

Humboldt-Universität zu Berlin – Geographisches Institut

# **Dengue disease in Malaysia: Vulnerability mapping and environmental risk assessment**

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## **Abstract**

Global changes to our earth system have impacts on human health; specifically vector-borne diseases such as dengue are of epidemiological importance. Dengue is a global disease burden. Little is known about the spatio-temporal distribution and environmental risk association of dengue disease. The main goal of this dissertation was to improve understanding of the etiology of dengue disease in a highly endemic region by focusing on, initially, vulnerability mapping of the disease occurrences and, next, environmental risk assessment between disease clusters and both weather and land use. First, a Spatio-temporal scan statistics approach was used to assess to what extent analyses that combine sub-district and address level data contribute to new insights into spatio-temporal dengue disease patterns to better inform health interventions. Second, a Poisson generalized additive model was used to assess the weather effects on dengue disease accounting for non-linear temporal effects. Third, a Boosted regression trees approach was used to account for nonlinearities and interactions between the land use factors and dengue disease and to generate a risk map. Results suggested that more than one geographical level was needed to confirm the disease clusters. Minimum temperature, rainfall and wind speed, were associated with the dengue cases in the study area. Spatial patterns of dengue cases could be explained by land use types, including human settlements, water bodies, mixed horticulture land, open land and neglected grassland. The predicted risk map depicted dengue risk in the study area. This dissertation provided compelling approaches that are highly valuable for dengue vector control policy advice; applicability is not confined to Malaysia but is transferable to other studies in similar settings.



## **Zusammenfassung**

Der Klimawandel hat weitreichende Folgen auf die Gesundheit der Menschen. Insbesondere Übertragungskrankheiten wie Dengue bekommen global gesehen eine zunehmende Bedeutung. Über die raumzeitliche Verteilung und das Umwelt-Dengue Risiko ist bisher wenig bekannt. Das Hauptziel dieser Dissertation war es daher, die Ätiologie von Dengue in einem hoch endemischen Gebiet besser zu verstehen. Es wurden räumliche Muster des Krankheitsauftretens untersucht, die anschließend in einer Umwelt-Risiko Analyse mit örtlichen Wetterdaten und Landnutzungsinformationen in Zusammenhang gebracht wurden. Zunächst wurde ein raumzeitlicher Ansatz durchgeführt, um herauszufinden, in wie weit Analysen, die verschiedene Aggregationsebenen miteinander kombinieren, zu neuen Erkenntnissen von raumzeitlichen Mustern von Dengue beitragen können. Anschließend wurde ein auf nicht-lineare zeitliche Einflüsse kontrolliertes, Poisson-generalisiertes additives Regressionsmodell genutzt, um herauszufinden, welchen Einfluss Wetterparameter auf die Verbreitung von Dengue haben. Schließlich wurden Boosted regression trees verwendet, um auf nicht-lineare Zusammenhänge und Interaktionen zwischen einzelnen Landnutzungsfaktoren und Dengue zu kontrollieren und um eine Risikokarte zu erstellen. Die Ergebnisse deuten darauf hin, dass mehr als eine geographische Ebene notwendig ist, um Krankheitscluster zu bestätigen. Minimaltemperatur, Regenmenge, und Windgeschwindigkeit waren mit der Verbreitung von Dengue im Untersuchungsgebiet assoziiert. Räumliche Dengue-Muster konnten durch Siedlungen, Wasser, gemischte Landwirtschaftsflächen, offene Flächen und stillgelegte Grünflächen erklärt werden. Dengue-Risiko ist auf der Ergebniskarte des Studiengebietes ersichtlich. Diese Dissertation liefert sowohl wertvolle Informationen für die Gesundheitspolitik in Malaysia als auch wichtige Herangehensweisen für die Entwicklung von Dengue-Kontrollmechanismen in und über die Untersuchungsregion hinaus.





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## List of Acronyms

AIC	Akaike's Information Criteria
API	Application Programming Interface
ARIMA	Autoregressive Integrated Moving Average
BRT	Boosted Regression Trees
Bti	Bacillus thuringiensis Israelensis
CI	Confidence intervals
COMBI	Communication for Behavioral Impact
DALYs	Disability adjusted life years
DF	Dengue fever
df	Degrees of freedom
DHF/DSS	Dengue hemorrhagic fever/dengue shock syndrome
DLNM	Distributed non-linear lag model
DV	Dengue virus
EIP	Extrinsic incubation period
ELISA	Enzyme-linked immunosorbent assay
ENM	Ecological niche modeling
ENSO	El Niño-Southern Oscillation
ESRI	Environmental Systems Research Institute
GAM	Generalized additive model
GIS	Geographical information system
GLM	Generalized linear model
IgM	Immunoglobulin M
IIP	Intrinsic incubation period
IVM	Integrated Vector Management
JUPEM	Department of Survey and Mapping in Malaysia
LIDAR	Light Detection and Ranging
lr	Learning rate
MAUP	Modifiable area unit problem
MoHM	Malaysia Ministry of Health
NCDC	National Climatic Data Center
PAC	Priority Area Classification
ppmv	Ppm by volume
ROC AUC	Area Under the Receiver Operator Characteristic Curve
RR	Relative risk
RSO	Rectified Skew Orthomorphic
SaTScan	Spatial and space-time scan statistics
SRTM	Shuttle Radar Topography Mission
tc	Tree complexity
UV	Ultraviolet
VBD	Vector-borne diseases
WG	Wettable granule
WMO	World Meteorological Organization





# **Chapter I: Introduction**

## **1 Global change and dengue**

Our earth system is subject to a wide range of planetary-scale forces that originate in human activities (Steffen et al. 2006). Human activities have changed the ecosystem more rapidly and extensively in the last 50 years than at any other time in human history, largely to meet rapidly growing demands for food, fresh water, timber, fiber and fuel (Millennium Ecosystem Assessment 2005). More than half of the Earth's land surface has been domesticated for direct human use (Hooke et al. 2012). Many of the world's fisheries are fully exploited, over-exploited or depleted (Vitousek et al. 1997). The atmospheric concentration of CO<sub>2</sub>, the major greenhouse gas, has risen by almost 30%, from 280 ppm by volume (ppmv) in the late 18th century to 358 ppmv in 1994 (Schimel et al. 1996). Human use has depleted 40% of known oil reserves, which took several hundred million years to generate (Steffen et al. 2006). Over the past few hundred years, extinction rates of species have increased by more than a thousand times compared to the fossil background rates that have existed throughout the planet's history (Wilson 1993).

The consequences of these changes for human health are of growing concern. Global change influences patterns of human health, international health care, and public health activities (McMichael 2013). Skin cancer risk has increased due to the increased duration and intensity of solar ultraviolet (UV) radiation resulting from ozone depletion (Jones 1987; Brian 2004). Prevalence of asthma, respiratory allergies, and airway diseases rises with increased human exposure to pollen in altered growing seasons, molds in extreme precipitation seasons, air pollution and dust from droughts (Beggs and Bambrick 2006; McMichael et al. 2006; Sciences 2010). Ocean-related human illness, e.g. fish poisoning and chronic liver disease, are primarily caused by consumption of contaminated seafood and inhalation of aerosolized toxins due to increases in harmful algal blooms (Tyson et al. 2004; Fleming et al. 2006). Increases in epidemics of vector-borne diseases, e.g. malaria, dengue fever, Chagas disease, Schistosomiasis and Lyme disease, are strongly influenced by temperature, rainfall, wind, extreme flooding or drought, sea level rise, and land use change (Foley et al. 2005; Patz et al. 2008).

To understand the challenges global change presents for human-environment systems and human health, vulnerability mapping and risk assessment are essentially applied (Jarup 2004). They describe the potential harm induced by a diverse range of risk-hazards at local, regional, national or global scales (Eakin and Luers 2006). In general, the concept has been

used to understand the impact of natural disasters and climate change hazards, to map out poverty, and to investigate human livelihoods and heat related illnesses (Cafiero and Vakis 2006; Dickin et al. 2013). In particular for vector-borne infectious disease, studies mainly focus on HIV, dengue, malaria and tuberculosis (Bates et al. 2004; Hagenlocher et al. 2013).

Vulnerability mapping of disease is applied to identify possible disease clusters, to define and monitor epidemics, to provide baseline data on health patterns and to show changes in disease patterns over time (Jarup 2004). However, the common problem for effective mapping of the disease clusters is the modifiable areal unit problem (MAUP) (Openshaw 1983) that causes differences in the analytical results of the same dataset compiled under different spatial aggregation levels. There is still a knowledge gap concerning the regional and local disease burden caused by a lack of detailed micro data at the address level (Sheehan et al. 2000; Goovaerts and Xiao 2011). Thus, in vulnerability mapping one of the upfront challenges is the uncertainties of selecting the appropriate geographical scales (Wilbanks and Kates 1999). Previous studies have dealt with the comparison of town level, zip code, census tract level and individual coordinates on cancer incidence (Sheehan et al. 2000; Gregorio et al. 2005), but not for dengue as a research subject.

In this dissertation, the focus is on two drivers of global change, i.e. climate change and land use change, in relation to their role as possible risk factors for dengue disease. Climate change is part of the larger Anthropocene syndrome of human-induced global environmental changes (McMichael 2013). Excessive greenhouse emissions are resulting in global warming that shifts global climate and local weather patterns (Erickson et al. 2012). Climate change can affect human health directly with extreme weather events (hurricanes, floods, droughts, wildfires and heat waves) (Ebi 2008). Indirectly, human health may be damaged by the alteration of natural systems brought on by climate change (crop failures, shifting pattern of vector-, water-, and food-borne diseases) or social responses to climate change (such as displacement of populations following prolonged drought) (Ebi et al. 2013; IPCC 2014).

Dengue disease transmission is climate sensitive for several reasons. Dengue mosquitos feed more often during their lifetimes and develop faster from larval to adult at higher temperatures (Focks et al. 2000; Hales et al. 2002; Lambrechts et al. 2011). Extreme heavy rainfall may flush away the dengue mosquitos, but residual water serves as a suitable breeding habitat for the dengue mosquito (Chen et al. 2010; Naish et al. 2014). Dengue is found to be associated with weather and climate variables, but with a different association

from place to place and from time to time as shown by previous studies (Hales et al. 1999; Eisen and Moore 2013; IPCC 2014). Therefore, a risk assessment of the associations between regional and microclimates and local dengue transmission is essential for estimating the disease burden under climate change.

Global economic acceleration and agricultural intensification induce land use change (Lambin and Meyfroidt 2011). Land use change represents another recent major human-caused global environmental change (Vitousek 1994). Land use activities, including deforestation, land cultivation, and various water structures and practices (storage, distribution, and irrigation) affect the incidence of vector-borne diseases (Sutherst 2004). Traditionally, ecologists have considered disease outbreaks as disturbances rather than inherent parts of the ecosystem, while most biomedical scientists have not considered the broader ecological contexts of disease (Ostfeld et al. 2010). To improve ability to predict the occurrence, dynamics and consequences of diseases, a systematic integration of ecology with traditional disease biology is urgently needed (Ostfeld et al. 2010; Keesing and Ostfeld 2012).

Risk assessments on the association between vector-borne diseases and ecological aspects have greatly enhanced our understanding and management of disease. For example, the increase of malaria incidence is attributed to the growing activities of deforestation, logging, forest fire and agricultural farming (Ye-Ebiyo et al. 2000; Stefani et al. 2013; Hahn et al. 2014). Tick-borne encephalitis in Europe and Lyme disease in the northeastern United States increased with proximity to the forest edge and abandoned agricultural fields (Bunnell et al. 2003; Šumilo et al. 2008). For dengue disease, the viral mosquitoes prefer not only to breed in domestic habitats, but also in the natural habitat of varying land use (Guzman et al. 2010). Many studies have discovered an association between land use and dengue based on the assessment of dengue mosquito density in different land use types (Rohani et al. 2001; Díaz-Nieto et al. 2013; Paily et al. 2013). However, to date, only few studies have focused on the association of land use with dengue incidence concerning aspects of geographic proximity regarding the flying capabilities of the dengue mosquitoes and neighborhood settings of human settlements (Patz and Norris 2004; Vanwambeke et al. 2007a).

Modern technologies, e.g. remote sensing, geographical information system (GIS), and spatial analysis have been the main tools for vulnerability mapping and environmental risk assessments of vector-borne disease (Hay 2000; Graham et al. 2004). Remotely sensed data have enabled the usage of civilian satellite imagery to evaluate changes in vegetation

type, land cover, land surface temperature, soil moisture etc. for spatial epidemiological studies at global scales (Vitousek et al. 1997; Graham et al. 2004; Reisen 2010). GIS has provided computational functionality such as input, management, analysis and presentation of spatial data, which is essential for health policy planning, decision making, and ongoing surveillance efforts (Clarke et al. 1996; Pfeiffer and Hugh-Jones 2002). Spatial analysis in epidemiology identifies and describes spatial patterns of exposure and disease clusters, and explains and predicts the disease risks (Pfeiffer et al. 2008; Gruebner et al. 2011).

Each year, there are 390 million dengue infections worldwide, of which about 96 million manifest with any level of clinical or subclinical severity symptoms (Bhatt et al. 2013). Currently, there are no licensed dengue vaccines and vector control efforts have not been able to stop the rapid emergence and global spread of dengue (Tatem et al. 2006; Bhatt et al. 2013). Particularly in Malaysia, little is known about environmental exposures and the dengue burden. Continuing improvements in vulnerability mapping and associated risk assessments of the dengue epidemic are urgently required. Detailed information on dengue disease, generally and locally, is covered in Chapter II.

## **2 Dengue studies in Malaysia**

The study area, Selangor, Kuala Lumpur and Putrajaya in Malaysia, is an area of high dengue occurrence. Dengue outbreaks appear to be uncontrollable despite current active implementations of vector control strategies in the study area. With limited resources, however, decision makers need to set priority areas (World Health Organization 1995) to focus the vector control efforts. Therefore, understanding the environmental risk including weather and land use factors helps better planning of the vector control strategies. To date, little is known about the geographical aspect of disease occurrence and environmental risk association with dengue disease from a state-wise perspective, in particular for the study area.

To date, most vulnerability mapping of dengue has been done in small local hotspot areas, e.g. in Subang Jaya, Selangor (Nazri et al. 2009; Dom et al. 2013) and Hulu Langat District, Selangor (Er et al. 2010). There is still a lack of evidence for dengue risk in a larger area including Selangor, Kuala Lumpur and Putrajaya. Hassan et. al. (2012) for example, conducted vulnerability mapping in Selangor and Kuala Lumpur, but only for an aggregated district level. Moreover, to our knowledge, there is no study that compares the

disease clustering pattern on different geographical scales, e.g. at sub-district and address level.

Regarding the assessment of regional and microclimate impacts on dengue, previous studies have reported varying associations at latitudes greater than 13 degrees north and south of the equator (Gagnon et al. 2001; Garcia et al. 2011; Gomes et al. 2012), but few studies have focused on the region close to the equator, particularly in Malaysia. Of these few, most examined the association of weather and dengue in Malaysia based on dengue mosquito density instead of dengue cases. Rozilawati et. al. (2007) found a strong correlation between rainfall and mosquito egg population in Penang, Malaysia. Nevertheless, Saifur et. al. (2012) argued that heavy rain resulted in mosquito population loss. In lag term association, Rohani et. al. (2011) showed that the previous week's rainfall played a significant role in increasing the mosquito population. Some studies have been conducted on the association between weather and dengue cases, but in a local area. In Jinjang, Selangor, Li et. al. (1985) found a lag time between the onset of heavy rain and dengue outbreak of about two to three months. Fairos et. al. (2010) found that daily temperature and wind speed significantly influence dengue incidence in terms of admittances to Putrajaya Hospital two and three weeks after their occurrence. To date, there is no study on short-term weather interaction with dengue cases at the state level that includes Selangor, Kuala Lumpur and Putrajaya.

Over the years, entomologists have conducted a number of important surveys and studies of the mosquito populations in Malaysia. These studies confirmed that *Ae. aegypti* and *Ae. albopictus* were found both indoors and outdoors (Rudnick 1986; Chen et al. 2005a; Lim et al. 2010). Hence, the risk of dengue transmission is not only high in indoor human settlement. The surrounded land use should not to be neglected as it functions as the ideal outdoor breeding ground for dengue mosquitoes. Since the 1950s, antibodies of dengue virus have been found in humans who lived in villages in close proximity to rice-growing valleys, rice-growing plains, coastal swamps and rubber plantations adjacent to swamp mangrove forest (Smith 1958; Rudnick 1986). In Subang Jaya, Selangor, Nazri et. al. (2009) found that people who lived in the urban area near construction sites faced the highest risk of becoming dengue patients. Shafie et. al. (2011) found that proximity to cemeteries, swamp and forest areas, river bank areas etc. influenced the probability of dengue cases in Georgetown, Penang. However, there is still a lack of studies assessing land use type in association with dengue cases at a state-wide level.

### **3 Overall aims, research questions and methodological approaches**

The global change impact on disease transmission at local or regional level is a complex issue that is still not understood. Increasing dengue epidemics are heightening the urgent need to study the risk of dengue disease. Currently, there is a lack of vulnerability mapping and risk assessments of dengue particularly in Malaysia. Hence, the overall aim of this dissertation was to improve understanding of the etiology of dengue disease in a highly endemic region. Therefore, it aims to provide new perspectives from which to address the two questions that are commonly asked in public health research. First, where and when can we find disease clusters of high-risk? Second, what are the relationships of the disease cluster with potential environmental risk factors? To answer the questions systematically, the structure of my cumulative dissertation is as follows:

First, spatio-temporal vulnerability mapping of disease occurrences at different aggregation level are targeted in the research questions (1), (2) and (3).

*Research question (1), (2) & (3) (Dissertation Chapter III):*

- (1) What is the spatio-temporal pattern of dengue cases at the address level in Selangor and Kuala Lumpur?*
- (2) What is the spatio-temporal pattern of dengue cases at the sub-district level in Selangor and Kuala Lumpur?*
- (3) What are the insights from both spatial levels to provide better information to assist health interventions?*

Many dengue vulnerability mapping studies have focused on the spatial or spatio-temporal analysis at one geographical level only (Er et al. 2010; Vanwambeke et al. 2011; Hassan et al. 2012). Previous studies that compared spatial clustering at two levels have focused on other diseases but not on dengue (Sheehan et al. 2000; Gregorio et al. 2005). Little is known about the extent to which the spatio-temporal mapping pattern of dengue occurrences at point and polygon level differs. This is the first spatio-temporal study combining address and sub-district level on dengue.

Dengue occurrences from the surveillance data were geocoded and mapped with Kulldorff's spatial scan statistic at address level and then aggregated to the sub-district level. The patterns were then compared at both levels to determine the proper scale to represent the underlying disease transmission.

Second, the relationships of the disease cluster with potential environmental risk factors are addressed. As a vector-borne disease, human and environment are closely linked, so environmental risk assessment is examined from two aspects, weather and land use. The weather association with dengue is addressed in research question (4).

Research question (4) (Dissertation Chapter IV):

- (4) *What are the relationships between weather effects and dengue disease in Selangor, Kuala Lumpur and Putrajaya at different lag periods?*

Dengue is influenced by local weather where variations can occur due to the impact of continental climate, monsoon seasons and local altitude on mosquito species adaptation capabilities (Patz et al. 1998; Eisen and Moore 2013). Many studies of the influences of weather on dengue disease focus on locations at latitudes more than 13 degrees north and south. There is still a lack of research examining the study area close to the equator. This study addresses this gap.

The weather parameters of strong correlation with dengue cases are selected with a Poisson generalized additive model. Subsequently, from the selected weather parameters, the lag effects are investigated using a distributed non-linear lag model adjusting with confounders to describe the non-linear and delayed dependencies of the complex relationship of weather with dengue cases, as has proved efficient in examination of weather effects on other diseases (Iñiguez et al. 2010; Tian et al. 2012). Time lags of up to 90 days are examined to account for the incubation period of the dengue vector and intrinsic incubation period of the dengue virus. The percentage change with the 95% confidence intervals was calculated to quantify the nonlinear exposure-response curves.

In addition to the weather aspect, the association of land use with dengue is addressed in research questions (5) and (6).

Research question (5) & (6) (Dissertation Chapter V):

- (5) *Which land use factors are associated with dengue cases in Selangor state, Malaysia?*
- (6) *What is the spatial pattern of dengue risk based on the identified correlative relationships?*

Human-induced changes in land use are key driving forces of emerging infectious disease and modify the transmission of endemic infections (Mackenzie et al. 2004; Patz et al. 2004). Human settlements are commonly known as areas with a high incidence of dengue



cases; however other land use types in the surrounding areas may be associated with the dengue cases. Many studies have focused on the relationship between the density of the dengue mosquitoes and the neighborhood in areas of local small outbreaks (Rohani et al. 2001; Chen et al. 2005a). Yet, to our knowledge, no study has assessed land use factors associated with dengue cases in a larger area.

The geocoded dengue cases are projected into a systematic 200 m grid and each grid cell is delineated between presence (1) and absence (0) of dengue cases. The spatial neighborhood analysis is performed to obtain the proportion of coverage of each land use factor within 1 km surrounding each grid cell to consider the maximum flight range of dengue mosquitoes. The machine learning method Boosted Regression Trees (BRT) is used for examining the correlative relationship between land use factors and dengue cases. A prediction risk map is generated from the 100 iterations model run.

#### 4 Structure of this dissertation

This dissertation consists of seven chapters. This introduction is followed by a literature review chapter (Chapter II) and three core research chapters (Chapter III-V). Chapter VI synthesizes the results of the preceding three chapters and summarizes the limitations. Finally, the main conclusions and future directions are drawn.

More specifically, the core research chapters (Chapters III-V) were published in international peer reviewed research journals.

Chapter III: Cheong, Y.L., Gruebner, O., Krämer, A. & Lakes, T. (2014). **Spatio-temporal patterns of dengue disease in Malaysia: combining address and sub-district level.** *Geospatial Health*. 9(1):131-140.

Chapter IV: Cheong, Y.L., Burkart, K., Leitão, P.J. & Lakes, T. (2013). **Assessing Weather Effects on Dengue Disease in Malaysia.** *International Journal of Environmental Research and Public Health*. 10(12):6319-6334.

Chapter V: Cheong, Y.L., Leitão, P.J. & Lakes, T. (2014). **Assessment of land use factors associated with dengue cases in Malaysia using Boosted Regression Trees.** *Spatial and Spatio-temporal Epidemiology*. 10:75-84.



## **Chapter II: Dengue disease and study area**

## 1 Dengue disease

Dengue fever (DF) is a global disease burden that infects an estimated 50-100 million individuals in tropical and sub-tropical countries every year (Halstead 2007). The common severe syndrome - Dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS) may lead to fatal hemorrhagic events (Halstead 2007). Dengue is a neglected tropical disease that has become the fastest growing mosquito-borne disease, with almost half the world's population now at risk. The epidemic of dengue stretches from America, Africa and Asia to Australia as shown in Figure II-1. The geographical limits correspond approximately to a winter isotherm of 10 °C, mostly between latitudes 35 °N and 35 °S (World Health Organization 2009). The Disease Control Priorities Project estimated the global burden of dengue disease cost as 528 000 disability adjusted life years (DALYs), a measure of the number of years lost due to ill-health, disability or early death, for the year 2001 (Cattand et al. 2006). The overall cost of a dengue case (both ambulatory and hospitalized patients) in several countries in Asia and the Americas is US\$828 (World Health Organization 2009). There has been a 30-fold increase in the number of dengue cases over the past 50 years (World Health Organization 2009). During comparable 5-year periods, Southeast Asia and the Americas experienced DHF cases at a proportion of 17:1 (Halstead 2006). In Southeast Asia, children are the principal vulnerable group (Halstead 2006).



Figure II-1: Map of areas at risk of dengue in the year 2011, source: World Health Organization Map Production: Public Health Information and Geographic Information Systems (GIS) World Health Organization 2012.

The first record suggesting potential cases of dengue fever is found in a Chinese medical encyclopedia from the Chin Dynasty for the years A.D. 265–420 (Nobuchi 1979). The possibly earliest reported dengue epidemics occurred on three continents (Asia, Africa and North America) in 1779 and 1780 (Rush 1951). In early years between 1948 and 1970, dengue was successfully controlled with the eradication program in the Americas and limited to the southeastern United States, islands in the Caribbean, and the northeastern corner of South America (Gubler 2004). Nevertheless, dengue has been reemerging and spreading to new geographic locations, with epidemics occurring in cycles of three to five years (Gubler 2004).

Known as a vector-borne disease, dengue virus (DENV) is mainly transmitted by the mosquito species *Aedes (Stegomyia) aegypti (Linnaeus)* (Lemon et al. 2008). DENV can also be transmitted by *Aedes (Stegomyia) albopictus*, also called the ‘Tiger mosquito’ because of its striped appearance (Shroyer 1986), *Aedes polynesiensis* and several species of the *Aedes scutellaris* complex. *Ae. aegypti* is a highly domesticated urban and rural mosquito (World Health Organization 2009). As a semi-domestic species, *Ae. albopictus* breeds in natural and man-made containers in both rural and suburban areas (Aiken and Leigh 1978). *Ae. polynesiensis* is only found in the islands of the South Pacific (Schmaedick et al. 2008). *Ae. scutellaris* is commonly found in Papua New Guinea (Penn 1947), the Philippine Islands, the South Pacific (Foote and Cook 1959), the Torres Strait Islands and on the Cape York Peninsular in Australia (Lee et al. 1987).

All male and female mosquitoes feed on plant nectars, fruit juices, and other plant sugars to acquire their main energy source. However, only female mosquitoes bite humans as they feed on human blood and other primates in the absence of humans in order to produce eggs (Harrington et al. 2001; Scott and Morrison 2010b). A female dengue mosquito takes several blood meals to lay a batch of eggs and it can lay multiple batches of eggs during its lifetime (Harrington et al. 2001). The dengue virus is transmitted by the infected female mosquito through its salivary glands through repeated feeding on the human blood of multiple persons. The repeated blood feeding provides a fitness advantage for female mosquitoes allowing them to transmit the dengue virus more efficiently (Scott and Morrison 2010b). This explains the reason for the high dengue reproduction rate even with a low number of dengue mosquitoes, as occurred in Singapore (Kuno 1995; Edman 2003).

Dengue is commonly caused by one of four dengue virus serotypes (DEN-1, DEN-2, DEN-3 and DEN-4) (Gubler and Clark 1995). Lifelong immunity is provided against re-infection by the same serotype but not against infection by the remaining three (Cattand et

al. 2006). Therefore, a person may be infected with the dengue virus up to four times during their lifetime (Ooi et al. 2006). Sequential infection with different DENV serotypes may cause severe DHF/DSS (Halstead 2006). The symptoms of normal dengue fever are frontal headache, retro-orbital pain, body aches, nausea and vomiting, joint pains, weakness, and rash (Gubler 1998a). Furthermore, DHF/DSF may be life threatening with the symptoms of high fever, spontaneous bleeding (through the skin, from the nose or gums, gastrointestinal bleeding, vomiting blood), circulatory failure with a rapid, weak pulse and narrowing of the pulse pressure with cold skin and shock with undetectable blood pressure or pulse (World Health Organization 2005).

The main clinical management of dengue fever is fluid therapy. Patients in early phases of dengue fever without DHF/DSF warning signs can be treated as out-patients with adequate bed-rest, fluid intake, paracetamol and daily laboratory tests of full blood count and haematocrit (World Health Organization 2009). For severe dengue patients, intravenous fluid therapy and fluid resuscitation with isotonic crystalloid solutions are given and are closely monitored in the hospital (World Health Organization 2009).

Dengue transmission had been eradicated (Gratz and Knudsen 1996) but re-emerged because of complex multiple factors including biological, socioeconomic, demographic, and environmental aspects (Wilson 2010). The trend of reported dengue cases differs between countries (Figure II-2). Cambodia, Lao People's Democratic Republic, Singapore and the Philippines exhibited peak dengue cases in the middle of the year 2011, whereas Malaysia and Australia reported higher dengue cases in the beginning and end of the year 2011. Many factors are associated with the reemergence of dengue disease, ranging from human herd immunity, behavior, density and mobility of human hosts, characteristics of mosquito-human interaction, virus introduction into the system, virulence of virus strains, and environmental and ecological connections (Gubler 1998a; Patz et al. 2004; Halstead 2008).

Temperature influences vector development rates, viral replication within the mosquito and survival (Watts et al. 1987). Durations of vector development to adult and viral replication decrease with increasing temperature (Scott and Morrison 2010b; Chan and Johansson 2012). Subsequently, more adult mosquitoes survive the shorter viral replication period and become infectious to humans (Watts et al. 1987). Rainfall influences the abundance of dengue mosquitoes in the winged (adult) and aquatic populations (eggs, larvae, pupae) (Wardekker et al. 2012). The flight activity and host-seeking behavior of the adult dengue mosquitoes become more active with the increased near-surface humidity associated with

rainfall (Wardekker et al. 2012). Increasing rainfall provides essential habitats for the immature development of the aquatic populations (Halstead 2008). Understanding the effect of climate-induced weather changes on mortality and occurrences of disease assists in suggesting relevant strategies that are urgently required (Yang et al. 2009; Burkart et al. 2011; Gabriel and Endlicher 2011).

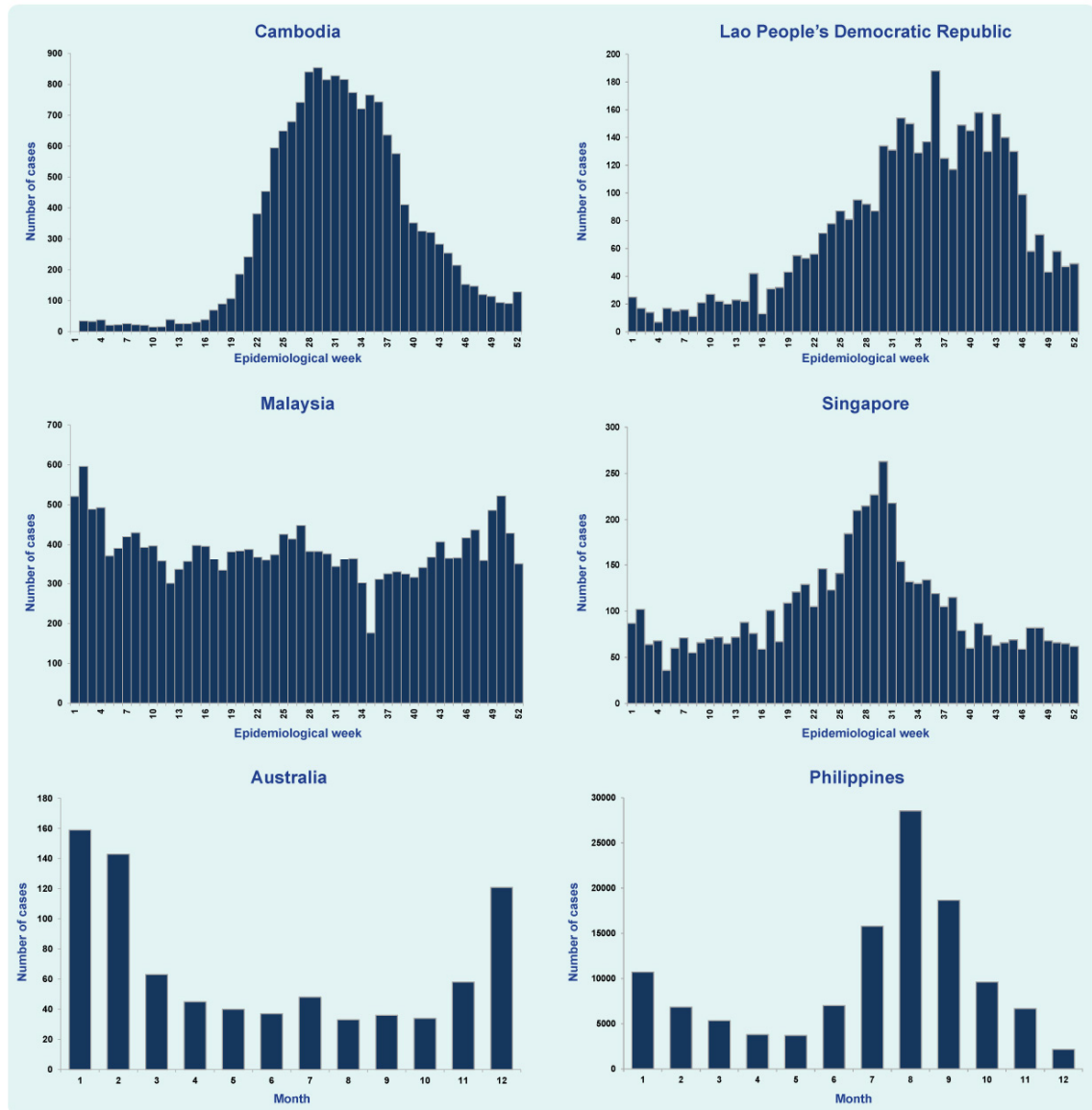


Figure II-2: Reported number of dengue cases by calendar week (Cambodia, the Lao People's Democratic Republic, Malaysia and Singapore) or month (Australia and the Philippines), 2011. Source: World Health Organization Western Pacific Regional Office based on data provided by the Member States.

Beside weather, land use change influences the suitability of habitats for *Aedes* mosquitoes (Patz et al. 2004; Vanwambeke et al. 2007a). *Aedes* mosquitoes are day biters that feed on humans in a wide range of indoor and outdoor environments in urban and rural areas (Gubler and Clark 1995; Chadee and Martinez 2000; Thavara et al. 2001). In addition to

domestic containers, vector ecology studies have identified outdoor breeding areas of *Aedes* mosquitoes in orchards, agricultural plantations, mining areas, forest fringes, and water bodies near human settlements (Rohani et al. 2001; Chareonviriyaphap et al. 2004; Vanwambeke et al. 2007b). Better understanding of the influence of local land use on the occurrences of dengue cases is important for vector control intervention.

Investigations into the interactions of the environmental factors with dengue disease are greatly complicated by inclusion of varying spatial and temporal issues. These factors change from place to place for varying study periods. Different weather lagged effect times in relation to high numbers of dengue cases were reported in Brazil (Gomes et al. 2012), Taiwan (Chen et al. 2012) and Australia (Bi et al. 2001). Varyingly suitable dengue mosquitoes habitats were found in Puerto Rico (Smith et al. 2009), China (Li et al. 2013) and Indonesia (Ishak et al. 1997). To better control the dengue disease locally, scrutiny at the local level in a specific high disease outbreak time frame is very much needed.

## **2 Dengue disease in Malaysia**

Dengue disease is highly endemic in several tropical countries especially in Southeast Asia and South Asia (Wiwanitkit 2014). In 2010 Malaysia reported 165.28 incidences per 100,000 populations, the second highest in the Western Pacific Region after the Lao People's Democratic Republic, and 134 deaths, the second highest in the Western Pacific Region after the Philippines (Table II-1). In Malaysia, dengue disease is a significant public health problem and the reported dengue cases have been increasing in recent years (Ministry of Health Malaysia 2012). The total reported number of dengue cases for the year 2008 to 2010 is 136,992, the highest over the century since the first reported cases (Department of Statistics Malaysia 2011a). The number of deaths for dengue and DHF is the highest compared to malaria, typhoid and cholera in Malaysia for the years 2006 to 2010 (Table II-2). The dengue prevalence in Malaysia is high: a national-cohort study on 1000 adults aged 35-74 reported 91.6% as dengue seropositive, i.e. showing a positive blood response in the dengue laboratory test (Muhammad Azami et al. 2011). The estimated immediate cost of dengue in Malaysia for the period 2001-2010 was US\$128 million per annum, more than in neighboring countries such as Cambodia, Myanmar, Singapore and Vietnam (Shepard et al. 2013).



Table II-1: Cases of dengue, including imported cases, and dengue-attributed deaths in the Western Pacific Region for 2010.

Countries/territories	Cases	Incidence per 100,000	No. of deaths	Case fatality rate (%)	Population (in thousands)
<i>Asia subregion</i>					
Brunei Darussalam	298	73.17	2	0.67	407
Cambodia	12,500	83.10	38	0.30	15,042
China	202	0.01	0	0	1,353,826
Hong Kong (China)	83	1.18	0	0	7,057
Japan	243	0.19	0	0	127,029
Republic of Korea	23	0.05	0	0	48,526
Lao People's Democratic Republic	22,929	356.36	46	0.20	6,434
Macao (China)	6	1.09	0	0	550
Malaysia	46,171	165.28	134	0.29	27,935
Mongolia	0	0	0	0	2,703
Philippines	135,355	144.55	793	0.59	93,639
Singapore	5,364	110.48	4	0.07	4,855
Viet Nam	128,831	144.69	55	0.04	89,038
<b>Total for subregion</b>	<b>352,005</b>	<b>19.81</b>	<b>1,071</b>	<b>0.31</b>	<b>1,777,041</b>

Note: Data of Pacific subregion is not shown. Source: World Health Organization Western Pacific Regional Office based on data provided by the Member States.

It is believed that the dengue mosquito was introduced from the forest of tropical Africa, transported to Malaysia through the merchant ships (Malaysia Institute for Medical Research 2010). The first reported dengue cases in Malaysia go back to December 1901 in Penang state, following reports of dengue in Hong Kong, Bangkok and Singapore in the same year (Skae 1902). Subsequently, a few outbreaks were reported in the urban areas of Penang and Kuala Lumpur (Smith 1956, 1957; Rudnick et al. 1965). Sixty years later, a DHF case was first laboratory-confirmed in Georgetown, a city on Penang island (Rudnick et al. 1965). In the 1960s, antibodies of dengue virus were also found in monkey in the forest in Malaysia (Rudnick 1986). Major national dengue outbreaks were reported in 1974, 1978, 1982 and 1990, exhibiting a 4-year cycle (Lam 1993). However, a significant increase in dengue cases occurred in full periods of 8 years, in 1974, 1982, 1987, 1991 and 1998 (Abubakar and Shafee 2002).

Table II-2: Number of deaths by type of diseases, Malaysia, 2006-2010.

Year	Dengue and dengue haemorrhagic fever	Malaria	Typhoid	Cholera
2006	67	21	5	2
2007	82	18	6	2
2008	112	30	3	2
2009	88	26	1	2
2010	134	33	-	6

Source: Department of Statistics Malaysia (2011a)

The co-circulating of the four dengue virus serotypes complicated the dengue epidemic in Malaysia. DEN-1 was the first serotype in Malaysia to be isolated, from an outbreak in a school hostel in March 1954 (Smith 1956). Subsequently, the presence of all four dengue virus serotypes was found and they were seen to co-circulate in Malaysia, with a predominance of DEN-4 (53.1%) isolated during the period 1967-1969 (Abubakar and Shafee 2002). DEN-2 had replaced DEN-4 by 1970, and all serotypes were present without one dominant type from 1971 to 1985 (Abubakar and Shafee 2002). However, DEN-3 then became the dominant serotype in 1986, but was replaced by DEN-1 and DEN-2 in subsequent years (Abubakar and Shafee 2002). From 1991 to 2007, all four serotypes were isolated; a sinusoidal pattern denotes the predominant circulating dengue serotype (Ministry of Health Malaysia 2010) as shown in Figure II-3. In the early 1990s, the predominant serotype was DEN-3 with a peak in 1993; but in recent years the DEN-2 serotype has been increasing.

The possible reasons for the increasing dengue cases were rapid urbanization, abandoned construction sites, improper waste management, acute shortage of water resulting in increases of water storage containers and the development of mosquito resistance to insecticide (Malaysia Institute for Medical Research 2010). Suitable breeding containers for dengue mosquitoes were often found in parks, empty land, industrial buildings, construction sites, and blocked cement drains and septic tanks (Chang et al. 2011). *Ae. albopictus* was found more in open spaces with shaded vegetation, for instance in car tires and garbage dumps (Malaysia Institute for Medical Research 2010).

As vaccine is currently in the developmental stage, dengue can at present only be controlled using vector-control methods (World Health Organization 1995). The current vector control strategies in Malaysia are adulticiding, larviciding, personal protection,

environmental management, community participation, legislation and integrated control. Adulticiding fogging of insecticide malathion and pyrethroids are conducted in an area of 200-meter radius from the suspected dengue cases, with repeat fogging conducted 7-10 days after the first fogging (Lee et al. 2008). Larviciding such as the application of the sand granule formulation of Temephos (Nazni et al. 2009) is encouraged in household water-storage containers. However, *Ae. albopictus* has showed low mortality against a diagnostic dosage of Temephos (Chen et al. 2005b). Alternative larviciding using a wettable granule (WG) formulation of *Bacillus thuringiensis Israelensis* (Bti) (Lee et al. 2008; Tan et al. 2012) is hence applied and has shown effective results, eliminating the potential breeding sites with dengue larvae (Lee et al. 2008). Personal protection includes the use of mosquito coils, insecticide mats, aerosols, and bed-nets especially during the day as *Aedes* mosquitoes feed on blood in the daytime.

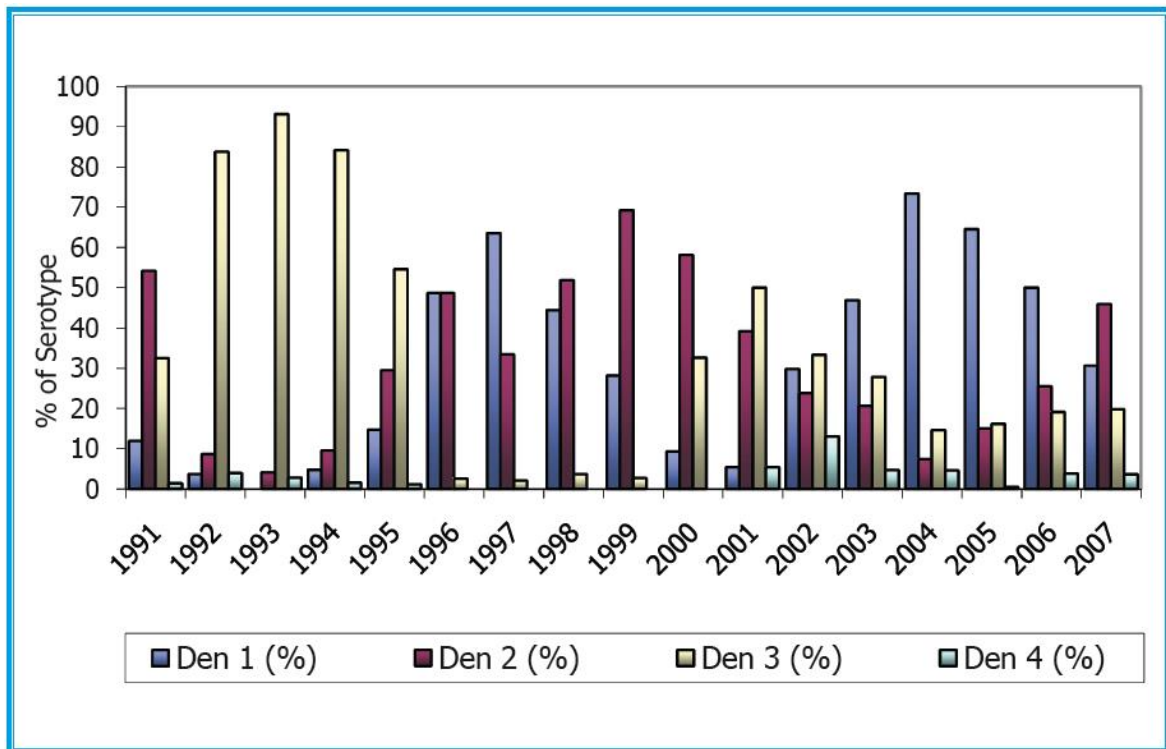


Figure II-3: Percentage of dengue serotype in Malaysia, 1991-2007. Source: Clinical Practice Guidelines on Management of Dengue Infection in Adults (Revised 2nd Edition) 2010.

Environmental management with the aim of source reduction, which involves community participation, is also applied in Malaysia. Malaysia is one of the countries conducting the communication for behavioral impact (COMBI) program in which the local community together with the authorities reduce or eliminate breeding sources of dengue mosquitoes

using the “search and destroy” method (Elder and Lloyd 2006; Malaysia Institute for Medical Research 2010; Ministry of Health Malaysia 2011a). First implemented in the Johor Bahru District, Johor State, COMBI showed a positive behavioral outcome and was further adopted as a national approach to encourage community participation and changes of human behavior at the household level (Elder and Lloyd 2006; Ministry of Health Malaysia 2011a). Beside community participation, practical control measures such as aedes-proofing of buildings and infrastructure are also implemented (Ministry of Natural Resources and Environment Malaysia 2011).

Prevention and control of vector-borne diseases are covered by legislation in Malaysia (Seng 2001). As part of the enforcement of the Destruction of Disease-Bearing Insects Act 1975, if *Aedes* mosquito larvae found in an *Aedes* survey in and around any premises are confirmed to be disease-bearing insects, the owner/occupier is issued a warning notice or a compound is offered. If the owner/occupier fails to abide by the instructions within a given time period, court prosecutions follow (Seng 2001). The Prevention and Control of Infectious Diseases Act 1988 mandated that all suspected dengue cases be notified by telephone to the nearest health office within 24 hours of diagnosis by health practitioners.

### **3 Study area**

Current vector control fails to address the dengue outbreak in Malaysia, in particular our study area including Selangor, Kuala Lumpur and Putrajaya (Figure II-4), that accounted for 50.9% (60,702 cases) of all nationally reported dengue cases from year 2008 to 2010 (Department of Statistics Malaysia 2011a). In 2012, the incidence rates were 175 per 100,000 population in Selangor and 104 per 100,000 population in Kuala Lumpur and Putrajaya (Ministry of Health Malaysia 2012), which are higher than the national target of less than 50 cases per 100,000 persons (Ministry of Health Malaysia 2010).

The climate of the study area is characterized by average daily temperature ranges from 21 to 32°C and mean annual temperatures of 26°C with a daily humidity level exceeding 80% (Olaniyi et al. 2012). The mean annual rainfall is about 2500 mm (Olaniyi et al. 2012). Figure II-5 exhibited the laboratory-confirmed dengue cases and weather (maximum temperature, mean temperature, minimum temperature, accumulated rainfall, humidity and wind speed) for the year 2008 to 2010 in the study area. The weather data was obtained from the Subang meteorological station in Selangor (World Meteorological Organization (WMO) no. 486470; North Latitude 3°07'01"; East Longitude 101°32'60"; 220 masl).

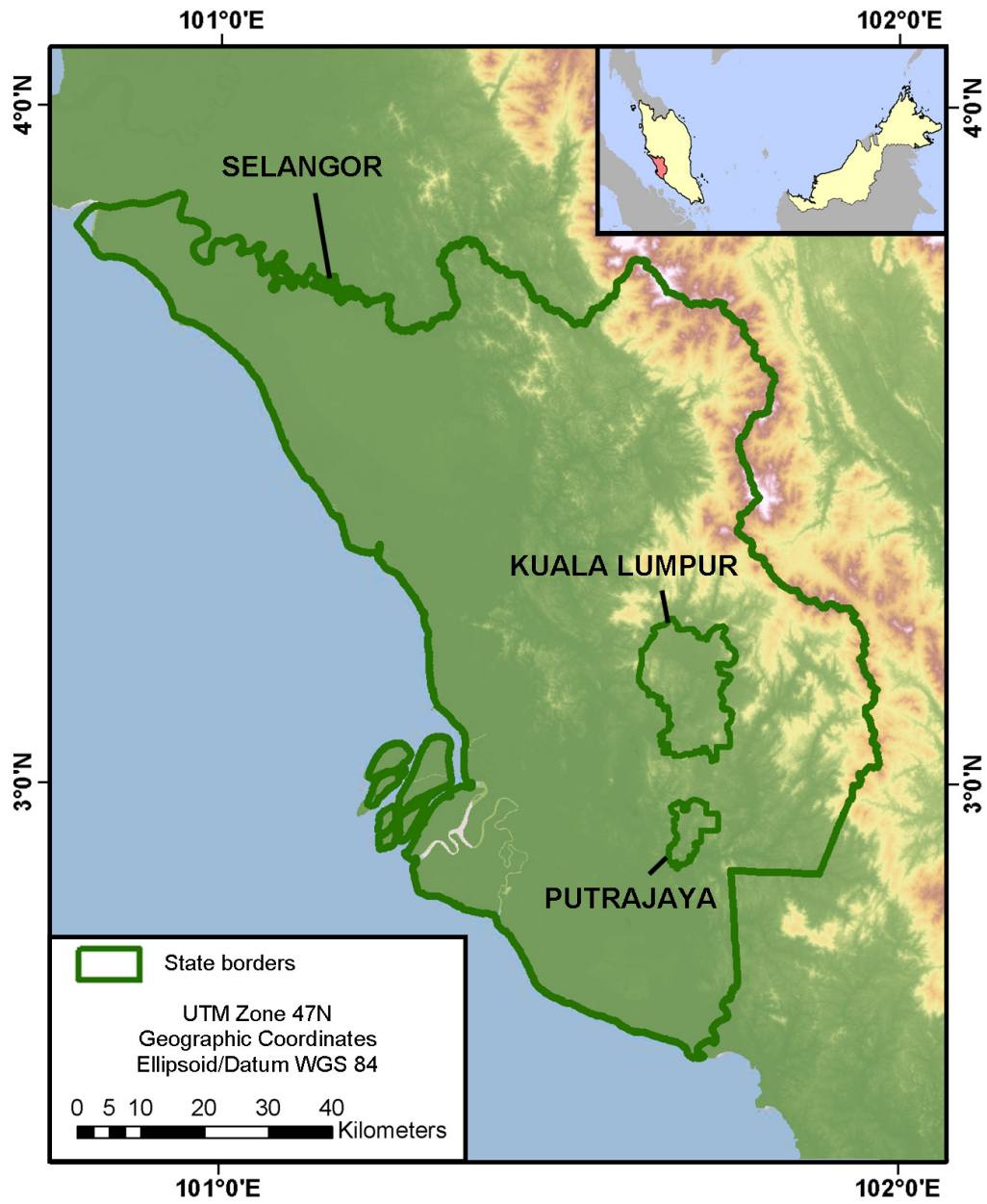


Figure II-4: Location of the Selangor, Kuala Lumpur and Putrajaya in Malaysia (altitudes range from approximately -54 to 2286m, source: Shuttle Radar Topography Mission (SRTM) Digital Elevation Model, ESRI Data and Maps Kit).

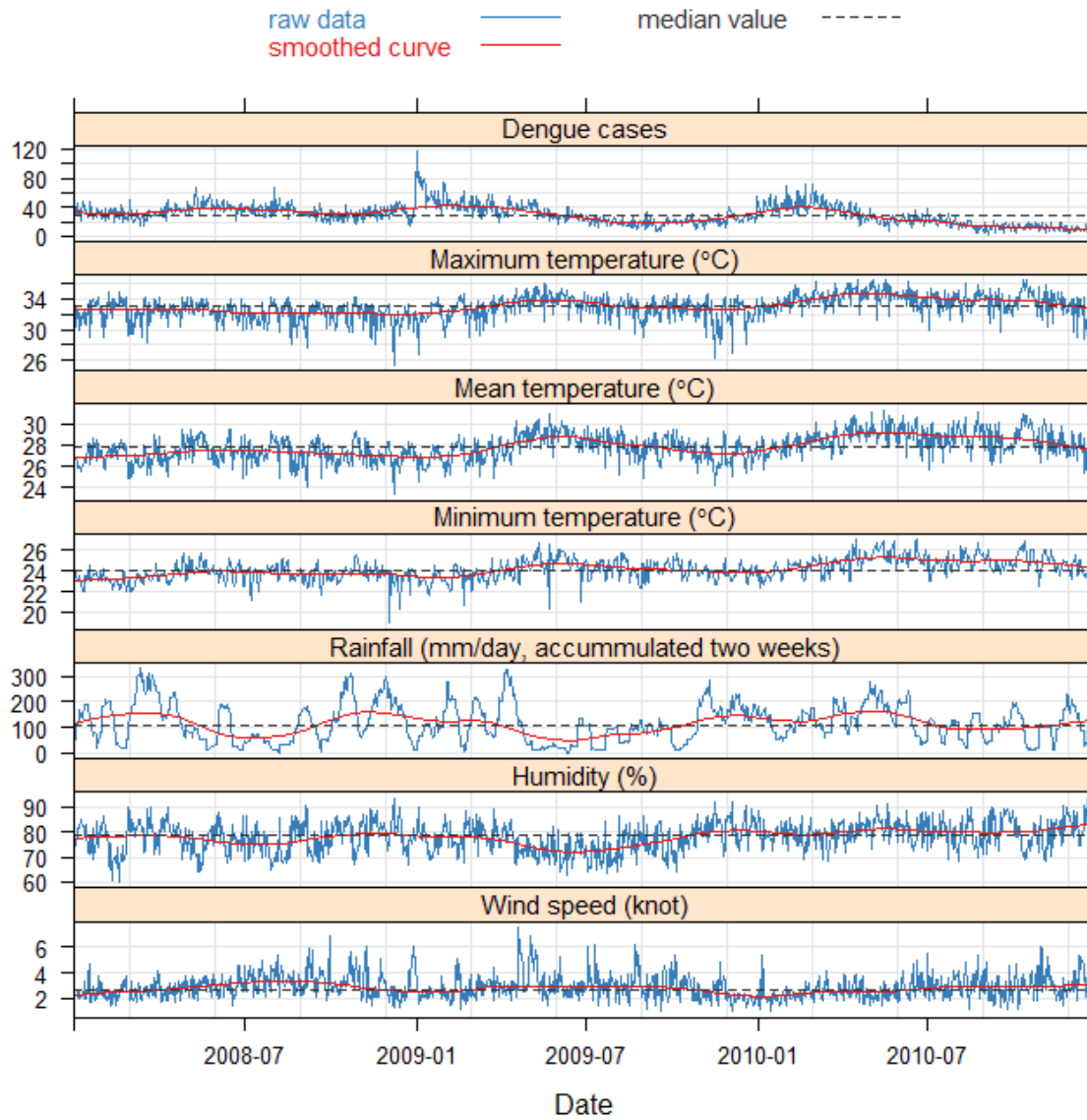


Figure II-5: Laboratory confirmed dengue cases and Selangor observatory weather for the year 2008-2010

**Chapter III:  
Spatio-temporal patterns of dengue disease in  
Malaysia: combining address and sub-district  
level**

*Geospatial Health 9/1 (2014) 131-140*

Yoon Ling Cheong, Oliver Gruebner,  
Alexander Krämer and Tobia Lakes

### **Abstract**

Spatio-temporal patterns of dengue risk in Malaysia were studied both at the address and the sub-district level in the province of Selangor and the Federal Territory of Kuala Lumpur. We geocoded laboratory-confirmed dengue cases from the years 2008 to 2010 at the address level and further aggregated the cases in proportion to the population at risk at the sub-district level. Kulldorff's spatial scan statistic was applied for the investigation that identified changing spatial patterns of dengue cases at both levels. At the address level, spatio-temporal clusters of dengue cases were concentrated at the central and south-eastern part of the study area in the early part of the years studied. Analyses at the sub-district level revealed a consistent spatial clustering of a high number of cases in proportion to the population at risk further confirming this pattern. Linking both levels assisted identification of differences and confirmed the presence of areas at high risk for dengue infection. Our results suggest that the observed dengue cases had both a spatial and a temporal epidemiological component, which needs to be acknowledged and addressed to develop efficient control measures and effective vector control. Our findings highlight the importance of detailed geographic analysis of disease cases in heterogeneous environments with a focus on clustered populations at different spatial and temporal scales. We conclude that bringing together information on the spatio-temporal distribution of dengue cases with a deeper insight of linkages between dengue risk, climate factors and land use constitutes an important step towards the development of an effective risk management strategy.



## 1 Introduction

Dengue fever (DF) and dengue haemorrhagic fever (DHF) are arguably the most important infectious diseases in tropical areas (Gubler 2006). Mainly distributed between latitudes 35°N and 35°S (World Health Organization 2009), almost two fifths of the world's population are at risk with about 50 million new cases emerging each year (Gubler 1998b; World Health Organization 2012a). Dengue outbreaks commonly occur in many parts of Africa, Australia, Latin America, Southeast Asia and throughout the Pacific Islands (Rogers et al. 2006). Vector control has proven difficult due to the biology of the mosquito and its ability to breed in domestic habitats (Eisen and Lozano-Fuentes 2009). Moreover, little is known about the true determinants of high dengue rates and research gaps include the detailed influence of complex climatic issues that vary over space and time. Main determinants include rainfall and temperature (Chadee et al. 2007), presence of suitable larval development sites (Vanwambeke et al. 2011), behaviour and mobility of humans (Gubler 1998a) and herd immunity (Halstead 2008). The distribution patterns of dengue cases reflect the multifaceted interaction of all these risk factors. The risk of this disease is expected to significantly increase in the near future, and the absence of effective treatment makes the development of adequate vector control strategies more important than ever (Vanwambeke et al. 2007a; Barrera et al. 2011).

In Malaysia, dengue disease has been endemic since the first case was found in Penang Island in 1901 (Skae 1902). Since then, peaks have been reported many times; more recently in 1974, 1978, 1982 and 1990, while the total number of infections has increased as well (Lam 1993). Out of the four serotypes, DEN-3 was predominant from 1992 to 1995 with DEN-1, DEN-2 and DEN-3 alternating in recent years (World Health Organization 2008a; Arima and Matsui 2011; Mulligan et al. 2012). In 2008, a Malaysian study that included 1,000 individuals aged between 35-74 years found a seropositive rate for dengue of 91.6% (Muhammad Azami et al. 2011). The incidence rate per 100,000 was the second highest in the Western Pacific region in 2010 (Arima and Matsui, 2011). For the year 2010, the Malaysia Ministry of Health (MoHM) reported a DF incidence rate of 148.7 per 100,000 population (Ministry of Health Malaysia 2010), which far exceeds the national target of not more than 50 cases per 100,000 population (Ministry of Health Malaysia 2010). To the best of our knowledge, the great majority of dengue studies in Malaysia have focused solely on spatial clustering on a yearly basis rather than spatial and temporal

distribution of the disease on a daily basis. The latest national dengue studies were purely spatial studies in Hulu Langat, a sub-district of Selangor in 2003 (Er et al. 2010), in Kuala Lumpur in 2009 (Aziz et al. 2012) and in both Selangor and Kuala Lumpur in 2010 (Hassan et al. 2012).

Effective vector control relies critically on the determination of the proper scale to address dengue virus transmission (Getis et al. 2003; Suaya et al. 2009). Different geographical scales have been suggested, ranging from finer scales based on the vector's flight range (Getis et al. 2003; Yoon et al. 2012) to larger scales due to the relative importance the closeness of neighbouring communities and human movement (Shepard et al. 2012). Fine-scale studies, i.e. at the address level, allow for detailed spatio-temporal analysis in linking the incidence to the local environment as the complex process of viral transmission is spatially continuous (Morrison et al. 1998; Siqueira-Junior et al. 2008). However, they do not account for the background population at risk of contracting a disease and therefore standard risk ratios cannot be calculated. In contrast, aggregation-level studies include the baseline risk population (Jeffery et al. 2009) but encounter the 'modifiable area unit problem' (MAUP) (Openshaw 1983) that causes differences in the analytical results of the same dataset compiled under different, spatial aggregation levels. Both levels provide significant advantages and disadvantages. Furthermore, previous studies that explicitly deal with comparisons of spatial clustering at two scales have been conducted for various diseases, e.g. cancer at the level of town, zip code and census tract (Sheehan et al. 2000) or the level of exact coordinates, census block group, census tract and town (Gregorio et al. 2005). However, these studies did not combine results of the different levels, e.g., the address and aggregation level, where the latter can vary between administrative limitations such as province, district, subdistrict, etc.

We selected the state of Selangor and the Federal Territory of Kuala Lumpur to study patterns of dengue since a large number of dengue cases (69,702 cases) occurred there between 2008 and 2010; indeed accounting for 50.9% of all reported cases in Malaysia according to the Department of Statistics in Malaysia (Department of Statistics Malaysia 2011). In addition, the area is geographically heterogeneous and includes the strongly urbanized Kuala Lumpur with 100% urban population (Department of Statistics Malaysia 2011) with surrounding suburban sub-districts and rural areas with great variations in population density. We aimed to investigate if a combination of two different geographical levels would provide new insights on dengue disease patterns. To our knowledge, this is the first spatio-temporal study combining address and sub-district level with respect to

dengue. We mapped the spatio-temporal distribution of dengue risk in Selangor and Kuala Lumpur by quantifying high-risk clusters of serologically confirmed dengue cases. Specifically, our research goals were (1) to assess the spatio-temporal patterns of dengue cases at the address level, (2) to assess the spatio-temporal patterns of dengue cases at the sub-district level, and (3) to combine insights from both spatial levels to provide better information to assist health interventions.

## **2 Materials and methods**

### **2.1 Study area**

As seen in Figure III-1, Selangor comprises nine districts: Klang, Petaling, Sepang, Gombak, Sabak Bernam, Hulu Langat, Hulu Selangor, Kuala Langat, Kuala Selangor, which are further divided into 54 ‘Mukims’ or sub-districts, the smallest local governing units. Kuala Lumpur is enclosed by the state of Selangor and has eight sub-districts, namely Ampang, Bandar Kuala Lumpur, Batu, Cheras, Kuala Lumpur, Petaling, Setapak and Ulu Klang. Both states covers an area of 8,222 km<sup>2</sup> with a location between 2°35’N to 3°60’N and 100°43’E to 102°5’E. The study area is thus geographically heterogeneous varying from Kuala Lumpur to the surrounding suburban sub-districts and rural areas along the boundaries of Selangor. The population density varies considerably from Kuala Lumpur at 6,891 persons per km<sup>2</sup> to Selangor at 674 persons per km<sup>2</sup> in 2010 (Department of Statistics Malaysia 2011a).

### **2.2 Case data and pre-processing**

We obtained dengue case data from the Vector Borne Disease Control Division, MoHM, where a passive surveillance was conducted. Passive surveillance is the routine notification of diseases by the state or local health departments to the health department based on the standardized reporting forms when cases of disease are detected (World Health Organization 2009). We used those dengue cases that were confirmed by serological tests with single positive IgM antibodies (IgM capture enzyme-linked immunosorbent assay; ELISA). These represent about 46.2% of all reported dengue cases for the years 2008 to 2010. For the address level, we geocoded the geographic location according to the residency: 11,664 cases in 2008; 10,482 in 2009; and 8,300 in 2010. The geocoding accounted for 92.16% (2008), 93.44% (2009) and 94.87% (2010) of the addresses, respectively, while the remainder had to be excluded due to missing addresses. The

addresses were geocoded using Google Maps Application Programming Interface (API) that has been shown to be a high-quality geocoding service (Roongpiboonsopit and Karimi 2010) and successfully used for the geocoding of the location of health care facilities (Gu et al. 2010) and for mosquito surveying (Neteler et al. 2011). For the sub-district level, we aggregated the confirmed cases of 12,424, 10,982 and 8,581 based on the onset date of the dengue occurrence by daily information at sub-district level for the year 2008 to 2010.

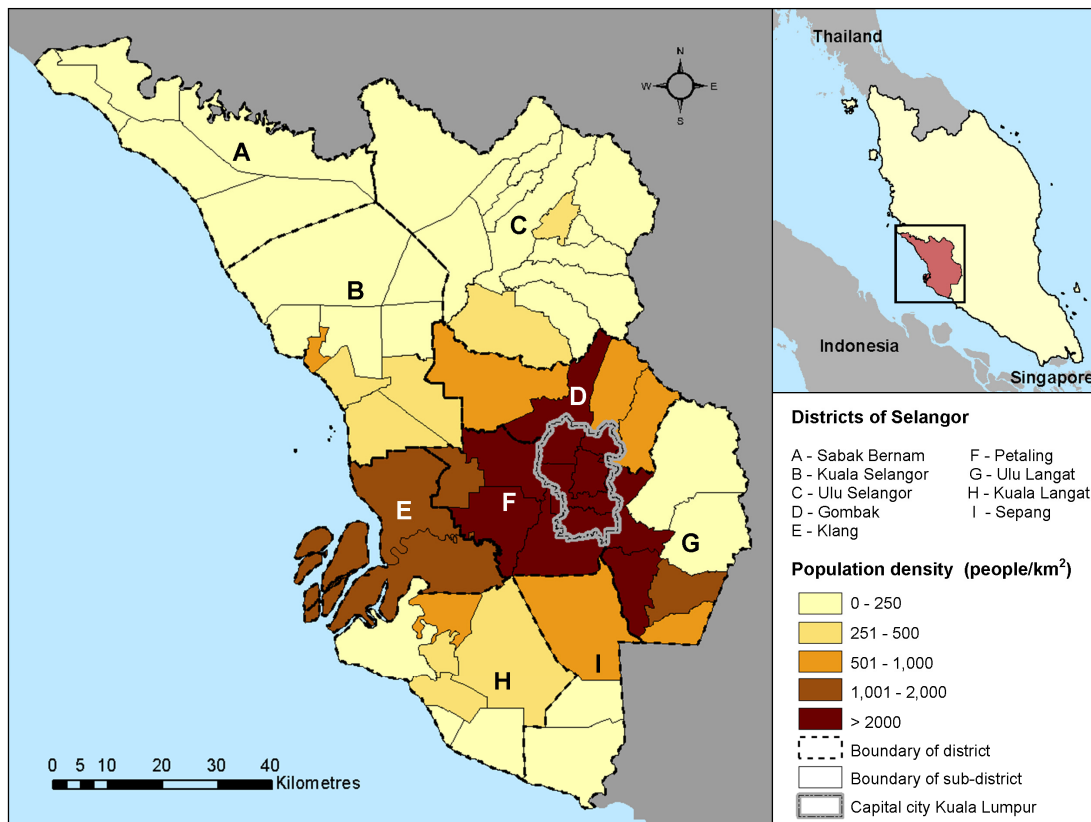


Figure III-1: Geographical distribution and population density (2010) in the 62 sub-districts of Selangor and Kuala Lumpur, Malaysia

### 2.3 Population and map data

We used population data at the sub-district level from the latest census in 2010 (Department of Statistics Malaysia 2011b). In addition, we applied the sub-district map of Selangor and Kuala Lumpur from the Department of Survey and Mapping in Malaysia (JUPEM). Putrajaya, the federal administrative capital that is located in the district Sepang was included in Selangor (Figure III-1). ArcGIS, version 10.0 (ESRI, Redlands, CA, USA) and R, version 2.15.0 with the 'maptools' package (Lewin-Koh et al. 2012) and 'ggplot2' package (Wickham 2009) were used for data pre-processing, spatial analysis and visualization.

## 2.4 Spatio-temporal pattern analysis

At the address level, we delineated clusters of dengue cases on a daily data basis using the software 'Spatial and Space-Time Scan Statistics' (SaTScan v9.1.1) (Kulldorff 2010). The scan statistic technique has been successfully applied in a number of studies (Kulldorff and Nagarwalla 1995; Song and Kulldorff 2003; Kulldorff et al. 2004). Space-time permutation models were employed to check for outbreaks at the address level where there was no population data available to assess the at risk population structure (Kulldorff et al. 2005). With reference to the official MoHM definition of an outbreak as the incidence of two or more dengue cases in a location where the onset date of the cases are less than 14 days apart and located within 200 m of each other (Ministry of Health Malaysia 1986; Ministry of Health Malaysia 2009), the maximum spatial cluster size was set at 200 m and the maximum temporal cluster size at 14 days. Only clusters with significant levels below 0.001 were reported after Monte Carlo simulation repeated 999 times. A window of a radius that can be varied up to 200 metres is moved across the study area with the aim of identifying potential clusters within various window settings. The assessment of a cluster was achieved by comparing the number of cases within the circle with the number of expected cases (assuming random distribution). The cluster with the maximum log likelihood ratio was taken as the most likely cluster, i.e. the cluster least likely to be due to chance. The secondary clusters are those that are in rank order after the most likely cluster, by their likelihood ratio value.

At the sub-district level, the same software SaTScan 9.1.1 was applied, but with slightly modified settings to better reflect the specific patterns encountered from the polygons of the study region. The analysis was done with the total number of cases observed and the estimated population numbers at each sub-district. A retrospective Poisson-based model was employed as the number of dengue cases in the study area is Poisson-distributed (Kulldorff et al. 2005). The circular scanning window was centred at the centroid of each sub-district polygon. To avoid unwanted effects linked to different sizes of the scanning window (Waller and Gotway 2004; Chen et al. 2008), we performed sensitivity tests and considered percentages of the population at risk from 1% to 50 %. To make it possible to discover small, homogeneous clusters within larger, heterogeneous ones, while at the same time not failing to detect significant, regional-level clusters due to small window sizes (Chen et al. 2008), the maximum spatial cluster was finally set at 15% of the total population at risk. The maximum temporal cluster size was set at 14 days similar to the address level for comparison purpose. With the availability of the total population at risk,

the relative risk can be estimated with the proportion of the estimation risk of dengue disease within the cluster to the estimated risk outside the cluster. To test the null hypothesis that the relative risk of dengue was the same between any sub-districts and remaining sub-districts, the Monte Carlo approach with 999 repetitions was used. A p-value  $<0.001$  was considered statistically significant.

To derive new insights on spatio-temporal patterns of dengue we focused on the two separate spatial scales, i.e., the address and the sub-district, and then visually compared the results by overlays.

### **3 Results**

#### **3.1 The address level**

Using the MoHM definition of an outbreak, our spatio-temporal analysis at the address level identified a total number of 107 outbreaks ( $p < 0.001$ ) for the whole study period from 2008-2010 (Figure III-2). Spatially, the outbreaks were concentrated in the central and south-eastern region of the study area. Temporally, they occurred most frequently in the period December to March over the three-year study period (Supplementary Figure A-1). The highest monthly number of outbreaks for the three-year period was observed in December 2009 with a total of 9 outbreaks and 54 cases. From September to November 2009 and from May to September 2010, we only observed occasional outbreaks (Supplementary Figure A-1).

With reference to the population density (Figure III-1), 67% of the detected address-level outbreaks occurred at sub-districts with more than 2,000 people per km<sup>2</sup>, while 21% occurred at sub-districts with population densities from 1,001 to 2,000 people per km<sup>2</sup>. The top-twenty of the outbreaks were found in high-density sub-districts, except the seventh largest cluster that occurred in a low population density sub-district, namely Bestari Jaya (Figure III-2).

#### **3.2 The sub-district level**

The spatio-temporal analysis discovered several significant high-risk clusters, again concentrated in the central and southern-eastern region of the study area (Figure III-2). Using the maximum temporal window of 14 days, we identified seven outbreak clusters ( $p < 0.001$ ) in total (Figure III-2). The most likely cluster, with a relative risk (RR) of 3.94 ( $p$

< 0.001, 13.98% of the total population), covered three out of Petaling's four sub-districts in the central region between 7 and 20 January 2010 (Figure III-1). One month later from 26 February to 11 March 2010, 2nd secondary cluster (Table III-1) was detected in the neighbouring Kuala Lumpur region (RR=3.69,  $p < 0.001$ , 14.42% of the total population). Both clusters occurred in the high-population density region with more than 2,000 people per km<sup>2</sup> (Figure III-1) and were close in space and time. The 1st secondary cluster in the districts of Sepang and Hulu Langat from 30 December 2008 to 12 January 2009 (RR=5.64,  $p < 0.001$ , 8.10% of the total population) and the 6th secondary cluster in Petaling and Kuala Lumpur from 1 January to 14 January 2009 (RR=2.44,  $p < 0.001$ , 12.48% of the total population) were similarly close in space and time (Table III-1).

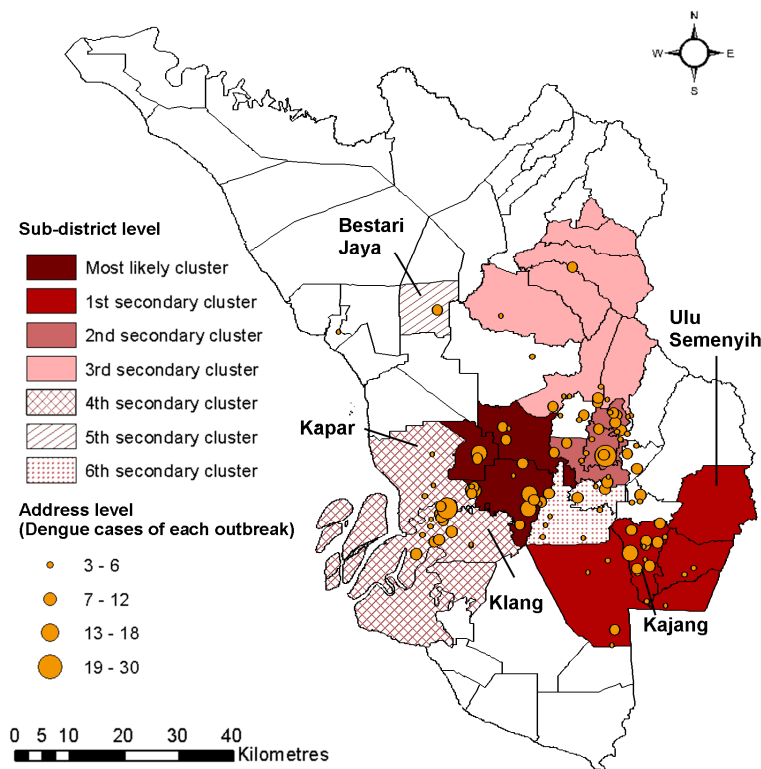


Figure III-2: Spatio-temporal clusters of dengue cases at the address level (circular shape) and sub-district level (shaded area) 2008-2010.

The cluster with the highest number of sub-districts was the 3rd secondary cluster in Hulu Selangor and Gombak with seven sub-districts and RR of 4.99 ( $p < 0.001$ , 7.19% of the total population). The extraordinary high RR of 16.32 compared to the average of 2.44 to 5.64 was observed in Bestari Jaya of Kuala Selangor (5th secondary cluster) from 27 April to 10 May 2008 ( $p < 0.001$ , 0.36% of the total population).

All clusters occurred in the first three months of the year except one in April and May 2008 (5th secondary cluster). Of all the clusters, 71.43% were seen in the same month (January)

of the three years (Table III-1). Three out of seven clusters (1st secondary cluster, 3rd secondary cluster and 6th secondary cluster) occurred in the end of 2008 stretching into the early part of 2009.

#### 4 Discussion

Our studies of outbreaks at the address level found that they occurred mainly in the central and south-eastern regions and that they peaked from December to March. This result supports the spatial mapping study in Hulu Langat district by (Er et al. 2010), who reported strong outbreaks at the south-eastern region. The address level dengue outbreaks were predominately located in the high-population density region ( $>1000$  people per  $\text{km}^2$ ) implying that the urbanized area play a major role in dengue epidemic. This also goes inline with earlier findings such as by Patz et al. (2005) and Cheong et al. (2014). Probable reasons for the varying areas of identified clusters in the three-year period reported here may be the complex interaction of vector abundance and herd immunity (Salje et al. 2012). Furthermore, an ovitrap surveillance conducted by Chen et al. (2006) in the study area indicate that mixed breedings of the two main dengue mosquitoes, *Aedes aegypti* and *Aedes albopictus* in a single ovitrap are known to lead to higher breeding rate and higher risk of dengue transmission. *Ae. albopictus* was found dominant in population compared to *Ae. aegypti* in the study area (Saleeza et al., 2011). Recent studies in Japan (Nihei et. al., 2014) and the Western United States (Kesavaraju et. al., 2014) have stressed that *Ae. Albopictus* was dominating other *Aedes* species representing an invasive vector that can lead to serious outbreaks of at least 22 arbovirus diseases including dengue (Gratz, 2004).

Spatio-temporal analysis at the address level allows for the detection of potential outbreaks but lacks information about the background population at risk (Kulldorff et al. 2005). However, by including the sub-district level, our analysis could also provide this information. At this level, we found that the dengue outbreaks covered a wide area from the central to the north-eastern and south-eastern regions and this identified spatial pattern not only supports, but also augment our findings at the address level. The most likely outbreak cluster was found to be in the Petaling District. The identified clusters at the sub-district level were close in space and time and may have been driven by human mobility rather than spatial action on the vector part (Stoddard et al. 2009; Teurlai et al. 2012) as there is a relatively high daily movement of commuters across the interconnecting sub-



Spatio-temporal patterns of dengue disease

Table III-1: Cluster analysis of dengue cases at the sub-district level in Selangor and Kuala Lumpur 2008-2010 (Space-time scan statistic using 15% of the maximum spatial window for population risk on a daily basis)

Cluster	Geographic area	Number of Sub-districts	Period	Radius (km)	Observed cases <sup>a</sup>	Expected cases <sup>b</sup>	RR <sup>c</sup>	Population at risk <sup>d</sup>	Significance level
Most likely cluster	Petaling	3	2010/1/7 - 2010/1/20	11.0	240	61.24	3.94	979,295	<0.001
1 <sup>st</sup> Secondary Cluster	Sepang, Hulu Langat	5	2008/12/30 - 2009/1/12	18.3	163	29.04	5.64	567,040	<0.001
2 <sup>nd</sup> Secondary Cluster	Kuala Lumpur	4	2010/2/26 - 2010/3/11	6.10	215	58.58	3.69	1,009,996	<0.001
3 <sup>rd</sup> Secondary Cluster	Hulu Selangor, Gombak	7	2008/12/28 - 2009/1/10	16.66	151	30.38	4.99	503,707	<0.001
4 <sup>th</sup> Secondary Cluster	Klang, Kuala Langat	4	2008/1/1 - 2008/1/14	13.23	154	53.83	2.88	905,030	<0.001
5 <sup>th</sup> Secondary Cluster	Kuala Selangor	1	2008/4/27 - 2008/5/10	0	25	1.53	16.32	25,360	<0.001
6 <sup>th</sup> Secondary Cluster	Petaling, Kuala Lumpur	2	2009/1/1 - 2009/1/14	7.04	122	50.05	2.44	873,867	<0.001

<sup>a</sup>Number of observed cases in cluster; <sup>b</sup>Number of expected cases in cluster; <sup>c</sup>Relative risk; <sup>d</sup>Number of population at risk in cluster.

districts (Barter 2002; Bunnell et al. 2002). The 2010 outbreak clusters in this area (Table III-1) clusters with rainfall. Special focus should be given to the dengue cluster with extremely high RR, which occurred in a low-population density sub-district, i.e. Bestari Jaya in 2008 (Figure III-2). A larvae surveillance study by Saleeza et al. (2011) in this area showed that the problem was artificial containers discarded outside houses thereby providing breeding places for mosquito larvae. Proper waste management from the authorities, as suggested by Saleeza et al. (2011) and more community participation (Gubler and Clark 1996) would improve the situation.

In our study, the sub-district level analysis overestimated of the cluster area. For example, the 3rd secondary cluster had a radius of 16.7 km and included seven sub-districts (Figure III-2), while clusters were only found in two sub-districts at the address level. Overestimation was also present with regard to the 1st secondary cluster where the Ulu Semenyih Sub-district, characterized by low numbers of dengue cases, was included only due to its adjacency to Kajang Sub-district that was found to have an excess number of outbreaks at the address level (Figure III-2). Jones and Kulldorff (2012) report that the aggregation (sub-district in our case) level has a greater likelihood to include areas that do not belong to the actual cluster in question. They state that as the scan statistics circle grows, it logically encloses more case observations in order to reach the relatively more spatial disparate aggregation level centroids. Hence, careful selection of scanning parameters is needed to better represent true outbreaks (Chen et al. 2008). Furthermore, the MAUP cause arbitrarily results at the aggregation level as the boundaries are not necessarily related to the spatial spread of dengue disease (Jeffery et al. 2009) and population density, land use, and breeding site availability. Additionally, meteorological parameters may vary distinctly within a sub-district. However, across the sub-district level, we were able to estimate the background population at risk for contracting dengue. Thus, this approach provided more valuable information than just looking at the address level, where the likelihood of the outbreak cluster stayed the same across the study area. Therefore, agree with Schwartz (Schwartz 1994), who states that information at the address level is not superior to the aggregation level and, conversely, the aggregation level is no substitute for the address level. In our study, overlying the address level results provided the exact location of the outbreaks. In one area we could even show that excess risk was concentrated at cross bordering regions, i.e. as depicted in the 4th secondary cluster, the border crossing regions of the two sub-districts Kapar and Klang (Figure III-2) showed excess numbers of address level outbreaks. This situation provides valuable input for the

local authorities of both sub-districts and it would be useful for them to intensify collaboration in vector control.

The observed spatio-temporal patterns of dengue cases may be linked to complex interacting factors, e.g., abundance of *Ae. aegypti* females, transportation network, land use change, human behavior and climate (Rogers et al. 2006; Halstead 2008; Eisen and Lozano-Fuentes 2009; Lambin et al. 2010). Many have tried to combine such influencing factors in the search for a way of predicting areas of dengue risk (Nakhapakorn and Tripathi, 2005; Kolivras, 2006; Porcasi et al., 2012). We have also done so and investigated the influence of weather and land use in association with dengue cases and reported the results in previous work (Cheong et al. 2013; Cheong et al. 2014). Cheong et al. (2013) showed that the relative risk of dengue cases is positively associated with increased minimum temperature and increased rainfall with the lag time of 51 days and 26-28 days, respectively, but is negatively associated with the wind speed. Cheong et al. (2014) found that the most important land use factors associated with dengue cases in the study area are human settlements, followed by water bodies, mixed horticulture, open land and neglected grassland. Due to the complexity of this disease, scrutinizing when and where the dengue outbreaks occurred in the past can be a useful guide for future outbreak prediction (World Health Organization 2012a). In addition, identification of high-risk dengue areas should focus public health activities such as immunization campaigns, once a vaccine against the dengue virus becomes reality (Lam et al. 2011).

This study has some limitations. Firstly, the dengue data used did probably not include all those infected in the area studied as reporting is commonly influenced by limitation in finding 100% of the cases (Shepard et al. 2012). However, the study is based on large number of laboratory-confirmed dengue cases, and even if there was some degree of under-reporting, our analyses still provide useful insights with regard areas at risk for infection. Secondly, we used circular scan statistic in this study, which implies that all detected outbreaks are approximately circular (Kulldorff et al. 2005), which is not always the case. Although the elliptic scan statistic performs well with non-circular true outbreak (Christiansen et al. 2006), longer computing times and the arbitrary setting of the eccentricity penalty must then be taken into account (Kulldorff et al. 2006). Thirdly, the home addresses used to allocate the dengue cases may not always be the correct ones, reflecting the mobility of patients with respect to recreation and work activities. Nevertheless, the higher probability of multiple infections in the household strengthens the home address as the main infection site (Halstead 2008; de Melo et al. 2012). Additional

illustrations of the monthly spatio-temporal clusters of dengue cases at the address level from year 2008 to 2010 can be found in the Supplementary Figure A-1.

## **5 Conclusions**

Combining address- and sub-district level information assists the identification of differences and coincidences of high-risk clusters of dengue. Although additional resources may be needed in assuring patient residencies, this strategy should improve routine epidemiological surveillance and vector control and initial high-risk cluster areas can be targeted before the disease spreads into a larger area. Further, studies on the geographical relationships between the various factors influencing the development of high-risk disease clusters would shed light regarding the aetiology of dengue.

The three main findings were: 1) that dengue outbreaks show a significant spatio-temporal pattern at the address level; 2) that the dengue risk show similar spatio-temporal patterns at the sub-district level; and 3) that a combination of the outbreak information from address and sub-district level facilitates the planning of effective health interventions.

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**Chapter IV:**  
**Assessing weather effects on dengue disease in**  
**Malaysia**

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## **Abstract**

The number of dengue cases has been increasing on a global level in recent years, and particularly so in Malaysia, yet little is known about the effects of weather for identifying the short-term risk of dengue for the population. The aim of this paper is to estimate the weather effects on dengue disease accounting for non-linear temporal effects in Selangor, Kuala Lumpur and Putrajaya, Malaysia, from 2008 to 2010. We selected the weather parameters with a Poisson generalized additive model, and then assessed the effects of minimum temperature, bi-weekly accumulated rainfall and wind speed on dengue cases using a distributed non-linear lag model while adjusting for trend, day-of-week and week of the year. We found that the relative risk of dengue cases is positively associated with increased minimum temperature at a cumulative percentage change of 11.92% (95% CI: 4.41–32.19), from 25.4 °C to 26.5 °C, with the highest effect delayed by 51 days. Increasing bi-weekly accumulated rainfall had a positively strong effect on dengue cases at a cumulative percentage change of 21.45% (95% CI: 8.96, 51.37), from 215 mm to 302 mm, with the highest effect delayed by 26–28 days. The wind speed is negatively associated with dengue cases. The estimated lagged effects can be adapted in the dengue early warning system to assist in vector control and prevention plan.

## 1 Introduction

The risk of mosquito-borne dengue infection has increased dramatically in tropical and sub-tropical regions around the World in recent decades (World Health Organization 2012b). Each year there are between 50 and 100 million dengue infections, and more than 500,000 cases are hospitalized (Gubler 2006). The pattern of dengue transmission is influenced by complex factors including the environment, climate and weather, human behavior and dengue virus serotype-specific herd immunity among the human population (Gubler and Rosen 1977; Hay et al. 2000; Halstead 2008). Here, we focus on weather, one of the fundamental driving forces behind dengue epidemics (Hales et al. 2002; Wardekker et al. 2012) that may allow us to narrow down the timeframe of high risk dengue infection.

Dengue disease transmission is sensitive to weather for several reasons: a warm ambient temperature is critical to adult dengue vectors' feeding behavior and gonotrophic cycle, as well as the rate of larval development and speed of virus replication; and rainfall-induced standing water are necessary for dengue vectors to breed (Focks et al. 1993a; Patz et al. 1998; Delatte et al. 2009). The entire immature or aquatic cycle from egg to adult is approximately 7–9 days (Focks et al. 1993b; Centers for Disease Control and Prevention 2012). Dengue vectors become infected by biting infected humans or non-human primates (viremic stage), and they can then transmit the infection to other uninfected people after an extrinsic incubation period (EIP) of 8–12 days (Gubler 1998a). The EIP is the time when dengue vectors take a viremic blood meal to the time of the first successful transmission of the DENV (Chan and Johansson 2012). After the intrinsic incubation period (IIP) of 4–10 days, the dengue symptoms begins unexpectedly sudden on the host (World Health Organization 2009). The dengue vectors fit to transmit DENV survives for 30 days (Yang et al. 2009). Hence, the estimated lagged time for the development of dengue vectors to the onset of dengue symptoms in human could be as short as 19 days if the dengue vectors bite a susceptible host on the first day after EIP.

Many studies have reported varying associations and lagged effects between climate and weather on dengue cases. Strong positive correlations were found between El Niño-Southern Oscillation (ENSO) and dengue epidemics in 10 island nations of the South Pacific (Hales et al. 1999), across the Indonesian archipelago and northern South America (Gagnon et al. 2001), and in Thailand (Cazelles et al. 2005). For temperature, a varying

lagged effect was reported in countries situated within 13 and 25 degrees latitude, both North and South. An increasing dengue risk was associated with increasing minimum and maximum temperature by a 1–2 month lag in Mexico (Garcia et al. 2011), Brazil (Gomes et al. 2012) and French West Indies (Gharbi et al. 2011), but with a longer lag time up to 3–4 months in Barbados (Depradine and Lovell 2004) and Australia (Bi et al. 2001). For countries closer to the equator, that is, within 1–6 degrees North and South, a shorter 2-week lag of temperature on dengue cases was reported in Singapore (Earnest et al. 2012), and a 1-month lag of temperature was reported in Indonesia (Arcari et al. 2007). Furthermore, rainfall interactions exhibited a mixture of influences, from a 2-week lag, a 4-week lag, a 7-week lag, to a 10-week lag on the increase of dengue cases in Mexico (Brunkard et al. 2008), Thailand (Jeefoo et al. 2010), Barbados (Depradine and Lovell 2004), and Taiwan (Chen et al. 2012), respectively. Wind speed also exhibited a disparate association with dengue cases, from the common negative association in Barbados (Depradine and Lovell 2004), Sri Lanka (Yasuoka and Levins 2007) and Guangzhou, China (Lu et al. 2009), to no association in Thailand (Tipayamongkhogul et al. 2009) and Taiwan (Shang et al. 2010). This study contributes to the overall estimation of the weather influence on dengue transmission in the area close to the equator.

Earlier studies have shown that Malaysia is dengue hyperendemic, with all four serotypes circulating concurrently (Chew et al. 2012), and with an abundance of both *Aedes aegypti* and *Aedes albopictus* (Chen et al. 2006; Saleeza et al. 2011). The potential contribution of the results in this work may help health workers and stakeholders to plan vector control activities. Few studies in Malaysia focus on the weather interaction with dengue vectors abundance (Rozilawati 2007; Dieng et al. 2010; Rohani et al. 2011; Saifur et al. 2012) and dengue cases in a local study site (Li et al. 1985; Shafie 2011). To date, there is no study on the short-term weather interaction with dengue cases in Selangor, Kuala Lumpur and Putrajaya, Malaysia. We aimed to estimate the weather effects on dengue disease accounting for non-linear temporal effects.

## **2 Materials and methods**

### **2.1 Study area**

The study area included the State of Selangor, the federal territory of Kuala Lumpur and the federal administrative capital of Putrajaya, and covered an area of 8,222 km<sup>2</sup>; the geographical location is between 2°35'N and 3°60'N, and 100°43'E and 102°5'E (Figure IV-1).



The tropical climate is characterized by fairly high but uniform average daily temperatures ranging from 21 °C to 32 °C, a mean annual temperature of 26 °C, average daily humidity levels exceeding 80%, and mean annual rainfall of about 2,500 mm. The climate of Selangor, Kuala Lumpur and Putrajaya is governed by two monsoonal winds, which originate from the northeast between October and February, and the southwest from May to September (Olaniyi et al. 2012).

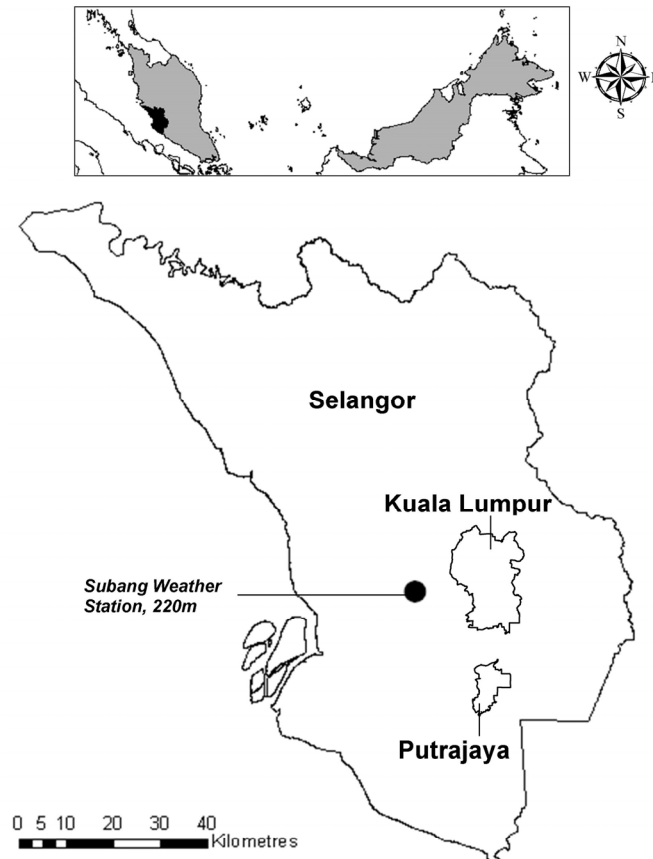


Figure IV-1: Study area: State of Selangor, including the federal territory of Kuala Lumpur and the federal administrative capital of Putrajaya.

## 2.2 Data

In Malaysia, dengue is a nationally notifiable disease and physicians must report every suspected case of dengue to the local health authority within 24 h (Ministry of Health Malaysia 2010). We obtained dengue data from the Disease Control Division, Ministry of Health Malaysia. We used only dengue cases that were confirmed by the serological tests IgM capture enzyme-linked immunosorbent assay (ELISA) with single positive IgM as also applied by other studies (Chadwick et al. 2006; Krishnan et al. 2012). For Selangor,

Kuala Lumpur and Putrajaya, 32,181 cases of dengue were found from 2008 to 2010. The number of dengue cases shows a mean of 29.4 per day, with a standard deviation of 13.7 (Table IV-1).

Table IV-1: Distribution of dengue cases and selected weather parameters in Selangor, Kuala Lumpur and Putrajaya, 2008–2010.

Variables (unit)	Mean	Standard deviation	Minimum	Percentiles			
				25th	50th	75th	100th
Daily total dengue cases	29.4	13.7	1.0	20.0	28.0	38.0	117.0
Daily minimum temperature (°C)	24.2	1.0	20.4	23.5	24.0	24.9	27.0
Daily maximum temperature (°C)	32.9	1.6	25.4	32.0	33.0	34.0	36.4
Daily mean temperature (°C)	27.8	1.3	23.3	26.9	27.8	28.8	31.3
Daily relative humidity (%)	78.0	6.0	59.9	73.6	78.5	82.6	93.5
Cumulative bi-weekly rainfall (mm)	117.4	72.9	1.3	55.6	108.2	170.4	329.2
Daily mean wind speed (knots)	2.9	0.9	1.0	2.3	2.7	3.4	6.2

We compiled the daily data for maximum, minimum and mean temperature (in degrees Celsius), cumulative bi-weekly rainfall (mm), relative humidity (percentage) and mean wind speed (knots) from the local weather station in Kuala Lumpur, Subang (WMO# 486470; North Latitude 3°07'01"; East Longitude 101°32'60"; 220 masl) from 2007–2010. The data distribution of dengue cases and weather parameters are shown in Table IV-1. We used cumulative bi-weekly rainfall to include the immature cycle of dengue vectors that takes at least seven days, which is consistent with previous studies (Barrera et al. 2011). One station data was used due to the availability of the data, the high number of dengue cases concentrated near the station, and the weather conditions would not vary significantly across space (Guo et al. 2013). Weather data were obtained from the National Climatic Data Center (NCDC) website (Guo et al. 2013).

### 2.3 Statistical analysis

Initially, we included daily minimum temperature, daily maximum temperature, daily mean temperature, daily relative humidity, daily mean wind speed and bi-weekly rainfall in our analysis. We assessed the correlation analyses between all weather parameters and dengue cases. Mean temperature was reported with a high positive correlation with maximum temperature, and was then excluded (Supplementary Table B-1).

We assessed the relationship between the weather parameters and the number of daily dengue cases using Poisson generalized additive models (GAM) (Hastie and Tibshirani 1990) in the “mgcv” R (R Development Core Team 2013) package, version 1.7–23 (Wood

2008) with natural cubic splines. The GAM are useful for identifying non-linear relationships and do not require an a priori knowledge of the shape of the response curves (Hastie and Tibshirani 1990; Wood 2006), which is determined by the data itself (Ferrier et al. 2002). We excluded outliers of 4 standard deviations from the mean for all weather parameters, as GAM modeling is outlier-sensitive (Alimadad and Salibian-Barrera 2011). Model construction was based on a stepwise forward and backward variable selection using the Akaike's Information Criteria (AIC) score (Burnham and Anderson 2004). The significance of the spline term(s) was assessed and fitted with linear interactions when non-significance was detected. The best parsimonious model was selected based on the Delta AICs (AIC—minimum AIC) (Burnham and Anderson 2004), and its accuracy was assessed by a 10-fold cross-validation. We assessed the autocorrelation and partial autocorrelation of the model residuals to adjust the need to account for seasonal trends.

To capture the delayed effects of weather parameters on the number of dengue cases, we used distributed lag non-linear models (DLNM) in the “dlnm” R (R Development Core Team 2013) package version 1.6.8 (Armstrong 2006; Gasparrini 2011) to simultaneously describe non-linear and delayed dependencies in the association between weather parameters and dengue cases based on a “cross-basis” function. Recent studies have shown promising modeling performances in the weather effects on inpatient mortality and outpatient visit with GAM and DLNM (Iñiguez et al. 2010; Thach et al. 2010; Tian et al. 2012; Zhang et al. 2013). We used lags up to 90 days to account for any potential lag period (i.e., the extrinsic incubation period of the dengue vector and intrinsic incubation period of dengue virus). The median value of weather parameters (Table IV-1) was defined as the baseline centering value for calculating relative risk. The relative risk was based on the Poisson regression models adjusting for various confounders following the work of Gasparrini et al. (Gasparrini et al. 2010). We compared the relative risk at specific lags to account for the effect of the current day's weather parameters on the current day's dengue cases (lag 0), weather parameters one month before (lag 30), two months before (lag 60), and three months before (lag 90) on the current day's dengue cases. To quantify the nonlinear exposure-response curves, we calculated the percentage change with the 95% confidence intervals (CIs) in the number of dengue cases for minimum temperature, cumulated rainfall and wind speed with the 99th percentile relative to the 90th percentile for high weather effect, and the 1st percentile relative to the 10th percentile, respectively, for low weather effect. The percentage change was calculated by the following formula (Equation 1)(Luo et al. 2013):

$$\text{Percentage Change} = (\text{Relative Risk} - 1) \times 100\% \quad (1)$$

Sensitivity analyses were performed by varying the degrees of freedom (df), using 3–7 df for trend adjustment. Moreover, we conducted the analysis for maximum lags of 60 and 90 days for the DLNM.

### 3 Results

#### 3.1 Best model selection and validation

By comparing the AIC and the Delta AIC values, we identified the best Poisson GAM model with minimum temperature, bi-weekly accumulated rainfall, and wind speed (AIC: 7367.23; deviance explained: 75.5%) (Supplementary Table B-2 and Supplementary Table B-3). The relative humidity and maximum temperature were not statistically significant and were thus not included in the model (Supplementary Table B-2). The model was adjusted with a natural cubic spline of the time per year using 4 df, a factor for day of week and a natural cubic spline of week of the year to control for seasonal and long-term trends. We found that the selected GAM model correctly described 66% of the withheld deviance in a 10-fold cross-validation without a lag effect. The deviance not described by the model may account for temporal fluctuations in the immunity status of host populations (Gubler and Clark 1995), socio-economical factors (Eisen and Lozano-Fuentes 2009), and other factors related to the population of dengue virus vectors (Halstead 2008). The autocorrelation and partial autocorrelations of residuals from our main models were free from systematic patterns and summed close to zero (Supplementary Figure B-1). This suggested our original choice of smoothing had adequately adjusted for seasonal trends.

In the sensitivity analyses for DLNM, the estimates for the results with varying df and lag changed little. Hence, we eventually used the natural cubic B-spline with 3 df for minimum temperature, 3 df for accumulated rainfall, and 3 df for wind speed to describe the association of weather parameters and dengue cases. For the lag stratification, we selected 3 df for minimum temperature, 3 df for accumulated rainfall, and 3 df for wind speed.

#### 3.2 Association of temperature and dengue

The estimated effects of minimum temperature were nonlinear for dengue cases, with increasing relative risk at a higher minimum temperature (Figure IV-2a).

The minimum temperature effect on dengue cases on the current day showed a different shape from the other specific lags of 30, 60 and 90 (Figure IV-3). The current day effect was basically not statistically significant, but the other lagged effect showed an increasing risk with an increase of minimum temperature. The increase of minimum temperature from 25.4 °C (90th percentile) to 26.5 °C (99th percentile) increased dengue cases by the highest amount, that is, 5.04% (95% CI: 3.58, 6.51) at a lag of 51 days (Supplementary Table B-4). The cumulative effect of the overall percentage change in the daily dengue cases exhibited a higher percentage value, of 11.92% (95% CI: 4.41–32.19) in warm temperature (an increase from 25.4 °C to 26.5 °C), than did the cold temperature (a decrease from 23 °C to 22 °C), at 0.10% (95% CI: 0.05–0.23) (Supplementary Table B-4).

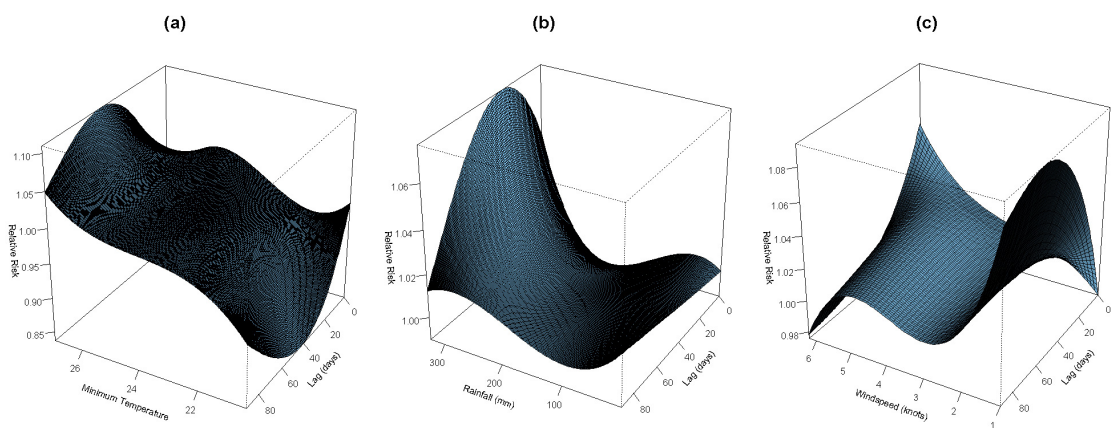


Figure IV-2: Relative risk of dengue cases by (a) minimum temperature (°C); (b) rainfall (mm) and (c) wind speed (knots) for a lag of 90 days, using a “natural cubic B-spline-natural cubic spline” DLNM with a 3 degrees of freedom natural cubic B-spline for minimum temperature, a 3 degrees of freedom natural cubic B-spline for accumulated rainfall, and a 3 degrees of freedom natural cubic B-spline for wind speed. The reference values were median of minimum temperature (24 °C), rainfall (108.20 mm), and wind speed (2.7 knots). (see also Supplementary Movie S1, Movie S2 and Movie S3).

### 3.3 Association between rainfall and dengue

The estimated effect of rainfall on dengue cases obviously differed for low and high cumulated rainfall for a lag period of 90 days in the three-dimensional plot (Figure IV-2b). There was a strong effect at high rainfall, but a rather small effect at low rainfall (Figure IV-2b). Further, Figure IV-3 exhibited the strongest effect of rainfall at a lag of 30 days with a rapid increase of risk above bi-weekly cumulated rainfall of 200 mm. The increase of cumulated rainfall from 215 mm (90th percentile) to 302 mm (99th percentile) increased dengue cases by the highest, 4.75% (95% CI: 3.50, 6.01) at a lag of 26 to 28 days (Supplementary Table B-4). Overall, high rainfall exhibited a higher cumulative percentage

value of 21.45% (95% CI: 8.96, 51.37) than the low rainfall level of 1.08% (95% CI: 0.94, 1.25) (Supplementary Table B-4).

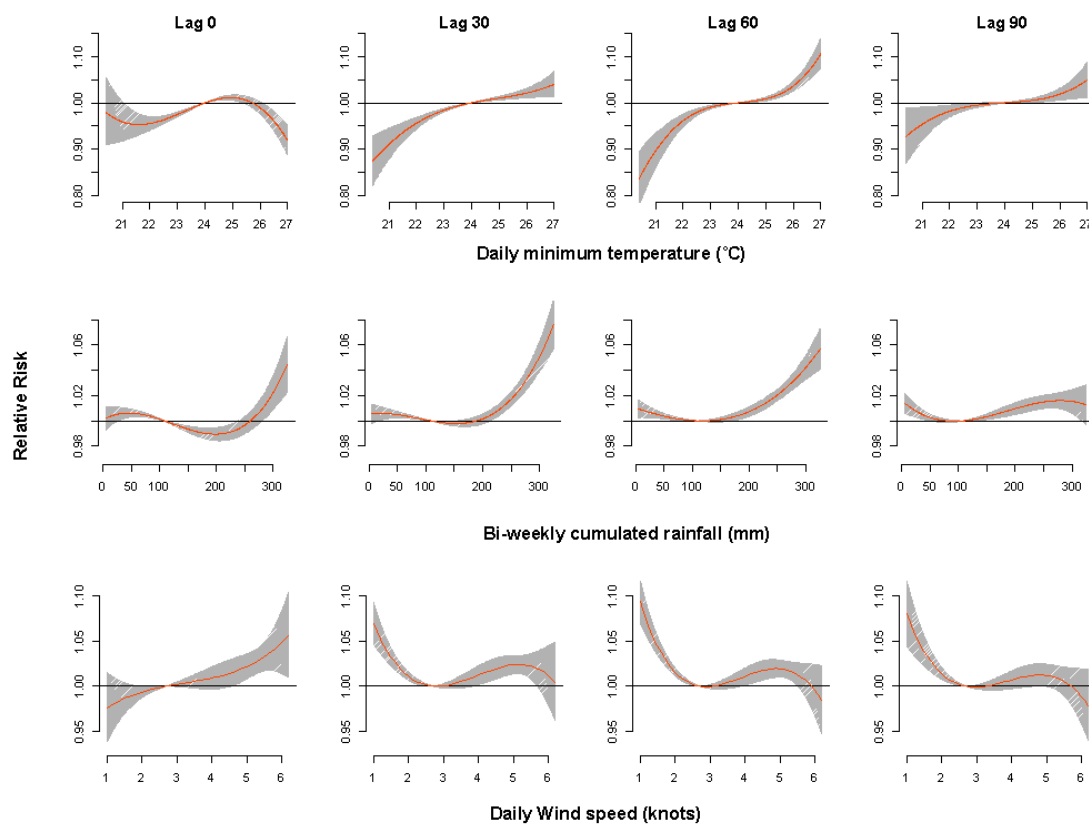


Figure IV-3: Relative risk of dengue cases by minimum temperature ( $^{\circ}\text{C}$ ), rainfall (mm) and wind speed (knots) at specific lags of 0, 30, 60 and 90 days, using a “natural cubic B-spline-natural cubic spline” DLNM with a 3 degrees of freedom natural cubic B-spline for minimum temperature, a 3 degrees of freedom natural cubic B-spline for accumulated rainfall, and a 3 degrees of freedom natural cubic B-spline for wind speed. The reference values were median of minimum temperature ( $24^{\circ}\text{C}$ ), rainfall (108.2 mm), and wind speed (2.7 knots).

### 3.4 Association of wind speed and dengue

The three-dimensional plot shows that the relative risk of dengue cases are inversely associated with the wind speed for longer lag periods (Figure IV-2c). The effect of low wind speed lasted for a longer period, while the effect of a high wind speed lasted for a shorter period (Figure IV-2c). For the high wind speed, the high effects were the largest at a lag of 0, and then declined gradually. Figure IV-3 exhibits the wind speed effect on dengue cases during the current day differed from the lagged effect. The relative risk of dengue cases increased with the increasing wind speed on the current day. At the lag of 1, 2 and 3 months, wind speed was negatively associated with dengue cases up to 3 knots, positively associated from 3–5 knots, followed by a negative association again at 5 knots and above.

Supplementary Table B-4 shows the percentage change of wind speed on dengue cases. The drop of wind speed from 2.7 knots (10th percentile) to 1.7 knots (1st percentile) increased dengue cases by the highest amount, 4.02% (95% CI: 2.99, 5.06) at a lag of 59 days (Supplementary Table B-4). However, the increase of wind speed from 4.1 knots (90th percentile) to 5.7 knots (99th percentile) showed the highest effect at the lag of 0, 2.80% (95% CI: 0.12, 5.56), and then decreasing with the lagged period (Supplementary Table B-4). Overall, low wind speed exhibited a higher cumulative percentage value of 13.63% (95% CI: 5.42, 34.25) than the high wind speed of 1.30% (95% CI: 0.20, 8.39) (Supplementary Table B-4).

#### **4 Discussion**

The aim of this study was to estimate the effects of weather parameters on dengue cases, with particular focus placed on lag times. Although the relationships between climate change effects on local weather and ecological systems is complex (Adger et al. 2008), it is encouraging that we found a short-term association of weather parameters, including minimum temperature, rainfall and wind speed with dengue cases at different lag periods.

We found the highest significant positive association between dengue cases and the minimum temperature with the lag time of 51 days, that is, close to two months. The significant association of dengue cases with minimum temperature was reported in numerous studies (Depradine and Lovell 2004; Chen et al. 2010; Gomes et al. 2012). Similar observations were also reported in Taiwan (Wu et al. 2007) and Mexico (Garcia et al. 2011), where minimum temperature at a lag of two months had the highest positive effect on dengue cases. The two-month lagged period may include time for dengue vectors to develop from eggs, become infected with the virus, EIP and biting activities in the gonotrophic cycle, and then IIP. Increasing temperatures shorten the gonotrophic cycle (Pant and Yasuno 1973; Halstead 2008) and reduce the EIP (Focks et al. 1995; Scott and Morrison 2010b; Chan and Johansson 2012). At higher but not extreme temperatures, adult infected vectors require more blood meal to complete the gonotrophic cycle, and more than one gonotrophic cycle throughout the survival life cycle may lead to an increasing risk of dengue transmission (Watts et al. 1987; Delatte et al. 2009). Furthermore, a recent incubation period review stated that EIP decreases with increases in temperature (Chan and Johansson 2012). In addition, a different pattern of risk observed for the current day and the lagged days might be due to the flying behavior of adult dengue vectors

(Figure IV-3). A higher risk of dengue cases in colder temperatures exists, as dengue vectors tend to fly farther at 15 °C than at 27 °C, which leads to greater dispersal and a higher biting rate of humans (Rowley and Graham 1968).

Rainfall season is positively associated with DENV adult abundance and higher dengue transmission (Moore et al. 1978; Halstead 2008; Pham et al. 2011). We found a higher risk of dengue cases reported during the lag of 26–28 days, or close to one month for bi-weekly cumulated rainfall (Supplementary Table B-4). This is in line with the studies that reported the highest risk of dengue cases related to rainfall 3 weeks prior in Veracruz, Mexico (Hurtado-Diaz et al. 2007), and one month prior in Rio de Janeiro, Brazil (Gomes et al. 2012), respectively. Rainfall influences the abundance of dengue vectors in the winged (adult) and aquatic populations (eggs, larvae, pupae) (Wardekker et al. 2012). Increased near-surface humidity associated with rainfall enhances adult dengue vectors flight activity and host-seeking behavior (Wardekker et al. 2012), whereas increased rainfall supports more suitable breeding sites for the immature development of the aquatic population (Lowe et al. 2011). Furthermore, prolonged rainfall that leads to flooding may increase the dengue risk (Bich et al. 2011; Hashizume et al. 2012). Aside from the indoor breeding habitats, probable rain filled breeding sites ranged from discarded car tires, animal watering dishes, tree holes, and discarded and neglected bottles and other containers are often found in parks, vacant land, blocked cement drains and septic tanks (Chang et al. 2011; Lowe et al. 2011; Wan-Norafikah et al. 2012). Moreover, the short lag period of one month indicated that the presence of a critical hyperendemic DENV environment in the study area may be due to the vertical dengue virus transmitting directly from adult to offspring (Adams and Boots 2010), and multiple DENV serotypes co-circulating (Chew et al. 2012).

We found that wind speed is inversely associated with the dengue cases (Figure IV-2c, Figure IV-3), which is in line with the study in Barbados (Depradine and Lovell 2004), Guangzhou, China (Lu et al. 2009) and Sri Lanka (Yasuoka and Levins 2007). This was further supported by the higher cumulative percentage change in low wind speed compared to high wind speed (Supplementary Table B-4). Wind suppresses dengue vectors host-seeking flying activity, which affects oviposition and contact with humans (Clements 1999; Hoffmann and Miller 2002; Kay et al. 2002). However, a slight increase of dengue risk was observed with an increase in wind speed from 3 knots to 5 knots, as this is still within the maximum threshold where dengue vectors can fly freely, which was reported to have a threshold of 4.4 knots in Wisconsin (Grimstad and DeFoliart 1975). The suitable wind



condition below the maximum threshold favors the dispersion of dengue vectors and their oviposition (Service 1997). Furthermore, there was a steep decrease of wind speed's effect on dengue cases for a short period of 10–15 lag days at high wind speeds (Figure IV-2c). This pattern suggests some harvesting phenomenon, as also reported by other studies (Gasparrini 2011; Turner et al. 2012). Therefore, short lags cannot adequately be used to assess risk effects (Guo et al. 2011). A maximum percentage increase from 1.7 knots to 2.7 knots was found at the lag of 59 days. This lag period of 59 days was reasonable if we include the period for immature development, EIP, DENV infection and transmission, and IIP.

Findings from our study can be adapted together with the other factors including population density, dengue virus circulating, efforts of vector control and vector density to assist in establishing a dengue early warning system. Current dengue disease control and prevention in Malaysia mainly based on the reported dengue cases in the passive surveillance system without predictive capabilities. For every notified dengue cases, adulticiding with space spraying is conducted. Other vector control strategies including larviciding with direct application of Temephos and misting of Bti (Nazni et al. 2009), communication for behavioral impact (COMBI) (Rozhan et al. 2006) and biological control (Chang et al. 2011) are applied for the selected outbreak areas or in areas where the outbreak cannot be controlled after long time period. In order to better control the dengue outbreak, an early warning system helps to alert on the increasing predicted risk of dengue based on the weather forecast and the other parameters to effectively target limited resources to the hotspot area (Lowe et al. 2013). This requires serious concern from local authorities, health professionals and the community to combine efforts for vector control and prevention.

However, our study also has some limitations. Firstly, there was under-reporting of dengue cases to an unknown degree (Shepard et al. 2012). Even if there were unreported dengue cases, our study still provides insights, the pattern of dengue occurrences were consistent over time when we compared with the clinically suspected dengue cases (results not shown) and this is the only national surveillance data that is available. Secondly, due to data limitations we could not include unmeasured confounders such as variation in virus serotype and variation in dengue vectors population density. Nevertheless, in hyperendemic areas, analytical models based on syndromic case surveillance can be more informative than the vector densities, as the dengue virus transmission can occur even when dengue vectors population densities are low because of the repeating feeding behavior (Kuno

1995; Scott and Morrison 2010b). Thirdly, we used the aggregated number of dengue cases and weather parameters from one principal weather station. Using weather parameters as close to the highly clustered dengue cases area could reduce the spatial discrepancies between the hotspot area and the location of weather station.

## **5 Conclusions**

Temperature, rainfall and wind speed all influence dengue transmission in high population density areas. The estimated lagged effects and patterns, in accordance with the time necessary for the development of the dengue vectors, the EIP, and the incubation period in human body, as well as the onset of dengue symptoms, can be adapted in the vector control and prevention plan. The relationship found in this study helps to shed light on the link between weather and dengue for the development of future dengue prediction models while vaccines are not available.

## **Acknowledgments**

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**Chapter V:**  
**Assessment of land use factors associated with  
dengue cases in Malaysia using Boosted  
Regression Trees**

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## **Abstract**

The transmission of dengue disease is influenced by complex interactions among vector, host and virus. Land use such as water bodies or certain agricultural practices have been identified as likely risk factors for dengue because of the provision of suitable habitats for the vector. Many studies have focused on the land use factors of dengue vector abundance in small areas but have not yet studied the relationship between land use factors and dengue cases for large regions. This study aims to clarify if land use factors other than human settlements, e.g. different types of agricultural land use, water bodies and forest are associated with reported dengue cases from 2008 to 2010 in the state of Selangor, Malaysia. From the correlative relationship, we aim to generate a prediction risk map. We used Boosted Regression Trees (BRT) to account for nonlinearities and interactions between the factors with high predictive accuracies. Our model with a cross-validated performance score (Area Under the Receiver Operator Characteristic Curve, ROC AUC) of 0.81 showed that the most important land use factors are human settlements (model importance of 39.2%), followed by water bodies (16.1%), mixed horticulture (8.7%), open land (7.5%) and neglected grassland (6.7%). A risk map after 100 model runs with a cross-validated ROC AUC mean of 0.81 ( $\pm 0.001$  s.d.) is presented. Our findings may be an important asset for improving surveillance and control interventions for dengue.

## 1 Introduction

Dengue fever (DF) and dengue haemorrhagic fever (DHF) are the most important vector-borne diseases (VBD) in tropical areas (Gubler 2006). In recent decades the risk of dengue infection has increased dramatically not only in tropical, but also in sub-tropical regions (World Health Organization 2012b). There are between 50 and 100 million dengue infections every year, and more than 500,000 cases are hospitalized (Gubler 2006). Dengue transmission is influenced by a complex set of factors including the environment, climate and weather, human behavior and dengue virus serotype-specific herd immunity among the human population (Hay et al. 2000; Halstead 2008; Cheong et al. 2013). Understanding the association between environmental factors and VBD is essential for better preventing and controlling disease transmission (Armien et al. 2008; Dambach et al. 2009).

In many countries, such as in Malaysia, dengue disease has been endemic (Halstead 2008). Since the first reported case in Malaysia in 1901 (Skae 1902) peaks of dengue cases have been reported in 1974, 1978, 1982 and 1990, and the total number of dengue cases has increased (Lam 1993). All four serotypes circulated, the predominant serotype identified was DEN-3 from 1992 to 1995, DEN-1, DEN-2 and DEN-3 alternated in recent years (Arima and Matsui 2011). According to the Ministry of Health Malaysia, the incidence rate of DF was the highest ever in 2010 (148.73 per 100,000 population) and the mortality rate of DHF was 0.42 per 100,000 population (Ministry of Health Malaysia 2011b). These figures significantly exceed the national target of Malaysia, which aims for the incidence rate of DF to be less than 50 cases per 100,000 population (Ministry of Health Malaysia 2011b).

Dengue disease is often called an “urban” disease, with the *Aedes* mosquitoes, both *Aedes aegypti* and *Aedes albopictus*, mainly found breeding in artificial containers in areas where high population density appears (Gubler and Clark 1995; Chen et al. 2005a). However, *Ae. albopictus* has also been found in natural environments (Gubler 1998a; World Health Organization 2008b). Entomological studies showed that dengue vectors have been captured in vegetated areas (Vezzani et al. 2005; Hayden et al. 2010), orchards (Vanwambeke et al. 2007b), rubber plantations (Sumodan 2003; Paily et al. 2013), marshy swamp (Sarfraz et al. 2012) and even in brackish waters (Ramasamy et al. 2011; Idris et al. 2013). In a study of dengue seroprevalence taken from the national database of the Malaysian cohort study of 2008 (Muhammad Azami et al. 2011), from the 1000 randomly

selected adults aged 35-74, there was no significant difference in the seroprevalence rate between adults living in urban and rural areas. Therefore, diverse land use types in the neighborhood of human settlements may also provide a suitable habitat for *Aedes* mosquitoes. Although human settlements have been identified in earlier studies as being highly associated with dengue cases (Gubler 2006), we hypothesized that other land use types are also associated with the occurrences of dengue cases. In this study, our research questions are:

- (1) Which land use factors are associated with dengue cases in Selangor state, Malaysia?
- (2) What is the spatial pattern of dengue risk based on the identified correlative relationships?

Many studies have focused on the relationship between *Aedes* mosquitoes density and environmental factors in specific local hotspots of dengue (Rohani et al. 2001; Chen et al. 2005a; Wan-Norafikah et al. 2012). There are also some studies that have evaluated the spatial risk factors of dengue cases on a local scale (Nazri et al. 2009; Shafie 2011). To our knowledge, this is the first study assessing the land use factors associated with dengue cases in Malaysia on a state-wide level.

## **2 Data and methods**

### **2.1 Study area**

Selangor covers an area of 7,930.20 km<sup>2</sup> and is located between 2°35'N to 3°60'N and 100°43'E to 102°5'E (Figure V-1). We selected the state of Selangor because of its large number of dengue cases, which accounted for 41.1% (56,305 cases) of all reported dengue cases in Malaysia (Department of Statistics Malaysia 2011a). Secondly, Selangor has the highest population density and gross domestic product per capita of all states in Malaysia (Abdullah and Nakagoshi 2006). Thirdly, Selangor is geographically heterogeneous and displays a large variety of land use and related environmental characteristics with large urban areas, agricultural use, forests and wetlands (Abdullah and Nakagoshi 2006).

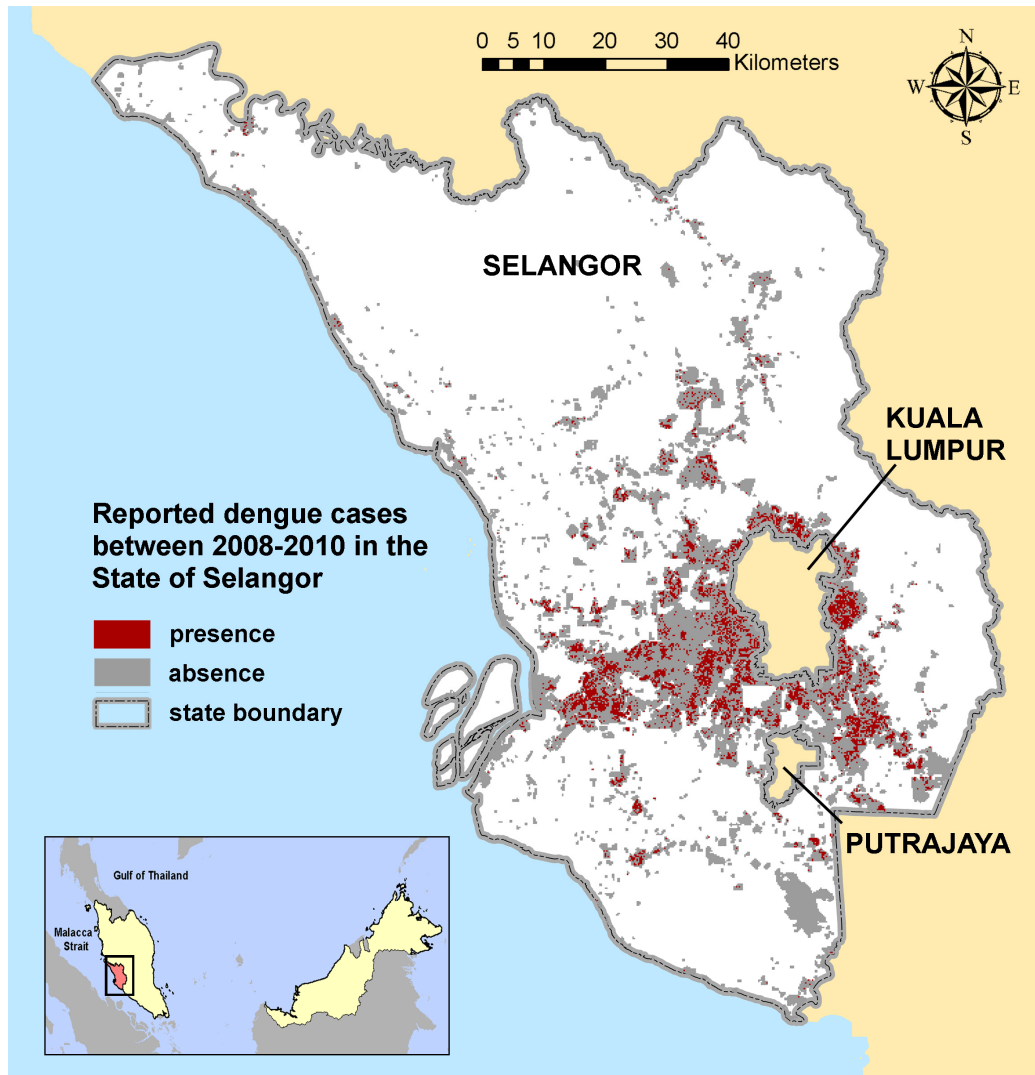


Figure V-1: Study area: State of Selangor, Malaysia with presence and absence of dengue cases in 200 m × 200 m grid cells

## 2.2 Data sources

We obtained dengue data for the state of Selangor for the years 2008, 2009 and 2010 from the Disease Control Division, Ministry of Health Malaysia. We used only those dengue cases that were confirmed by the serological tests IgM capture enzyme-linked immunosorbent assay (ELISA) with single positive IgM, following earlier studies (Chadwick et al. 2006; Krishnan et al. 2012).

We obtained a land use map of the year 2006 from the Department of Agriculture Malaysia. This map is based on imagery from Landsat 7 (30 m × 30 m resolution) and SPOT 4 (20 m × 20 m resolution) satellite imagery, a topographic map (L7030, 1:50,000) and reference data from field trips. According to the official accuracy assessment, less than 5% of the land use classes have been incorrectly classified.

### 2.3 Explanatory variables

We selected 15 land use variables that could be associated with suitable habitats for *Aedes* mosquitoes according to a detailed literature review and dengue expert knowledge. The land use variables are coconut and cocoa plantation, animal husbandry, mixed horticulture, orchard and farm, tea plantation, mining, oil palm plantation, neglected grassland, rubber plantation, paddy field, swamp forest, forest, open land, human settlements and water bodies. The detailed map of each land use variable is shown in Supplementary Figure C-1.

In coconut and cocoa plantations, natural breeding habitats such as plant axils, coconut husks, coconut shells and coconut floral spathes containing organic debris were identified as suitable habitats for *Aedes* mosquitoes (Rohani et al. 2001; Thavara et al. 2001; Chareonviriyaphap et al. 2004). Land being used for animal husbandry is a potential habitat for the dengue vector as *Ae. albopictus* also feed on domestic chickens (Richards et al. 2006). Mixed horticulture describes the area of mixed cultivation of gardens, orchards and nurseries with flowers, fruits, vegetables and ornamental plants surrounding the human settlements where mosquitoes find several suitable breeding possibilities (Nazri et al. 2009). Furthermore, *Aedes* mosquitoes have been found in ornamental plants (Wan-Norafikah et al. 2012) including the water-holding bromeliad axils (Mocellin et al. 2009) in mixed horticulture. The presence of fruit trees and vegetable farms – which is classified here as orchard and farm land including vegetation farming, fruit trees and mixed cropland – has been seen to increase the probability of finding *Aedes* mosquitoes (Chareonviriyaphap et al. 2004; Vanwambeke et al. 2007b). In tea plantation areas *Aedes* mosquitoes have been found in discarded tires, tins and plastic cups near human inhabitations (Amala and Anuradha 2011).

*Aedes* mosquitoes have also been found in old mining areas, in particular in flooded disused gold mine shafts and wells (Russell et al. 1996). They have been identified in suburban areas surrounded by oil palm plantation (Ponlawat and Harrington 2005) and in the neglected grassland of a cemetery (Vezzani et al. 2005). Furthermore, *Aedes* mosquitoes have also been found in rubber plantations, particularly in the rubber tree hole (Paily et al. 2013), in suspended sap-collecting containers without rain guards (Sumodan 2003) and discarded water storage containers (Chareonviriyaphap et al. 2004). Paddy fields and swamp forest containing standing water from 2.5 cm to 30 cm in depth serve as a rainfall catchment area, and are another suitable habitat for the dengue vector (Sarfraz et al. 2012). *Aedes* mosquitoes have been captured from sites inside the forest, as far as 1 km



from houses (Lourenco-de-Oliveira et al. 2004), and in tree holes, bamboo stumps and rock pools in the forest area (Amala and Anuradha 2011).

Artificial water containers that provide nutrients for the *Aedes* mosquitoes have been found in open land, i.e. areas that are ready for construction or agriculture and have only little or no vegetation coverage with a dominance of sand and rocks (Chang et al. 1997; Gleiser and Zalazar 2010; Dom et al. 2012). In several studies, *Aedes* mosquitoes were identified in human settlements where they were found to breed in a variety of water filled containers (Nyamah et al. 2010). Another favorable dengue vector habitat is natural reservoirs including various types of water bodies, e.g. roadside ponds, pools, streams and other containers found on river banks (Uribe et al. 2008).

#### **2.4 Data preprocessing**

In a first step, we geocoded the addresses of the dengue cases with totals of 11,664, 10,482 and 8,300 for the years 2008, 2009 and 2010. The geocoding accounted for 92.16% (2008), 93.44% (2009) and 94.87% (2010) of the addresses; the others had to be excluded due to missing values. We used the Google Maps Application Programming Interface (API) that showed high quality geocoding services (Roongpiboonsopit and Karimi 2010; Cui 2013) and has successfully been used for the geocoding of health care facility locations (Gu et al. 2010) and mosquito survey in earlier studies (Neteler et al. 2011).

Secondly, we calculated a systematic 200 m grid of the projected coordinate system Kertau (RSO)/RSO Malaya (m) for the state of Selangor. This follows the official definition of the Ministry of Health Malaysia that a dengue outbreak is constituted by an incidence of two or more dengue cases in a location where the onset dates of the cases are less than 14 days apart and the cases are within 200 m of each other (Ministry of Health Malaysia 1986, Ministry of Health Malaysia 2009). Next, only those grids that are at least partly covered by human settlements were included in the model. We hereby avoid a modeling bias of dengue absence data in areas where no human settlement and therefore no potential cases could be recorded because we analyse the patient's home address that falls into the human settlements class of land use. We then classified 6,344 grid cells as presence data (1) where at least one dengue case was reported between 2008 to 2010. The remaining 29,662 grid cells with a certain proportion of human settlements but no reported dengue cases were considered as absence (0) data. Hence, our target, i.e. response variable, is a binary

presence/absence value of at least one reported dengue case in a 200 m grid cell that includes human settlement area.

We then used the focal statistics geoprocessing function of ArcGIS's Spatial Analyst (Environmental Systems Research Institute, Inc.) to obtain the proportion of coverage of each land use factor (Supplementary Figure C-1) within a rectangular moving window of 1 km radius surrounding each grid cell for the spatial neighborhood analysis. The radius was used in order to consider the maximum flight range of the mosquito during its life span and the potential dengue virus (DV) transmission with human mobility that has also been applied in other studies (Maciel-de-Freitas et al. 2006; Sarfraz et al. 2012). After data compilation, and in order to avoid using highly correlated variables in the subsequent models, we checked for the pair-wise Spearman rank correlation between all predictor variables.

## **2.5 Boosted Regression Tree analysis**

To identify the association between the land use factors and the reported dengue cases we apply Boosted Regression Trees (BRT), a machine learning algorithm developed by Friedman et al. (2000). BRT are very flexible and capable of dealing with complex responses, including nonlinearities and interactions (Elith et al. 2008). Compared to generalized linear model (GLM) and generalized additive model (GAM) models they have been shown to yield better results e.g. in terms of prediction capability (Oppel et al. 2012; Coutts and Yokomizo 2014). BRT have performed well in disease modeling (Stevens and Pfeiffer 2011) and have been applied in various study domains, from predicting the distribution of organisms (Elith et al. 2008), to comparing the factors of cropland abandonment (Müller et al. 2013). We applied the BRT using the R version 3.0.2 (R Development Core Team 2013), package "dismo" version 0.8-17 (Hijmans et al. 2013) and package "gbm" version 2.1 (Ridgeway 2013).

BRT combine boosting and regression trees in a single algorithm. Regression trees grow with recursively binary splits of the data until some stopping criterion is met. Despite its easier visual interpretation of the interactions, capability to adapt predictor variables of any type (numeric, binary, categorical, etc.), and insensitivity to outliers, decision trees are prone to bias and not as accurate as other statistical methods (e.g. GAM). Boosting based on the stochastic gradient boosting (Friedman 2002) improves the decision trees by minimizing the loss function (deviance) at each tree split. Stochastic gradient boosting

applies randomness into the sequential fitting (De'ath 2007). We use a bagging factor of 0.5 as suggested by Friedman (2001). The stagewise approach means that the first regression tree is fitted to the dependent variable while randomly selecting 50% of the training data (bagging). The following tree is then fitted to the residuals of the first tree and the fitted values are added to the logit of the fitted probability. The model is then updated to contain two trees and the residuals from this updated model are calculated. This process is then further iterated until reaching the defined stopping criterion (Elith et al. 2008).

The model building process is best with slower learning rates (*lr*), also known as shrinking rate. The number of splits levels of each tree, also called tree complexity (*tc*), determines the degree to which predictors may interact with each other in relation to the response. More levels of interactions are explained with a higher *tc*. In this study, we fit the model with a “bernoulli” distribution as we are dealing with presence and absence data, as explained above. We test for several combinations of the *lr* (0.025, 0.05, 0.1) and *tc* (3, 4, 6, 8, 9, 10) parameters. The model with the highest cross-validated Receiver Operating Characteristic Area Under the Curve (ROC AUC) score was selected as the most optimal settings (Hastie et al. 2009).

To obtain a more valid and reliable result, the BRT model runs were repeated in 100 iterations (Bhatt et al. 2013). The mean and standard deviation of the ROC AUC scores among the 100 iterations were reported. We then calculated a risk map to show the spatial pattern of probability of occurrence of dengue cases on the 200 m grid level for the state of Selangor, Malaysia. We therefore get the mean of the 100 iterations of prediction value. As a result we receive a risk value scaled between 0 and 1 where 0 means low risk for dengue and 1 means high risk for dengue based on the identified associations between land use variables and dengue cases.

BRT delivers the relative importance of the predictor variables in the model (Friedman 2001). The relative importance is based on the number of times a variable is selected for splitting, weighted by the squared improvement and averaged over all trees (Friedman and Meulman 2003). The relative importance of each variable is then scaled so that the sum adds to 100 as percentages. A higher percentage of a variable indicates a stronger relative importance of this variable on the response. With 15 predictor variables in our model, only the relative contribution above the randomness threshold ( $100\%/\text{number of predictor variables}$ ,  $100\%/15 = 6.67\%$ ) can be interpreted (Müller et al. 2013). To better interpret the fitted functions, we used partial dependence plots to visualize the relative importance of the predictor variables on dengue cases (Friedman 2001), as well as rug plots to show the

percentile distribution of the response variables. To aid interpretation, all plots were smoothed using a spline function.

### 3 Results

From the correlation analysis we found no high rank correlations ( $\rho > 0.70$ ) between any pair of predictor variables so that we continued with a model that included all land use variables. The selected model was fitted using a  $lr$  of 0.05,  $tc$  of 9 and a total of 2,150 decision trees, and showed a cross-validated ROC AUC score of 0.81. The ensemble prediction map after the 100 iterations resulted in a performance ROC AUC score of 0.81 ( $\pm 0.001$  s.d.). These predictions were represented in the risk map of dengue where we identify distinct spatial patterns of different probabilities of occurrence of dengue cases for each grid cell (Figure V-2). The spatial patterns of predicted dengue cases overall coincide very well with the observed cases that are shown in Figure V-1. Most of the reported high dengue risk areas are identified, while only few are not correctly identified. Our predictions of high dengue risk (Figure V-2) seems to be more focused on the central region of Selangor, with clusters at the border to Kuala Lumpur, west and south-east of Selangor. The presence of dengue cases that were scattered in the northern and southern part of Selangor (Figure V-1) is mainly predicted with low dengue risk (Figure V-2). Besides, a large share of the presence of dengue cases in the central region of Selangor is predicted with the probability of occurrences of dengue cases between high and low risk (Figure V-2).

In addition to the spatial pattern of probability of occurrence of dengue cases we identified the relative importance of the predictors in the BRT model (Figure V-3) and the correspondent partial dependence plots for each predictor and the risk of dengue presence (Figure V-4). The selected model demonstrated that only 5 out of 15 predictor variables had a considerable importance, i.e. above the randomness threshold of 6.67% (Figure V-3). The partial dependence plots in Figure V-4 further show the influence of each of the five predictor variables on the dengue occurrences, taken that every other variable has been kept to its mean value. We observed that the proportion of cover of human settlements in a grid cell substantially contributed to the models with a relative importance of 39.2% (Figure V-3), with a nearly linear increasing association with the occurrence of dengue cases (Figure V-4(a)). Water bodies including drains, lakes and rivers followed as the second most important predictor of the dengue cases (relative importance of 16.1%)

(Figure V-3) with a slightly decreasing non-linear association (Figure V-4(b)). The model indicates an optimum for the occurrence of dengue in a grid cell with the presence of water bodies of around the value of 25 to 50 ha of area (ca. 5 to 10% of the 1 km grid cell) (Figure V-4(b)). Mixed horticulture, normally related to the suburban orchards and gardens surrounding the human settlements, showed a relative importance of 8.7%, with an increasing non-linear association with the reported dengue cases (Figure V-3 and V-4(c)). The coverage of mixed horticulture, particularly above ca. 200 ha (ca. 40% of the 1 km grid cell) depicted a sudden increase of dengue risk. Similarly, the proportion of area covered by open land, with a relative importance of 7.5% (Figure V-3), also showed an increasing non-linear association with the occurrence of dengue cases (Figure V-4(d)), with particularly higher dengue risk in grid cells with ca. 150–200 ha of open land (ca. 30% to 40% of the 1 km grid cell). Finally, neglected grassland, with a relative importance of 6.7% (Figure V-3) in the model, showed a decreasing linear association with the occurrence of dengue (Figure V-4(e)).

The other predictor variables with relative importance below the randomness threshold are coconut and cocoa, animal husbandry, orchard and farm, tea plantation, mining area, oil palm, rubber plantation, paddy field, swamp forest, and forest. The dependency profiles for these predictor variables are not shown in the Figure V-4.

#### **4 Discussion**

In this study, we aimed to characterize associations between different land use factors and dengue cases in Selangor state, Malaysia. Moreover, we wished to show the spatial patterns of dengue risk based on the identified correlative relationships. Our results demonstrate that we are able to explain the different associations between land use factors and dengue cases from a state level perspective.

The study showed that human settlements and non-agricultural areas largely determined the occurrence of dengue cases. Larger shares of human settlement coverage in the neighborhood are associated with higher numbers of dengue cases. One of the reasons for this may be higher population density in areas with more human settlements, leading to higher human biting rates. Increased human biting rates offer opportunities for the *Aedes* mosquitoes to acquire DV by biting an infected person and then to transmit the virus after becoming infected (Scott and Morrison 2010a). Our findings are in line with those of other authors, such as e.g. a study in one suburban city in Selangor, Subang Jaya, where they

found that most dengue cases occurred in urban areas (Nazri et al. 2009). The habitats of *Aedes* mosquitoes were found in artificial containers in areas related to human activities, but disparities were identified between types of human settlements (Vanwambeke et al. 2007a). Although no variation of human settlements was investigated in this study, previous entomological surveillance has provided insightful information. *Aedes* mosquitoes were found indoors and outdoors in human settlements, especially in culverts, water compartments, metal drums, plastic drums, pails, gully traps, discarded containers, construction sites, solid-waste dumps, open spaces and factories (Teng and Singh 2001; Chen et al. 2009; Nyamah et al. 2010).

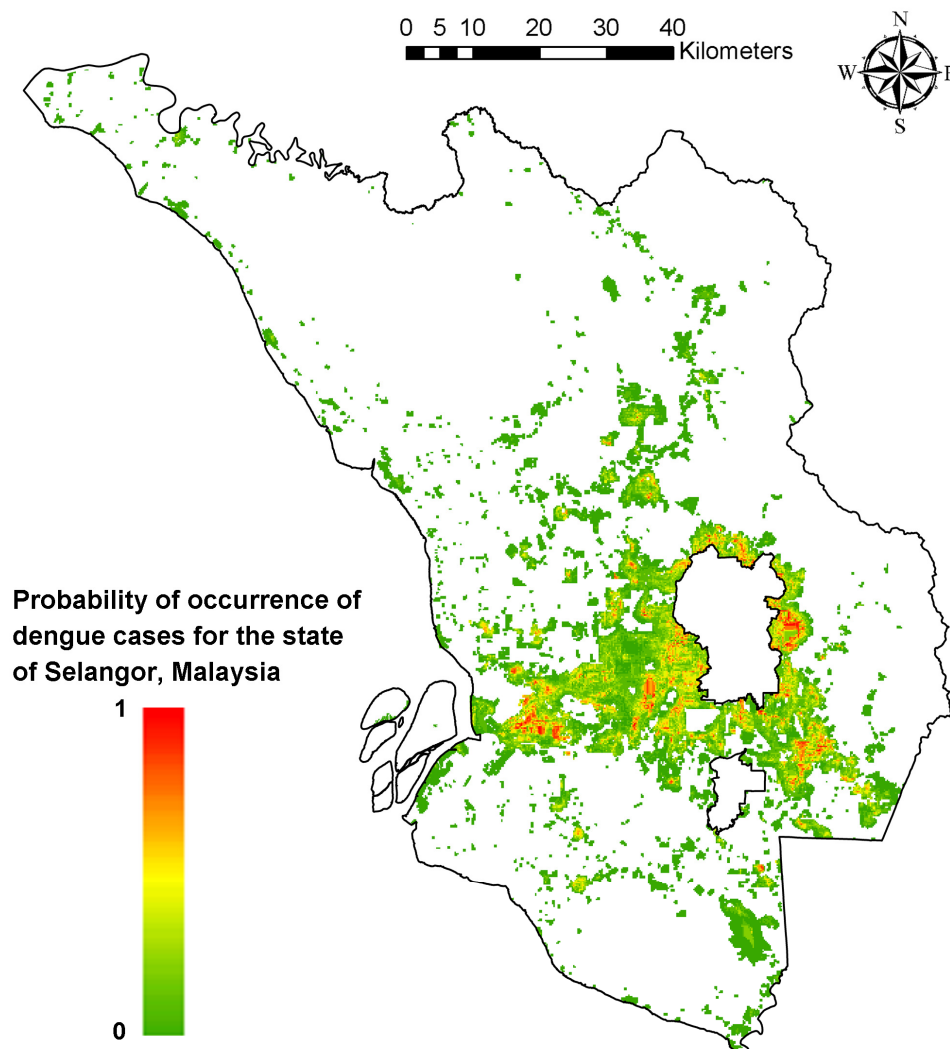


Figure V-2: Probability of dengue occurrence at  $200 \text{ m} \times 200 \text{ m}$  spatial resolution of the mean predicted map area under the receiver operator curve of  $0.81 (\pm 0.001 \text{ s.d.})$  from 100 boosted regression tree model iterations. High probability of dengue occurrences area is shown in red and low probability of dengue occurrences area in green.

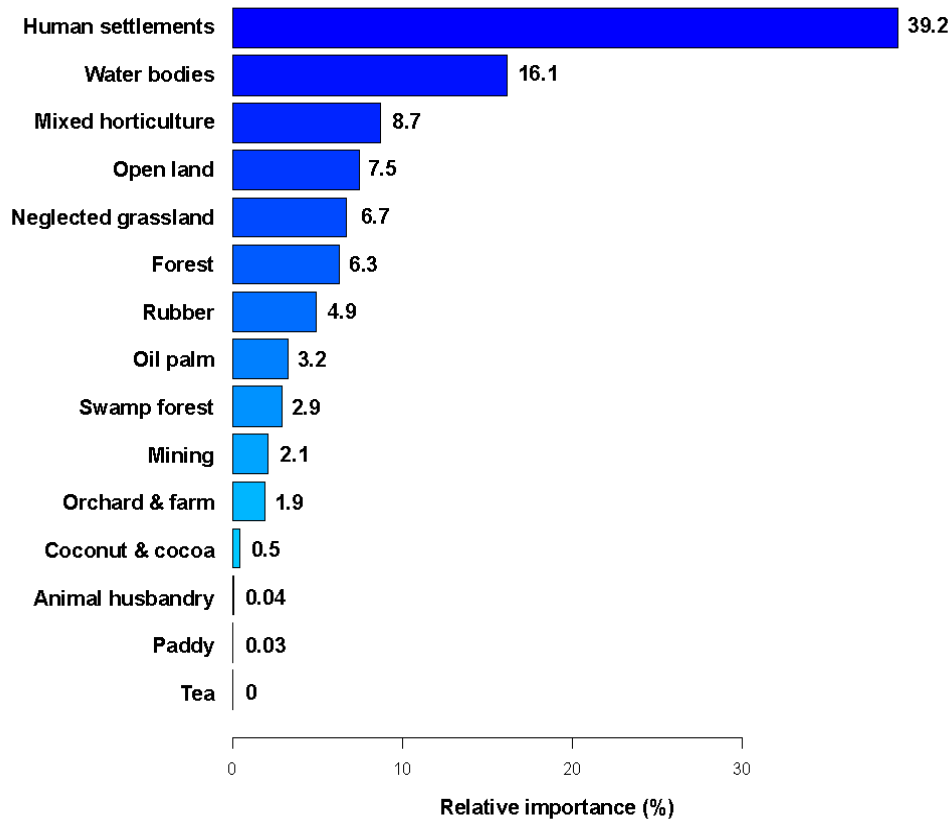


Figure V-3: Relative importance of explanatory variables.

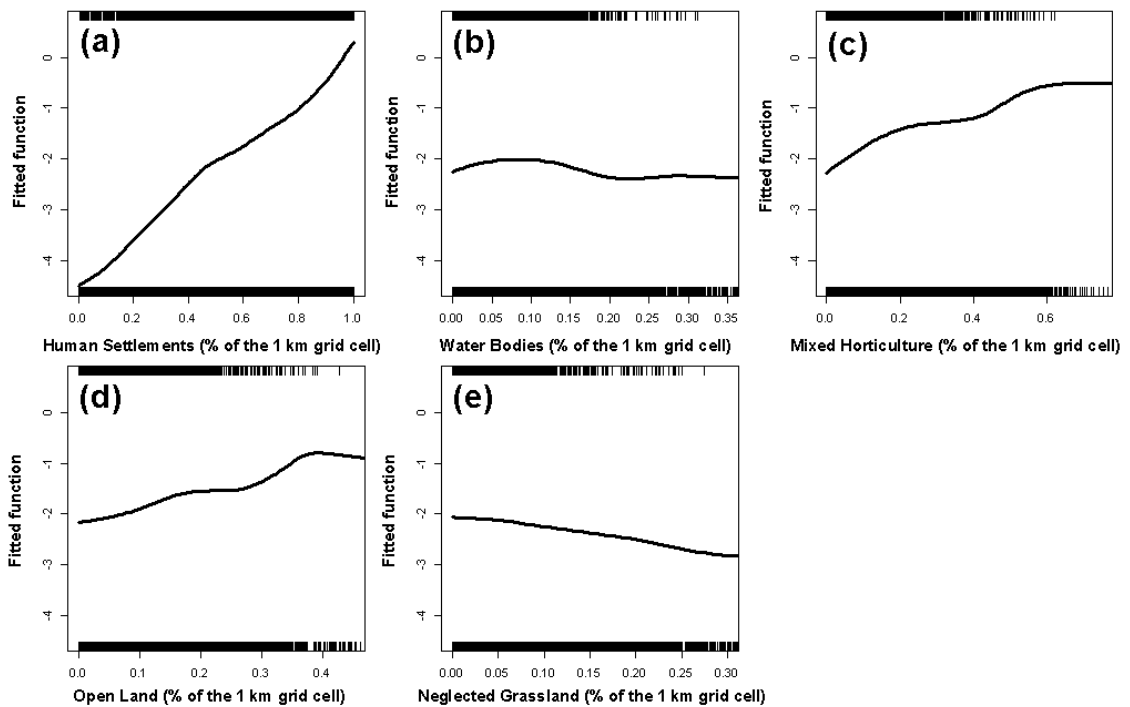


Figure V-4: Smoothed partial dependence plots for the five most influential land use factors for dengue cases; (a) human settlements, (b) water bodies, (c) mixed horticulture, (d) open land, (e) neglected grassland. The density of presence and absence of dengue cases are represented in rug plots on the top and bottom along the variable axis.

In addition to human settlements, the spatial patterns of occurrence of dengue cases were also greatly influenced by water bodies. In a 1 km buffer zone surrounding dengue cases, a share of water bodies of about 25-50 ha exercise the highest influence on the occurrences of dengue cases. Although delineation of the type of water bodies was not possible in this study, we infer that drains, small ponds and streams would be the water bodies of about 25-50 ha. Of particular relevance in this regard is the fact that Malaysia has an open concrete drainage system (Ghani et al. 2000; Zakaria et al. 2004). Our study is hence in line with other entomological studies in Malaysia that found that shallow clean stagnant water in drains served as a suitable habitat for the *Aedes* mosquitoes (Lee 1991; Chen et al. 2005a; Wan-Norafikah et al. 2012). Other water bodies including roadside ponds, pools and streams are also considered as natural reservoirs for *Aedes* mosquitoes (Uribe et al. 2008).

Mixed horticulture also contributes to the high frequency of dengue cases. The higher the coverage of mixed horticulture, particularly above ca. 200 ha, the higher the influence on dengue cases. Mixed horticulture is distributed throughout the suburban area. Orchards provide shade and temporary stagnant water on plants or in artificial containers that are suitable habitats for *Aedes* mosquitoes (Vanwambeke et al. 2007a). Vanwambeke et al. (2007a) also showed that the probability of finding the *Ae. albopictus* mosquito larvae in orchards, peri-urban settlements or villages was higher than in other land cover types. Furthermore, the gardens or ornamental plants surrounding the human settlements were also positively associated with dengue cases. Teng et al. (1999) found that containers used for planting and containers for watering plants formed part of the breeding habitats for *Aedes* mosquitoes.

More open land coverage in the 1 km vicinity shows a positive association with dengue cases, especially when open land covers an area of 150 to 200 ha. Natural gullies filled with rainfall are a good reservoir for *Aedes* mosquitoes (Delatte et al. 2013). Such natural reservoirs are available all year round and are often neglected as vector control largely targets human settlements (Delatte et al. 2013). Furthermore, potential breeding sites have been found in artificial containers discarded by workers in open land (Chang et al. 2011).

*Aedes* mosquitoes are free to proliferate without much dengue control intervention, especially in abandoned land cover types such as neglected grassland. Our study shows that a small patch of neglected grassland of ca. 25 ha would be a suitable reservoir for *Aedes* mosquitoes. Microhabitats that are shaded and vegetated are favourable habitats for *Aedes* mosquitoes to breed in (Tun-Lin et al. 1995; Vezzani et al. 2005). Another study



also found that wet grassland was associated with suitable habitats for dengue vector reproduction (Li et al. 2013).

Our results suggest that land use factors are an important component to be considered in the strategic planning and implementation of vector control. This finding can be used as empirical evidence from the environmental perspective for Integrated Vector Management (IVM) (World Health Organization 2012c) at the state level. IVM has been found more effective than other vector control approaches in that it represents a rational decision-making process that allows the optimal use of resources for vector control, addressing all risk factors from parasite to vector, human to environment (Erlanger et al. 2008; World Health Organization 2012c). Although Malaysia is now adopting this strategy, there is still a lot to be done to ensure effective management with cost-effective programmes, intersectoral action, regulatory and operational standards, subsidiarity and sustainability (Mnzava et al. 2006; Horstick et al. 2010). For Selangor, we suggest more combined vector control intervention should be focused on human settlements, water bodies, mixed horticulture, open land and neglected grassland.

The risk map that we provide can offer a helpful resource for the local vector control programme for the state of Selangor (Figure V-2). The prediction map differentiates between areas of higher and lower risk. Moreover, the prediction model can be transferred to other locations with similar environmental settings as applied in other studies for predicting avian influenza risk (Van Boeckel et al. 2012) and fish species distribution (Pittman and Brown 2011).

However, our study is constrained by four main aspects. Firstly, we use correlative models which cannot define a causal relationship. Although the relationships identified are not causal, they are suggestive for vector control intervention and are in line with earlier studies that use field knowledge and focus on the processes within the disease cycle (Martin et al. 2011; Bhatt et al. 2013). Secondly, special care needs to be taken in interpreting the relationship between land use factors, dengue cases and habitats of *Aedes* mosquitoes. The link between habitat and land cover characteristics is not always straightforward and is influenced by landscape structure (Vanwambeke et al. 2007b). Nevertheless, knowledge of mosquito ecology from other studies helps explain this relationship. Thirdly, we could not include human lifestyles and habits in the study due to a lack of data, e.g. on housing with air-conditioning, human mobility from house to workplace, recreational habits both outdoor or indoor, and self-awareness of personal protection – all of which could influence the occurrence of dengue cases and would be

worth including in a more detailed study (Barmak et al. 2011). Fourthly, this study focused on the spatial and did not consider temporal effects associated with rapid climatic changes, changes in the composition of animal host population, abrupt land use/cover change, political and economic change (Lambin et al. 2010). However, our study indicated that there is a significant relationship between land use factors associated with higher frequencies of dengue cases and, moreover, we further quantified these relationships and depicted the risk of dengue on a state-wide level.

## **5 Conclusions**

Our study has shown that BRT are a useful tool to model the nonlinear and complex association between dengue and land use factors and to derive a risk map. This approach can not only be applied to other vector-borne diseases, but may also be transferred to other endemic regions. More detailed consideration of processes related to each land use type is a possible direction for future research. An equal focus on parasite, vector, human and environmental factors is needed for planning, implementing and evaluating the vector control interventions to reduce or eliminate dengue transmission.

## **Acknowledgments**

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## **Chapter VI: Synthesis**

## 1 Summary

Global change has a great impact on human health. One of the impacts is the epidemic nature of vector-borne disease, specifically dengue disease that is also known as a global disease burden. This dissertation provides a new strategy and perspective to address the two questions that are commonly asked in public health research. First, where and when is the high-risk disease cluster? Chapter III showed that vulnerability mapping at more than one aggregation level provided insights to confirm and compare the potential disease clusters. This can assist health interventions particularly in highly endemic large regions. Second, what are the relationships of the disease cluster with environmental factors? Chapter IV suggested that dengue was associated with weather, showing a nonlinear temporal effect. The lag period of weather that preceded high dengue occurrences could be identified. This can be an essential input parameter for early warning systems. Chapter V identified several land use types that spatially determined disease occurrences. Risk maps were generated based on the correlative relationship. This is important so as to suggest better preventive measures and vector control planning at a time when dengue vaccine is still not available. The suggested strategies can be transferred to other diseases or study areas in similar settings.

My dissertation addressed the research questions in three core chapters. In the following, I summarize both the study results and discussion for each research question.

Research questions (1), (2) & (3) (Dissertation Chapter III):

- (1) *What is the spatio-temporal pattern of dengue cases at the address level in Selangor and Kuala Lumpur?*
- (2) *What is the spatio-temporal pattern of dengue cases at the sub-district level in Selangor and Kuala Lumpur?*
- (3) *What are the insights from both spatial levels that provide better information to assist health interventions?*

In Chapter III, disease mapping and clustering methods were employed to study the spatio-temporal pattern of dengue cases at both the address and sub-district levels. At address level, outbreaks were concentrated in the central and south-east region of the study area mainly from December to March for the three-year period. From the entire detected outbreak, two-thirds occurred in the sub-district with a population density of more than

2000 people per kilometer square. The results at sub-district level showed that the most likely cluster was also concentrated in the central region and in the high population density region with more than 2000 people per kilometer square. Six out of seven sub-district clusters occurred from January to March in the study period. Both levels showed similar high risk areas in general but differed in detail.

Comparing both the address and sub-district level assisted in identifying differences and coincidences of high-risk cluster dengue areas. Mapping at the address level alone identified only the individual cluster of outbreak areas but with no underlying background population to provide complete risk estimation and comparison. In contrast, the sub-district level considered the background population density, but suffered from possible overestimation by including non-high risk areas in clusters due to the non-flexible circular buffer shape and modifiable area unit problem resulted from the varying aggregation scale. Therefore, this study exhibited the advantages of combining both levels in a two-fold procedure that can improve the ability to identify the outbreak clusters. First, by overlaying the spatio-temporal patterns of each level, the clusters are targeted in more precise locations. Second, the excess risks which concentrated at cross-border regions are identified, e.g. more overlapping high-risk clusters at the border of sub-districts.

Disease mapping and clustering as demonstrated in Chapter III identified the high-risk cluster dengue area. Most dengue disease spatio-temporal studies suggest disease clusters on one geographical level (Mondini and Chiaravalloti-Neto 2008; Cuong et al. 2013). By combining more than one geographical level, close to the real situations, spatio-temporal cluster analysis can be included in local scale routine operational epidemiological surveillance (Eisen and Lozano-Fuentes 2009). This strategy can be applied to routine dengue surveillance in order to improve the detection of high risk areas that guide continuous vector control planning. Even if additional resources may be needed for patient residencies, the initial high-risk cluster areas are better targeted.

Research question (4) (Dissertation Chapter IV):

- (4) *What are the relationships between weather effects and dengue disease in Selangor, Kuala Lumpur and Putrajaya?*

In Chapter IV, the relationship between the weather parameters and the number of daily dengue cases is assessed. The minimum temperature, bi-weekly accumulated rainfall and wind speed are included in the model, based on the significant GAM relationship. In the study area the highest significant positive association between minimum temperature and

dengue cases is delayed by 51 days. This almost two-month lag period includes the time for the mosquitoes to develop from eggs, mosquitoes to become infected with the dengue virus through a blood meal, EIP, the transmittance of the virus to humans in the gonotrophic cycle, and the intrinsic incubation period of the virus in the infected human until dengue symptoms are observed. Higher temperatures shorten the EIP and the gonotrophic cycle (Chan and Johansson 2012) and may lead to an intensification of the dengue outbreak.

Chapter IV also showed that bi-weekly cumulated rainfall is positively associated with dengue cases and that the highest effect is delayed by 26-28 days. The one-month lag period showed that rainfall not only affects the aquatic mosquito populations, but also the adult mosquito, with flight activity and host-seeking behavior becoming more active with rainfall-induced increased near-surface humidity. Suitable breeding sites such as discarded containers, car tires, tree holes, and blocks of cement are increased with higher rainfall.

Results also showed that dengue cases are negatively associated with increased wind speed. This is due to strong wind suppressing the host-seeking flying activity of dengue mosquitoes in oviposition and contact with humans. However, there was a slight increase in dengue cases within the threshold where dengue mosquitoes can fly freely, from 3 knots to 5 knots.

The effects of temperature, rainfall and wind speed on dengue cases discovered in Chapter IV are important parameters for designing the local dengue early warning system, alongside other factors such as population density, dengue virus circulation, effort of vector control and vector density. In the study area, two months after high minimum temperature and one month after high rainfall higher dengue cases may be triggered. Therefore, the temporal information is valuable for planning dengue vector control intervention based on the weather forecast.

This study demonstrated a new perspective for the study of the non-linear lag-effect interaction between short-term weather and infectious disease cases. DLNM is a newly developed method and has been used to study the association of climate and mortality (Armstrong 2006; Guo et al. 2010), but is still not widely applied in the study of infectious disease. In particular, it is a very helpful tool for dealing with lag effects that describe simultaneous non-linear and delayed dependencies. Many studies have estimated lag effects using regression function GLM (Sriprom et al. 2010; Gomes et al. 2012), GAM (Chen et al. 2012; Colón-González et al. 2013) and ARIMA (Wu et al. 2007; Luz et al.

2008). DLNM combines the non-linear exposure-response regression function with the additional lag-response function. The associations are further exhibited with an animated movie clip as included in the online published version of Chapter IV.

Research questions (5) & (6) (Dissertation Chapter V):

- (5) *Which land use factors are associated with dengue cases in Selangor state, Malaysia?*
- (6) *What is the spatial pattern of dengue risk based on the identified correlative relationships?*

In Chapter V, the relationships of dengue disease with land use factors were assessed and discussed. The selected model showed a cross-validated ROC AUC score of 0.81 ( $\pm 0.001$  s.d.) after 100 iterations. The most important land use factors are human settlements (model importance of 39.2%), followed by water bodies (16.1%), mixed horticulture land (8.7%), open land (7.5%) and neglected grassland (6.7%).

This study demonstrated that, in addition to human settlement areas that are already the focus of vector control and research, neighboring land uses like water-bodies, horticulture land, open land and neglected grassland should not be ignored for the planning of vector control. Human settlement substantially contributed to the models as the habitats of *Aedes* mosquitoes were found in artificial containers in areas related to human dwelling and activities. Beside human settlement, about 25-50 ha water bodies were considered important reservoirs for dengue mosquitoes, which might be due to the stagnant water in the open concrete drains and rainfall-filled small ponds, pools and streams. Mixed horticulture land, estimated at ca. 200 ha and distributed throughout the study area, contributes suitable habitats for dengue mosquitoes particularly in the form of ornamental plants, plant containers and watering containers in orchards or gardens. Furthermore, natural gullies filled with rainfall and containers discarded by workers in open land that covers an area of 150-200 ha should also not be neglected. Abandoned land cover such as small patches of neglected grassland covering ca. 25 ha provides suitable shaded and vegetated conditions for dengue mosquitoes to proliferate freely.

The prediction risk map after 100 model iterations with high predictive accuracies was anticipated based on the correlative relationships found in research question (5). The prediction risk map depicted the high risk dengue distribution in the central region of Selangor, with clusters at the border of Kuala Lumpur, west and south-east of Selangor. The presence of dengue cases scattered in the northern and southern part of Selangor is

mainly predicted as reflecting low dengue risk. The risk map offered a helpful resource for the local vector control program at state level.

The potential land use types that influence the dengue occurrences as shown in Chapter V should be given more focus in the planning of vector control strategies. Integrated Vector Management (IVM) strategy has been found more effective than other vector control strategies (Erlanger et al. 2008; World Health Organization 2012c). Hence, this strategy as also applied in Malaysia, should focus not only in human settlements area, also to the surrounding land use, i.e. water bodies, mixed horticulture, open land and neglected grassland that may provide suitable habitats for dengue mosquitoes.

This study demonstrated the potential of using BRT, the ecological niche modeling (ENM) approach to account for nonlinearities and interactions between the distributions of disease occurrences and the environmental land use type with high predictive accuracies. This approach can not only be applied to other vector-borne diseases, but can also be transferred to other endemic regions. The correlative relationships found provide important input for a dengue early warning system or prediction model to assist in planning and targeting potential dengue outbreaks.

## **2 Limitations**

This dissertation is limited in a number of ways. First, there is under-reporting of dengue cases in the surveillance data, especially in the ambulatory and private sectors (Shepard et al. 2012). This is common in the disease surveillance system elsewhere (Chairulfatah et al. 2001; Beatty et al. 2010). However, even if there is under-reporting, this dissertation still provides insights to the disease distribution and the relationship with environmental factors as a large number of laboratory confirmed dengue cases are employed within the three-year periods.

There are also issues of delayed case reporting in the current dengue surveillance system (Ministry of Health Malaysia 2009), even though the legislation mandated that all suspected dengue cases be notified to the nearest health office within 24 hours of diagnosis by health practitioners (Zakaria et al. 2013). As this dissertation does not focus on discussing the framework of the early warning system, the onset date of the dengue occurrences is used to study the patterns and relationship. Hence, the delay issue does not directly influence the outcome of this dissertation.



Besides, the single home address of the patient as documented in the surveillance system was not sufficient to reflect the daily mobility of patients from home to work, from work to recreational areas and from recreational areas back home. Nevertheless, multiple case infections in one household due to the repeated feeding behavior of dengue mosquitoes implied that the probability of getting infected is higher at home than elsewhere.

This dissertation does not include other confounders, such as vector population density, virus serotype, water storage habits of inhabitants, housing condition and design, self-awareness of personal protection, immunity status and effectiveness of the vector control program. Even so, the syndromic case surveillance provides basic information to estimate the pattern and distribution of dengue transmission in the hyperendemic and complex disease surroundings.

### **3 Main conclusions**

It is undeniable that global change of our earth system impacts on human health in various ways. One of these aspects is the emergence and re-emergence of vector-borne disease, specifically dengue disease. This dissertation provided empirical evidence to assess where and when higher risk of dengue cases occurs, and further related this to possible environmental risk factors, i.e. weather and land use. This is a fundamental step in better understanding the etiology of dengue disease so that relevant prevention and control of the disease can be implemented.

This dissertation showed a feasible way to better utilize the disease surveillance records and environmental information for the study of spatio-temporal disease patterns and environmental risk assessment. The surveillance records of previous years can be studied retrospectively to look for a trend or pattern that can provide advice for future decision making in disease prevention and control. Due to weakness of management and limited resources, many countries are yet to implement a disease surveillance mechanism that is robust in predicting epidemics (Harrington et al. 2013). Therefore, continuously monitoring and improving of the disease surveillance system is a valuable asset for understanding the impact and risk factors of disease epidemic.

The approach discussed in Chapter III ensured better spatio-temporal cluster information as more than one geographical level was used for comparison. This approach can be adopted in vector-borne disease operational prevention, surveillance and control. In periods of high dengue transmission, these findings can be used to suggest priority subareas to be

treated for vector control as depicted in the scheme of Priority Area Classification (PAC) (Eisen and Lozano-Fuentes 2009). In periods of low transmission, these findings assist in improving the guidelines for setting priority areas for *Aedes* surveillance (World Health Organization 2003).

The results of Chapter IV underpinned the need to study local influences of weather effect on dengue to aid local preventive measures and vector control. The dengue strategic plan for the Asia Pacific region 2008-2015 published by WHO South-East Asia region and WHO Western Pacific region stated that environmental data such as temperature and rainfall are important indicators for developing and scaling up early warning systems for dengue outbreak response (World Health Organization 2008c). The survival, oviposition and flying activities of dengue mosquitoes are sensitive to temperature and water (Bidlingmayer et al. 1985; Chan and Johansson 2012). Contradictory interpretations obtained from many studies of the weather effect on dengue cases were due to the complications of local underlying factors of population density, host immunity status, human and vector mobility, preventive control and resistance to drugs (Chowell and Sanchez 2006; Wu et al. 2007; Colon-Gonzalez et al. 2011). Thus, studies at local area level add to knowledge of the relationship between dengue and weather (Sutherst 2004).

The application of ENM in understanding the geographical and landscape epidemiology of dengue disease was demonstrated in Chapter V. The complexity of disease-host-vector transmission serves as a black box, but ENM assists in relating this to environmental variation, characterizing geographical distributions that meet the ecologic requirements of the disease, and predicting other regions with a similar risk of transmission (Peterson 2006). Increasing ENM studies have been applied to study the transmission of vector-borne disease in recent years (Martin et al. 2011; Sinka et al. 2011), but not many in dengue disease (Machado-Machado 2012; Bhatt et al. 2013). The global dengue burden using BRT aimed at grid cells of 5 km spatial resolution (Bhatt et al. 2013), while the study in Mexico focused on municipality level (Machado-Machado 2012). However, this dissertation exhibited the potential of ecological study at a lower spatial resolution of 200 m spatial resolution.

Besides ecological niche modeling, remote sensing, GIS and spatial analysis technologies influence the study of vector-borne disease in broad-area coverage. Local entomological surveillance with the limit of small sample sizes is not sufficient to produce an overall picture of environmental influence, particularly in the broad-area with high rates of endemic dengue cases (Peterson 2006). These findings encourage epidemiologists,

ecologists and public health researchers to apply the broad-area land use map derived from the remote-sensing technologies and GIS spatial analyzing power to study disease transmission.

The risk map generated in this dissertation serves as a resource with predictive capabilities that may contribute to the planning of vector control interventions. High and low risk area was delineated with the prediction capabilities. This dissertation defined the probability of occurrence of dengue risk within each 200 m × 200 m pixel at the state level. The prediction models can be transferred to other endemic regions. Cartographic refinements can be applied to differentiate endemic from epidemic-prone areas (Bhatt et al. 2013).

Overall, this dissertation has demonstrated new perspectives in vulnerability mapping and environmental risk assessment. A new methodology has been discussed that can better identify the spatio-temporal clustering pattern using an analysis at more than one geographical level. A relevant approach of non-linear exposure-response regression with lag-response function was demonstrated to assess the weather effects on dengue disease. Another relevant approach of ecological niche modeling was applied to assess the land use correlative relationship with dengue disease. Better understanding of disease high risk areas and assessing the association with environmental factors help in the planning of interventions to control dengue disease.

#### **4 Future research and outlook**

This dissertation has demonstrated a new approach and relevant findings that add to the existing knowledge of dengue disease in highly epidemic areas. To better understand the etiology of disease, several interesting research issues beyond the scope of this work are worth brief discussion.

More parameters should be captured and extracted from the surveillance system for further investigation. First, geographical coordinates of the patient address should be collected and validated in the surveillance system. In this dissertation, much effort and time has been dedicated to cleaning, geocoding and validating patient addresses manually offline. A mechanism for recording geographical coordinates in the surveillance system may increase efficiency for future research both locally and regionally. The second type of parameters that should be captured in the surveillance system is the dengue virus serotypes. This is due to the fact that subsequent infection with different serotypes may cause serious complications that may lead to death. Therefore, the spatio-temporal cluster mapping of

risk areas that may be attacked by complicated DHF/DSS seems important and should be included in future disease mapping research.

Further breakdown of land use categories delineates better land use types. In Chapter V, the land use categories were limited to general groups such as water bodies, open land etc. More detailed land use types should be used in future research to enable better understanding of the correlative relationship between land use and dengue disease, i.e. water bodies should be broken down into river, pond, stream and drainage, and human settlements into factories, housing areas, schools, office buildings and religious areas.

Population data provide a good underlying basis for disease rate comparison. In Chapter V, presence/absence of cases per grid cell was employed rather than the rate of disease (cases/population) per grid cell. This was due to the population data provided by the statistical department being at administrative level so that it was impossible to estimate for grid cells. The use of rate of disease per grid cell in future research is anticipated with a growing body of research using high-spatial-resolution remote sensing Light Detection and Ranging (LIDAR) images for population estimation methods (Wu et al. 2005; Wang and Cardenas 2011; Upegui and Viel 2012). This will provide detail and better modeling results.

Studies define the complexes of environment, culture and behavior and their relations to disease causation as being important (Mayer 1982). This dissertation focuses on vulnerability mapping and environmental aspects of the disease. Future research should take into account other disciplines, including health care service, and cultural and social geographical aspects. In this way, the available health care services, community behavior and public awareness of vector control strategies can be included.

Besides, studies of different risk factors could be combined and integrated in one mode for future research. One way to respond to global change is the development of integrated assessment (McMichael et al. 2006). "Integrated assessment is an interdisciplinary process of combining, interpreting, and communicating knowledge from diverse scientific disciplines in such a way that the whole set of cause-effect interactions of a problem can be evaluated from a synoptic perspective with two characteristics: it should have added value compared to single disciplinary oriented assessment; and it should provide useful information to decision-makers" (Rotmans and Dowlatabadi 1998). Therefore, future research with integrative assessment including pathogen transmission dynamics, demographic population movement, changing land use, changing weather and other risk

factors may evaluate the potential impacts of global change on infectious diseases (McMichael et al. 2006).

It would also be interesting to develop scenarios of the effect of weather changes and land use changes on dengue disease in future research. General circulation model based scenarios can be constructed in which the frequency and intensity of ENSO events impact the transmission of infectious disease (Patz et al. 2003). The scenarios on land use changes can also be developed, as human-induced land use changes are primary drivers for infectious disease outbreaks and modifiers of the transmission of endemic infections (Patz et al. 2000). Vanwambeke et. al. (2007b) demonstrated a scenario on land use change where high numbers of dengue cases may be found if the area of orchard increased. Scenarios may contribute to the assessment of future developments in complex systems that are often inherently unpredictable (IPCC 2001).



## References

## References

- Abdullah, S.A., & Nakagoshi, N. (2006). Changes in landscape spatial pattern in the highly developing state of Selangor, peninsular Malaysia. *Landscape and Urban Planning*, 77, 263-275.
- Abubakar, S., & Shafee, N. (2002). Outlook of dengue in Malaysia: a century later. *Malaysian Journal of Pathology*, 24, 23-28.
- Adams, B., & Boots, M. (2010). How important is vertical transmission in mosquitoes for the persistence of dengue? Insights from a mathematical model. *Epidemics*, 2, 1-10.
- Adger, W.N., Eakin, H., & Winkels, A. (2008). Nested and teleconnected vulnerabilities to environmental change. *Frontiers in Ecology and the Environment*, 7, 150-157.
- Aiken, S.R., & Leigh, C.H. (1978). Dengue haemorrhagic fever in South-east Asia. *Transactions of the Institute of British Geographers*, 476-497.
- Alimadad, A., & Salibian-Barrera, M. (2011). An Outlier-Robust Fit for Generalized Additive Models With Applications to Disease Outbreak Detection. *Journal of the American Statistical Association*, 106, 719-731.
- Amala, S., & Anuradha, V. (2011). A study on diversity of mosquitoes in the forest ecosystem of Sirumalai Hills, Dindigul, Tamilnadu. *The ECOSCAN - An Int Quarterly J of Environ Sci*, 1, 219-222.
- Arcari, P., Tapper, N., & Pfueller, S. (2007). Regional variability in relationships between climate and dengue/DHF in Indonesia. *Singapore Journal of Tropical Geography*, 28, 251-272.
- Arima, Y., & Matsui, T. (2011). Epidemiologic update on the dengue situation in the Western Pacific Region, 2010. *Western Pacific Surveillance and Response Journal*, 2, 4-8.
- Armien, B., Suaya, J.A., Quiroz, E., Sah, B.K., Bayard, V., Marchena, L., Campos, C., & Shepard, D.S. (2008). Clinical characteristics and national economic cost of the 2005 dengue epidemic in Panama. *American Journal of Tropical Medicine and Hygiene*, 79, 364-371.
- Armstrong, B. (2006). Models for the relationship between ambient temperature and daily mortality. *Epidemiology*, 17, 624-631.
- Aziz, S., Ngui, R., Lim, Y.A., Sholehah, I., Nur Farhana, J., Azizan, A.S., & Wan Yusoff, W.S. (2012). Spatial pattern of 2009 dengue distribution in Kuala Lumpur using GIS application. *Trop Biomed*, 29, 113-120.
- Barmak, D.H., Dorso, C.O., Otero, M., & Solari, H.G. (2011). Dengue epidemics and human mobility. *Physical Review E*, 84, 011901.
- Barrera, R., Amador, M., & MacKay, A.J. (2011). Population dynamics of *Aedes aegypti* and dengue as influenced by weather and human behavior in San Juan, Puerto Rico. *PLoS Negl Trop Dis*, 5, 1371-1379.



- Barter, P. (2002). Transport and Housing Security in the Klang Valley, Malaysia. *Singapore Journal of Tropical Geography*, 23, 268-287.
- Bates, I., Fenton, C., Gruber, J., Laloo, D., Medina Lara, A., Squire, S.B., Theobald, S., Thomson, R., & Tolhurst, R. (2004). Vulnerability to malaria, tuberculosis, and HIV/AIDS infection and disease. Part 1: determinants operating at individual and household level. *Lancet Infect Dis*, 4, 267-277.
- Beatty, M.E., Stone, A., Fitzsimons, D.W., Hanna, J.N., Lam, S.K., Vong, S., Guzman, M.G., Mendez-Galvan, J.F., Halstead, S.B., Letson, G.W., Kuritsky, J., Mahoney, R., Margolis, H.S., & Preventio, A.-P.A.D. (2010). Best Practices in Dengue Surveillance: A Report from the Asia-Pacific and Americas Dengue Prevention Boards. *Plos Neglected Tropical Diseases*, 4.
- Beggs, P.J., & Bambrick, H.J. (2006). Is the global rise of asthma an early impact of anthropogenic climate change? *Ciência & Saúde Coletiva*, 11, 745-752.
- Bhatt, S., Gething, P.W., Brady, O.J., Messina, J.P., Farlow, A.W., Moyes, C.L., Drake, J.M., Brownstein, J.S., Hoen, A.G., Sankoh, O., Myers, M.F., George, D.B., Jaenisch, T., Wint, G.R., Simmons, C.P., Scott, T.W., Farrar, J.J., & Hay, S.I. (2013). The global distribution and burden of dengue. *Nature*, 496, 504-507.
- Bi, P., Tong, S., Donald, K., Parton, K.A., & Hobbs, J. (2001). Climate Variability and the Dengue Outbreak in Townsville, Queensland, 1992-93. *Environmental Health*, 1, 54-60.
- Bich, T.H., Quang, L.N., Ha le, T.T., Hanh, T.T., & Guha-Sapir, D. (2011). Impacts of flood on health: epidemiologic evidence from Hanoi, Vietnam. *Glob Health Action*, 4, 21-28.
- Bidlingmayer, W.L., Evans, D.G., & Hansen, C.H. (1985). Preliminary study of the effects of wind velocities and wind shadows upon suction trap catches of mosquitoes (DIPTERA: CULICIDAE). *Journal of Medical Entomology*, 22, 295-302.
- Brian, D. (2004). Climate change, ozone depletion and the impact on ultraviolet exposure of human skin. *Physics in Medicine and Biology*, 49, R1.
- Brunkard, J.M., Cifuentes, E., & Rothenberg, S.J. (2008). Assessing the roles of temperature, precipitation, and ENSO in dengue re-emergence on the Texas-Mexico border region. *Salud Publica De Mexico*, 50, 227-234.
- Bunnell, J.E., Price, S.D., Das, A., Shields, T.M., & Glass, G.E. (2003). Geographic information systems and spatial analysis of adult *Ixodes scapularis* (Acari: Ixodidae) in the middle Atlantic region of the USA. *Journal of medical entomology*, 40, 570-576.
- Bunnell, T., Barter, P.A., & Morshidi, S. (2002). Kuala Lumpur metropolitan area: A globalizing city-region. *Cities*, 19, 357-370.
- Burkart, K., Schneider, A., Breitner, S., Khan, M.H., Kramer, A., & Endlicher, W. (2011). The effect of atmospheric thermal conditions and urban thermal pollution on all-cause and cardiovascular mortality in Bangladesh. *Environ Pollut*, 159, 2035-2043.

- Burnham, K.P., & Anderson, D.R. (2004). Multimodel inference - understanding AIC and BIC in model selection. *Sociological Methods & Research*, 33, 261-304.
- Cafiero, C., & Vakis, R. (2006). Risk and vulnerability considerations in poverty analysis: Recent advances and future directions. In Social Protection Unit, H.D.N., The World Bank (Ed.), *Document de discussions sur la Protection sociale*. Washington, D.C.
- Cattand, P., Desjeux, P., Guzman, M., Jannin, J., Kroeger, A., Médict, A., Musgrove, P., Nathan, M.B., Shaw, A., & Schofield, C. (2006). Tropical diseases lacking adequate control measures: dengue, leishmaniasis, and African trypanosomiasis. *Disease Control Priorities Project*, 451-466.
- Cazelles, B., Chavez, M., McMichael, A.J., & Hales, S. (2005). Nonstationary Influence of El Niño on the Synchronous Dengue Epidemics in Thailand. *Plos Medicine*, 2, 101-106.
- Centers for Disease Control and Prevention (2012). Dengue and the Aedes aegypti mosquito [online]. Available from: <http://www.cdc.gov/dengue/resources/30Jan2012/aegyptifactsheet.pdf> [accessed November 2012].
- Chadee, D.D., & Martinez, R. (2000). Landing periodicity of Aedes aegypti with implications for dengue transmission in Trinidad, West Indies. *Journal of vector Ecology*, 25, 158-163.
- Chadee, D.D., Shivnauth, B., Rawlins, S.C., & Chen, A.A. (2007). Climate, mosquito indices and the epidemiology of dengue fever in Trinidad (2002-2004). *Annals of Tropical Medicine and Parasitology*, 101, 69-77.
- Chadwick, D., Arch, B., Wilder-Smith, A., & Paton, N. (2006). Distinguishing dengue fever from other infections on the basis of simple clinical and laboratory features: Application of logistic regression analysis. *Journal of Clinical Virology*, 35, 147-153.
- Chairulfatah, A., Setiabudi, D., Agoes, R., van Sprundel, M., & Colebunders, R. (2001). Hospital based clinical surveillance for dengue haemorrhagic fever in Bandung, Indonesia 1994-1995. *Acta tropica*, 80, 111-115.
- Chan, M., & Johansson, M.A. (2012). The Incubation Periods of Dengue Viruses. *Plos One*, 7, 50971-50977.
- Chang, M.S., Christophel, E.M., Gopinath, D., & Abdur, R.M. (2011). Challenges and future perspective for dengue vector control in the Western Pacific Region. *Western Pacific Surveillance and Response Journal*, 2, 9-16.
- Chang, M.S., Hii, J., Buttner, P., & Mansoor, F. (1997). Changes in abundance and behaviour of vector mosquitoes induced by land use during the development of an oil palm plantation in Sarawak. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 91, 382-386.
- Chareonviriyaphap, T., Akratanakul, P., Huntamai, S., Nettanomsak, S., & Prabaripai, A. (2004). Allozyme patterns of *Aedes albopictus*, a vector of dengue in Thailand. *Journal of Medical Entomology*, 41, 657-663.

- Chen, C.D., Benjamin, S., Saranam, M. M., Chiang, Y. F., Lee, H.L., Nazni, W.A., Sofian-Azirun, M. (2005a). Dengue vector surveillance in urban residential and settlement areas in Selangor, Malaysia. *Tropical Biomedicine*, 22, 39-43.
- Chen, C.D., Nazni, W.A., Lee, H.L., & Sofian-Azirun, M. (2005b). Weekly variation on susceptibility status of *Aedes* mosquitoes against temephos in Selangor, Malaysia. *Trop Biomed*, 22, 195-206.
- Chen, C.D., Nazni, W.A., Lee, H.L., Seleena, B., Mohd Masri, S., Chiang, Y.F., & Sofian-Azirun, M. (2006). Mixed breeding of *Aedes aegypti* (L.) and *Aedes albopictus* Skuse in four dengue endemic areas in Kuala Lumpur and Selangor, Malaysia. *Trop. Biomed.*, 23, 224-227.
- Chen, C.D., Teoh, P.S., Othman, W.-N., Sofian-Azirun, M., & Lee, H.L. (2009). The effectiveness of a floor gully with grating to prevent the oviposition of *Aedes* (*Stegomyia*) *aegypti* (Linnaeus): a laboratory study. *Jurnal Sains Kesihatan Malaysia*, 7, 73-80.
- Chen, J., Roth, R., Naito, A., Lengerich, E., & MacEachren, A. (2008). Geovisual analytics to enhance spatial scan statistic interpretation: an analysis of U.S. cervical cancer mortality. *International Journal of Health Geographics*, 7, 57.
- Chen, M.J., Lin, C.Y., Wu, Y.T., Wu, P.C., Lung, S.C., & Su, H.J. (2012). Effects of Extreme Precipitation to the Distribution of Infectious Diseases in Taiwan, 1994–2008. *Plos One*, 7, 34651-34658.
- Chen, S.C., Liao, C.M., Chio, C.P., Chou, H.H., You, S.H., & Cheng, Y.H. (2010). Lagged temperature effect with mosquito transmission potential explains dengue variability in southern Taiwan: Insights from a statistical analysis. *Science of the Total Environment*, 408, 4069-4075.
- Cheong, Y.L., Burkart, K., Leitão, P.J., & Lakes, T. (2013). Assessing Weather Effects on Dengue Disease in Malaysia. *International Journal of Environmental Research and Public Health*, 10, 6319-6334.
- Cheong, Y.L., Leitão, P.J., & Lakes, T. (2014). Assessment of land use factors associated with dengue cases in Malaysia using Boosted Regression Trees. *Spat Spatio-tempor Epidemiol*, 10, 75-84.
- Chew, M.H., Rahman, M.M., Jelip, J., Hassan, M.R., & Isahak, I. (2012). All Serotypes of Dengue Viruses Circulating in Kuala Lumpur, Malaysia. *Curr. Res J. Biol. Sci.*, 4, 229-234.
- Chowell, G., & Sanchez, F. (2006). Climate-based descriptive models of Dengue fever: The 2002 epidemic in Colima, Mexico. *Journal of Environmental Health*, 68, 40-44.
- Christiansen, L., Andersen, J., Wegener, H., & Madsen, H. (2006). Spatial scan statistics using elliptic windows. *Journal of Agricultural, Biological, and Environmental Statistics*, 11, 411-424.

## References

- Clarke, K., McLafferty, S., & Tempalski, B. (1996). On epidemiology and geographic information systems: a review and discussion of future directions. *Emerg Infect Dis*, 2, 85-92.
- Clements, A.N. (1999). *The biology of mosquitoes: Sensory reception and behaviour*. Wallingford, England: CABI.
- Colón-González, F.J., Fezzi, C., Lake, I.R., & Hunter, P.R. (2013). The Effects of Weather and Climate Change on Dengue. *PLoS Negl Trop Dis*, 7, e2503.
- Colon-Gonzalez, F.J., Lake, I.R., & Bentham, G. (2011). Climate Variability and Dengue Fever in Warm and Humid Mexico. *American Journal of Tropical Medicine and Hygiene*, 84, 757-763.
- Coutts, S.R., & Yokomizo, H. (2014). Meta-models as a straightforward approach to the sensitivity analysis of complex models. *Population Ecology*, 56, 7-19.
- Cui, Y. (2013). A systematic approach to evaluate and validate the spatial accuracy of farmers market locations using multi-geocoding services. *Applied Geography*, 41, 87-95.
- Cuong, H.Q., Vu, N.T., Cazelles, B., Boni, M.F., Thai, K.T., Rabaa, M.A., Quang, L.C., Simmons, C.P., Huu, T.N., & Anders, K.L. (2013). Spatiotemporal dynamics of dengue epidemics, southern Vietnam. *Emerging infectious diseases*, 19, 945.
- Dambach, P., Sie, A., Lacaux, J., Vignolles, C., Machault, V., & Sauerborn, R. (2009). Using high spatial resolution remote sensing for risk mapping of malaria occurrence in the Nouna district, Burkina Faso. *Glob Health Action*, 2.
- De'ath, G. (2007). Boosted trees for ecological modeling and prediction. *Ecology*, 88, 243-251.
- de Melo, D.P.O., Scherrer, L.R., & Eiras, Á.E. (2012). Dengue Fever Occurrence and Vector Detection by Larval Survey, Ovitrap and MosquiTRAP: A Space-Time Clusters Analysis. *Plos One*, 7, e42125.
- Delatte, H., Gimonneau, G., Triboire, A., & Fontenille, D. (2009). Influence of Temperature on Immature Development, Survival, Longevity, Fecundity, and Gonotrophic Cycles of *Aedes albopictus*, Vector of Chikungunya and Dengue in the Indian Ocean. *Journal of Medical Entomology*, 46, 33-41.
- Delatte, H., Toty, C., Boyer, S., Bouetard, A., Bastien, F., & Fontenille, D. (2013). Evidence of Habitat Structuring *Aedes albopictus* Populations in Réunion Island. *PLoS Negl Trop Dis*, 7, e2111.
- Department of Statistics Malaysia (2011a). Compendium of Environment Statistics Malaysia (pp. 176-185). Putrajaya, Malaysia: Department of Statistics Malaysia.
- Department of Statistics Malaysia (2011b). Population and Distribution by Local Authority Areas and Mukims, 2010 (pp. 389-417). Putrajaya, Malaysia: Department of Statistics Malaysia.

- Depradine, C.A., & Lovell, E.H. (2004). Climatological variables and the incidence of Dengue fever in Barbados. *International Journal of Environmental Health Research*, 14, 429-441.
- Díaz-Nieto, L.M., Maciá, A., Perotti, M.A., & Berón, C.M. (2013). Geographical Limits of the Southeastern Distribution of *Aedes aegypti* (Diptera, Culicidae) in Argentina. *PLoS Negl Trop Dis*, 7, e1963.
- Dickin, S.K., Schuster-Wallace, C.J., & Elliott, S.J. (2013). Developing a vulnerability mapping methodology: applying the water-associated disease index to dengue in Malaysia. *PloS one*, 8, e63584.
- Dieng, H., Saifur, R.G.M., Abu Hassan, A., Salmah, M.R.C., Boots, M., Satho, T., Jaal, Z., & AbuBakar, S. (2010). Indoor-Breeding of *Aedes albopictus* in Northern Peninsular Malaysia and Its Potential Epidemiological Implications. *Plos One*, 5, 11791-11799.
- Dom, N.C., Ahmad, A.H., Latif, Z.A., Ismail, R., & Pradhan, B. (2013). Coupling of remote sensing data and environmental-related parameters for dengue transmission risk assessment in Subang Jaya, Malaysia. *Geocarto International*, 28, 258-272.
- Dom, N.C., Latif, Z.A., Ahmad, A.H., Ismail, R., & Pradhan, B. (2012). Manifestation of GIS Tools for Spatial Pattern Distribution Analysis of Dengue Fever Epidemic in the City of Subang Jaya, Malaysia. *EnvironmentAsia*, 5, 82-92.
- Eakin, H., & Luers, A.L. (2006). Assessing the Vulnerability of Social-Environmental Systems. *Annual Review of Environment and Resources*, 31, 365-394.
- Earnest, A., Tan, S.B., & Wilder-Smith, A. (2012). Meteorological factors and El Niño Southern Oscillation are independently associated with dengue infections. *Epidemiology & Infection*, 140, 1244-1251.
- Ebi, K., Berry, P., Campbell-Lendrum, D., Corvalan, C., & Guillemot, J. (2013). *Protecting health from climate change: vulnerability and adaptation assessment*. Switzerland: World Health Organization.
- Ebi, K.L. (2008). Effects of global change on human health. *Analyses of the effects of global change on human health and welfare and human systems* (pp. 1-78). EPA.
- Edman, J.D. (2003). Fitness advantages in multiple blood-feeding: the *Aedes aegypti* example. *Ecological Aspects for Application of Genetically Modified Mosquitoes*, 2, 63-74.
- Eisen, L., & Lozano-Fuentes, S. (2009). Use of Mapping and Spatial and Space-Time Modeling Approaches in Operational Control of *Aedes aegypti* and Dengue. *Plos Neglected Tropical Diseases*, 3, 411-417.
- Eisen, L., & Moore, C.G. (2013). *Aedes* (*Stegomyia*) *aegypti* in the Continental United States: A Vector at the Cool Margin of Its Geographic Range. *Journal of Medical Entomology*, 50, 467-478.
- Elder, J., & Lloyd, L. (2006). Achieving behaviour changes for dengue control: methods scaling-up and sustainability. Geneva, Switzerland: World Health Organization.

## References

- Elith, J., Leathwick, J., & Hastie, T. (2008). A working guide to boosted regression trees. *Journal of Animal Ecology*, *77*, 802-813.
- Er, A.C., Rosli, M.H., Asmahani, A., Mohamad Naim, M.R., & Harsuzilawati, M. (2010). Spatial Mapping of Dengue Incidence: A Case Study in Hulu Langat District, Selangor, Malaysia. *International Journal of Human and Social Sciences*, *5*, 410-414.
- Erickson, R.A., Hayhoe, K., Presley, S.M., Allen, L.J.S., Long, K.R., & Cox, S.B. (2012). Potential impacts of climate change on the ecology of dengue and its mosquito vector the Asian tiger mosquito ( *Aedes albopictus*). *Environmental Research Letters*, *7*, 034003.
- Erlanger, T.E., Keiser, J., & Utzinger, J. (2008). Effect of dengue vector control interventions on entomological parameters in developing countries: a systematic review and meta-analysis. *Medical and Veterinary Entomology*, *22*, 203-221.
- Fairos, W.W., Azaki, W.W., Alias, L.M., & Wah, Y.B. (2010). Modelling Dengue Fever (DF) and Dengue Haemorrhagic Fever (DHF) Outbreak Using Poisson and Negative Binomial Model. *Int J Math Comput Sci Eng*, *4*, 809-814.
- Ferrier, S., Watson, G., Pearce, J., & Drielsma, M. (2002). Extended statistical approaches to modelling spatial pattern in biodiversity in northeast New South Wales. I. Species-level modelling. *Biodiversity and Conservation*, *11*, 2275-2307.
- Fleming, L.E., Broad, K., Clement, A., Dewailly, E., Elmir, S., Knap, A., Pomponi, S.A., Smith, S., Solo Gabriele, H., & Walsh, P. (2006). Oceans and human health: Emerging public health risks in the marine environment. *Marine Pollution Bulletin*, *53*, 545-560.
- Focks, D., Daniels, E., Haile, D., & Keesling, J. (1995). A simulation model of the epidemiology of urban dengue fever: literature analysis, model development, preliminary validation, and samples of simulation results. *The American journal of tropical medicine and hygiene*, *53*, 489-506.
- Focks, D.A., Brenner, R.J., Hayes, J., & Daniels, E. (2000). Transmission thresholds for dengue in terms of *Aedes aegypti* pupae per person with discussion of their utility in source reduction efforts. *The American Journal of Tropical Medicine and Hygiene*, *62*, 11-18.
- Focks, D.A., Haile, D.G., Daniels, E., & Mount, G.A. (1993a). Dynamic life table model for *Aedes aegypti* (Diptera: Culicidae): analysis of the literature and model development. *Journal of medical entomology*, *30*, 1003-1017.
- Focks, D.A., Haile, D.G., Daniels, E., & Mount, G.A. (1993b). Dynamic life table model for *Aedes aegypti* (diptera: Culicidae): simulation results and validation. *Journal of medical entomology*, *30*, 1018-1028.
- Foley, J.A., DeFries, R., Asner, G.P., Barford, C., Bonan, G., Carpenter, S.R., Chapin, F.S., Coe, M.T., Daily, G.C., Gibbs, H.K., Helkowski, J.H., Holloway, T., Howard, E.A., Kucharik, C.J., Monfreda, C., Patz, J.A., Prentice, I.C., Ramankutty, N., & Snyder, P.K. (2005). Global consequences of land use. *Science*, *309*, 570-574.

- Foote, E., & Cook, D. (1959). Mosquitoes of medical importance. *Mosquitoes of medical importance*. Agricultural Research Service, U.S. Department of Agriculture.
- Friedman, J.H., Hastie, T., & Tibshirani, R. (2000). Additive logistic regression: A statistical view of boosting. *Annals of Statistics*, 28, 337 - 374.
- Friedman, J.H. (2001). Greedy function approximation: A gradient boosting machine. *Annals of Statistics*, 29, 1189-1232.
- Friedman, J.H. (2002). Stochastic gradient boosting. *Computational Statistics & Data Analysis*, 38, 367-378.
- Friedman, J.H., & Meulman, J.J. (2003). Multiple additive regression trees with application in epidemiology. *Statistics in Medicine*, 22, 1365-1381.
- Gabriel, K.M., & Endlicher, W.R. (2011). Urban and rural mortality rates during heat waves in Berlin and Brandenburg, Germany. *Environ Pollut*, 159, 2044-2050.
- Gagnon, A.S., Bush, A.B.G., & Smoyer-Tomic, K.E. (2001). Dengue epidemics and the El Niño Southern Oscillation. *Clim Res*, 19, 35-43.
- Garcia, C., Garcia, L., Espinosa-Carreón, L., & Ley, C. (2011). Abundance and distribution of *Aedes aegypti* (Diptera: Culicidae), and dengue dispersion in Guasave Sinaloa, Mexico. *Revista De Biología Tropical*, 59, 1609-1619. In Spanish.
- Gasparri, A. (2011). Distributed Lag Linear and Non-Linear Models in R: The Package dlnm. *Journal of Statistical Software*, 43, 1-20.
- Gasparri, A., Armstrong, B., & Kenward, M.G. (2010). Distributed lag non-linear models. *Statistics in Medicine*, 29, 2224-2234.
- Getis, A., Morrison, A.C., Gray, K., & Scott, T.W. (2003). Characteristics of the spatial pattern of the dengue vector, *Aedes aegypti*, in Iquitos, Peru. *The American journal of tropical medicine and hygiene*, 69, 494-505.
- Ghani, A.A., Zakaria, N.A., Kassim, M., & Nasir, B.A. (2000). Sediment size characteristics of urban drains in Malaysian cities. *Urban Water*, 2, 335-341.
- Gharbi, M., Quenel, P., Gustave, J., Cassadou, S., Ruche, G., Girdary, L., & Marrama, L. (2011). Time series analysis of dengue incidence in Guadeloupe, French West Indies: Forecasting models using climate variables as predictors. *BMC Infectious Diseases*, 11, 161-113.
- Gleiser, R.M., & Zalazar, L.P. (2010). Distribution of mosquitoes in relation to urban landscape characteristics. *Bull Entomol Res*, 100, 153-158.
- Gomes, A.F., Nobre, A.A., & Cruz, O.G. (2012). Temporal analysis of the relationship between dengue and meteorological variables in the city of Rio de Janeiro, Brazil, 2001-2009. *Cadernos De Saude Publica*, 28, 2189-2197.

- Goovaerts, P., & Xiao, H. (2011). Geographical, temporal and racial disparities in late-stage prostate cancer incidence across Florida: A multiscale joinpoint regression analysis. *International journal of health geographics*, *10*, 63.
- Graham, A., Atkinson, P., & Danson, F. (2004). Spatial analysis for epidemiology. *Acta tropica*, *91*, 219-225.
- Gratz, N., & Knudsen, A. (1996). The rise and spread of dengue, dengue haemorrhagic fever and its vectors. *A historical review (up to 1995)*. *CTD/FIL (DEN)*, *96*.
- Gregorio, D., DeChello, L., Samociuk, H., & Kulldorff, M. (2005). Lumping or splitting: seeking the preferred areal unit for health geography studies. *International Journal of Health Geographics*, *4*, 6.
- Grimstad, P.R., & DeFoliart, G.R. (1975). Mosquito nectar feeding in Wisconsin in relation to twilight and microclimate. *Journal of medical entomology*, *11*, 691-698.
- Gruebner, O., Khan, M.M.H., & Hostert, P. (2011). Spatial epidemiological applications in public health research: examples from the megacity of Dhaka. In Krämer, A., Khan, M.M.H. & Kraas, F. (Eds.), *Health in Megacities and Urban Areas* (pp. 243-261). Springer.
- Gu, W., Wang, X., & McGregor, S. (2010). Optimization of preventive health care facility locations. *International Journal of Health Geographics*, *9*, 17.
- Gubler, D.J. (1998a). Dengue and Dengue Hemorrhagic Fever. *Clin Microbiol Rev*, *11*, 480-496.
- Gubler, D.J. (1998b). Resurgent vector-borne diseases as a global health problem. *Emerging Infectious Diseases*, *4*, 442-450.
- Gubler, D.J. (2004). The changing epidemiology of yellow fever and dengue, 1900 to 2003: full circle? *Comparative Immunology Microbiology and Infectious Diseases*, *27*, 319-330.
- Gubler, D.J. (2006). Dengue/dengue haemorrhagic fever: history and current status. *Novartis Found Symp*, *277*, 3-16.
- Gubler, D.J., & Clark, G.G. (1995). Dengue/dengue hemorrhagic fever: the emergence of a global health problem. *Emerg Infect Dis*, *1*, 55-57.
- Gubler, D.J., & Clark, G.G. (1996). Community involvement in the control of *Aedes aegypti*. *Acta Tropica*, *61*, 169-179.
- Gubler, D.J., & Rosen, L. (1977). Quantitative aspects of replication of dengue viruses in *Aedes albopictus* (Diptera: Culicidae) after oral and parenteral infection. *Journal of medical entomology*, *13*, 469-472.
- Guo, Y., Barnett, A., Zhang, Y., Tong, S., Yu, W., & Pan, X. (2010). The short-term effect of air pollution on cardiovascular mortality in Tianjin, China: comparison of time series and case-crossover analyses. *Sci Total Environ*, *409*, 300 - 306.



- Guo, Y., Barnett, A.G., Pan, X., Yu, W., & Tong, S. (2011). The impact of temperature on mortality in Tianjin, China: a case-crossover design with a distributed lag nonlinear model. *Environ Health Perspect*, *119*, 1719-1725.
- Guo, Y.M., Barnett, A.G., & Tong, S.L. (2013). Spatiotemporal model or time series model for assessing city-wide temperature effects on mortality? *Environmental Research*, *120*, 55-62.
- Guzman, M.G., Halstead, S.B., Artsob, H., Buchy, P., Farrar, J., Gubler, D.J., Hunsperger, E., Kroeger, A., Margolis, H.S., & Martínez, E. (2010). Dengue: a continuing global threat. *Nature Reviews Microbiology*, *8*, S7-S16.
- Hagenlocher, M., Delmelle, E., Casas, I., & Kienberger, S. (2013). Assessing socioeconomic vulnerability to dengue fever in Cali, Colombia: statistical vs expert-based modeling. *International Journal of Health Geographics*, *12*, 36.
- Hahn, M.B., Gangnon, R.E., Barcellos, C., Asner, G.P., & Patz, J.A. (2014). Influence of Deforestation, Logging, and Fire on Malaria in the Brazilian Amazon. *PLoS ONE*, *9*, e85725.
- Hales, S., de Wet, N., Maindonald, J., & Woodward, A. (2002). Potential effect of population and climate changes on global distribution of dengue fever: an empirical model. *Lancet*, *360*, 830-834.
- Hales, S., Weinstein, P., Soares, Y., & Woodward, A. (1999). El Nino and the dynamics of vectorborne disease transmission. *Environ Health Perspect*, *107*, 99-102.
- Halstead, S.B. (2006). Dengue in the Americas and Southeast Asia: do they differ? *Rev Panam Salud Publica*, *20*, 407 - 415.
- Halstead, S.B. (2007). Dengue. *The Lancet*, *370*, 1644-1652.
- Halstead, S.B. (2008). Dengue virus-mosquito interactions. *Annual Review of Entomology*, *53*, 273-291.
- Harrington, J., Kroeger, A., Runge-Ranzinger, S., & O'Dempsey, T. (2013). Detecting and Responding to a Dengue Outbreak: Evaluation of Existing Strategies in Country Outbreak Response Planning. *Journal of tropical medicine*, *2013*.
- Harrington, L.C., Edman, J.D., & Scott, T.W. (2001). Why do female *Aedes aegypti* (Diptera: Culicidae) feed preferentially and frequently on human blood? *Journal of medical entomology*, *38*, 411-422.
- Hashizume, M., Dewan, A., Sunahara, T., Rahman, M., & Yamamoto, T. (2012). Hydroclimatological variability and dengue transmission in Dhaka, Bangladesh: a time-series study. *BMC Infectious Diseases*, *12*, 91-99.
- Hassan, H., Shohaimi, S., & Hashim, N.R. (2012). Risk mapping of dengue in Selangor and Kuala Lumpur, Malaysia. *Geospat Health*, *7*, 21-25.
- Hastie, T., & Tibshirani, R. (1990). *Generalized Additive Models*. London/Boca Raton: Chapman & Hall/CRC Press.

## References

- Hastie, T., Tibshirani, R., & Friedman, J. (2009). *The elements of statistical learning: data mining, inference and prediction*. New York: Springer-Verlag.
- Hay, S. (2000). An overview of remote sensing and geodesy for epidemiology and public health application. *Adv Parasitol*, 47, 1-35.
- Hay, S.I., Myers, M.F., Burke, D.S., Vaughn, D.W., Endy, T., Ananda, N., Shanks, G.D., Snow, R.W., & Rogers, D.J. (2000). Etiology of interepidemic periods of mosquito-borne disease. *Proceedings of the National Academy of Sciences*, 97, 9335-9339.
- Hayden, M.H., Uejio, C.K., Walker, K., Ramberg, F., Moreno, R., Rosales, C., Gameros, M., Mearns, L.O., Zielinski-Gutierrez, E., & Janes, C.R. (2010). Microclimate and Human Factors in the Divergent Ecology of *Aedes aegypti* along the Arizona, US/Sonora, MX Border. *Ecohealth*, 7, 64-77.
- Hijmans, R.J., Phillips, S., Leathwick, J., & Elith, J. (2013). dismo: Species distribution modeling. R package version 0.8-17 [online]. Available from: <http://cran.r-project.org/web/packages/dismo/index.html> [accessed August 2013].
- Hoffmann, E.J., & Miller, J.R. (2002). Reduction of mosquito (Diptera: Culicidae) attacks on a human subject by combination of wind and vapor-phase DEET repellent. *Journal of medical entomology*, 39, 935-938.
- Hooke, R.L., Martín-Duque, J.F., & Pedraza, J. (2012). Land transformation by humans: a review. *GSA Today*, 22, 4-10.
- Horstick, O., Runge-Ranzinger, S., Nathan, M.B., & Kroeger, A. (2010). Dengue vector-control services: how do they work? A systematic literature review and country case studies. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 104, 379-386.
- Hurtado-Diaz, M., Riojas-Rodriguez, H., Rothenberg, S., Gomez-Dantes, H., & Cifuentes, E. (2007). Short communication: impact of climate variability on the incidence of dengue in Mexico. *Tropical Medicine and International Health*, 12, 1327-1337.
- Idris, F.H., Usman, A., Surendran, S.N., & Ramasamy, R. (2013). Detection of *Aedes albopictus* pre-imaginal stages in brackish water habitats in Brunei Darussalam. *Journal of Vector Ecology*, 38, 197-199.
- Iñiguez, C., Ballester, F., Ferrandiz, J., Pérez-Hoyos, S., Sáez, M., & López, A. (2010). Relation between Temperature and Mortality in Thirteen Spanish Cities. *International Journal of Environmental Research and Public Health*, 7, 3196-3210.
- IPCC (2001). Developing and Applying Scenarios, *Climate change 2001: impacts, adaptation, and vulnerability: contribution of Working Group II to the third assessment report of the Intergovernmental Panel on Climate Change*, 0521015006. Cambridge University Press.
- IPCC (2014). Human Health: Impacts, Adaptaion, and Co-Benefits. *Climate Change 2014: Impacts, Adaptation and Vulnerability. Contribution of Working Group II to the Fifth Assessment Report of the Intergovernmental Panel on Climate Change*.

- Ishak, H., Miyagi, I., Toma, T., & Kamimura, K. (1997). Breeding habitats of *Aedes aegypti* (L) and *Aedes albopictus* (Skuse) in villages of Barru, South Sulawesi, Indonesia. *The Southeast Asian journal of tropical medicine and public health*, *28*, 844-850.
- Jarup, L. (2004). Health and environment information systems for exposure and disease mapping, and risk assessment. *Environ Health Perspect*, *112*, 995-997.
- Jeefoo, P., Tripathi, N.K., & Souris, M. (2010). Spatio-Temporal Diffusion Pattern and Hotspot Detection of Dengue in Chachoengsao Province, Thailand. *International Journal of Environmental Research and Public Health*, *8*, 51-74.
- Jeffery, C., Ozonoff, A., White, L.F., Nuno, M., & Pagano, M. (2009). Power to detect spatial disturbances under different levels of geographic aggregation. *J Am Med Inform Assoc*, *16*, 847-854.
- Jones, R. (1987). Ozone depletion and cancer risk. *The Lancet*, *330*, 443-446.
- Jones, S.G., & Kulldorff, M. (2012). Influence of spatial resolution on space-time disease cluster detection. *Plos One*, *7*, e48036.
- Kay, B.H., Ryan, P.A., Lyons, S.A., Foley, P.N., Pandeya, N., & Purdie, D. (2002). Winter Intervention Against *Aedes aegypti* (Diptera: Culicidae) Larvae in Subterranean Habitats Slows Surface Recolonization in Summer. *Journal of Medical Entomology*, *39*, 356-361.
- Keesing, F., & Ostfeld, R.S. (2012). Disease ecology. *Integrating Ecology and Poverty Reduction* (pp. 217-230). Springer.
- Krishnan, N., Purswani, M., & Hagmann, S. (2012). Severe dengue virus infection in pediatric travelers visiting friends and relatives after travel to the Caribbean. *American Journal of Tropical Medicine and Hygiene*, *86*, 474-476.
- Kulldorff, M., Heffernan, R., Hartman, J., Assuncao, R., & Mostashari, F. (2005). A space-time permutation scan statistic for disease outbreak detection. *Plos Medicine*, *2*, 216-224.
- Kulldorff, M., Huang, L., Pickle, L., & Duczmal, L. (2006). An elliptic spatial scan statistic. *Statistics in Medicine*, *25*, 3929-3943.
- Kulldorff, M., & Nagarwalla, N. (1995). Spatial disease clusters: detection and inference. *Stat Med*, *14*, 799-810.
- Kulldorff, M., Zhang, Z., Hartman, J., Heffernan, R., Huang, L., & Mostashari, F. (2004). Benchmark data and power calculations for evaluating disease outbreak detection methods. *MMWR Morb Mortal Wkly Rep*, *53 Suppl*, 144-151.
- Kulldorff, M. (2010). SaTScan<sup>TM</sup>: Software for the spatial and space-time scan statistics, version 9.0.1 *Information Management Services*.
- Kuno, G. (1995). Review of the factors modulating dengue transmission. *Epidemiologic Reviews*, *17*, 321-335.

- Lam, S.K. (1993). Two Decades of Dengue in Malaysia. *Tropical Medicine*, 35, 195-200.
- Lam, S.K., Burke, D., Capeding, M.R., Chong, C.K., Coudeville, L., Farrar, J., Gubler, D., Hadinegoro, S.R., Hanna, J., Lang, J., Lee, H.L., Leo, Y.S., Luong, C.Q., Mahoney, R., McBride, J., Mendez-Galvan, J., Ng, L.C., Nimmannitya, S., Ooi, E.E., Shepard, D., Smit, J., Teyssou, R., Thomas, L., Torresi, J., Vasconcelos, P., Wirawan, D.N., & Yoksan, S. (2011). Preparing for introduction of a dengue vaccine: Recommendations from the 1st Dengue v2V Asia-Pacific Meeting. *Vaccine*, 29, 9417-9422.
- Lambin, E., Tran, A., Vanwambeke, S., Linard, C., & Soti, V. (2010). Pathogenic landscapes: Interactions between land, people, disease vectors, and their animal hosts. *International Journal of Health Geographics*, 9, 54.
- Lambin, E.F., & Meyfroidt, P. (2011). Global land use change, economic globalization, and the looming land scarcity. *Proceedings of the National Academy of Sciences*, 108, 3465-3472.
- Lambrechts, L., Paaijmans, K.P., Fansiri, T., Carrington, L.B., Kramer, L.D., Thomas, M.B., & Scott, T.W. (2011). Impact of daily temperature fluctuations on dengue virus transmission by *Aedes aegypti*. *Proceedings of the National Academy of Sciences*, 108, 7460-7465.
- Lee, D.J., Hicks, M.M., Griffiths, M., Debenham, M., Bryan, J., Russell, R., Geary, M., & Marks, E. (1987). *The Culicidae of the Australasian Region*. Australian Government Publishing Service.
- Lee, H.L. (1991). A nationwide resurvey of the factors affecting the breeding of *Aedes aegypti* (L.) and *Aedes albopictus* (Skuse) (Diptera: Culicidae) in urban town of peninsular Malaysia-1988-1989. *Tropical Biomedicine*, 8, 185-189.
- Lee, H.L., Chen, C.D., Masri, S.M., Chiang, Y.F., Chooi, K.H., & Benjamin, S. (2008). Impact of larviciding with a *Bacillus thuringiensis israelensis* formulation, VectoBac WG, on dengue mosquito vectors in a dengue endemic site in Selangor State, Malaysia. *Southeast Asian J Trop Med Public Health*, 39, 601-609.
- Lemon, S.M., Sparling, P.F., Hamburg, M.A., Relman, D.A., Choffnes, E.R., & Mack, A. (2008). *Vector-Borne Diseases: Understanding the Environmental, Human Health, and Ecological Connections, Workshop Summary (Forum on Microbial Threats)*. National Academies Press.
- Lewin-Koh, N.J., Bivand, R., Pebesma, E.J., Archer, E., Baddeley, A., & al., e. (2012). maptools: tools for reading and handling spatial objects. R package version 0.7-26.
- Li, C.F., Lim, T.W., Han, L.L., & Fang, R. (1985). Rainfall, abundance of *Aedes aegypti* and dengue infection in Selangor, Malaysia. *The Southeast Asian journal of tropical medicine and public health*, 16, 560-568.
- Li, S., Tao, H., & Xu, Y. (2013). Abiotic determinants to the spatial dynamics of dengue fever in Guangzhou. *Asia-Pacific Journal of Public Health*, 25, 239-247.

- Lim, K.W., Sit, N.W., Norzahira, R., Sing, K.W., Wong, H.M., Chew, H.S., Firdaus, R., Suria, M., Mahathavan, M., Nazni, W.A., Lee, H.L., McKemy, & A., V., S., S. (2010). Dengue vector surveillance in insular settlements of Pulau Ketam, Selangor, Malaysia. *Tropical Biomedicine*, 27, 185-192.
- Lourenco-de-Oliveira, R., Castro, M.G., Braks, M.A.H., & Lounibos, L.P. (2004). The invasion of urban forest by dengue vectors in Rio de Janeiro. *Journal of Vector Ecology*, 29, 94-100.
- Lowe, R., Bailey, T.C., Stephenson, D.B., Graham, R.J., Coelho, C.A.S., Carvalho, M.S., & Barcellos, C. (2011). Spatio-temporal modelling of climate-sensitive disease risk: Towards an early warning system for dengue in Brazil. *Computers & Geosciences*, 37, 371-381.
- Lowe, R., Bailey, T.C., Stephenson, D.B., Jupp, T.E., Graham, R.J., Barcellos, C., & Carvalho, M.S. (2013). The development of an early warning system for climate-sensitive disease risk with a focus on dengue epidemics in Southeast Brazil. *Statistics in Medicine*, 32, 864-883.
- Lu, L., Lin, H., Tian, L., Yang, W., Sun, J., & Liu, Q. (2009). Time series analysis of dengue fever and weather in Guangzhou, China. *Bmc Public Health*, 9, 395-400.
- Luo, Y., Zhang, Y., Liu, T., Rutherford, S., Xu, Y., Xu, X., Wu, W., Xiao, J., Zeng, W., Chu, C., & Ma, W. (2013). Lagged effect of diurnal temperature range on mortality in a subtropical megacity of china. *Plos One*, 8, e55280.
- Luz, P.M., Mendes, B.V.M., Codeco, C.T., Struchiner, C.J., & Galvani, A.P. (2008). Time Series Analysis of Dengue Incidence in Rio de Janeiro, Brazil. *American Journal of Tropical Medicine and Hygiene*, 79, 933-939.
- Machado-Machado, E.A. (2012). Empirical mapping of suitability to dengue fever in Mexico using species distribution modeling. *Applied Geography*, 33, 82-93.
- Maciél-de-Freitas, R., Neto, R.B., Goncalves, J.M., Codeco, C.T., & Lourenco-de-Oliveira, R. (2006). Movement of dengue vectors between the human modified environment and an urban forest in Rio de Janeiro. *J Med Entomol*, 43, 1112-1120.
- Mackenzie, J.S., Gubler, D.J., & Petersen, L.R. (2004). Emerging flaviviruses: the spread and resurgence of Japanese encephalitis, West Nile and dengue viruses. *Nature Medicine*, 10, S98-S109.
- Malaysia Institute for Medical Research (2010). *Dengue Fever Studies (1981-2010)*. Kuala Lumpur, Malaysia: Institute for Medical Research Malaysia.
- Martin, V., Pfeiffer, D.U., Zhou, X., Xiao, X., Prosser, D.J., Guo, F., & Gilbert, M. (2011). Spatial distribution and risk factors of highly pathogenic avian influenza (HPAI) H5N1 in China. *Plos Pathogens*, 7, e1001308.
- Mayer, J.D. (1982). Relations between two traditions of medical geography: health systems planning and geographical epidemiology. *Progress in Human Geography*, 6, 216-230.

## References

- McMichael, A.J. (2013). Globalization, climate change, and human health. *New England Journal of Medicine*, 368, 1335-1343.
- McMichael, A.J., Woodruff, R.E., & Hales, S. (2006). Climate change and human health: present and future risks. *Lancet*, 367, 859-869.
- Millennium Ecosystem Assessment (2005). Ecosystems and human well-being: synthesis. *Washington, DC: Island Press*.
- Ministry of Health Malaysia (1986). Prevention and control guide for dengue fever/dengue hemorrhagic fever. Kuala Lumpur, Malaysia: Ministry of Health Malaysia.
- Ministry of health Malaysia (2009). Pelan Strategik Pencegahan dan Kawalan Denggi 2009-2013. Putrajaya, Malaysia: Ministry of Health Malaysia.
- Ministry of Health Malaysia (2010). Management of Dengue Infection in Adults. In *Clinical Practice Guidelines*. Putrajaya, Malaysia: Ministry of Health Malaysia [online]. Available from: <http://www.moh.gov.my/attachments/5502.pdf> [accessed October 2011]
- Ministry of Health Malaysia (2011a). Communication for Behavioral Impact Community Guidelines. In Division, H.E. (Ed.). Putrajaya, Malaysia: Ministry of Health Malaysia.
- Ministry of Health Malaysia (2011b). Health Facts 2010. In (p. 5). Putrajaya, Malaysia: Ministry of Health Malaysia.
- Ministry of Health Malaysia (2012). Annual Report Ministry of Health 2012. Putrajaya, Malaysia: Ministry of Health Malaysia.
- Ministry of Natural Resources and Environment Malaysia (2011). Malaysia Second National Communication to the United Nations Framework Convention on Climate Change (UNFCCC). Putrajaya, Malaysia: Ministry of Natural Resources and Environment Malaysia.
- Minzava, A., Curtis, C., Manga, L., & Touré, Y. (2006). Application of genetically modified mosquitoes in national vector control programmes: thoughts on integrated control. In B. G. J. Knols, C.L. (Ed.) *Bridging laboratory and field research for genetic control of disease vectors* (pp. 211-214). The Netherlands.: Springer.
- Mocellin, M.G., Simoes, T.C., do Nascimento, T.F.S., Teixeira, M.L.F., Lounibos, L.P., & de Oliveira, R.L. (2009). Bromeliad-inhabiting mosquitoes in an urban botanical garden of dengue endemic Rio de Janeiro. Are bromeliads productive habitats for the invasive vectors *Aedes aegypti* and *Aedes albopictus*? *Memorias Do Instituto Oswaldo Cruz*, 104, 1171-1176.
- Mondini, A., & Chiaravalloti-Neto, F. (2008). Spatial correlation of incidence of dengue with socioeconomic, demographic and environmental variables in a Brazilian city. *Science of The Total Environment*, 393, 241-248.
- Moore, C.G., Cline, B.L., Ruiz-Tiben, E., Lee, D., Romney-Joseph, H., & Rivera-Correa, E. (1978). *Aedes aegypti* in Puerto Rico: environmental determinants of larval

- abundance and relation to dengue virus transmission. *The American journal of tropical medicine and hygiene*, 27, 1225-1231.
- Morrison, A.C., Getis, A., Santiago, M., Rigau-Perez, J.G., & Reiter, P. (1998). Exploratory space-time analysis of reported dengue cases during an outbreak in Florida, Puerto Rico, 1991-1992. *American Journal of Tropical Medicine and Hygiene*, 58, 287-298.
- Muhammad Azami, N.A., Salleh, S., Neoh, H.m., Syed Zakaria, S., & Jamal, R. (2011). Dengue epidemic in Malaysia: Not a predominantly urban disease anymore. *BMC Research Notes*, 4, 216.
- Müller, D., Leitão, P.J., & Sikor, T. (2013). Comparing the determinants of cropland abandonment in Albania and Romania using boosted regression trees. *Agricultural Systems*, 117, 66-77.
- Mulligan, K., Elliott, S.J., & Schuster-Wallace, C.J. (2012). Global public health policy transfer and dengue fever in Putrajaya, Malaysia: a critical discourse analysis. *Critical Public Health*, 22, 407-418.
- Naish, S., Dale, P., Mackenzie, J., McBride, J., Mengersen, K., & Tong, S. (2014). Climate change and dengue: a critical and systematic review of quantitative modelling approaches. *BMC Infectious Diseases*, 14, 167.
- Nazni, W.A., Lee, H.L., Rozita, W.M.W., Lian, A.C., Chen, C.D., Azahari, A.H., & Sadiyah, I. (2009). Oviposition behaviour of *Aedes albopictus* in temephos and *Bacillus thuringiensis israelensis*-treated ovitraps. *Dengue Bulletin*, 33, 209-217.
- Nazri, C., Hashim, A., & Rodziah, I. (2009). Distribution pattern of a dengue fever outbreak using GIS. *Journal of Environmental Health Research*, 9, 89-96.
- Neteler, M., Roiz, D., Rocchini, D., Castellani, C., & Rizzoli, A. (2011). Terra and Aqua satellites track tiger mosquito invasion: modelling the potential distribution of *Aedes albopictus* in north-eastern Italy. *International Journal of Health Geographics*, 10, 49.
- Nobuchi, H. (1979). The symptoms of a dengue-like illness recorded in a Chinese medical encyclopedia. *Kanpo no Rinsho*, 26, 422-425.
- Nyamah, M.A., Sulaiman, S., & Omar, B. (2010). Categorization of potential breeding sites of dengue vectors in Johor, Malaysia. *Trop Biomed*, 27, 33-40.
- Olaniyi, A.O., Abdullah, A.M., Ramli, M.F., & Sood, A.M. (2012). Factors affecting agricultural land use for vegetables production - a case study of the state of Selangor, Malaysia. *Afr. J. Agric. Res.*, 7, 5939-5948.
- Ooi, E.-E., Goh, K.-T., & Gubler, D.J. (2006). Dengue prevention and 35 years of vector control in Singapore. *Emerging infectious diseases*, 12.
- Openshaw, S. (1983). *The Modifiable Areal Unit Problem*. England: Geo Books.

## References

- Oppel, S., Meirinho, A., Ramírez, I., Gardner, B., O'Connell, A.F., Miller, P.I., & Louzao, M. (2012). Comparison of five modelling techniques to predict the spatial distribution and abundance of seabirds. *Biological Conservation*, *156*, 94-104.
- Ostfeld, R.S., Keesing, F., & Eviner, V.T. (2010). *Infectious disease ecology: effects of ecosystems on disease and of disease on ecosystems*. New Jersey, United States of America: Princeton University Press.
- Paily, K.P., Chandhiran, K., Vanamail, P., Kumar, N.P., & Jambulingam, P. (2013). Efficacy of a mermithid nematode *Romanomermis iyengari* (Welch) (Nematoda: Mermithidae) in controlling tree hole-breeding mosquito *Aedes albopictus* (Skuse) (Diptera: Culicidae) in a rubber plantation area of Kerala, India. *Parasitology Research*, *112*, 1299-1304.
- Pant, C.P., & Yasuno, M. (1973). Field studies on the gonotrophic cycle of *Aedes aegypti* in Bangkok, Thailand. *Journal of medical entomology*, *10*, 219-223.
- Patz, J., Githeko, A., McCarty, J., Hussein, S., Confalonieri, U., & De Wet, N. (2003). Climate change and infectious diseases. *Climate change and human health: risks and responses*, 103-137.
- Patz, J., Graczyk, T., Geller, N., & Vittor, A. (2000). Effects of environmental change on emerging parasitic diseases. *Int J Parasitol*, *30*, 1395-1405.
- Patz, J., Martens, W., Focks, A., & Jetten, T. (1998). Dengue Fever Epidemic Potential as Projected by General Circulation Models of Global Climate Change. *Environmental Health Perspective*, *6*, 147-153.
- Patz, J., & Norris, D. (2004). Land use change and human health. *DeFries, Asner, and Houghton, Note*, *6*, 159-167.
- Patz, J., Olson, S., Uejio, C., & Gibbs, H. (2008). Disease emergence from global climate and land use change. *Med Clinics of North Am*, *92*, 1473-1491.
- Patz, J.A., Daszak, P., Tabor, G.M., Aguirre, A.A., Pearl, M., Epstein, J., Wolfe, N.D., Kilpatrick, A.M., Foutoupoulos, J., Molyneux, D., Bradley, D.J., & Dis, W.G.L.U.C. (2004). Unhealthy landscapes: Policy recommendations on land use change and infectious disease emergence. *Environmental Health Perspectives*, *112*, 1092-1098.
- Penn, G.H. (1947). The larval development and ecology of *Aedes* (*Stegomyia*) *scutellaris* (Walker, 1859) in New Guinea. *The Journal of parasitology*, *33*, 43-50.
- Peterson, A.T. (2006). Ecologic niche modeling and spatial patterns of disease transmission. *Emerging infectious diseases*, *12*, 1822.
- Pfeiffer, D., & Hugh-Jones, M. (2002). Geographical information systems as a tool in epidemiological assessment and wildlife disease management. *Revue scientifique et technique-Office international des épizooties*, *21*, 91-102.
- Pfeiffer, D., Robinson, T., Stevenson, M., Stevens, K.B., Rogers, D.J., & Clements, A.C. (2008). *Spatial analysis in epidemiology*. Oxford University Press New York.



- Pham, H., Doan, H., Phan, T., & Tran Minh, N. (2011). Ecological factors associated with dengue fever in a central highlands Province, Vietnam. *BMC Infectious Diseases*, *11*, 171-176.
- Pittman, S.J., & Brown, K.A. (2011). Multi-scale approach for predicting fish species distributions across coral reef seascapes. *PloS one*, *6*, e20583.
- Ponlawat, A., & Harrington, L.C. (2005). Blood feeding patterns of *Aedes aegypti* and *Aedes albopictus* in Thailand. *Journal of Medical Entomology*, *42*, 844-849.
- R Development Core Team (2013). R: a language and environment for statistical computing. R foundation for statistical computing. In, *R Development Core Team*. Vienna, Austria.
- Ramasamy, R., Surendran, S.N., Jude, P.J., Dharshini, S., & Vinobaba, M. (2011). Larval Development of *Aedes aegypti* and *Aedes albopictus* in Peri-Urban Brackish Water and Its Implications for Transmission of Arboviral Diseases. *PLoS Negl Trop Dis*, *5*, e1369.
- Reisen, W.K. (2010). Landscape Epidemiology of Vector-Borne Diseases. *Annual Review of Entomology*, *55*, 461-483.
- Richards, S., Ponnusamy, L., Unnasch, T., Hassan, H., & Apperson, C. (2006). Host-feeding patterns of *Aedes albopictus* (Diptera: Culicidae) in relation to availability of human and domestic animals in suburban landscapes of central North Carolina. *J Med Entomol*, *43*, 543.
- Ridgeway, G. (2013). Gbm: Generalized boosted regression models. R package version 2.1 [online]. Available from: <http://cran.r-project.org/web/packages/gbm/> [accessed June 2013].
- Rogers, D.J., Wilson, A.J., Hay, S.I., & Graham, A.J. (2006). The global distribution of yellow fever and dengue. *Advances in Parasitology*, *62*, 181-220.
- Rohani, A., Abdullah, A., Ong, Y., Saadiyah, I., Zamree, I., & Lee, H. (2001). Survey of mosquito larvae distribution in container habitats collected from urban and rural areas in major towns of Malaysia. *Trop Biomed*, *18*, 41-49.
- Rohani, A., Suzilah, I., Malinda, M., Anuar, I., Mazlan, I.M., Maszaitun, M.S., Topek, O., Tanrang, Y., Ooi, S.C., Rozilawati, H., & Lee, H.L. (2011). *Aedes* larval population dynamics and risk for dengue epidemics in Malaysia. *Trop Biomed*, *28*, 237-248.
- Roongpiboonsopit, D., & Karimi, H.A. (2010). Comparative evaluation and analysis of online geocoding services. *International Journal of Geographical Information Science*, *24*, 1081-1100.
- Rotmans, J., & Dowlatabadi, H. (1998). *Integrated assessment modeling*. Columbus, Ohio, USA: Batelle Press.
- Rowley, W., & Graham, C. (1968). The effect of temperature and relative humidity on the flight performance of female *Aedes aegypti*. *Journal of Insect Physiology*, *14*, 1251-1257.

## References

- Rozhan, S., Jamsiah, M., Rahimah, A., & Ang, K.T. (2006). The COMBI (Communication for Behavioural Impact) in the Prevention and Control of Dengue-The Hulu Langat Experience. *Journal of Community Health, 12*, 19-32.
- Rozilawati, H., Zairi, J. & Adanan, C.R. (2007). Seasonal abundance of *Aedes albopictus* in selected urban and suburban areas in Penang, Malaysia. *Trop Biomed, 24*, 83-94.
- Rudnick, A. (1986). Dengue virus ecology in Malaysia. *Inst. Med. Res. Malays. Bull, 23*, 51-152.
- Rudnick, A., Tan, E.E., Lucas, J.K., & Omar, M.B. (1965). Mosquito-borne haemorrhagic fever in Malaya. *British medical journal, 1*, 1269.
- Rush, B. (1951). An account of the bilious remitting fever: As it appeared in philadelphia, in the summer and autumn of the year 1780. *The American Journal of Medicine, 11*, 546-550.
- Russell, B.M., Muir, L.E., Weinstein, P., & Kay, B.H. (1996). Surveillance of the mosquito *Aedes aegypti* and its biocontrol with the copepod *Mesocyclops aspericornis* in Australian wells and gold mines. *Medical and Veterinary Entomology, 10*, 155-160.
- Saifur, R.G.M., Hassan, A.A., Dieng, H., Ahmad, H., Salmah, M.R.C., Satho, T., Saad, A.R., & Vargas, R.E.M. (2012). Update on Temporal and Spatial Abundance of Dengue Vectors in Penang, Malaysia. *Journal of the American Mosquito Control Association, 28*, 84-92.
- Saleeza, S.N.R., Norma-Rashid, Y.M., & Sofian-Azirun (2011). Mosquitoes Larval Breeding Habitat in Urban and Suburban Areas, Peninsular Malaysia. *World Acad. Sci. Eng. Technol., 58*, 569-573.
- Salje, H., Lessler, J., Endy, T.P., Curriero, F.C., Gibbons, R.V., Nisalak, A., Nimmannitya, S., Kalayanarooj, S., Jarman, R.G., Thomas, S.J., Burke, D.S., & Cummings, D.A.T. (2012). Revealing the microscale spatial signature of dengue transmission and immunity in an urban population. *Proceedings of the National Academy of Sciences, 109*, 9535-9538.
- Sarfraz, M.S., Tripathi, N., Tipdecho, T., Thongbu, T., Kerdthong, P., & Souris, M. (2012). Analyzing the spatio-temporal relationship between dengue vector larval density and land-use using factor analysis and spatial ring mapping. *Bmc Public Health, 12*, 853.
- Schimel, D., Alves, D., Enting, I., Heimann, M., Joos, F., Raynaud, D., Wigley, T., Prather, M., Derwent, R., & Ehhalt, D. (1996). Radiative forcing of climate change. In Houghton, J., Meira-Filho, L., Callander, B., Harris, N., Kattenberg, A. & Maskell, K. (Eds.), *Climate change 1995: The science of climate change* (pp. 65-131). Cambridge, UK: Cambridge Univ. Press.
- Schmaedick, M.A., Ball, T.S., Burkot, T.R., & Gurr, N.E. (2008). Evaluation of three traps for sampling *Aedes polynesiensis* and other mosquito species in American Samoa. *J Am Mosq Control Assoc, 24*, 319-322.
- Schwartz, S. (1994). The Fallacy of the Ecological Fallacy - the Potential Misuse of a Concept and the Consequences. *American Journal of Public Health, 84*, 819-824.

- Sciences, N.I.o.E.H. (2010). A human health perspective on climate change: A report outlining the research needs on the human health effects of climate change. *A Human Health Perspective On Climate Change: A Report Outlining the Research Needs on the Human Health Effects of Climate Change*. Environmental Health Perspectives (EHP); National Institute of Environmental Health Sciences.
- Scott, T.W., & Morrison, A.C. (2010a). Longitudinal field studies will guide a paradigm shift in dengue prevention. In Atkinson, P.W. (Eds.), *Vector Biology, Ecology and Control* (pp. 139-161). The Netherlands: Springer.
- Scott, T.W., & Morrison, A.C. (2010b). Vector dynamics and transmission of dengue virus: implications for dengue surveillance and prevention strategies: vector dynamics and dengue prevention. *Curr. Top. Microbiol. Immunol.*, 338, 115-128.
- Seng, T.A. (2001). Legislation for Dengue Control in Malaysia. *From the Editor's desk*, 25, 109.
- Service, M.W. (1997). Mosquito (Diptera : Culicidae) dispersal - The long and short of it. *Journal of Medical Entomology*, 34, 579-588.
- Shafie, A. (2011). Evaluation of the Spatial Risk Factors for High Incidence of Dengue Fever and Dengue Hemorrhagic Fever Using GIS Application. *Sains Malaysiana*, 40, 937-943.
- Shang, C.S., Fang, C.T., Liu, C.M., Wen, T.H., Tsai, K.H., & King, C.C. (2010). The Role of Imported Cases and Favorable Meteorological Conditions in the Onset of Dengue Epidemics. *PLoS Negl Trop Dis*, 4, 771-779.
- Sheehan, T.J., Gershman, S.T., MacDougall, L.A., Danley, R.A., Mroszczyk, M., Sorensen, A.M., & Kulldorff, M. (2000). Geographic assessment of breast cancer screening by towns, zip codes, and census tracts. *J Public Health Manag Pract*, 6, 48-57.
- Shepard, D.S., Undurraga, E.A., & Halasa, Y.A. (2013). Economic and disease burden of dengue in Southeast Asia. *PLoS neglected tropical diseases*, 7, e2055.
- Shepard, D.S., Undurraga, E.A., Lees, R.S., Halasa, Y., Lum, L.C., & Ng, C.W. (2012). Use of multiple data sources to estimate the economic cost of dengue illness in Malaysia. *The American journal of tropical medicine and hygiene*, 87, 796-805.
- Shroyer, D. (1986). *Aedes albopictus* and arboviruses: a concise review of the literature. *Journal of the American Mosquito Control Association*, 2, 424.
- Sinka, M.E., Bangs, M.J., Manguin, S., Chareonviriyaphap, T., Patil, A.P., Temperley, W.H., Gething, P.W., Elyazar, I.R., Kabaria, C.W., & Harbach, R.E. (2011). The dominant Anopheles vectors of human malaria in the Asia-Pacific region: occurrence data, distribution maps and bionomic précis. *Parasit Vectors*, 4, 89.
- Siqueira-Junior, J., Maciel, I., Barcellos, C., Souza, W., Carvalho, M., Nascimento, N., Oliveira, R., Morais-Neto, O., & Martelli, C. (2008). Spatial point analysis based on dengue surveys at household level in central Brazil. *Bmc Public Health*, 8, 361.
- Skae, F.M.T. (1902). Dengue Fever in Penang. *British Medical Journal* 2, 1581-1582.

## References

- Smith, C. (1956). Isolation of three strains of type 1 dengue virus from a local outbreak of the disease in Malaya. *Journal of Hygiene*, 54, 569-580.
- Smith, C. (1957). A localized outbreak of dengue fever in Kuala Lumpur: serological aspects. *Journal of Hygiene*, 55, 207-223.
- Smith, C.E.G. (1958). The distribution of antibodies to Japanese encephalitis, dengue, and yellow fever viruses in five rural communities in Malaya. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 52, 237-252.
- Smith, J., Amador, M., & Barrera, R. (2009). Seasonal and Habitat Effects on Dengue and West Nile Virus Vectors in San Juan, Puerto Rico. *Journal of the American Mosquito Control Association*, 25, 38-46.
- Song, C., & Kulldorff, M. (2003). Power evaluation of disease clustering tests. *Int J Health Geogr*, 2, 9.
- Sriprom, M., Chalvet-Monfray, K., Chaimane, T., Vongsawat, K., & Bicout, D.J. (2010). Monthly district level risk of dengue occurrences in Sakon Nakhon Province, Thailand. *Science of the Total Environment*, 408, 5521-5528.
- Stefani, A., Dusfour, I., Correa, A.P., Cruz, M., Dessay, N., Galardo, A., Galardo, C., Girod, R., Gomes, M., Gurgel, H., Lima, A.C., Moreno, E., Musset, L., Nacher, M., Soares, A., Carme, B., & Roux, E. (2013). Land cover, land use and malaria in the Amazon: a systematic literature review of studies using remotely sensed data. *Malaria Journal*, 12, 192.
- Steffen, W., Sanderson, R.A., Tyson, P.D., Jäger, J., Matson, P.A., Moore III, B., Oldfield, F., Richardson, K., Schellnhuber, H.J., & Turner, B.L. (2006). *Global change and the earth system: a planet under pressure*. Germany: Springer.
- Stevens, K.B., & Pfeiffer, D.U. (2011). Spatial modelling of disease using data- and knowledge-driven approaches. *Spat Spatiotemporal Epidemiol*, 2, 125-133.
- Stoddard, S.T., Morrison, A.C., Vazquez-Prokopec, G.M., Soldan, V.P., Kochel, T.J., Kitron, U., Elder, J.P., & Scott, T.W. (2009). The Role of Human Movement in the Transmission of Vector-Borne Pathogens. *Plos Neglected Tropical Diseases*, 3, e481.
- Suaya, J.A., Shepard, D.S., Siqueira, J.B., Martelli, C.T., Lum, L.C., Tan, L.H., Kongsin, S., Jiamton, S., Garrido, F., Montoya, R., Armien, B., Huy, R., Castillo, L., Caram, M., Sah, B.K., Sughayyar, R., Tyo, K.R., & Halstead, S.B. (2009). Cost of dengue cases in eight countries in the Americas and Asia: a prospective study. *The American journal of tropical medicine and hygiene*, 80, 846-855.
- Šumilo, D., Bormane, A., Asokliene, L., Vasilenko, V., Golovljova, I., Avsic-Zupanc, T., Hubalek, Z., & Randolph, S.E. (2008). Socio-economic factors in the differential upsurge of tick-borne encephalitis in central and Eastern Europe. *Reviews in Medical Virology*, 18, 81-95.
- Sumodan, P.K. (2003). Potential of Rubber Plantations as Breeding Source for *Aedes albopictus* in Kerala, India *Dengue Bull*, 27, 197-198.

- Sutherst, R.W. (2004). Global change and human vulnerability to vector-borne diseases. *Clinical microbiology reviews*, 17, 136-173.
- Tan, A.W.A., Loke, S.R., Benjamin, S., Lee, H.L., Chooi, K.H., & Sofian-Azirun, M. (2012). Spray application of *Bacillus Thuringiensis* Israelensis (BTI Strain AM65-52) against *Aedes Aegypti* (L.) and *Ae. Albopictus* SKUSE populations and impact on dengue transmission in a dengue endemic residential site in Malaysia. *Southeast Asian Journal of Tropical Medicine and Public Health*, 43, 296-310.
- Tatem, A.J., Hay, S.I., & Rogers, D.J. (2006). Global traffic and disease vector dispersal. *Proceedings of the National Academy of Sciences*, 103, 6242-6247.
- Teng, A.K., & Singh, S. (2001). Epidemiology and new initiatives in the prevention and control of dengue in Malaysia. *Dengue Bull*, 25, 7-14.
- Teng, H.J., Wu, Y.L., & Lin, T.H. (1999). Mosquito fauna in water-holding containers with emphasis on dengue vectors (Diptera : Culicidae) in Chungho, Taipei County, Taiwan. *Journal of Medical Entomology*, 36, 468-472.
- Teurlai, M., Huy, R., Cazelles, B., Duboz, R., Baehr, C., & Vong, S. (2012). Can Human Movements Explain Heterogeneous Propagation of Dengue Fever in Cambodia? *Plos Neglected Tropical Diseases*, 6, e1957.
- Thach, T.-Q., Wong, C.-M., Chan, K.-P., Chau, Y.-K., Chung, Y.-N., Ou, C.-Q., Yang, L., & Hedley, A.J. (2010). Daily visibility and mortality: Assessment of health benefits from improved visibility in Hong Kong. *Environmental Research*, 110, 617-623.
- Thavara, U., Tawatsin, A., Chansang, C., Kong-ngamsuk, W., Paosriwong, S., Boon-Long, J., Rongsriyam, Y., & Komalamisra, N. (2001). Larval occurrence, oviposition behavior and biting activity of potential mosquito vectors of dengue on Samui Island, Thailand. *Journal of Vector Ecology*, 26, 172-180.
- Tian, Z., Li, S., Zhang, J., Jaakkola, J., & Guo, Y. (2012). Ambient temperature and coronary heart disease mortality in Beijing, China: a time series study. *Environmental Health*, 11, 51-57.
- Tipayamongkhogul, M., Fang, C.T., Klinchan, S., Liu, C.M., & King, C.C. (2009). Effects of the El Nino-Southern Oscillation on dengue epidemics in Thailand, 1996-2005. *Bmc Public Health*, 9, 421-415.
- Tun-Lin, W., Kay, B.H., & Barnes, A. (1995). The Premise Condition Index: a tool for streamlining surveys of *Aedes aegypti*. *American journal of tropical medicine and hygiene*, 53, 591-594.
- Turner, L.R., Connell, D., & Tong, S. (2012). Exposure to hot and cold temperatures and ambulance attendances in Brisbane, Australia: a time-series study. *BMJ Open*, 2, 001071-001078.
- Tyson, F.L., Rice, D.L., & Dearry, A. (2004). Connecting the oceans and human health. *Environmental health perspectives*, 112, A455.

- Upegui, E., & Viel, J. (2012). GeoEye imagery and Lidar technology for small-area population estimation: An epidemiological viewpoint. *Photogrammetric Engineering and Remote Sensing*, 78, 693-702.
- Uribe, L.A.A., Pineda, S.V., Martinez, O.G., Flores, J.L., Davila, M.F., & Harris, M.K. (2008). Culicid Distribution in Coahuila, Mexico. *Southwestern Entomologist*, 33, 219-222.
- Van Boeckel, T.P., Thanapongtharm, W., Robinson, T., Biradar, C.M., Xiao, X., & Gilbert, M. (2012). Improving Risk Models for Avian Influenza: The Role of Intensive Poultry Farming and Flooded Land during the 2004 Thailand Epidemic. *PloS one*, 7, e49528.
- Vanwambeke, S.O., Bennett, S.N., & Kapan, D.D. (2011). Spatially disaggregated disease transmission risk: land cover, land use and risk of dengue transmission on the island of Oahu. *Tropical Medicine & International Health*, 16, 174-185.
- Vanwambeke, S.O., Lambin, E.F., Eichhorn, M.P., Flasse, S.P., Harbach, R.E., Oskam, L., Somboon, P., van Beers, S., van Benthem, B.H.B., Walton, C., & Butlin, R.K. (2007a). Impact of land-use change on dengue and malaria in northern Thailand. *Ecohealth*, 4, 37-51.
- Vanwambeke, S.O., Somboon, P., Harbach, R.E., Isenstadt, M., Lambin, E.F., Walton, C., & Butlin, R.K. (2007b). Landscape and land cover factors influence the presence of Aedes and Anopheles larvae. *J Med Entomol*, 44, 133-144.
- Vezzani, D., Rubio, A., Velazquez, S.M., Schweigmann, N., & Wiegand, T. (2005). Detailed assessment of microhabitat suitability for *Aedes aegypti* (Diptera : Culicidae) in Buenos Aires, Argentina. *Acta Tropica*, 95, 123-131.
- Vitousek, P.M. (1994). Beyond global warming: ecology and global change. *Ecology*, 75, 1861-1876.
- Vitousek, P.M., Mooney, H.A., Lubchenco, J., & Melillo, J.M. (1997). Human domination of Earth's ecosystems. *Science*, 277, 494-499.
- Waller, L.A., & Gotway, C.A. (2004). Spatial Clustering of Health Events: Regional Count Data. In Shewhart, W.A. & Wilks, S.S. (Eds.), *Applied Spatial Statistics for Public Health Data* (pp. 200-271). John Wiley & Sons, Inc.
- Wan-Norafikah, O., Nazni, W.A., Noramiza, S., Shafa'ar-Ko'Ohar, S., Heah, S.K., Nor-Azlina, A.H., Khairuh-Asuad, M., & Lee, H.L. (2012). Distribution of Aedes Mosquitoes in Three Selected Localities in Malaysia. *Sains Malaysiana*, 41, 1309-1313.
- Wang, L., & Cardenas, J.S. (2011). Small Area Population Estimation with High-Resolution Remote Sensing and Lidar. (pp. 183-193). John Wiley and Sons.
- Wardekker, J., de Jong, A., van Bree, L., Turkenburg, W., & van der Sluijs, J. (2012). Health risks of climate change: An assessment of uncertainties and its implications for adaptation policies. *Environmental Health*, 11, 67:61-67:16.

- Watts, D.M., Burke, D.S., Harrison, B.A., Whitmire, R.E., & Nisalak, A. (1987). Effect of temperature on the vector efficiency of *Aedes aegypti* for dengue 2 virus. *The American journal of tropical medicine and hygiene*, *36*, 143-152.
- Wickham, H. (2009). *ggplot2: elegant graphics for data analysis*. New York: Springer.
- Wilbanks, T., & Kates, R. (1999). Global Change in Local Places: How Scale Matters. *Climatic Change*, *43*, 601-628.
- Wilson, E.O. (1993). Is humanity suicidal? *BioSystems*, *31*, 235-242.
- Wilson, M.E. (2010). Re-emerging Diseases. In Killewo, J., Heggenhougen, K. & Quah, S.R. (Eds.), *Epidemiology and Demography in Public Health* (p. 115). Access Online via Elsevier.
- Wiwanitkit, V. (2014). Lessons learned from previous dengue outbreaks. *Asian Pacific Journal of Tropical Disease*, *4*, 67-70.
- Wood, S. (2006). *Generalized Additive Models: An Introduction with R*. London/Boca Raton: Chapman & Hall/CRC Press.
- Wood, S.N. (2008). Fast stable direct fitting and smoothness selection for generalized additive models. *Journal of the Royal Statistical Society Series B-Statistical Methodology*, *70*, 495-518.
- World Health Organization (1995). Global Strategy for Prevention and Control of Dengue Fever and Dengue Haemorrhagic Fever: report of the consultation on key issues in dengue vector control towards the operationalization of a global strategy. Geneva, Switzerland: World Health Organization.
- World Health Organization (2003). Guidelines for dengue surveillance and control. Geneva: World Health Organization.
- World Health Organization (2005). Dengue, dengue haemorrhagic fever and dengue shock syndrome in the context of the integrated management of childhood illness [online]. Available from: [http://whqlibdoc.who.int/hq/2005/WHO\\_FCH\\_CAH\\_05.13\\_eng.pdf](http://whqlibdoc.who.int/hq/2005/WHO_FCH_CAH_05.13_eng.pdf) [accessed January 2012].
- World Health Organization (2008a). Asia Pacific Dengue Program Managers Meeting. World Health Organization Western Pacific Region (p. 84).
- World Health Organization (2008b). Dengue and dengue haemorrhagic fever. *Health in Asia and the Pacific*, 244-255.
- World Health Organization (2008c). The dengue strategic plan for the asia pacific region 2008-2015. Geneva, Switzerland: World Health Organization.
- World Health Organization (2009). *Dengue Guidelines for Diagnosis, Treatment, Prevention and Control*. Geneva, Switzerland: World Health Organization.
- World Health Organization (2012a). Dengue and dengue haemorrhagic fever. In *Factsheet No 117, revised November 2012*. Geneva, Switzerland: World Health Organization

- [online]. Available from: <http://www.who.int/mediacentre/factsheets/fs117/en/> [accessed March 2013].
- World Health Organization (2012b). DengueNet database and geographic information system [online]. Available from: <http://www.who.int/globalatlas> [accessed January 2013].
- World Health Organization (2012c). Handbook for integrated vector management. *WHO Library Cataloguing-in-Publication Data*.
- Wu, P.C., Guo, H.R., Lung, S.C., Lin, C.Y., & Su, H.J. (2007). Weather as an effective predictor for occurrence of dengue fever in Taiwan. *Acta Tropica*, 103, 50-57.
- Wu, S.-s., Qiu, X., & Wang, L. (2005). Population estimation methods in GIS and remote sensing: a review. *GIScience & Remote Sensing*, 42, 80-96.
- Yang, H.M., Macoris, M.L.G., Galvani, K.C., Andrighetti, M.T.M., & Wanderley, D.M.V. (2009). Assessing the effects of temperature on the population of *Aedes aegypti*, the vector of dengue. *Epidemiology and Infection*, 137, 1188-1202.
- Yasuoka, J., & Levins, R. (2007). Ecology of vector mosquitoes in Sri Lanka--suggestions for future mosquito control in rice ecosystems. *The Southeast Asian journal of tropical medicine and public health*, 38, 646-657.
- Ye-Ebiyo, Y., Pollack, R.J., & Spielman, A. (2000). Enhanced development in nature of larval *Anopheles arabiensis* mosquitoes feeding on maize pollen. *The American journal of tropical medicine and hygiene*, 63, 90-93.
- Yoon, I.K., Getis, A., Aldstadt, J., Rothman, A.L., Tannitisupawong, D., Koenraadt, C.J., Fansiri, T., Jones, J.W., Morrison, A.C., Jarman, R.G., Nisalak, A., Mammen, M.P., Jr., Thammapalo, S., Srikiatkachorn, A., Green, S., Libraty, D.H., Gibbons, R.V., Endy, T., Pimgate, C., & Scott, T.W. (2012). Fine Scale Spatiotemporal Clustering of Dengue Virus Transmission in Children and *Aedes aegypti* in Rural Thai Villages. *PLoS Negl Trop Dis*, 6, e1730.
- Zakaria, N.A., Ghani, A.A., Abdullah, R., Sidek, L.M., Kassim, A., & Ainan, A. (2004). MSMA—A New Urban Stormwater Management Manual for Malaysia. In Altinakar, M.S., Wang, S.S.Y., Holz, K.P., & Kawahara, M. (Eds.) *Proceedings of 6th International Conference on Hydro-Science and Engineering (ICHE)*, May 31-June 2, 2004 (pp. 1-10). Brisbane, Australia.
- Zakaria, S.Z.S., Roslan, N.A.M., Mokhtar, M., Hadi, A.S., Razman, M.R., Jahi, J.M., Ramli, Z., & Nordin, N.H. (2013). Environmental Maagement in Dealing with Dengue Fever Cases Towards Urban Sustainability: Study on the Prevention and Control of Infectious Diseases Act 1998 (Act 342). . *The Social Sciences*, 8, 295-299.
- Zhang, F., Krafft, T., Ye, B., Zhang, J., Luo, H., Li, M., Zhang, Y., Zhou, L., Xu, J., & Wang, W. (2013). The lag effects and seasonal differences of air pollutants on allergic rhinitis in Beijing. *Sci Total Environ*, 442, 172-176.



**Appendix A:**  
**Supplementary material for Chapter III**

### Monthly temporal clusters of dengue cases at the address level 2008-2010

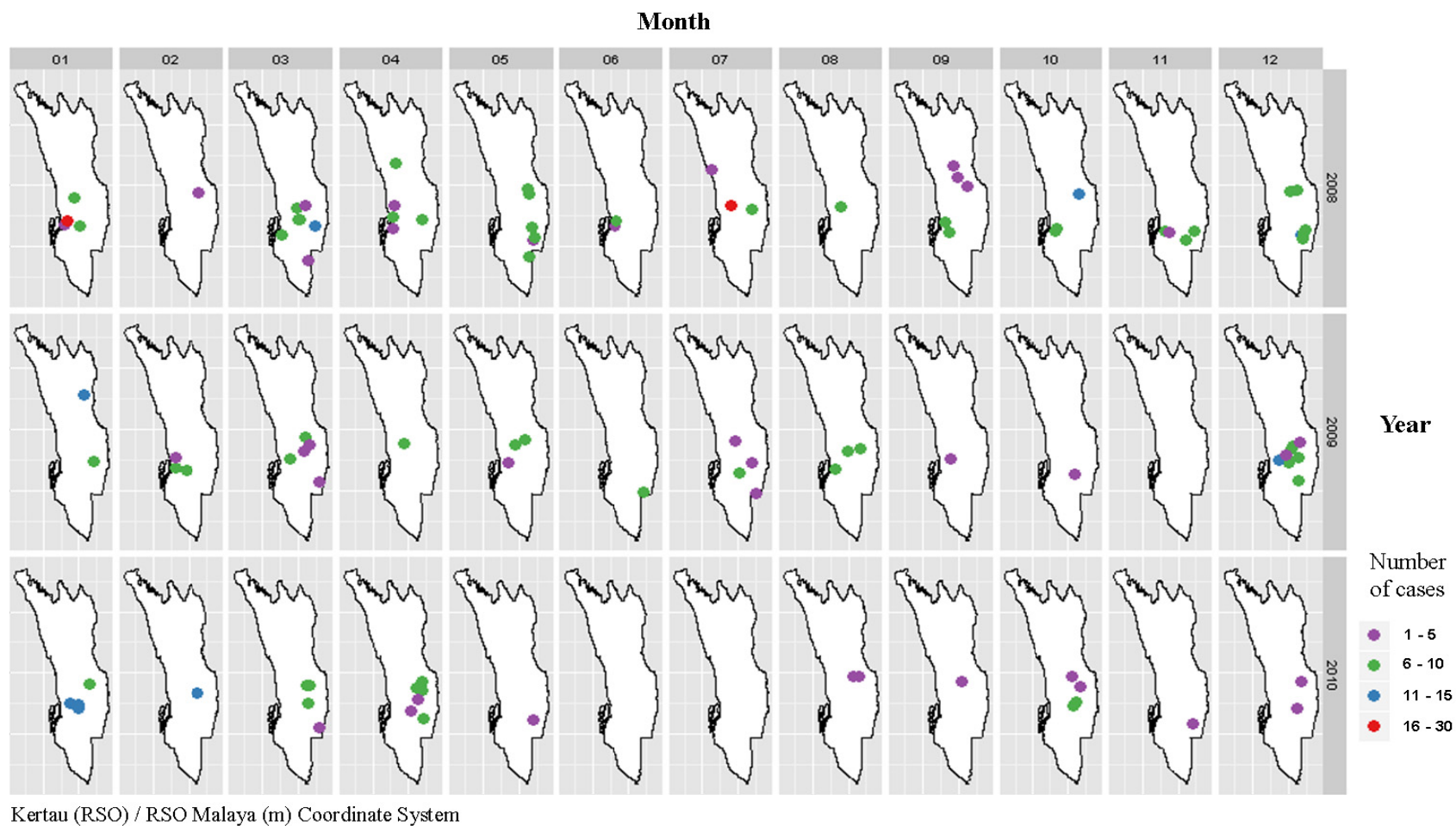


Figure A-1: Monthly temporal clusters of dengue cases at the address level 2008-2010

**Appendix B:**  
**Supplementary material for Chapter IV**

Appendix B

We used 3D visualization device system (OpenGL rgl) in the “rgl” R (R Development Core Team 2013) package, version 0.93.986 (Adler and Murdoch 2012) and software ImageMagick version 6.8.7 Q16 (ImageMagick Studio 1999) to convert the result of Figure IV-2 to the animated movie. The movies can be downloaded from Cheong et al. (2013).

Movie S1. Relative Risk of dengue cases by minimum temperature (°C) for a lag of 90 days, using a “natural cubic B-spline-natural cubic spline” DLNM with a 3 degrees of freedom natural cubic B-spline. The reference median value was 24 °C.

Movie S2. Relative Risk of dengue cases by bi-weekly accumulated rainfall (mm) for a lag of 90 days, using a “natural cubic B-spline-natural cubic spline” DLNM with a 3 degrees of freedom natural cubic B-spline. The reference median value was 108.20 mm.

Movie S3. Relative Risk of dengue cases by wind speed (knots) for a lag of 90 days, using a “natural cubic B-spline-natural cubic spline” DLNM with a 3 degrees of freedom natural cubic B-spline. The reference median value was 2.7 knots.

Table B-1: Pearson correlation coefficients between dengue cases and weathers parameters, Selangor, Kuala Lumpur and Putrajaya 2008–2010.

	<b>Daily Minimum Temperature (°C)</b>	<b>Daily Maximum Temperature (°C)</b>	<b>Daily Mean Temperature (°C)</b>	<b>Daily Relative Humidity (%)</b>	<b>Daily Wind Speed (Knot)</b>	<b>Cumulative Bi-Weekly Rainfall (mm)</b>	<b>Daily Total Dengue Cases</b>
Daily minimum temperature	1.00	0.47	0.64	-0.09	0.11	-0.11	-0.29
Daily maximum temperature		1.00	0.79	-0.44	0.15	-0.11	-0.14
Daily mean temperature			1.00	-0.60	0.28	-0.18	-0.22
Daily relative humidity				1.00	-0.38	0.33	-0.09
Daily wind speed					1.00	-0.19	-0.09
Cumulative bi-weekly rainfall						1.00	-0.01
Daily total dengue cases							1.00

Table B-2: Diagnostics of dengue-weather parameters models.

Variable in the Model	AIC	Deviance Explained	Remarks
MinT	7418.645	74.4	All parameters statistically significant
MaxT	7435.730	74.1	All parameters statistically significant
WDSP	7423.545	74.3	All parameters statistically significant
RH	7427.296	74.3	All parameters statistically significant
RF	7398.850	74.6	All parameters statistically significant
RF, MinT	7382.249	75.0	All parameters statistically significant
RF, MaxT	7396.225	74.7	MaxT is not statistically significant
RF, RH	7393.082	74.9	All parameters statistically significant
RF, WDSP	7383.954	75.0	All parameters statistically significant
RF, MinT, MaxT	7380.956	75.2	MaxT is not statistically significant
RF, MinT, RH	7378.860	75.3	RH is not statistically significant
RF, MinT, WDSP	7367.231	75.5	All parameters statistically significant
RF, MinT, WDSP, RH	7365.200	75.7	RH is not statistically significant
RF, MinT, WDSP, MaxT	7365.544	75.6	MaxT is not statistically significant

Models also include a natural cubic spline of time per year using 4 df, a factor of day of the week and a natural cubic spline of week of the year. MinT = Minimum temperature; MaxT = Maximum temperature; WDSP = Wind speed; RH = Relative humidity; RF = Cumulative bi-weekly rainfall.

Table B-3: Model selection based on delta AIC.

Model	AIC	Delta AIC	Model Likelihood	Akaike Weight
minimum AIC model: RF, MinT, WDSP	7367.231	0.000	1.000	0.996
RF, MinT, RH	7378.860	11.629	0.003	0.003
RF, MinT, MaxT	7380.956	13.725	0.001	0.001

MinT = Minimum temperature; MaxT = Maximum temperature; WDSP = Wind speed;  
RH = Relative humidity; RF = Cumulative bi-weekly rainfall.

The delta AIC ( $\Delta_i$ ) is a measure of each model relative to the best model (Equation (1)).

$$\text{Delta AIC} = \Delta_i = \text{AIC}_i - \text{min AIC} \quad (1)$$

Appendix B

where  $AIC_i$  is the AIC value for model  $i$ , and  $\min AIC$  is the AIC value of the best model that is with lowest AIC value. As a guideline, a  $\Delta_i < 2$  suggests substantial evidence for the model, values between 3 and 7 indicate that the model has considerably less support, whereas a  $\Delta_i > 10$  indicates that the model is very unlikely (Burnham and Anderson 2004).

The delta AIC is 11.629, suggesting the model with  $AIC_i$  is very unlikely to be selected as the best model. Hence, the best model (minimum temperature, rainfall and wind speed) is selected as the Akaike weight is 0.996.

Table B-4: All percentage change (and 95% CIs) in the number of dengue cases for minimum temperature, cumulated rainfall and wind speed, with 99th percentile relative to 90th percentile and with 1st percentile relative to 10th percentile, respectively.

Lag (Days)	Overall Percentage Change (95% CI)					
	Minimum Temperature (°C)		Cumulated Rainfall (mm)		Wind Speed (knots)	
	1st Percentile (22 °C) Relative to 10th Percentile (23 °C)	99th Percentile (26.5 °C) Relative to 90th Percentile (25.4 °C)	1st Percentile (11 mm) Relative to 10th Percentile (24 mm)	99th Percentile (302 mm) Relative to 90th Percentile (215 mm)	1st Percentile (1.7 kn) Relative to 10th Percentile (2.7 kn)	99th Percentile (5.7 kn) Relative to 90th Percentile (4.1 kn)
Cumulative	0.10(0.05,0.23)	11.92(4.41,32.19)	1.08(0.94,1.25)	21.45(8.96,51.37)	13.63(5.42,34.25)	1.30(0.20,8.39)
0	-2.00(-3.21, -0.78)	-4.69(-6.31, -3.05)	-0.19(-0.43,0.05)	3.39(1.93,4.86)	-0.98(-2.74,0.81)	2.80(0.12,5.56)
1	-2.06(-3.23, -0.89)	-4.30(-5.86, -2.72)	-0.18(-0.41,0.05)	3.48(2.06,4.93)	-0.79(-2.49,0.93)	2.70(0.09,5.38)
2	-2.12(-3.25, -0.98)	-3.91(-5.42, -2.39)	-0.18(-0.40,0.05)	3.58(2.18,4.99)	-0.61(-2.26,1.06)	2.61(0.06,5.22)
3	-2.18(-3.27, -1.08)	-3.53(-4.98, -2.05)	-0.17(-0.39,0.05)	3.67(2.30,5.05)	-0.43(-2.02,1.19)	2.51(0.02,5.06)
4	-2.24(-3.30, -1.16)	-3.14(-4.55, -1.72)	-0.17(-0.38,0.05)	3.76(2.42,5.12)	-0.25(-1.79,1.32)	2.41(-0.03,4.91)
5	-2.29(-3.33, -1.25)	-2.77(-4.13, -1.38)	-0.16(-0.37,0.05)	3.85(2.53,5.18)	-0.07(-1.56,1.44)	2.32(-0.09,4.78)
6	-2.35(-3.36, -1.32)	-2.40(-3.73, -1.05)	-0.16(-0.36,0.05)	3.93(2.63,5.25)	0.10(-1.34,1.57)	2.22(-0.15,4.65)
7	-2.40(-3.40, -1.39)	-2.04(-3.34, -0.73)	-0.15(-0.35,0.05)	4.01(2.73,5.31)	0.27(-1.13,1.69)	2.13(-0.22,4.53)
8	-2.45(-3.43, -1.45)	-1.69(-2.96, -0.40)	-0.14(-0.34,0.05)	4.09(2.82,5.37)	0.44(-0.93,1.82)	2.04(-0.29,4.43)
9	-2.49(-3.47, -1.51)	-1.35(-2.60, -0.08)	-0.14(-0.33,0.05)	4.16(2.90,5.43)	0.60(-0.73,1.94)	1.95(-0.37,4.33)
10	-2.54(-3.51, -1.56)	-1.02(-2.26,0.23)	-0.13(-0.32,0.06)	4.22(2.97,5.49)	0.75(-0.54,2.06)	1.87(-0.45,4.24)
11	-2.58(-3.55, -1.60)	-0.70(-1.93,0.54)	-0.13(-0.31,0.06)	4.29(3.05,5.54)	0.90(-0.36,2.18)	1.79(-0.53,4.16)
12	-2.62(-3.59, -1.64)	-0.39(-1.61,0.85)	-0.12(-0.31,0.06)	4.34(3.11,5.59)	1.05(-0.18,2.30)	1.70(-0.62,4.08)
13	-2.66(-3.63, -1.68)	-0.09(-1.31,1.15)	-0.12(-0.30,0.07)	4.40(3.17,5.64)	1.20(-0.01,2.42)	1.63(-0.70,4.01)
14	-2.69(-3.67, -1.71)	0.20(-1.02,1.44)	-0.11(-0.29,0.07)	4.45(3.22,5.69)	1.33(0.15,2.53)	1.55(-0.79,3.94)
15	-2.73(-3.71, -1.73)	0.48(-0.75,1.73)	-0.10(-0.29,0.08)	4.49(3.27,5.73)	1.47(0.31,2.64)	1.47(-0.88,3.88)

Table B-4. Cont.

Lag (Days)	Overall Percentage Change (95% CI)					
	Minimum Temperature (°C)		Cumulated Rainfall (mm)		Wind Speed (knots)	
	1st Percentile (22 °C) Relative to 10th Percentile (23 °C)	99th Percentile (26.5 °C) Relative to 90th Percentile (25.4 °C)	1st Percentile (11 mm) Relative to 10th Percentile (24 mm)	99th Percentile (302 mm) Relative to 90th Percentile (215 mm)	1st Percentile (1.7 kn) Relative to 10th Percentile (2.7 kn)	99th Percentile (5.7 kn) Relative to 90th Percentile (4.1 kn)
16	-2.76(-3.75, -1.76)	0.76(-0.48,2.01)	-0.10(-0.28,0.09)	4.54(3.31,5.77)	1.60(0.46,2.76)	1.40(-0.97,3.83)
17	-2.79(-3.79, -1.78)	1.02(-0.23,2.29)	-0.09(-0.28,0.09)	4.57(3.35,5.81)	1.73(0.60,2.87)	1.33(-1.06,3.77)
18	-2.81(-3.82, -1.80)	1.28(0.01,2.56)	-0.09(-0.27,0.10)	4.61(3.38,5.85)	1.85(0.74,2.98)	1.26(-1.15,3.72)
19	-2.84(-3.86, -1.81)	1.52(0.24,2.82)	-0.08(-0.27,0.11)	4.64(3.41,5.88)	1.97(0.87,3.08)	1.19(-1.24,3.67)
20	-2.86(-3.89, -1.82)	1.76(0.46,3.07)	-0.07(-0.26,0.11)	4.66(3.43,5.91)	2.08(0.99,3.19)	1.12(-1.33,3.63)
21	-2.89(-3.92, -1.83)	1.98(0.67,3.31)	-0.07(-0.26,0.12)	4.69(3.45,5.93)	2.19(1.11,3.29)	1.05(-1.41,3.59)
22	-2.90(-3.96, -1.84)	2.20(0.87,3.55)	-0.06(-0.25,0.13)	4.71(3.47,5.95)	2.30(1.23,3.39)	0.99(-1.50,3.54)
23	-2.92(-3.98, -1.85)	2.41(1.06,3.77)	-0.06(-0.25,0.13)	4.72(3.48,5.97)	2.41(1.34,3.48)	0.93(-1.58,3.50)
24	-2.94(-4.01, -1.85)	2.61(1.25,3.99)	-0.05(-0.24,0.14)	4.73(3.49,5.99)	2.50(1.44,3.58)	0.87(-1.66,3.46)
25	-2.95(-4.04, -1.86)	2.80(1.42,4.20)	-0.04(-0.24,0.15)	4.74(3.50,6.00)	2.60(1.54,3.67)	0.81(-1.73,3.42)
26	-2.97(-4.06, -1.86)	2.98(1.59,4.39)	-0.04(-0.23,0.15)	4.75(3.50,6.01)	2.69(1.64,3.76)	0.75(-1.81,3.38)
27	-2.98(-4.08, -1.86)	3.16(1.75,4.58)	-0.03(-0.23,0.16)	4.75(3.50,6.01)	2.78(1.73,3.84)	0.70(-1.88,3.34)
28	-2.98(-4.09, -1.86)	3.32(1.90,4.76)	-0.03(-0.22,0.17)	4.75(3.50,6.01)	2.87(1.82,3.93)	0.64(-1.95,3.30)
29	-2.99(-4.11, -1.86)	3.48(2.04,4.93)	-0.02(-0.22,0.18)	4.74(3.49,6.01)	2.95(1.90,4.01)	0.59(-2.01,3.26)
30	-3.00(-4.12, -1.86)	3.63(2.18,5.10)	-0.01(-0.21,0.18)	4.73(3.48,6.00)	3.03(1.98,4.08)	0.54(-2.07,3.22)
31	-3.00(-4.13, -1.86)	3.77(2.31,5.25)	-0.01(-0.21,0.19)	4.72(3.47,5.99)	3.10(2.06,4.16)	0.49(-2.13,3.19)
32	-3.00(-4.14, -1.85)	3.90(2.43,5.39)	0.00(-0.20,0.20)	4.70(3.45,5.97)	3.17(2.13,4.23)	0.44(-2.19,3.15)
33	-3.00(-4.15, -1.85)	4.02(2.55,5.52)	0.00(-0.19,0.20)	4.69(3.43,5.95)	3.24(2.20,4.29)	0.40(-2.24,3.11)
34	-3.00(-4.15, -1.84)	4.14(2.65,5.65)	0.01(-0.19,0.21)	4.67(3.41,5.93)	3.30(2.26,4.36)	0.35(-2.29,3.07)
35	-3.00(-4.15, -1.84)	4.25(2.76,5.76)	0.02(-0.18,0.22)	4.64(3.39,5.91)	3.37(2.32,4.42)	0.31(-2.34,3.02)
36	-3.00(-4.15, -1.83)	4.35(2.85,5.87)	0.02(-0.18,0.22)	4.61(3.37,5.88)	3.42(2.38,4.48)	0.26(-2.39,2.98)
37	-2.99(-4.15, -1.83)	4.44(2.94,5.97)	0.03(-0.17,0.23)	4.58(3.34,5.85)	3.48(2.44,4.53)	0.22(-2.43,2.94)
38	-2.99(-4.14, -1.82)	4.53(3.02,6.06)	0.04(-0.16,0.24)	4.55(3.31,5.81)	3.53(2.49,4.58)	0.18(-2.47,2.90)
39	-2.98(-4.13, -1.81)	4.61(3.10,6.14)	0.04(-0.16,0.24)	4.52(3.28,5.77)	3.58(2.54,4.63)	0.14(-2.50,2.86)
40	-2.97(-4.12, -1.80)	4.68(3.17,6.21)	0.05(-0.15,0.25)	4.48(3.24,5.73)	3.63(2.59,4.68)	0.10(-2.54,2.81)

Table B-4. Cont.

Lag (Days)	Overall Percentage Change (95% CI)					
	Minimum Temperature (°C)		Cumulated Rainfall (mm)		Wind Speed (knots)	
	1st Percentile (22 °C) Relative to 10th Percentile (23 °C)	99th Percentile (26.5 °C) Relative to 90th Percentile (25.4 °C)	1st Percentile (11 mm) Relative to 10th Percentile (24 mm)	99th Percentile (302 mm) Relative to 90th Percentile (215 mm)	1st Percentile (1.7 kn) Relative to 10th Percentile (2.7 kn)	99th Percentile (5.7 kn) Relative to 90th Percentile (4.1 kn)
41	-2.96(-4.11, -1.79)	4.75(3.24,6.28)	0.05(-0.15,0.26)	4.44(3.21,5.68)	3.67(2.63,4.72)	0.07(-2.57,2.77)
42	-2.94(-4.09, -1.78)	4.80(3.30,6.33)	0.06(-0.14,0.26)	4.39(3.17,5.64)	3.71(2.67,4.76)	0.03(-2.59,2.73)
43	-2.93(-4.07, -1.77)	4.85(3.35,6.38)	0.07(-0.13,0.27)	4.35(3.13,5.58)	3.75(2.71,4.79)	0.00(-2.62,2.68)
44	-2.92(-4.06, -1.76)	4.90(3.40,6.42)	0.07(-0.12,0.27)	4.30(3.08,5.53)	3.78(2.75,4.83)	-0.04(-2.64,2.64)
45	-2.90(-4.03, -1.75)	4.94(3.44,6.45)	0.08(-0.12,0.28)	4.25(3.04,5.47)	3.81(2.78,4.86)	-0.07(-2.66,2.59)
46	-2.88(-4.01, -1.74)	4.97(3.48,6.48)	0.09(-0.11,0.28)	4.20(2.99,5.41)	3.84(2.81,4.89)	-0.10(-2.68,2.55)
47	-2.86(-3.99, -1.73)	4.99(3.51,6.50)	0.09(-0.10,0.29)	4.14(2.95,5.35)	3.87(2.84,4.91)	-0.13(-2.70,2.50)
48	-2.84(-3.96, -1.72)	5.01(3.54,6.51)	0.10(-0.10,0.30)	4.08(2.90,5.28)	3.90(2.87,4.93)	-0.16(-2.71,2.46)
49	-2.82(-3.93, -1.70)	5.03(3.56,6.52)	0.11(-0.09,0.30)	4.02(2.84,5.21)	3.92(2.89,4.95)	-0.19(-2.72,2.41)
50	-2.80(-3.90, -1.69)	5.03(3.57,6.52)	0.11(-0.08,0.31)	3.96(2.79,5.14)	3.94(2.91,4.97)	-0.22(-2.73,2.36)
51	-2.78(-3.87, -1.68)	5.04(3.58,6.51)	0.12(-0.07,0.31)	3.90(2.73,5.07)	3.95(2.93,4.99)	-0.24(-2.74,2.32)
52	-2.75(-3.83, -1.66)	5.03(3.59,6.50)	0.13(-0.07,0.32)	3.83(2.68,5.00)	3.97(2.90,4.50)	-0.27(-2.74,2.27)
53	-2.73(-3.80, -1.65)	5.02(3.59,6.48)	0.13(-0.06,0.32)	3.76(2.62,4.92)	3.98(2.96,5.02)	-0.29(-2.75,2.23)
54	-2.70(-3.76, -1.63)	5.01(3.58,6.45)	0.14(-0.05,0.33)	3.69(2.56,4.84)	3.99(2.97,5.03)	-0.32(-2.75,2.18)
55	-2.68(-3.73, -1.61)	4.99(3.57,6.42)	0.15(-0.04,0.33)	3.62(2.50,4.76)	4.00(2.98,5.04)	-0.34(-2.75,2.14)
56	-2.65(-3.69, -1.60)	4.96(3.56,6.39)	0.15(-0.03,0.34)	3.55(2.43,4.67)	4.01(2.98,5.04)	-0.36(-2.75,2.09)
57	-2.62(-3.65, -1.58)	4.93(3.54,6.35)	0.16(-0.03,0.35)	3.47(2.37,4.59)	4.01(2.99,5.05)	-0.38(-2.75,2.05)
58	-2.59(-3.61, -1.56)	4.90(3.51,6.31)	0.17(-0.02,0.35)	3.39(2.30,4.50)	4.01(2.99,5.05)	-0.40(-2.75,2.00)
59	-2.56(-3.56, -1.54)	4.86(3.48,6.26)	0.17(-0.01,0.36)	3.31(2.23,4.41)	4.02(2.99,5.06)	-0.42(-2.75,1.96)
60	-2.53(-3.52, -1.52)	4.82(3.45,6.21)	0.18(0.00,0.36)	3.23(2.16,4.32)	4.01(2.98,5.06)	-0.44(-2.75,1.92)
61	-2.49(-3.48, -1.50)	4.77(3.41,6.16)	0.19(0.00,0.37)	3.15(2.08,4.23)	4.01(2.97,5.06)	-0.46(-2.74,1.88)
62	-2.46(-3.43, -1.48)	4.72(3.36,6.10)	0.19(0.01,0.37)	3.07(2.01,4.14)	4.01(2.97,5.06)	-0.48(-2.74,1.84)
63	-2.42(-3.39, -1.45)	4.67(3.31,6.04)	0.20(0.02,0.38)	2.98(1.93,4.05)	4.00(2.95,5.06)	-0.49(-2.73,1.80)
64	-2.39(-3.34, -1.43)	4.61(3.25,5.98)	0.21(0.03,0.38)	2.90(1.86,3.95)	3.99(2.94,5.06)	-0.51(-2.73,1.76)
65	-2.35(-3.30, -1.40)	4.54(3.19,5.91)	0.21(0.03,0.39)	2.81(1.78,3.86)	3.98(2.92,5.05)	-0.53(-2.73,1.73)
66	-2.32(-3.25, -1.38)	4.48(3.13,5.85)	0.22(0.04,0.40)	2.72(1.69,3.76)	3.97(2.91,5.05)	-0.54(-2.72,1.69)



Table B-4. Cont.

Lag (Days)	Overall Percentage Change (95% CI)					
	Minimum Temperature (°C)		Cumulated Rainfall (mm)		Wind Speed (knots)	
	1st Percentile (22 °C) Relative to 10th Percentile (23 °C)	99th Percentile (26.5 °C) Relative to 90th Percentile (25.4 °C)	1st Percentile (11 mm) Relative to 10th Percentile (24 mm)	99th Percentile (302 mm) Relative to 90th Percentile (215 mm)	1st Percentile (1.7 kn) Relative to 10th Percentile (2.7 kn)	99th Percentile (5.7 kn) Relative to 90th Percentile (4.1 kn)
67	-2.28(-3.20, -1.35)	4.41(3.06,5.78)	0.23(0.05,0.40)	2.63(1.61,3.66)	3.96(2.88,5.05)	-0.56(-2.72,1.66)
68	-2.24(-3.16, -1.32)	4.34(2.98,5.71)	0.23(0.06,0.41)	2.54(1.53,3.57)	3.95(2.86,5.05)	-0.57(-2.72,1.63)
69	-2.20(-3.11, -1.29)	4.26(2.90,5.64)	0.24(0.06,0.42)	2.45(1.44,3.47)	3.93(2.83,5.04)	-0.58(-2.72,1.60)
70	-2.17(-3.07, -1.26)	4.18(2.82,5.56)	0.25(0.07,0.42)	2.36(1.35,3.37)	3.92(2.81,5.04)	-0.60(-2.72,1.58)
71	-2.13(-3.02, -1.22)	4.10(2.73,5.49)	0.25(0.08,0.43)	2.26(1.26,3.27)	3.90(2.78,5.03)	-0.61(-2.72,1.55)
72	-2.09(-2.98, -1.19)	4.02(2.64,5.42)	0.26(0.08,0.44)	2.17(1.17,3.17)	3.88(2.74,5.03)	-0.62(-2.73,1.53)
73	-2.05(-2.93, -1.15)	3.93(2.54,5.34)	0.27(0.09,0.44)	2.07(1.07,3.08)	3.86(2.71,5.03)	-0.63(-2.73,1.51)
74	-2.00(-2.89, -1.11)	3.84(2.44,5.27)	0.27(0.10,0.45)	1.97(0.98,2.98)	3.84(2.67,5.02)	-0.64(-2.74,1.50)
75	-1.96(-2.85, -1.07)	3.75(2.33,5.19)	0.28(0.10,0.46)	1.88(0.88,2.88)	3.82(2.64,5.02)	-0.65(-2.75,1.49)
76	-1.92(-2.81, -1.03)	3.66(2.22,5.12)	0.29(0.11,0.47)	1.78(0.78,2.78)	3.80(2.59,5.02)	-0.67(-2.76,1.48)
77	-1.88(-2.77, -0.98)	3.56(2.11,5.04)	0.29(0.11,0.47)	1.68(0.68,2.69)	3.78(2.55,5.01)	-0.68(-2.78,1.47)
78	-1.84(-2.73, -0.94)	3.47(1.99,4.97)	0.30(0.12,0.48)	1.58(0.58,2.59)	3.75(2.51,5.01)	-0.69(-2.79,1.47)
79	-1.79(-2.69, -0.89)	3.37(1.87,4.90)	0.31(0.12,0.49)	1.48(0.48,2.50)	3.73(2.46,5.01)	-0.70(-2.81,1.46)
80	-1.75(-2.65, -0.84)	3.27(1.74,4.82)	0.31(0.13,0.50)	1.38(0.37,2.40)	3.70(2.42,5.00)	-0.70(-2.83,1.47)
81	-1.71(-2.61, -0.79)	3.17(1.62,4.75)	0.32(0.13,0.51)	1.28(0.26,2.31)	3.68(2.37,5.00)	-0.71(-2.85,1.47)
82	-1.66(-2.58, -0.73)	3.07(1.48,4.68)	0.33(0.14,0.52)	1.18(0.16,2.21)	3.65(2.32,5.00)	-0.72(-2.88,1.48)
83	-1.62(-2.55, -0.68)	2.97(1.35,4.60)	0.34(0.14,0.53)	1.08(0.05,2.12)	3.62(2.27,5.00)	-0.73(-2.91,1.49)
84	-1.57(-2.51, -0.62)	2.86(1.22,4.53)	0.34(0.15,0.54)	0.98(-0.06,2.03)	3.60(2.22,5.00)	-0.74(-2.94,1.51)
85	-1.53(-2.48, -0.56)	2.76(1.08,4.46)	0.35(0.15,0.55)	0.87(-0.18,1.94)	3.57(2.16,5.00)	-0.75(-2.97,1.52)
86	-1.48(-2.45, -0.50)	2.65(0.94,4.39)	0.36(0.16,0.56)	0.77(-0.29,1.85)	3.54(2.11,4.99)	-0.76(-3.01,1.54)
87	-1.44(-2.42, -0.44)	2.55(0.80,4.32)	0.36(0.16,0.57)	0.67(-0.40,1.76)	3.51(2.05,4.99)	-0.77(-3.05,1.57)
88	-1.39(-2.40, -0.38)	2.44(0.66,4.26)	0.37(0.16,0.58)	0.57(-0.52,1.67)	3.49(2.00,5.00)	-0.77(-3.09,1.59)
89	-1.35(-2.37, -0.32)	2.33(0.51,4.19)	0.38(0.17,0.59)	0.47(-0.63,1.58)	3.46(1.94,5.00)	-0.78(-3.13,1.62)
90	-1.30(-2.34, -0.25)	2.23(0.37,4.12)	0.38(0.17,0.60)	0.36(-0.75,1.49)	3.43(1.89,5.00)	-0.79(-3.17,1.65)

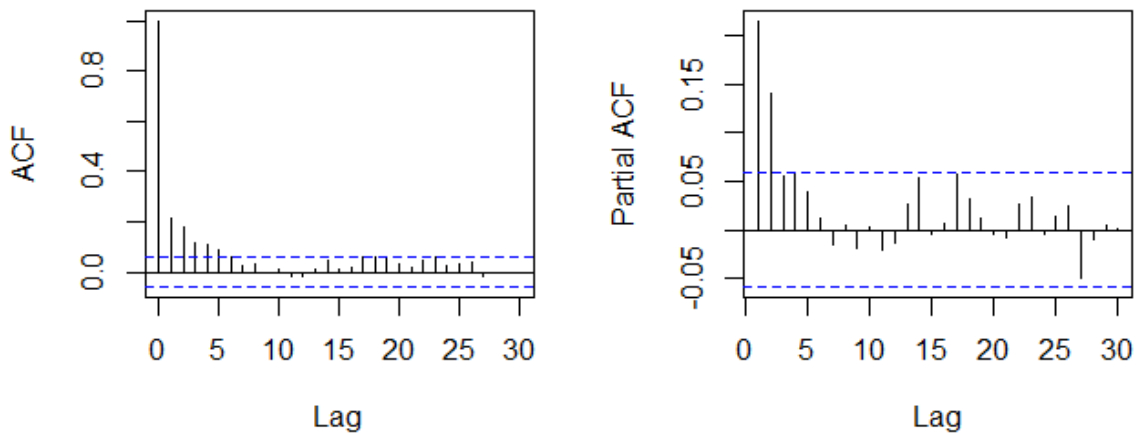


Figure B-1: Autocorrelation and partial autocorrelations of residuals for the selected model.

## References

- Adler, D. & Murdoch, D. (2012). 3D Visualization Device System (OpenGL) [online]. Available from: <http://rgl.neoscientists.org/about.shtml> [accessed October 2013].
- Cheong, Y.L., Burkart, K., Leitão, P.J., & Lakes, T. (2013). Assessing Weather Effects on Dengue Disease in Malaysia. *International Journal of Environmental Research and Public Health*, *10*, 6319-6334 [online]. Available from: <http://www.mdpi.com/1660-4601/10/12/6319> [accessed January 2014].
- ImageMagick Studio (1999). ImageMagick Studio LLC [online]. Available from: <http://www.imagemagick.org> [accessed January 2012].
- R Development Core Team (2013). R: a language and environment for statistical computing. R foundation for statistical computing. In, *R Development Core Team*. Vienna, Austria.

**Appendix C:**  
**Supplementary material for Chapter V**

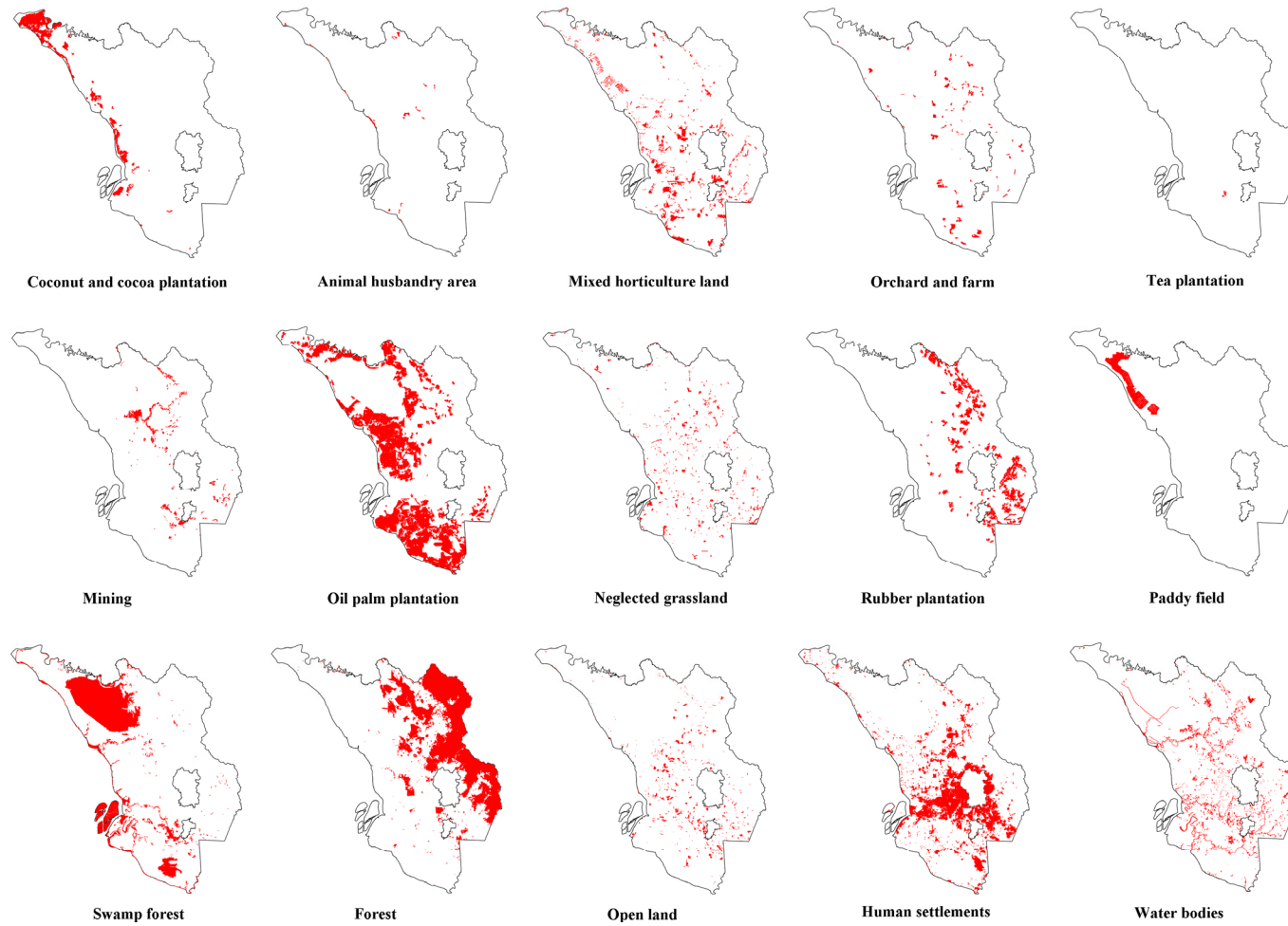


Figure C-1: Map of land use parameters highlighted in red.

## Publikationen

### Veröffentlichte Artikel (peer-reviewed)

---

- Cheong, Y.L., Burkart, K., Leitão, P.J., & Lakes, T. (2013). Assessing Weather Effects on Dengue Disease in Malaysia. *International Journal of Environmental Research and Public Health*, 10(12), 6319-6334.
- Cheong, Y.L., Leitão, P.J., & Lakes, T. (2014). Assessment of land use factors associated with dengue cases in Malaysia using Boosted Regression Trees. *Spatial and Spatio-temporal Epidemiology*, 10, 75-84.
- Cheong, Y.L., Gruebner, O., Krämer, A., & Lakes, T. (2014). Spatio-temporal patterns of dengue disease in Malaysia: combining address and sub-district level. *Geospatial Health*, 9(1), 131-140.

### Konferenzbeiträge (Artikel mit peer-review)

---

- Azizah, S., Alicia, T.Y.C., Cheong, Y.L., & Marini, O. (2002). A Traditional Expert System with a GUI Interface. In *Proceedings of National Conference of Graphics and Multimedia (CoGRAMM'02)*, Melaka, Malaysia.

### Konferenzbeiträge (Vorträge und Poster)

---

- Cheong, Y.L., Leitão, P.J., & Lakes, T. (2013). Assessing environmental risk factors of Dengue in Malaysia using boosted regression trees. *GEOMED 2013, the 8th international interdisciplinary conference on spatial epidemiology, spatial statistics and geomedical systems*, Sheffield, United Kingdom. Poster presentation.
- Cheong, Y.L. & Lakes, T. (2012). Spatio-temporal study on the risk of dengue disease in Malaysia. *Climate and Health Meeting*, Potsdam, Germany. Oral presentation.
- Cheong, Y.L. & Lakes, T. (2012). Spatio-temporal study on dengue disease in Malaysia. *Mini Workshop on Dengue*, Heidelberg, Germany. Oral presentation.
- Cheong, Y.L. & Lakes, T. (2011). Spatial and temporal cluster of dengue disease in a heterogeneous land cover state. *GEOMED 2011, the 7th international interdisciplinary conference on spatial epidemiology, spatial statistics and geomedical systems*, Victoria, Canada. Poster presentation.
- Cheong, Y.L. & Lakes, T. (2011). Spatial mapping of vector borne disease with RapidEye map. *RapidEye Science Archive (RESA) 3rd Workshop*, Neustadt, Germany. Oral presentation.



## **Eidesstattliche Erklärung**

Hiermit erkläre ich, die vorliegende Dissertation selbstständig und ohne Verwendung unerlaubter Hilfe angefertigt zu haben. Die aus fremden Quellen direkt oder indirect übernommenen Inhalte sind als solche kenntlich gemacht. Die Dissertation wird erstmalig und nur an der Humboldt-Universität zu Berlin eingereicht. Weiterhin erkläre ich, nicht bereits einen Dokortitel im Fach Geographie zu besitzen. Die dem Verfahren zu Grunde liegende Promotionsordnung ist mir bekannt.

Cheong Yoon Ling

Malaysia, den 22.08.2014