.

Overall, dengue brings economic losses to Brazil. The productivity losses in this study were substantial for the five years, accounting for over 60% of the total cost of illness. These results are consistent with other studies in the country. For instance, Martelli et al (2015) found an estimated national total cost of $468 million in 2013 on actual reported cases which is slightly higher than the 2013 figure in our study of $ 345 million considering 2013 exchange rate of (1$ =2.36 R$). This is due to the fact that the current study did not consider other additional costs illustrated in the conceptual framework, such as the costs due to premature death cases, indirect costs of caregivers and value of school days lost due to illness. They also found out that the indirect costs accounted for a significant proportion of the total costs. Similarly, Shepard et al (2011) indicate that productivity losses were 60% of the total costs while the share of indirect costs was higher (72%) of total cost in the ambulatory group in Suaya et al (2009) economic study. These results illustrate that indirect costs due to illness should not be neglected and excluded in analysis but rather properly valued and quantifying when undertaking health economic studies of diseases to avoid underestimations.

Although, it was noticeable that the share of the productivity losses that went to the public sector was minimal, that was not the case for direct costs. The government of Brazil ensures universal health coverage and most of the direct costs in public health care system notably, medical treatment and laboratory may be covered by the government through the Unified Health System (SUS). On the other hand, Massuda *et a*l (2018) state that despite significant increases in the total and per capita health expenditure in Brazil to 8.3% of GDP and US$ 947 respectively in 2014, expenditure of public health is lowest in Brazil in comparison with other Latin American countries. This means that individuals or households must still take care of associated costs related to health treatment. Our results further indicated that individuals living in northern states bore the huge proportion of indirect costs when they have dengue fever. This region is the poorest in Brazil and Massuda *et al* (2018) emphasize the existence of inequalities in health resource allocation for the northern marginalized people which has its healthcare needs unmet while higher per capita expenditure is recorded in southeast, Central west and south west respectively. Above all, the results imply that the poorest are the most disadvantaged when affected with dengue, when they are not covered by official employment and/or have facilitate access to healthcare services, incurring to them a huge economic burden.

7. Conclusion

Temperature is a climate factor that can influence dengue occurrence in Brazil, in both historical and future scenario, especially for central-west and southeast states, with a potential future shift of increased dengue occurrence from southern to northern states. Precipitation was not determinant, but urbanization has shown an important role in the development and transmission of the disease. Even though it was not possible to identify a strong historically correlation for all states between climate and dengue, it is crucial to look back to climate data to build the future ones. Furthermore, knowing more about distribution patterns of this disease may be useful in guiding the states towards prevention measures against the vector, which can also intensify the decrease of diseases such chikungunya, zika and yellow fever.

In general, there is no consensus concerning which factors have more influence on the increase in dengue cases in a given area, which is probably the result of multidimensional combination of climate variables, human behaviour and other socio-ecological factors that influence the dengue vector. As a result, there is variations of the economic costs across the states in both direct and indirect costs for dengue fever consequences. The costs in the Northern and Northeast states were very low as compared with those in southern East, Central west and South over the five years. Despite that, an annual average cost of 707 R$ million over the five year, indicate that dengue disease imposes huge economic burden to the society and different sectors especially through productivity losses which are often overlooked.

While the dengue cases decreased in 2017 indicating a relief of the economic burden, the efforts must continue focused on the fight against the vector *Aedes aegypti* through proper epidemiological surveillance, educational campaigns, vigilance and research which are the current most effective way of eradicating the disease. Improving the preventive actions will need the collaboration between different economic sectors (public, private and individuals) and between the states, to prevent economic losses described in this study.

8. Limitations

The study presented limitations mentioned over the paper but in further details here. Regarding data availability, it was reported missing dengue incidence data in Brazil from the years 2008-2012 and monthly precipitation and temperature data for years before 1995 by several meteorological stations. The data for temperature and precipitation used for the analysis by state were obtained from stations located at the main cities in each state. However, for a more precise analysis, it is recommended gathering data from all stations available or making the analysis using land cells, to represent the temperature and precipitation conditions of one state. It is worth to mention one more time that the aggregation of the variables by state and by year may hide results according to the latitudes and seasonality, respectively.

This paper utilized the dengue surveillance data from SINAN which is the main source for this type of data in the country. However, it is important to emphasize that case reports may not be precise under high endemicity periods, tending to be overestimated from the effect of the midia attention on the outbreaks, and underestimated in low outbreaks' periods. In this case, literature suggests alternative indices for dengue incidence, which can be helpful to balance the errors on reporting dengue cases.

Regarding the economic losses analysis, the current study did not consider additional costs such as costs of caregivers and indirect costs for children under 14 years, productivity loss due to presenteeism of the patients (attending work but reduced performance due to illness), costs and loss of income from death cases, prevention, research, campaigns and surveillance expenditures on dengue were not estimated due to data and time limitations. Intangible costs associated with social stress, pain, anxiety and depression due to the illness were not also captured due to difficulties in measurement. Furthermore, other socio-economic data on the potential dengue cases such as age, gender, residence, occupation, number of days absent, wage rate and medical expenditures were missing especially for the years 2014-2018. These data could only be estimated from other literature and secondary sources and perhaps led to underestimation or overestimation of the economic costs.

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Annex 1. Result of Jackknife Test for Bioclimatic Variable Importance for Training, Model Testing and Bioclimatic Variable Importance for AUC, respectively.