Climate Change and Dengue:

Analysis of historical health and environment data for Peru

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Abstract

Dengue, a mosquito-borne virual infection that is the most common cause of hemorrhagic fever globally, is rapidly spreading worldwide. An estimated 40% of the world's population is at risk for this disease that is transmitted by *Aedes sp*. mosquitos. The *Aedes* mosquito-dengue virus lifecycle varies with temperature, and climate change may increase the risk of dengue epidemics in the future. We examined whether changes in sea surface temperature (SST) along the Peruvian coast were associated with dengue incidence from 2002-2010. In Peru the effects of the El Niño cycle on weather conditions are pronounced, providing an ideal place to study fluctuations in climate and dengue incidence.

Negative binomial models were used to examine the relationship between dengue cases and changes in SST across regions of Peru. Spearman's rank test was used to determine the lagged SST term that was most correlated with dengue incidence in each region. The negative binomial models included terms for the optimum lagged SST and a term for the trend of increasing dengue incidence over the study period.

The magnitude and sign of the correlation coefficient of dengue and SST varied between the 15 regions of Peru with dengue cases. 9 provinces had positive correlations between the two while 6 had negative correlations. The optimum lag ranged from 0 months to 6 months. In all of the regions lagged SST was a significant predictor of dengue cases in the negative binomial model.

The relationship between dengue and sea surface temperature in Peru appears to be significant across the country. Given the varied nature of the relationship between regions it is not possible to make accurate generalisations about this relationship in Peru. Accounting for additional climatic variables such as precipitation may help in improving the predictive model.

Résumé

La dengue, une infection virale transmise par les moustiques étant la cause la plus fréquente de fièvre hémorragique au niveau mondial, se propage rapidement dans le monde entier. On estime que 40% de la population mondiale est à risque pour cette maladie qui est transmise par les moustiques *Aedes sp*. Le cycle de vie du virus dengue des moustiques *Aedes* varie avec la température, et le changement climatique peut accroître le risque d'épidémies de dengue dans le futur. Nous avons examiné si les changements de température de surface de la mer (SST) sur le long de la côte péruvienne ont été associés à l'incidence de dengue de 2002 à 2010. Au Pérou les effets du cycle El Niño sur les conditions météorologiques sont prononcés, offrant un endroit idéal pour étudier les fluctuations du climat et de l'incidence de la dengue.

Des modèles binomiaux négatifs ont été utilisés pour examiner la relation entre les cas de dengue et des changements de SST dans toutes les régions du Pérou. Le test de Spearman a été utilisé pour déterminer le terme retardé de SST qui était la plus corrélée avec l'incidence de dengue dans chaque région. Les modèles binomiaux négatifs comprenaient des termes pour optimiser la SST et un terme à la tendance de l'incidence de la dengue augmente au cours de la période d'étude.

L'amplitude et le signe du coefficient de corrélation de la dengue et le SST varient entre les 15 régions du Pérou. Neuf provinces avaient des corrélations positives entre les deux, tandis que six avaient des corrélations négatives. Le décalage optimal varie de 0 à 6 mois. Dans toutes les régions retardées, le SST était un prédicateur important de cas de dengue dans le modèle binomial négatif.

La relation entre la dengue et la température de surface de la mer au Pérou semble être significatif à travers le pays. Étant donné la nature variée de la relation entre les régions, il n'est pas possible de faire des généralisations exactes à propos de cette relation au Pérou. Tenant compte des autres variables climatiques comme la précipitation pourrait aider à améliorer le modèle prédictif.

Chapter 1: Introduction

1.1 Background

Vector borne diseases such as malaria and yellow fever have been the focus of many prevention efforts and studies; however, other pervasive diseases, such as dengue, remain neglected[1]. The incidence of dengue, a virus transmitted through the bite of an infected *Aedes* species mosquito, has been increasing throughout the world during the last few decades, and is now thirty times higher than it was just fifty years ago[2]. The relationship between human vector borne disease and its determinants is complex, but it has become clear that climate is an important determinant for many of these diseases. Changing temperatures may allow for the spread of disease into previously unaffected areas by making environmental conditions more favourable for the propagation of disease-carrying vectors including *Aedes* species mosquitoes [3-5].

1.1.1 What is Dengue?

Dengue is an acute febrile illness caused by a virus transmitted through the bite of an infected *Aedes* species mosquito, mainly *Aedes aegypti*[2]. The dengue virus was first isolated in the 1940s and was classified as a member of the genus *Flavivirus*, family Flaviviridae[6]. By 1956, four different serotypes had been identified. Since then thousands of dengue viruses have been isolated and all fit into one of the four serotypes (dengue types 1-4) [6-7]. The main vector of dengue, the *Aedes aegypti* mosquito, is highly domesticated and lives mainly in urban areas. These mosquitoes lay their eggs in standing water, usually in an artificial container such as cisterns, flower pots and even old tires and trash[7]. The larvae then mature in the water until adulthood, and it is believed that as adults, females remain in close proximity to where they grew as larvae[2]. Humans become infected with the dengue virus when they are bitten by an infected adult female mosquito.[2] After the virus' intrinsic incubation period (IIP) of anywhere from three to fourteen days (typically four to ten)[2] the symptons of dengue become noticeable. Once a person is symptomatic they can infect any mosquito that bites them while the virus is circulating in the bloodstream (usually a period of two to ten days)[2]. After the mosquito acquires the disease the virus replicates during the extrinsic incubation period (EIP) of eight to twelve days, after which the mosquito can infect any human it subsequently bites[8] . Overall, the time from when a mosquito first acquires dengue to the time a human it bites can transmit dengue to another mosquito is between two weeks and slightly over a month. Since female mosquitoes remain in the same area for their entire lives, dengue moves by traveling from place to place in the blood of infected humans[2]. The general time line of the human-mosquito transmission process is pictured in Figure 1.

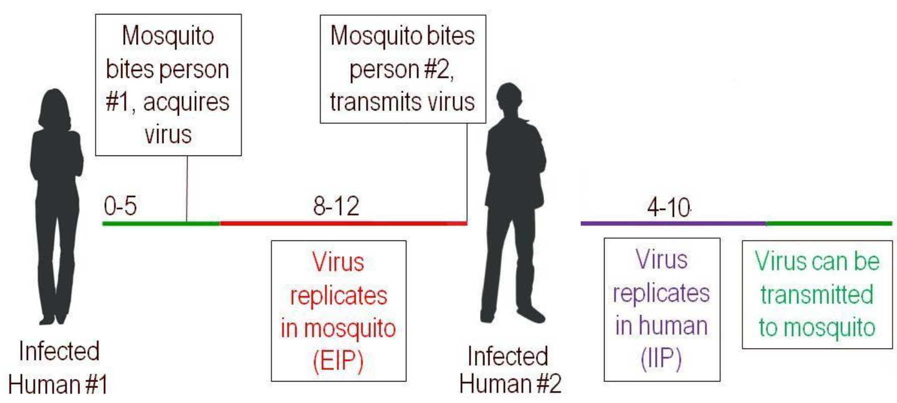


Figure 1: The human-mosquito dengue transmission cycle, the length of each stage is marked in days.

Currently, dengue causes more illness and death than any other arthropod-borne disease in the world, and the number of cases reported to the World Health Organization (WHO) has been steadily increasing over the last twenty years. Their records indicate that dengue is now the most rapidly spreading mosquito-transmitted disease in the world with between 400,000 and 1.3 million cases reported each year between 1994 and 2005. The organization believes underreporting to be significant, with an estimated 50 million dengue cases actually occurring globally each year[2]. In 2010, dengue was endemic to every continent except Europe, putting the 2.5 billion people residing in the globe's 'dengue belt', between the latitudes of 35^{o} North and 35^{o} South, at risk for dengue infection[9,10]. Dengue cases place a high economic burden on the patient, family and community in general wherever they occur; a study completed in Central America and Asia showed that a each person sick with dengue costs a household an average of 14.8 to 18.9 days of productivity, or US$514 to US$149 [2]. Widespread dengue epidemics can cause economic hardship beyond the household level, placing a burden on the health sector and economy of a country[2].

According to the WHO, a typical dengue case begins with the sudden onset of a fever that can last from two to seven days[2]. The fever is accompanied by flu-like symptoms including body aches, headache, flushing, and sore throat. Other common symptoms include bone and joint pain, rash and pain behind the eyes. In some cases more severe complications arise, leading to dengue hemorrhagic fever (DHF). These complications include bleeding of the nose, gums and gastrointestinal tract and severe vaginal bleeding, respiratory distress and organ impairment that may lead to death. DHF is also characterized by fever, hemorrhagic episodes, thrombocytopenia, and plasma loss. Plasma loss occurs once the patient's initial fever drops and remains below 38^{o}C and blood capillaries become permeable. Mortality from dengue fever is low, but if the disease progresses to DHF, mortality increases. If a large amount of plasma is lost during the 7-10 day duration of DHF, shock can occur. Dengue shock syndrome is the most serious form of dengue and can result in circulatory failure and death[2]. There is currently no treatment to eliminate the virus from an infected person. The symptoms are managed by treating the patient's pain and intravenous fluid replacement[11].

Since there is currently no cure or preventative vaccine for dengue, all control efforts are aimed at reducing the population of the mosquito vector, or at limiting human-mosquito exposure and mosquito biting rates[7]. Spraying inside homes where mosquitoes typically rest and treating larval habitats such as water containers are two of the most effective measures that are currently available to control the spread of the vector and disease[12-14]. Longer term solutions suggested by the WHO include environmental management programs to reduce suitable habitats for mosquito larva, such as the modification of water supply systems, waste removal programs and changing building structures. Efforts to reduce contact between humans and mosquitoes can also be effective, including adding screens to all windows and doors and the use of mosquito nets.[8]

1.1.2 Dengue in Peru

In recent years the epidemiology of dengue has changed dramatically. In the 1950s dengue was present in Peru[15], but during the next two decades dengue transmission was effectively stopped due to the *Aedes aegypti* mosquito eradication program implemented in the WHO region of the Americas[8,12,16]. After the eradication program was discontinued in the 1970s mosquitoes reinvaded the area via surrounding countries where there were no successful eradication programs in place, including the United States, Cuba, Venezuela and some Caribbean islands[7,15]. Dengue returned along with the mosquitoes, and by 1990 Peru had been affected by a major epidemic of dengue serotype 1[15] that infected 25% of the 300,000 residents of the city of Iquitos[17]. Dengue 1 caused additional outbreaks in Peru throughout the 1990s; dengue 2 infections followed soon after and were the cause of a major outbreak in 1995-1996. During the next Peruvian outbreak in 2000-2001, all four dengue serotypes were circulating in the population[18].

The speed at which dengue re-emerged in the Americas may be due in part to the rapid population growth in this area, as well as the increase in urbanization that resulted in increased population density and more suitable habitats for *Aedes aegypti* and travel that increased the movement of infected people and mosquitoes from place to place[15]. By 2000-2007 the Andean region, which includes Peru, was home to 19% of the dengue cases in all of the Americas and had the highest number of DHF cases of any country in the region[8]. In a study completed during those same years, serology showed that 26% of patients reporting with febrile illness at clinics in Peru, Bolivia, Ecuador and Paraguay had dengue[19]. The circulation of all four dengue serotypes in the population puts Peruvians at greater risk of developing dengue hemorrhagic fever since re-infection with a different serotype increases the risk of this complication[17]. Clearly dengue is a pressing health issue in this region.

1.1.3 The role of climate

Arthropods such as mosquitoes are extremely sensitive to climate. *Aedes* mosquitoes can survive over a large geographic range but temperature is a key factor in their development[20]. Public health researchers now accept that climate is an important determinant of the distribution of mosquito-borne diseases and that weather can impact not only the timing but the intensity of outbreaks[21]. This principle has been observed in laboratory and population level epidemiologic studies. The first laboratory study that showed that there was a relationship between the behaviour of the mosquito and temperature was completed in 1970 by Yasuno and Pant, who demonstrated that when the mosquito habitat is warmer the female *Aedes* mosquito feeds more often[22]. At the other extreme, at temperatures cooler than 17 degrees Celsius mosquitoes cease feeding, lowering the chances of contact with a human and eventually lowering the rate of dengue transmission[23]. Even if mosquitoes were to survive and feed, the virus itself stops replicating in the vector at temperatures below 11.0^{o}C[24].

Higher temperatures also affect the spread of disease by decreasing the extrinsic incubation period (EIP) needed for the dengue virus to replicate within the mosquito, influencing the survival and reproduction rates of mosquitoes themselves and increasing their biting rates[24-26]. A two to five degree Celsius increase in ambient temperature from 30 degrees Celsius to 32 to 35 degrees Celsius, for example, decreases the EIP from 12 to 7 days, so a mosquito can transmit the disease for a greater proportion of their lifetime[24]. This five day decrease in the extrinsic incubation period of the dengue virus has been equated with a 300% increase in dengue transmission in Mexico[26]. Not only are the mosquitoes infective for a greater amount of time but they also bite humans more frequently when temperatures rise. Warmer temperatures are associated with smaller mature mosquito populations that must feed more frequently in order to reproduce. These adult mosquitoes also digest blood meals more quickly in warmer temperatures, again leading to more frequent feeding[27]. Together the increased feeding rates and decreased EIP result in higher probabilities of dengue infection in human populations.

There is an apparent association between temperature and the behaviour and biology of dengue's mosquito vector. Preliminary studies have also indicated that there may be a relationship between climate and disease incidence[28-32]. It is believed that, in recent years, anthropogenic increases in global temperature and overall climate change have increased the severity and incidence of weather events including, but not limited to, El Niño Southern Oscillation (ENSO) cycles [33-34]. It is predicted that, over the next ninety years, temperatures will increase by 1.4 to 5.8^{o}C on average around the globe, making the expected rate of warming more than ten times what it has been in recent years[35]. Models have been developed that include 'temperature dependent insect reproductive and biting rates' consistently show that there is potential for a spread in geographical areas that can sustain vector-borne disease transmission. The same researchers that developed these models believe that warming may also result in longer seasons of transmission, when conditions are suitable for the spread of disease by insects.

In the short term, climate cycles like the El Niño-Southern Oscillation phenomenon may be useful in providing clues as to how future climate change might affect vector-borne disease incidence[21]. During an El Niño-Southern Oscillation event, global mean temperatures fluctuate due to large exchanges of heat between the ocean and atmosphere, making ENSO a driving force behind short term climate variability[34, 36-37]. These effects can be observed even far from the Pacific region where ENSO indices are measured[37]. Warmer sea surface temperatures (an indicator of the ENSO cycle) are related to increased air temperature in the tropics, as well as the upward shift in elevations which reach freezing temperatures that has occurred over the last forty years[38-39]. During the warm part of the ENSO cycle (the El Niño phase) temperatures around the globe increase, sometimes by as much as 0.5°C [37]. For example, one of the most dramatic ENSO events in recent history increased the annual global mean temperatures by an estimated 0.17^{o} Celsius[40]. These fluctuations already affect the distribution of disease vectors like *Aedes aegypti*[21]. Continued warming could allow mosquitoes to survive year-round in new areas, making these places vulnerable to dengue transmission. The climate of Peru is especially influenced by the El Niño-Southern Oscillation cycle [41]. Since global cycles like ENSO have a large effect on local weather patterns they may be useful, along with local topography and environmental conditions, in predicting what conditions might be conducive to epidemics or outbreaks and other 'biological surprises'[21,31].

In the context of these changes, it is important to understand the relationship between climate and infectious disease. The WHO already recommends that dengue prevention and response programs include early warning systems and environmental surveillance[2]. As more is understood about the relationship between climate and disease, warning systems including monitoring of climatic conditions that are favourable for outbreaks may become feasible, allowing early preventative action to protect populations against disease[21].

1.2 Research Objectives

The aim of this research project is to analyze the relationship between sea surface temperature (SST) and the incidence of dengue fever in Peru in two steps.

1. **Describe the general relationship between temperature and dengue throughout the world**. The first objective will be achieved by completing a systematic review of the existing peer-reviewed literature on the relationship between temperature and dengue. Examining studies that have been completed around the globe will facilitate the evaluation and general understanding of the dynamics of the dengue transmission cycle and factors that might influence it. This knowledge will help to guide this research project with regard to appropriate methodology for studying the relationship between SST and dengue as well as understand what potentially important covariates might need to be examined.
2. **Characterize the relationship between sea surface temperature and dengue in Peru from 2002-2010.** The regression models will help to elucidate the relationship, if any,

between SST and dengue in Peru. The relationship found through these analyses can then be compared to results of similar studies included in the systematic review.

1.3 Thesis outline

This thesis consists of four chapters. This chapter focuses on the background and context for the research. Chapter two is a systematic review of the relationship between temperature and dengue incidence around the world. The results of this review are used to develop a summary of the relationship around the world and clarify if there are patterns and commonalities across regions, as well as to give an overview of the statistical methods that are being used to explore these relationships. Chapter three presents the data and the statistical analysis methods used in this study. The methods used to clean the data are presented first, and then the descriptive statistics used to examine the data for patterns are presented. In chapter four, models are constructed for each region of Peru that reported dengue cases during the study period and then they are compared and summarized. Chapter five includes the discussion of the results, limitations of the project and recommendations for future research.

Chapter 2: Systematic Review

2.1 Introduction and Research Question

A systematic review of the literature was conducted in order to characterize the relationship between temperature and dengue around the world. The main goal of this review was to determine the impacts of the variability of climate on dengue incidence around the world, and to compile the methods that were used to evaluate the relationships between climate and dengue. The variables representing climate variability in the review were ENSO indices and temperature measures. These two types of measures are closely related since ENSO has a large impact on local-scale weather conditions such as temperature[37,40]. Additionally, the studies are presented according to geographic regions as defined by the WHO[42], in order to clarify any trends or potential relationships within the same areas of the globe.

A similar review on climate change and vector-borne diseases was completed by Zhang *et al*. and published in 2008, but this review only included studies published prior to 2007 while focusing on various vector-borne diseases[35]. This review therefore adds to the scientific literature by including more databases in the literature search, reviewing additional studies published between 2007 and 2010, while focusing specifically on the relationship between dengue and temperature.

2.1.1 Methods

A keyword search was performed in the eight databases shown in Appendix 1 using the listed search terms related to temperature and dengue.

Articles not written in English or Spanish were excluded. The search of the databases yielded 5,032 results which were reviewed by title and abstract and screened based on the inclusion and exclusion criteria listed in Table 1. Only studies of five years and over were included to ensure that the studies could detect long term patterns and changes in dengue incidence, possibly associated with El Niño, a cycle that typically has a duration of two to seven years[41]. The focus of this study was whether or not there was a population level association between dengue infection incidence in humans and temperature measures, so laboratory based studies were excluded since most of these studies focused on the dengue virus alone or its proliferation in mosquitoes. When it was not clear whether an article should be included from the title and abstract alone, the full text was reviewed. The results of the overall search process are outlined in Appendix 2.

Table 1. The inclusion and exclusion criteria used to select papers for the systematic review.

Include	Exclude
• Dengue occurrence is a measured outcome • Temperature is a determinant or ENSO is a determinant • Peer reviewed article • Longitudinal study 5 years or greater in length • Published in English or Spanish • Analysis examines the relationship between dengue and temperature or dengue and ENSO via regression, correlation or wavelet analysis	• Lab based study, vaccine focused study, diagnostic study • No statistics included that directly compare temperature and dengue occurrence • Conference proceedings, meeting abstracts, editorials, reviews, commentaries, books • Non-peer reviewed documents • Resolution of data is coarser than monthly (i.e. annual data)

The data extraction form that was developed included sections for the data and results from the articles, the methodologies used by the authors, and the variations between the studies (shown in Appendix 3). The completed forms were then examined and compared.

2.2 Results

There were sixteen studies that met the eligibility criteria for the systematic review (summarized in Table 2). Twelve of the sixteen studies used monthly dengue and climate data[25,29,32,43-52], while only four[53-56] used weekly data in their final analyses. All of the papers examined some measure of temperature in the study areas. Many also included some measure of El Niño, in the form of sea surface temperature or an El Niño index from the National Oceanic and Atmospheric Administration (NOAA) or other national office[25,29,43,47,49,53-55,57].

The results are presented according to geographic area to see if there are trends within regions of the world. Nine of the included studies took place in the Americas; five studies took place in South-East Asia or the Western Pacific, one study included sites in both regions. No studies meeting the inclusion criteria were found in any of Europe, the Eastern Mediterranean, or Africa.

2.2.1 Statistical methods

The authors of the studies included in this review employed a wide variety of statistical methods to evaluate the relationship between climate measures and dengue. Some investigators used a log transformation of dengue incidence to approximate a normal distribution[25,53-54,56], while others used the raw case counts[31,43,45-47,50,55], or incidence[29,44,48-49,51].

Due to the complex nature of the relationship between climate and dengue, a change in climate may result in a change in dengue only after a period of time has passed. In order to determine how long this lag time was, most of the authors first performed some test of correlation between climate and dengue at various lags. The lag at which the correlation was the greatest was chosen as the optimum lag and was then used in the regression. Most authors used the cross correlation function[47,51,53-54,56] or Pearson product-moment correlation[31,49]; others used the Spearman's rank correlation[50] since as a non-parametric test it is less affected by non-normal distributions[58].

After determining if the variables were related via correlation, the lagged climate variable was typically used in a regression model appropriate to the distribution. For transformed dengue incidence (dengue cases standardized by population) with a normal distribution, multiple regression[44,47-49,54,56] or autoregressive integrated moving average (ARIMA) models were used[51,53]. For case count data, Poisson and negative binomial models were used[43,46,55]. Generalized estimating equations (GEE) were used in one instance[50]. Both ARIMA models and GEE methods can incorporate autocorrelation [59-60]. Autocorrelation is an intrinsic property of most infectious disease time series, since the current disease incidence is related to previous disease incidence. Two studies used wavelet analysis to determine if the patterns of climate and dengue incidence were similar[25,29]. Wavelet analysis involves breaking down variables into two separate oscillating functions of time. The two wavelets are then examined for commonalities in phase, also known as coherence[61].

Table 2. A description of the studies that were included in the systematic review.

Study number	Study reference	Study Period	Time resolution	Correlation method	Regression method	Other methods
1	Nakhapakorn and Tripathi, 2005[45]	1997-2001	Monthly	None	Multiple linear regression	None
2	Tipayamongkholgul *et al*., 2009[43]	1996-2004	Monthly	None	Multiple negative binomial regression	None
3	Thammapalo *et al*., 2005[44]	1978-1997	Monthly	None	Multiple linear regression	None
4	Cazelles *et al*. 2005[29]	1983-1997	Monthly	None	None	Wavelet Analysis
5	Johansson *et al*., 2009a[25]	1983-2006	Monthly	None	None	Wavelet Analysis
6	Brunkard *et al*., 2008[53]	1995-2005	Weekly	cross correlation	ARMAX	None
7	Hurtado-Diaz *et al*., 2007[54]	1995-2002	Weekly	cross correlation	Multiple regression with polynomial terms	None
8	Johansson *et al*., 2009b[46]	1986-2006	Monthly	None	Poisson regression	None
9	Rifakis *et al*., 2005[47]	1998-2004	Monthly	cross correlation	Multiple linear regression	None
10	Depradine and Lovell, 2004[56]	1995-2000	Weekly	cross correlation	Multiple regression with polynomial terms	None
11	Hales *et al*., 1999[32]	1973-1994	Monthly	Pearson correlation	None	None
12	Sia Su, 2008[48]	1996-2005	Monthly	None	Multiple linear regression	None
13	Hii *et al*., 2009[55]	2000-2007	Weekly	None	Poisson regression	None
14	Arcari *et al*., 2007[49]	1992-2001	Monthly	Pearson correlation	Multiple linear regression	None
15	Lu *et al*., 2009[50]	2001-2006	Monthly	Spearman's rank	Generalized estimating equation	None
16	Wu *et al*., 2007[51]	1988-2003	Monthly	cross correlation	ARIMA	None

2.2.2 Temperature

There was a positive association between dengue and temperature measures in all of the studies, with the strongest correlations between rising temperature and increased dengue at a lag of zero and four months[25,29,32,43-56]. None of the studies found an inverse association between temperature and dengue according to the correlation coefficients. When the investigators created regression models and controlled for other variables, the coefficients for temperature were negative in some instances[44-45,49,51]. However, the majority of the results suggest that there is a positive relationship between dengue incidence and temperature[43,46-47,50,53-56].

The Americas

The was no lag between temperature and changes in dengue in San Andres, Mexico, Veracruz, Mexico, Puerto Rico, and Caracas, Venezuela; all of which showed a significant association between temperature and dengue. However, most of the studies examining the same geographical areas did not use the same statistical techniques and controlled for different covariates, making it difficult to compare relationships across studies. For example, in Mexico increased temperature was a significant predictor of dengue at lags of 0-1 week at three study sites[53-54] when regression was used in the analysis, but in the study by Johansson *et al*.[25], wavelet analysis showed that it was not a significant predictor of dengue.

In the other study sites in the western hemisphere (Puerto Rico, Venezuela and Barbados), the results were varied. In Puerto Rico, Johansson *et al.* found that temperature was a significant predictor of dengue incidence using Poisson regression[46], but not when using wavelet analysis[25]. In Venezuela and Barbados, temperature was positively associated with dengue incidence at lags of zero months and twelve weeks respectively[47,56].

South-East Asia and the Western Pacific

The longest optimum lag times of three to four months were all found in studies in Asia, including studies in Thailand, Taiwan, Indonesia, Singapore and China. In Singapore, the relationship between temperature and dengue was positive at lags up to four months[55]. In China and Taiwan, the relationship was also positive at short lags as shown by correlation analysis[50-51]. However, when adjusted for relative humidity, the beta coefficient was negative in Taiwan at a lag of two months[51]. There was an inverse relationship in other areas as well, for example, in the study by Naphapakorn and Tripathi in Sukhothai, Thailand, increased maximum temperature was associated with decreased dengue incidence at a lag of one month[45]. In the various studies that used data from Thailand the relationship between temperature and dengue was mostly positive using regression[29,43-44], except in Sukothai and Phetchabum, where it was negative[44-45]. In the study by Tipayamongkholgul *et al*. the authors chose to look at provinces in two different geographical regions, some facing the Gulf of Thailand and some in the northern mountainous regions of the country[43]. Thammapalo *et al*. examined all 73 Thai provinces[44]. Across the different geographical areas in Thailand that were examined, the relationship between temperature and dengue was usually positive. However, in other areas the relationship is quite different even within one country.

In Indonesia, Arcari *et al*. found that temperature was also associated with increased and decreased dengue incidence across different provinces according to regression analysis[49]. The varied nature of the relationships in Indonesia might be due to the fact that Arcari *et al*. chose to examine provinces that represented different geographical and climatic types within the country, as did Tipayamongkholgul *et al*. although with less varied results. Overall, the relationship between dengue and temperature was usually significant and positive, with short lags from zero to four months. The few inverse relationships may be statistical artifacts in the data and not reflect the actual relationships.

Table 3: The associations between temperature and dengue in each study site, as determined by correlation testing and regression.

Study	Location	Dengue measure	Temperature Measure	Correlation coefficient or wavelet relationship†	Optimum lag according to correlation	Regression Coefficient/other relationship	Optimum lag according to regression*
1	Sukothai, Thailand	Incidence	Maximum temperature	NA	NA	-	1
2	Petchaburi, Thailand	Incidence	Mean temperature	NA	NA	+	1
	Prachuap Khirikhan, Thailand					NS	NS
	Chumpon, Thailand					NS	NS
	Surat Thani, Thailand					NS	NS
	Nakhon Sithammarat, Thailand					NS	NS
	Chaingmai, Thailand					+	2
	Lamphun, Thailand					+, +	1, 3
	Lamphang, Thailand					+	2
	Phrae, Thailand					NS	NS
	Nan, Thailand					+	1
	Phayao, Thailand					NS	NS
	Chaingrai, Thailand					+, +	1, 2
	Maehongson, Thailand					+	1
3	Nakhon Nayok, Thailand	Incidence	Maximum temperature	NA	NA	+	
	Chanthaburi, Thailand					+	
	Mukdahan, Thailand					+	
	Sukothai, Thailand					+	
	Krabi, Thailand					+	
	Yala, Thailand					+	
	Narathiwat, Thailand					+	
	Prachuap Khiri Khan, Thailand					+	
	64 other provinces, Thailand					NS	

Study	Location	Dengue measure	Temperature Measure	Correlation coefficient or wavelet relationship†	Optimum lag according to correlation	Regression Coefficient/ other relationship	Optimum lag according to regression*
4	Bangkok, Thailand other areas of Thailand	Incidence	Temperature	+	NA	NA	NA
5	Thailand Puerto Rico Mexico	Cases	Temperature	NS NS NS	NS NS NS	NA	NA
6	Matamoros, Mexico	Incidence	Maximum temperature	NA	NA	+	1
7	San Andres, Mexico Veracruz, Mexico	log(cases+1)	Minimum temperature	+ +	0 0	+ +	0 0
8	Puerto Rico	Cases	Mean temperature	NA	NA	+, +, +	0, 1, 2
9	Caracas, Venezuela	Cases	Maximum temperature	NA	NA	+	0
10	Barbados	Incidence	Maximum, average, minimum temperature	+, +, +	16, 15, 12	+	12
12	Manila, Philippines	Incidence	Mean temperature	NA	NA	NS	NS
13	Singapore	Cases	Mean temperature	NA	NA	+, +, +	5-8, 9-12, 13-16
14	(All in Indonesia) Jakarta Aceh NTB East Kalimantan Central Sulawesi West Kalimantan, Central Java Maluku	Incidence	Temperature	+ + NS + + + + NS	1 1 NS 1 3 0 0 NS	+ - - + - - NS -	1 0 0 0 3 0 NS 0
15	Guangzhou, China	Cases	Minimum temperature	+, +, +, +	0, 1, 2, 3	+	1
16	Kaohsiung, Taiwan	Incidence	Temperature deviation	NA	NA	-	2

† + indicates a coefficient greater than 0, - indicates a coefficient less than 0. *Lags are in the same time scale as temperature and dengue cases **NS= not significant

2.2.3 ENSO

ENSO is a global process that has local and regional effects on short term weather[33]. ENSO activity can be measured by many different indices, each being a unique combination of various indicators such as barometric pressure, temperature and precipitation. The seven measures used in the studies reviewed here include sea level pressure (SLP), sea surface temperature (SST), the Oceanic Niño Index (ONI) the Southern Oscillation Index (SOI), the North Atlantic Oscillation (NAO), and the Multivariate ENSO Index (MEI). The SLP and SST are composite measures of the barometric pressure above or the temperature at certain ocean sites. The ONI is a measurement of three month averages of SST departures from the average SST in the Niño 3.4 region[62]. The SOI is made up of the difference in mean monthly sea level pressure at two sites[62]. The NAO is based on air pressure differences at various sites in the Atlantic Ocean. MEI is an index made up of six variables measured over the Pacific Ocean including sea level pressure, air temperature, sea surface temperature, cloudiness fraction of the sky and two wind components[62]. Since these indices all measure different aspects of the ENSO process, relationships between all of the indices and dengue will not be the same. Therefore, the direction of relationship (positive or negative correlation) will not always be the same from study to study even if the actual relationship is similar. There was not a consistent relationship between the presence or magnitude of El Niño and dengue incidence across the studies that examined it[25,29,32,43,47,49,53-54]. The lag times for the correlation between El Niño and dengue ranged from zero to six months. This range was greater than that of lags between temperature and dengue.

The Americas

In Mexico, the optimum lag times for ENSO at the three study sites where the relationship was significant were similar, ranging from sixteen to twenty weeks[53-54]. At all three study sites, the correlation between SST and dengue incidence was positive. Interestingly, the coastal sites of Matamoros and Veracruz had longer optimal lag times than the site inland at San Andres. One might expect that being closer to the ocean would result in shorter lag times. The only study that did not find that ENSO was related to dengue incidence was the study by Johansson *et al.*[25] It should also be noted that this was the only study that used wavelet analysis. In Puerto Rico, there was also a significant relationship between ENSO and dengue, but at a longer lag of 6 months[25]. In Venezuela, the relationship was not significant[47], and the second study in Puerto Rico[46] and the study in Barbados[56] did not examine this relationship.

South-East Asia and the Western Pacific

In the Pacific Community, the same measure of El Niño was used across the study sites and the island nations studied were all in close proximity[32]. Even though one might expect the close proximity to result in similar relationships between SOI and dengue the relationship differed between them. Five of the islands had a positive association between dengue and SOI, while two had a negative one and results from the other study sites were not significant. This study did not account for a lag, assuming there was a lag of zero. Within Indonesia, there was similar variation between the 8 provinces that were studied[49]. Three of the provinces had a positive association with SOI, with lags ranging from 0-5 months, while 2 provinces had a negative association at a lag of 1 month. In Jakarta, even though there was no significant correlation between SOI and dengue incidence, SOI was a significant predictor in the final model selected to describe the relationship between climate and dengue. Five of the eight Indonesian provinces that were studied had SOI as a significant predictor of dengue with negative coefficients in their final models after adjusting for temperature, rainfall and humidity. Both of these study sites are south of the equator.

The study in Thailand by Tipayamongkholgul *et al*. studied the correlations of both MEI and SLP with dengue[43]. There were negative correlations between SLP and positive correlations between MEI and dengue in all of the provinces. The difference in the directions of the relationships was probably due to the use of the two different ENSO indices. After adjusting for seasonality, mean temperature and relative humidity, the sign of the regression coefficient for MEI became non-significant and even negative in some areas. In the regression models at shorter lags of 1 and 2 months and in one province at six months, the regression coefficients for MEI were positive in ten provinces and non-significant in three. At longer lags of 3 to 5 months the coefficient was negative. This reiterates the importance of taking into account the ENSO index used when considering results. The relationship can be positive or negative in the same study, depending on the measure used.

2.2.4 Other relationships

Some studies looked for a correlation between the ENSO cycle and local climate conditions, such as temperature and rainfall[25,32,43]. Tipayamongkholgul examined the relationship between MEI as an ENSO indicator and local climate parameters in two groups of provinces in Thailand. They found that MEI was positively associated with temperature but negatively associated with relative humidity in tropical coastal areas, and positively associated with temperature in mountainous areas but not significantly associated with relative humidity in mountainous areas. Johansson *et al*. [25] found that ENSO was associated with local temperature and rainfall in Puerto Rico and Thailand. In both areas, the association with temperature was positive, with a lag of five months in Puerto Rico and three months in Thailand. Hales *et al*. found significant positive correlations between SOI and local temperature in Fiji, New Caledonia, French Polynesia, Tonga and Vanuatu[32]. In the other countries examined in that study, the association was weak or negative.

Table 4: The relationship between various ENSO measures and dengue incidence in each study site.

Study	Location	ENSO measure	Correlation coefficient or wavelet relationship	Optimum lag	Regression Coefficient	Optimum lag
2	Petchaburi, Thailand	MEI, SLP	+ (MEI) - (SLP)	1-11	+, - (MEI)	2, 5
	Prachuap, Thailand				+, - (MEI)	2, 3
	Chumpon, Thailand				+ (MEI)	6
	Surat Thani, Thailand				NS	NS
	Nakhon Sithammarat, Thailand				NS	NS
	Chaingmai, Thailand				+ (MEI)	1
	Lamphun, Thailand				+ (MEI)	1
	Lamphang, Thailand				+ (MEI)	1
	Phrae, Thailand				+, - (MEI)	2, 3
	Nan, Thailand				+ (MEI)	1
	Phayao, Thailand				+ (MEI)	2
	Chaingrai, Thailand				+ (MEI)	1
	Maehongson, Thailand				NS	
4	Bangkok, Thailand	SOI			NA	NA
	other areas of Thailand	SOI			+	0
5	Thailand	SST	NA	NA	NS	NS
	Puerto Rico		NA	NA	+	6
	Mexico		NA	NA	NS	NS
6	Matamoros, Mexico	SST	+	18	+	18
7	San Andres, Mexico	SST	+	16	+	16
	Veracruz, Mexico	SST	+	20	+	20
9	Caracas, Venezuela	NAO, SOI, ONI	NA	NA	NS	NS

Study	Location	ENSO measure	Correlation coefficient or wavelet relationship	Optimum lag	Regression Coefficient	Optimum lag according to regression
11	Tokelau	SOI	+	0	NA	NA
	Western Samoa		+	0		
	Fiji		+	0		
	American Samoa		+	0		
	Tonga		+	0		
	Nauru		NS	0		
	Vanuatu		NS	0		
	Wallis		NS	0		
	French Polynesia		NS	0		
	New Caledonia		NS	0		
	Kiribati		NS	0		
	Niue		NS	0		
	Tuvalu		-	0		
	Cook Islands		-	0		
14	Jakarta, Indonesia	SOI	NS	NS	-	0
	Aceh, Indonesia		-	1	-	1
	NTB, Indonesia		+	5	-	1
	East Kalimantan, Indonesia		NS	NS	NS	NS
	Central Sulawesi, Indonesia		+	0	-	5
	West Kalimantan, Indonesia		NS	NS	NS	NS
	Central Java, Indonesia		NS	NS	NS	NS
	Maluku, Indonesia		+	1	-	1

† + indicates a coefficient greater than 0, - indicates a coefficient less than 0. *Lags are in the same time scale as temperature and dengue cases **NS= not significant. NA = the authors did not examine this relationship

2.3 Discussion

Sixteen studies met the inclusion criteria for this systematic review. A wide variety of methodologies was used by each author and each study examined different combinations of covariates. Even though the studies were quite different one can try to look for insights into the relationship between temperature changes and dengue cases by examining the results as a whole.

2.3.1 Temporal Scale Issues

The majority of the studies focused on intra-annual variations in climate and dengue despite the five year plus time scale. Within years, there were typically obvious differences in temperature and dengue incidence coinciding with the various seasons throughout the year. Usually, when temperatures increased, the occurrence of dengue in the area increased as well following a short lag.

In order to better understand the effect of the El Niño/La Niña cycle, one would have to examine the inter-annual trends as well as trends within years, since this cycle usually occurs over two to five years[41]. El Niño itself influences local temperatures so one would expect that where there is a significant relationship between temperature and dengue there would also be a relationship between El Niño and dengue. However, El Niño does not only affect temperature, it also influences other weather conditions such as precipitation that may act along with temperature to influence the behavior and biology of mosquitoes as well as dengue patterns and transmission.

2.3.2 Spatial scale issues

The results of this review showed great variation in the relationship of climate and dengue, even across nearby regions, demonstrating that different regions will not have the same relationship with changing temperature and El Niño conditions. The majority of the studies used weather and dengue measurements that had been aggregated over space. Either multiple temperature measurements from different weather stations were averaged together to obtain one measurement used for one area, or the data from a single weather station was used for a larger area. The areas were defined according to political boundaries and, in the case of nationwide studies, were quite large. It is reasonable to assume that in many cases the geography and weather conditions vary across a country and perhaps the aggregated weather data was not an accurate reflection of the conditions in all areas. Since the effect of ENSO on climate differs across areas, confounding could result when examining the area as a whole, if for example, temperatures increased in one location within the country but decreased in another.

In addition, the strength and effects of the relationship between El Nino and weather varies across different regions of the world. This might explain the nature of the differing associations between El Niño and dengue in the studies. El Niño does not create the same weather conditions from place to place, so while an El Niño year may make the environment more favorable for dengue transmission in one area, another area might become unable to support mosquitoes or disease transmission.

Measurement of ENSO is also done at much larger scales than measuring local temperature. Most of the indices are aggregated from conditions across large areas of the ocean so they might not be as straight forward to study as temperature. The longer lag times for the effect of ENSO might also be due to the fact that ENSO influences weather, which then influences dengue, and it takes longer for the effects to trickle down. There also must be sufficient population to sustain transmission, since mosquitoes pick up the virus from biting humans.

Given that the typical *Aedes* mosquito only lives for a short time it seems surprising that climate was related to dengue at lags of one month or more. However, the studies that used weekly data, which would have been able to detect optimal lag times closer to the lifespan of a mosquito, found similar lags to those that used monthly data. It is possible that increased temperature at one time could increase dengue transmission by decreasing the incubation time of the virus and increasing mosquito biting rates, infecting more people with the virus and later infecting more mosquitoes. If the temperature were to decrease, the next generation of mosquitoes would bite less frequently and so transmission would decrease again. Prolonged periods of unusually high temperatures might be related to increased rates of dengue infection but it seems unlikely that brief periods of high temperatures would result in large, lasting dengue outbreaks. However, these long lags are due to the delay between all stages of disease, including notification. Even if the duration of the mosquito/dengue cycle is less than a month, some time still passes prior to the patient visiting a doctor and being diagnosed and reported to the proper authorities.

2.3.3 Measuring independent variables

There were multiple ways in which temperature and the El Nino cycle were measured in the studies presented here. After examining all of these studies in detail there seem to be merits and deficiencies to each measurement. There is no definitively best way to measure these determinants. Maximum temperature measurements might best reflect the limiting effect of high temperature on the behavior of both the dengue virus and mosquitoes, but low temperatures, perhaps better reflected by minimum temperature measures, are equally influential [20, 23-24]. The different ways in which ENSO can be measured also reflect the variety of climatic conditions associated with the process (beyond temperature alone), and in this review, one measurement does not seem to reflect a stronger relationship with dengue incidence than the others.

2.3.4 Conclusions

It is clear that in most areas there is some statistically significant relationship between climate and dengue around the world. This review, however, makes it apparent that studying the relationship between climate and dengue at a local scale (finer than national) can be beneficial to properly understanding how the incidence of this disease might change in the future. The significant results across studies show that dengue is highly climate-sensitive across the globe. However, the extent of this relationship and any geographical trends had not yet been described before this review. The continuing need for small-scale studies is due to the inconsistent results across studies. These inconsistencies make it difficult to make predictions about the relationships in other areas such as Peru. If predictions about how climate change will affect dengue incidence in an affected area are to be made it is still necessary to complete a study specific to that site.

Chapter 3: Modeling the effects of sea surface temperature on Dengue in Peru

3.1 Research objectives

In order to determine if there was a relationship between dengue and SST in Peru for the years 2002-2010, regression models were created for each region of the country that reported dengue cases.

3.2 Methods

3.2.1 Data collection and sources

Dengue

The case counts used in these analyses were extracted from weekly epidemiological bulletins (*Boletines Epidemiológicos*) that are published by the Department of Epidemiology of the Peruvian Ministry of Health in Lima, Peru[63]. The Department of Epidemiology runs the epidemiological surveillance program for the country via a network of 6,000 notifying units[64]. A notifying unit is required to report any suspected dengue case to the intermediate level reporting center, it is then reported to the regional Epidemiology Office, who then reports it to the Ministry of Health Department of Epidemiology. Cases reported to the Ministry of Health by the following Tuesday at two o'clock are then recorded and reported in the weekly Epidemiologic Bulletin[65]. Dengue cases are reported as confirmed and probable dengue and dengue hemorrhagic fever cases in each region of the country according to the World Health Organization Guidelines. Probable dengue cases are cases with a history of fever lasting between two and seven days and having two of more of the following symptoms: rash, signs of haemorrhage, headache, retro-orbital pain, muscle or joint pain. Confirmed dengue cases are any probable cases that have been confirmed via serology or that come from a region where the vector is present and there has been transmission of dengue confirmed by a laboratory during the previous fifteen days[66-67]. A third type of cases, discounted, is also reported; this is the number of cases that were originally diagnosed as dengue but then were identified as some other disease. Only dengue cases that were reported to the Ministry of Health were examined in this study. Only data from fifteen of twenty five regions was analyzed as the other regions did not report any dengue cases during the study period.

Sea surface temperature (SST)

Sea surface temperature was chosen to represent the climatic determinants of dengue incidence in this study. Sea surface temperature is a measure of the ENSO process. This process has a large influence on local climate, not just in temperature but also in other climatic factors related to mosquito biology, such as precipitation[34, 36-37]. Therefore, SST was chosen to be used since it is one simple, easy to measure, determinant that reflects a variety of complex climatic conditions related to dengue incidence in Peru. Monthly sea surface temperature records for El Niño Region 1.2 were obtained from the National Oceanic and Atmospheric Administration of the United States[68]. The El Niño 1.2 region lies directly along the coast of Peru. The SST records for this region come from satellite and *in situ* data (from ships and buoys) recorded for each 1^{o} latitude and longitude square across the El Niño region. The satellite data and in situ data are combined using an algorithm to correct for cloud cover and reflection of sunlight during the day that may create bias in the satellite data. The records across the Niño region 1.2

grid are area-averaged over time and space to give one average SST record for the month[69].

3.2.2 Preparing the data

Dengue

Throughout the study period weekly cases were reported according to geographical area. The regions that were reported changed over time, with some regions being subdivided and reported separately. Total dengue case counts for the twenty five greater regions of Peru as currently defined by the Peruvian government were calculated from the counts from sub-regions reported in the bulletins. For this analysis, only dengue (not DHF) cases were considered and the probable and confirmed accumulated cases were combined into one total weekly count. DHF cases were rare and the vast majority of the weeks had zero cases so they were not included in the analysis.

In order to find the incident cases each week the previous week's accumulated cases were subtracted from the current week's accumulated cases. In some cases this created negative incident cases. The negative cases were due to the fact that in the records it was possible for the accumulated cases to decrease over time. This is because of the presence of discounted cases, cases that might have originally been recorded as probable but upon receiving the serology results were determined not to be actual dengue cases. Since the bulletins did not denote which cases from which weeks were discounted, the total of the appropriate week could not simply be corrected. Instead, when negative case counts arose the negative number was added to the previous week's incident case counts and changed the negative week's count to zero. If the previous week's case count was then negative, it was changed to zero and the negative cases were moved to the week before that. This process was repeated until the negative count became positive. Linear interpolation was used to fill in the missing weeks, except for the first thirteen weeks of the study period, which were left as missing.

In the systematic review in chapter 2, using monthly instead of weekly data did not seem to result in different lag times or results. In order to cut down on the noise in this dataset, the weekly counts were aggregated to monthly counts. After the negative cases and missing weeks were removed from the series the data was combined into four week totals starting with weeks 4-8 of 2002, resulting in 13 epidemiological months per year. If any weeks in the epidemiological month were missing the month was considered a missing data point.

SST

The sea surface temperature data were complete and had already been cleaned at the source. There were no missing data.

3.2.3 Descriptive statistics

Dengue

Each region was examined over the study period. First, histograms of the case counts were created in order to visualize the distribution of the data. Then time series graphs of the case counts were created to see if there were any obvious patterns or trends. In order to clarify the seasonality of annual dengue incidence, box plots were created of the monthly cases over all the years. The autocorrelation of the cases in each region, at lags up to 13 months (1 year), was also examined to see if autocorrelation was an issue in this data set. The

Portmanteau Q statistic was used to determine if the autocorrelation in each region was significant and if so, at what lags[60].

SST

Histograms of SST over the study period were used to visualize the distribution of the data. A time series plot was also created to see how SST varied over the study period.

3.2.4 Building the models

Finding the optimum lag time

SST along the Peruvian coast affects the local weather throughout the country; in turn those weather conditions affect the life-cycle and behaviour of the mosquito and therefore the rate at which it transmits dengue. Once a person is infected the intrinsic incubation period must pass before they develop symptoms and seek medical attention. Although dengue is a reportable disease, it is unlikely that incident cases are reported to the Ministry of Health in Lima immediately. Some time may pass before the news of new cases reaches the capital and they are recorded. Therefore, it is reasonable to assume that a change in SST might not be associated with a simultaneous change in dengue cases but that the shift in cases might occur after a lag time. In order to determine at what lag time SST was most correlated with dengue cases, Spearman's rank test was used to find the correlation coefficient and its significance level in each region at each lag from zero to six months. From the systematic review in chapter 2, it is apparent that it is customary to examine lags in that range. The optimum lag time was the lag at which the correlation coefficient was significant and if more than one lag was significant the highest correlation coefficient was chosen.

Regression

After finding the optimum lag time for each region, various regression models were created and compared to determine which was the most appropriate for the data. First the incidence data were log transformed in order to approximate a normal distribution. Then an ARIMA (AutoRegressive Integrated Moving Average) model was fit to the data with lagged SST and year as predictor. This model was extended to a seasonal ARIMA model in order to account for the seasonality of the data. This method accounts for the correlation of the incidence in the current month with the incidence in previous months (autocorrelation). As an alternative, Poisson regression was performed for each region. Including a term to account for seasonality was also considered, both as monthly indicator variables and as a sine and cosine function. A year term was also included in the model in order to account for the long term trends in dengue cases. The outcome of the Poisson regression was examined to determine if some other method might be appropriate. One alternative regression method was a negative binomial model to account for over-dispersion in the data. The best regression method and combination of covariates was chosen by examining Akaike information criterion (AIC) and the Bayesian information criterion (BIC) for each model; the lowest scores indicated the best fitting model. Using a generalized estimating equation, or GEE, is the easiest way to account for autocorrelation in count data, as it allows using both a negative binomial distribution and autocorrelation residuals. This method is usually used for clustered data or repeated measures over time like the data in this study, but a GEE is used typically used to examine the average of multiple regions at once.[59] A GEE for a negative binomial distribution and autocorrelated errors was then employed to see if accounting for the autocorrelation of the errors would change the results.

Chapter 4: Results

4.1 Descriptive statistics

4.1.1 SST

In Figure 2 there is a clear annual cycle of SST. It is high at the beginning of the year, decreases in the middle of the year and then increases again. There was an exceptionally warm annual minimum in 2006 and an exceptionally cold minimum the following year and again in 2010. The highest annual maximums occurred in 2002, 2006 and 2008 while the lowest maximums occurred in 2004 and 2005.

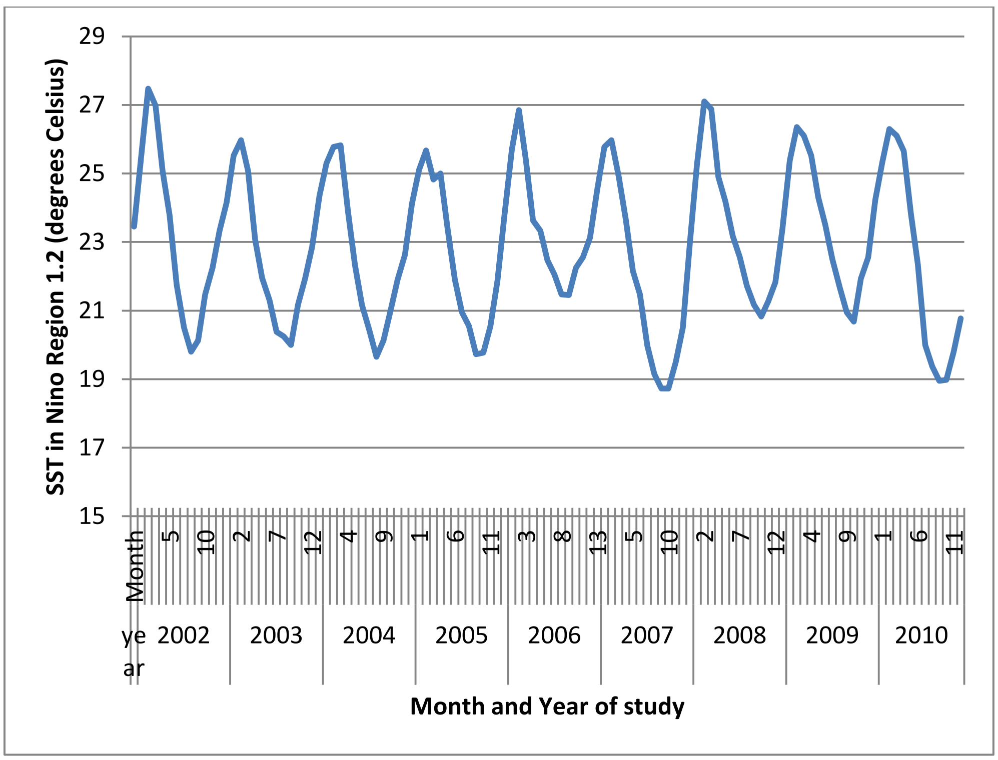


Figure 2. Time series of sea surface temperature in El Nino regions 1 and 2 for 2002-2010.

In Figure 3 the distribution of SST during 2002-2010 appears approximately normal.

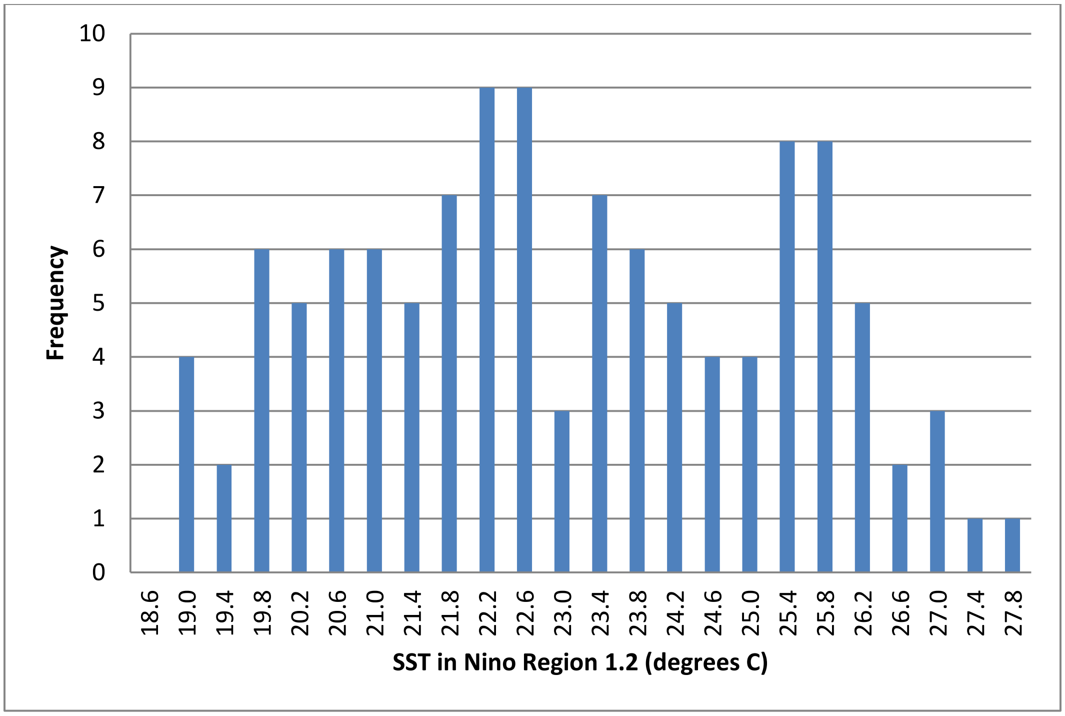


Figure 3. Histogram of sea surface temperature in El Nino Region 1 and 2 for 2002-2010.

4.1.2 Dengue

Examination of the yearly plots of monthly dengue cases and the box plots of cases by month (Figure 4 - Figure 18) shows that there is a seasonal pattern of dengue incidence. The majority of cases occur in the first six months of the year, then there are fewer cases during the middle of the year and in some regions cases begin to rise again in month thirteen. The peak dengue months seem to occur later in the year in Cajamarca, Pasco and Piura and earliest (sometimes starting to increase in month 13 of the previous year) in Amazonas, Junin, Loreto and San Martin. The largest numbers of cases occur in the regions of Loreto, Lambayeque, and Piura.

a) b)

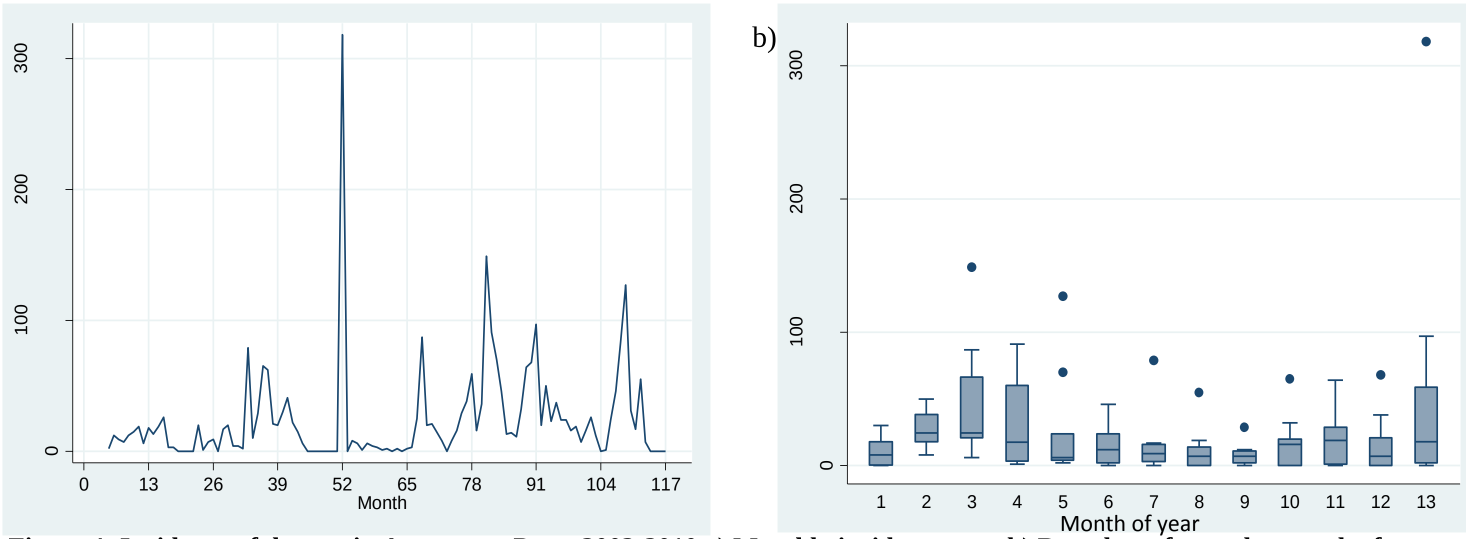


Figure 4: Incidence of dengue in Amazonas, Peru, 2002-2010 a) Monthly incident cases. b) Box plots of cases by month of year.

a) b)

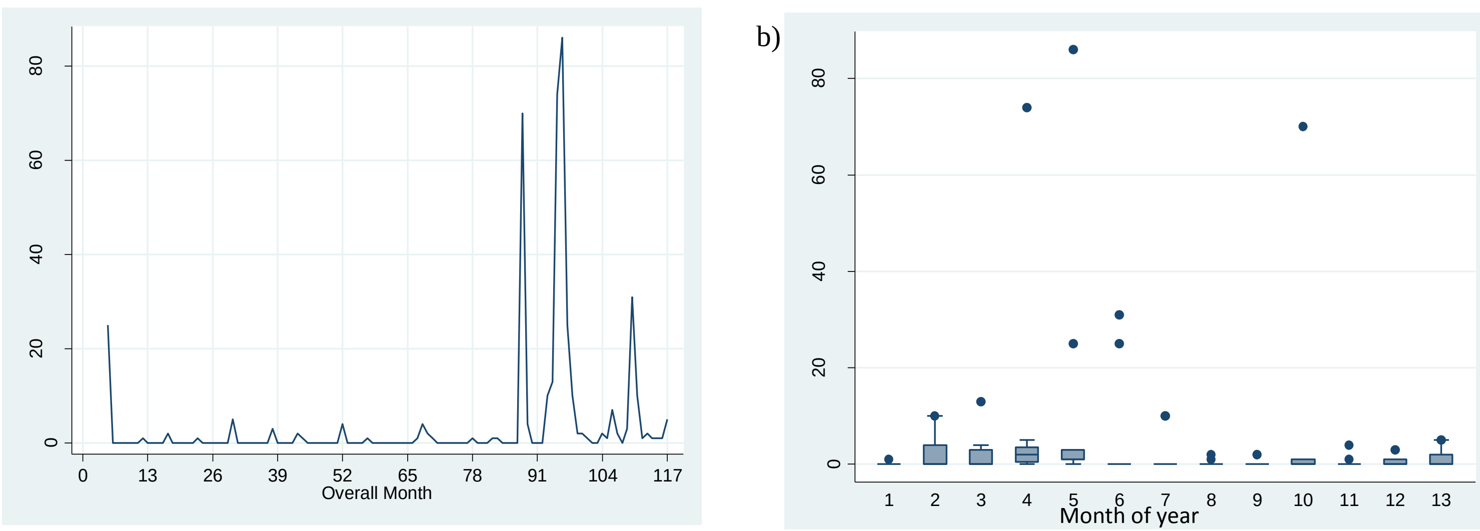
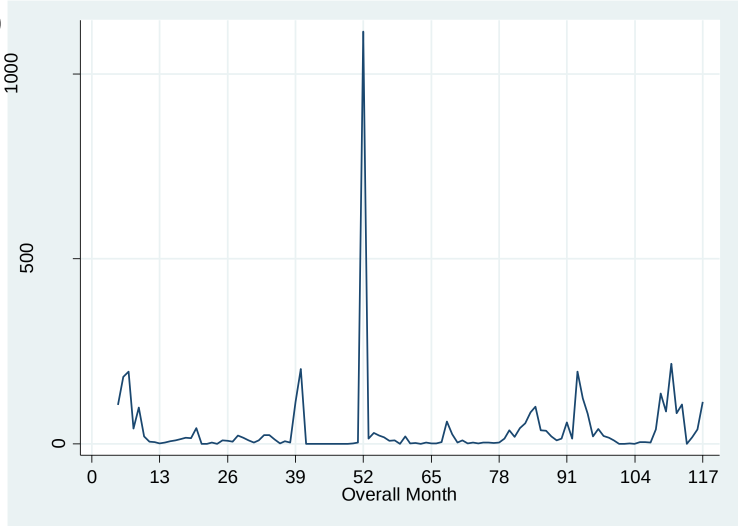


Figure 5: Incidence of dengue in Ancash, Peru, 2002-2010 a) Monthly incident cases. b) Box plots of cases by month of year.

a)



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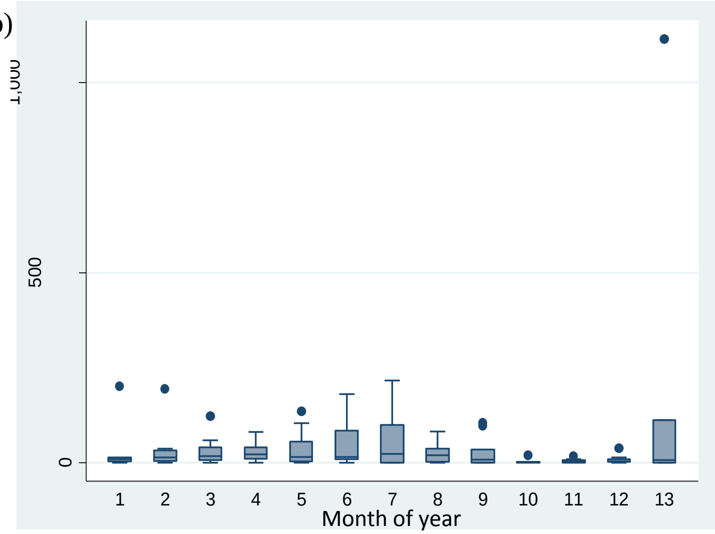
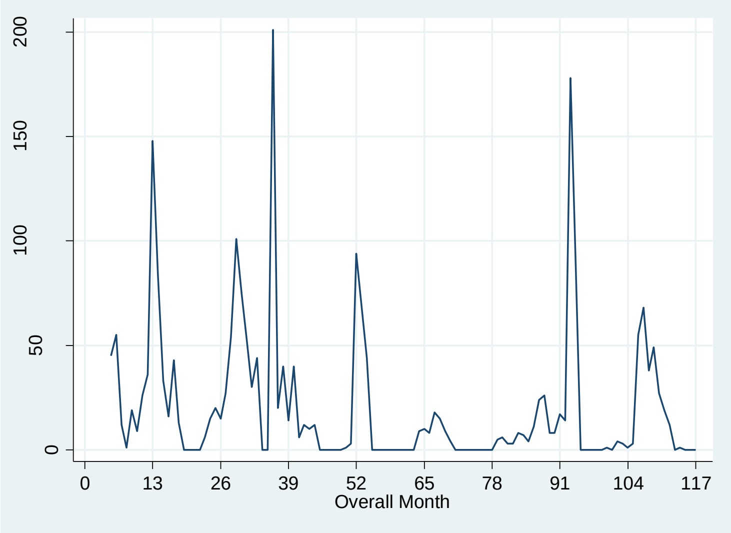


Figure 6: Incidence of dengue in Cajamarca, Peru, 2002-2010. a) Monthly incident cases. b) Box plot of cases by month of year.

a)



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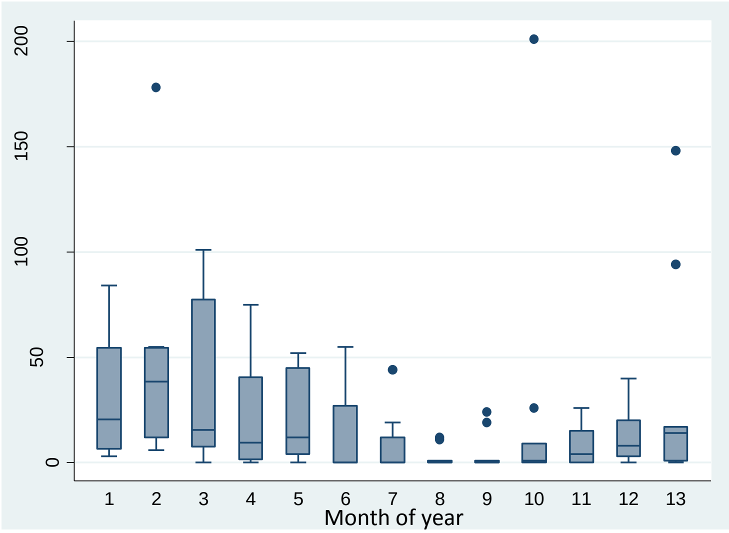


Figure 7: Incidence of dengue in Huanuco, Peru, 2002-2010. a) Monthly incident cases. b) Box plots of cases by month of year.

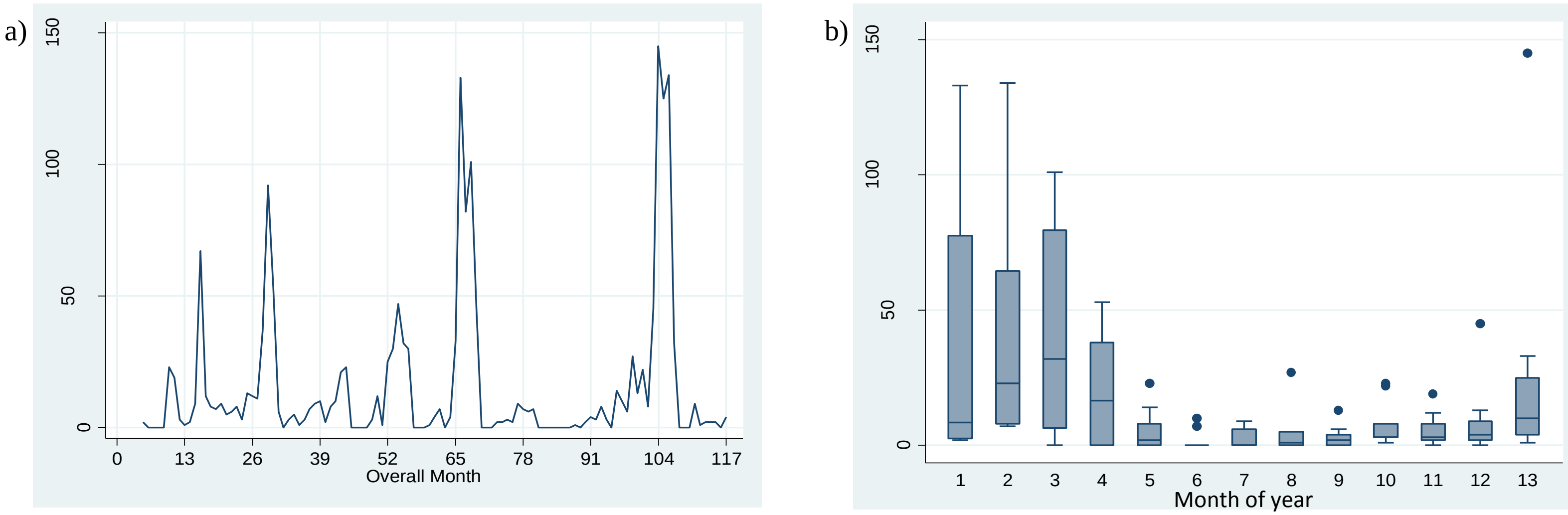


Figure 8: Incidence of dengue in Junin, Peru, 2002-2010. a) Monthly incident cases. b) Box plots of cases by month of year.

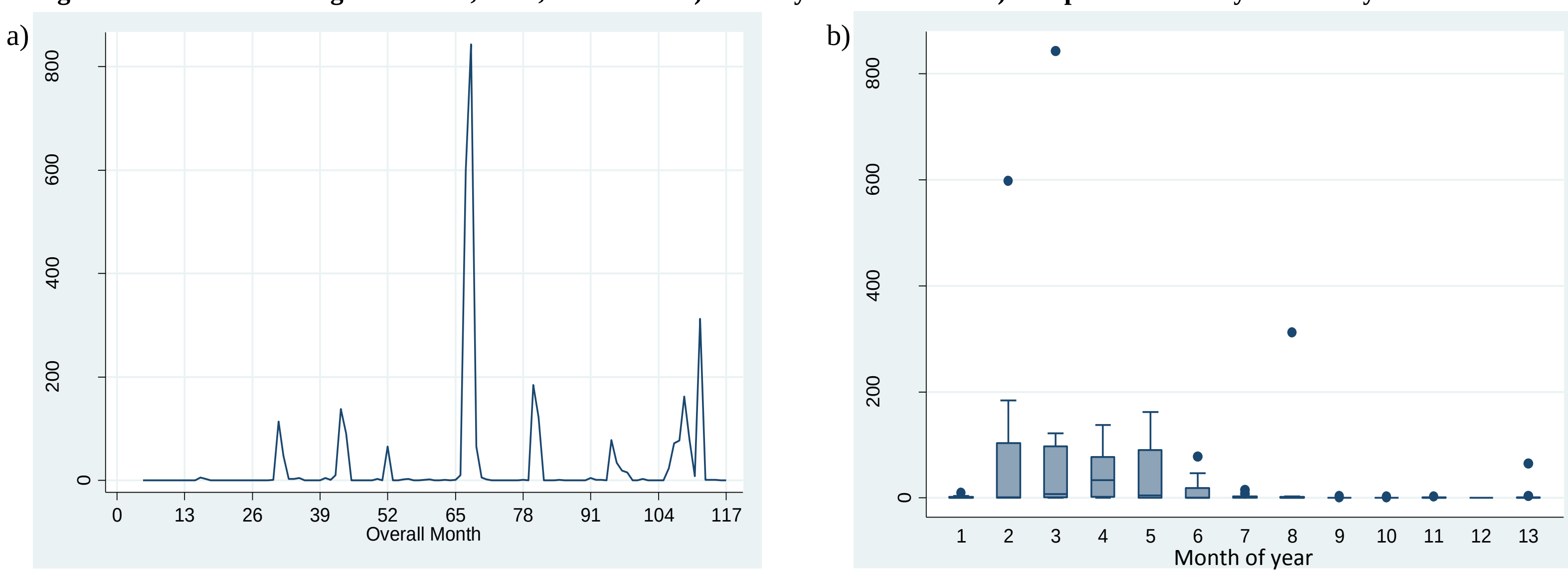


Figure 9: Incidence of dengue in La Libertad, Peru, 2002-2010. a) Monthly incident cases. b) Box plots of cases by month of year.

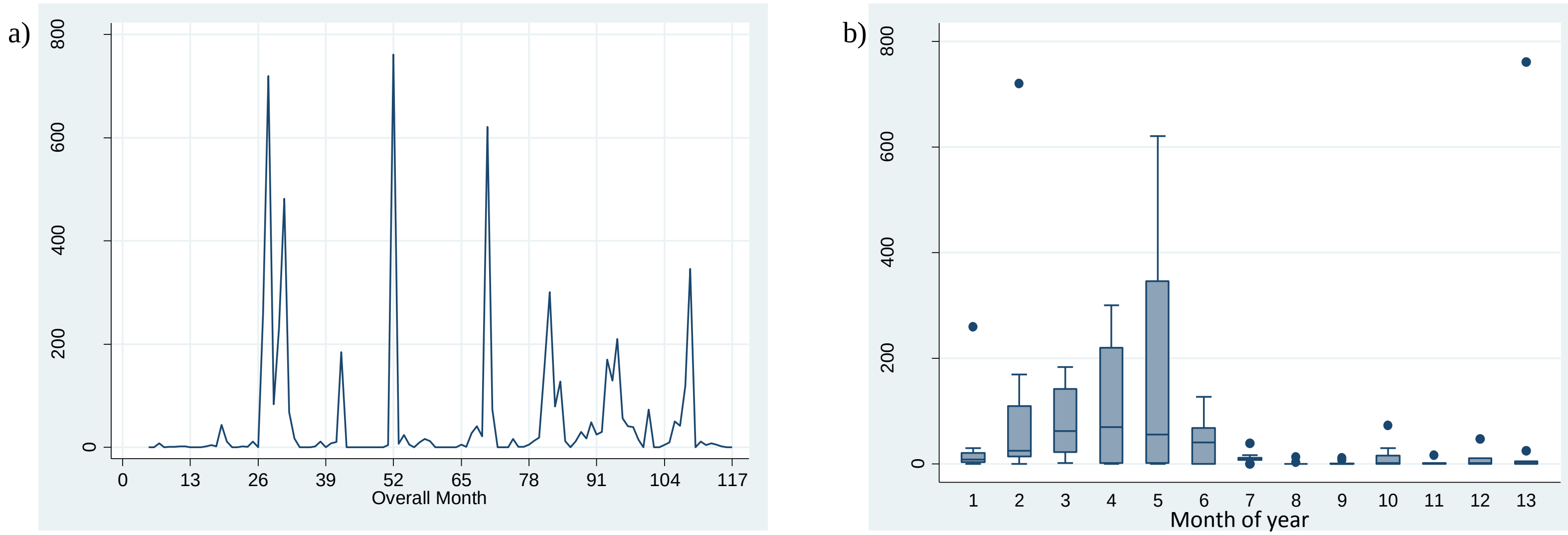


Figure 10: Incidence of dengue in Lambayeque, Peru, 2002-2010. a) Monthly incident cases. b) Box plots of cases by month of year.

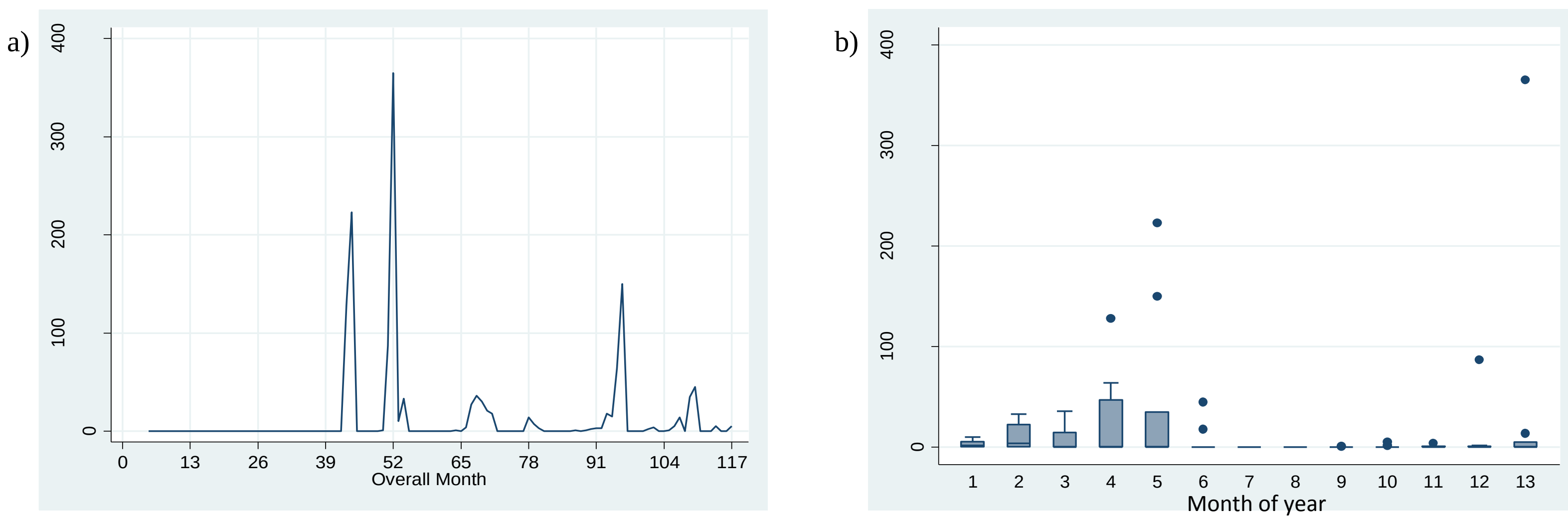
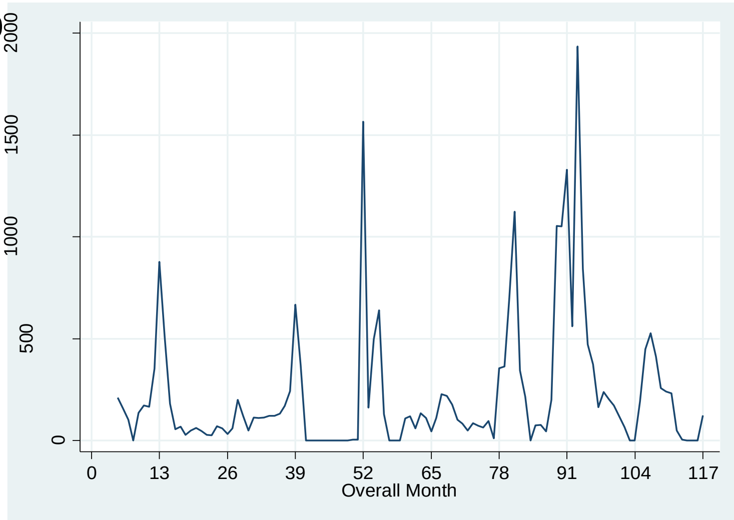


Figure 11: Incidence of dengue in Lima, Peru, 2002-2010. a) Monthly incident cases. b) Box plots of cases by month of year.

a)


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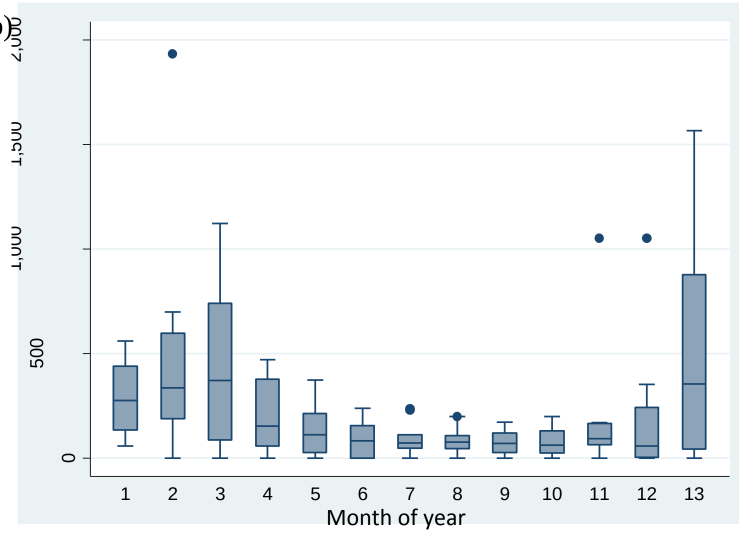
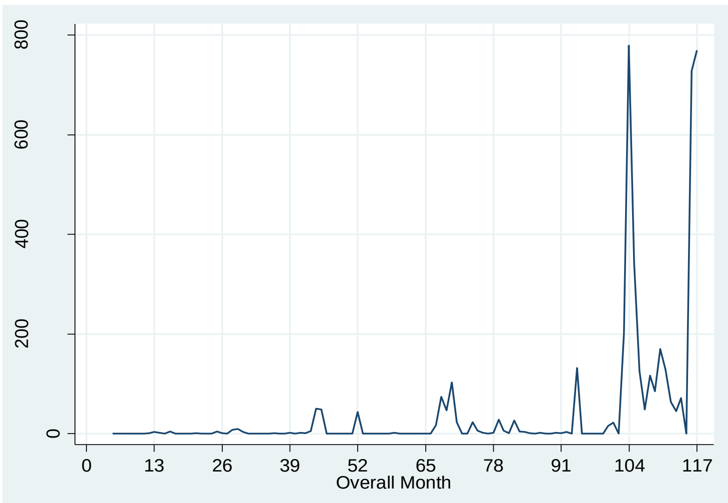


Figure 12: Incidence of dengue in Loreto, Peru, 2002-2010. a) Monthly incident cases. b) Box plots of cases by month of year.

a)


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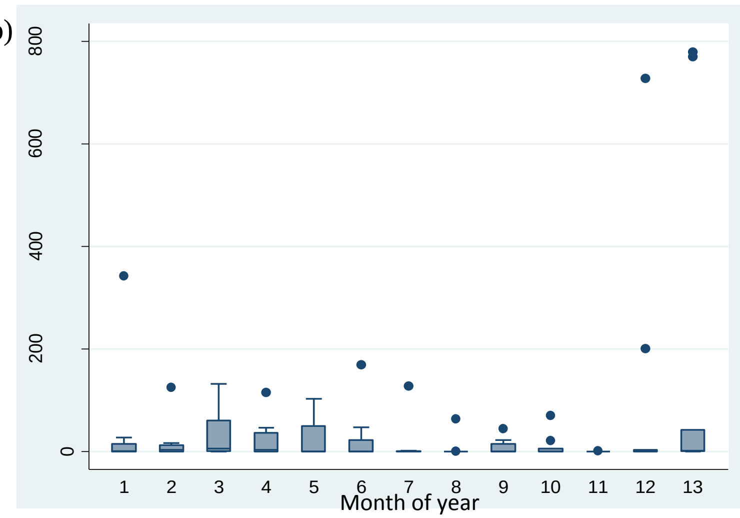


Figure 13: Incidence of dengue in Madre de Dios, Peru, 2002-2010. a) Monthly incident cases. b) Box plots of cases by month of year.

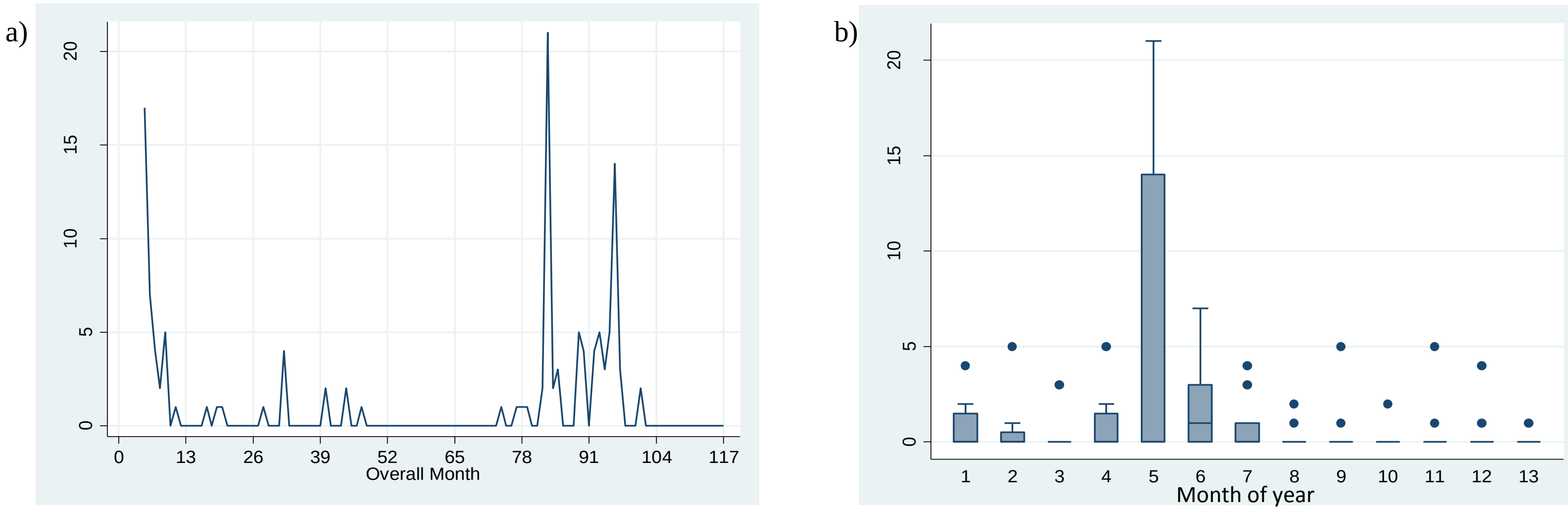


Figure 14: Incidence of dengue in Pasco, Peru, 2002-2010. a) Monthly incident cases. b) Box plots of cases by month of year.

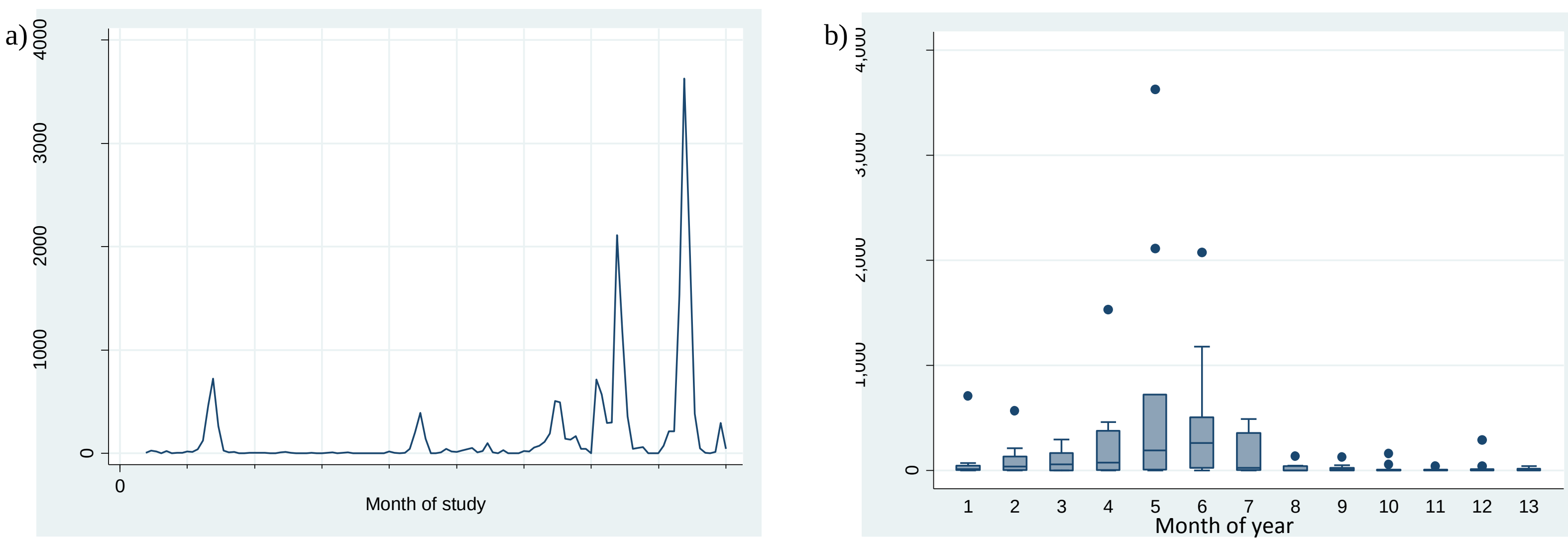


Figure 15: Incidence of dengue in Piura, Peru, 2002-2010. a) Monthly incident cases. b) Box plots of cases by month of year.

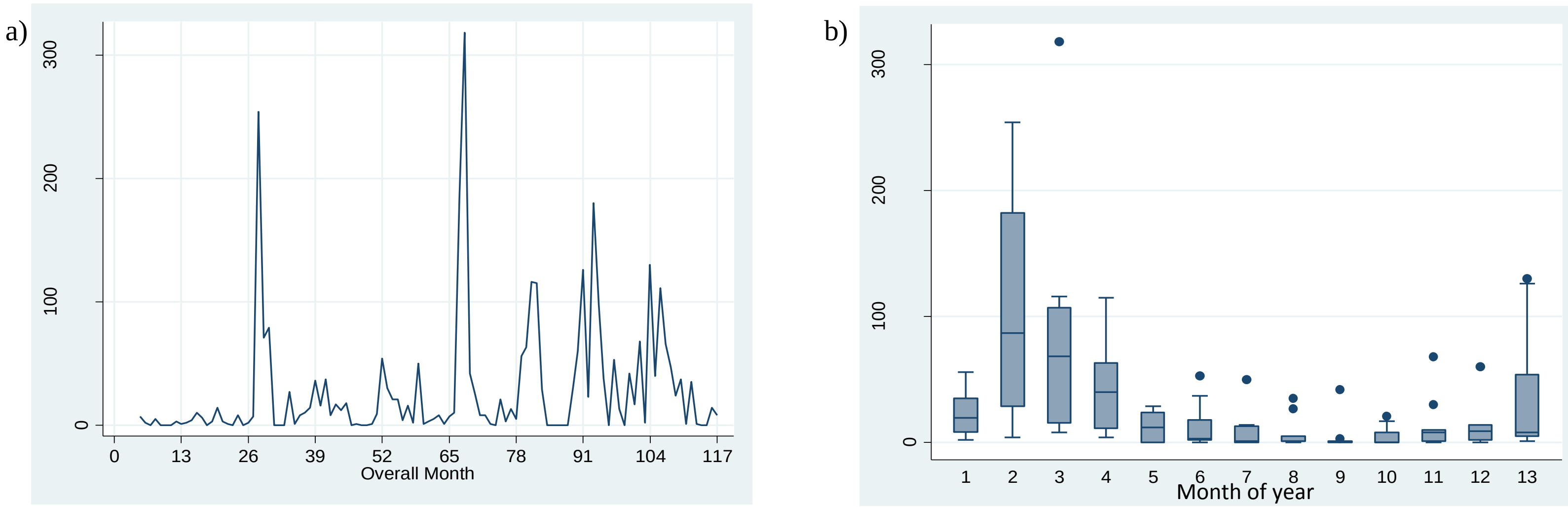


Figure 16: Incidence of dengue in San Martin, Peru, 2002-2010. a) Monthly incident cases. b) Box plots of cases by month of year.

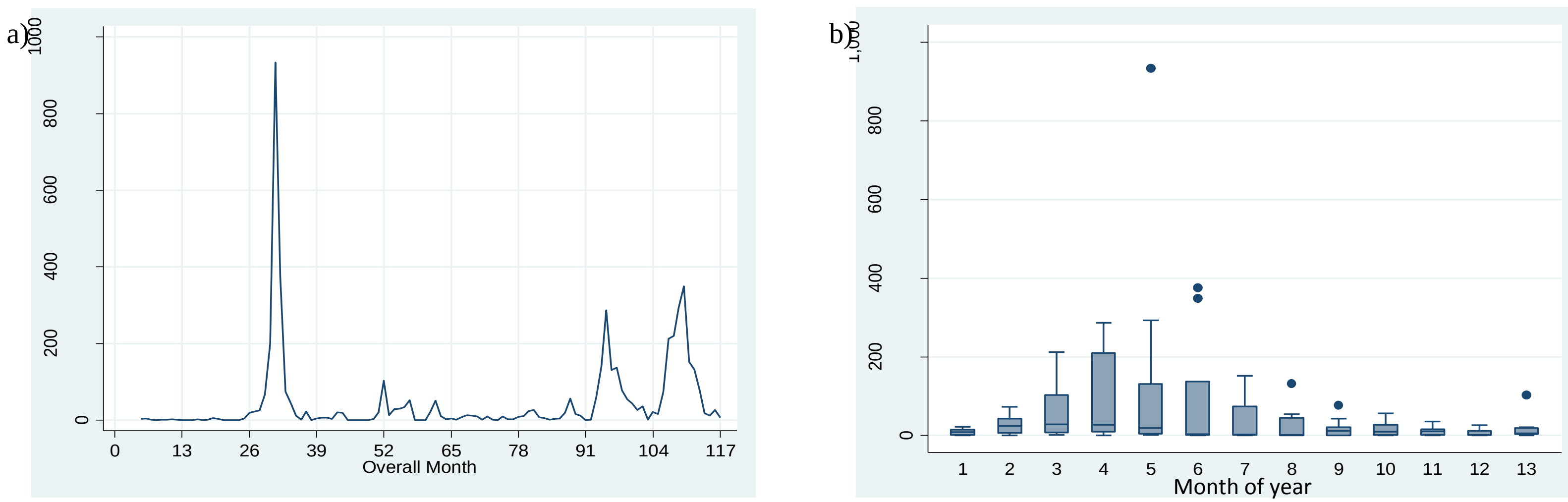
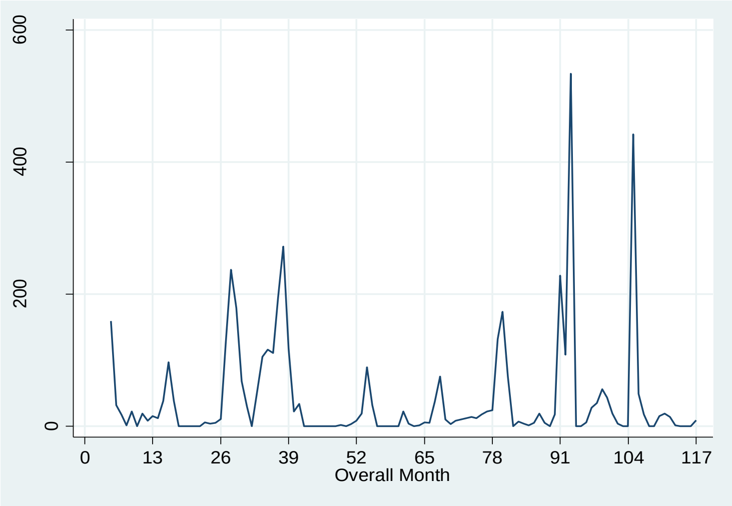


Figure 17: Incidence of dengue in Tumbes, Peru, 2002-2010. a) Monthly incident cases. b) Box plots of cases by month of year.

a)


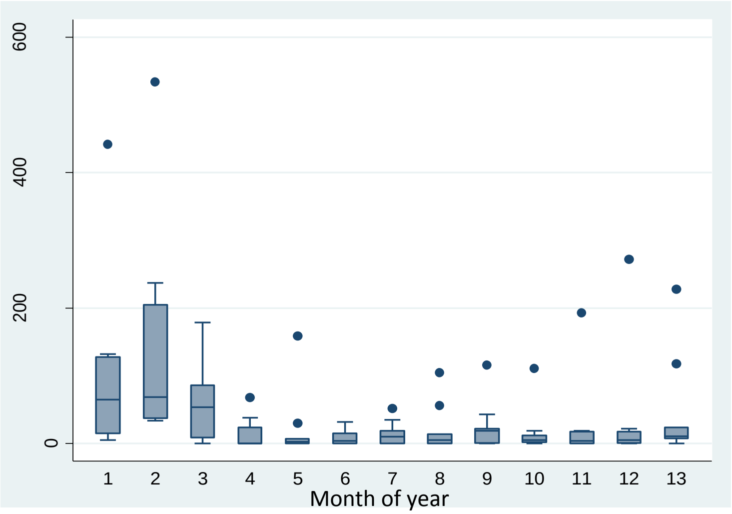
b)


Figure 18: Incidence of dengue in Ucayali, Peru, 2002-2010. a) Monthly incidence cases. b) Box plots of cases by month of year.

Loreto, Tumbes, Ucayali and Madre de Dios had the greatest incidence of dengue per 1000 people. These regions lie along Peru's eastern border in the jungle region (Loreto, Ucayali, and Madre de Dios) and along the northern coastal region (Tumbes), as pictured in Appendix 4. The incidence of dengue seems to be increasing over time in Madre de Dios and Piura and to a lesser extent in Loreto, but seems to be steadier in Ucayali and Tumbes. Among the regions with dengue, the incidence is lowest in Ancash, Huanuco, Pasco and Junin. These regions also lie near each other in the southwest region of Peru, mostly in the mountains, except Ancash, which lies on the coast. Many of the regions saw a noticeable spike in cases at the end of 2005 and at the beginning of 2004 and 2009.

According to the Portmanteau Q statistic there was significant autocorrelation at a lag of one month in every region but Cajamarca (Table 5). In some regions, there was significant autocorrelation at longer lags, suggesting that longer seasonal or yearly cycles exist. For example, there was significant autocorrelation at 7 and 8 month lags in Ancash and 13 and 14 month lags in Madre de Dios, Piura, San Martin and Ucayali. It is obvious from the time series graphs in Figure 4 - Figure 18 that there is a disease cycle that is about one year, or 13 months in this data set.

4.2 Models

The optimal lag times and the corresponding correlation coefficients for each region are pictured below (Figure 19). There seems to be a pattern in the optimum lag times across the country. The regions along the coast of Peru have shorter lag times of zero or one month and the regions farther inland have longer lag times. All of the negative correlations are also at longer lag times and do not occur in the regions on the coast, except for Lima. Strangely, Madre de Dios is surrounded by regions that have a negative correlation coefficient, and while its optimum lag time is five months just like its neighbours, its correlation coefficient is positive.

Table 5. Lags in months at which the autocorrelation of dengue cases was significantly different from zero.

Region	Lags at which there was significant autocorrelation
Amazonas	1
Ancash	1, 7, 8
Cajamarca	None
Huanuco	1, 16
Junin	1, 2
La Libertad	1
Lambayeque	1, 24
Loreto	1, 2
Madre de Dios	1, 13, 14
Pasco	1
Piura	1, 4, 14
San Martin	1, 14
Tumbes	1, 2
Ucayali	1, 13

The descriptive statistics show that there is a large amount of variation in dengue incidence from year to year; therefore, an indicator variable for year was included in the model with the reference category being 2002, the first year of the study. This is similar to a trend term, but it does not assume that the increase or decrease in dengue over the study period is linear. There was also obvious seasonality in both the dependent variable and SST, so tests were performed to determine if controlling for seasonality improved the model. Seasonality was modelled in two ways: by including an indicator variable for season or by including sine and cosine terms. Using an indicator variable for season assigns one category as the reference category (in this case month 1 of the year) and the coefficients for the other categories can be transformed into risk ratios relative to that indicator. In this study the years were made up of thirteen epidemiological months, so adding a monthly indicator added 13 terms to the model. Including sine and cosine terms added only two terms, resulting in a more parsimonious model.

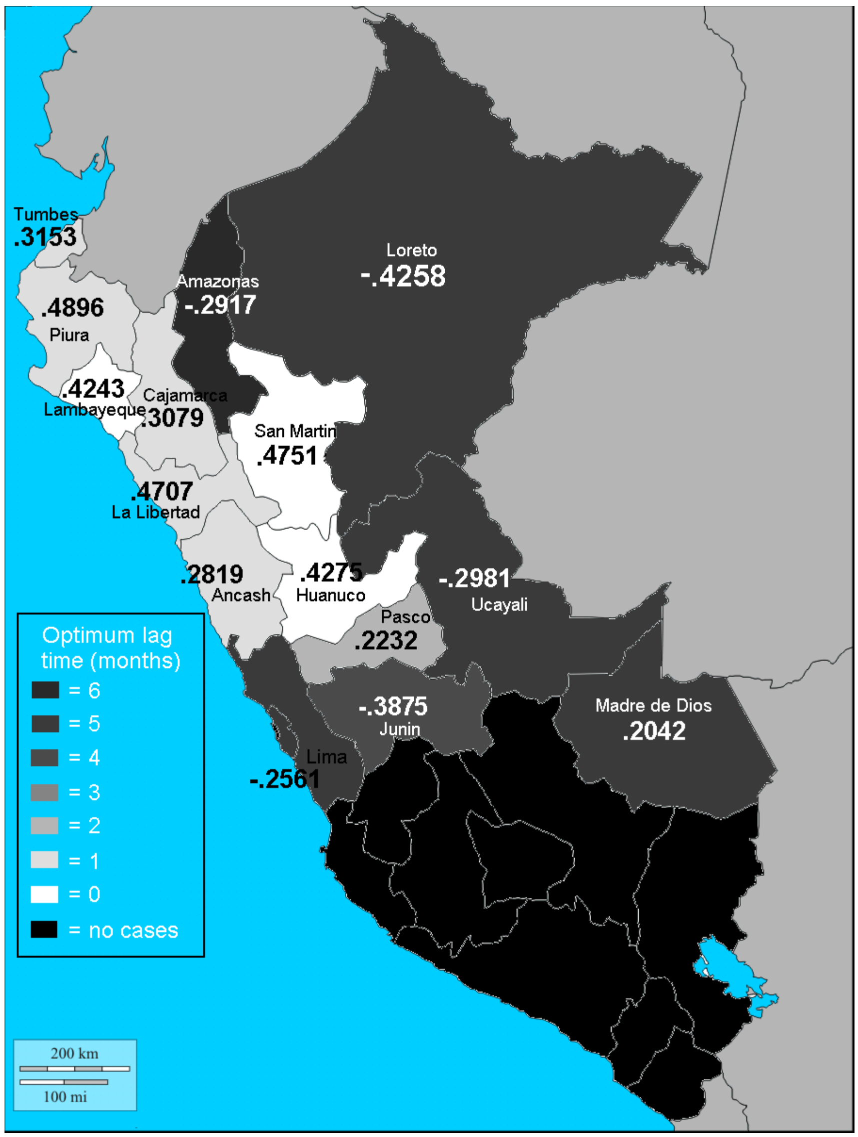


Figure 19: Map of correlation coefficients and optimum lag between cases and sea surface temperature for each region of Peru.

In order to model dengue incidence as influence by SST the disease data was first log transformed and an ARIMA model was applied. Unfortunately

ARIMA models (and variations of it, including SARIMA) are most appropriate for normal data. When an ARIMA model was fitted to the log transformed incidence data the residuals were not normally distributed, so the models were considered inappropriate for this dataset. Then, Poisson models were fit to the data as they are more appropriate for count data, but it was evident that the data was over-dispersed, so negative binomial models were considered more appropriate. A GEE model was then compared to the negative binomial model in order to examine the effect of accounting for the autocorrelation of dengue on the estimated coefficients and the results were nearly identical to those obtained using the negative binomial model and were still significant (Table 6). Since there was no difference between the results of the negative binomial model and the GEE the negative binomial model is presented here since it is the simpler of the two because it does not account for the correlation structure.

Table 6. The results of the negative binomial model and the generalized estimating equation for sea surface temperature, controlling for inter-annual variation in dengue incidence by including an indicator term for year.

	Negative binomial model with i.year and lagged SST	GEE with negative binomial distribution, i.year, lagged SST and AR(1) correlation structure
Region	IRR_{SST} (95% CI)	IRR_{SST} (95% CI)
Amazonas	0.841 (0.748,0 .945)	0.842 (0.769, 0.922)
Ancash	1.434 (1.177, 1.747)	1.443 (1.278, 1.630)
Cajamarca	1.195 (1.032, 1.385)	1.198 (1.086, 1.321)
Huanuco	1.590 (1.333, 1.896)	1.517 (1.344, 1.712)
Junin	0.639 (0.547, 0.746)	0.662 (0.582, 0.754)
La Libertad	2.198 (1.639, 2.946)	2.068 (1.859, 2.301)
Lambayeque	1.609 (1.325, 1.954)	1.603 (1.459, 1.760)
Lima	did not converge	did not converge
Loreto	0.733 (0.648, 0.828)	0.745 (0.673, 0.826)
Madre de Dios	1.297 (1.04, 1.618)	1.248 (1.115, 1.396)
Pasco	1.338 (1.151, 1.555)	1.363 (1.156, 1.606)
Piura	1.490 (1.297, 1.712)	1.489 (1.349, 1.643)
San Martin	1.373 (1.222, 1.543)	1.372 (1.254, 1.503)
Tumbes	1.226 (1.087, 1.382)	1.285 (1.148, 1.439)
Ucayali	0.689 (0.601, 0.790)	0.702 (0.636, 0.775)

When the negative binomial models were examined, the AIC did not differ between the models that accounted for seasonality as monthly indicator terms and those that accounted for it by using sine and cosine terms, but the BIC was lower when sine and cosine were used. The AIC and BIC were lowest (indicating the best fitting model) for the negative binomial model for each region that did not account for seasonality, as seen in Table 7. The best model for each region included SST at the optimum lag and an indicator term for year as follows:

$$cases(t) \sim Negative\ Binomial(\mu_t, k)$$

$$\log(\mu_t) = \log(population_t) + \beta_0 + \beta_{SST} SST_{t-lag} + \sum_{i=2002}^{2010} \beta_i\, year_i$$

The coefficients for SST from each region's best model are shown in Table 8. The accompanying incidence rate ratios (IRRs) show the estimated rate ratios, or expected percentage change in dengue, for an increase of 1^{o}C in SST at the optimum lag. The magnitude of the expected change varies between regions.

In Junin the incidence rate of dengue would be expected to decrease by a factor of .64 if SST increased by 1^{o}C. On the other extreme, the incidence rate of dengue in La Libertad would be expected to be 2.2 times greater after a 1^{o}C increase in SST. In regions where incidence was expected to decrease, the percentage decreases were between 37 and 15%. The range of factors of expected increases was much wider, between 19.5% and about 120%. The model for Lima did not converge; this might be due to the large amount of variation in the data –

there were many weeks when zero cases were reported and a small number of weeks with a high number of cases.

The coefficients for the year indicators relative to 2002 are graphed by region in Appendix 5. After adjusting for sea surface temperature, dengue incidence decreased in 2003 relative to 2002 in the majority of provinces, but increased in La Libertad, Lambayeque, San Martin, Tumbes, Madre de Dios and Junin. In 2004 dengue incidence increased from 2003 in all of the regions. For the most part there were increases again in 2005 and then the incidence decreased in 2006. Dengue incidence increased again in 2007 before falling in 2008 and rising again after. All of the regions follow a similar general pattern with regards to their coefficients for year.

4.3 Residual analysis

If the models are well fitted to the data there should not be patterns or remaining autocorrelation in the residuals. In order to evaluate the autocorrelation, the residuals were graphed against time, the covariates in the model, and the outcome and the Q statistics of the residual series were examined. It appeared that there were patterns present in the residuals. Residuals around the same times appeared clustered when they should have been random. There was also significant autocorrelation in the residuals in some regions, (Table 9), meaning that the assumption that the observations are independent over the study period does not hold in all of the regions. The long lag time at which there is significant autocorrelation suggests that there might be multiyear cycles involved in dengue incidence that have not been accounted for in this analysis.

Table 7. **The AIC/BIC for each negative binomial model. The lowest scores indicate the best fitting model.***

Region	Optimum lag time	NB model with i.year, sine, cos, with SST	NB model with i.year, sin, cos, without SST	NB model with i.month, i.year, with SST	NB model without seasonality, with i.year, with SST	NB model with i.month, with i.year, without SST
Amazonas	6	7.88/-344.19	7.87/-348.91	7.94/-296.56	7.87/-353.77	7.94/-301.23
Ancash	1	3.08/-396.52	3.14/-402.33	3.0/-358.9	3.09/-406.13	3.08/-361.09
Cajamarca	1	8.37/-344.76	8.37/-349.37	8.35/-298.28	8.42/-353.48	8.33/-302.95
Huanuco	0	6.85/-356.62	6.86/-361.67	6.97/-308.64	6.99/-364.75	6.99/-313.58
Junin	4	6.47/-352.44	6.46/-357.66	6.50/-306.84	6.63/-363.08	6.52/-312.01
La Libertad	1	4.75/-390.08	4.74/-394.55	did not converge	4.72/-399.93	4.73/-350.38
Lambayeque	0	7.6/-354.69	7.58/-359.36	7.61/-308.29	7.62/-363.78	7.59/-313.03
Lima	5	did not converge				3.53/-371.94
Loreto	5	12.03/-339.7	12.01/-344.43	12.12/-292.61	12.03/-349.14	12.11/-297.33
Madre de Dios	0	5.44/-376.38	5.43/-381.32	5.47/-329.58	5.49/-386.85	5.45/-334.34
Pasco	2	2.1/-404.63	2.09/-411.55	2.16/-349.92	2.07/-415.04	2.14/-355.33
Piura	1	9.81/-345.14	9.17/-349.85	9.21/-299.78	9.23/-354.59	9.2/-304.34
San Martin	0	7.62/-346.41	7.60/-351.11	7.70/-299.81	7.66/-356.2	7.68/-304.47
Tumbes	1	7.91/-347.38	7.92/-352.01	7.93/-301.99	7.88/-356.62	7.91/-306.73
Ucayali	5	7.94/-349.63	7.92/-354.38	7.93/-302.80	7.98/-359.06	7.93/-307.15

*i.year and i.month refer to the indicator variables representing each month and year respectively. Sine and cos refer to the sine and cosine terms representing seasonality.

Table 8. The results from the multivariate negative binomial regression of seas sea surface temperature on the incidence of dengue by region of Peru, controlling for inter-year variability from 2002-2010.

Region	β_{SST}	**S.E. (β_{SST})**	**95% CI (β_{SST})**	**IRR(SST)**
Amazonas	-0.174	0.060	-0.291, -0.056	0.841
Ancash	0.360	0.101	.163, .558	1.434
Cajamarca	0.178	0.075	.0311,.326	1.195
Huanuco	0.464	0.090	.288, .640	1.590
Junin	-0.448	0.079	-0.603, -0.293	0.639
La Libertad	0.787	0.150	.494, 1.081	2.198
Lambayeque	0.476	0.099	.281, .670	1.609
Lima		did not converge		
Loreto	-0.311	0.063	-0.434, -0.189	0.733
Madre de Dios	0.260	0.113	.039, .481	1.297
Pasco	0.291	0.077	.141, .441	1.338
Piura	0.399	0.071	.26, .538	1.49
San Martin	0.317	0.059	.200, .433	1.373
Tumbes	0.176	0.064	.050, .301	1.226
Ucayali	-0.372	0.070	-0.509, -0.236	0.689

Table 9. Lags in months at which the autocorrelation of the residuals from the negative binomial model were significantly different from zero.

Region	**Lags at which there was significant autocorrelation**
Amazonas	None
Ancash	36
Cajamarca	None
Huanuco	1
Junin	1
La Libertad	28
Lambayeque	None
Lima	NA
Loreto	28
Madre de Dios	None
Pasco	10, 12
Piura	None
San Martin	3, 5
Tumbes	26
Ucayali	3

Chapter 5: Discussion

5.1 What do these findings mean?

This study appears to be the first to address the relationship between climate and dengue in Peru through regression. The results of this study indicate that there is a significant relationship between lagged SST and dengue across Peru. These findings agree with the findings of other, similar studies completed around the world in that the relationship is not consistently positive or negative even within countries. The scale of this study is similar to that of the studies completed in Indonesia[49] and Thailand[43-44] in that it examined the relationship between ENSO and dengue in smaller regions across a country. In these other studies, it was evident that the optimum lag time for both temperature and ENSO varied on a smaller scale within Thailand and Indonesia[43-44,49]. This relationship also varies between regions with regard to the direction of the relationship. The results in both studies are similar, with the optimum lag time for the relationship between ENSO (as measured by SST) and dengue cases varying between 0 and 6 months and the correlation being positive in some areas and negative in others.

The variation in the relationship between climate and dengue within Peru, as well as Indonesia and Thailand, may be related to the differing environments across geographic regions within the country. The effects of temperature and ENSO cycles may interact with the ecological characteristics of an area on a surprisingly small scale. This is probably related to the interaction of climatic fluctuations with the existing environmental conditions across regions. For example, if there is an increase in standing water that can serve as a habitat for mosquito larva, decreased precipitation levels due to ENSO can dry up the water and make the habitat unsuitable. If there is flowing water present lower precipitation levels might dry up the source enough to create standing water, creating more places for mosquitoes to breed. The complex relationship of multiple climate factors that are related to ENSO, (including, precipitation and temperature) might explain the great variation in results.

Understanding the correlation between this disease and variables like SST may help in predicting how dengue incidence might change with fluctuating climate in the future[35]. Regions with endemic dengue, like, Peru will be especially susceptible to future shifts in climate, as it and other countries at temperate latitudes are predicted to bear the brunt of the effects of global warming[70]. In the future, if global warming continues as anticipated, the results of this analysis suggest that dengue will be impacted in Peru; in most areas, the incidence will increase, but in some areas will decrease. If climate change continues, dengue may spread to the southern regions of Peru as new geographic areas become suitable for transmission. Overall, public health programs will have to adjust to changing patterns in this potentially fatal disease. The 95% confidence intervals for the incidence rate ratios for SST in each province cover a range of changes in dengue incidence that are of interest to public health officials. The intervals include an increase of only a few percentage points in Cajamarca and Madre de Dios, but the upper limits include an increase in risk of over a third. In areas where health resources are scarce, an increase in dengue cases of even a small percentage may have a large impact on health services.

Models that can incorporate climate variables like SST may be used to predict outbreaks and allow local governments to prepare vector control measures or to fortify public health centers that may have an influx of dengue patients.

Although the direction of the relationship and the lag time between SST and dengue varies across Peru, the relationship was significant in every region except Lima, where the regression model did not converge. The correlation coefficient was generally highest in the northern regions and lower in the more southern areas of Peru. The lag times were also shorter on the coast and longer inland. Considering that Peru is home to a variety of ecosystems, it is surprising that the results are so consistently significant across all of them. There are some trends across Peru that may help to guide further research about how and why this relationship varies.

5.2 Limitations

Data

Using an administrative data set poses many challenges for analysis. The quality of dengue surveillance data may vary across Peru and it is difficult to judge the completeness of this type of dataset. However, the risk of this issue producing bias towards significance in the results is low since it is unlikely that accuracy of reporting is related to SST[31]. Also, the reporting of dengue incidence might not be timely, and there is also no way of knowing when the cases that were reported actually occurred. If a case is reported after the deadline for that week's epidemiological bulletin it will not be reported until the next week. There is also the possibility that the clinics that diagnose the patients do not report each individual case to the Ministry of Health immediately. A lag was incorporated into the analysis to help account the time lapse between onset of a dengue case and reporting, but this lapse is not necessarily constant over time even within the same region. Using the date of dengue onset rather than the date of reporting might improve the results of this analysis by indicating a more exact lag time, but surveillance data does not usually include this information and determining the date of onset for each reported case would be resource intensive and difficult.

Dengue is typically an underreported disease[2]. This might be due to the fact that people who are infected with dengue may not even visit a doctor since symptoms can be mild and flu-like. However, it is unlikely that rates of underreporting are related to climate or time, therefore the risk of bias is minimal. In any case, if a patient presents at a hospital or clinic there is no guarantee that the case will be accurately diagnosed since serological testing for dengue is not the norm in many places in Peru. So some patients may be misdiagnosed, but there are also many people who never see a doctor at all when they are infected with dengue, so cases that are incorrectly identified probably do not significantly affect the results. It was not possible to determine if the cases reported by each region originated in that region, but, it is unlikely that the number of imported cases was so large that it would have a dramatic impact on the results of the regression.

Methods

Various regression methods were used to model the data. The nature of the data made finding an appropriate model difficult. There are many different methods that are used for analyzing time series data. The major issue in this analysis was that the dengue dataset contained a large number of zeros. First adding .001 to the incidence each week and taking the natural log of the incidence was attempted in order to obtain a normal distribution. Because of the large number of weeks with zero cases the histogram of the data was still not normal even after this transformation. For this same reason the mean number of monthly cases was quite low and the count data could not be approximated by a normal distribution.

The incidence of an infectious disease during one period is highly related to the incidence in previous time periods, resulting in autocorrelation that needs to be accounted for in the analysis. Not accounting for this issue should not affect the magnitude of the estimated regression coefficients, but the estimated standard errors will be biased, leading to incorrect conclusions that SST is a significant predictor of dengue cases[31,71]. In this preliminary analysis the final negative binomial model that was reported did not account for the autocorrelation of the disease series. In this case, the results were the same in the GEE and the simpler negative binomial model, suggesting that autocorrelation does not meaningfully affect estimates of the relationship between SST and dengue or their significance.

5.3 Future Research

The models used in this study can be improved upon in various ways. Most studies that examine the relationship between ENSO as measured by SST or other indices also included local scale weather variables such as temperature, precipitation, relative humidity and vapor pressure. Additional weather variables were not included in the models here because local weather is highly correlated with SST and therefore adding these variables might result in collinearity. However, investigating local temperatures and precipitation could lead to better predictive models and more information about the climatological processes that affect mosquitoes and dengue. It might also be useful to examine interactions between local conditions, both climatic and environmental, with SST. For example, local land use and land cover might be one of the factors that account for the differences that were seen between regions. Obtaining detailed land cover data such as annual measures might be useful over a longer study period (since land cover data is unlikely to change drastically from year to year).

In coming years, it is unlikely that the climatic conditions are the only thing that will change in Peru and other places affected by dengue. Dengue outbreaks are not caused by climate alone. There must be infected humans present in order to infect new mosquitoes, the environment must remain appropriate for the virus itself to survive and replicate, and susceptible people must be exposed to mosquitoes.[72] In addition, mosquito control programs have eradicated dengue in the past and it is likely that new programs could affect the number of mosquitoes present in Peru as well as people's exposure to them. There is a myriad of other factors that will determine dengue incidence in Peru including not just environmental factors but demographics as well[73]. Population growth could result in higher population density throughout Peru, making it easier for dengue transmission to be maintained. An influx of people to cities will not only increase population density but may result in new breeding grounds for mosquitoes, especially *Aedes aegypti,* which prefer urban areas[73]. Other researchers have also theorized that the multi-annual cycle that dengue incidence seems to follow might also be due to factors such as the temporary immunity to one strain of dengue induced by infection by another[74]. It will be important to consider incorporating these and other covariates into the analysis of SST and dengue as it may help to improve the ability of models to predict dengue outbreaks and focus control efforts at vulnerable areas and populations.

It is clear from the literature review and this analysis that the relationship between climate and dengue is best described on a less- than- global scale since the effects of ENSO and climate change vary greatly between regions. Understanding the relationships between ENSO, climate and dengue on a small scale, within countries if possible, might be a valuable part of dengue prevention programs in the future. The models presented here could be developed into predictive models that could provide insight to the future of dengue under various climate change scenarios as well as being useful as early warning systems for public health officials. Considering the significant relationships that appear to exist in other regions, similar models might be effective around the globe, which could prove useful as an increasing proportion of the global population will be at risk of dengue infection as climate changes in the future.

References

1. World Health Organization. Neglected tropical diseases, hidden successes, emerging opportunities. Geneva: WHO Press, 2009.
2. World Health Organization. Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control. Geneva: WHO Press, 2009.
3. Chinga-Alayo E, Huarcaya E, Nasarre C, del Aguila R, A L-C. The influence of climate on the epidemiology of bartonellosis in Ancash, Peru. Transactions of the Royal Society of Tropical Medicine and Hygiene 2004;98(2):116-124.
4. Corwin AL, Larasati RP, Bangs MJ, Wuryadi S, Arjoso S, Sukri N, Listyaningsih E, Hartati S, Namursa R, Anwar Z, Chandra S, Loho B, Ahmad H, Campbell JR, P K. Epidemic dengue transmission in southern Sumatra, Indonesia. Transactions of the Royal Society of Tropical Medicine and Hygiene 2001;95(3):257-265.
5. Chaves LF, Pascual M. Climate Cycles and Forecasts of Cutaneous Leishmaniasis, a Nonstationary Vector-Borne Disease. PLoS Medicine 2006;3(8):e295. doi:10.1371/journal.pmed.0030295.
6. ICTV. Virus taxonomy: classification and nomenclature of viruses. In: C.M. Fauquet MAM, J. Maniloff, J. Desselberger, L.A. Ball, ed. San Diego: Elsevier Academic Press, 2005.
7. Gubler DJ. Dengue/Dengue Haemorrhagic Fever: History and Current Status. New Treatment Strategies for Dengue and Other Flaviviral Diseases John Wiley & Sons, Ltd, 2008.
8. World Health Organization (WHO). Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control. Geneva: WHO Press, 2009.
9. Chadee DD, Shivnauth B, Rawlins SC, Chen AA. Climate, mosquito indices and the epidemiology of dengue fever in Trinidad (2002-2004). Annals of Tropical Medicine & Parasitology 2007;101(1):69-77.
10. World Health Organization (WHO). Dengue. International Travel and Health. Geneva: WHO Press, 2011;63-64.
11. Ross TM. Dengue Virus. Clinics in Laboratory Medicine 2010;30(1):149-160.
12. Gubler DJ. Aedes aegypti and Aedes aegypti-borne disease control in the 1990s: top down or bottom up. American Journal of Tropical Medicine and Hygiene 1989;40:571-578.
13. Newton EAC, Reiter P. A Model of the Transmission of Dengue Fever with an Evaluation of the Impact of Ultra-Low Volume (ULV) Insecticide Applications on Dengue Epidemics. American Journal of Tropical Medicine and Hygiene 1992;47(6):709-720.
14. World Health Organization (WHO). Strengthening implementation of the global strategy for dengue fever/dengue hemorrhagic fever prevention and control. Report of the Informal Consultation. Geneva, 2000.
15. Pinheiro FP, Corber SJ. Global situation of dengue and dengue hemorhaggic fever, and its emergence in the Americas. World Health Statistics Quarterly 1997;50(3-4):161-169.

16. Pinheiro FP. Dengue in the Americas. 1980-1987. Epidemiological Bulletin 1989;10(1):1-8.
17. Torres JR, Castro J. The health and economic impact of dengue in Latin America. Cadernos de Saúde Pública 2007;23(Suppl 1):S23-S31.
18. Montoya Y, Holechek S, Caceres O, Palacios A, Burans J, Guevara C, Quintana F, Herrera V, Pozoy E, Anaya E, Mamani E, Gutierrez V, Guevara ALd, Fernandez E, Asmat P, Alva-Davalos V, Hoguin C, Laguna VA, Morales AM, Minaya P, Kochel T. Circulation of Dengue Viruses in North-Western Peru, 2000-2001. Dengue Bulletin 2003;27:52-62.
19. Forshey BM, Laguna-Torres VA, Vilcarromero S, Bazan I, Rocha C, Morrison AC, Stoddard ST, Alegre Y, Gomez J, Scott TW, Kochel TJ. Epidemiology of influenza-like illness in the Amazon Basin of Peru, 2008–2009. Influenza and Other Respiratory Viruses 2010;4(4):235-243.
20. Gubler D.J., Reiter P., Ebi K., Yap W., Nasci R., J P. Climate variability and change in the United States: potential impacts on vector- and rodent-borne diseases. Environmental Health Perspectives 2001;109(Suppl. 2):223-233.
21. Epstein PR, Diaz HF, Elias S, Grabherr G, Graham NE, Martens WJM, Mosley-Thompson E, Susskind J. Biological and Physical Signs of Climate Change: Focus on Mosquito-borne Diseases. Bulletin of the American Meteorological Society 1998;9(3):409-417.
22. Yasuno M, Pant C. Seasonal changes in biting and larval infestation rates of Aedes aegypti in Bangkok, Thailand in 1969. Bulletin of the World Health Organization 1970; 43:319-325.
23. W. Reed., Carroll J., A. A. Experimental Yellow Fever. Mil. Med 2001;166(Suppl. 9):55-60.
24. Watts DM BD, Harrison BA, Whitmire RE, Nisalak A,. Effect of Temperature on the Vector Efficiency of Aedes aegypti for Dengue 2 Virus. American Journal of Tropical Medicine and Hygiene 1987;36(1):143-152.
25. Johansson MA, Cummings DAT, Glass GE. Multiyear Climate Variability and Dengue—El Niño Southern Oscillation, Weather, and Dengue Incidence in Puerto Rico, Mexico, and Thailand: A Longitudinal Data Analysis. PLoS Medicine 2009;6(11):e1000168.
26. Koopman JS, Prevots DR, Mann MAV, Dantes HG, Aquino MLZ, Longini IM, JS A. Determinants and Predictors of Dengue Infection in Mexico. American Journal of Epidemiology 1991;133(11):1168-1178.
27. Scott TW, Amerasinghe PH, Morrison AC, Lorenz LH, Clark GG, Strickman D, Kittayapong P, JD E. Longitudinal Studies of Aedes aegypti (Diptera: Culicidae) in Thailand and Puerto Rico: Blood Feeding Frequency. Journal of Medical Entomology 2000;37(1):89-101.
28. Bangs M, Larasati R, Corwin A, Wuryadi S. Climatic factors associated with epidemic dengue in Palembang, Indonesia: implications of short-term meteorological events on virus transmission. Southeast Asian Journal of Tropical Medicine and Health 2006;37(6):1103-1116.

29. Cazelles B, Chavez M, McMichael AJ, Hales S. Nonstationary Influence of El Niño on the Synchronous Dengue Epidemics in Thailand. PLoS Med 2005;2(4):e106. doi:10.1371/journal.pmed.0020106.
30. Gagnon AS, Bush ABG, Smoyer-Tomic KE. Dengue epidemics and the El Niño Southern Oscillation. Climate Research 2001;19:35-43.
31. Hales S, Weinstein P, Souares Y, Woodward A. El Niño and the dynamics of vectorborne disease transmission. Environmental Health Perspectives 1999;107(2):99-102.
32. Hales S, Weinstein P, Woodward A. Dengue fever epidemics in the South Pacific: driven by El Nino Southern Oscillation? Lancet 1996;348(9024):1664-1665.
33. Timmermann A, Oberhuber J, Bacher A, Esch M, Latif M, Roeckner E. Increased El Nino frequency in a climate model forced by future greenhouse warming. Nature 1999;398:694 - 697.
34. Solomon S, D. Qin, M. Manning, Z. Chen, M. Marquis, K.B. Averyt, M. Tignor, H.L. Miller, eds. Contribution of Working Group I to the Fourth Assessment Report of the Intergovernmental Panel on Climate Change. New York, NY: Cambridge University Press, 2007.
35. Ying Zhang, Peng Bi, Hiller JE. Climate Change and the Transmission of Vector-Borne Diseases: A Review. Asia-Pacific Journal of Public Health 2008;20(1):64-76.
36. Stern PC, Easterling WE. Making Climate Forecasts Matter. Panel on the Human Dimensions of Seasonal-to-Interannual Climate Variability National Research Council, 1999.
37. Kovats RS, Bouma MJ, Hajat S, Worrall E, Haines A. El Niño and health. The Lancet 2003;362(9394):1481-1489.
38. Graham NE. Simulation of Recent Global Temperature Trends. Science 1995;267(5198):666-671.
39. Diaz HF, Graham NE. Recent changes in tropical freezing heights and the role of sea surface temperature. Nature 1996;383(6596):152-155.
40. Trenberth KE, Caron JM, Stepaniak DP, Worley S. Evolution of El Niño–Southern Oscillation and global atmospheric surface temperatures. Journal of Geophysical Research 2002;107(D8):4065. doi:10.1029/2000JD000298.
41. Checkley W, Epstein LD, Gilman RH, Figueroa D, Cama RI, Patz JA, Black RE. Effects of EI Niño and ambient temperature on hospital admissions for diarrhoeal diseases in Peruvian children. The Lancet 2000;355(9202):442-450.
42. World Health Organization (WHO). The World Health Report. Geneva: WHO Press, 2002.
43. Tipayamongkholgul M, Fang C-T, Klinchan S, Liu C-M, King C-C. Effects of the El Nino-Southern Oscillation on dengue epidemics in Thailand, 1996-2005. BMC Public Health 2009;9(1):422. doi:10.1186/1471-2458-9-422.
44. Thammapalo S, Chongsuwiwatwong V, McNeil D, Geater A. The climatic factors influencing the occurrence of dengue hemorrhagic fever in

Thailand. Southeast Asian Journal of Tropical Medicine and Health 2005;36(1):191-196.
45. Nakhapakorn K, Tripathi NK. An information value based analysis of physical and climatic factors affecting dengue fever and dengue haemorrhagic fever incidence. International Journal of Health Geographics 2005;4(13). doi:10.1186/1476-072X-4-13.
46. Johansson MA, Dominici F, Glass GE. Local and Global Effects of Climate on Dengue Transmission in Puerto Rico. PLoS Neglected Tropical Diseases 2009;3(2):e382. doi:10.1371/journal.pntd.0000382.
47. Rifakis P, Gonçalves N, Omaña W, Manso M, Espidel A, Intingaro A, Hernández O, Rodríguez-Morales A. Asociacion entre las variaciones climaticas y los casos de Dengue en un Hospital de Caracas, Venezuela, 1998 – 2004 Revista Peruana de Medicina Experimental y Salud Publica 2005;22(3):183-190.
48. Sia Su G. Correlation of Climatic Factors and Dengue Incidence in Metro Manila, Philippines. AMBIO: A Journal of the Human Environment 2008;37(4):292-294.
49. Arcari P, Tapper N, Pfueller S. Regional variability in relationships between climate and dengue/DHF in Indonesia. Singapore Journal of Tropical Geography 2007;28:251-272.
50. Lu L, Lin H, Tian L, Yang W, Sun J, Liu Q. Time series analysis of dengue fever and weather in Guangzhou, China. BMC Public Health 2009;9:395. doi:10.1186/1471-2458-9-395.
51. Wu P-C, Guo H-R, Lung S-C, Lin C-Y, Su H-J. Weather as an effective predictor for occurrence of dengue fever in Taiwan. Acta Tropica 2007;103:50-57.
52. Wu P-C, Lay J-G, Guo H-R, Lin C-Y, Lung S-C, Su H-J. Higher temperature and urbanization affect the spatial patterns of dengue fever transmission in subtropical Taiwan. Science of the Total Environment 2009;407(7):2224-2233.
53. Brunkard JM, Cifuentes E, Rothenberg SJ. Assessing the the Roles of Temperature, Precipitation, and ENSO in Dengue Re-emergence on the Texas-Mexico Border Region. Salud Pública de México 2008;50(3):227-234.
54. Hurtado-Díaz M, Riojas-Rodríguez H, Rothenberg SJ, Gomez-Dantés H, Cifuentes E. Short communication: Impact of climate variability on the incidence of dengue in Mexico. Tropical Medicine & International Health 2007;12(11):1327-1337.
55. Hii YL, Rocklov J, Ng N, Tang CS, Pang FY, Sauerborn R. Climate variability and increase in intensity and magnitude of dengue incidence in Singapore. Global Health Action 2009;2(10). doi: 10.3402/gha.v2i0.2036.
56. Depradine CA, Lovell EH. Climatological variables and the incidence of Dengue fever in Barbados. International Journal of Environmental Health Research 2004;14(6):429-441.

57. Hales S, Weinstein P, Souares Y, Woodward A. El Nino and the dynamics of vectorborne disease transmission. Environmental Health Perspectives 1999;107(2):99-102.
58. Moore DS, McCabe GP, Craig BA. Nonparametric Tests. Introduction to the Practice of Statistics. New York, MY: W.H. Freeman and Company, 2009.
59. Hilbe J. Negative Binomial Regression. Cambridge: Cambridge University Press, 2007.
60. Wei WS. Time Series Analysis: Univariate and Multivariate Analysis. Redwood City, California: Addison-Wesley Publishing Company, 1994.
61. Torrence C, Compo GP. A Practical Guide to Wavelet Analysis. Bulletin of the American Meteorological Society 1999;79(1):61-78.
62. Laing A, Evans JL. Introduction to Tropical Meteorology Cooperative Program for Operational Meteorology, Education and Training, 2010.
63. Oficina General de Epidemiologia MdS. Boletine Epidemiologico. Lima, Peru: Oficina General de Epidemiologia, Ministerio de Salud, 2002-2010. http://www.dge.gob.pe/boletin.php Accessed January 10, 2011.
64. Chowell G, Torre CA, Munayco-Escate C, Suárez-Ognio L, López-Cruz R, Hyman JM, C. C-C. Spatial and temporal dynamics of dengue fever in Peru: 1994-2006. Epidemiology and Infection 2008;136(12):1667-1677.
65. Ministerio de Salud - Oficina General de Epidemiología. Etapas de la vigilancia epidemiológica. Vol. 2011. Lima, Peru, 2010.
66. More LB, Alban FC, Champe RC, Anticona CM. Dengue y dengue hemorrágico. Protocolos de vigilancia epidemiológica - Parte I. Lima, Peru: Oficina General de Epidemiología - Ministerio de Salud, 2005.
67. World Health Organization Department of Communicable Disease SaR. WHO Recommended Surveillance Standards. 2 ed, 1999.
68. National Oceanic and Atmospheric Administration (NOAA). National Weather Service Climate Prediction Center - Atmospheric and SST Indices. 2011. http://www.cpc.ncep.noaa.gov/data/indices/ Accessed January 11, 2011.
69. Reynolds RW, Rayner NA, Smith TM, Stokes DC, Wang W. An Improved In Situ and Satellite SST Analysis for Climate. Journal of Climate 2002;15:1609-1625.
70. Patz JA, Campbell-Lendrum D, Holloway T, Foley JA. Impact of regional climate change on human health. Nature 2005;438(7066):310-317.
71. Pindyck RS, Rubinfeld DL. Econometric models and economic forecasts. Boston, MA: Irwin/McGraw-Hill, 1998.
72. Kuno G. Review of the factors modulating dengue transmission. Epidemiology Reviews 1995;17:321 - 335.
73. Hales S, de Wet N, Maindonald J, Woodward A. Potential effect of population and climate changes on global distribution of dengue fever: an empirical model. Lancet 2002;360:830 - 834.

74. Hay S, Myers M, Burke D, Vaughn D, Endy T, Ananda N, Shanks G, Snow R, Rogers D. Etiology of interepidemic periods of mosquito-borne disease. Proceedings of the National Academy of Sciences 2000;97:9335 - 9339.

Appendix 1

Keywords and subject headings for searched databases.

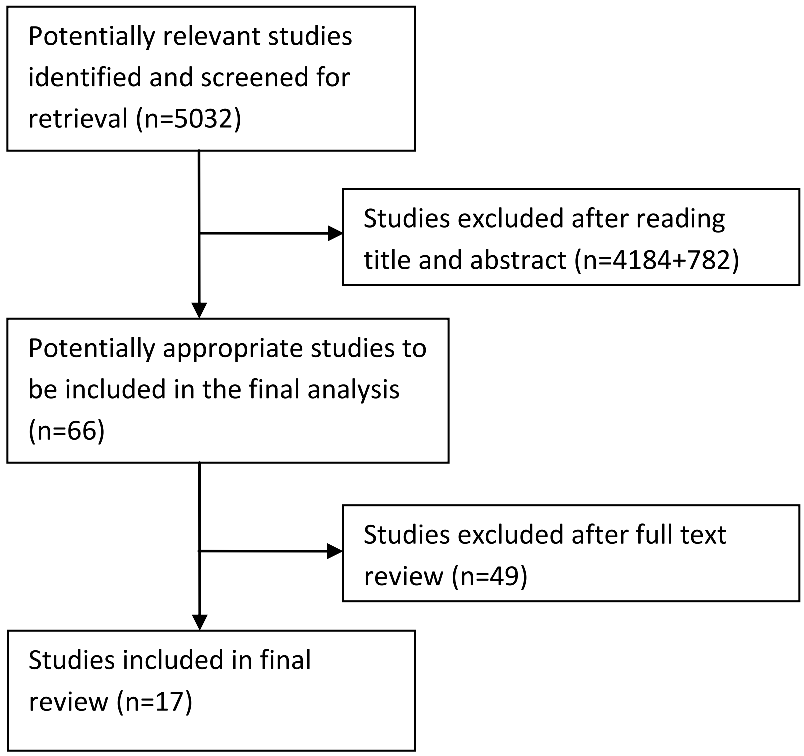
Searches were based on the Boolean function: [‘exposure1’ OR’ exposure2’ OR ‘exposure3’…] AND [‘outcome1’ OR ‘outcome2’ OR ‘outcome3’…]

Database	**Exposure**	**Outcome**
Keywords for Medline, Global Health, EMBASE, Web of Science and BIOSIS	Air temperature Atmosphere Climate Climate change El Niño El Niño-Southern Oscillation ENSO Environmental temperature Global Climate Global warming Greenhouse Greenhouse effect Heat* Sea surface temperature SOI Soil temperature Southern Oscillation Southern Oscillation Index Temperature warm* Water temperature Weather Weather patterns	Bouquet fever Break-bone fever Break bone fever Dandy fever Date fever Dengue Dengue Fieber Dengue hemorrhagic fever Dengue shock syndrome Dengue virus DHF Duengero Flaviviridae Flavivirus Giraffe fever Petechial fever Polka fever
Medline (via Ovid)	MeSH terms: Atmosphere Climate Climate change Global Warming Greenhouse effect Heating Hot temperature Temperature Weather	MeSH terms: Dengue Dengue Hemorrhagic Fever Dengue Virus Flavivirus

Global Health (via Ovid) 1910-May 2010	Subject headings: Air temperature Atmosphere Climate Climatic change Climatic factors El Niño-Southern Oscillation Environmental temperature Global warming Greenhouse effect Heat Heating Soil temperature Temperature Water temperature Weather Weather patterns	Subject headings: Dengue Dengue 1 virus Dengue 2 virus Dengue 3 virus Dengue 4 virus Dengue hemorrhagic fever Dengue shock syndrome Flavivirus
EMBASE Classic+EMBASE (via Ovid) 1947-2010 Week 26	Subject headings: Air temperature Atmosphere Climate Climate change El Niño Environmental temperature Global Climate Greenhouse effect Heat Heating Sea surface temperature Soil temperature Temperature Warming Water temperature Weather	Subject headings: Dengue Dengue virus Flavivirus
Web of Science with Conference Proceedings	Keywords only	Keywords only

BIOSIS Previews (via Ovid) 1969 to 2010 Week 30	Subject headings: Temperature – General measurements and methods External effects: temperature as a primary variable Environmental sciences Ecology: environmental biology-bioclimatology Climatology	Subject headings: Flaviviridae
PAHO		Dengue
LILACS	Weather Temperature El Niño	Dengue
	Climate change and synonyms, and specific relevant climatic processes	*Dengue and synonyms*

Appendix 2


Potentially relevant studies identified and screened for retrieval (n=5032)
Studies excluded after reading title and abstract (n=4184+782)
Potentially appropriate studies to be included in the final analysis (n=66)
Studies excluded after full text review (n=49)
Studies included in final review (n=17)

Appendix 3

Questionnaire used for data extraction from the articles included in the systematic review.

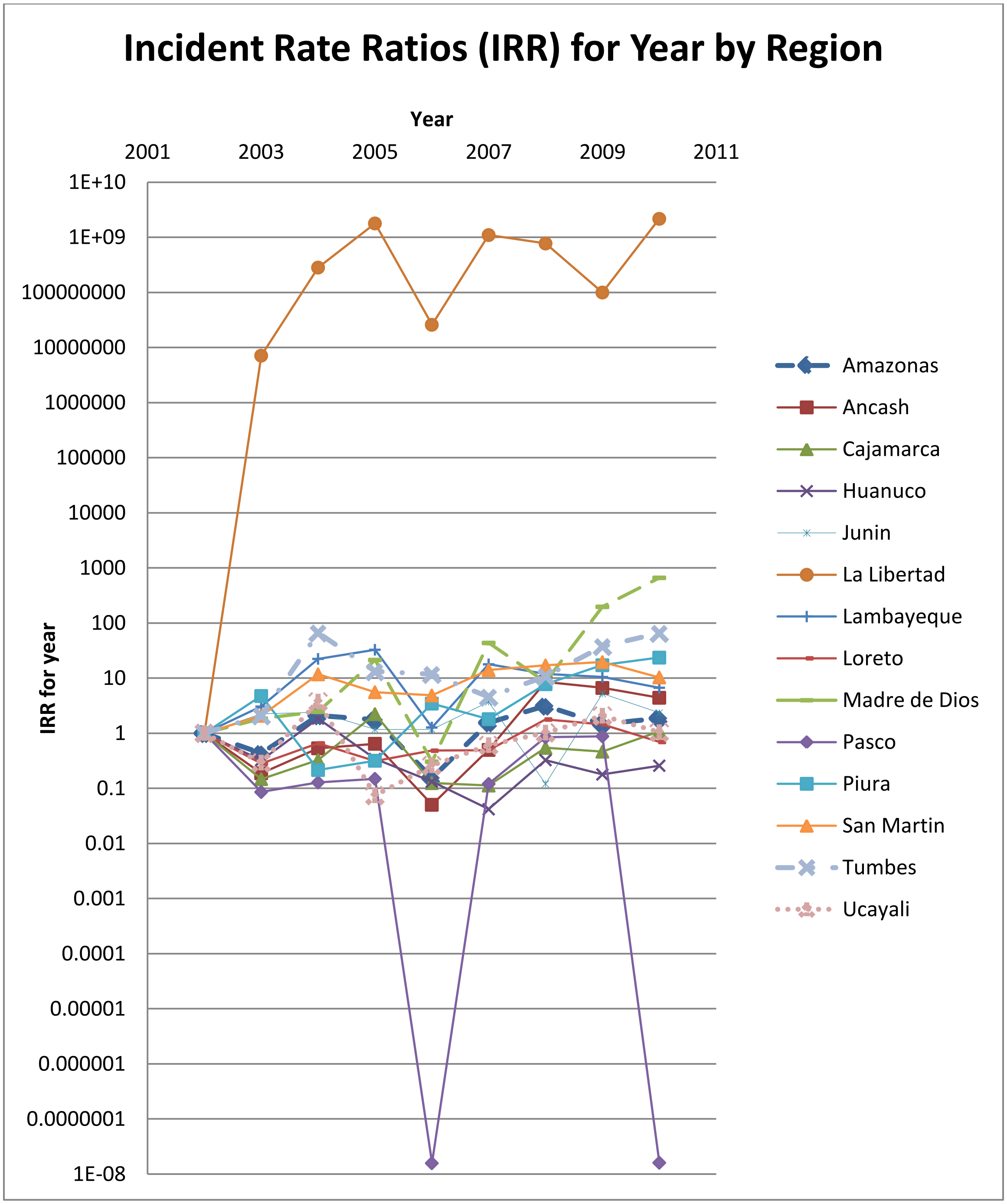
Study reference	
Population	
Time period	
Source of dengue data	
Source of weather data	
Time resolution of data (monthly, weekly etc.)	
Spatial resolution of data (by city, province, region)	
Exposure measure (temperature)	
Outcome measure (disease)	
Type of correlation analysis	
Was there significant correlation? What lags did the authors consider?	
Type of regression performed	
Is there a statistically significant association between temperature and dengue according to regression?	
What is the lag time?	

Is there a statistically significant association between ENSO and dengue according to correlation? What lags did the authors consider?	
What is the lag?	
Is there a significant association between ENSO and dengue according to regression?	
What is the lag?	
Were other covariates considered? What are they? Are there significant relationships between the covariates and dengue?	
Was seasonality controlled for? How?	
Was autocorrelation controlled for? How?	

Appendix 4

Labeled regions of Peru according to administrative boundaries

Appendix 5



Incident Rate Ratios (IRR) for Year by Region
Year
2001
2003
2005
2007
2009
2011
IRR for year
1E+10
1E+09
100000000
10000000
1000000
100000
10000
1000
100
10
1
0.1
0.01
0.001
0.0001
0.00001
0.000001
0.0000001
1E-08
Amazonas
Ancash
Cajamarca
Huanuco
Junin
La Libertad
Lambayeque
Loreto
Madre de Dios
Pasco
Piura
San Martin
Tumbes
Ucayali