Weather, climate change and dengue in Mexico

By

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To Nuriya and Carlos Kamil who are the most precious to me

Abstract

Many studies have estimated empirical relationships between dengue, weather, and El Niño in several regions of the world. Some of these studies used their model estimations to predict the potential impacts of climate change on the future distribution of dengue. Often, these studies have sidestepped elements that are key to the estimation of the effects of climate variables on dengue with statistical confidence. For example, they fail to incorporate covariates that may confound the empirical associations between dengue, weather, El Niño, and climate undermining their model estimations. Additionally, several studies used nationally or supra-nationally aggregated data which remove the spatial variability in all variables making it difficult to detect complex associations between dengue and climate variables. Other studies were conducted in small geographical areas with the problem of having low numbers of disease cases posing problems for their analysis with statistical confidence.

Here, we used the most comprehensive dengue-related datasets analysed to date and several statistical methods to investigate the effects of weather, climate, and El Niño on dengue incidence. We demonstrate that such effects are robust to the confounding effects of socioeconomic development and other non-climatic factors such as seasonal trends and inter-annual variability. Our results reveal that the effects weather and El Niño are significantly heterogeneous between provinces influenced by the underlying climate. With the exception of access to piped water, we could not identify significant effects of socioeconomic status on dengue occurrence. This result is likely related to human behaviour or the lack of protective measures against mosquitoes. We used our model estimations to project the potential impacts of climate change on dengue incidence by 2030, 2050 and 2080 with greater statistical confidence than previous studies. Our projections indicate that climate change is likely to increase dengue incidence mainly in already endemic areas.

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Chapter 1

Introduction

It has been suggested that climate change will affect global health mainly in an adverse way (Costello et al., 2009). For example, extreme-temperature events may take the human body beyond its weather-coping range increasing mortality among some segments of the population (Githeko and Woodward, 2003; Cowie, 2007). Also, because of the ectothermic nature of arthropods, vector-borne diseases, such as dengue and malaria, are highly sensitive to variations in the climate system, particularly in temperature and precipitation (Gage et al., 2008; Jansen and Beebe, 2010).

The study of the likely impacts of climate change on the transmission and distribution dynamics of vector-borne diseases such as dengue and malaria has received a great deal of attention because of this sensitivity to changes in the climate system (e.g. Reiter, 2001; Confalonieri et al., 2007; Reiter, 2008; Gething et al., 2010; Sriprom et al., 2010; Béguin et al., 2011). Changes in ambient temperature, humidity and rainfall for example, may potentially influence the risk of dengue by modulating the population size and host-seeking activity of the vector, as well as the development rate of both the dengue vector and the dengue viruses (Watts et al., 1987; Focks et al., 2000; Bicout et al., 2002; Gage et al., 2008; Halstead, 2008).

Many studies have estimated the effects of weather and El Niño on dengue, and used their model outputs as a baseline for predicting the potential impact of climate change on the future distribution of dengue (e.g. Hales et al., 2002; Sriprom et al., 2010). However, often these studies have failed to incorporate non-climatic confounders in their models, have aggregated data to large geographical boundaries, or have been conducted over short periods of time greatly undermining their estimations (Robins and Morgenstern, 1987; Gething et al., 2010; Jansen and Beebe, 2010; Santer et al., 2011).

In this thesis, we investigate the effects of weather, El Niño, and climate change on dengue using several statistical methods and the most comprehensive dengue-related dataset analysed to date to ensure the robustness of our estimations. We demonstrate that the effects of weather and El Niño on dengue are not only statistically significant, but also robust to the confounding effects of socioeconomic development and other non-climatic factors such as seasonal trends and interannual variability. Additionally, we reveal that the effects of weather on dengue vary significantly between provinces, and that such effects are largely determined by the local conditions. Finally, we use our model estimations to project the potential effects of climate change on dengue incidence under three emission scenarios.

1.1 Dengue burden

Dengue is the most rapidly spreading mosquito-borne viral disease in the world (TDR, 2007). Before 1970, only nine countries experienced severe dengue epidemics, but it is now endemic in over a hundred countries (Figure 1.1) in Africa, the Americas, the Eastern Mediterranean, South-east Asia and the Western Pacific (WHO, 2012). Dengue has become a major public health concern (WHO, 2012). Its incidence rate has dramatically increased over the last six decades (from about 900 annual cases reported to the World Health Organization over 1955–1959 to about 926 thousand annual cases over 2000–2007) and continues to rise (WHO, 2002, 2009).

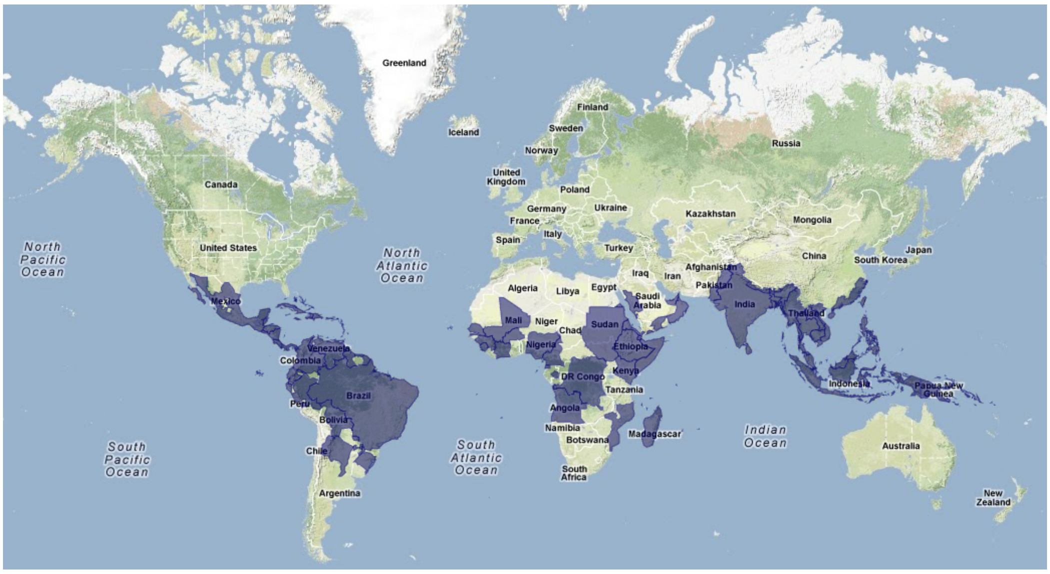

Figure 1.1: Areas of ongoing dengue transmission risk (shaded) as defined by the Center for Disease Control and Prevention (CDC). Based on data from Ministries of Health, international health organizations, journals, and knowledgeable experts (2010). Source: `http://www.healthmap.org`

Such increase in dengue incidence has been influenced by numerous mechanisms such as population growth, unplanned urbanisation (commonly associated with insufficient waste collection that provides potential breeding sites for the mosquito), increased transportation of goods (that facilitates the movement of infected mosquitoes across regions), and lack of political will (which has caused the re-direction of resources for dengue control to other programmes) (Gubler and Wilson, 2005; Al-Muhandis and Hunter, 2011). Such increases have also been associated with variations in the climate system, including climate change (e.g. Jetten and Focks, 1997; Sriprom et al., 2010; Lowe et al., 2011). The World Health Organization estimates that approximately 40% of the global population (i.e. 2.5 billion people) are at risk from dengue transmission, with about 50 million new dengue infections (WHO, 2009), and approximately 12,000 deaths, mainly among children, occurring worldwide every year (WHO, 1997, 2002).

Dengue is characterized by a sudden onset of high-grade fever, severe headache, pain behind the eyes, nausea, vomiting, rash and a low white blood cell count (TDR, 2012; WHO, 2012). In a small proportion of cases, life-threatening complications such as circulatory compromise and shock occur (Alexander et al., 2011; WHO, 2012). The burden of dengue at the global scale has been estimated in 750,000 disability-adjusted life years (the number of lost years of healthy life) per annum lost due to absenteeism, immobilisation, debilitation or medication (Murray and Lopez, 1996a,b; Clark et al., 2005). The economic losses caused by dengue are similar to the losses attributed to malaria and tuberculosis in some regions of the world such as the Americas (e.g. Torres and Castro, 2007). The annual cost of dengue has been estimated to be 2.1 billion US dollars (USD) across Latin America and the Caribbean (Shepard et al., 2011), and 89 million USD in Cambodia, Malaysia and Thailand (Suaya et al., 2009). As there are no specific antiviral medicines treating or vaccines preventing dengue, the only way to control or prevent the disease is through the management of mosquito populations (Eisen and Lozano-Fuentes, 2009; Al-Muhandis and Hunter, 2011).

Public health systems are already overburdened in many countries, and increases in the distribution and intensity of vector-borne diseases, especially within populations with little or no immunity to dengue, could quickly lead to situations very difficult or impossible to cope with. Understanding the epidemiology of the disease and the role of its drivers is important for understanding past outbreaks, as well as for estimating future risks in order to facilitate an early response and allow the effective allocation of resources.

1.2 Dengue overview

Dengue causes an acute febrile syndrome that affects all age groups (WHO, 1997). The World Health Organization traditionally classified dengue as Dengue Fever (DF), Dengue Hemorrhagic Fever (DHF), and Dengue Shock Syndrome (DSS) (WHO, 1997). This classification posed major difficulties for the application of the clinical guidelines to diagnose severe cases in many countries (e.g. Santamaria et al., 2009; Alexander et al., 2011). Consequently, this classification has been revised and recently modified to the new categories 'Dengue' (with or without warning signs) and 'Severe Dengue'.

Dengue symptoms are charaterized by sudden onset and last two to seven days. Symptoms range from mild to incapacitating severe fever, intense headache, pain behind the eyes (retro-orbital), muscle pain (myalgia), joint pain (arthralgia), nausea, gastrointestinal problems, swollen glands, and rash (WHO, 2012; TDR, 2012). Severe Dengue is a potentially lethal complication of Dengue, and is characterized by plasma leakage, fluid accumulation, severe hemorrhage, respiratory distress, or organ impairment (WHO, 2012; TDR, 2012). Warning signs of likely progression to Severe Dengue usually occur three to seven days after the initial symptoms, in conjunction with temperature decrease ($< 38°$C), and include: severe abdominal pain (acute abdomen), persistent vomiting, rapid breathing (tachypnea), mucosal bleeding, fatigue, restlessness, blood in vomit (hematemesis), and decreasing platelet count (Alexander et al., 2011; WHO, 2012).

Dengue is caused by four antigenically distinct but genetically related single-stranded RNA viruses of the family *Flaviviridae*, genus flavivirus (Heinz et al., 2000), designated DEN-1, DEN-2, DEN-3, and DEN-4 (WHO, 1997). Infection with one type of dengue virus or 'serotype' produces life-long immunity against reinfection with that serotype (homologous immunity) (WHO, 1997). Experiments conducted on human volunteers suggest that infections with one serotype may also produce temporary (two to nine months) and partial protection against secondary infections with other serotypes (WHO, 1997; Wearing and Rohani, 2006). After this period of temporary 'cross-immunity', a second infection with a different serotype may result in a process known as antibody-dependent enhancement (ADE) where the cross-reactive antibodies enhance viral replication (increasing infection of cells) and may lead to Severe Dengue instead of preventing a later infection (Wearing and Rohani, 2006).

1.2.1 Dengue transmission and control

Dengue viruses are transmitted to humans through the bite of infected female *Aedes (Stegomyia) aegypti* mosquitoes. Other species (e.g. *A. albopictus*, *A. polynesiensis*, and some members of the *A. scutellaris* complex) have been associated with dengue outbreaks, but they are not as efficient as *A. aegypti* for dengue transmission (WHO, 1997; OPS, 2001). The anthropophilic (preference for humans) habits of *A. aegypti* are a major contributing factor to its public health impact.

Aedes mosquitoes become infected after biting human carriers (Figure 1.2), and remain infected for life (typically ten days) (WHO, 1997). Mosquitoes usually become infective (able to transmit dengue viruses) 8–12 days after an infectious bloodmeal (OPS, 2001). This time between an infectious bloodmeal and the time when the vector can transmit a dengue virus is known as the extrinsic incubation period (EIP). The transovarian transmission of dengue viruses (from a female mosquito to its offspring by infection of the eggs in its ovaries) is also possible (Salas-Luévano and Reyes-Villanueva, 1994; Orta-Pesina et al., 2005); however, it is infrequent and apparently does not contribute significantly to human transmission (WHO, 1997).

Infected humans are the main carriers of dengue viruses, and are the source of such viruses for uninfected mosquitoes (WHO, 2012). The intrinsic incubation period (the period required for the development of the virus in a human host before it can be transmitted to a mosquito, and before such host develops symptoms) averages 4.5–7 days, with a maximum of ten days in a few cases (Halstead, 2008). Infected humans may transmit the virus to susceptible mosquitoes for 4-5 days, with a maximum of 12 days (Halstead, 2008). The length of viremia (presence of viruses in blood) may be a function of the viral titer (concentration) delivered by the vector (Halstead, 2008). Long viremic periods may increase the likelihood of transmission to susceptible infected mosquitoes.

As previously stated, the prevention and control of dengue transmission greatly depends on the management of mosquito populations (Eisen and Lozano-Fuentes, 2009; Al-Muhandis and Hunter, 2011). Such control is mainly achieved by eliminating water-holding

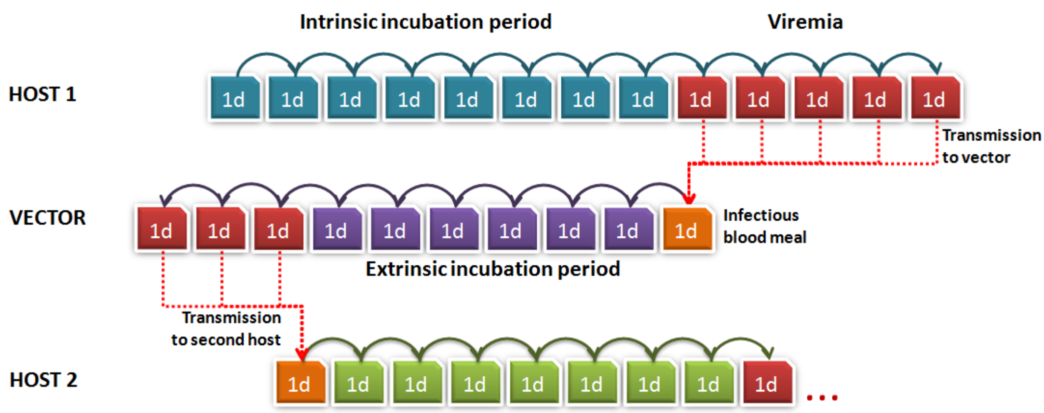

Figure 1.2: Schematic representation of dengue virus transmission. Each box represents one day. Red boxes indicate when both the host and the vector become infective. Orange boxes indicate when both the host and the vector become infected.

containers that may become oviposition sites allowing the development of aquatic stages of the mosquito cycle (WHO, 2009). Carrying out vector control measures, however, is rather complex because *A. aegypti* effectively exploits a wide range of habitats, both natural and man-made. The habitats are eliminated by preventing access of mosquitoes to water-holding containers, by frequently emptying and cleaning them, by removing the developing stages using biological agents such as copepods (Vu et al., 1998), by killing immature and adult mosquitoes using insecticides, or by combinations of these methods (WHO, 2009). Attempting to control immature stages in all the possible habitats in a community may not be feasible or cost-effective as some of these habitats are considerably more productive than others (WHO, 2009).

1.3 Climatic determinants of dengue

1.3.1 Temperature

Weather has obvious influences on the ecology of dengue and greatly determines the timing and magnitude of dengue outbreaks. The major climatic factors influencing dengue transmission are temperature and rainfall. Temperature affects the dengue system through numerous biological mechanisms. For example, because of its ectothermic (cold blooded) nature, the behaviour and distribution of *A. aegypti* is greatly influenced by temperature (Gage et al., 2008; Jansen and Beebe, 2010).

Dengue transmission declines with cold temperatures in regions with clear seasonal changes in temperature (Kuno, 1995). Temperatures below 16°C prevent *Aedes* mosquitoes from transmitting dengue viruses (Blanc and Caminopetros, 1930). Moreover, low temperatures affect the development of immature stages of the vector (Focks and Barrera, 2006). In tropical areas, mosquito abundance does not seem to vary with temperature but with changes in the abundance and productivity of water-holding containers (Focks and Barrera, 2006).

Temperature modulates the development time of *A. aegypti* immatures (Halstead, 2008). For example, the duration of the development from egg hatching to adult is inversely related to temperature, ranging from seven days at 35°C to 40 days at 15°C (Tun-Lin et al., 2000). Additionally, the pupal development time period at 32°C, is only half of that at 28°C (Focks et al., 2000).

Female mosquitoes bite humans to get blood for completing their gonotrophic cycle (the time period between two consecutive egg-production acts, which involve two consecutive bloodmeals) and lay eggs. The length of the gonotrophic cycle is also temperature dependent (Christophers, 1960). The speed of egg development is steered by temperature. Mosquitoes at 32°C will attempt to take more than twice as many replete bloodmeals than mosquitoes at 24°C (Focks et al., 2000). As a consequence, the percentage of infected mosquitoes may rise with high temperatures, as well as the likelihood of successful transmission to a human host (Reiter, 2001; Wu et al., 2009). Dengue transmission is more efficient at temperatures above 20°C (Blanc and Caminopetros, 1930). The maximum transmission efficiency of *A. aegypti* has been reported at 32–35°C under laboratory conditions (Watts et al., 1987).

The length of the EIP is also steered by temperature. In laboratory conditions, temperatures around 32–35°C produced and EIP of about 6–7 days, whilst temperatures around 27–30°C substantially increased the EIP to 12–13 days (McLean et al., 1974; Watts et al., 1987). Additionally, mosquitoes incubating the virus at about 32°C are approximately 2.6 times more likely to survive long enough to potentially infect human hosts than those at 22°C (Focks et al., 2000).

Aedes mosquitoes are less susceptible to dengue infection and also die faster under large diurnal temperature ranges (DTR) around the same mean temperature (Lambrechts et al., 2011). The underlying mechanism for such negative impact of the DTR on vector competence is still unclear but might be related to short periods of time spent at high or low temperatures under large DTRs adversely impacting the possibilities of midgut infection by limiting entry into midgut epithelial cells or initial replication in midgut cells as observed in *Culex tarsalis* mosquitoes infected with western equine encephalitis virus (Lambrechts et al., 2011). Climate change has decreased the amplitude of the global DTR over the period 1950 to 2004 in many parts of the world, at a rate of -0.07°C per decade (Trenberth et al., 2007), a situation that may favour dengue transmission.

Extremely high temperatures decrease mosquito survival and may hamper dengue transmission (Gage et al., 2008). Adult *Aedes* mosquitoes gradually begin to die at temperatures over 36°C, whereas the survival of immature mosquitoes (larvae and pupae) begins to decrease only at temperatures above 39–40°C (Focks et al., 2000).

The viral titer in *Aedes* mosquitoes is also temperature dependent (Gage et al., 2008). High viral titers in infected mosquitoes may result in high viral loads in human hosts (Halstead, 2008). High viral titers may augment the duration of viremia in such hosts (Halstead, 2008), affecting the likelihood of secondary transmission. Also, high viremia levels have been associated with increased dengue severity (Vaughn et al., 2000).

Human behaviour is also influenced by temperature and may affect the ecology of dengue. Humans may spend more time indoors sheltering from the seasonal warm temperatures and heatwaves. If people seek refuge in sealed buildings with window screening and air conditioning during these periods, the risk of dengue transmission may decrease because they are less exposed to mosquito bites (Reiter, 2001; Gage et al., 2008; Jansen and Beebe, 2010). However, if such protective measures are nonexistent, as typically happens in the tropics (Reiter, 2001), *A. aegypti* may gain access to the indoor environment and dengue transmission may occur (Reiter, 2001; Jansen and Beebe, 2010).

1.3.2 Precipitation

Dengue incidence is strongly associated with the wet season in many countries across Latin America, the Caribbean and South-east Asia (e.g. Moore et al., 1978; Aiken et al., 1980; Koopman et al., 1991; Depradine and Lovell, 2004; Cazelles et al., 2005; Focks and Barrera, 2006; Chadee et al., 2007; García et al., 2008; Sia Su, 2008). Research indicates that increases in mosquito populations tend to recur after the onset of the wet season (Moore et al., 1978; Aiken et al., 1980).

The influence of precipitation on the dengue system is complex and highly nonlinear. The creation (or wash-out) of breeding sites for the vector may be greatly influenced by rainfall depending on the prevailing climatic, socioeconomic and cultural conditions of a region. For example, rising precipitation may increase the number of breeding sites for the vector only if there are enough water-holding containers available (Gage et al., 2008; Jansen and Beebe, 2010). Low levels of precipitation may equally contribute to the creation of breeding sites by slowing rivers and causing ponding and stagnation (Patz et al., 2003). Heavy rainfall, on the other hand, may wash-out the breeding sites (Gage et al., 2008) resulting in a decreasing number of circulating adults and reduced dengue transmission.

Natural water-holding containers such as tree holes, leaves, and fruit zests may become potential breeding sites for the vector (Focks and Barrera, 2006). However, *A. aegypti* prefers to breed in man-made containers such as swimming pools, water storage drums, discarded tyres, cans and bottles, fountains, trash, domestic ant-traps, boreholes and washing machines (Ibáñez and Gómez, 1995; Tsuzuki et al., 2009). Toilet concrete basins, flower vases, wells, jars, and plastic buckets seem to have a higher pupal productivity than other types of water-holding containers (Tsuzuki et al., 2009).

The reduced or zero precipitation for long periods observed in dry regions may provoke the dormancy of mosquito eggs (diapause) for several months reducing the presence of adult stages of the vector (Bicout et al., 2002) which may decrease dengue transmission. Yet, dengue outbreaks have been reported over dry periods in Singapore, Indonesia and the Philippines (Aiken et al., 1980) possibly reflecting the abundance of breeding sites due to water storage practices (Aiken et al., 1980; Gage et al., 2008; Jansen and Beebe, 2010; Padmanabha et al., 2010). Wet areas, on the other hand, may observe little variation in dengue incidence throughout the year because there may always be enough water to produce oviposition sites (Williams et al., 2010).

1.3.3 El Niño Southern Oscillation

El Niño Southern Oscillation (ENSO) is an anomalous condition of ocean temperature that originates in the eastern tropical Pacific Ocean (Magaña, 2004). ENSO is a dominant source of interannual climate variability around the world (Trenberth, 1997). The warm phase of ENSO is known as El Niño and occurs every few years when the sea surface temperature (SST) anomalies (relative to the base period climatology of 1950–1979) in the Niño-3.4 region (5°N–5°S, 170°-120°W) exceed 0.4°C for at least six consecutive months (Trenberth, 1997). Opposite reverse anomaly patterns occur during the La Niña phase of ENSO (Trenberth, 1997). El Niño modulates the regional and local ecology of the affected areas which may experience extreme meteorological events such as heavy rain, floods or heat (Hurtado-Díaz et al., 2007). However, each El Niño event has a distinct character (Trenberth and Stepaniak, 2001).

The effects of El Niño on weather are most commonly observed on precipitation, but ambient temperature is also affected (Magaña et al., 2004). The effects of El Niño are not the same every year, and may vary between summer and winter (Magaña et al., 2004). In our study case area of Mexico, for example, the El Niño winters are colder than usual in most of the country and precipitation increases in the north and northwest, and decreases in the south (Magaña et al., 2004). El Niño summers, on the other hand, register above-normal temperatures (with some exceptions mainly in the north-west) and decreased precipitation in the majority of the country (with some exceptions mainly in the south-east) (Magaña et al., 2004).

Research suggests that El Niño increases the risk of dengue infection in regions with poor disease control measures where the local climate is associated with the ENSO cycle (Hurtado-Díaz et al., 2007). Statistically significant associations between dengue and El Niño have been detected in many countries such as Mexico, Puerto Rico, Thailand, French Guyana, Suriname, Indonesia, Colombia, Brazil, Australia and Tahiti (e.g. Hales et al., 1996; Gagnon et al., 2001; Cazelles et al., 2005; Hurtado-Díaz et al., 2007; Johansson et al., 2009a; Lowe et al., 2011). However, the links behind such associations have not been clearly established (Hurtado-Díaz et al., 2007) partly because of the challenge to disentangle the relative influence of intrinsic mechanisms (such as host-virus interactions) and external mechanisms (such as climate variability and El Niño). On the other hand, as will be discussed in Section 1.5, many studies analysing the effects of El Niño on dengue have used country level data in which the spatial variability of all variables is largely removed making it difficult to detect the complex associations between these variables.

1.4 Non-climatic determinants of dengue

1.4.1 Human behaviour and access to protective measures

As previously mentioned, when temperatures increase, humans may seek refuge in sealed air-conditioned buildings where they are less exposed to mosquito bites, resulting in decreased dengue transmission (Gage et al., 2008). In the United States for example, people spend much of their time in sealed, air-conditioned buildings where the low ambient temperature and dry atmosphere lessen the survival rate of *A. aegypti* and extend the EIP of the dengue viruses reducing the likelihood of successful transmission (Reiter, 2001).

Conversely, in tropical countries people often seek the coolness of shaded, well ventilated areas where *A. aegypti* prefers to feed (Reiter, 2001). In these countries, windows and doors are often kept open and many buildings do not have protective measures such as window screens (Reiter, 2001). Furthermore, these buildings often have gaps between the top of the wall and the underside of the roof that provide mosquitoes potential routes to enter the indoor space where they can bite humans (Reiter, 2001). The adoption of protective measures may be driven by economic instead of climatic factors (Jansen and Beebe, 2010; Reiter, 2001). For example, poor housing design is more frequent in lower socioeconomic strata.

1.4.2 Mosquito behaviour

The contemporary distribution of dengue does not reflect its maximum potential range according to the historical records (Jansen and Beebe, 2010). For example, *A. aegypti* has been found beyond the theoretical latitude range (Figure 1.3) of 35°N–35°S (Ibáñez and Gómez, 1995; CENAVECE, 2003; Jansen and Beebe, 2010), and has been associated with dengue outbreaks in temperate areas such as Philadelphia, New York and Boston (Gage et al., 2008).

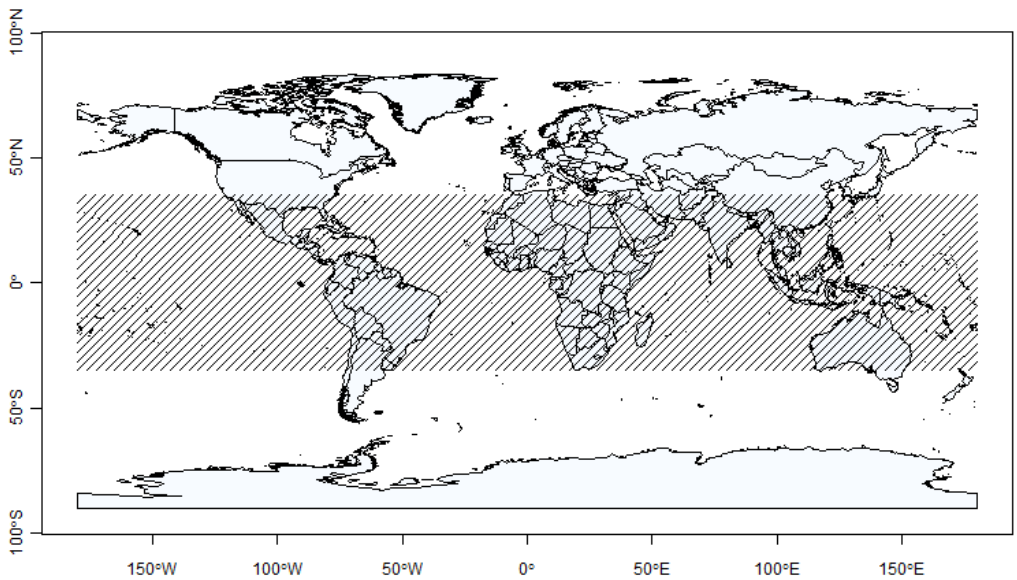

Figure 1.3: Theoretical geographical limits for the distribution of *Aedes aegypti* (shaded area).

A. aegypti is typically found at altitudes below 1,200 metres above sea level (Gómez-Dantés, 1991) presumably due to the low temperatures characteristic of high altitudes. However, it has also been found indoors at altitudes as high as 1,700 and 2,200 metres above sea level in Mexico and Colombia respectively where it has been able to effectively transmit dengue (Herrera-Basto et al., 1992; Montesano and Ruíz, 1995; Yoganathan and

Rom, 2001). Such large potential originates from the remarkable ability of *A. aegypti* to accommodate adverse conditions by exploiting the local microclimates (Jansen and Beebe, 2010). Adult *Aedes* mosquitoes readily feed and rest indoors where they are less exposed to the external meteorological conditions (Jansen and Beebe, 2010). Its geographical distribution may not necessarily correlate with outdoor conditions (Kuno, 1995). Thus, climate and weather do not determine the geographical distribution of dengue and *A. aegypti* alone (Jansen and Beebe, 2010; Reiter, 2001).

1.4.3 Population density and unplanned urbanisation

Population density also modulates dengue dynamics, and so dengue is associated with unplanned urbanisation. High population densities per household allow mosquitoes to find available human hosts (sources of blood) without the need of flying long distances. This increases the likelihood of multiple infections in a single household (Halstead, 2008). Such clustering of blood sources contributes to the development of urban pockets of dengue infections (Halstead, 2008).

Large population growth in major cities and the rising urbanisation of rural areas in the tropics over the past decades has significantly contributed to the contemporary increase in dengue incidence (Kuno, 1995). Rising urbanisation place high demands on infrastructure and public services, particularly in developing countries (Jansen and Beebe, 2010). The response of each settlement to these demands may significantly influence its suitability for mosquito breeding (Jansen and Beebe, 2010). Unplanned urbanisation is usually accompanied by overburdened water systems (Al-Muhandis and Hunter, 2011) that may lead to increased domestic or peri-domestic water storage providing potential breeding sites for *Aedes* mosquitoes (Gage et al., 2008; Jansen and Beebe, 2010; Padmanabha et al., 2010).

Access to piped water may significantly modify the ecology of dengue transmission (Schmidt et al., 2011). For example, if the water supply service is unreliable, people may store water to cope with the intermittent service, providing mosquitoes potential breeding sites, even in the absence of precipitation (Aiken et al., 1980; Gage et al., 2008; Jansen and Beebe, 2010; Padmanabha et al., 2010). Also, stand pipes often leak or have puddles below them that may be effectively exploited by *A. aegypti* for laying eggs. Cultural differences in water use and storing practices may also influence dengue transmission (Kuno, 1995). For example, in a study conducted in Vietnam, the absence of tap water in the household increased the dengue hospital admission rate by a factor (rate ratio) of 1.2 (Schmidt et al., 2011).

It is likely that emptying water-holding containers washes away the aquatic stages of the mosquito (Subra, 1983). However, people may be unwilling to empty such containers as result of limited or intermittent water supplies (Ibáñez and Gómez, 1995; Chareonsook et al., 1999; Cifuentes and Sánchez-Arias, 2007; Tran et al., 2010), or as an adaptive response to increased drought conditions (Beebe et al., 2009). Such emptying will be effective in reducing mosquito populations only if it occurs before immature stages complete their development (Padmanabha et al., 2010).

If the containers are not covered and are exposed to the environment, they readily become potential breeding sites for the vector even during months of low precipitation (Ibáñez and Gómez, 1995). The use of lids may avoid mosquito infestations of water-holding containers (Morrison et al., 2004); however, this action may be undermined by the effects of frequent water usage and result in high mosquito infestation rates (Kittayapong and Strickman, 1993; Phuanukoonnon et al., 2005). In some regions, despite routine maintenance water-holding containers become colonized breeding large numbers of mosquito larvae (Hemme et al., 2009).

Unplanned urbanisation is also commonly associated with insufficient waste collection services that generate numerous artificial water-holding containers that *Aedes* mosquitoes prefer for laying eggs (WHO, 2009; Al-Muhandis and Hunter, 2011). The combination of an increasing use of man-made containers, and poor sanitation services results in the accumulation of potential breeding sites that facilitate the expansion of mosquito populations (Jansen and Beebe, 2010). As previously mentioned, *A. aegypti* prefers to breed in water-storage drums, discarded tyres, cans and bottles (Ibáñez and Gómez, 1995; Tsuzuki et al., 2009). Efforts to reduce solid waste should be directed against those water-holding containers identified as important for mosquito production within each community (WHO, 2009).

The association between dengue and urbanisation is by no means unequivocal. Dengue has been also reported in rural areas with low population densities in Thailand and Vietnam (e.g. Chareonsook et al., 1999; Nagao et al., 2008; Nguyen et al., 2011; Schmidt et al., 2011). Furthermore, in Thailand dengue has shown greater incidence rates in rural areas (compared to urban ones) presummably due to lack of a reliable water source in the immediate vicinity of a household, and increased water storage over the wet season (Chareonsook et al., 1999; Schmidt et al., 2011). In some rural settings, tree holes, fruit zests, and leaves, as well as the rutting and pot-holing of trackways associated with agricultural settlements may provide breeding sites for the vector when wetted (Focks and Barrera, 2006).

1.4.4 International travel and transportation of commodities

In previous times, both *A. aegypti* and the dengue viruses were spread via sailing ships because the water storage containers in such ships served as mosquito breeding sites, allowing the continuation of the transmission cycle even on long trips (Gubler, 2002). Both the mosquito and the virus were introduced when ships called at port (Gubler, 2002). Modern transportation has facilitated and increased the international travel and transportation of goods within and beween countries, resulting in the constant movement of infected individuals and vectors from endemic areas to susceptible ones (Gubler, 2002; WHO, 2009; Al-Muhandis and Hunter, 2011).

For many years, public health authorities have tried to limit the spread of dengue-infected mosquitoes and implemented vector control programmes at international airports spraying adulticides into arriving aircrafts (Halstead, 2008). However, viremic humans are the most likely source of dengue virus importation across the world, and not the mosquitoes within the aircrafts (Halstead, 2008). Susceptible individuals moving into dengue-endemic regions (for holidays, for example) increase their risk to dengue infection and may introduce the virus or a new serotype into dengue-receptive areas on their return.

1.4.5 Human conflicts and politics

The dynamics of dengue substantially changed in Southeast Asia during World War II due to the disruption in the ecology caused by the war (Gubler, 2002). Such disruption expanded the geographical distribution and increased the population densities of *A. aegypti*, making many countries in the region highly susceptible to dengue epidemics (Gubler, 2002). The movement of troops accelerated the spread of viruses between populations, causing major epidemics (Gubler, 2002). By the end of the war, most countries in Southeast Asia were hyperendemic and had multiple dengue serotypes co-circulating in their communities, a few years later epidemic DHF emerged in the region (Gubler, 2002).

Lack of political will and limited resources for implementing effective control measures have played a key role in the contemporary distribution of dengue in many regions (e.g. Gubler, 2002; Al-Muhandis and Hunter, 2011). For example, in the 1950s the elimination of the yellow fever and dengue vector, *A. aegypti*, became the goal of a regional eradication programme led by the Panamerican Health Organization (Gubler and Wilson, 2005). This programme initially succeeded in many Latin American and Caribbean countries, and dengue was successfully eliminated from all but a few countries in the region (Gubler and Wilson, 2005). However, complacency, and lack of political will resulted in the redirection of resources to other programmes causing changes in the vector control strategies, and ultimately the reinfestation of the region by the early 1970s (Gubler, 2002; Gubler and Wilson, 2005), and the aspiration of a regional eradication was abandoned. To date, the eradication of dengue remains elusive.

1.4.6 Resistance to insecticides

Insecticide-resistant *A. aegypti* populations have been detected in several countries such as Cuba, Brazil, Venezuela and Vietnam (e.g. Rodríguez et al., 2001; Huong et al., 2004; Lima et al., 2011). Such resistance poses serious threats to the effective management of *A. aegypti* (WHO, 2009). Routine monitoring of insecticide susceptibility should be a key component of any vector control programme.

1.4.7 Viral titer

The viral titer of an individual carrier, and the amount of blood taken by each biting mosquito greatly determine the probability that the virus will disseminate to the mosquito's salivary glands and, in consequence, the likelihood and size of the virus inoculum to further human hosts (Halstead, 2008). The levels of human viremia required to infect *Aedes* mosquitoes have not been accurately determined (Halstead, 2008).

1.5 State of research on the empirical modelling of dengue occurrence as a function of climatic factors

The potential role of weather, climate and climate change in the contemporary and future geographical distribution of dengue is a highly topical issue (Gubler et al., 2001; Reiter, 2001; Gage et al., 2008; Jansen and Beebe, 2010). Understanding and ultimately being able to predict the spatiotemporal dynamics of dengue at different spatial scales is critical to effectively prevent and control the disease (Eisen and Lozano-Fuentes, 2009), and to target the timing and location of public health interventions in a timely fashion (Kovats et al., 2003).

Many studies have estimated empirical relationships between dengue, weather, and climate using a wide range of methods (e.g. Gagnon et al., 2001; Cazelles et al., 2005; Hurtado-Díaz et al., 2007; Lowe et al., 2011; Machado-Machado, 2012). The methods used range in complexity, from simple bivariate correlation and contingenty tables, to the application of more sophisticated methods such as Generalized Linear Mixed Models with random effects and species distribution modelling (e.g. Gagnon et al., 2001; Hales et al., 2002; Hurtado-Díaz et al., 2007; Johansson et al., 2009a; Machado-Machado, 2012). Weather and climate variables generally included temperature, rainfall, humidity, and an El Niño index. These variables were used as predictors for the distribution or occurrence of dengue across several geographical areas. Ocassionally, the outputs of empirical models were used as a baseline to predict the potential impacts of climate change on the future distribution and risk of dengue at different spatial and temporal scales (e.g. Hales et al., 2002; Sriprom et al., 2010). Often, however, the influence of non-climatic confounders was neglected, undermining the relationships estimated by these models (Robins and Morgenstern, 1987; Gething et al., 2010).

We identified and analysed 16 studies that used empirical modelling methods to estimate relationships between dengue and various climatic variables in order to identify gaps in the literature. Table A.1 presents those studies in a chronological order, and summarizes their main features. In this section, we (i) present an overview to the statistical methods used in the identified studies, and (ii) detail the key findings of the identified studies analysing their strengths and limitations for the estimation of empirical associations between dengue, weather and climate. Studies using similar statistical methods (e.g. autoregressive models) and model structures were grouped to facilitate their analysis. Whenever possible, studies are discussed together to avoid unnecessary repetition (e.g. Hurtado-Díaz et al., 2007; Brunkard et al., 2008; Luz et al., 2008).

1.5.1 Bivariate correlation

Bivariate correlation measures the strength of the relationship (ranging from zero to one, where one represents a perfect relationship, and zero no relationship) between two variables (Cohen et al., 2003). The purpose is to determine whether as one variable increases, the other variable tends to increase or decrease. Spearman correlation is used when one or both of the variables are not normally distributed, or consist of ordinal data or ranks. If the variables are not already ranks, these are converted into ranks and then correlated (Cohen et al., 2003).

Hales et al. (1996) studied the relationship between dengue epidemics and ENSO in South Pacific island countries over the period 1970–1995. ENSO was measured with the Southern oscillation index (SOI). Using Spearman's rank correlation, the number of dengue epidemics (obtained from searches on peer-reviewed journals) starting in a given year was compared with the mean SOI value for that same year. Dengue epidemics were positively correlated with ENSO (r_s = 0.58, P = 0.002).

This study represents one of the first attempts to correlate dengue data with El Niño, which as previously mentioned, is one major source of interannual climate variability (Trenberth, 1997). The study, however, does not look at associations between dengue, weather and climate. One strength of this study is that it uses a relatively long time-series including more than one El Niño event. Evidence of statistical associations between dengue and ENSO are more robust when the studies use long time-series including more than one El Niño event (Kovats et al., 2003). Another strength is that the SOI index (together with the Niño-3.4, and Niño-4 indices) chosen by Hales et al. (1996) is one of the most sensitive indices for determining an El Niño event, compared to the Japan Meteorological Agency (JMA), Niño-1+2, and Niño-3 indices (Hanley et al., 2003).

One drawback is that looking only at epidemic periods, the model ignores subtler changes in dengue dynamics that may originate from El Niño. The aggregation of data at the supra-national level may have caused aggregation bias issues (Theil, 1954; Grunfeld and Griliches, 1960) because such aggregation removes the spatial variability in the local climate, leading to flawed estimates and conclusions. Additionally, the authors fail to incorporate the effects of potential confounders (e.g. population data, urbanisation trends, access to public services; see Section 1.4) which may explain variations in dengue occurrence. Such confounders are required to produce reliable estimations of statistical relationships between disease outcome variables and climatic factors (Robins and Morgenstern, 1987; Gething et al., 2010).

1.5.2 Fisher's exact tests

The Fisher's exact test is used in the analysis of contingency tables (cross tabulation), to estimate the significance of the association (contingency) between two categorical variables similarly to the chi-squared test of independence (Weinberg and Abramowitz, 2008). The Fisher's exact test is more precise than chi-squared test when the expected numbers are small (Weinberg and Abramowitz, 2008). As with the chi-squared test, the most common use of Fisher's exact test is for 2 by 2 contingency tables.

Gagnon et al. (2001) analysed associations between dengue epidemics and ENSO events in Colombia, French Guiana, Suriname, and the Indonesian archipelago. Annual dengue epidemics were defined as anomalous increases (i.e. increase in disease transmission greater than 0.5 standard deviations above the mean) in the rate of change (i.e. the number of dengue cases/1,000 people in one year minus the number of cases/1,000 people in the previous year, Gagnon et al. 2001). ENSO events were measured with three dichotomous variables for: (a) the development phase of El Niño (Niño 0), (b) the year immediately after the peak of El Niño (Niño +1), and (c) La Niña years.

The authors used Fisher's exact tests to determine wether dengue epidemics were more likely to occur during: El Niño (0) versus other years, El Niño (+1) versus other years, and La Niña years versus other years. Their results suggest that dengue epidemics are significantly associated with El Niño events at the 0.05 level in French Guiana and Indonesia. In Colombia and Suriname, however, the association between dengue epidemics and El Niño was significant only at the 0.1 level. Furthermore, the risk to dengue epidemics was high in French Guiana and Suriname during El Niño (0) years, whilst in Colombia and Indonesia it was high during El Niño (+1) years.

Although both the ENSO and dengue series are long enough to include more than one El Niño events, and the study area is relatively large and diverse, one drawback is that the extent of spatial heterogeneity may be substantially large in the studied regions (e.g. Colombia is characterized by five natural regions including the Andes, the Amazon, and the Caribbean and Pacific coast lowlands). As in Hales et al. (1996), this study focuses on epidemics ignoring subtler changes in dengue incidence that may result from El Niño variability. Additionally, as previously mentioned, the aggregation of data at the national level may have caused aggregation bias issues (Theil, 1954; Grunfeld and Griliches, 1960) leading to flawed estimates and conclusions.

The use of El Niño years as a time-related explanatory variable of dengue epidemics is imprecise because the El Niño events do not run according to the calendar year (Kovats et al., 2003; Hurtado-Díaz et al., 2007). An El Niño event may start in one year and end in another, but its effects on the local climate may be restricted to only one of those years (Hurtado-Díaz et al., 2007). In addition, the authors fail to incorporate the effects of potential confounders (see Section 1.4) required to produce reliable estimations statistical relationships between disease and climate variables (Robins and Morgenstern, 1987; Gething et al., 2010).

1.5.3 Multiple linear regression

Multiple linear regression is used to model the linear relationship between a dependent variable and a set of independent variables (Cohen et al., 2003). Multiple linear regression could be a powerful approach in situations when appropriately applied. However, it is limited by the following assumptions. First, linear regression assumes a constant variance (Cohen et al., 2003). Second, linear regression assumes that the errors are identically and independently distributed (Guisan et al., 2002). Third, it assumes that the residuals follow a Gaussian distribution (Guisan et al., 2002; Cohen et al., 2003) which makes them inappropriate for modelling count data with small counts and with periods of no case occurrence as commonly observed in dengue data. Fourth, linear regression assumes that the regression function in the predictors is linear (Guisan et al., 2002); although this limitation can be easily overcome incorporating different functional forms of the independent variables.

Chowell and Sánchez (2006) analysed associations between dengue incidence and a range of climatic variables (see Table A.1) in Colima (Figure 1.4), Mexico during the 2002 outbreak. Cross-correlation analysis was initially used to study the lagged effects of the climatic variables on dengue incidence. Univariate and multivariate regression models were then fitted both with and without the lagged climatic variables.

Figure 1.4: Geographical location of the Mexican province of Colima (shaded area)

The multivariate model with the greatest explanatory variable (94% of the observed variance, $P < 0.001$) indicated that dengue incidence shows a positive association with minimum temperature, maximum temperature, precipitation and evaporation, and a negative association with mean temperature. Positive associations indicate that, for example, as temperature increases, so too does dengue incidence. Reduced versions of this model including only two explanatory variables at the time were also fitted. The estimated associations of the reduced models were consistent with those of the full model, and were significant at the 0.01 level. Adjusting the maximum temperature and evaporation time series for the lags at which they were most highly correlated to dengue incidence did not improve the percentage of variance explained by the previous models.

Sia Su (2008) studied the influence of weather on dengue incidence in the Metro Manila region, Philippines for the period 1996–2005. The selected method was step-wise multiple linear regression. Monthly dengue incidence per 100,000 people was regressed on mean monthly temperature and mean monthly precipitation. Precipitation showed a small, positive and significant relationship with dengue incidence (B = 0.004, $r^2 = 0.337$, $P < 0.05$). No significant relationship was detected for temperature.

Critique to Chowell and Sánchez (2006) and Sia Su (2008). Dengue transmission involves one person's infection leading to one or more secondary infections, situation that may lead to serial autocorrelation in the residuals. Both Chowell and Sánchez (2006) and Sia Su (2008) failed to incorporate autocorrelation components in their models to avoid such autocorrelation, even though such autocorrelation effect would be apparent from the results of the regression models. The estimated effects of temperature in Chowell and

Sánchez (2006) suggest that the inclusion of several temperature covariates may have lead to overfitting issues because whilst minimum and maximum temperature were positively associated with dengue, mean temperature showed a negative association.

Both studies estimated correlations between dengue and climatic time series that exhibit strong seasonal patterns while neglecting the seasonal trend components of such series, making it difficult to disentangle true weather from other seasonal effects (e.g. holidays, seasonal water storage). This situation greatly undermines their estimations because the seasonality in both dengue and climatic series is high (e.g. Cazelles et al., 2005; Johansson et al., 2009a). Consequently, if the seasonal components are not eliminated from the time series, almost any variable with a similar temporal behaviour will inevitably produce highly significant coefficients even if no real association exists between the two time series (Bowie and Prothero, 1981).

The time span of both studies is short ($\leq$ 10 years); and short time series are problematic for the identification of climatic signals with high statistical confidence due to their small signal-to-noise ratios (Santer et al., 2011). Furthermore, the studies were conducted in small geographical areas which are likely to be climatically and socioeconomically homogeneous (Elliott and Wartenberg, 2004; Eisen and Lozano-Fuentes, 2009), making it hard to extrapolate their results to areas with greater climatic or socioecnomic variability. Also, small populations commonly result in low numbers of disease cases leading to unstable risk estimations (Olsen et al., 1996). As in previous cases, both studies fail to incorporate the effects of likely sources of spurious relationships (see Section 1.4) greatly undermining their estimations (Robins and Morgenstern, 1987; Gething et al., 2010).

1.5.4 Autoregressive models

Autoregressive models (AR) are frequently used in time series analysis. In these AR models, a time series is explained by past terms (lags) of itself, a constant, and an error process (Cowpertwait and Metcalfe, 2008). The order of an AR model indicates the number of lag observations of the analysed series, so that a first order model AR(1) would include the outcome variable lagged one month as a time period explanatory variable. As in multiple linear regression, the major shortcomings of autoregressive models are the assumption of a constant variance (Xiao and Abdurrahman, 2007), and the assumption of normality on the residuals (Fonseca-Nobre et al., 2001; Xiao and Abdurrahman, 2007). In practice, AR models are commonly related to moving average (MA) models which conceptually are linear regressions of the values of one series against previous white noise (independent and identically distributed terms, with zero mean) error terms (Pfaff, 2008). When a time series exhibits non-stationarity (i.e. the mean and variance change over time), the time series must be differenced until a stationary one is obtained (Pfaff, 2008). This model class is termed autoregressive integrated moving average (ARIMA) model.

Hurtado-Díaz et al. (2007) estimated the impact of both weather and El Niño on dengue incidence in two municipalities of the State of Veracruz (Figure 1.5), Mexico, over the period 1995–2003. The dengue series were autoregressed until there was no evidence of serial correlation in the residuals. The optimal time lag of the independent meteorological variables was estimated cross-correlating the meteorological series against the auto-regressed dengue series. Then, associations between dengue, weather and El Niño were analysed including the climatic variables into the auto-regressive models. Models were adjusted by population growth. The predictive ability of the fitted models was evaluated using data from 1995–2002, and validated using the 2003 data.

Figure 1.5: Geographical location of the Mexican municipalities of Veracruz (blue pushpin), San Andrés Tuxtla (red pushpin), and Matamoros (green pushpin)

The models' results suggest that increases in the weekly number of dengue cases in the municipalities of San Andrés Tuxtla and Veracruz are positive and significantly associated with SST (used as a proxy of El Niño) with a lag of 16 and 20 weeks respectively. Similar associations were estimated for minimum temperature during the same week, and precipitation with a lag of two weeks in both municipalities. No significant differences in the estimated coefficients of weather and climate was detected between the two municipalities.

Brunkard et al. (2008) analysed the role of climate and weather variables (see Table A.1) on dengue incidence in the city of Matamoros, Tamaulipas, Mexico over the period 1995–2005. The dengue series were autoregressed until there was no evidence of serial correlation in the residuals as in Hurtado-Díaz et al. (2007). Additionally, the optimal time lags for the meteorological variables were determined using cross-correlation functions with each meteorological variable tested against the residuals of the auto-regressed dengue series. The dengue autoregressive terms and the lagged weather and climate variables were entered into an ARMA model. Model validation was performed using the first ten years of data and predicting the values for the remaining year.

The autoregressive components in the model exerted a strong influence in the model fit; however, adding the climatic variables significantly improved it (Chi-squared(3) = 11.12, $P = 0.011$) when using the full 11 years series. Dengue incidence was positive and significantly associated with maximum temperature with a lag of one week, precipitation with a lag of two weeks, and SST in the Niño 3.4 region with a lag of 18 weeks. No significant association was estimated with minimum temperature, and consequently, it was dropped from the model.

Critique to Hurtado-Díaz et al. (2007) and Brunkard et al. (2008). Like in previous sections, these two studies neglect the effects of potential confounders of the associations between dengue, weather and El Niño undermining their estimations (Robins and Morgenstern, 1987; Gething et al., 2010). Also, they were conducted across relatively short time periods (see Table A.1) which, as previously explained, pose challenges for the identification of climatic signals with high statistical confidence (Santer et al., 2011). Moreover, these studies were conducted in small greographical areas which may lead to biased risk estimations due to low number of cases (Olsen et al., 1996).

Luz et al. (2008) fitted ARIMA models to monitor dengue incidence in Rio de Janeiro over the period 1997–2004. The results of the fitted model were used to predict dengue incidence by 2005. The authors further evaluated whether incorporating climatic variables in the models would increase their predictive power. The climatic variables were selected using Pearson's correlation tests and univariate ARIMA models between such variables and a 'pre-whitened' dengue series over a range of lags. This pre-whitening consisted in removing the trend and seasonal components of the dengue series using ARIMA models. The climatic variables that correlated with dengue incidence were tested as additional regressors in further ARIMA models. Incorporating independently maximum temperature during the same month, and number of rainy days with a lag of one month improved predictive power of the fitted ARIMA models. However, the predictions computed with the results of these climate-informed models were not significantly better than the estimated with the ARIMA model without external regressors.

The model's predictions of this study were significantly close to the observed dengue incidence in the study region making it very useful as a decision-making tool. However, for the understanding of associations between dengue and weather, the model is not as reliable as it fails to incorporate potential confounders (see Section 1.4). Thus, the estimated associations between dengue and weather are likely to be biased (Robins and Morgenstern, 1987; Gething et al., 2010). The study was conducted over a short period of time (8 years) and across a small geographical area which, as previously explained, pose challenges for the identification of climatic signals with high statistical confidence (Elliott and Wartenberg, 2004; Santer et al., 2011), and may lead to biased risk estimations due to low disease counts (Olsen et al., 1996).

1.5.5 Wavelet analyses

Wavelet analysis allows the study of nonstationary time series by decomposing them into time-frequency domains (Liu, 1994; Torrence and Compo, 1998). The method allows the investigation and quantification of the temporal evolution of different periodic components of a given time series (Cazelles et al., 2005, 2007). Signals can vary both in frequency and amplitude over time. For example, sea surface temperature in the Niño-3.4 Region shows both high-frequency spikes on a time scale of two to seven years, as well as longer interdecadal fluctuations. Wavelet analysis allows the time-frequency decomposition, and the identification of these cycles on an ENSO series with a trade-off between time and frequency resolution (e.g. Torrence and Compo, 1998). One major drawback of wavelet analysis is that it assumes a linear functional form making it inappropriate for analysing data describing nonlinear phenomena (Cummings et al., 2004). As with other methods, this problem may be solved by transforming the variables to linearize their relationship (Cohen et al., 2003).

Wavelet coherency analysis is an extension of this method. Unlike conventional statistical methods (i.e. spectral density analysis), wavelet coherence measures the cross-correlation between two time series as a function of their frequencies (Torrence and Compo, 1998), providing information about those periods where two nonstationary signals are linearly correlated with each other (Cazelles et al., 2005). More specifically, wavelet coherence analysis determines if the presence of a particular frequency in a disease series at a specific time is related to the same frequency, and at the same time in a given covariate (Chaves et al., 2008). However, research indicates that a significant level of wavelet coherence between two series does not necessarily correspond to a statistically significant dependence between random signals (Bigot et al., 2011).

Cazelles et al. (2005) estimated associations between severe dengue (henceforth dengue) incidence in Bangkok and the averaged incidence for the rest of Thailand, and the Niño-3 index, the Southern Oscillation Index, and average monthly temperature and precipitation over the period 1983–1997. Wavelet analysis was selected because, as previously explained, it allows the quantification of the temporal evolution of a time series with different cyclic components (Cazelles et al., 2007). Statistical relationships between the dengue and climatic time series were estimated using wavelet coherence analysis.

The dengue series showed strong seasonal oscillations, indicating a strong influence of the annual cycle on dengue dynamics. The El Niño series on the other hand, was dominated by cycles of about 4–6 years. Both dengue series have in-phase cycles of about 2–3 years (with a mean delay of three months in the rest of Thailand with respect to Bangkok) only over the period 1984–1992 where there is high coherence with El Niño cycles. Over the periods 1983–1986 and 1991–1997 the annual oscillations are dominant, showing a mean delay of one month in Bangkok with respect to the rest of Thailand.

Dengue and precipitation were significantly associated with each other at the annual scale. Both series are in-phase in most of the country; however, dengue incidence in Bangkok follows the seasonal peak of precipitation after a short lag time (length not specified by the authors). Over the period 1986–1991, dengue and precipitation were significantly associated for cycles of about 2–3 years. Similar but weaker patterns of oscillation were observed for temperature in both series.

Johansson et al. (2009a) analyzed statistical relationships between dengue incidence, ENSO, and local weather across Puerto Rico, Mexico, and Thailand over different time periods (see Table A.1). Wavelet coherence analysis was used to estimate the relationships between dengue incidence, ENSO, and the local weather on annual and multiyear scales. ENSO and dengue showed significantly associated cycles of approximately 3.6 years in Puerto Rico, with a delay of about six months on the dengue cycles with respect to ENSO.

No significant associations were detected between dengue and ENSO in Mexico and Thailand at interannual scales.

Dengue, temperature and precipitation showed significantly associated modes of oscillation on the annual scale in the three countries. Temperature was not significantly associated with dengue incidence in any of the studied countries at interannual scales. Associations between dengue and precipitation varied between countries at interannual scales. In Puerto Rico, precipitation and dengue cycles of about 1.8 years were significantly associated with each other with a lead of approximately four months in the dengue series with respect to precipitation. Since it is impossible for dengue incidence to influence precipitation, Johansson et al. (2009a) hypothesize that such phase difference indicates that decreased precipitation leads to increased dengue seven months later due to increased water storage (see Section 1.4.3). Similar associations were observed in Thailand for cycles of about 2.5 years, with delay of about two months in the dengue series with respect to precipitation. In Mexico, no significant associations were estimated between dengue incidence and precipitation on multi-year scales.

Chowell et al. (2011) estimated associations between dengue incidence and climatic factors across the jungle, coast, and mountain regions of Peru, over the period 1994–2008. Two time periods were assessed to partially account for the introduction of new serotypes (1994–1999 and 2000–2008). The time series were square root transformed to stabilize their variance. Wavelet coherence revealed significant coherence between dengue and mean temperature at the annual level. The coherence pattern for precipitation was less clear.

Critique to Cazelles et al. (2005); Johansson et al. (2009a) and Chowell et al. (2011). One advantage of wavelet analyses is that they allow the analysis of nonstationary data, as well as the estimation of transient relationships between two signals (Cazelles et al., 2007). One major drawback, however, is that wavelet coherence analysis only allows the estimation of statistical associations between two time series at the time. Consequently it is not possible to account for the potential effects of confounding variables. Also, because only two series can be analysed at a given time, the analysis of panels of cross-sectional data is not feasible. Therefore, series from multiple administrative units should be either analysed individually, which can be tedious; or aggregated at a greater scale which may lead to aggregation bias (Theil, 1954; Grunfeld and Griliches, 1960). Johansson et al. (2009a) acknowledge this situation and state that the estimated lack of association between dengue and El Niño in Mexico may be due to the aggregation of data at the national level.

1.5.6 Generalized Linear Model and Generalized Linear Mixed Model

The Generalized Linear Model (GLM) is a broad class of regression models developed to address multiple regression when the variance on the outcome variable is not constant, or when the errors are not normally distributed such as count data (e.g. the number of dengue cases in a given region at a given time), or binary response variables (e.g. dengue epidemics or non-epidemic) (Cohen et al., 2003; Crawley, 2007). In count data, there are often lots of zeros in the outcome variable, and the variance may increase linearly with the mean

(Crawley, 2007). The Generalized Linear Mixed Model (GLMM) is an extension to the GLM which includes random effects (where the study subjects are random samples of a larger population, and therefore their variance may tell us something about the population) in the linear predictor in addition to the usual fixed effects (where both the study subjects and their variance are identical) (Crawley, 2007).

Unlike linear regression models which assume a normal distribution, the distribution of the outcome variable in the GLM and GLMM may arise from any exponential family distributions (e.g. Gamma, Poisson or binomial) (Guisan et al., 2002). Also, when the dispersion (or scale parameter) of the data is expected to be higher than would be expected based on a chosen distribution, their scale parameters can be estimated using quasilikelihood (Guisan et al., 2002). Although both GLMM and GLM models can handle nonlinear relationships, the identification of the appropriate polynomial terms and transformations of predictors to improve the model's fit can be tedious and imprecise (Guisan et al., 2002).

Logistic, Poisson, and negative-binomial regression models are included within the GLM framework (Gelman and Hill, 2007). Logistic regression is a form of nonlinear regression where the dependent variable is not continuous, and where regression coefficients are expressed in odd ratios (ratio of the probability that an event happens to the probability that it does not happen) (Cohen et al., 2003). The dependent variable may be dichotomous as when one person is diagnosed with dengue fever or not; or may be a count like the number of dengue epidemics in a given period of time.

The Poisson model is used for count data such as the number of disease cases characterized by following a Poisson distribution (Gelman and Hill, 2007). The Poisson distribution expresses the probability of a number of relatively rare events taking place in a given time if such events take place with a known average rate, and are independent of the time since the last event (Levin, 1988). The negative binomial model is used to fit overdispersed (i.e. the variance appears to be greater than the mean) count data that cannot be encompassed by a Poisson model (Gelman and Hill, 2007).

Koopman et al. (1991) conducted a serosurvey in individuals under 25 years across 3,408 households in 70 Mexican localities from March to October 1986. Within each household, various aspects were registered (e.g. construction, access to mosquito protective measures, history of clinical dengue). Locality level variables were then created for each of the variables registered at the household level (Table A.1). Additionally, population size, socioeconomic level, and meteorologic variables were obtained for each locality.

The authors used stepwise logistic regression for selecting a final set of variables in a multivariate analysis. Even though some of the variables fell out of this regression, they were included in the final model because they were considered to be potential confounding variables (Koopman et al., 1991).

The median temperature during the rainy season showed a stronger association with dengue than the other variables with a four times greater odds ratio of infection (95% CI 2.5–6.6) in communities with a median temperature of 30°C compared to communities with a median temperature of 17°C over the rainy season (Koopman et al., 1991). This finding supports the notion that variations in temperature greatly influence many aspects of the biology of both *A. aegypti* and the dengue viruses (Watts et al., 1987; Gage et al., 2008; Jansen and Beebe, 2010). The authors do not report a quantification of the estimated dengue risk associated with mean annual precipitation pressumably because this variable fell out of the initial screening.

Temperature and altitude are negative and significantly correlated. Therefore, not surprisingly altitude showed the second strongest association with dengue with the odds ratio of dengue infection at 10m above sea level being two times (95% CI 1.6–2.6) the odds ratio of infection at 1,200m. Humid climates were associated with a 1.4 greater risk of infection (95% CI 1.1–1.7) compared to dry climates.

The presence of uncovered water-holding containers and mosquito larvae were both significantly associated with a 1.9 times greater risk of infection (95% CI 1.4–2.7, and 1.4–2.5 respectively) when comparing communities with high and low levels (Koopman et al., 1991). The presence of tyres in the household, on the other hand, was associated with a 1.1 times greater risk of dengue infection in communities with high levels of this factor.

With the exception of the use of sleeping nets, the use of protective measures (i.e. insecticide use, complete screening, use of smoke for mosquitoes) decreased the odds ratio of infection. The use of sleeping nets was found to be a risk factor with a 2 times (95% CI 1.4–3.1) greater odds ratio of infection when used. This finding may be explained by human and mosquito behaviours, because people may use sleeping nets when mosquito populations are high, but *A. aegypti* prefers to feed in the early morning and late afternoon (Koopman et al., 1991). The main strenghts of this study rely on the unique dataset of epidemiological, environmental, and socioeconomic variables at a very refined scale, and their inclusion as covariates in a single model for the whole study area.

To our knowledge, this study is unique in its design. The amount of covariates included in the model and the high resolution of the data constitute two of its main strengths. However, the time span of the Koopman et al. (1991) study is very short which is problematic for the identification of climatic signals with high statistical confidence (Santer et al., 2011). This could possibly explain the lack of significant associations between dengue and mean annual precipitation. Also, logistic regression requires an *a priori* knowledge of the functional form of the associations between dengue and each modelled variable (Schimek, 2009). The incorrect specification of the functional form of the associations between dengue and weather may lead to residual confounding (Benedetti and Abrahamowicz, 2004).

Hales et al. (2002) estimated empirical relationships linking the global spatial distribution of dengue outbreaks (dengue occurrence in excess of what would normally be expected) and local humidity, and extrapolated their results to predict future changes in the geographic distribution of the disease under the IS92a climate change scenario. The number of dengue outbreaks was collected by country, unless subnational information were available, for the period 1975–1996. Climate information (see Table A.1) was retrieved from the Intergovernmental Panel on Climate Change (IPCC) data distribution centre for the period 1961–1990.

Two logistic regression models were fitted by the method of maximum likelihood to predict the presence or absence of dengue outbreaks at the global scale (Hales et al., 2002). The models results were then used to project the potential effects of climate change on the geographical limits of dengue by 2055 and 2085 using the outputs of a range of global circulation models (ECHAM4, HADCM2, CGCMA2, and CGCMA1). The outputs of the regression models were used to estimate the population at risk of dengue under the baseline and climate change scenarios.

The first model only included local humidity (defined as vapour pressure or specific humidity) as explanatory variable. There is no indication about why temperature and precipitation variables were dropped from the model. It is likely that these variables had a poor or nil association with dengue, but this is not explicit in the paper. This initial model explained 89% of the variation on the outcome variable. Humidity was significantly associated with dengue outbreaks with a 1.3 greater risk (95% CI 1.29–1.31) of outbreaks in areas with high levels of humidity. The final model included local humidity, maximum humidity within a radius of ten grid squares (grid size 0.5°) to reduce the spatial patterning of the residuals, and an interaction term between these two variables. The model explained of 92% of the variation on the outcome variable, a sensitivity (the proportion of dengue outbreaks accurately predicted by the model) of 85% and a specificity (the proportion of non-outbreaks accurately predicted by the model) of 93%. This model represents one of the first and few attempts to model the geographical limits of dengue at the global scale using empirical modelling methods.

As in other studies, Hales et al. (2002) fail to acknowledge the effects of potential confounders (see Section 1.4) in their models, something that greatly undermines their results (Robins and Morgenstern, 1987; Gething et al., 2010). The use of national level data may result in aggregation bias issues (Theil, 1954; Grunfeld and Griliches, 1960) which are particularly problematic when estimating nonlinear relationships (Fezzi and Bateman, 2012). This bias has severe implications for their prediction of climate change impacts because such predictions could be significantly distorded and lead to flawed conclusions (Fezzi and Bateman, 2012). Additionally, the univariate analysis performed is likely to produce erroneous results if a region experiences increases in two climatic variables with opposite effects of similar magnitude on the disease outcome (Rohr et al., 2011).

Johansson et al. (2009b) analyzed associations between dengue incidence, temperature and precipitation across 77 Puerto Rican municipalities over the period July 1986 to December 2006. One municipality (Culebra) was excluded from the analyses because of relatively sporadic transmission. A hierarchical GLM was fitted to estimate local associations over time as well as spatial heterogeneity.

The first modelling stage consisted in fitting municipality-specific GLM models with Poisson specification, regressing dengue incidence on either monthly average temperature or monthly average precipitation, to estimate their local short-term associations. These models included a population offset and a natural cubic spline function of time to adjust for seasonal confounding. Distributed lag models were used to assess effects of weather on dengue, up to six months later, to account for the delayed effects of weather on mosquito populations. The second stage consisted in estimating global associations by averaging the short-term associations across municipalities and identifying local climatic and socioeconomic factors (see Table A.1) that may potentially modify the previously estimated local short-term associations. This stage allowed the characterization of the spatial heterogeneity on the relationships between dengue and weather. The model was fitted using a Bayesian framework.

Temperature lagged zero, one, and two months were positive and significantly associated with dengue incidence in most municipalities. The global association (i.e. the average of local short-term associations) was positive and statistically significant at all three lags. Short-term associations were weaker for mean temperature compared to maximum and minimum temperatures. Precipitation lagged one, and two months were significantly associated with dengue in some municipalities. The global association with precipitation was positive and significant only after having accounted for the effect modification of long-term climate. Municipalities with a higher poverty index showed a stronger short-term association between dengue and weather; however, such an effect was not consistent across lags.

The smooth function used in this study greatly reduces the observed interannual variability in dengue incidence, and effectively isolates the associations with weather on the temporal scale (Johansson et al., 2009b). As previously mentioned, removing the seasonal trends from the analysis is critical to differentiating the effects of potential confounders with smooth seasonal trends (Bowie and Prothero, 1981; Johansson et al., 2009b). However, such spline contains more variation than can be really attributed to weather making the associations evident, but at the same time, likely underestimating the magnitude of the true effects of weather (Johansson et al., 2009b). The model fit would have benefitted from the extension of flexible smooth functions to the climatic factors as it could have allowed the estimation of highly nonlinear relationships with dengue incidence.

The findings of Johansson et al. (2009b) provide the first piece of quantitative evidence for understanding why local associations between dengue and weather are spatially heterogeneous. Unfortunately, these findings arise from a rather small geographical area, with a low range of climatic conditions posing difficulties for their generalization to other regions with greater climatic variability. It is possible that the relatively low variation in climate would have prevented the model from detecting complex nonlinearities in the relationships between dengue, weather and climate.

Sriprom et al. (2010) developed a GLM to estimate associations between dengue incidence, weather and socioeconomic conditions across the Sakon Nakhon province of Thailand over the period 2005-2007. The GLM model was adjusted for the effects of each year, and included a multiplicative interaction term for minimum temperature and precipitation. Then, the authors assessed the potential impact of climate change on dengue incidence using their model's output and multi-model averages based on the temperature and precipitation predictions for the A1B emissions scenario, for the period 2090–2099.

The results indicated that dengue was positive and significantly associated with minimum temperature. The relationship with precipitation, however, was negative for temperatures smaller than 23.2°C, and positive for temperatures above that threshold. For monthly minimum temperatures lower than 23.2°C, the combined effect of minimum temperature and precipitation is heterogeneous across districts, whereas for monthly minimum temperatures above 23.2°C, the impact of climatic factors is positive and homogeneous across districts. The number of children of 0–4 years old, was positive and significantly associated with dengue incidence, whilst both the proportion of villages with primary schools and per capita number of public small water wells showed negative associations. The projections under the A1B scenario assumptions suggest that climate change may increase the spatial distribution of dengue in the region from the most populated districts to less populated ones. It may also increase the dengue transmission period to include part of the winter, summer, and the rainy seasons (February to November).

Sriprom et al. (2010) explicitly accounted for the effects of some socioeconomic confouders, and controlled for the effects of year-specific omitted variable bias and un-modelled confounders (e.g. the introduction of a new dengue serotype). As a consequence, their estimations of future dengue risk under climate change are more reliable than those from previous studies (e.g. Hales et al., 2002). One drawback, however, is that the study is restricted to a small temporal frame which, as has been mentioned, is problematic for the identification of climatic signals with high statistical confidence due to their small signal-to-noise ratios (Santer et al., 2011). Furthermore, although both GLM models can handle nonlinear data relationships, the authors did not seem to have attempted identifying complex nonlinear structures in their study.

Lowe et al. (2011) estimated empirical relationships between dengue, weather and ENSO across 558 microregions of Brazil over the period 2001–2008. The main objective of their study was to analyse the potential for incorporating climate information into a spatio-temporal early warning system for Brazil. In an early stage, the authors fitted a series of GLM models with a negative binomial specification because dengue data showed substantial extra-Poisson variation (overdispersion). Stepwise regression algorithms were used to select the most appropriate and parsimonious model. Interactions between a categorical variable for an ad-hoc zone classification and month were included to account for non-climatic confounders that may produce an observed spatially varying annual cycle in dengue incidence.

The initial model failed to capture much of the spatio-temporal variability in dengue incidence. Therefore, Lowe et al. (2011) further developed their model fitting a Generalized Linear Mixed Model (GLMM) within a Bayesian framework. This model was generated just for a subset of the dataset (the South East region), and included the same set of covariates selected in the previous stage with the exception of the zone factor. Random effects were included in the linear predictor to allow for unobserved structures in the model that may vary both temporally and spatially (e.g. serotype introduction). Additionally, a first order autoregressive component was included to avoid serial correlation in the residuals. The GLMM model captured substantially more spatio-temporal variation in dengue than did the GLM. The estimated relationships between dengue and the covariates in the model were similar for both the GLM and the GLMM. Both temperature and precipitation at lags of one and two months showed a positive and significant association with dengue. Associations with ENSO, on the other hand, were negative using the Niño-3.4 index at a lag of six months. No information is provided about the estimated relationships with the non-climatic covariates.

The spatially refined dataset across a large geographical area used by Lowe et al. (2011), as well as the use of random effects in the linear predictor, allowed them the estimation of both local and global associations between dengue and weather based on great range of climatic variations, while assuming that the differences between micro-regions are of interest. Thus, the global associations estimated by Lowe et al. (2011) could potentially be generalized to other regions with climatic, socioeconomic and epidemiological features within the range of their dataset. Lowe et al. (2011) accounted for a considerable amount of observed and unobserved confounders because of their model specification, increasing the reliability of their estimations (Robins and Morgenstern, 1987; Gething et al., 2010). Unfortunately, there is no indication as to whether these confounders showed significant associations with dengue.

Although both GLMM and GLM models can handle nonlinear data relationships, Lowe et al. (2011) did not attempt to identify the form of complex nonlinear structures in their dataset. The short time span of the study poses problems for the identification of climate signals due to low signal-to-noise ratios (Santer et al., 2011).

El Niño has a strong effect on the local weather of many countries and it is believed that this effect ultimately influences dengue (Kovats et al., 2003). Therefore, including the Niño-3.4 index in the same model as weather covariates (e.g. Lowe et al., 2011) prevents the identification of the effects of both on dengue incidence due to partial redundancy (Cohen et al., 2003). A thorough estimation of the effects of El Niño should include models with and without the effects of weather.

1.5.7 Species distribution modelling: Maxent

Maxent is a species distribution modelling method that allows the modelling and mapping of diseases by establishing relationships between the conditions where the disease has been observed and a series of predictors (Machado-Machado, 2012). Theoretically, this method is similar to GLM and generalized additive models (GAM) (Phillips et al., 2006). One advantage however, is that while both GLM or GAM require absence data when used to model probability of disease occurrence, Maxent does not need case absences; instead the probability distribution is determined using background environmental data for the region under study (Phillips et al., 2006). Like GAM models, Maxent is able to fit complex nonlinear relationships between the outcome and predictor variables, including interactions between the predictors (Phillips et al., 2006; Elith and Graham, 2009).

Some drawbacks of the method are that it can give very large predicted values for environmental conditions outside the range observed in the study area. Therefore, extrapolating to other areas or to future or past climatic conditions could be problematic (Phillips et al., 2006). Furthermore, there are few guidelines for its use, and fewer methods for estimating the amount of error in its predictions, compared to those available for GLM or GAM (Phillips et al., 2006). Also, Maxent is not available in standard statistical packages (Phillips et al., 2006).

Machado-Machado (2012) aimed to identify suitable areas for dengue occurrence based on the relative influence of climatic and socioeconomic covariates as determinants of dengue across Mexico. Mean annual dengue incidence (1999–2006) was calculated for each Mexican municipality, and then averaged. Climate data was obtained from weather stations for the period 1950–2000, and interpolated using smoothing splines and elevation data. The modelling followed a three-stage approach using the Maxent method (Phillips et al., 2004). In the first stage, two models were fitted. The first one included the full set of climatic variables, and the second one both climatic and socioeconomic variables.

The second modelling stage consisted of producing independent predictor variables using principal components analysis (PCA). Two models were generated, the first of which used four principal components derived from climatic variables; whilst the second used the five components derived from both, climatic and socioeconomic variables. The third set of models was based on variables identified as limiting factors of dengue fever distribution by previous research, as well as inferences drawn from cumulative frequency plots for each predictor.

Low elevation coastal areas were identified as the most suitable for dengue occurrence. In all the models, minimum temperature of the coldest month, mean temperature of the coldest quarter, annual precipitation, and to a lesser extent, precipitation of the coldest quarter, consistently contributed the most to defining suitabile dengue areas. The first principal component was the variable that contributed the most to both of the models based on PCA, and was highly correlated with annual precipitation, minimum temperature of the coldest month, mean temperature of the coldest quarter, and temperature annual range. The contribution of the socioeconomic variables was minor compared to that of the climatic ones. Minimum temperature of the coldest month and mean temperature of the coldest quarter were the variables that gave the highest gain to the model when used in isolation. When omitted, these variables decreased the overall gain of the model. However, such decrease was not significantly large, indicating that part of their information is shared by other covariates.

As with other statistical methods, the efficacy of the Maxent models depends on the dataset under analysis. While Machado-Machado (2012) explicitly incorporates a wide range of climatic and socioeconomic covariates, one major drawback of this model is that the coarse aggregation of data at the temporal scale neglects both the intra- and interannual variability in both the dengue and climatic series. Therefore, the model is not able to estimate (i) the suitability of dengue occurrence for different seasons, and (ii) the complex nonlinear relationships characteristic of the dengue, temperature, and precipitation interactions, and cannot be extrapolated to other climatic conditions with confidence. The model was generated under the assumption that dengue occurred exclusively in urban areas. However, as previously mentioned, dengue has also been reported in peri-urban and rural areas (Chareonsook et al., 1999; Nagao et al., 2008; WHO, 2009; Nguyen et al., 2011; Schmidt et al., 2011)

1.5.8 Summary

The previous analysis shows that most studies have failed to incorporate non-climatic confounders greatly undermining their estimations of dengue risk (Robins and Morgenstern, 1987; Gething et al., 2010; Jansen and Beebe, 2010). Also, it is not clear how the specification of the functional form of the associations between dengue, weather, and El Niño was conducted in many of these studies. Several studies were conducted across large geographical areas using data aggregated at national or supra-national scales (e.g. Hales et al., 1996; Johansson et al., 2009a) which may have caused aggregation bias issues (Theil, 1954; Grunfeld and Griliches, 1960). Some other studies were conducted across small geographical areas (e.g. Hurtado-Díaz et al., 2007; Brunkard et al., 2008), which tend to be climatically and socioeconomically homogeneous (Elliott and Wartenberg, 2004), and commonly result in low numbers of disease cases that lead to unstable risk estimations (Olsen et al., 1996). Just a few studies attempted estimating associations between dengue, weather and El Niño across large geographical areas using data aggregated at the sub-national scale (e.g. Lowe et al., 2011).

About half of the studies spanned short time periods ($\leq$ 10 years), and only a few spanned over 20 years. Such short time series are problematic for the identification of climatic signals with high statistical confidence because of their small signal-to-noise ratios (Santer et al., 2011). Some studies have failed to incorporate the potential effects of both climatic and non-climatic confounders when estimating associations between dengue and El Niño (e.g. Gagnon et al., 2001). Other studies estimated associations between dengue and El Niño including weather variables in the same model (e.g. Lowe et al., 2011). Including both El Niño and weather variables in a single model may prevent the identification of the effects of El Niño on dengue incidence due to partial redundancy (Cohen et al., 2003). To our knowledge, no previous efforts have been directed at estimating relationships between dengue and El Niño above and below the effects of ENSO on the local weather. Only one study (i.e. Johansson et al., 2009a) investigated potential climatic and non-climatic causes of between-regions heterogeneity observed in dengue incidence across a single country.

Research suggests that the transmission and distribution of vector-borne diseases is likely to change in the next decades as a result of climate change (Confalonieri et al., 2007). Initial studies suggested that hosts and parasites in temperate regions were expected to be the most affected by climate change (in comparison to hosts and parasites in other parts of the world) due to the disproportionate increases in temperature expected in such regions (Rohr et al., 2011). However, recent studies suggest that tropical hosts and parasites might be as affected by such temperature increases because they are adapted to narrower temperature ranges (Rohr et al., 2011). Thus, there is still high uncertainty about the potential effects of such climate change on vector-borne diseases such as dengue.

Understanding the relationships between dengue, weather and climate is problematic because of the complex interactions between hosts, viruses, vectors, climatic and non-climatic determinants of the disease. The state of research suggests that there is a need for

(i) good quality data including epidemiological, socioeconomic, climatic, environmental, and demographic information (ii) long-term datasets that do not compromise the applicability of statistical methods, and (iii) reliable statistical models for revealing the relationships between dengue dynamics, weather and climate, ideally in conjunction with that from potential confounding factors.

1.6 Contribution

This thesis builds on previous research and arguable provides elements towards filling the gaps identified in the literature review. We generated a long dataset containing 23 years of laboratory confirmed dengue case observations, aggregated at the province level, with a monthly resolution. The dataset includes information about weather, climate, environmental, socioeconomic, and demographic determinants of dengue ocurrence also aggregated at the province level. To our knowledge, this is the most comprehensive dengue-related dataset analysed to date.

Using Mexico as a study case, this study investigates the effects of weather and climate on dengue across a greater geographical area (1.96 million km^2), time frame (276 months), and number of dengue cases (417,668) compared to the vast majority of previous studies. Mexico was selected as a study case for various reasons. Mexico is both a tropical and subtropical country with a large climatic diversity due to its geographical location (14°32'–32°43' N), wide range of altitudes, and complex orography (Mosiño and García, 1974). The Mexican weather is highly influenced by the ENSO cycles (Magaña et al., 2004). Moreover, the Mexican climate shows a wide range of climatic features observed in numerous low and middle latitude countries (Mosiño and García, 1974) affected by dengue. Mexico has a large socioeconomic heterogeneity (GINI index 0.48, The World Bank 2012), and shares a range of socioeconomic features that are common to various countries affected by dengue (OECD, 2009).

This variability in climate and socioeconomic conditions allows the estimation of relationships between dengue, climatic and non-climatic factors, which can be potentially extrapolated to other regions with climatic and socioeconomic features within the range of our dataset to plan the allocation of resources, and to target intervention needs as appropriate. Dengue is a real public health problem in Mexico. It has been continuously present in the country since the 1970s (SSA, 2008). The disease is present nationwide with the majority of cases occurring in low elevation coastal areas and during the rainy season (Machado-Machado, 2012). The four dengue serotypes have been co-circulating in the country since 1995 (Guzmán and Kouri, 2003). The mean annual incidence rate shows great interannual variability (Figure B.1), with the period 1995–1999 (which coincides with the introduction of the DEN-3 serotype into Mexico, and strongest El Niño in our period of study), and the period 2006–2007 showing the largest increases across provinces.

We produced a wide range of empirical models generated taking into consideration the confounding effects of both climatic and non-climatic factors, the lagged effects of the climatic variables, the influence of long-term and seasonal trends, and autocorrelation in the dengue series. We investigated the nonlinear effects of weather on dengue using smooth functions which estimate the optimal degree of nonlinearity of the model directly from the data, resolving the subtle task of determining the model flexibility *a priori* (Wood, 2006). By demonstrating that there is a great deal of between-province heterogeneity in the effects of weather and El Niño on dengue, we highlight the importance of using spatially disaggregated data for modelling disease outcomes in regions with great climatic and socioeconomic heterogeneity such as Mexico.

Our results also reveal that the effects of El Niño on dengue in some regions are largely influenced by the 1997–1998 El Niño event. In addition, we argue that previous attributions of increases in dengue incidence the 1997–1998 period solely to El Niño may be overestimating the real relative influence of El Niño on dengue due to the concurrent introduction of the DEN-3 serotype to the country. Additionally, we demonstrate that El Niño has different effects on dengue incidence during summer and winter.

We demonstrate that, contrary to what intuition would indicate, rising access to piped water is associated to significant increases in dengue incidence. We argue that such an effect is related to the the scarcity or lack or reliable water supply services that force people to store water in domestic and peri-domestic containers that may potentially become breeding sites for *A. aegypti* (Jansen and Beebe, 2010; Nguyen et al., 2011). In addition, we show that the effects of socioeconomic status of people do not seem to play a significant role on dengue transmission. Finally, we used some of our model estimations to project the potential impact of climate change on dengue incidence, accounting for the confounding effects of socioeconomic development. To our knowledge, this is the first study estimating the impacts of climate change in Mexico at the national scale.

1.7 Thesis structure

The core of this thesis is divided into three data chapters. Each chapter is structured as a paper for publication in an academic journal.

Chapter 2 estimates associations between dengue incidence, minimum temperature, maximum temperature, precipitation, and El Niño in the warm and humid region of Mexico, over the period 1985–2007. The effects of El Niño were analysed with and without controlling for the effects of weather to estimate associations with dengue above and below such effects. Significant increases in dengue incidence coincided with the strongest El Niño event in our records (1997–1998), as well as with the introduction of a new dengue virus serotype (DEN-3); therefore, we re-computed all our estimated relationships excluding the months coinciding with this El Niño event from the series.

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[1]http://www.ajtmh.org/content/84/5/757.full (Accessed 24 Aug 2012)

Chapter 3 analyses associations between dengue incidence, weather, and El Niño across Mexico using a two-stage approach. In the first stage, we fitted a series of province-specific GLMs with Poisson specification to estimate local associations between dengue and weather. Then, we determine the significant level of between-province variation in the strength of such associations using meta-analytic regression methods. Finally, we assess the effect modification of the underlying climate and a range of socioeconomic moderators.

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Chapter 4 investigates the relationships between dengue and weather adopting a semi-parametric modelling approach, estimating the relative influence of weather and socioeconomic development on dengue with a Generalized Additive Model (GAM) (Wood, 2006). Then, we extrapolated dengue risk into the future for the years 2030, 2050 and 2080, under the A1B, A2 and B1 climate change scenarios. The GAM mdoel was coupled with penalized likelihood function and an automated smoothing selection criterion, which estimated the optimal degree of nonlinearity of the model directly from the data (Wood, 2006). This specification resolves the subtle task of determining the model flexibility *a priori* by incorporating this choice into the actual estimation process.

This chapter will be submitted for consideration to Nature Climate Change. Paper details: Colón-González, F. J., Fezzi, C., Lake, I. R., and Hunter, P. R. The Potential Impact of Climate Change on Dengue. *Nat Clim Chang*. Authors' contributions: Conception and design: FJCG, CF. Dataset creation: FJCG. Data analysis: FJCG, CF. Preparation of the paper: FJCG. Paper revision: CF IRL, PRH.

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Chapter 2

The effects of weather and El Niño on dengue incidence in warm and humid Mexico

2.1 Abstract

Dengue is an acute viral disease caused by four distinct but genetically related viruses. Dengue viruses are transmitted through the bite of infective *Aedes aegypti* mosquitoes. Dengue dynamics is highly sensitive to changes in weather because of the ectothermic nature of such mosquitoes and their physiological sensitivity to the presence of water. In this chapter, we fitted multiple linear regression models to estimate associations between dengue incidence, weather and El Niño in the warm and humid region of Mexico. Data were collected for 12 Mexican provinces over a 23 years period (January 1985 to December 2007). Our results show that the incidence rate of dengue is higher during El Niño events and over the warm and wet season. We provide evidence to demonstrate that dengue incidence is positively associated with the strength of El Niño as well as minimum temperature, particularly during the cool and dry season. Our study complements the understanding of dengue dynamics in the region and may be useful for the effective allocation of resources.

2.2 Introduction

Dengue is an infectious disease caused by the dengue virus, with *Aedes aegypti* acting as the main vector. Symptoms include headaches, rashes, joint and muscle pains, and in a small proportion of cases, life-threatening complications such as dengue hemorrhagic fever and dengue shock syndrome (Reiter, 2001). It is present in over 100 tropical and subtropical

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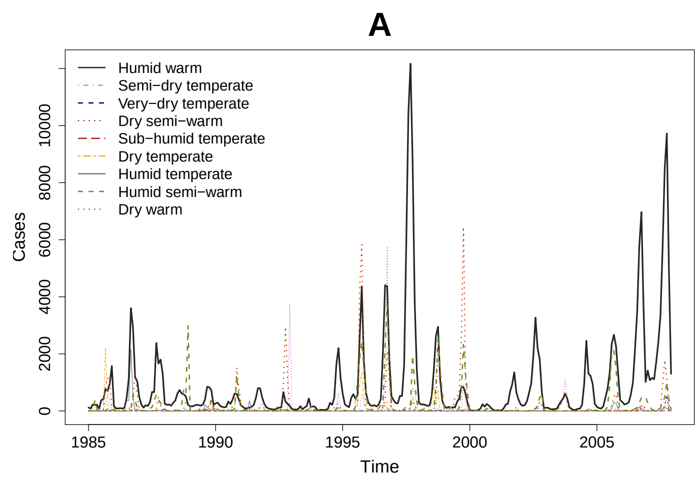
countries, (Hsieh and Chen, 2009) where approximately 50–100 million cases are reported every year (Günther et al., 2009). The global burden of dengue has been estimated in 750,000 disability-adjusted life years (the number of lost years of healthy life, WHO 2012) per annum lost due to absenteeism, immobilisation, debilitation or medication (Murray and Lopez, 1996a,b; Clark et al., 2005). Moreover, its economic burden has been estimated in 2.15 billion US dollars per year just in the Americas (Shepard et al., 2011). In Mexico, dengue is endemic all over the country. However, almost 60% of the cases occur in the southern part of the country (Figure 2.1) characterized by a warm and humid climate.



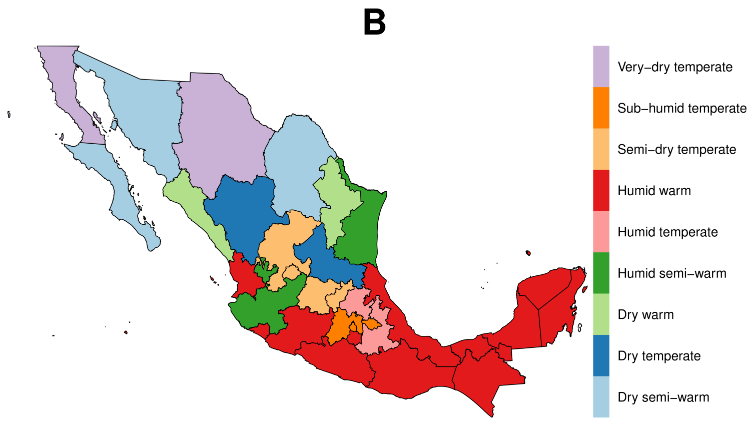


Figure 2.1: (A) Monthly dengue cases aggregated by dominant climate (1985–2007); (B) dominant climates by province.

The absence of cold winters, the high concentration of population in urban areas (INEGI, 2005), and the large inequality (GINI index 0.48, The World Bank 2012) observed in the country allow the development of the disease throughout the year (Reiter, 2001). Behavioural and cultural factors also play a key role in the prevalence of dengue (Reiter, 2001). For example, the close proximity and poor construction of houses and buildings in the cities, the use of natural ventilation instead of air conditioning, and low access to health services and health education interact to facilitate the transmission of the dengue viruses (Reiter, 2001).

Research indicates that dengue shows both strong inter-annual and intra-annual variability (Cazelles et al., 2005, 2007), that is the result of both extrinsic (e.g., climate variability) and intrinsic (e.g., host–virus interactions mediated by herd immunity and host susceptibility) factors (Wearing and Rohani, 2006). Both these factors drive the serotype-specific dynamics and may increase the incidence rate of the disease (Nisalak et al., 2003).

Significant efforts have been made to understand the effects of weather and El Niño on dengue transmission (e.g. Hurtado-Díaz et al., 2007; Lowe et al., 2011). Variations in temperature and precipitation, as well as the occurrence of El Niño have been associated with changes in dengue incidence in Mexico (e.g. Hurtado-Díaz et al., 2007; Brunkard et al., 2008) and other countries (e.g. Focks et al., 2000; Cazelles et al., 2007; Chadee et al., 2007).

Previous studies relating weather to dengue incidence in Mexico have analysed time series of dengue cases up to one year (e.g. Koopman et al., 1991; Chowell and Sánchez, 2006; García et al., 2008), and only a few have analysed series of up to ten years (e.g. Hurtado-Díaz et al., 2007; Brunkard et al., 2008). Such short series pose problems for disentangling the overall associations between weather and dengue with high statistical confidence due to their small signal-to-noise ratios (Santer et al., 2011). Our study analyzes 23 years of reported dengue cases to estimate associations with temperature, precipitation and El Niño. We also analyze a larger geographical area than previous studies by including data from 12 provinces in comparison to previous studies that focused on smaller areas such as a few cities or municipalities (e.g. Chowell and Sánchez, 2006; Brunkard et al., 2008).

The aim of this paper was to examine if changes in dengue incidence are statistically associated with weather and El Niño in the warm and humid region of Mexico. The null hypothesis was that the cumulative incidence rate (CIR) of dengue is not statistically associated with weather or El Niño.

2.3 Materials and methods

2.3.1 Data

Monthly dengue notifications were obtained from the web page of the National System of Epidemiologic Surveillance (SINAVE)[1] for the period January 1985 to December 2007 (Figure 2.1). Dengue notifications were defined as any legal notification of confirmed dengue and severe dengue referred to SINAVE by the health authorities (CENAVECE, 2008). Because severe dengue is only a severe presentation of dengue, both dengue and severe dengue cases were analysed together.

Data were obtained for all Mexican provinces with a dominant warm and humid or subhumid climate. Such provinces comprised Campeche, Colima, Chiapas, Guerrero, Michoacán, Morelos, Nayarit, Oaxaca, Quintana Roo, Tabasco, Veracruz and Yucatán. The

[1]http://www.dgepi.salud.gob.mx/anuario/html/anuarios.html (Accessed 12 Mar 2009)

dominant climate of each province was retrieved from the web page of the National Institute of Statistics and Geography (INEGI)[2]. These provinces have a joint population of over 31 million people. Moreover, the warm and humid region of Mexico contains the majority (59.8%) of the total dengue cases occurring in Mexico. A total of 249,618 dengue cases were reported in this region over the period from 1985 to 2007.

To obtain an estimate of the strength of El Niño we retrieved monthly sea surface temperature (SST) data from the website of the Climate Prediction Center of the National Oceanic and Atmospheric Administration[3]. We chose the Niño-3.4 Index because it is one of the most sensitive indices for determining an El Niño event (Trenberth and Stepaniak, 2001; Hanley et al., 2003). These data are presented in Figure 2.2. An El Niño or a La Niña occur when the SST anomalies relative to the 1950–1979 climatology in the Niño-3.4 region (5°N–5°S, 120°–170°W) exceed either 0.4°C or -0.4°C for a minimum of six consecutive months (Trenberth, 1997). We identified seven El Niño and six La Niña events in the series based on this definition (Figure 2.2). Periods in between El Niño and La Niña events were classified as neutral. Further explanations on what constitutes an El Niño or La Niña event can be found elsewhere (e.g. Trenberth, 1997, 2001).

Mean monthly minimum and maximum temperature, and mean monthly accumulated precipitation were obtained from the Mexican National Meteorological Service for each Mexican Province. These meteorological data corresponded to province-wide average values estimated from all meteorological stations within each province. The province-specific data were averaged to provide overall mean monthly temperature (minimum and maximum) and accumulated monthly precipitation time series for the region. The number of dengue cases within each province was summed to provide overall epidemiological time series data for the region.

Within this warm and humid region, our data show that the year-round climate has two distinct seasons (Figure 2.3B): warm and wet from May to October, and cool and dry from November to April (Mosiño and García, 1974). During the warm and wet season, accumulated precipitation averages 178mm, average maximum temperature (Tmax) is 31°C and average minimum temperature (Tmin) is 18°C. In the cool and dry season, precipitation averages 37mm, mean Tmax is 30°C and mean Tmin 14°C.

Dengue data were converted to a CIR (expressed in cases/100,000 people) based on the region population as suggested by Bonita et al. (2006). Province-specific population data were obtained from INEGI[4] for 1990, 1995, 2000 and 2005. Population estimates for the intervening years were calculated using linear interpolation. We stabilized the variance in the series taking the natural logarithm of the CIR (henceforth LnCIR).

Temporal analyses of the aggregated dengue cases (including all serotypes) revealed inter-annual fluctuations with a strong seasonal component. The seasonality of the transmission shows a peak occurring in October (Figure 2.3). The aggregation of the in- and out-of-phase inter-annual cycles of each serotype and their seasonal components may be

[2]http://www.inegi.org.mx/sistemas/sisept/default.aspx?t=mamb22&c=21443&s=est (Accessed 8 May 2012)

[3]http://www.cpc.ncep.noaa.gov/data/indices/sstoi.indices (Accessed 12 Mar 2009)

[4]http://www.inegi.org.mx/inegi/ (Accessed 23 Mar 2009)

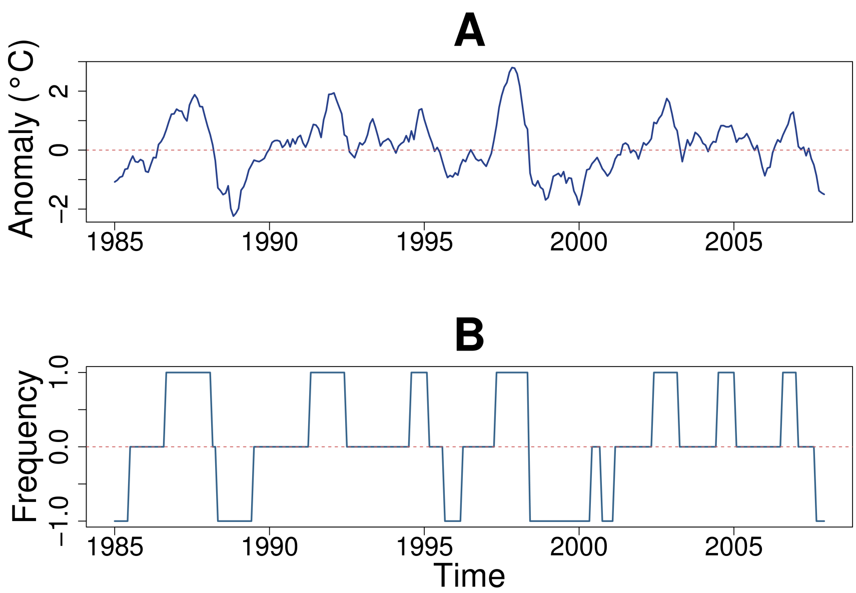


Figure 2.2: (A) SST anomalies in the Niño-3.4 region over the study period; and (B) El Niño (peaks) and La Niña (troughs) events occurring over the study period. El Niño and La Niña events were defined according to Trenberth (1997) as SST anomalies ±0.4°C for six or more consecutive months.

responsible for the seasonal peaks (Wearing and Rohani, 2006) observed in the aggregated serotype time series.

2.3.2 Optimal lagged meteorological variables

The first stage of the analysis was to establish the associations between the LnCIR with the various lags of the explanatory variables to determine the optimal time lag for the final models. Dengue shows a nonlinear dynamics, with strong seasonality and interannual oscillations (Cazelles et al., 2005) that may result from the interaction of intrinsic and extrinsic factors (Johansson et al., 2009a). In these regression models, we controlled for long-term trends by including an index variable of time in the model, and we controlled for seasonal effects by including a categorical variable for calendar month. This is because long-term changes in dengue incidence may result from non-climatic factors such as changes in the reporting practices, or resistance of the mosquitoes to insecticides. Similarly, seasonal changes may be caused by non-climatic factors such as holidays, seasonal water storage, or seasonal mosquito control campaigns. Similar approaches have been used elsewhere (e.g. Lake et al., 2009). We estimated associations between the LnCIR of dengue and each of our meteorological variables lagged 1 to 12 months fitting linear regression models as follows:

$$\log(\mathrm{y}_t) = \beta_0 + \beta_1 t' + \sum_{k=2}^{12} \beta_k D_{kt} + \beta_2 X_{t-l} + u_t \qquad (2.1)$$

where $\log(y_t)$ denotes the LnCIR of dengue for time t = 1,...,276; β_0 is the intercept; β_1, β_2, and β_k are the regression coefficients (slopes) for each explanatory variable (regressor); t' is an index variable for time (from month 1 to month 276); D_{kt} denote a categorical variable for calendar month, where k = 2,...,12 with January set as a reference level; X_t denotes a

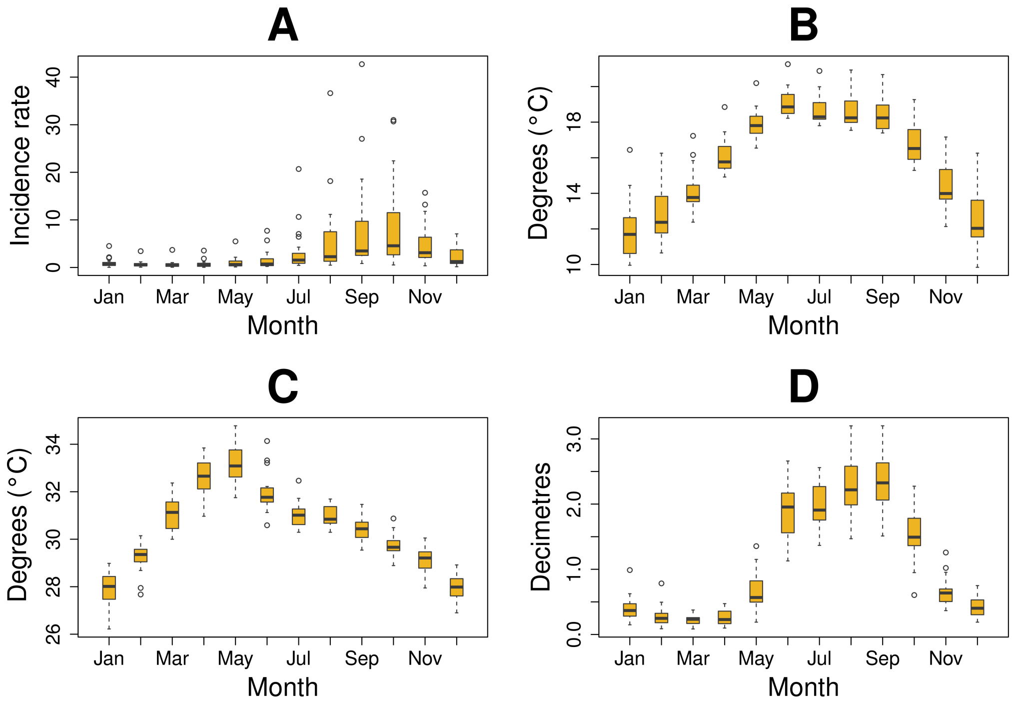


Figure 2.3: Box-and-whisker plots of the annual cycle of (A) dengue incidence, (B) minimum temperature, (C) maximum temperature, and (D) precipitation in the warm and humid region of Mexico for the period 1985–2007. The boxes indicate the 25% and 75% quantiles, and the whiskers give the minimum and maximum values. Outliers are shown as dots above or below the whiskers.

meteorological regressor at l-th lags, and u_t corresponds to the discrepancy or disturbance (the net influence of everything other than the regressors, Johnston and DiNardo 1997). Analyses were conducted in SPSS version 16.0 and R version 2.13.1 (R Development Core Team, 2010).

Many lagged meteorological variables were significantly correlated with the outcome variable (Table 2.1). Including all the related lagged variables in a model would have led to significant collinearity. Consequently, we created new explanatory variables using the mean values of the two lags with the highest significant regression coefficients. The new variables were Tmin lagged 1 and 2 months ($Tmin_{1:2}$), Tmax and SST in the current and present months ($Tmax_{0:1}$ and $SST_{0:1}$), and precipitation lagged 6 and 7 months ($Precipitation_{6:7}$).

Before using these variables in the final models, non-stationarity was examined, because the statistical properties of epidemiological time series commonly vary with time (Cazelles et al., 2007) and may lead to biased estimations (Hsieh and Chen, 2009). We conducted Phillips-Perron tests to verify the stationarity of all variables. The outcome variable and all four independent variables were stationary and consequently, were included in the final regression models.

2.3.3 Final regression models

We fitted different multiple linear regression models using the LnCIR as the outcome variable. The normal distribution of the series was corroborated with a Jarque-Bera test of composite normality (Jarque and Bera, 1980). All models were adjusted for long-term

Lag (in months)	SST (95% C.I)	Tmin (95% C.I)	Tmax (95% C.I)	Precipitation (95% C.I)
0	**0.24 (0.11 – 0.37)**	**0.44 (0.34 – 0.53)**	**0.47 (0.26 – 0.67)**	-0.31 (-0.72 – 0.10)
-1	**0.23 (0.10 – 0.36)**	**0.46 (0.36 – 0.56)**	**0.44 (0.23 – 0.65)**	-0.36 (-0.77 – 0.05)
-2	**0.22 (0.08 – 0.35)**	**0.46 (0.36 – 0.56)**	**0.41 (0.19 – 0.62)**	-0.40 (-0.82 – 0.15)
-3	**0.20 (0.06 – 0.33)**	**0.46 (0.36 – 0.56)**	**0.43 (0.22 – 0.64)**	**-0.53 (-0.94 – -0.11)**
-4	**0.17 (0.03 – 0.30)**	**0.44 (0.33 – 0.54)**	**0.41 (0.20 – 0.62)**	**-0.68 (-1.09 – -0.27)**
-5	**0.14 (0.00 – 0.28)**	**0.39 (0.28 – 0.50)**	**0.33 (0.12 – 0.54)**	**-0.71 (-1.13 – -0.30)**
-6	0.11 (-0.02 – 0.25)	**0.34 (0.23 – 0.45)**	**0.28 (0.07 – 0.50)**	**-0.73 (-1.15 – -0.31)**
-7	0.10 (-0.04 – 0.24)	**0.31 (0.19 – 0.42)**	0.22 (-0.00 – 0.43)	**-0.81 (-1.13 – -0.39)**
-8	0.10 (-0.04 – 0.24)	**0.31 (0.20 – 0.43)**	0.14 (-0.08 – 0.36)	**-0.54 (-0.97 – -0.11)**
-9	0.10 (-0.04 – 0.24)	**0.35 (0.23 – 0.47)**	0.20 (-0.02 – 0.42)	-0.40 (-0.83 – 0.04)
-10	0.10 (-0.04 – 0.23)	**0.36 (0.24 – 0.49)**	0.22 (-0.00 – 0.43)	-0.37 (-0.81 – 0.06)
-11	0.09 (-0.05 – 0.23)	**0.40 (0.28 – 0.53)**	0.19 (-0.03 – 0.41)	-0.38 (-0.81 – 0.06)
-12	0.10 (-0.04 – 0.24)	**0.46 (0.33 – 0.59)**	0.13 (-0.09 – 0.35)	-0.28 (-0.71 – 0.15)

Table 2.1: Regression coefficients of four climatic variables versus the log-transformed cumulative incidence rate (LnCIR) of dengue. Models were controlled for long-term trends and seasonality. Values in bold font were statistically significant at the 0.05 level.

trend and seasonality as described earlier. These were included in the model even if not significant.

The final models were produced in a series of stages. Initial models included $\mathrm{SST}_{0:1}$ as the explanatory variable. The next stage of models examined the impact of weather on the LnCIR by fitting monthly $\mathrm{Tmin}_{1:2}$, $\mathrm{Tmax}_{0:1}$, and $\mathrm{Precipitation}_{6:7}$ as explanatory variables. In all models Durbin-Watson tests were conducted to detect autocorrelation in the residuals. When the residuals were autocorrelated, an adjustment was included incorporating a first-order autocorrelation term (LnCIR lagged 1 month). Higher order terms were not required. However, this could not be achieved for models including SST because this variable is highly autocorrelated. Including such an adjustment for autocorrelation would have removed all the variability coming from the El Niño signal. We estimated associations between dengue and the optimal lagged meteorological variables as follows:

$$\log(\mathrm{y}_t) = \beta_0 + \beta_1 t' + \sum_{k=2}^{12} \beta_k D_{kt} + \sum_{n=1}^{3} \beta_n X_{nt-l} + y_{t-1} + u_t \tag{2.2}$$

where β_n denotes the regression coefficients for each meteorological regressor in the model (i.e. $\mathrm{SST}_{0:1}$, $\mathrm{Tmin}_{1:2}$, $\mathrm{Tmax}_{0:1}$, and $\mathrm{Precipitation}_{6:7}$); X_{nt-l} indicates a meteorological variable at l-th lags; y_{t-1} is a first-order autocorrelation term; and the other variables are specified as in Equation 2.1.

El Niño is a dominant source of inter-annual climate variability in the world (Trenberth, 1997), and a major source of temperature and precipitation variability in Mexico (Magaña et al., 2004). We stratified the models for the presence of El Niño events and the rainy season to assess if the association between the variables increased during these events. Having produced models for first SST and subsequently, temperature and precipitation, the final stage was to fit models with SST and any weather variable significant in the earlier models. This would examine whether the effects of SST on dengue incidence are fully explained by weather.

In the dataset, we observed a significant increase in the number of dengue cases (from about 6,700 cases per year from 1985 to 1996 to about 45,100 in 1997) coinciding with the exceptionally strong 1997–1998 El Niño. This period also saw the introduction of the DEN-3 serotype which may have led to elevated dengue incidence because of low herd immunity. We tested the influence of this extreme event on the model results by excluding the 13 months coinciding with this period from the series and fitting regression models as before.

2.4 Results

The averaged CIR increases from 1.99 cases/100,000 people during the neutral period, to 5.52 (ratio = 2.8) during El Niño, and to 3.10 (ratio = 1.6) during La Niña (Table 2.2). Excluding the months coinciding with the 1997–1998 El Niño decreases the CIR to 4.10 (26% reduction) during the El Niño events.

Parameters	**CIR difference**	**CIR ratio**
El Niño vs. Neutral period	5.52–1.99	2.77
El Niño vs. La Niña	5.52–3.10	1.78
La Niña vs. Neutral period	3.10–1.99	1.56
Without the 1997–1998 El Niño		
El Niño vs. Neutral period	4.10–1.99	2.06
El Niño vs. La Niña	4.10–3.10	1.32
La Niña vs. Neutral period	3.10–1.99	1.56

Table 2.2: CIR (cases/100,000 people) differences and ratios per SST period.

The CIR increases from 1.6 cases/100,000 people in the cool and dry season, to 4.8 cases/100,000 people (ratio: 2.9) during the warm and wet season (Table. 2.3). The annual cycle of dengue incidence is similar to that of Precipitation but with an onset about two months later (Figure 2.3).

Parameters	**CIR difference**	**CIR ratio**
Rainy season vs. Dry season	4.8–1.6	2.9

Table 2.3: CIR (cases/100,000 people) differences and ratios per season.

The results from the first multiple regression are presented in Table 2.4 and indicate that a 1°C increase in $SST_{0:1}$ results in monthly increases in the LnCIR (B = 0.238; $P < 0.001$). When the model was stratified by El Niño months $SST_{0:1}$ was significantly associated with the LnCIR during the El Niño months (B = 0.463; $P = 0.028$) but not during the non-El Niño months (B = -0.126; $P = 0.301$). However, after removing the data coinciding with the 1997–1998 El Niño, $SST_{0:1}$ was not significantly associated with dengue. This observation was consistent for models non-stratified (B = 0.125; $P = 0.095$), and stratified by El Niño (B = -0.216; $P = 0.512$), and non-El Niño months (B = -0.133; $P = 0.275$), suggesting that the previously observed association is highly influenced by the 1997–1998 event. The introduction of the DEN-3 serotype to the country in 1995 and the lack of serotype identification of each case makes it almost impossible to disentangle whether the El Niño or the introduction of a new dengue serotype is responsible for thin peak in incidence observed in 1997.

Model	N	B ($P < \|t\|$)	95% C.I.	Adj. R^2
Whole year	276	**0.24(0.00)**	0.11 – 0.37	0.46
El Niño				
Present	75	**0.46(0.03)**	0.05 – 0.88	0.56
Absent	201	-0.13(0.30)	-0.36 – 0.11	0.38
Without 1997–1998 El Niño				
Whole year	263	0.13(0.10)	-0.02 – 0.27	0.44
El Niño				
Present	62	-0.22(0.51)	-0.87 – 0.44	0.54
Absent	201	-0.13(0.28)	-0.37 – 0.11	0.38

Table 2.4: Regression coefficients of the LnCIR of dengue as a function of $SST_{0:1}$. Models were controlled for long-term trends and seasonality. Values in bold font were statistically significant.

Table 2.5 examines the impact of weather ($Tmin_{1:2}$, $Tmax_{0:1}$ and $Precipitation_{6:7}$) on dengue and indicates that monthly increases in the LnCIR (B = 0.079; $P = 0.019$) result after every 1°C increase in $Tmin_{1:2}$. Such increases can be expected during the non-El Niño months (B = 0.108; $P = 0.008$) and the cool and dry season (B = 0.080; $P = 0.049$). Similar results were obtained after removing data coinciding with the months during the 1997–1998 El Niño. No significant associations were found between the LnCIR and $Tmax_{0:1}$ or $Precipitation_{6:7}$ in the models (Table 2.5).

Previous studies used shorter time lags for estimating the effects of precipitation on dengue incidence (e.g. Hurtado-Díaz et al., 2007; Brunkard et al., 2008). Our results were robust to the use of shorter lags of precipitation for higher biological plausibility (i.e. $Precipitation_{2:3}$ and $Precipitation_{4:5}$).

Table 2.5 shows that the effects of $Tmin_{1:2}$ on dengue incidence are statistically significant. In the final model, we examined whether there was a significant association between dengue and El Niño after controlling for weather. This model is presented in Table 2.6 and includes $SST_{0:1}$ and $Tmin_{1:2}$ as explanatory variables. The results indicate that even after controlling for weather, there is still a significant association between SST and dengue. The results show that monthly increases in the LnCIR occur after every increase by 1°C in SST (B = 0.311; $P < 0.001$) indicating an influence of SST above and below its effects on temperature. The association is stronger (B = 0.714; $P < 0.001$) during El Niño. There were no associations between $SST_{0:1}$ and dengue during non-El Niño periods (B = 0.058; $P = 0.558$). The overall association between SST and dengue incidence persisted after the removal of the 1997–1998 El Niño. However, after the series was stratified by El Niño months, the association during El Niño disappeared.

Model	N	Tmin$_{1:2}$ B $(P < \lvert t \rvert)$	95% C.I.	Tmax$_{0:1}$ B$(P < \lvert t \rvert)$	95% C.I.	Precipitation$_{6:7}$ B $(P < \lvert t \rvert)$	95% C.I.	Adj. R^2
Whole year	274	**0.08(0.02)**	0.03–0.15	0.12(0.07)	-0.01–0.24	-0.26(0.06)	-0.53–0.01	0.88
El Niño								
Present	75	0.00(0.97)	-0.14–0.14	0.16(0.19)	-0.08–0.40	-0.32(0.31)	-0.94–0.31	0.87
Absent	199	**0.11(0.01)**	0.03–0.19	0.10(0.22)	-0.06–0.26	-0.27(0.10)	-0.60–0.06	0.87
Rainy season								
Present	115	0.05(0.43)	-0.07–0.16	0.06(0.10)	-0.13–0.26	-0.58(0.06)	-1.18–0.02	0.86
Absent	159	**0.08(0.05)**	0.00–0.16	0.13(0.13)	-0.04–0.30	-0.14(0.37)	-0.46–0.17	0.86
Without 1997–1998 El Niño								
Whole year	261	**0.11(0.00)**	0.04–0.18	0.13(0.06)	-0.00–0.26	-0.25(0.07)	-0.53–0.02	0.87
El Niño								
Present	62	0.11(0.35)	-0.12–0.34	0.22(0.13)	-0.07–0.51	-0.32(0.36)	-1.07–0.37	0.84
Absent	200	**0.11(0.01)**	0.03–0.19	0.10(0.23)	-0.06–0.25	-0.27(0.10)	-0.60–0.05	0.87
Rainy season								
Present	110	**0.15(0.04)**	0.01–0.29	0.10(0.35)	-0.11–0.30	-0.42(0.17)	-1.02–0.18	0.85
Absent	152	0.08(0.07)	0.01–0.17	0.13(0.16)	-0.05–0.31	-0.14(0.40)	-0.47–0.19	0.85

Table 2.5: Regression coefficients of the LnCIR of dengue as a function of Tmin$_{1:2}$, Tmax$_{0:1}$, and Precipitation$_{6:7}$. Models were controlled for long-term trends, seasonality and autocorrelation. Values in bold font were statistically significant.

Model	N	B $(p < \lvert t \rvert)$	95% C.I.	Adj. R^2
Whole year	275	**0.31(0.00)**	0.20–0.42	0.62
El Niño				
Present	75	**0.71(0.00)**	0.31–1.12	0.70
Absent	200	0.06(0.56)	-0.13–0.27	0.63
Without 1997–1998 El Niño				
Whole year	262	**0.15(0.01)**	0.04–0.27	0.68
El Niño				
Present	62	-0.09(0.72)	-0.60–0.42	0.73
Absent	200	0.05(0.60)	-0.14–0.25	0.61

Table 2.6: Regression coefficients of the LnCIR of dengue as a function of SST$_{0:1}$. Models were controlled for long-term trends and seasonality, and adjusted for the confounding effects of Tmin$_{1:2}$. Values in bold font were statistically significant.

2.5 Discussion

2.5.1 Effects of El Niño

The results show that in the presence of El Niño, the risk of dengue infection is 2.8 times higher in the warm and humid region of Mexico compared with the neutral phase. This is corroborated in the multiple regression analysis indicating a significant and positive effect of the strength of El Niño on dengue. However, there is some uncertainty as to the validity of this result, because when the exceptionally strong 1997–1998 El Niño is removed from the analyses, associations between dengue and El Niño become marginally insignificant. This suggests that the impacts of El Niño are only apparent above a threshold exceeded by the strongest events.

When some of the variability in the series is controlled for by including temperature as a covariate, the association between dengue and El Niño becomes significant in the models with an without the 1997–1998 El Niño. We, therefore, conclude that El Niño has an association with dengue in the warm and humid region of Mexico, and this corroborates previous studies (e.g. Hurtado-Díaz et al., 2007; Brunkard et al., 2008). This also indicates that El Niño modulates the dynamics of the disease through mechanisms that are not fully explained by its influence on the local weather. These mechanisms may be related to changes in environmental factors (e.g. vegetation cover), human behaviour, or cultural artifacts (e.g. water-storage practices).

The concurrent introduction of the DEN-3 serotype and the exceptionally strong 1997–1998 El Niño makes it difficult to separate these two effects and questions the linking of the unusual increases in the levels of dengue incidence observed in 1997, which have been previously attributed to weather conditions related to the 1997–1998 El Niño (Kovats, 2000). The importance of the introduction of the DEN-3 serotype is strengthened by the observation that, throughout Mexico, 88% of the dengue cases in 1997 were related to the DEN-3 serotype (CENAVECE, 2003). It could, therefore, be argued that the introduction of DEN-3 was entirely responsible for the peak in dengue incidence seen in 1997. However, we have shown that El Niño was positive and significantly associated with dengue during other time periods, and therefore, it is likely that both the introduction of DEN-3 and El Niño were responsible for the unusually large increase in dengue incidence observed in 1997. Disentangling extrinsic from intrinsic factors in a quantitative fashion requires serotype-specific data. However, these data were not available from SINAVE.

2.5.2 Effects of temperature

The results also showed that increases in $\mathrm{Tmin}_{1:2}$ are positive and significantly associated with dengue incidence. When we removed the 1997–1998 El Niño, $\mathrm{Tmin}_{1:2}$ remained significant. This corroborates previous studies conducted in other regions of Mexico and the world (e.g. Brunkard et al., 2008; Sriprom et al., 2010).

When the model was subdivided by rainy season, $\mathrm{Tmin}_{1:2}$ was significant during the cool and dry season, which is when temperatures in the region are at their lowest. This could indicate that low temperatures in the cool and dry season hamper the biology of the mosquito or the virus, diminishing the likelihood of effective transmission.

Low temperatures have been previously associated with increased mosquito development rates and mosquito larvae mortality which result in decreased transmission (Hemme et al., 2009). At temperatures below 16°C, the length of the larval stages of the vector increases (CENAVECE, 2003). Besides, *Aedes* mosquitoes stop feeding in ambient temperatures lower than 17°C (Wu et al., 2009) resulting in lower transmission rates. Additionally, the virus cannot amplify within the vector in temperatures below 18°C (Watts et al., 1987), and low temperatures increase the time of the extrinsic incubation period (EIP) of the virus increasing its likelihood of exceeding the time span of the vector (Reiter, 2001).

Conversely, rising temperatures shorten the EIP and the development rate of the vector, and increase the biting and contact rates (Keating, 2001). This increases the percentage of infected mosquitoes and the likelihood of successful transmission (Reiter, 2001; Wu et al., 2009). High temperatures generate reductions in the larval sizes resulting in smaller adults (Focks et al., 2000) that feed more often than the larger ones (Martens, 1998; Focks et al., 2000). Additionally, mosquitoes digest blood faster at higher temperatures increasing their need and persistence of feeding (Hemme et al., 2009).

Temperature-influenced human behaviour may also play a key role on dengue dynamics. During the warm and wet season, individuals spend more time indoors sheltering from the rain, the high humidity and the warm temperatures. This increase in the time spent indoors interacts with the lack of sealed doors and windows, and air conditioning, increasing the vector-host contact rate and the risk of transmission (Reiter, 2001). During the cool and dry season, temperatures are cooler and the relative humidity lower and people spend more time outdoors. This may lead to lower levels of dengue and is corroborated by the fact that warmer minimum temperatures in the cool and dry season are associated with elevated dengue incidence.

Tmax is not associated with dengue incidence in the region. However, in the time series, $\mathrm{Tmax}_{0:1}$ is less variable (σ = 1.6) than Tmin (σ = 2.7) making it statistically less likely for an effect to be apparent throughout the analyses.

2.5.3 Effects of precipitation

The risk of infection is higher during the warm and wet season corroborating previous studies conducted in Mexico (e.g. Koopman et al., 1991; Hurtado-Díaz et al., 2007; Brunkard et al., 2008; García et al., 2008) and some other countries (e.g. Lowe et al., 2011; Johansson et al., 2009b). After the long-term trend and seasonality are controlled for in the model, precipitation is not statistically associated with dengue incidence. This could indicate that, although water is required for mosquito breeding, there is enough rainfall in the region all year to create breeding sites, and therefore, variations in monthly precipitation do not affect dengue incidence.

This result could also indicate that rainfall does not influence the survival of adult vectors directly (Patz et al., 1998) because of their indoor activity, or that water-holding containers used as breeding sites in the region may be mainly man-filled containers (Focks and Barrera, 2006; Tsuzuki et al., 2009). Another plausible explanation is that effects of precipitation are obscured by summarizing weather and dengue data to large political boundaries because such aggregation removes much of the variability in the data. Alternatively, it could be argued that the use of a categorical variable for seasonal trends (variable that is critical to differentiate the true effects of weather) may have removed much of the precipitation-related information preventing the model from estimating a significant effect.

Population increases in urban areas, uncontrolled urbanisation, and lack of adequate public services are common in Mexico (INEGI, 2005). High levels of urbanization seem to increase the risk of dengue incidence (e.g. Narro and Gómez, 1995; Gómez-Dantés, 2007). Inadequate or inefficient water supply and sewage, and poor solid waste disposal services increase the likelihood of water stagnation and offer potential breeding sites for the vector (Escobar and Gómez, 2003; Cifuentes and Sánchez-Arias, 2007; Gómez-Dantés, 2007). Inefficient or intermittent water supply leads to people having to store water for domestic usage (Hemme et al., 2009). In other cases, people store water “just in case” (Padmanabha et al., 2010). These situations create of potential breeding sites for mosquitoes independent of precipitation.

The lack of association of precipitation with dengue incidence may, therefore, be intrinsically linked to the presence of confounding factors (e.g. social, political and cultural features) in the region. At least part of the effects of these confounding factors is captured by our long-term trend (e.g. rising urbanisation trends) and season variables (e.g. seasonal water storage). Understanding the role of each of these factors in the dynamics of the disease requires detailed entomological, epidemiological and socioeconomic data and more advanced statistical methods, and is beyond the scope of this study.

This study explores a larger time series and geographical area than previous studies conducted in the region (e.g. Hurtado-Díaz et al., 2007). Our large time series allowed the estimation of associations between dengue and a large number of El Niño events with greater statistical confidence than previous studies that analysed dengue series of up to 10 years. The large geographical area of study allowed us to reduce problems of small numbers in dengue incidence observed at the provincial level. The stratification of models into El Niño, non-El Niño, warm and wet and cool and dry seasons also allowed us to explore differential associations between dengue and weather at different periods.

2.6 Limitations

In this study we have presented an analysis of the relationships between dengue incidence and three key climatic variables (temperature, precipitation and SST) in the warm and humid region of Mexico. Although in this study we have reached the established aims, there were some limitations.

There is large undereporting and misclassification of dengue cases because of lack of specificity of the symptoms, low awareness of health practitioners, limited access to diagnostic tests, and poor systematic surveillance (Suaya et al., 2007; WHO, 2012). Previous research suggests that for every official dengue report included in the official surveillance systems, there are 10–27 cases unreported (Meltzer et al., 1998; Clark et al., 2005). Consequently, our estimations were very likely conducted on a fraction of the total cases. This situation is likely to have increased the uncertainty of our estimations (Lake et al., 2008). However, this undereporting and misclassification is unlikely to have biased our results they are unlikely to be a correlated with our variables of interest (e.g. precipitation).

We removed the seasonal trend components on both the predictors and the oucome variable to identify their relationships as suggested by previous research (Bowie and Prothero, 1981). To do so, we used categorical variables for each month for the period which is a strict approach to control for seasonality. Previous research conducted on the epidemiology of enteric diseases suggests that stringent control methods for seasonality may bias the effects of weather towards the null effect (Charron et al., 2005). The use of sinusoidal terms with sine and cosine functions (Cowpertwait and Metcalfe, 2008) are a less stringent way to account for seasonal trends in regression models.

As previously stated dengue series usually exhibit strong inter-annual variability (Cazelles et al., 2005), as a result of both extrinsic and intrinsic factors (Wearing and Rohani, 2006). Although our models were adjusted by the effects of log-linear long-term trends, this is not enough to control for the effects of inter-annual variability. This lack of control may have increased the residual confounding in our study. Additionally, we did not account for the confounding effects of socioeconomic development in the models, situation that may also increase residual confounding. As a consequence, our models could have overestimated the true effects of weather on dengue incidence.

Data were aggregated to large political boundaries. Such coarse aggregation may have caused aggregation bias issues (Theil, 1954; Grunfeld and Griliches, 1960) because it averages out variations in all predictors, making them less likely to show associations with the outcome variable (Johansson et al., 2009a).

In this study we have assumed that the relationships between the log-transformed CIR of dengue and the meteorological predictors are linear. In reality however, the effects of weather on the dengue system are complex and highly nonlinear. One example of such nonlinearities is a threshold response (Rohr et al., 2011). The ability of mosquitoes to survive and transmit dengue, decreases in either direction as one moves away from the optimal temperature and precipitation levels. For example, adult *Aedes* mosquitoes gradually die at temperatures beyond 36°C Focks et al. (2000). The use of smooth functions for the predictors could be helpful for testing the assumptions of linearity.

2.7 Conclusions

In this study, we used multiple linear regression to estimate associations between dengue incidence, weather and El Niño in the warm and humid region of Mexico. We found that dengue incidence was positively associated with El Niño. This association however, is largely influenced by the exceptionally strong 1997–1998 El Niño, suggesting that the impacts of an El Niño are only apparent above a specific threshold exceeded by the strongest events.

We also found a concurrence between the same 1997–1998 El Niño and the introduction of the DEN-3 serotype, which would have increased dengue incidence because of low herd immunity. Such concurrence questions previous attributions of the 1997–1998 outbreak to climatic conditions and could indicate that previous studies on the associations between dengue incidence and El Niño may have overestimated its relative influence on dengue. It is likely that both the introduction of DEN-3 and El Niño were responsible for the unusual increase in dengue incidence observed in 1997.

The mechanisms by which El Niño influences dengue dynamics are still unclear, because El Niño shows a statistical association above and below its influence on the local weather. We provide robust evidence that SST excerts an influence on dengue incidence in accordance with previous studies (Hurtado-Díaz et al., 2007; Brunkard et al., 2008).

Increases in minimum temperature, especially during the cool and dry season, were associated with elevated dengue incidence levels. There are a number of biologically plausible reasons for this association: (i) increased development time and larval mortality of the vector at low temperatures, (ii) alterations in the feeding behaviour of the vector, (iii) amplification problems and increased EIP of the virus, and (iv) reduction in the time spent indoors during the dry season.

Precipitation does not show a statistical association, suggesting that there are suitable places for mosquito breeding all year. Socio-cultural, biological or epidemiological conditions may be of great importance in ensuring that there are enough breeding sites all year.

The effects of weather and El Niño on dengue of dengue remain controversial. However, our study complements the understanding of dengue dynamics in the region and may help in the effective allocation of resources in targeted areas.

There is no consistent evidence of likely changes in the amplitude or frequency of El Niño because of climate change in the 21^{st} century (Meehl et al., 2007). However, climate change is likely to increase temperatures in the region (Christensen et al., 2007), increasing the spatial and geographical distribution of the disease as well as the length of the transmission period (Confalonieri et al., 2007). Our results suggest that this might worsen dengue incidence in the region, especially during the cool and dry season when incidence is currently low. Long-term surveillance and research will play a key role in the study of changes in dengue behaviour and distribution. Our results can be used to determine future incidence trends in the region, giving the opportunity to improve the control measures for the disease and strengthen the adaptive capacity of the population.

2.8 Acknowledgments

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Chapter 3

Marked heterogeneity in the effects of weather and ENSO on dengue across Mexico

3.1 Abstract

Variations in dengue incidence have been associated with weather in many countries, but there is little evidence on how such associations vary across different geographical or climatic regions. Here, we present one of the first studies analyzing how and why the effects of weather and El Niño on dengue vary across a single country. We estimated the effects of weather and El Niño on dengue across Mexico; assessed the level of between-province heterogeneity; and examined climatic and socioeconomic sources of such heterogeneity. Associations between dengue, weather, and El Niño were estimated fitting province-specific Poisson models regressing dengue incidence on a range of meteorological variables. The results of the Poisson models were used to fit random-effects meta-analytic models to assess the presence of heterogeneity in the strength of such associations. Where significant heterogeneity was identified, we fitted mixed-effects meta-analytic models to estimate the effect modification of climate and socioeconomic status on this heterogeneity. Dengue incidence was significantly associated with El Niño, mean monthly temperature, and precipitation at various time lags. These associations were significantly heterogeneous between provinces. The underlying climate significantly modulated the strength of the associations between dengue incidence and all meteorological variables. This association was corroborated using, average annual mean temperature, average annual mean precipitation, and latitude. The socioeconomic status did not show a significant modulating effect. We conclude that there is significant heterogeneity in the associations between dengue incidence and weather across provinces in Mexico. This result highlights the disadvantages of using country-level averaged values to investigate the relative effects of climate on health in a country with large geographic and climatic variability.

3.2 Introduction

Dengue is the most rapidly spreading mosquito-borne viral disease in the world (TDR, 2007). It is an acute febrile disease that affects all age groups (WHO, 1997). The World Health Organization classifies the disease as Dengue (with and without Warning Signs) and Severe Dengue (previously known as Dengue Haemorrhagic Fever or DHF) (WHO, 2009). Both Dengue and Severe Dengue are caused by the same four antigenically distinct but genetically related viruses of the genus flavivirus (Heinz et al., 2000), designated DEN-1, DEN-2, DEN-3, and DEN-4 (WHO, 1997). Dengue viruses are transmitted to humans through the bite of infected female mosquitoes, being *Aedes aegypti* the primary vector. Every year, dengue causes approximately 50–100 million cases (Günther et al., 2009) and at least 12,000 deaths, mainly among children (WHO, 2002), worldwide. The economic burden of dengue has been recently estimated in 2.1 billion US dollars per annum just in the Americas (Shepard et al., 2011). One country greatly affected by dengue is Mexico. The disease has been reported throughout the country where the four serotypes co-circulate since 1995 (Guzmán and Kouri, 2003). The mean annual incidence rate of dengue in Mexico shows great inter-annual variability (Figure B.1), with the periods 1995–1999 and 2006–2007 showing the largest increases in incidence across provinces.

Dengue incidence has dramatically increased globally over the last six decades (WHO, 2009) influenced by population growth, unplanned urbanisation, increased travel and transportation of goods, lack of political will and limited resources for implementing effective control measures (Al-Muhandis and Hunter, 2011). Variations in dengue incidence have also been associated with changes in weather and the occurrence of El Niño events (Hurtado-Díaz et al., 2007; Brunkard et al., 2008; Colón-González et al., 2011; Lowe et al., 2011; Sriprom et al., 2010).

El Niño phenomenon is a dominant source of inter-annual climate variability around the world (Trenberth, 1997). An El Niño event occurs every few years when the sea-surface temperature (SST) anomalies (relative to the climatology of the base period 1950–1979) in the Niño-3.4 region (5°N–5°S, 170°W–120°W) exceed 0.4°C for at least six consecutive months (Trenberth, 1997). The effects of El Niño on the Mexican weather are mainly observed on precipitation, but ambient temperature is also affected (Magaña et al., 2004). The effects of El Niño are not the same every year, and also vary between summer and winter (Magaña et al., 2004).

The El Niño winters (El Niño$_w$) are colder than usual in most of the country and precipitation increases in the north and northwest, and decreases in the south (Magaña et al., 2004). The El Niño summers (El Niño$_s$) register above-normal temperatures (with some exceptions mainly in the north-west) and decreased precipitation in the majority of the country (with some exceptions mainly in the south-east) (Magaña et al., 2004). Figure 3.1 shows the mean temperature and precipitation anomalies for El Niño$_s$ and El Niño$_w$ across Mexico based on the 1958–1999 climatology. The definition of an El Niño event (Niño-3.4 SST anomalies exceeding 0.4°C for a minimum of six consecutive months, Trenberth 1997) is the same for both summer and winter.

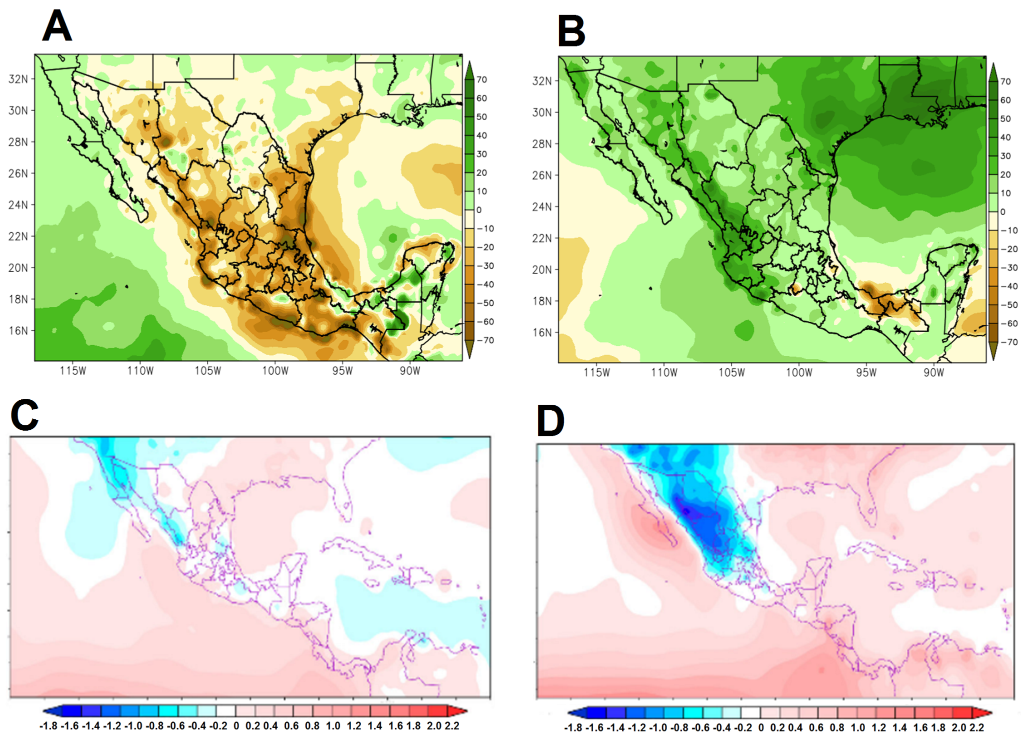

Figure 3.1: Mean precipitation anomalies (mm/day) during (A) El Niño summers (El Niño$_s$) and (B) El Niño winters (El Niño$_w$); and mean temperature anomalies (°C) during (C) El Niño$_s$ and (D) El Niño$_w$ for the 1965–1966, 1972–1973, 1982–1983, 1986–1987, 1991–1992, and 1997–1998 events based on the 1958–1999 climatology. Reproduced with the consent of Magaña et al. (2004).

Research conducted in Mexico, Brazil and Thailand showed that rising ambient temperature and SST (used as a proxy of El Niño) are associated with increasing dengue incidence at different time lags (Hurtado-Díaz et al., 2007; Brunkard et al., 2008; Sriprom et al., 2010; Colón-González et al., 2011; Lowe et al., 2011). The effects of rising precipitation on the other hand, have been largely inconsistent between studies. For example, meanwhile Hurtado-Díaz et al. (2007) and Brunkard et al. (2008) found a positive and statistically significant association between dengue and precipitation lagged 2–3 weeks in some eastern and northern Mexican municipalities, Colón-González et al. (2011) found a negative and not statistically significant association at various time lags in the warm and humid region of Mexico (situated in the southern half of the country). Lowe et al. (2011) found that precipitation lagged 1 and 2 months was positive and significantly associated with dengue incidence throughout Brazil, whereas in north-east Thailand, Sriprom et al. (2010) estimated a negative and statistically significant association between dengue and precipitation using the same time lags.

Johansson et al. (2009b) found that the strength of the local associations between dengue and weather varies significantly across municipalities in Puerto Rico, and that such variation is associated with differences in the local climate. The effect modification of socioeconomic factors (population density, median household income, and share of families living below the poverty line), on the other hand, was not consistent across a range of lagged meteorological variables (Johansson et al., 2009b). These findings provide the first piece of quantitative evidence for understanding why local associations between dengue and weather are spatially heterogeneous. Yet, this study is limited to a small geographical area, and to a low range of climatic conditions.

Variations in the strength of the associations between dengue and weather may arise from the complex interplay between the ecological determinants of dengue (Gage et al., 2008). For example, the high temperatures characteristic of tropical and subtropical regions may reduce the development time of *Aedes* mosquitoes and the extrinsic incubation period (EIP) of the virus (the period between the infection of an *Aedes* mosquito with a dengue virus and its ability to transmit it to a human host) (Watts et al., 1987; Jansen and Beebe, 2010) enhancing dengue transmission. However, if humans seek refuge in air-conditioned buildings the low temperatures and dry atmosphere lessen the survival rate of *Aedes* mosquitoes and increase the EIP of the virus reducing the likelihood of successful transmission (Reiter, 2001).

Low temperatures characteristic of temperate regions increase the development time, the EIP, and the length of the gonotrophic cycle (Focks et al., 2000; Jansen and Beebe, 2010) resulting in decreased or zero transmission. Above-normal temperatures in such regions (resulting from El Niño or heatwaves) on the other hand, may produce favourable local climate conditions for dengue transmission (Gage et al., 2008).

In dry areas, adult stages of the vector may disappear if the eggs of the mosquito have their development interrupted (diapause) due to desiccation (Bicout et al., 2002). Nevertheless, increased domestic or peri-domestic water storage in these areas may provide numerous oviposition sites that are effectively exploited by the vector (Gage et al., 2008; Al-Muhandis and Hunter, 2011). Wet areas may observe little variation in dengue incidence throughout the year because there may always be enough water to produce oviposition sites (Williams et al., 2010). Access to window screening, sealed buildings, and air-conditioning may limit dengue transmission in the region because people are less exposed to mosquito bites (Reiter, 2001; Gage et al., 2008; Jansen and Beebe, 2010).

The socioeconomic status (SES) of the affected populations is also important for determining dengue occurrence. Dengue is more common to impoverished urban and peri-urban areas where the poor building construction offers the vector access to the indoor environment, and the high population density facilitates the vector-human contact (Reiter, 2001; Eisen and Lozano-Fuentes, 2009). However, there is no evidence as to whether SES modulates the strength of the associations between dengue and weather.

We further developed the work of Johansson et al. (2009b) analysing a larger geographical area (1.96 million km^2), greater climatic diversity (Mexico has 9 major differentiable climatic regions, see Figure 2.1), and slightly larger time frame (276 months of dengue reports). We also quantitatively assessed whether the observed between-province variation is statistically significant or due to random, and evaluated the effect modification of the underlying climate accounting for the potential confounding effects of SES. The aims of this paper were three-fold: First, to estimate the effects of weather and El Niño on dengue across Mexico. Second, to assess whether there is statistically significant between-province variation in the strength of such effects. Finally, to examine the effect modification of the underlying climate and SES as moderators of such between-province variation.

3.3 Materials and methods

3.3.1 Data

We obtained two sets of data for our analyses. The first set of data (Table 3.1) was collected to understand the effects of weather and El Niño on dengue in each Mexican province. These data comprised monthly dengue reports, population size, and monthly observations of our meteorological variables.

The monthly number of confirmed dengue cases was obtained for the period January 1985 to December 2007 from the website of the the National System of Epidemiologic Surveillance[1] for all Mexican provinces (Table A.2). Notifications comprised dengue and severe dengue reports. Cases were aggregated because severe dengue is just a severe presentation of dengue. A total of 417,668 dengue cases were reported in Mexico (Figure 3.2) over the study period (1985–2007).

Annual province-specific population data were obtained from the website of the National Institute of Statistics and Geography (INEGI)[2] for 1990, 1995, 2000, 2005 and 2010. Monthly population estimates for the intervening years were computed using linear interpolation.

Information was then obtained on meteorological variables for each province. The first meteorological variable was monthly SST anomalies in the Niño-3.4 region as an estimate of the strength of El Niño. SST data were obtained from the website of the US Climate Prediction Center[3]. Monthly SST anomalies were then transformed into two categorical variables each of them indicating the presence of an El Niño$_s$ or an El Niño$_w$ episode. These variables were created to assess whether the presence (and not the strength) of an El Niño in a given season has a different effect on dengue incidence than the other season. We selected the Niño-3.4 region because it is one of the most sensitive indices for determining an El Niño event (Hanley et al., 2003). SST data were the same for each of the provinces.

Province-specific observations of average monthly minimum temperature, average monthly maximum temperature and accumulated monthly precipitation were obtained from the Mexican National Meteorological System. These data comprised province-wide averaged values from observations of all meteorological stations within each province.

The second set of data collected (Table 3.1) was used to examine the influence of underlying climate (Figure 3.2) and SES on the effects of weather and El Niño on dengue across provinces. The dominant underlying climate of each province (very-dry temperate, dry semi-warm, dry temperate, dry warm, semi-dry temperate, humid semi-warm, humid

[1] http://www.dgepi.salud.gob.mx/anuario/html/anuarios.html (Accessed 12 Mar 2009)
[2] http://www.inegi.org.mx/inegi/ (Accessed 23 Mar 2009)
[3] http://www.cpc.ncep.noaa.gov/data/indices/sstoi.indices (Accessed 12 Mar 2009)

Variable	Mean	SD	Median	Minimum	Maximum
Dengue cases	47.29	233.77	1.00	0.00	6322.00
Tmin	13.29	5.58	13.41	-2.87	24.88
Tmax	28.50	4.39	28.71	13.32	39.95
Precipitation	72.73	88.49	35.72	0.00	802.45
Tmean$_q$	20.94	3.32	21.43	14.25	26.97
Precipitation$_q$	72.95	38.90	64.47	14.87	189.24
Latitude	21.68	3.62	20.71	16.21	30.21
GDP	4,798.11	3,300.75	3,881.92	755.74	25,410.97
Urbanisation	71.72	15.59	73.23	35.72	100.00
Population	2,809,833.95	2,449,218.98	2,154,671.50	244,470.00	14,474,842.00

Table 3.1: Descriptive statistics of scale parameters (n = 8,832).

temperate, humid warm, and semi-humid temperate) were obtained from INEGI[4]. Average annual mean temperature (Tmean$_q$), and average annual precipitation (Precipitation$_q$) were estimated from the monthly data for the period of study.

The latitude of the approximate centroids of each province were extracted from a website of the Mexican National Institute of Ecology[5] because latitude is important for determining the climate of the Mexican provinces (Mosiño and García, 1974).

As already mentioned, SES may modulate dengue transmission (Reiter, 2001). Thus, for each province, indicators for wealth and demography were obtained to assess whether these influence the effects of the meteorological variables on dengue. The wealth data used was the gross domestic product per capita (GDP) which was obtained from INEGI[6] for the year 2005. The proportion of the population living in urban areas (urbanisation) was used as the measure of demography, and was obtained from the Chamber of Deputies[7] for the year 2004. The spatial distribution of these socioeconomic variables is illustrated in Figure 3.2.

3.3.2 Estimation of the optimal lagged meteorological variables

To estimate the effects of each meteorological variable (as defined in Section 3.3.1) at different time lags it was necessary to account for the confounding effects of both seasonal trends and inter-annual variability components of the series involved as suggested by Bowie and Prothero (1981). We estimated the optimal (biologically plausible) lagged meteorological variables fitting province-specific models as follows:

$$y_t \sim \text{Poisson}(\mu_t) \tag{3.1}$$

$$\log(\mu_t) = \beta_0 + \sum_{j=1986}^{2007} \beta_j D_{jt} + \beta_1 \sin(t') + \beta_2 X_{t-l} + \log(W_t) \tag{3.2}$$

[4]http://www.inegi.org.mx/sistemas/sisept/default.aspx?t=mamb22c=21443s=est (Accessed 7 Nov 2010)
[5]http://zimbra.ine.gob.mx/escenarios/ (Accessed 10 Nov 2011)
[6]http://www.inegi.org.mx/sistemas/productos/ (Accessed 18 Apr 2010)
[7]http://www.cefp.gob.mx/intr/bancosdeinformacion/estatales/ (Accessed 18 Apr 2009)

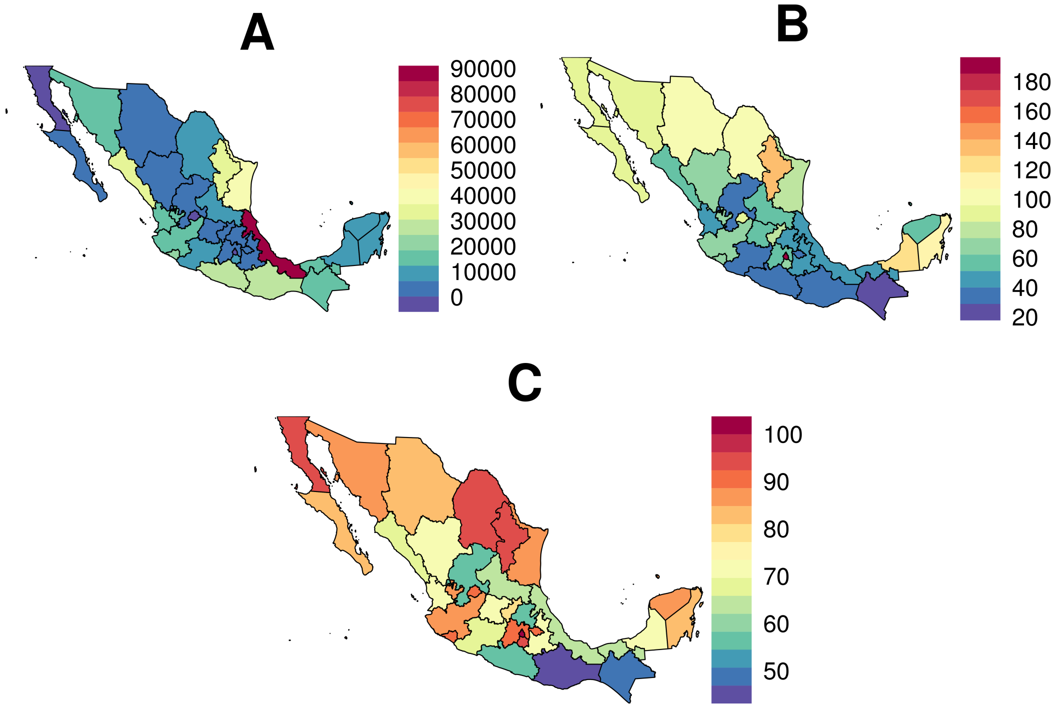

Figure 3.2: (A) Total number of dengue cases by province (1985–2007); (B) Gross Domestic Product per capita (2005) in thousand Mexican Pesos; and (C) percentage of the population living in urban areas.

$$\sin(t') = \sin(2\pi t/12) \tag{3.3}$$

where $\log(\mu_t)$ denotes the logarithm of the expected number of dengue cases for time t = 1,...,n; β_0 is the intercept; β_j, β_1, and β_2 are the regression coefficients (slopes) for each explanatory variable (regressor); D_{jt} denotes a categorical variable for calendar year, where j = 1986,...,2007 and 1985 is set as a reference level; X_t denotes each meteorological covariate at the l-th lags, and $\log(W_t)$ corresponds to the logarithm of the population size included as an offset variable.

For temperature and precipitation variables we only considered time lags from zero to three months based on previous research (Hurtado-Díaz et al., 2007; Brunkard et al., 2008; Colón-González et al., 2011) and biological plausibility. For SST we considered time lags from zero to six months (Hurtado-Díaz et al., 2007; Brunkard et al., 2008; Colón-González et al., 2011; Lowe et al., 2011). The year-specific categorical variables controls for independent inter-annual variability that may arise from real changes in dengue incidence or from changes in reporting rates over time, improved diagnostic techniques or micro-evolutionary changes in mosquito populations. Such variable also control for the potential inter-annual effects of omitted variables such as social behaviour or socioeconomic development that may confound the associations between dengue and the meteorological variables. The sinusoidal term (Equation 3.3) controls for the potential confounding effects of seasonal trends that may be related to non-climatic factors such as holidays and seasonal water storage practices. This led to a Poisson model with log link function. To account for possible over-dispersion, we allowed the scale parameter to be different from its mean (Cameron and Trivedi, 1990). Estimations were conducted in R version 2.13.1 (R Development Core Team, 2010). Our preferred models were those that produced the minimal residual deviance in each province.

3.3.3 Associations between dengue and the optimal lagged meteorological variables

To estimate the effects of the optimal lagged meteorological variables on dengue, we specified the expected number of dengue cases during month *t* in each province as:

$$\log(\mu_t) = \beta_0 + \sum_{j=1986}^{2007} \beta_j D_{jt} + \beta_1 \sin(t') + \sum_{i=1}^{2} \beta_i X_{it} + \log(W_t) \tag{3.4}$$

where X_{it} denotes the optimal lagged *i*-th meteorological covariates, and the rest of variables and the model specification (i.e. a Poisson model with log link function) are as defined on Equation 3.2.

3.3.4 Meta-analytic models

After the associations between dengue and the optimal lagged meteorological variables were established for each province, we assessed whether there was statistically significant between-province variation (heterogeneity) in the strength of such associations. Providing that the associations between dengue, weather and El Niño in each province are independent, we analysed their summary measures (regression coefficients and their corresponding standard errors in this case) using standard methods as suggested by Kirkwood and Sterne (2003).

We calculated the mean true "overall" association (with variance τ^2) between dengue and each meteorological variable fitting random-effects meta-analyses using the *metafor* package for R (Viechtbauer, 2010). We assessed the between-province heterogeneity of effect estimates using Cochran's *Q*-tests as defined by DerSimonian and Laird (1986) and the H^2 and I^2 statistics as described by Higgins and Thompson (2002).

Whenever we observed significant between-province heterogeneity (i.e. *Q*-test $P < 0.001$, $H^2 > 1.5$, and $I^2 > 50\%$, Higgins and Thompson 2002) in the associations between dengue and the meteorological variables, we included moderators (province-level variables) into the meta-analytic models to examine possible sources of such heterogeneity. It was expected that such moderators would account for at least part of the between-province heterogeneity (Viechtbauer, 2010). This led to a series of mixed-effects models given by:

$$\theta = \beta_0 + \sum_{j=1}^{4} \beta_j X_j \tag{3.5}$$

where θ corresponds to the expected true effect on each model, β_0 is the intercept, β_j is the effect size of each *j*-th moderator variable, and X_j denotes the value of the *j*-th moderator in the model.

To examine moderators of the associations between dengue, weather and El Niño, we fitted mixed-effects models in three stages. First, we estimated the influence of the prevailing climatic regime including categorical variables for underlying climate in the model, using procedures described in Viechtbauer (2010). We performed omnibus tests for these models to estimate the between-region homogeneity (Q_m) using the humid warm climatic region (β_0) as a reference. A significant Q_m indicates that effect sizes are significantly different between climatic regions.

Second, we replaced the climate-related categorical variables with continuous variables to account for subtle differences between provinces with similar climate that would not otherwise be captured by including a categorical variable. The first two variables were Tmean_q, and Precipitation_q. Then, we explored the influence of latitude. Third, we estimated the effect modification of SES (GDP per capita, and urbanisation).

The proportion of the total amount of heterogeneity (ω) that can be accounted by including X_j moderators in the model (Equation 3.5) was specified as:

$$\omega = (\hat{\tau}_r^2 - \hat{\tau}_m^2) \; / \; \hat{\tau}_r^2 \tag{3.6}$$

where $\hat{\tau}_r^2$ denotes the estimated amount of residual heterogeneity of a given random-effects model, and $\hat{\tau}_m^2$ corresponds to the estimated amount of residual heterogeneity of its corresponding mixed-effects model.

3.4 Results

3.4.1 Optimal lagged meteorological variables

We estimated significant correlation between minimum temperature and maximum temperature in 63% of the provinces (Table 3.2); consequently, we computed average monthly mean temperature (Tmean) for our analyses. The optimal lagged meteorological variables were SST lagged 5 months (SST_5), and averaged Tmean and accumulated precipitation lagged 1 and 2 months. Because temperature and precipitation variables were significantly associated with dengue incidence at more than one time lag, such lagged variables were averaged before their inclusion in the final models (i.e. $\text{Tmean}_{1:2}$, and $\text{Precipitation}_{1:2}$) to avoid collinearity issues. We created categorical variables for the presence of El Niño_s and El Niño_w episodes respecting the 5 months time lag determined for SST.

3.4.2 Province-specific associations between dengue incidence, weather, and El Niño

Table A.3 reports the parameter estimates of the province-specific models for associations between dengue, weather, and El Niño. The estimated relationship between dengue incidence and El Niño (both El Niño_s and El Niño_w) was positive in 15 out of 32 provinces. Positive associations indicate that as the value of the meteorological variable increases so

Province	Tmin-Tmax	Tmin-Precipitation	Tmax-Precipitation
Aguascalientes	0.701	0.736	0.192
Baja California	0.964	-0.618	-0.683
Baja California Sur	0.951	0.395	0.252
Campeche	0.713	0.649	0.186
Chiapas	0.535	0.688	-0.030
Chihuahua	0.926	0.617	0.379
Coahuila	0.949	0.617	0.492
Colima	0.287	0.742	-0.107
Distrito Federal	0.509	0.788	0.206
Durango	0.860	0.662	0.291
Guanajuato	0.703	0.756	0.219
Guerrero	0.351	0.707	-0.260
Hidalgo	0.594	0.759	0.168
Jalisco	0.456	0.793	-0.027
México	0.356	0.865	0.018
Michoacán	0.432	0.746	-0.130
Morelos	0.346	0.743	-0.173
Nayarit	0.569	0.741	0.062
Nuevo León	0.943	0.535	0.414
Oaxaca	0.645	0.582	0.006
Puebla	0.624	0.707	0.206
Querétaro	0.715	0.734	0.292
Quintana Roo	0.770	0.520	0.226
San Luis Potosí	0.836	0.731	0.399
Sinaloa	0.826	0.639	0.211
Sonora	0.919	0.523	0.254
Tabasco	0.837	0.292	-0.085
Tamaulipas	0.936	0.617	0.447
Tlaxcala	0.371	0.886	0.143
Veracruz	0.891	0.644	0.341
Yucatán	0.753	0.692	0.374
Zacatecas	0.729	0.749	0.215

Table 3.2: Province-specific Spearman rank correlations between meteorological predictors.

too does dengue. Significant and negative associations between dengue and El Niño$_s$ were only observed in two provinces where precipitation and temperature greatly decrease during an El Niño$_s$ and may hamper the vector's biology. The statistically significant associations between dengue and Tmean$_{1:2}$ were mainly negative, meanwhile statistically significant associations with Precipitation$_{1:2}$ were mainly positive. Figure 3.3 shows the spatial distribution of statistically significant associations between dengue, weather and El Niño.

3.4.3 Categorical moderator analyses

The meta-analytic random-effects models provided evidence of statistically significant heterogeneity between provinces in the strength of the associations between dengue and our four meteorological variables (Table 3.3). Given the statistically significant variation, it is inappropriate to report the average associations with any of these variables (Fine, 1995).

We therefore proceeded to explore sources of between-province variation. Results of the categorical moderator analysis are shown in Table 3.4. The omnibus test (Q_m) indicated that the underlying climate significantly influences the average strength of the associations

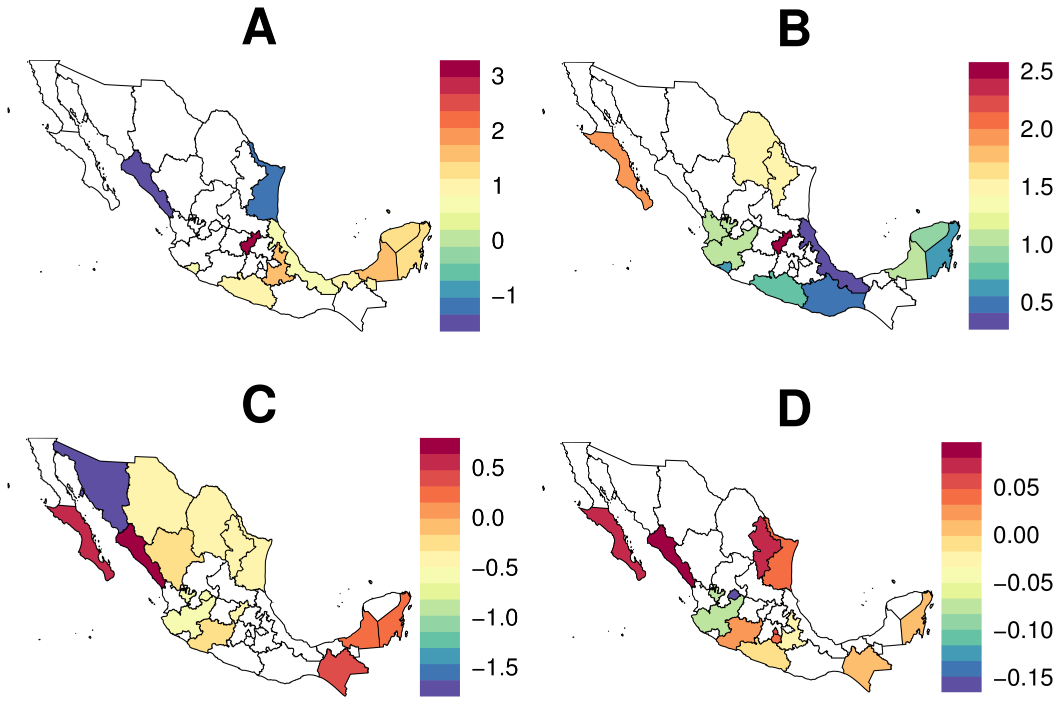

Figure 3.3: Statistically significant associations between log-transformed dengue cases, and (A) El Niño$_s$, (B) El Niño$_w$, (C) Tmean$_{1:2}$, and (D) Precipitation$_{1:2}$. Colors represent the relative strength and direction (i.e. positive or negative) of the estimated associations. Blank polygons indicate a non-significant association in the corresponding province.

	Q			H^2		I^2	
	Estimate	d.f.	*P*	Estimate	95% CI	Estimate	95% CI
Niño$_s$	**164.981**	31	< 0.001	**5.322**	3.734 – 11.716	**81.210**	73.216 – 91.464
Niño$_w$	**92.273**	31	< 0.001	**2.977**	2.130 – 7.994	**66.404**	53.056 – 87.491
Tmean$_{1:2}$	**201.444**	31	< 0.001	**6.498**	5.801 – 21.830	**84.611**	82.762 – 95.419
Precipitation$_{1:2}$	**164.555**	31	< 0.001	**5.308**	8.674 – 41.301	**81.161**	88.471 – 97.579

Table 3.3: Parameter estimates of the between-province heterogeneity in the associations between dengue and weather. Values in bold font were statistically significant at the 0.05 level

between dengue and all four meteorological variables. Very dry temperate, semi-dry temperate and humid temperate climates were found to yield significantly larger associations between dengue and El Niño$_s$ than other climatic regions, whereas dry warm climates yield significantly lower associations. The estimations obtained for the very dry temperate climates in this and other models should be considered cautiously as the very low numbers of disease cases observed in those provinces led to very unstable estimations (see Table A.3).

Very-dry temperate, semi-dry temperate and dry semi-warm climates appear to significantly yield larger associations between dengue and El Niño$_w$ than in other climates. Only sub-humid temperate and humid warm climates appear to yield larger associations between dengue and Tmean$_{1:2}$, whilst semi-dry temperate, humid-semi warm and very-dry temperate climates appear to yield significantly lower associations between dengue and Tmean$_{1:2}$. Associations between dengue and Precipitation$_{1:2}$ seem to be significantly greater than the rest of the country in dry warm, dry semi-warm and humid-warm regions.

Underlying climate	Niño$_s$ B (95% CI)	Niño$_w$ B (95% CI)	Tmean$_{1:2}$ B (95% CI)	Precipitation$_{1:2}$ B (95% CI)
Humid warm	**0.608 (0.286 – 0.929)**	**0.536 (0.328 – 0.744)**	0.009 (-0.109 – 0.127)	**0.009 (0.001 – 0.018)**
Humid semi-warm	-0.127 (-1.120 – 0.866)	0.623 (-0.085 – 1.330)	**-0.469 (-0.778 – -0.159)**	0.006 (-0.020 – 0.032)
Humid temperate	**1.468 (0.379 – 2.556)**	-0.414 (-1.426 – 0.598)	-0.113 (-0.479 – 0.254)	-0.024 (-0.059 – 0.011)
Subhumid temperate	-0.0134(-1.015 – 0.988)	-0.194 (-0.585 – 0.972)	0.033 (-0.280 – 0.346)	0.022 (-0.016 – 0.059)
Dry semi-warm	-0.315 (-1.272 – 0.643)	**1.629 (0.916 – 2.341)**	-0.135 (-0.449 – 0.180)	**0.054 (0.018 – 0.091)**
Dry temperate	0.223 (-1.508 – 1.062)	0.996 (-0.084 – 2.075)	-0.224 (-0.539 – 0.091)	0.014 (-0.015 – 0.044)
Dry warm	-0.858 (-1.888 – -0.171)	0.720 (-0.033 – 1.473)	-0.044 (-0.374 – 0.287)	**0.075 (0.048 – 0.103)**
Semi-dry temperate	**2.965 (1.652 – 4.277)**	**2.130 (1.233 – 3.027)**	**-0.520 (-0.890 – -0.151)**	-0.021 (-0.070 – 0.029)
Very dry temperate	-15.163 (-4604.822 – 4574.496)	-1.910 (-4.677 – 0.857)	-0.389 (-0.841 – 0.063)	-0.005 (-0.057 – 0.067)
Model statistics				
$\hat{\tau}_r^2$	0.455	0.191	0.047	0.003
$\hat{\tau}_m^2$	0.271	0.088	0.038	0.002
ω	0.405	0.535	0.196	0.379
Q_m	**43.623**	**79.703**	**22.408**	**46.323**

Table 3.4: Effect modification of underlying climate on the average log relative associations between dengue and weather. Values in bold font were statistically significant at the 0.05 level.

The El Niño$_w$, Tmean$_{1:2}$, and Precipitation$_{1:2}$ models accounted for 54%, 20% and 38% of the total amount of between-provinces heterogeneity, respectively.

3.4.4 Continuous moderator analyses

To corroborate the influence of underlying climate on the effects of weather and El Niño, we fitted new mixed-effects meta-analytic models replacing the categorical variables for underlying climate with continuous variables for Tmean$_q$ and, Precipitation$_q$ (see Section 3.3). None of these two moderators showed a significant influence on the strength of the associations between dengue and El Niño$_s$ in disagreement with the results obtained with the previous model specification (Table 3.5). Furthermore, this model specification did not seem to account for any of the total amount of residual heterogeneity.

The strength of the associations between dengue and El Niño$_w$, and between dengue and Precipitation$_{1:2}$, on the other hand, appear to be negative and significantly influenced by Precipitation$_q$, but not significantly influenced by Tmean$_q$. This finding suggests that greater levels of Precipitation$_q$ lead to increasingly smaller associations with both El Niño$_s$ and Precipitation$_{1:2}$. Neither Tmean$_q$ nor Precipitation$_q$ seemed to significantly influence the strength of the associations between dengue and Tmean$_{1:2}$.

We then fitted new mixed-effects models replacing Tmean$_q$ and, Precipitation$_q$ with latitude. Latitude was highly correlated with Precipitation$_q$ (Spearman's rank Rho = -0.8), but not with Tmean$_q$ (Spearman's rank Rho = -0.2). Latitude showed a significant negative influence on the associations between dengue and El Niño$_s$ and Tmean$_{1:2}$ suggesting increasingly smaller associations with dengue at higher latitudes. On the other hand, latitude appears to have significant negative effects on the associations between dengue, El Niño$_w$ and Precipitation$_{1:2}$.

Moderator	Niño$_s$ B (95% CI)	$\hat{\tau}_m^2$	Niño$_w$ B (95% CI)	$\hat{\tau}_m^2$	Tmean$_{1:2}$ B (95% CI)	$\hat{\tau}_m^2$	Precipitation$_{1:2}$ B (95% CI)	$\hat{\tau}_m^2$
Tmean$_q$	-0.015 (-0.119 – 0.089)	0.486	0.058 (-0.007 – 0.123)	0.114	0.026 (-0.001 – 0.053)	0.037	0.003 (-0.001 – 0.007)	0.000
Precipitation$_q$	0.056 (-0.034 – 0.146)	0.486	**-0.097 (-0.152 – -0.042)**	0.114	0.015 (-0.010 – 0.040)	0.037	**-0.003 (-0.005 – -0.001)**	0.000
Latitude	**-0.128 (-0.236 – -0.020)**	0.466	**0.089 (0.018 – 0.160)**	0.134	**-0.037 (-0.062 – -0.012)**	0.032	**0.004 (0.002 – 0.006)**	0.000
GDP	1.002 (-0.325 – 2.329)	0.423	0.272 (-0.732 – 1.276)	0.195	0.132 (-0.287 – 0.551)	0.049	0.034 (-0.005 – 0.073)	0.000
Urbanisation	-0.138 (-0.412 – 0.136)	0.423	0.069 (-0.269 – 0.131)	0.195	-0.075 (-0.163 – 0.013)	0.049	-0.000 (-0.008 – 0.008)	0.000

Table 3.5: Effect modification of Tmean$_q$, Precipitation$_q$, latitude, and SES on the mean log-associations between dengue and weather. Values in bold font were statistically significant at the 0.05 level.

We finally examined the influence of SES as source of heterogeneity. The results indicated that neither GDP or urbanisation seem to significantly influence the associations between dengue and our meteorological variables (Table 3.5).

3.5 Discussion

The results of this study demonstrate that weather and El Niño have statistically significant effects on dengue in Mexico corroborating previous research in the country (Hurtado-Díaz et al., 2007; Brunkard et al., 2008; Colón-González et al., 2011) and other regions (e.g. Johansson et al., 2009b; Lowe et al., 2011). The identified optimal lagged meteorological variables also were in accordance with previous studies conducted in Mexico (Hurtado-Díaz et al., 2007; Brunkard et al., 2008). Such range of time lags account for the time required by El Niño to modulate the Mexican weather (Hurtado-Díaz et al., 2007), the time taken for ambient temperature and precipitation to influence the ecology of the vector, and the corresponding diagnosis and reporting time lags of the disease.

To our knowledge, this is one of the first studies to demonstrate that the underlying climate exerts a statistically significant influence on the strength of the associations between dengue, weather and El Niño across different provinces in a single country; and the first one establishing differentiable associations between dengue and El Niño in different seasons.

We estimated the influence of the underlying climate including categorical variables in the model. Our models accounted for about 20-50% of the total amount of between-provinces heterogeneity. Thus, the underlying climate seems to have a modest but statistically significant effect modification in the associations between dengue, weather and El Niño. These results are in accordance with those from Johansson et al. (2009b) that indicated that the heterogeneity in the strength of the associations between dengue and weather is significantly influenced by the local climate but not by SES. The modest effect modification of underlying climate on the relationships between dengue, weather and El Niño suggests that other factors not considered in the model may explain the observed variation in such relationships.

When we replaced the categorical variables with continuous variables for long-term Tmean and precipitation, only Precipitation$_q$ showed a significant effect modification. Furthermore, the effect modification of Precipitation$_q$ was statistically significant only for the El Niño$_s$ and Precipitation$_{1:2}$ models. The effect modification of Precipitation$_q$ was negative suggesting a greater effect in areas with low long-term precipitation levels. Much of this effect may be due to the physiological sensitivity of *Aedes* mosquitoes to water abundance (Gage et al., 2008; Jansen and Beebe, 2010). As previously stated, humid provinces may always be wet enough to provide potential breeding sites for the vector (Williams et al., 2010) and consequently, precipitation may play a less important role than in dry provinces where increases in precipitation may trigger the development of dormant eggs (Bicout et al., 2002). Dry provinces are mainly located at high latitudes where El Niño$_w$ generally cause increases in precipitation (Magaña et al., 2004).

Johansson et al. (2009b) suggest that the effects of long-term mean temperature (Tmean$_q$

in our study) significantly influences the associations between dengue and weather. However, our dataset was unable to show it. One possible explanation for the lack of an effect modification of Tmean_q is that the aggregation of data to large political boundaries significantly reduces the spatiotemporal heterogeneity preventing the models to detect the effects of Tmean_q. Another explanation could be that Tmean_q (coefficient of variation = 0.2) is considerably less variable than Precipitation_q (coefficient of variation = 0.5) making it statistically less likely for an effect to be apparent throughout the analyses.

The effect modification of latitude was also considerably small, yet it was statistically significant in all models. The associations between dengue, El Niño_w and $\text{Precipitation}_{1:2}$ were increasingly greater at high latitudes despite the low temperatures experienced during the El Niño_w events in some regions. As previously explained, this situation may be the result of the effects of monthly precipitation being minimized in regions where mean annual precipitation is high as observed in Puerto Rico (Johansson et al., 2009b), demonstrating the relative greater importance of precipitation in dry provinces (possibly due to its importance for the creation of breeding sites, Gage et al. 2008; Jansen and Beebe 2010). These results were highly consistent across models. Associations between dengue and $\text{Tmean}_{1:2}$ were increasingly smaller at high latitudes. A possible explanation is that, as previously explained, at high latitudes, precipitation seems to play a greater role than temperature presumably because of its importance for the creation of rain-filled breeding sites (Gage et al., 2008; Jansen and Beebe, 2010).

Associations between dengue and El Niño_s were also increasingly smaller at high latitudes. This could be the results of extreme temperatures (either very high or very low) and low precipitation observed during an El Niño_s hamper the vector's biology (Watts et al., 1987; Focks et al., 2000; Bicout et al., 2002; Jansen and Beebe, 2010), and may result in negative associations with dengue. Much of this effect may be due to the ectothermic nature and the physiological sensitivity to water abundance of the *Aedes* mosquitoes (Gage et al., 2008; Jansen and Beebe, 2010). At low latitudes, several humid provinces experience warmer and wetter conditions during an El Niño_s, enhancing the vectorial development and activity, and resulting in increasingly stronger associations with dengue.

Previous studies indicate that SES plays a key role in dengue transmission (Reiter, 2001; Gage et al., 2008). Regions with high population densities and poor construction of buildings in the cities, using natural ventilation instead of air conditioning, and with low access to health services and education show higher incidence rates than well developed ones irrespective of their climate and vector prevalence (Reiter, 2001; WHO, 2009). Although less privileged regions may have higher incidence rates than well developed ones, something not examined in our study, SES differences do not seem to affect the strength of the associations between dengue and climate. Our results suggests that although socioeconomic factors may be important for the transmission dynamics of the disease (Reiter, 2001), associations between dengue, weather, and El Niño seem to be independent from variations in the SES.

3.6 Limitations

In this study we have assumed that the relationships between the logarithm of the number of dengue cases, weather and El Niño are linear. As previously explained, in reality these associations are likely to be nonlinear. The significant heterogeneity observed in this study may arise from the presence of such nonlinear relationships between dengue, weather, and El Niño; something not accounted for in our models. The use of flexible smooth functions for the predictors (see Chapter 4) could help in testing these assumptions.

Although the dataset used for this study has a greater spatial resolution than the one used in Chapter 2, data were still aggregated to rather large political boundaries. As previously explained, this aggregation may is likely to remove a great deal of variability in both the predictors and the outcome variable making it difficult to estimate statistically significant relationships between them (Johansson et al., 2009a).

Dengue transmission involves one person's infection leading to one or more secondary infections (see Figure 1.2). This situation results in a violation of independence as the number of dengue cases at a given time depends on the number of cases ocurring in previous periods. While the temporal autocorrelation does not bias our estimated regression coefficientes, it tends to underestimate the standard errors of the predictors (Cohen et al., 2003). Consequently, our models may have overestimated the statistical significance of the relationships between dengue, weather and El Niño. Figure 3.4 shows the partial autocorrelations for each of our province-specific models. These plots indicate that there has been a violation of independence in some provinces. Incorporating a temporal dependence structure between the observations in the province-specific models may help to prevent such violation (Zuur et al., 2009).

We used a sinusoidal term (Equation 3.3) characterized by a sine function to control for the effects of seasonal trends that may be related to non-climatic factors in our models. However, the seasonal patterns observed in our dataset may not have the shape or the phase of the sine function specified in our models. The use of pairs of sine and cosine functions may be helpful for relaxing this assumption.

Here, we did not account for the confounding effects of socioeconomic development in the regression models. As a consequence, our models are subject to have large residual confounding. Moreover, we could have overestimated the true effects of weather and El Niño on dengue incidence. Some of the effect of socioeconomic development (e.g. variations in GDP) may have been accounted for by the categorical variable for year in the model.

Our meta-analytic approach is one of the simplest and valid ways to compare summary measures between clusters (Kirkwood and Sterne, 2003). However, a more powerful and succinct analysis could have been obtained by fitting a single model to the data from all provinces together. We take this approach in the following Chapter.

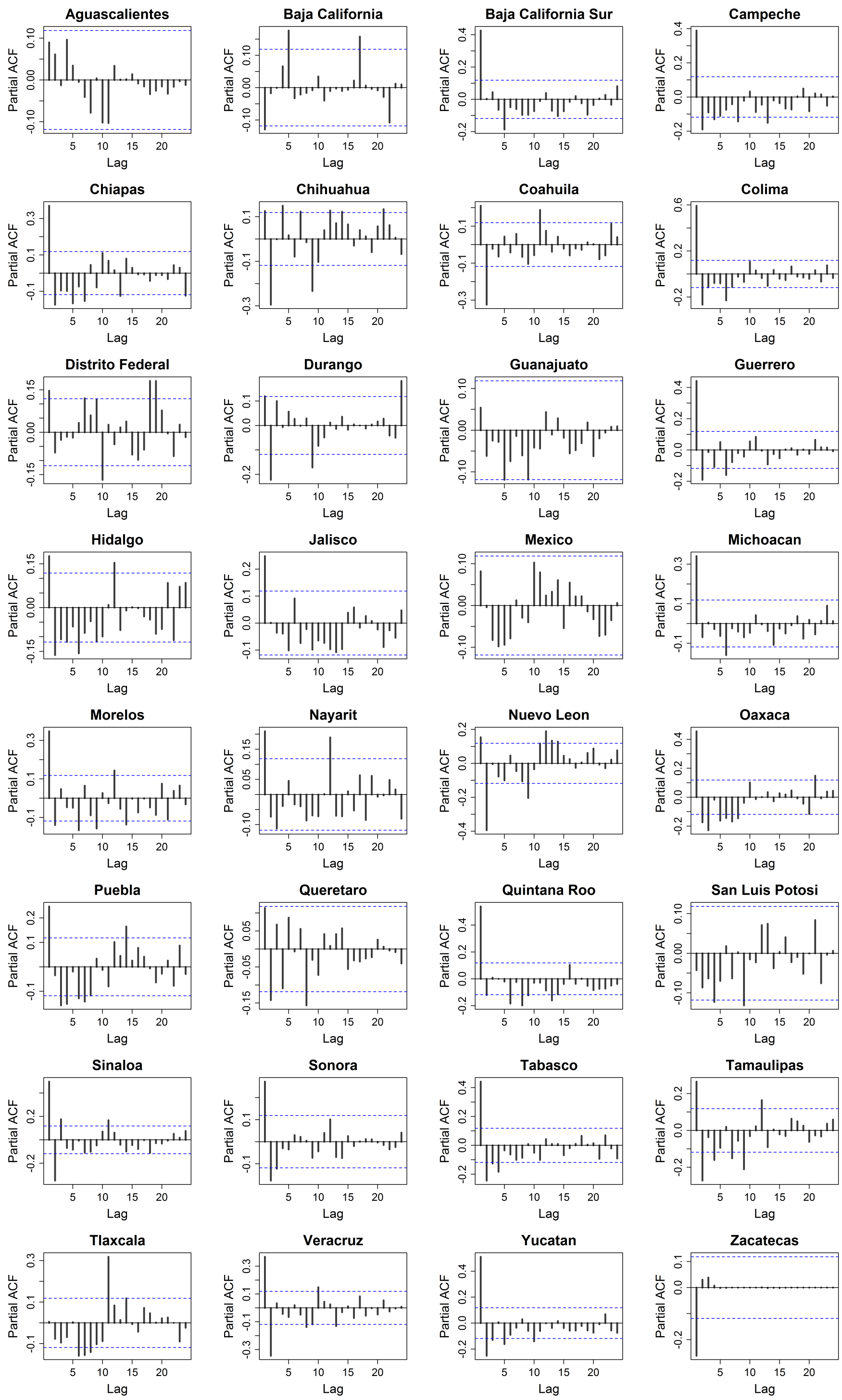

Figure 3.4: Partial autocorrelations of the province-specific models' deviance residuals.

3.7 Conclusions

Many infectious diseases share the common feature of being spatially heterogeneous in their transmission (Johansson et al., 2009b). The approach used in this study offers an alternative for overcoming the difficulties posed by spatial heterogeneity in the development of statistical models for the spatiotemporal analysis of the effects of weather on a range of vector-borne diseases.

In this study, meta-analytic regression analysis revealed that the effects of weather and El Niño on dengue across provinces in Mexico are significantly heterogeneous across provinces. These findings corroborate that dengue dynamics is determined at the local level and significantly influenced by the underlying local climate. Furthermore, they highlight the disadvantages of using country-level aggregated values for estimating the empirical relationships between climate variables and health indicators in a country with large geography and climatic variability.

3.8 Acknowledgments

Wolfgang Viechtbauer provided technical assistance for the use of the 'metafor' Meta-Analysis Package for R. The Mexican Meteorological Service kindly provided the temperature and precipitation data to conduct this study. Dr. Víctor Magaña et al. kindly provided the maps for Figure 3.1. Felipe J. Colón González received a scholarship from the Mexican National Council for Science and Technology (CONACYT).

Chapter 4

The potential impact of climate change on dengue incidence

4.1 Abstract

There is still uncertainty about the potential impact of climate change on vector-borne diseases. Such uncertainty reflects the difficulties to model the complex interactions between climatic and socioeconomic determinants of the disease. Here, we use a large panel of monthly province-specific data covering 23 years of dengue observations to estimate the relative importance of weather on contemporary dengue trends after accounting for the confounding effects of several non-climatic factors. We estimate statistically significant effects of weather and access to piped water on dengue. The effects of weather are highly nonlinear. These findings highlight the importance of using flexible model specifications when analysing weather-health interactions. We use our model estimations to project the potential impact of climate change on dengue incidence under three emission scenarios by 2030, 2050 and 2080. Our projections indicate that climate change could increase the national average annual dengue incidence by up to 42% by 2080. Rising access to piped water could aggravate the problem if it leads to increased domestic water storage. Climate change may therefore influence the success or failure of future efforts against dengue.

4.2 Introduction

Dengue is the most widely distributed and rapidly spreading mosquito-borne viral disease in the world (TDR, 2007). This acute febrile disease affects all age groups (WHO, 1997), and is caused by four antigenically distinct but genetically related viruses (serotypes) (Wearing and Rohani, 2006). Dengue has become endemic in over 100 countries (Figure 1.1) in Africa, the Americas, the Eastern Mediterranean, South-east Asia and the Western Pacific (WHO, 2009). Approximately 2.5 billion people are at risk from dengue transmission. About 50 million new dengue infections (WHO, 2009) and at least 12,000 deaths, mainly among children, occur worldwide every year (WHO, 2002). The economic burden of dengue has been estimated to be about 2.1 billion US dollars per annum in Latin America and the Caribbean alone (Shepard et al., 2011). The economic losses caused by dengue are similar to those attributed to malaria and tuberculosis in some regions such as the Americas (Torres and Castro, 2007). As there are no specific antiviral medicines treating or vaccines preventing dengue, the only way to control or prevent the disease is through the control of vector populations (Al-Muhandis and Hunter, 2011).

The global incidence rate of dengue has substantially increased over the last six decades (from about 900 annual cases reported to WHO over 1955–1959 to about 926 thousand annual cases over 2000–2007, WHO 2009, 2002) influenced by numerous mechanisms including population growth, unplanned urbanisation, increased travel and transportation of goods, lack of political will and limited resources for implementing effective control measures (Al-Muhandis and Hunter, 2011). The spatial distribution of the main dengue vector, *Aedes aegypti*, has also increased over the last 25 years (Jansen and Beebe, 2010). Increases in the distribution of both dengue incidence and *A. aegypti* have also been associated to variations in the climate system, including climate change (e.g. Sriprom et al., 2010).

In this chapter, we estimate the relative effects of weather (minimum and maximum temperature, and precipitation) on dengue accounting for the confounding effects of several of non-climatic factors (e.g. access to piped water, urbanisation, gross domestic product, inter-annual variability, and seasonal trends). Our model estimations are then used to estimate the potential effects of climate change on dengue incidence for the years 2030, 2050 and 2080 under three of the emission scenarios described by Nakicenovic and Swart (IPCC, 2000).

Several empirical models have been developed for estimating associations between dengue and weather (e.g. Sriprom et al., 2010; Johansson et al., 2009b), and some of these have been used as a baseline to predict the potential impacts of climate change on the future distribution and risk of dengue infection (e.g. Confalonieri et al., 2007; Sriprom et al., 2010). However, although non-climatic factors greatly confound the associations between dengue and weather, the majority of these studies have failed to incorporate such confounders greatly undermining their estimations (Robins and Morgenstern, 1987; Gething et al., 2010). Furthermore, most previous research has been conducted in small geographical areas or covered relatively short periods of time (e.g. Johansson et al., 2009b; Sriprom et al., 2010; Schmidt et al., 2011) leading to several limitations. For example, short series (10 years or less) pose challenges for the identification of climatic signals with high statistical confidence because of their small signal-to-noise ratios (Santer et al., 2011); small populations commonly result in low disease numbers leading to unstable risk estimations (Olsen et al., 1996); small areas are also more likely to be climatically and socioeconomically homogeneous (Elliott and Wartenberg, 2004; Eisen and Lozano-Fuentes, 2009), making it harder to extrapolate the results to areas with greater climatic or socioeconomic variability.

Our study case has various unique features that minimize the identified problems. First, we used a large panel of province-specific data with a refined temporal resolution (monthly) covering the entirety of Mexico to investigate a greater geographical area (1.96 million km^2), time frame (276 months), and number of cases (417,668) than previous studies. Second, the great climatic diversity (Mexico is a tropical and subtropical country, Mosiño and García 1974) and socioeconomic heterogeneity (GINI index 0.48, The World Bank 2012) of Mexico allowed us to estimate robust and generalized relations between dengue, weather and socioeconomic development, which can be extrapolated to a variety of regions with similar climatic and socioeconomic features. Third, we allowed for nonlinear relationships between dengue and weather by adopting a semi-parametric modelling approach.Specifically, we implemented a Generalized Additive Model (GAM) coupled with penalized likelihood function and an automated smoothing selection criterion, which estimated the optimal degree of nonlinearity of the model directly from the data (Wood, 2006). Such specification resolves the subtle task of determining the model flexibility *a priori* by incorporating this choice into the actual estimation process. This method has been described in detail elsewhere (Wood, 2006). Finally, we incorporate province-specific fixed-effects into our model to account for the confounding effects of time invariant unobserved variables.

4.3 Materials and methods

4.3.1 Data

Province-specific monthly reports of laboratory confirmed dengue cases were collected from the Mexican National System of Epidemiologic Surveillance website[1] for the period 1985–2007 (Table 4.1). Dengue and dengue hemorrhagic fever cases were aggregated because they correspond to different presentations of the disease. Higher incidence rates were observed during the wet season (May to October), and in provinces with low elevation coastal zones.

Variable	Units	Mean	sd	Min	Max
Dengue	Cases	47.3	233.8	0.0	6322.0
$\text{Tmin}_{1:2}$	°C	13.3	5.5	-1.9	24.8
$\text{Tmax}_{1:2}$	°C	28.5	4.3	15.0	39.3
$\text{Precipitation}_{1:2}$	mm	146.2	161.4	0.0	1167.0
Access to piped water	%	81.8	12.2	44.5	98.1
GDP	Thousand USD	26.8	58.1	2.8	744.0
Urbanisation	%	71.7	15.6	35.7	100.0
Population	million	2.8	2.4	0.2	14.5

Table 4.1: Descriptive statistics.

Monthly average minimum and maximum temperature, and monthly accumulated precipitation data were obtained from the Mexican National Meteorological Service for each province for the period 1971–2007 (Table 4.1). Data comprised province-specific averages from observations from all meteorological stations within each province.

Provincial population data were retrieved from the website of the National Institute of Statistics and Geography (INEGI)[2] for 1990, 1995, 2000 and 2005. The proportion of the population with access to piped water was also obtained from INEGI for 1990, 2000, 2005

[1] http://www.dgepi.salud.gob.mx/anuario/html/anuarios.html (Accessed 12 Mar 2009)
[2] http://www.inegi.org.mx/default.aspx (Accessed 23 Mar 2009)

and 2010. The share of the population living in urban areas (urbanisation) was obtained from the Chamber of Deputies[3] for 1980, 1990, 1995, 2000 and 2004 (Table 4.1). Intervening years for these variables were estimated using linear interpolation.

GDP per capita was estimated using annual deflated GDP data from the World Bank[4] and population data from INEGI (Table 4.1). Because GDP was aggregated at the national level, we distributed national GDP to each province proportionally to the provincial distribution for which GDP information were available (1993–2005) from INEGI.

4.3.2 GAM model

We specified the expected number of dengue cases during month *t* in provice *i* as:

$$y_{it} \sim \text{Poisson}(\mu_{it}) \tag{4.1}$$

$$\log(\mu_{it}) = \beta_0 + \sum_{j=1}^{3} s_j(X_{jit}) + \sum_{k=1}^{3} \beta_k(Z_{kit}) + s_1(t) + d_i + \log(\text{Pop}_{it}) \tag{4.2}$$

where μ_{it} denotes the expected number of dengue cases at time *t* = 1985,...,2007.917; β_0 is the intercept; X_{jit} denotes the *j*-th meteorological variables; $s_j(.)$ and $s_1(.)$ are smooth functions for the meteorological variables and the time trend defined via penalized cubic regressions splines; Z_{kit} is a vector of *k*-th socio-economic variables (GDP per capita, proportion of people living in urban areas, proportion of people with access to piped water) which enter the model linearly; d_i are province-specific fixed effects as described by Johnston and DiNardo (1997) to allow for the potential effects of unobserved confounders in the model. Log(Pop$_{it}$) indicates the logarithm of the total population included as an offset variable. This led to a Poisson model with log link function. To account for possible over-dispersion, we allowed the scale parameter to be different from the mean (Cameron and Trivedi, 1990).

The province-specific fixed effects control for province-specific omitted variable bias and un-modelled confounders such as the differences in reporting or control measures between provinces. The smooth function of time controls for inter-annual variability and seasonal trends that could arise from non-climatic factors such as resistance of the vector to insecticides, changes in the diagnostic techniques, holidays and seasonal water storage practices. To ensure the robustness of our results, we tested other specifications to account for inter-annual variability and seasonal trends including: categorical variables for calendar year, and for calendar month for the period; categorical variables for each year with a sinusoidal term; and a linear trend with a sinusoidal term (Table 4.4). The results presented here were robust to all these specifications.

Because the modulating effects of the climate system on vector populations do not immediately result in changes on dengue transmission, we specified our meteorological

[3]http://www.cefp.gob.mx/intr/bancosdeinformacion/estatales/ (Accessed 18 Apr 2009)
[4]http://data.worldbank.org/indicator/NY.GDP.MKTP.CD (Accessed 21 May 2011)

variables within time lags that were both biologically and physically plausible based on literature reports in Mexico (e.g. Hurtado-Díaz et al., 2007; Brunkard et al., 2008; Colón-González et al., 2011). We also considered the delays in laboratory confirmation of suspected cases and their reporting. We only report results for the GAM with the greater explanatory power, which is also the most consistent with the ecology of the disease. Optimal lagged climatic variables comprised monthly average minimum temperature, average monthly maximum temperature and accumulated monthly precipitation lagged one and two months. To avoid colinearity between both lagged variables, we created new variables ($\text{Tmin}_{1:2}$, $\text{Tmax}_{1:2}$ and $\text{Precipitation}_{1:2}$) taking the mean of the values of the two lagged variables. Estimations were conducted using the *mgcv* package (Wood, 2006) for R version 2.13.1 (R Development Core Team, 2010).
The smooth functions are represented by regression splines, which can be written as linear-combinations of known basis functions of the regressors.

$$s_j(X_{jit}) = \sum_{l=1}^{q} \delta_l b_l(X_{jit}) = \delta' b \tag{4.3}$$

where $b_l(.)$ denotes the basis functions and δ_l the parameters to be estimated. The number of basis functions q determines the maximum possible flexibility of the relation between X_{jit} and $\log(\mu_{it})$; the greater the value of q, the more flexible is the estimated effect. Here, we used Cubic Regression Splines (CRS) in which the basis functions $b_l(.)$ are constructed by dividing the range of values of the independent variable into segments separated by knots. A local cubic regression is fitted to each segment. The continuity and smoothness at the knots is ensured imposing conditions on the first and second-order derivatives (Keele, 2008).

4.3.3 Climate change scenarios

We generated extrapolations of projected dengue risk based on our fitted GAM model parameters for the years 2030, 2050 and 2080, under the A1B, A2 and B1 climate change scenarios. The storylines behind these scenarios are described in detail elsewhere (IPCC, 2000). Briefly, the A1B scenario relates to a future with very rapid economic growth, global population peaking in mid-century, and the introduction of more efficient technologies with a balance in energy-sources-related technological change (IPCC, 2000). The A2 scenario describes a future with a continuously increasing global population, economic development regionally oriented, and a slower and fragmented per capita economic growth and technological change than other scenarios (IPCC, 2000). Lastly, the B1 scenario considers a similar global population growth as the A1B, but with an economic structure towards a service and information economy, reductions in material intensity, and the introduction of clean and resource-efficient technologies (IPCC, 2000).

To project the potential impact of climate change on dengue (with Monte Carlo 95% confidence intervals), we retrieved province-specific historical values (relative to the 1970–1999 climatology) and projected changes for the years 2030, 2050 and 2080 under three climate change scenarios (A1B, A2 and B1) for monthly mean temperature and precipitation from the National Institute of Ecology web page[5]. Data were retrieved using the coordinates of the approximate centroids of each province. Data correspond to a multi-model ensemble of downscaled spatial climate change scenarios for Mexico. The methodology and outputs of these ensembles have been described by Magaña and Caetano (2007).

Average monthly minimum temperature, maximum temperature and precipitation were estimated as the monthly averages of the baseline period based on the observational data obtained from the Mexican National Meteorological Service. To generate new temperature values for each scenario, we added the corresponding projected changes to the historical values. Precipitation was rescaled multiplying the historical value by the corresponding projected percentage of variation. The average of minimum temperature, maximum temperature and precipitation values (historical and projected) lagged one and two months were then used for the climate change projections.

Briefly, the used scenarios (A1B, A2, B1) describe rising temperature at an increasing rate all over the country. The north-west region is the most greatly affected by temperature by the end of the century (Magaña and Caetano, 2007). In these scenarios, changes in precipitation are be very irregular; although they agree that decreases are expected mainly in the north and north-west, followed by the Yucatan Peninsula and central Mexico (Magaña and Caetano, 2007). Changes in both temperature and precipitation are expected to be greater under the A2 scenario (high emissions) followed by the A1B and B1 (Magaña and Caetano, 2007).

To conduct our estimations, we used future projections of climate holding all the other driving forces constant (fixed to the baseline year 2000) to isolate the climatic effects on dengue. Although the isolation of the effects of climate is a simplification of the complex interaction of dengue dynamics, our approach is justified because unlike malaria, which shows a contemporary decreasing trend even in the presence of climate change (Gething et al., 2010), dengue transmission has substantially increased over the past six decades (WHO, 2002, 2009); furthermore, our model is robust to the confounding effects of observed and un-observed non-climatic factors giving validity to our estimations. These projections, are not predictions of the future but show the potential impact of climate change on dengue incidence whilst keeping the other driving forces constant.

4.4 Results

4.4.1 GAM model

Table 4.2 presents the estimates of our GAM model for the logarithm of dengue incidence per province. This specification explained 62% of the deviance of the log-transformed dengue incidence. The high values of the effective degrees of freedom (*edf*) of the smooth functions indicate that associations between dengue and weather are highly nonlinear. The effects of all meteorological variables and access to piped water on dengue were found to

[5]http://zimbra.ine.gob.mx/escenarios/ (Accessed 10 Nov 2011)

be significant. The estimate of the scale parameter was very high (> 80) indicating extra-Poisson variability.

Smooth terms	*edf* (F)
s(Time)	**44.540 (58.950)**
s($\text{Tmin}_{1:2}$)	**3.776 (19.850)**
s($\text{Tmax}_{1:2}$)	**2.972 (58.480)**
s($\text{Precipitation}_{1:2}$)	**3.697 (57.860)**
Linear terms	Estimate (SE)
Constant	**-23.325 (2.918)**
Access to piped water	**0.054 (0.007)**
Urbanisation	0.011 (0.010)
GDP per capita	-0.799 (0.801)
Fixed-effects	Included
Log-Likelihood	-383696.5
Explained deviance	62.4%
GCV	88.144
Scale parameter	85.459

Table 4.2: Model estimates of the effects of weather and socioeconomic development on dengue across Mexico. Values in bold font were significant at the 0.001 level. *edf* = effective degrees of freedom of the smooth function terms (*edf* >1 indicate nonlinear relationships); F-value is an approximate F-test as in (Wood, 2006), maximum number of spline basis for the meteorological terms = 5. SE = asymptotic standard error; GCV = Generalized Cross Validation. Estimation via Poisson Iteratively Reweighted Least Squares (P-IRLS) and GCV score minimization by outer iteration.

Figure 4.1 depicts the relationships estimated by our model. The figure reveals that with our GAM specification, $\text{Tmin}_{1:2}$ appears to have the greatest relative importance in the model (notice the differences in the 'y' axes. Figure 4.1A shows a modest response of dengue to $\text{Tmin}_{1:2}$ below 10°C, which progressively becomes greater at higher temperatures. At temperatures above 18°C the response of dengue to $\text{Tmin}_{1:2}$ increases sharply providing a partial explanation for the strong seasonality observed in tropical provinces where seasonal variations in temperature are not greater than a few degrees (Focks et al., 2000) but are close to this mean value. These effects are consistent with the biology of both the mosquito and the virus because rising temperatures shorten the extrinsic incubation period (EIP), the development time and the gonotrophic cycle resulting in an increased likelihood of dengue transmission (Jansen and Beebe, 2010; Focks et al., 2000; Watts et al., 1987).

Dengue incidence also increases gradually with rising $\text{Tmax}_{1:2}$ (Figure 4.1B), showing a peak at approximately 32°C. The decay in the association with dengue at high levels of $\text{Tmax}_{1:2}$ may be explained by the maximum transmission efficiency of *A. aegypti* achieved above 32°C (Watts et al., 1987), and by adult mosquitoes gradually dying at temperatures above 36°C (Focks et al., 2000). Figure 4.1C shows a quadratic relationship between dengue incidence and $\text{Precipitation}_{1:2}$ with a peak at approximately 590 mm. The progressive increase in dengue incidence at low $\text{Precipitation}_{1:2}$ levels suggests the creation of rain-filled (outdoors) breeding sites, whereas the decay observed at high levels, may be due to the wash-out of such breeding sites (Gage et al., 2008).

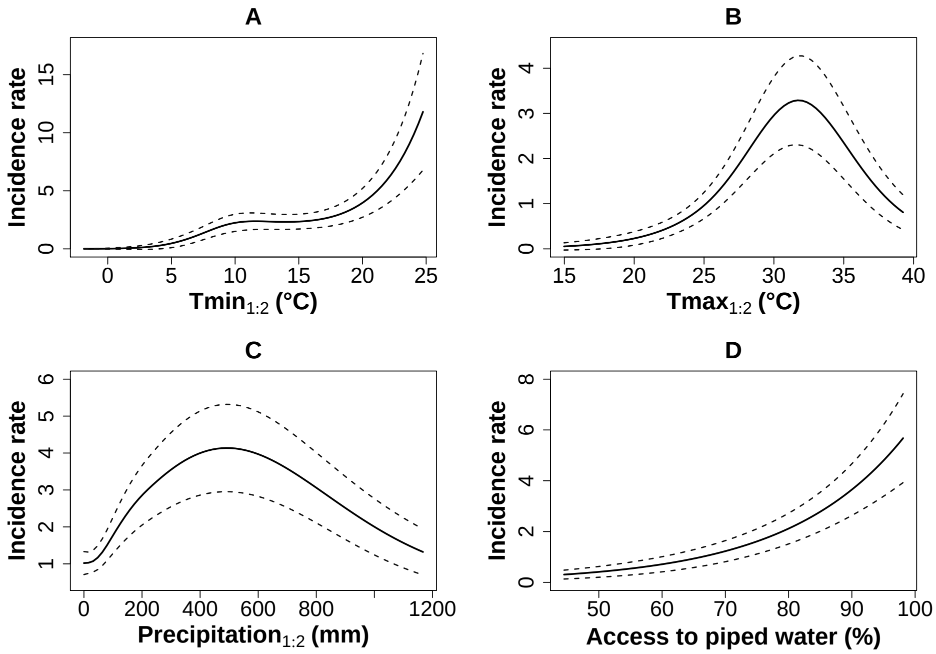

Figure 4.1: Estimated response of the average monthly dengue incidence to (A) $\mathrm{Tmin}_{1:2}$, (B) $\mathrm{Tmax}_{1:2}$, (C) $\mathrm{Precipitation}_{1:2}$, and (D) access to piped water. Solid lines indicate the average expected number of dengue cases (cases/100,000 people per month); dotted lines indicate the estimated 95% Bayesian prediction intervals.

Figure 4.1D depicts a positive relationship between dengue incidence and the proportion of the population with access to piped water, indicating that as access to piped water rises so too does dengue. Such relationship could result from unplanned urbanisation overburdening water systems (Al-Muhandis and Hunter, 2011), and forcing people to store water due to fear to limited or intermittent water supply. Rising water storage increases the number of potential breeding sites that could be effectively exploited by the vector (Jansen and Beebe, 2010; Padmanabha et al., 2010). Urbanisation and GDP did not show a significant association with dengue. This may indicate that these variables do not play a key role in determining dengue transmission in Mexico or that our data, after the removal of time invariant characteristics by the province-specific fixed-effects, do not contain enough variability for estimating meaningful relationships for these variables.

$\mathrm{Tmin}_{1:2}$ and $\mathrm{Tmax}_{1:2}$ were highly correlated with each other (Table 4.3). To ensure the robustness of our estimations, we re-fitted the model and obtained estimations for $\mathrm{Tmin}_{1:2}$ and $\mathrm{Tmax}_{1:2}$ when they were not mutually adjusted, keeping the other variables as described in the original model (Equation 4.2).

$\mathrm{Tmin}_{1:2}$–$\mathrm{Tmax}_{1:2}$	**$\mathrm{Tmin}_{1:2}$–$\mathrm{Precipitation}_{1:2}$**	**$\mathrm{Tmax}_{1:2}$–$\mathrm{Precipitation}_{1:2}$**
0.876	0.538	0.196

Table 4.3: Spearman rank correlations between meteorological predictors.

Figure 4.2 depicts the relationships estimated by these models and shows that although the shapes of the relationships between dengue and weather were consistent in all three models, there are changes in the oder of magnitude and the thresholds of the response of dengue to both $\text{Tmin}_{1:2}$ and $\text{Tmax}_{1:2}$. More specifically, $\text{Tmin}_{1:2}$ showed a smaller effect and $\text{Tmax}_{1:2}$ a greater effect on dengue incidence when they were not adjusted for the effects of each other. The threshold at which the response of dengue to $\text{Tmin}_{1:2}$ increased sharply was estimated at approximately 15°C in the un-adjusted model and not at about 18°C as in the adjusted model. Additionally, the response of dengue to $\text{Tmax}_{1:2}$ showed a peak at about 34°C compared to 32°C in the adjusted model.

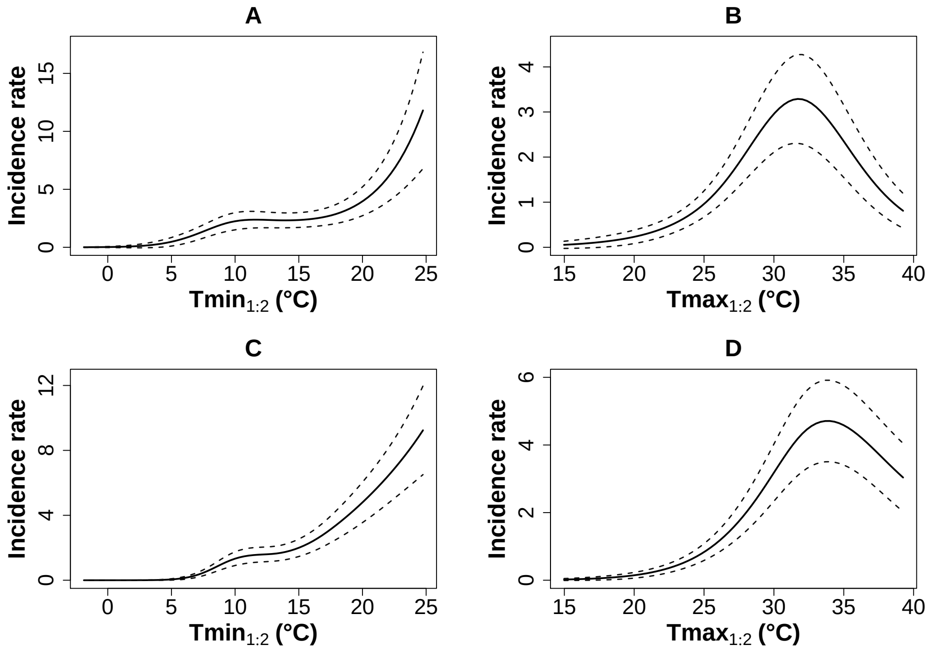

Figure 4.2: Estimated response of average monthly dengue incidence to (A) $\text{Tmin}_{1:2}$ and (B) $\text{Tmax}_{1:2}$ when mutually adjusted, and estimated response of average monthly dengue incidence to (C) $\text{Tmin}_{1:2}$ and (D) $\text{Tmax}_{1:2}$ when entered independently into the Poisson GAM. Solid lines indicate the average expected number of dengue cases (cases/100,000 people per month); dotted lines indicate the estimated 95% Bayesian prediction intervals.

We tested different specifications to control the model for inter-annual variability and seasonal trends. Table 4.4 reports the results of the different model specifications tested. Generally, the results of all models were consistent with our Poisson GAM estimations. GDP and urbanisation became significant in some of the models presumably due to the more stringent control for interannual variability and seasonal trends than in the original model.

We compared the model predictions with the observed data for the whole year, and the wet (May to October) and dry seasons (November to April). The model captured much of the spatiotemporal variability observed in dengue incidence (Figure B.2) providing evidence that our estimates are robust. We tested the influence of the province with the greatest incidence rate on the model fit excluding it from the model. The results presented in this chapter were robust to these changes.

Specification	Original model	Model 2	Model 3	Model 4	Model 5
Smoothers (edf)					
$\text{Tmin}_{1:2}$	**3.776**	**3.625**	**3.561**	**3.367**	**3.802**
$\text{Tmax}_{1:2}$	**2.972**	**2.917**	**2.958**	**3.021**	**2.972**
$\text{Precipitation}_{1:2}$	**3.697**	**3.618**	**3.709**	**3.793**	**3.448**
Linear (Coef.)					
Acc. water	**0.544**	**0.063**	**0.063**	**0.021**	**0.063**
Urbanisation	0.011	0.004	0.005	**0.039**	0.017
GDP	-0.799	**-2.802**	-2.857	0.026	-3.365
AIC	767573.1	747277.6	835574.2	756850.4	957771.4
GCV	88.144	85.285	95.212	86.056	108.488
Adj. R^2	0.385	0.402	0.332	0.393	0.243
Deviance explained	62.416	63.436	58.993	62.954	52.844

Table 4.4: Model estimates using different representations of inter-annual variability and seasonal trends. Values in bold font were significant at the 0.001 level. The original model is as in Equation 4.2. Model 2 replaces the smooth variable of time (Equation 4.2) with categorical variables for calendar year and month. Model 3 uses categorical variables for calendar year and season. Model 4 includes a categorical variable for calendar year and a sinusoidal term for season. The sinusoidal term can be expressed as $sin(2 \times \pi \times \text{time}/12) + cos(2 \times \pi \times \text{time}/12)$, where $time$ is an index variable 1,...,n. Model 5 includes a linear trend and a sinusoidal function.

4.4.2 Climate change projections

Our projections suggest that mean annual dengue incidence may increase about 12–18% by 2030, 22–31% by 2050, and 33–42% by 2080 across Mexico indicating an increasing effect of climate change on dengue (Table 4.5). Such increasing effect was also evident when we compared the projected impact of climate change on dengue incidence in Nuevo León (semi-warm and semi-dry climate) and Veracruz (warm and humid climate) characterized by intense transmission but with periods of no transmission during the dry season, and Querétaro (temperate and semi-dry) characterized by very intermittent transmission (Table 4.5). Although the proportional increase under future climate change was estimated to be substantially greater in Querétaro by 2080 (A1B: 95%, A2: 102%, B1: 71%) compared to Nuevo León (A1B: 51%, A2: 58%, B1:42%) and Veracruz (A1B: 70%, A2: 63%, B1: 60%), the absolute incidence rate in Querétaro is much lower than that of the other two provinces (0.042 vs. 1.682 and 2.630 cases/100,000 people respectively). This situation implies that the projected net dengue incidence by the end of the century is expected to be considerably greater in already endemic provinces characterized by intense transmission.

Figure B.3 shows that the majority of provinces across Mexico are expected to undergo an increase in dengue transmission under future climate change. The difference in mean annual dengue incidence between the projections and the baseline scenario are likely to be greater in already endemic provinces (with year-round transmission or with periods of no transmission during the dry season), and particularly stronger in southern and eastern provinces characterized by warm and humid climates. Some north-western provinces and the north of the Yucatan Peninsula are likely to observe decreases in dengue incidence by 2080 presumably due to the impact of reduced precipitation on the creation of breeding sites and the development of immature stages of the vector (Bicout et al., 2002; Gage et al.,

Scenario	Region	Baseline	95% CI	2030	95% CI	2050	95% CI	2080	95% CI
A1B	National	1.001	0.708–1.466	1.177	0.832–1.723	1.315	0.926–1.961	1.411	1.001–2.078
A2	National	1.001	0.708–1.466	1.118	0.798–1.640	1.258	0.894–1.863	1.412	1.016–2.093
B1	National	1.001	0.708–1.466	1.149	0.814–1.702	1.222	0.870–1.813	1.333	0.942–2.003
A1B	Nuevo León	1.683	1.141–2.589	2.092	1.427–3.208	2.296	1.555–3.510	2.539	1.757–3.874
	Querétaro	0.042	0.014–0.138	0.056	0.018–0.179	0.067	0.022–0.227	0.082	0.026–0.278
	Veracruz	2.630	1.801–3.961	3.358	2.292–5.067	3.388	2.653–5.901	4.470	3.104–6.836
A2	Nuevo León	1.683	1.141–2.589	2.001	1.360–3.082	2.240	1.520–3.430	2.654	1.801–4.043
	Querétaro	0.042	0.014–0.138	0.053	0.017–0.181	0.067	0.020–0.223	0.085	0.026–0.274
	Veracruz	2.630	1.801–3.961	3.005	2.067–4.568	3.377	2.556–5.731	4.289	2.934–6.578
B1	Nuevo León	1.683	1.141–2.589	1.950	1.330–2.997	2.248	1.539–3.399	2.392	1.617–3.601
	Querétaro	0.042	0.014–0.138	0.056	0.018–0.200	0.062	0.194–0.202	0.072	0.023–0.251
	Veracruz	2.630	1.801–3.961	3.250	2.235–4.892	3.522	2.399–5.363	4.216	2.823–6.345

Table 4.5: GAM-estimated average annual dengue incidence (cases/100,000 people) under climate change.

2008; Jansen and Beebe, 2010).

4.5 Discussion

In this study, we estimated the influence of weather and a socioeconomic development across a larger and more heterogeneous geographical area, and longer time frame than previous studies. Our GAM approach revealed that associations between dengue, weather and access to piped water are statistically significant in accordance with previous research (Sriprom et al., 2010; Colón-González et al., 2011; Lowe et al., 2011). Furthermore, associations with weather are highly nonlinear as previously observed in other regions (e.g. Beebe et al., 2009). These results highlight the importance of using flexible model specifications for analysing weather-health interactions.

$\text{Tmin}_{1:2}$ had the biggest impact on dengue with almost no risk below 5°C, a modest increased risk above this temperature, and a rapid increasing risk when average minimum temperatures rose above 18°C. Maximum temperature also showed an effect independently from Tmin. The risk of dengue increased as $\text{Tmax}_{1:2}$ rose above about 20°C to a peak around 32°C after which the risk declines. There is some uncertainty as to the validity of these thresholds because when we fitted models in which $\text{Tmin}_{1:2}$ and $\text{Tmax}_{1:2}$ were not mutually adjusted, we obtained slightly different thresholds. We also observed an increasing risk as $\text{Precipitation}_{1:2}$ rose to about 550mm beyond which risk declines. Our findings are consistent with the results of other studies (e.g. Sriprom et al., 2010; Lowe et al., 2011). However, previous studies using OLS, GLM, or ARIMA methods are unlikely to have fully captured the nonlinearities that we have demonstrated here.

The estimated relationships suggest that climate change may result in greater dengue transmission by the end of the century under the three used scenarios (A1B: 41%, A1: 42%, and B1: 33%) with a more conspicuous effect in already endemic provinces. The increasing trends in access to piped water (INEGI, 2010) may aggravate the projected impact of climate change if it leads to domestic or peri-domestic water storage as it could provide with potential breeding sites even in the absence of precipitation (Gage et al., 2008; Jansen and Beebe, 2010).

The use of regional climate model outputs represent a significant source of such uncertainty as they are based on the probability that one event may or not take place. To address model uncertainty, we used multimodel ensembles because they have shown greater forecast quality compared to single model ensembles (e.g. Stephenson et al., 2005).

4.6 Limitations

Our projections of dengue incidence under climate change are subject to some limitations. For example, there is large underreporting and misclassification of dengue cases because of lack of specificity of the symptoms, low awareness of health practitioners, limited access to diagnostic tests, and poor systematic surveillance (Suaya et al., 2007; WHO, 2012). Thus, our estimations were conducted on a fraction of the total cases, and may be biased towards larger standard errors (Lake et al., 2008). Also, the proportion of unreported cases may vary between provinces biasing our estimates (Lake et al., 2008). However, variation in reporting would be accounted by the province-specific fixed effects in our model.

The use of smooth functions for seasonal trends and inter-annual variability is required to differentiate the effects of weather from other covariates that may also exhibit a seasonal trend (Bowie and Prothero, 1981; Johansson et al., 2009b). However, because such smooth functions likely contain more variability that can attributable to weather, they may cause an underestimation of the magnitude of the true effects of weather on dengue (Johansson et al., 2009b).

We have assumed that dengue incidence has the same temporal trend all over the country. However, Mexico has a large number of climatic regions with different temperature and precipitation patterns (Mosiño and García, 1974). Consequently, this assumption needs to be tested to reinforce our results.

Our assumption of an invariant dengue-weather relationship is at odds with the results of Chapter 3 that estimated significant heterogeneity in the associations between dengue and weather. However, such heterogeneity may be arise from the nonlinear structures we have demonstrated here. This is because, on the one hand, we have not looked for nonlinear structures on previous chapters; and on the other hand, as will be later illustrated, analysing a short range of meteorological data poses problems for the detection of nonlinearities.

As explained in previous chapters, dengue transmission involves at least, two mosquito bites. As a consequence, dengue time series violate the assumption of independence required for regression analyses. Although this serial dependency does not lead to biased regression coefficients, our model may have underestimated the standard erros of the predictors. Figure 4.3 shows the partial autocorrelations of our Poisson GAM residuals. This plot indicates a serial dependency which could be prevented by incorporating a temporal dependence structure between the observations in the model (Zuur et al., 2009).

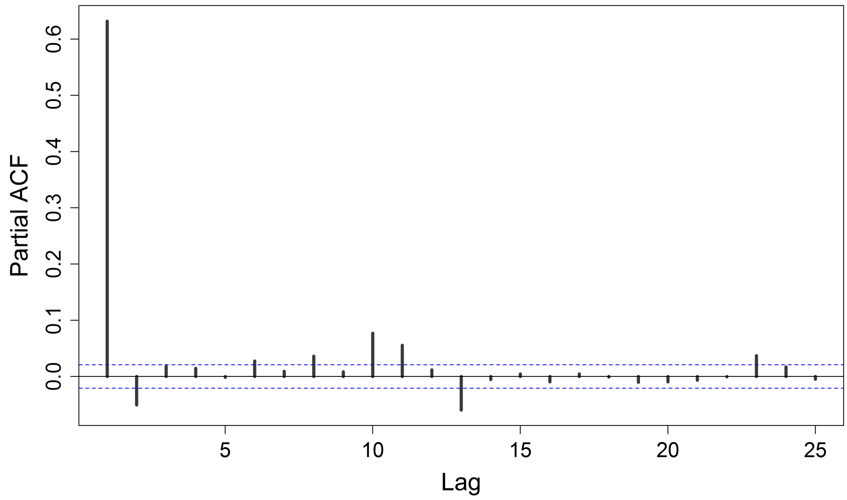

Figure 4.3: Partial autocorrelations of the Poisson GAM's deviance residuals.

4.7 Conclusion

In conclusion, we have reported on the association between dengue incidence in Mexico and climate variables using one of the longest and more spatially diverse dengue and climate datasets yet assembled. We argue that our results provide, a much improved empirical model of the relationship between the dengue and climate than has been presented to date, because of the much longer data set and the use of GAM regression to better model the nonlinear nature of the relationships. Such an improved model is critical to help make better predictions of the impact of climate change on dengue into the future. Consequently, we further argue that this dataset can be used to draw conclusions about the relationship between dengue and climate elsewhere in the world. We have estimated the impact that future climate change will increase dengue incidence by about 40%, but that the proportional increase in severe dengue forms may be greater.

4.8 Acknowledgments

This chapter benefitted from the thoughtful comments of Dr. Corinne Le Quéré (Tyndall Centre for Climate Change Research, University of East Anglia, Norwich, UK). The Mexican Meteorological Service kindly provided the temperature and precipitation data to conduct this study. Felipe J. Colón González received a scholarship from the Mexican National Council for Science and Technology (CONACYT).

Chapter 5

Conclusions

This final chapter summarizes the main contributions of this thesis. The sources of uncertainty and their implications are briefly discussed in relation with the empirical chapters. The chapter concludes with some general suggestions for future work.

5.1 Summary of research gaps

Research suggests that variations in dengue incidence are significantly influenced by climatic variables such as temperature, precipitation, humidity and El Niño (e.g. Sriprom et al., 2010; Lowe et al., 2011). As a consequence, many studies have estimated empirical relationships between dengue, weather, El Niño, and climate change in several regions of the world such as the Americas, south-east Asia, and the South Pacific (e.g. Hales et al., 1996; Sriprom et al., 2010; Lowe et al., 2011). In some of these studies, authors used their model outputs as a baseline to predict the potential impact of climate change on the future distribution of dengue (e.g. Hales et al., 2002; Sriprom et al., 2010). However, these studies have been largely criticized (e.g. Reiter, 2001; Gage et al., 2008; Jansen and Beebe, 2010) because the majority of them sidestep elements that are key to the estimation of the effects of climate variables on disease outcomes with statistical confidence.

One common problem to most of these studies is that they fail to incorporate the effects of likely sources of spurious relationships (e.g. seasonal trends and socioeconomic development) greatly undermining their estimations (Robins and Morgenstern, 1987; Gething et al., 2010). Some studies were conducted across large geographical areas but using data aggregated at national or supra-national scales (e.g. Hales et al., 1996; Johansson et al., 2009a). The use of national or supranational data removes the spatial variability in all variables making it difficult to detect the complex associations between dengue and the local weather. Other studies were conducted in small geographical areas (e.g. Hurtado-Díaz et al., 2007; Brunkard et al., 2008) which commonly have low numbers of disease cases posing problems in producing sufficient numbers for their analysis with great statistical confidence, situation that may lead to unstable risk estimations (Olsen et al., 1996).

Many studies were conducted over periods spanning less than 10 years, and just a few spanned over 20 years. One major issue of such short time series is that they have small signal-to-noise rations that are problematic for the identification of climatic signals on dengue data with high statistical confidence (Santer et al., 2011). Furthermore, little research have been conducted to understand the potential causes of the between-regions variation observed in dengue incidence.

5.2 Main contributions

With this thesis we arguable filled some of these knowledge gaps enabling us to gain a better understanding of the effects of weather, El Niño, and climate change on dengue. We developed one of the most comprehensive dengue-related datasets analysed to date including epidemiological, geographical and socioeconomic data for a larger geographical area and period of time than previous studies (e.g. Hurtado-Díaz et al., 2007; Brunkard et al., 2008; Sriprom et al., 2010). Such a comprehensive dataset provides robustness to our estimations because it allows empirical models capture much more epidemiological, climatic, and socioeconomic variability than studies using data aggregated over different geographical areas, conducted across very small geographical areas, or carried out over short time periods. This dataset may be useful to other studies for modelling dengue incidence through a variety of statistical methods. In addition, data may be also be used for the validation of process-based (dynamical) models for dengue in Mexico.

One novel aspect of this thesis is that we investigated and revealed the nonlinear functional form of the effects of weather on dengue using smooth functions across a larger geographical area and time frame than previous studies. The estimated nonlinear relationships between dengue and weather were robust to the confounding effects of socioeconomic development, seasonal trends, and time-invariant unobserved covariates such as variations in reporting between provinces. The robustness of our estimations allowed us to project the potential effects of climate change on dengue incidence with greater statistical confidence than previous research (e.g. Hales et al., 2002; Sriprom et al., 2010).

The presence of such nonlinearities highlights the need for the correct specification of the functional form of the relationships between dengue and weather to avoid residual confounding issues (Benedetti and Abrahamowicz, 2004). These nonlinearities also stress the need for using comprehensive datasets because when nonlinearities are present, analysing a small range of meteorological data may pose problems for extrapolating the estimated relationships outside the range of the analysed values. Figure 5.1 illustrates this situation, and indicates that in three hypothetical regions, a short range of values (in red) of a given meteorological variable ($Tmax_{1:2}$ in this example) prevents the detection of nonlinear relationships.

Throughout this thesis, we highlighted the importance of using spatially disaggregated data for modelling disease outcomes in regions with great climatic and socioeconomic heterogeneity such as Mexico. Such disaggregation is important because, as we demonstrated in Chapter 4, the effects of weather on dengue are largely determined by the local conditions. Data aggregated at the regional, national and supra-national levels may mask the real effects of the predictors on dengue incidence, increasing the likelihood of aggregation bias

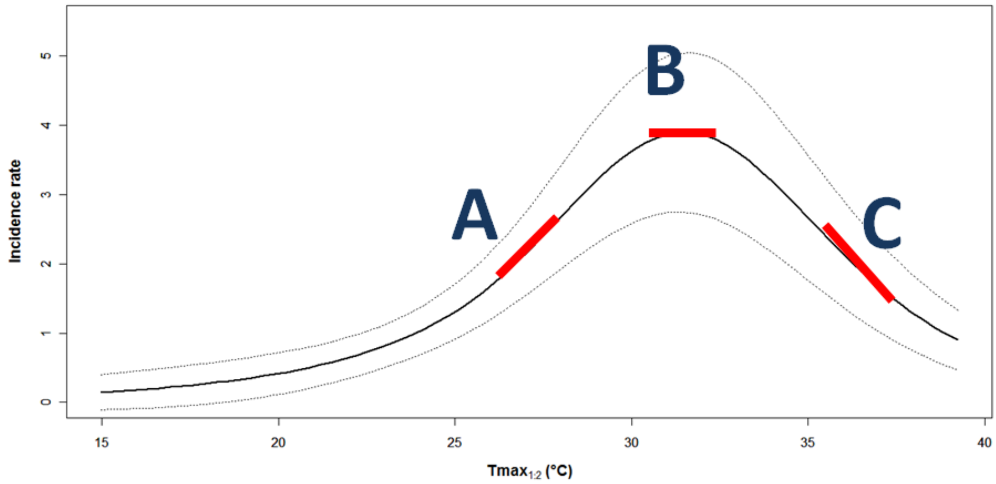

Figure 5.1: Representation of the estimated nonlinear effect of maximum temperature lagged 1 and 2 months ($Tmax_{1:2}$) on dengue incidence in Mexico (black continuous line). Lines A, B, and C (in red) represent the estimated effects of $Tmax_{1:2}$ under a short range of values in three hypothetical regions. Dotted lines indicate the estimated 95% Bayesian prediction intervals of the estimated effect of $Tmax_{1:2}$.

issues (Theil, 1954; Grunfeld and Griliches, 1960). Using Figure 5.1 as an example, it can be observed that the aggregation of data from these three hypothetical regions may cancel out the effect of $Tmax_{1:2}$ on dengue biasing the estimations. We hypothesize that the lack of association between dengue and precipitation observed in the warm and humid region of Mexico (Chapter 2) may have been caused by the aggregation of data at the regional level, because such aggregation could have averaged out the large between-province variation in rainfall, making it less likely to show significant associations with dengue.

This thesis also revealed that the effects of El Niño on dengue in the warm and humid region of Mexico, are not only statistically significant, but also largely influenced by the 1997–1998 El Niño. However, these results should be cautiously interpreted because increases in dengue incidence over the 1997–1998 period concurred with the introduction of a new viral serotype (DEN-3). The lack of serotype-specific information from the Mexican health authority makes it impossible to disentangle the effects of these two events. Previous research (e.g. Hurtado-Díaz et al., 2007; Brunkard et al., 2008) conducted in Mexico seems to obviate the concurrence of these events and has attributed increases in dengue incidence over this period solely to El Niño. Such studies may be overestimating the real influence of El Niño on dengue.

We also showed that El Niño has different effects on dengue incidence during summer and winter (Chapter 3). This between-season variation, provides evidence to support the notion that the different effects of El Niño on the local weather during summer and winter (Magaña et al., 2004) may ultimately lead to different responses from dengue incidence, a situation that previous research has failed to acknowledge. This result emphasizes the need for more in-depth research in the topic as new data and methods become available.

Contrary to what intuition would indicate, we demonstrated that rising access to piped water is associated to significant increases in dengue incidence. Dengue is essentially an urban problem (WHO, 2009), and although it may be believed that urban residents enjoy better access to basic public services such as water, and sanitation than rural people, water distribution systems in many cities in developing countries are inadequate, typically serving the city's wealthiest sectors (Cohen, 2006). We hypothesize that the scarcity and/or lack of reliable water supply services force people to store water in domestic and peri-domestic containers (a situation that is facilitated by the access to a tap) that may potentially become breeding sites for *A. aegypti* (Jansen and Beebe, 2010; Nguyen et al., 2011). This result has serious implications for dengue conrol because access to piped water is likely to increase over the next decades (INEGI, 2010), and may significantly aggravate dengue incidence if water supply is not more reliable than it is now.

Finally, we demonstrated that the effects of socioeconomic status of people are not significant for dengue occurrence in Mexico. We therefore conclude that dengue equally affects both the rich and the poor. Although this situation seems counterintuitive, it is likely because as explained in Section 1.4, in tropical countries such as Mexico, people often seek the coolness of shaded, well ventilated areas where *A. aegypti* prefers to feed (Reiter, 2001), windows and doors are often kept open, and many buildings do not have protective measures such as window screens (Reiter, 2001). An alternative hypothesis is that, after removing time invariant characteristics (e.g. differences in the reporting between provinces) by fixed effects, our data do not contain enough variability for estimating meaningful relationships for these socioeconomic variables. Further research including data from regions with similar climatic conditions but with different human behaviour and access to protective measures is used to test this hypothesis.

5.3 Sources of uncertainty

Our results are subject various sources of uncertainty. The aggregation of data to large political boundaries areas removes a great deal of spatial variability in both the outcome variable and the predictors making it difficult to detect the complex associations between dengue, weather and socioeconomic development. This aggregation constitutes a main source of bias in provinces such as Chiapas which, albeit being a medium sized province (74,210 km^2), shows large socioeconomic variability (GINI index = 0.54 in 2005).[1] It is also comprised of a variety of geographic such as tropical rainforest, highlands, valleys, and low elevation coastal zones.[2] There is also a large climatic variability accross the regions (e.g. warm and humid with rains all year, semiwarm and humid with rains in summer, and and temperate subhumid with rains in summer).[3] We were unable to address this variability because data were only released at the province level.

As has been previously mentioned, epidemiological surveillance systems do not capture all dengue cases taking place in a region (Shepard et al., 2011) because of the unspecific dengue symptoms, low awareness about the disease, or lack of equipment (Suaya et al.,

[1] http://www.coneval.gob.mx/cmsconeval/rw/pages/medicion/index.es.do (Accessed 16 Sep 2012)
[2] http://www.zonainfantil.chiapas.gob.mx/geografia/orografia.php (Accessed 16 Sep 2012)
[3] http://www.zonainfantil.chiapas.gob.mx/geografia/clima.php (Accessed 16 Sep 2012)

2007; WHO, 2012). Consequently, reported cases represent only a fraction of the total number of cases in a given province as illustrated in Figure 5.2 (Lake et al., 2008). This situation implies that our studies were conducted on a fraction of the total cases, situation that bias our estimations due to larger standard errors (Lake et al., 2008). The proportion of unreported cases may also vary between provinces and may also be correlated with our predictors biasing our estimates (Lake et al., 2008). However, such differences in reporting would be accounted by incorporating province-specific fixed effects in our model (Johnston and DiNardo, 1997). Although there may be some geographic biases on our estimations, it is unlikely that there will be time ones, as there is no reason to believe that reporting practices will vary over time. We therefore, we assume that our time series are correct, even if they vastly underestimate the disease burden.

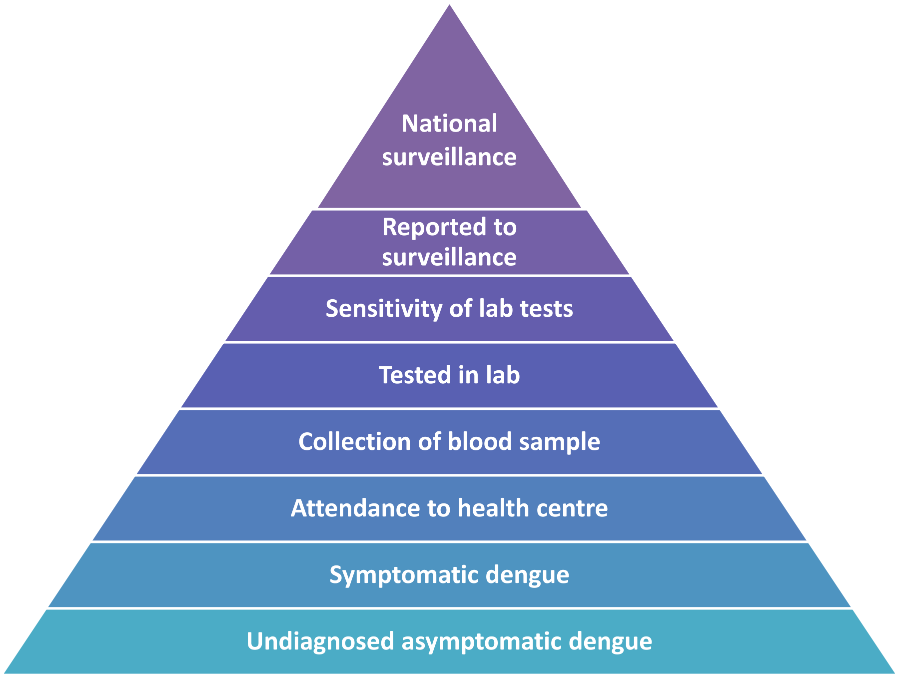

Figure 5.2: Schematic representation of the dengue surveillance pyramid. Modified from Lake et al. (2008) with consent of the authors.

Dengue data in Mexico are only made available by the health authority aggregated at political boundaries. Consequently, there is no attribute information associated to each dengue case making it impossible to differentiate between indigenous and foreign cases (Lake et al., 2008). This situation implies that our province-specific dengue records are likely to include foreign cases (e.g. people from temperate provinces going on holidays to low elevation coastal areas where dengue is more common).

The instruments and methods used to measure each the variables used in our study are diverse and subject to different sources of bias that introduce uncertainty to our estimations. For example, meteorological stations are not only subject to environmental hazards (lightings, fires, earthquakes) that may affect their precision, but also to vandalism.

Although El Niño-3.4 index is one of the most sensitive indices for determining an El Niño event (Trenberth and Stepaniak, 2001; Hanley et al., 2003), its robustness needs to be verified as more data become available. We suggest that future models should report findings with and without adjustments for weather and socioeconomic predictors, make use of different El Niño indices, and consider the use of smooth flexible functions to allow for nonlinearities in the associations between dengue and El Niño.

The possible spatial autocorrelation in the dengue data was not considered. Such consideration is important because spatially autocorrelated data cannot be considered as a series of independent observations (Kleinschmidt et al., 2000). If spatial correlation exists, the estimates obtained from the empirical modelling of dengue data may be inaccurate (Kleinschmidt et al., 2000). We expect spatial autocorrelation to be an issue only for the GAM model estimations in Chapter 4 because we analysed our panel of province data as a whole. However, in Chapter 2 we aggregated data at the regional level, and in Chapter 3 we fitted province-specific models and, therefore, spatial autocorrelation is not an issue of concern for those studies.

Finally, to project the impacts of climate change on dengue incidence we made the assumption that the values of the non-climatic predictors in the model remained constant. This situation may be unrealistic and requires a re-evaluation incorporating projections for future socioeconomic development. We also assumed that the relationships between dengue and weather remained the same. However, factors such as adaptation, micro-evolution and mosquito control measures are likely to modify such relationships resulting in outcomes different to those predicted by our model. Therefore, our estimated effects of weather and climate change on dengue give us an indication of what their effects may be if everything else remains the same. However, the models should be revised as new data become available.

5.4 Reflections on the Thesis chapters

In this thesis we used several modelling approaches to estimate empirical relations between dengue, weather and El Niño. In each chapter we have made different assumptions related to the modelling approach selected for the analysis of data. In Chapters 2 and 3, for example, we assumed that the relationships between the logarithm of dengue incidence and our climatic predictors are linear. However, as demonstrated in Chapter 4, the relationships between dengue and such climatic predictors are highly nonlinear. The presence of nonlinearities in the dengue-weather associations suggests that the relationships estimated in Chapters 2 and 3 may be biased. However, because our models focussed on small geographical areas with restricted temperature and precipitation variation (e.g. the warm humid region of Mexico) such bias may not have been a large source of concern.

In Chapter 3, we estimated significant between-province heterogeneity in the relationships between dengue, weather and El Niño. In this chapter we fitted province-specific models in which meteorological data had a small range of variation. We hypothesize that such heterogeneity may arise from the presence of nonlinear structures not detected by our models. As can be observed on Figure 5.1, analysing a small range of meteorological data poses problems for the identification of non-linear structures. In Chapter 4, not only we have relaxed the assumption of linearity by including smooth functions for the meteorological predictors, but also we fitted a single model to the data from all provinces put together. This approach allowed us to analyse a larger range of weather variations and to estimate global associations between dengue and weather.

Conversely to what we did in Chapter 2, we did not include an autocorrelation term in Chapters 3 and 4 to account for the effects of dengue incidence in the previous month. Whilst temporal autocorrelation does not bias our estimated regression coefficients, it biases the estimated standard erros of our predictors. As a consequence, our models may have overestimated the statistical significance of the predictors.

In Chapter 2 we hypothesized that the concurrent introduction of the DEN-3 serotype and the exceptionally strong 1997–1998 El Niño may be both responsible for the large incidence rates observed in 1997. As previously mentioned, the lack of serotype-specific information from the Mexican health authorities makes it impossible to disentangle the effects of these two events or to further explore this hypothesis in further chapters. Including 1,0 categorical variables into the province-specific or Poisson GAM models to account for the introduction of the new serotype into the Mexican provinces was not feasible because this information was only available at the national level.

Data were aggregated to very large political boundaries in Chapter 2. This coarse aggregation of data may have caused aggregation bias issues (Theil, 1954; Grunfeld and Griliches, 1960) because it averages out variations in all predictors, making them less likely to show associations with the outcome variable (Johansson et al., 2009a). An improvement in further chapters was the use of province-specific data.

Compared to previous chapters, Chapter 4 is likely to have smaller residual confounding issues because of the inclusion of socioeconomic predictors in the Poisson GAM. The lack of adjustment for the effects of socioeconomic development in previous chapters may have caused an overestimation of the true effects of weather on dengue incidence. However, some of the effect of socioeconomic development (e.g. variations in GDP) may have been accounted for by the variables used to control for long-term trends and inter-annual variability in the models (Chapters 2 and 3).

5.5 Suggestions for future research

This thesis has demonstrated that weather, El Niño, and climate change have significant effects on dengue incidence in Mexico. Despite the described uncertainties and limitations in our data and modelling approaches, we believe that the results of the empirical chapters provide elements that are useful for public health decision-making. The modelling approach developed here could be applied to other geographical regions to increase the understanding of the effects of weather, El Niño, and climate change on dengue and other vector-borne diseases that affect the health and economy of people. For instance, the model framework developed in Chapter 4 is being used to estimate the effects of climate and socioeconomic development on malaria incidence in Uganda and Rwanda as part of the Healthy Futures Project of the European Union. This project is funded through the seventh framework programme (FP7) project.

Interactions between variables were not explored in this thesis. It would be interesting to incorporate such interactions in the GAM model developed in Chapter 4 to have a better representation of the reality. Boosted Regression Tree (BRT) models are being explored as an alternative for analysing these data because these models select relevant variables, fit flexible differentiable functions, and automatically identify and model interactions (Elith et al., 2008). In addition, unlike GAM models, BRT models are not sensitive to over-fitting, missing data or outliers (Elith et al., 2008). The results of these models, coupled with the use of climate forecasts would be a great input for the creation of climate-informed early warning systems.

We investigated the potential impacts of climate change on future dengue incidence. However, there is still a need for understanding whether the contemporary dengue trends can be attributed to such climate change. This situation is being evaluated by an interdisciplinary research group at the Tyndall Centre for Climate Change Research, School of Environmental Sciences, University of East Anglia.

Some research efforts have been made to estimate the cost of ambulatory and hospitalized cases of dengue in several regions such as the Americas (Suaya et al., 2009). However, we could not identify studies comparing the costs of dengue preventive measures versus the cost of treating the disease. Preliminary analyses for such a study have begun at the School of Environmental Sciences of the University of East Anglia.

Appendix A

Supplementary tables

Table A.1

Reference	Country	Time frame	Spatial aggregation	Method	Variables selected	Climate change impacts estimation
Koopman et al. (1991)	Mexico	March-October 1986 (8m)	Community	Logistic regression	Median temperature (rainy season) Mean annual precipitation Rainy months per year Climate type Altitude Insecticide use Complete screens Closed doors and windows Smoke for mosquitoes Sleeping net Over 5 junk pieces Uncovered containers (50–200 l) Tyres Larvae	Not considered
Hales et al. (1996)	South Pacific islands	1970-1995 (26y)	Supra-national region	Spearman's rank correlation	Southern Oscillation Index (SOI)	Not considered
Gagnon et al. (2001)	Colombia French Guiana Indonesia Suriname	1981–1998 (18y) 1965–1993 (29y) 1969–1998 (30y) 1978–1992 (15y)	Country	Contingency tables with Fisher's exact test	El Niño years La Niña years	Not considered
Hales et al. (2002)	Global	1975–1996 (22y)	Country	Logistic regression	Minimum temperature Maximum temperature Mean temperature Precipitation Vapour pressure	Estimated under the IS92a scenario for the years 2055 and 2085
Cazelles et al. (2005)	Thailand	1983–1997 (15y)	Country (except for Bangkok)	Wavelet coherence analysis	Niño 3 Index Southern Oscillation Index Temperature (unspecific) Precipitation (unspecific)	Not considered

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Table A.1 – Continued

Reference	Country	Time frame	Spatial aggregation	Method	Variables selected	Climate change impacts estimation
Chowell and Sánchez (2006)	Mexico	2002 (1y)	Province	Multiple linear regression	Minimum temperature Maximum temperature Mean temperature Precipitation Evaporation	Not considered
Hurtado-Díaz et al. (2007)	Mexico	1995–2003 (9y)	Municipality	Adjusted auto-regressive models	Minimum temperature Maximum temperature Accumulated precipitation Sea surface temperature	Not considered
Brunkard et al. (2008)	Mexico	1995–2005 (11y)	City	Autoregressive-moving average model	Minimum temperature Maximum temperature Accumulated precipitation Sea surface temperature	Not considered
Luz et al. (2008)	Brazil	1997–2004 (8y)	City	Autoregressive integrated moving average model	Minimum temperature Maximum temperature Accumulated precipitation Number of rainy days	Not considered
Sia Su (2008)	Philippines	1996–2005 (10y)	Region	Multiple linear regression	Mean temperature Mean precipitation	Not considered
Johansson et al. (2009a)	Mexico Thailand Puerto Rico	1985–2006 (22y) 1983–1996 (14y) Jul 1986–Dec 2006 (20.5y)	Country	Morlet wavelet analysis	Minimum temperature Maximum temperature Mean temperature Accumulated precipitation Oceanic Niño Index	Not considered
Johansson et al. (2009b)	Puerto Rico	Jul 1986–Dec 2006 (20.5y)	Municipality	Hierarchical model	Minimum temperature Maximum temperature Mean temperature Accumulated precipitation Time (smooth function)	Not considered

Continued on next page . . .

Table A.1 – Continued

Reference	Country	Time frame	Spatial aggregation	Method	Variables selected	Climate change impacts estimation
					Population density Median house income Share of families below poverty line	
Sriprom et al. (2010)	Thailand	2005–2007 (3y)	District	Generalized linear model with Markov Chain Monte Carlo	Minimum temperature Accumulated precipitaiton Population (0–4 yrs) Water wells per capita Share of villages with primary school Year	Estimated under the A1B scenario for the period 2090-2099
Chowell et al. (2011)	Peru	1994–2008 (15y)	Region	Morlet wavelet analysis & cross-correlation	Mean temperature Precipitation (unspecific)	Not considered
Lowe et al. (2011)	Brazil	2001–2008 (8y)	Micro-region	Generalized linear model & Generalized linear mixed model with Markov Chain Monte Carlo	Mean air surface temperature Mean precipitation Sea surface temperature Altitude Urban population share Water supply share Waste collection Presence of one bathroom Time	Not considered
Machado-Machado (2012)	Mexico	1999-2006 (8y)	Municipality	Species distribution modelling (Maxent)	Annual mean temperature Mean diurnal range Isothermality Temperature seasonality Max temperature of warmest month Min temperature of coldest month Temperature annual range Mean temperature of wettest quarter Mean temperature of driest quarter	Not considered

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Table A.1 – Continued

Reference	**Country**	**Time frame**	**Spatial aggregation**	**Method**	**Variables selected**	**Climate change impacts estimation**
					Mean temperature of warmest quarter	
					Mean temperature of coldest quarter	
					Annual Precipitation	
					Precipitation of wettest month	
					Precipitation of driest month	
					Precipitation seasonality	
					Precipitation of wettest quarter	
					Precipitation of driest quarter	
					Pecipitation of warmest quarter	
					Pecipitation of coldest quarter	
					Population with income up to two minimum wages	
					Population without sewage and sanitary system	
					Population without piped water	
					Private housing with crowding	

Table A.1: Summary of empirical models available in the literature that estimate associations between dengue, weather and climate

Table A.2

Province	**Dengue cases**	**Tmeanlt (°C)**	**Preciplt (mm)**	**GDP (thousand MXN Pesos)**	**Urbanisation (%)**	**Latitude (°N)**	**Dominant climate**
	μ	μ	μ			μ	
Aguascalientes	11	17.4	40.6	85.6	90.2	22.2	Semi-dry temperate
Baja California	78	18.9	15.5	93.0	93.5	30.2	Very-dry temperate
Baja California Sur	4550	22.4	14.9	89.2	82.5	25.2	Dry semi-warm
Campeche	7815	26.2	112.6	121.7	72.5	19.2	Humid warm
Chiapas	13412	24.0	156.1	28.6	48.4	16.2	Humid warm
Chihuahua	199	17.4	36.5	102.9	83.8	28.7	Very-dry temperate
Coahuila	6865	20.1	33.4	98.3	94.1	27.2	Dry semi-warm
Colima	19327	25.3	72.7	70.0	89.6	19.7	Humid warm
Distrito Federal	27	16.1	66.4	185.5	100.0	19.2	Sub-humid temperate
Durango	1396	17.4	37.6	65.0	72.8	25.2	Dry temperate
Guanajuato	662	18.3	56.5	52.0	70.4	21.2	Semi-dry temperate
Guerrero	29124	25.1	84.9	39.4	55.9	17.7	Humid warm
Hidalgo	1636	16.5	60.0	41.6	55.9	20.2	Humid temperate
Jalisco	15963	20.5	65.5	69.5	86.9	20.7	Humid semi-warm
México	311	14.6	60.3	51.3	91.2	19.2	Sub-humid temperate
Michoacán	6271	19.5	63.0	39.9	67.1	19.2	Humid warm
Morelos	8514	21.5	76.3	64.9	92.9	18.7	Humid warm
Nayarit	13088	25.0	92.8	42.1	71.8	21.7	Humid warm
Nuevo León	31491	19.6	52.7	133.1	95.1	25.7	Dry warm
Oaxaca	28555	22.4	119.6	32.5	46.9	17.2	Humid warm
Puebla	5917	17.5	118.1	50.8	70.7	18.7	Humid temperate
Querétaro	190	18.2	46.1	83.3	78.6	20.7	Semi-dry temperate

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Table A.2 – Continued

Province	Dengue cases	Tmeanlt (°C)	Preciplt (mm)	GDP (thousand MXN Pesos)	Urbanisation (%)	Latitude (°N)	Dominant climate
	μ	μ	μ			μ	
Quintana Roo	10870	25.8	110.0	107.5	84.1	19.2	Humid warm
San Luis Potosí	11015	21.0	70.9	57.2	65.2	22.2	Dry temperate
Sinaloa	30867	24.9	56.4	55.1	68.1	24.7	Dry warm
Sonora	14172	22.2	33.7	85.4	85.3	29.2	Dry semi-warm
Tabasco	17417	27.0	188.8	47.6	65.0	17.7	Humid warm
Tamaulipas	41965	23.6	66.0	83.1	87.6	24.2	Humid semi-warm
Tlaxcala	522	14.3	61.1	37.3	90.2	19.2	Sub-humid temperate
Veracruz	85017	22.9	129.3	44.2	65.4	19.2	Humid warm
Yucatán	10208	26.2	86.7	59.1	85.4	20.7	Humid warm
Zacatecas	213	17.1	42.3	39.7	57.2	23.2	Semi-dry temperate

Table A.2: Descriptive statistics

Table A.3

Province	**Niño$_s$** B (95% CI)	**Niño$_w$** B (95% CI)	**Tmean$_{1:2}$** B (95% CI)	**Precipitation$_{1:2}$** B (95% CI)
Aguascalientes	0.800 (-7728.028 – 7729.628)	0.672 (-1.433 – 2.777)	**-0.628 (0.289 – 967)**	**-0.150 (0.060 – 0.220)**
Baja California	6.929 (-29771.580 – 29785.440)	26.019 (-13282.820 – 13334.850)	-0.689 (-2372.289 – 2370.911)	-2.040 (-699.800 – 695.720)
Baja California Sur	-0.009 (-0.703 – 0.685)	**1.862 (1.194 – 2.530)**	**0.502 (0.220 – 0.784)**	**0.070 (0.037 – 0.103)**
Campeche	**1.588 (1.118 – 2.058)**	**0.989 (0.540 – 1.438)**	**0.220 (0.044 – 0.396)**	0.007 (-0.009 – 0.023)
Chiapas	-0.198 (-0.612 – 0.216)	-0.205 (-0.611 – 0.201)	**0.332 (0.209 – 0.455)**	**0.010 (0.002 – 0.018)**
Chihuahua	-15.660 (-4668.765 – 4637.445)	-1.908 (-4.617 – 0.801)	**-0.389 (-0.634 – -0.144)**	0.005 (-0.052 – 0.062)
Coahuila	-0.853 (-2.221 – 0.515)	**1.548 (0.429 – 2.667)**	**-0.503 (-0.740 – -0.266)**	0.048 (-0.017 – 0.113)
Colima	**0.653 (0.255 – 1.051)**	**0.667 (0.279 – 1.055)**	-0.090 (-0.186 – 0.006)	0.008 (0.000 – 0.016)
Distrito Federal	0.826 (-0.244 – 1.896)	-0.366 (-1.485 – 0.753)	0.009 (-0.258 – 0.276)	**0.057 (0.004 – 0.110)**
Durango	0.397 (-1.332 – 2.126)	1.307 (-0.365 – 2.979)	**-0.323 (-0.631 – -0.015)**	-0.001 (-0.075 – 0.073)
Guanajuato	-0.864 (-24.490 – 22.762)	-0.299 (-19.613 – 19.611)	-0.683 (-29.495 – 28.129)	-0.108 (-2.264 – 2.048)
Guerrero	**0.812 (0.479 – 1.145)**	**0.735 (0.417 – 1.053)**	-0.111 (-0.223 – 0.001)	**-0.016 (-0.027 – -0.004)**
Hidalgo	0.977 (-1.747 – 3.701)	0.784 (-2.246 – 3.814)	-0.219 (-0.687 – 0.249)	0.005 (-0.064 – 0.074)
Jalisco	0.773 (-0.085 – 1.631)	**1.083 (0.321 – 1.845)**	**-0.640 (-0.948 – -0.332)**	**-0.076 (-0.117 – -0.035)**
México	-0.719 (-1.625 – 0.187)	0.539 (-0.259 – 1.337)	0.129 (-0.121 – 0.380)	-0.021 (-0.071 – 0.030)
Michoacán	0.113 (-0.469 – 0.695)	0.237 (-0.296 – 0.770)	**-0.261 (-0.398 – -0.124)**	**0.023 (0.001 – 0.045)**
Morelos	0.112 (-0.311 – 0.535)	0.176 (-0.261 – 0.613)	0.012 (-0.084 – 0.108)	**0.037 (0.023 – 0.051)**
Nayarit	0.251 (-0.292 – 0.794)	**1.021 (0.525 – 1.517)**	-0.012 (-0.282 – 0.258)	0.006 (-0.008 – 0.020)
Nuevo León	-0.345 (-1.390 – 0.700)	**1.477 (0.587 – 2.367)**	**-0.411 (-0.566 – -0.256)**	**0.069 (0.040 – 0.098)**
Oaxaca	-0.027 (-0.460 – 0.406)	**0.444 (0.038 – 0.850)**	-0.095 (-0.226 – 0.036)	0.005 (-0.005 – 0.015)
Puebla	**1.548 (0.966 – 2.130)**	-0.558 (-1.456 – 0.340)	-0.051 (-0.312 – 0.210)	**-0.032 (-0.061 – 0.003)**
Querétaro	**2.976 (2.147 – 3.805)**	**2.432 (1.638 – 3.226)**	**-0.400 (-0.780 – -0.020)**	0.047 (-0.008 – 0.102)
Quintana Roo	**1.287 (0.952 – 1.622)**	**0.621 (0.341 – 901)**	**0.217 (0.046 – 0.388)**	**0.011 (0.001 – 021)**
San Luis Potosí	-0.653 (-1.978 – 0.672)	0.812 (-0.419 – 2.043)	-0.153 (-0.312 – 0.006)	0.017 (-0.001 – 0.035)

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Table A.3 – Continued

Province	**Niño$_s$** B (95% CI)	**Niño$_w$** B (95% CI)	**Tmean$_{1:2}$** B (95% CI)	**Precipitation$_{1:2}$** B (95% CI)
Sinaloa	**-1.366 (-2.399 – -0.333)**	-0.038 (-0.930 – 0.854)	**0.634 (0.226 – 1.042)**	**0.081 (0.054 – 0.108)**
Sonora	-0.497 (-3.698 – 2.704)	-1.657 (-5.287 – 1.973)	**-1.640 (-2.796 – -0.483)**	-0.144 (-0.315 – 0.027)
Tabasco	**0.813 (0.215 – 1.411)**	0.349 (-0.249 – 0.947)	-0.040 (-0.218 – 0.138)	0.002 (-0.006 – 0.010)
Tamaulipas	**-1.250 (-2.334 – -0.166)**	0.077 (-0.791 – 0.945)	**-0.354 (-0.477 – -0.231)**	**0.036 (0.022 – 0.050)**
Tlaxcala	-3.494 (-30.773 – 23.785)	-1.584 (-32.803 – 29.635)	-0.436 (-1.524 – 0.652)	0.040 (-0.105 – 0.185)
Veracruz	**0.571 (0.228 – 0.914)**	**0.402 (0.034 – 0.770)**	-0.090 (-0.186 – 0.006)	0.008 (0.000 – 0.016)
Yucatán	**1.259 (0.802 – 1.716)**	**0.950 (0.513 – 1.387)**	0.063 (-0.102 – 0.228)	0.017 (-0.003 – 0.037)
Zacatecas	-35.080 (-4376.480 – 4306.320)	-14.590 (-2964.390 – 2935.210)	-7.327 (-156.469 – 141.815)	-3.301 (-45.770 – 39.168)

Table A.3: Parameter estimates of the associations between log-transformed dengue, weather and El Niño. Models were controlled for long-term trends, seasonality and autocorrelation. Values in bold font were statistically significant at the 0.05 level.

Appendix B

Supplementary figures

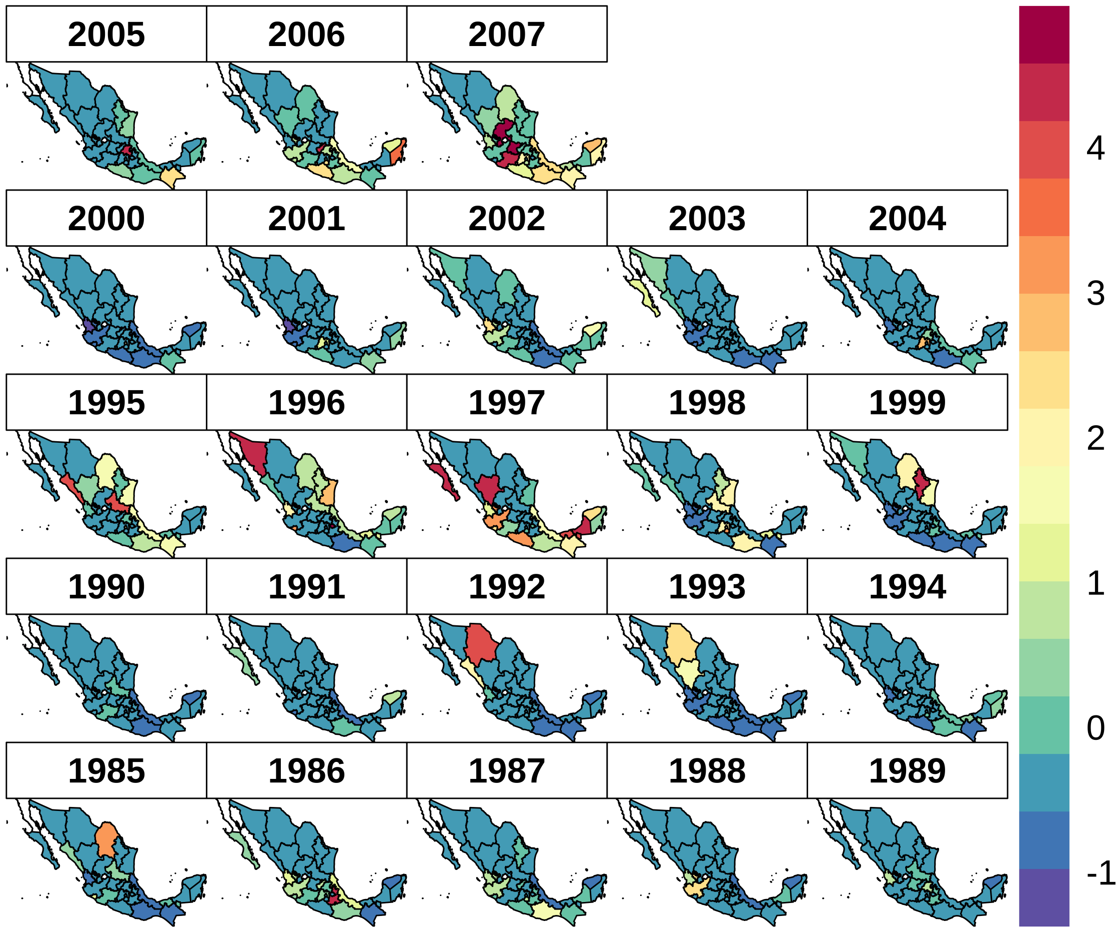

Figure B.1: Dengue incidence normalized anomalies (in standard deviations) for October (month of highest incidence) with respect to the 1985–2007 base period.

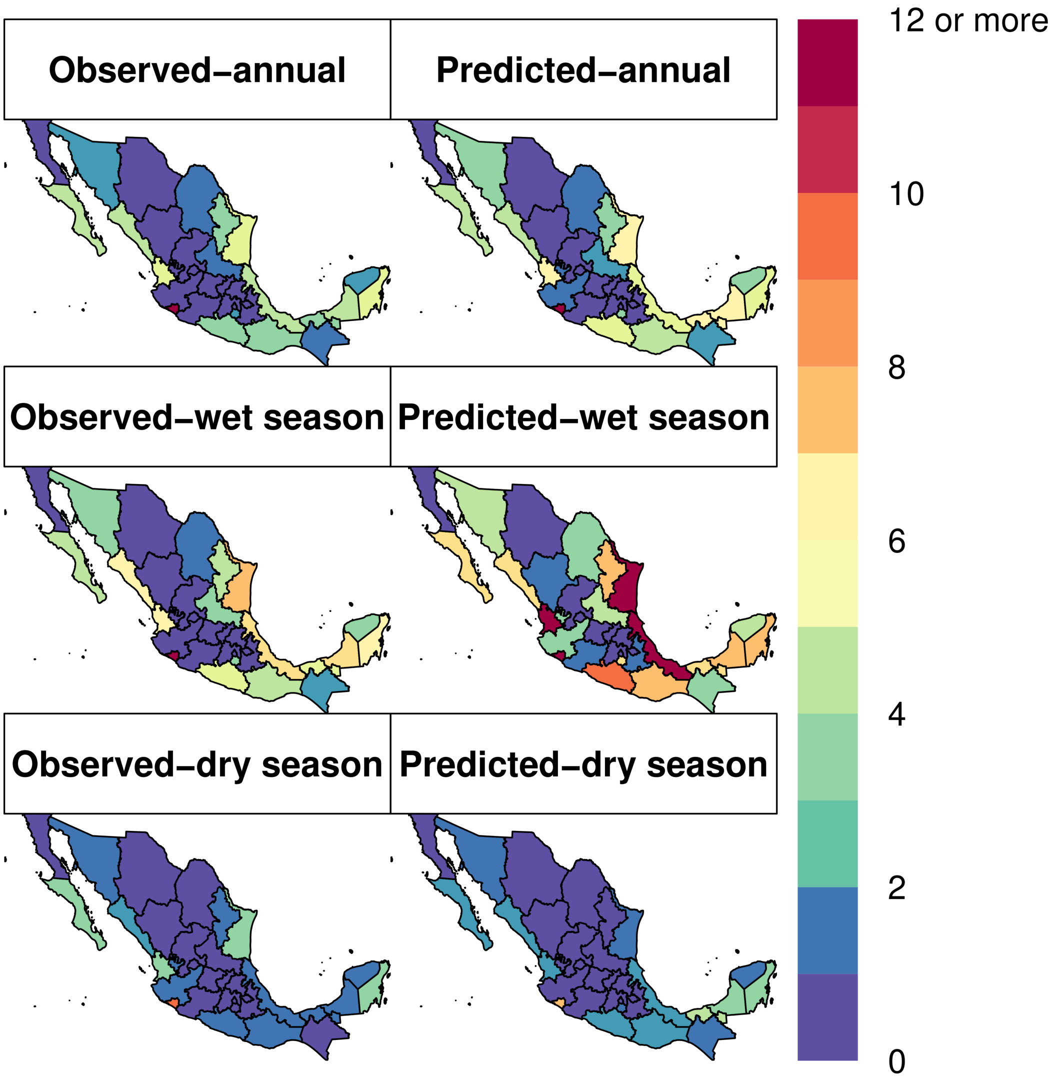

Figure B.2: Observed and GAM-estimated mean monthly dengue incidence (cases/100,000 people per month) across Mexico during the whole year, the wet season (Nov–Apr), and the dry season (May–Oct)

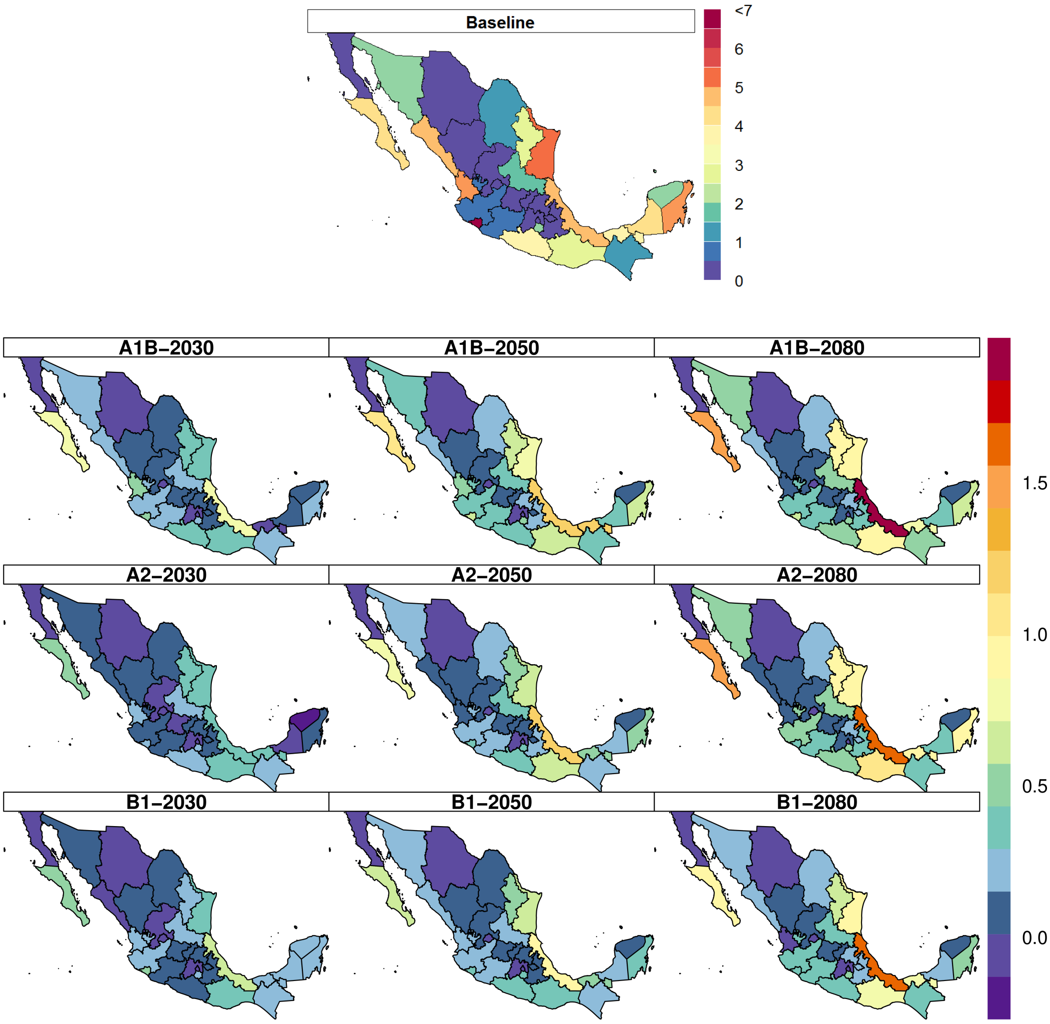

Figure B.3: Estimated 1970–1999 average annual dengue incidence (cases/100,000 people) across Mexico (Baseline) and difference in mean annual dengue incidence relative to the baseline scenario (cases/100,000 people) by 2030, 2050, and 2080 under the A1B, A2, and B1 climate change scenarios.

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