EVALUATING THE EFFECTS OF CLIMATE ON DENGUE CASES IN KELANTAN

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BY

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LIST OF ABBREVIATIONS

BI	Breteau Index
CPRC	Crisis Preparedness and Response Centre
DENV	Dengue virus
EIP	Extrinsic incubation period
EWAR	Early Warning and Response System
GAM	Generalized Additive Model
GIS	Geographical Information System
IgM	Immunoglobulin M
MOH	Ministry of Health
NS1	Non-structural protein 1
WHO	World Health Organization

PENILAIAN KESAN CUACA KE ATAS KES DENGGI DI KELANTAN

ABSTRAK

Pengenalan: Denggi masih endemik di negeri Kelantan meskipun banyak sumber telah dilaburkan dalam aktiviti kawalan vektor. Cuaca mempengaruhi taburan kes denggi dan telah dimasukkan di dalam beberapa Sistem Amaran dan Tindak Balas Awal untuk pemantauan denggi. Untuk menggunakan faktor cuaca secara proaktif dalam jangkaan peningkatan kes denggi di Kelantan, penilaian kesan cuaca ke atas kes denggi perlu dilaksanakan.

Objektif: Kajian ini bertujuan untuk menilai kesan cuaca terhadap kes denggi di Kelantan dari tahun 2016 hingga 2018. Tujuan ini dicapai melalui analisa trend kes denggi di Kelantan, pemetaan kadar insiden kes dan gugusan ruangan kes denggi berdasarkan daerah serta penilaian kesan suhu, hujan dan kelajuan angin terhadap kes denggi di Kelantan.

Metodologi: Kajian dijalankan menggunakan data sekunder retrospektif kes denggi yang diambil daripada sistem eDengue. Data cuaca, iaitu data harian bagi suhu minimum, suhu maksimum, suhu purata, hujan dan kelajuan angin dari tahun 2016 hingga 2018 telah diambil daripada stesen kajicuaca Kota Bharu. Pensampelan universal melibatkan kesemua 10,645 data dilaksanakan mengambilkira saiz sampel yang diperlukan adalah 10,704. Aplikasi ArcMap digunakan untuk memeta kadar insiden denggi dan gugusan ruangan kes denggi melalui analisis titik panas (*hotspot)*. Pengaruh cuaca terhadap kes denggi dianalisis dengan menggunakan model aditif Poisson umum (*generalized additive model*) dalam paket "mgcv" perisian R.

Keputusan: Purata kes denggi harian di Kelatan adalah sebanyak 9.8 kes. Trend kes denggi menunjukkan corak kitaran dengan kes puncak berlaku pada bulan April dan bulan Oktober setiap tahun. Kadar insiden denggi menunjukkan tren penurunan dengan kadar tertinggi dan lokaliti panas yang ketara telah dikenal pasti dicatatkan di daerah Kota Bharu. Suhu maksimum, suhu purata, hujan dan kelajuan angin menunjukkan kesan tidak linear yang signifikan terhadap kes denggi di Kelantan. Kes denggi tertinggi dicatatkan pada suhu maksimum antara 31.5˚C hingga 34˚C, suhu purata antara 23˚C hingga 26˚C, taburan hujan antara 20mm hingga 30mm dan kelajuan angin antara 0 m/s hingga 2 m/s.

Kesimpulan: Tempoh sebelum bermulanya musim antara dua monsun merupakan peluang untuk mempertingkatkan aktiviti kawalan vektor bagi mengurangkan magnitud kenaikan kes denggi. Perubahan pada gugusan ruangan juga perlu diambil kira untuk memastikan aktiviti kawalan ditujukan kepada kumpulan sasaran yang sewajarnya. Kolaborasi antara Jabatan Meteorologi Malaysia dan Kementerian Kesihatan Malaysia dalam memantau cuaca akan meningkatkan keberkesanan Sistem Amaran dan Tindak Cepat terhadap kes denggi.

KATA KUNCI: denggi; iklim; analisis ruangan; model tambah umum

EVALUATING THE EFFECTS OF CLIMATE ON DENGUE CASES IN KELANTAN

ABSTRACT

Introduction: Dengue remains endemic in Kelantan despite considerable investment in vector control activities. Climate plays an integral role in affecting the magnitude of dengue incidences and has been integrated into some local Early Warning and Response System for dengue. In order to enhance the proactive usage of climate factors for a state-specific, time-based estimation of dengue incidence in Kelantan, the effects of climate on dengue cases needs to be evaluated.

Objective: The study aims to evaluate the effects of climate on dengue cases in Kelantan from 2016 to 2018 by analysing the trend of dengue cases in Kelantan, mapping of incidence rate and spatial clustering of dengue by district, and estimating the effects of temperature, rainfall and wind speed on dengue cases in Kelantan.

Methodology: The study design uses a retrospective secondary data review of daily dengue case obtained from the eDengue system and daily minimum temperature, maximum temperature, mean temperature, cumulative rainfall and average wind speed obtained from Kota Bharu Weather station from the year 2016 to 2018. Universal sampling of the 10,645 data obtained was applied following sample size calculation of

10,704. The ArcMap application was used to analyse and map the dengue incidence rate and spatial clustering of dengue cases through hotspot analysis. The effect of climate on dengue cases was analysed by using a *Poisson* generalized additive model in the “mgcv” package of R software.

Results: There was an average of 9.8 dengue cases daily in Kelantan. A cyclical pattern was observed with peak cases occurring between April and October annually. The dengue incidence rate shows a reducing trend with the highest incidence and significant hotspot identified being in Kota Bharu district. The maximum temperature, mean temperature, rainfall, and wind speed shown significant non-linear effect on dengue incidence. The highest peak of dengue incidence found at the maximum temperature between 31.5˚C to 34˚C, the mean temperature between 23˚C to 26˚C, rainfall between 20mm to 30mm, and wind speed between 0 m/s to 2 m/s.

Conclusion: There is a limited window of opportunity before the start of the inter-monsoon period for enhanced vector control activities in order to reduce the magnitude of dengue cases. The changing geography of spatial clusters should also be considered for a targeted approach. Monitoring of climate variables through interagency collaboration between the Malaysian Meteorology Department and the Ministry of Health Malaysia provides an improved early warning system for dengue.

KEYWORDS: dengue; climate; spatial analysis; generalized additive model

CHAPTER 1

INTRODUCTION

1.1. Background

Dengue is a vector-borne viral illness transmitted by the *Aedes* mosquito, mainly by *Aedes aegypti* and to a smaller degree by *Aedes albopictus.* Originally from Africa, *Aedes aegypti* is also responsible for other illnesses including Zika, chikugunya and urban yellow fever. However, due to factors such as globalization, trade, urbanization and travel, these vectors have vastly spread from their original habitat over the past 50 years (Ebi and Nealon, 2016). Some were transported overland as adult mosquitoes in rubber tires whilst some were transported as eggs in egg-laden containers (Murray *et al.*, 2013).

Dengue has shown a dramatic increase in recent years, especially in the tropical and sub-tropical regions. However, rural areas in some countries are also being affected by dengue putting nearly half of the global population at risk of contracting the disease. The dengue virus (DENV) has been rapidly spreading through increased international tourism as infected travellers brings and introduces the virus to susceptible environment (Foley *et al.*, 2020). The interplay of vector abundance and virus availability is further attenuated by a changing climate which leads to higher dengue transmission in tropical and sub-tropical countries such as Malaysia.

1.1.1 Dengue Prevention and Control

Dengue cases are being treated symptomatically as there is still no definite treatment for dengue. Therefore, the mainstay of dengue management is through the prevention of the disease. One proposed approach is through increasing the host's immunity against dengue. Studies have shown that a dengue infection provides host immunity for decades against the infecting serotype but increases the risk of severe disease if infected by a different serotype (Biswal *et al.*, 2019). To overcome this issue, a tetravalent vaccine by Takeda has been developed based on a live attenuated DENV2 virus as the genetic backbone. Although the phase three clinical trial has shown an overall positive vaccine efficacy of 80.9% in the vaccinated group, the results differ according to serotype with a similar incidence of adverse events between vaccinated and placebo group (Biswal *et al.*, 2019). Hence, the vaccine is still not integrated into the national immunisation schedule.

Another method being researched to break the chain of transmission of dengue virus is through infecting *Aedes aegypti* with *Wolbachia* endosymbionts. This causes the mosquito to be less susceptible to dengue viruses and other medically important arboviruses. However, the effectiveness of the strategy to release *Wolbachia* infected mosquitoes are locality specific. Effectivity is dependent on the local mosquito population density and environmental conditions which cannot be replicated consistently in different infected areas (Nguyen *et al.*, 2015).

The mainstay of dengue prevention in most countries is through integrated vector control. This includes larviciding activities, reduction of breeding sites and the killing of adult mosquitoes. An estimated US$73.5 million was spent in 2010 in Malaysia on prevention and vector control activities alone, of which 33% is invested for fogging operations (Packierisamy *et al.*, 2015). Despite the involvement by all level of government through the National Dengue Vector Control Program, outbreaks of dengue cases still occur.

1.1.2 Dengue and Climate

Environmental variables such as climate, land use, vegetation index and slope of the terrain highly impacts the geographical distribution and seasonal abundance of dengue vectors (Palaniyandi *et al.*, 2014). Out of these factors, recent studies in Malaysia has shown that climate plays an integral role in affecting the magnitude of dengue incidences (Hii *et al.*, 2016; Jayaraj *et al.*, 2019). The increase is secondary to the direct impact of climate, especially temperature and rainfall, on mosquitoes breeding sites, life cycle, biting range, host activity, and vector incubation period (Cheong *et al.*, 2013; Hii *et al.*, 2016; Jayaraj *et al.*, 2019).

Climate variables were also reported to be associated with dengue outbreaks. In Malaysia, a dengue outbreak is defined when two or more dengue cases were reported from the same locality within seven days. Evidence of the association between climate variables and dengue outbreak or spatial clustering of dengue, however, is relatively inconsistent in the literature. In Thailand, for example, urbanization, rather than rainfall or temperature, was associated with spatial clustering of dengue (Phanitchat *et al.*, 2019). Another study by Tian *et al.* (2016) in Guangzhou China determines that increased surface water is associated with dengue outbreaks irrespective of the amount of rainfall in the area. However, Aziz *et al.* (2012) reported in their study that the amount of rainfall has correlation with spatial clustering or dispersion of dengue cases in Kuala Lumpur.

1.2. Statement of problem

Dengue is still endemic in Malaysia with periodic epidemics despite extensive vector control, thus causing a constant strain on public health resources. Some studies have been conducted to predict dengue occurrences through climate change. However, these studies are location specific and centre around the west coast of peninsular Malaysia. To the best of our knowledge, limited study has been conducted in Kelantan despite Kelantan being ranked first in the east coast of peninsular Malaysia and ranked fourth in Malaysia with the highest number of dengue cases in 2019.

Since no definitive treatment for dengue has yet been discovered, the mainstay of disease control is through effective vector control and preventive activities. Despite the importance of climate being mentioned as part of the Early Warning, Alert, and Response System in Malaysia (Ministry of Health, 2016), proactive measures against an increase in dengue cases predicted by climate change have not been fully utilized. Proactive measures include activities such as timely search and destroy activities during the inter-monsoon period or targeted distribution of health education materials to cover water-holding containers during the dry season. The reactive response towards notified cases remains as the bulk of preventive and control activities.

1.3. Rationale

The result of this study will provide a time-based estimate of possible dengue increases following changes in climate. The relative risks will contribute to a tailored dengue Early Warning and Response System (EWARS) in Kelantan, thus providing a mean for targeted resource allocation for vector control strategy recommendation. Disease prevention strategy can also be personalized for the public to suit different climate conditions. By knowing when an increase in dengue cases is expected, we can control the magnitude of the epidemic.

Big data analysis has become the cornerstone of the fourth industrial revolution. To keep abreast with the current revolution, agencies such as the Malaysian Meteorological Department and even the Ministry of Health Malaysia has started data mining for environmental surveillance as well as disease forecasting. This study can broaden the dimension for future collaboration between the Malaysian Meteorological Department and the Ministry of Health Malaysia in combating dengue. It will give the department a state-specific estimate on the level of temperature, rainfall, or wind speed that needs to be monitored to highlight potential dengue outbreaks or indicate increased risk for dengue incidences.

1.4. Research question

1. What is the trend of dengue cases in Kelantan from 2016 to 2018?

2. Is there spatial clustering of dengue cases in Kelantan?

3. Can temperature, rainfall and wind speed data be used to predict dengue cases and suggest proactive measures to reduce dengue incidence?

1.5. Objectives

1.5.1 General objective

To evaluate the effects of climate on dengue cases in Kelantan for the year 2016 to 2018.

1.5.2 Specific objectives

a. To describe the trend of dengue cases in Kelantan from 2016 to 2018 in relation to temperature, rainfall and wind speed.
b. To determine and map the incidence rate of dengue cases in Kelantan from 2016 to 2018 based on district.
c. To map the spatial clustering of Dengue in Kelantan from 2016 to 2018.
d. To model for dengue prediction based on temperature, rainfall and wind speed.

CHAPTER 2

LITERATURE REVIEW

All the literature search on dengue and climate were widely done by using search engines such as PubMed, Scopus, and Google Scholar. Various searching strategy was applied, such as a combination of terms with the use of Boolean operators (AND or OR). The entire literature searches published from 2010-2020 were included. Keywords used were dengue, vector-borne disease, environment, climate, weather, spatial analysis and generalized additive model.

2.1. Epidemiology of Dengue

Dengue has shown a 30-fold increase in global incidence in the past 50 years (Guo *et al.*, 2017). This vector-borne disease favours tropical climate and is endemic in more than 100 countries mainly in the tropical belt of Asia, Latin America, the Pacific and across Africa (Katzelnick *et al.*, 2017; World Health Organization, 2020). Globally, an estimated 100 to 400 million dengue virus infections are occurring per year (World Health Organization, 2020). Out of these, Asia alone contributes 75% of the global burden of dengue (Shepard *et al.*, 2013b) whereas 16% occurred in America and the remaining 14% are reported in Africa (Phanitchat *et al.*, 2019). Expansion of dengue to new geographical regions such as the United States and part of Europe has been seen since the 1960s secondary to globalization, population growth, trade, urbanization, inadequate domestic water supply, increased in travel and warming temperature (Caldwell, 2018; Ebi and Nealon, 2016; Katzelnick *et al.*, 2017). Due to the increase in number of countries affected, dengue has developed from a sporadically occurring disease of the tropics into a global major public health concern in recent decades (Phanitchat *et al.*, 2019).

Despite the staggering number of cases, only 17% to 35% of these infections manifested clinically whilst the vast majority were asymptomatic, which makes the actual number of dengue cases possibly under-reported (World Health Organization, 2020). Although most of the cases are asymptomatic or mild and recovers completely, nearly 5% of the patients developed severe dengue which is a lethal complication of dengue (Castro *et al.*, 2017). Severe illness and mortality among adults and children in some Asian and Latin American countries are mainly attributable to severe dengue (World Health Organization, 2020). The case fatality rate is estimated at 2.5% annually worldwide.

The causative agent in dengue is a positive single-stranded RNA virus from the Flaviviridae family. There are four distinct, but closely related serotypes of this virus family that causes dengue which are DENV1 to DENV4. These four different virus serotypes lead to a wide spectrum of disease ranging from asymptomatic to debilitating febrile illnesses associated with severe headache, retro-orbital pain, arthralgia, myalgia, rash, nausea and vomiting (Rahman, 2012; World Health Organization, 2020). Although dengue infection may cause severe flu-like illnesses, they seldom cause death (World Health Organization, 2020). However, in untreated dengue patients, the case fatality rate was reported by Guo *et al.* (2017) to reach up to 20% with increasing lethality in severe dengue patients from 5% (Campos *et al.*, 2019) to more than 7% (San Martin *et al.*, 2010) of cases. Early detection and expert clinical management through careful fluid therapy have shown to decrease the fatality rate to less than 1% (Guo *et al.*, 2017). Despite developing life-long immunity against a specific infecting serotype upon recovery, subsequent infections by other serotypes may increase the risk of developing severe dengue in the patient (World Health Organization, 2020).

2.2. Dengue situation in Malaysia

Dengue is a major public health concern in Malaysia (Shepard *et al.*, 2013a). The first dengue case reported in Malaysia was in 1901 (Shepard *et al.*, 2013a) whilst the first major dengue outbreak in Malaysia occurred in 1970 with 2,200 cases and 104 deaths (Aziz *et al.*, 2012). Since then, dengue had become endemic in the country (Hii *et al.*, 2016). There is a notable increase in dengue incidence as shown in Figure 2.1from 31 cases per 100,000 population in 2000 to 361 cases per 100,000 population in 2014 (Hii *et al.*, 2016). The case fatality rate is less than 0.2% annually since 2013 with the exception of the year 2015, where fatality rate almost doubled due to spill over cases from the 2014 nationwide dengue epidemic (Hii *et al.*, 2016).

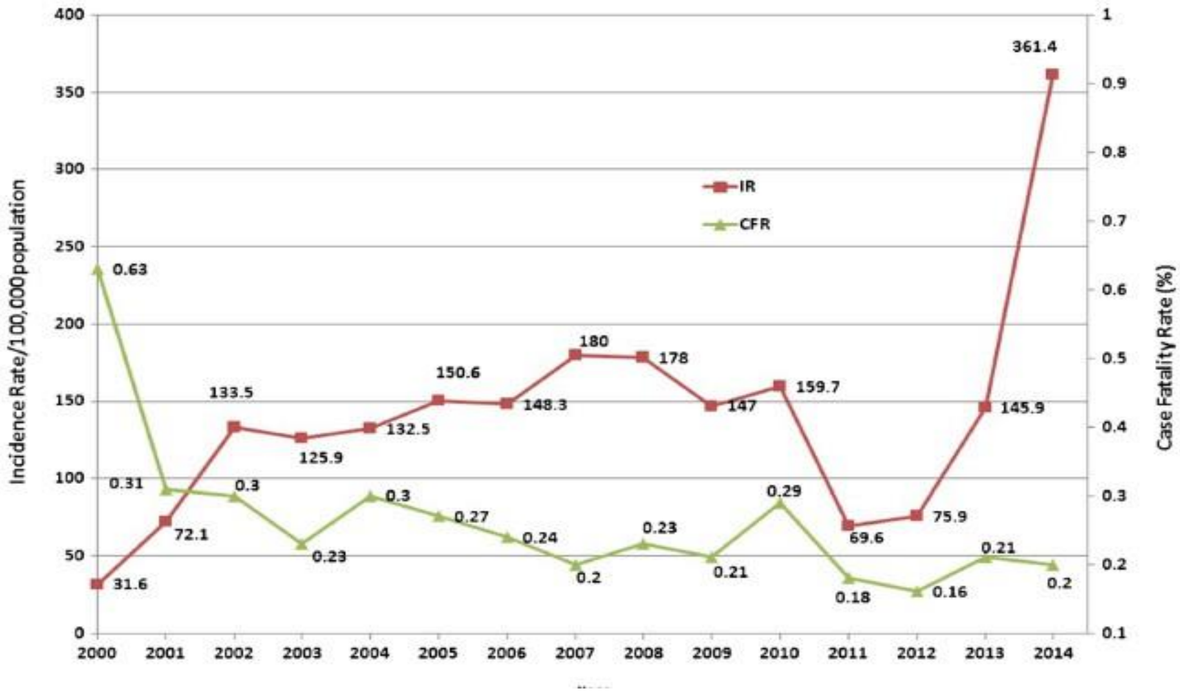

Figure 2.1 Dengue incidence rate and case fatality rate in Malaysia from the year 2000 to 2014 (source of data: Hii *et al*, 2016)

Dengue has now become a mandatory notifiable disease in Malaysia. It is hyperendemic in Malaysia for the past 20 years with all four serotypes, namely DENV1, DENV2, DENV3, and DENV4 circulating concurrently (Cheong *et al.*, 2013; Md-Sani *et al.*, 2018). The dengue trend in Malaysia shows a cyclical pattern of every three to five years, resulting in nationwide epidemics. More than RM120 million is spent yearly in Malaysia on treating dengue cases, either ambulatory (RM2,222,200.00) or hospitalized (RM118,354,400.00) (Shepard *et al.*, 2013a).

Dengue is predominantly an urban disease in Malaysia secondary to the close proximity between the abundance of vector and high density of susceptible host in the urban setting (Gill, 2017). This situation is reflected in the states which are largely affected by dengue namely the state of Selangor, Kuala Lumpur and Johor hence reporting a high number of dengue cases. The state of Selangor recorded the highest dengue incidence rate in 2019 followed by the Federal State of Kuala Lumpur and Putrajaya and Kelantan. Nearly 90% of all dengue notifications nationwide originated from Peninsular Malaysia. Table 2.1 shows the distribution of dengue cases and dengue incidence rate by states for 2019.

Table 2.1: Distribution of dengue cases and incidence rate by state in 2019

State	**Number of dengue cases**	**Incidence rate / 100,000**
Selangor	72,543	1,111.19
Federal State of Kuala Lumpur and Putrajaya	15,424	818.47
Johor	10,873	288.85
Kelantan	6,003	318.34
Sabah	5,478	140.34
Penang	4,119	232.11
Perak	3,226	128.42
Pahang	2,873	171.56
Sarawak	2,648	94.14
Negeri Sembilan	2,305	203.93
Melaka	2,156	231.65
Kedah	1,587	72.78
Terengganu	542	43.51
Perlis	288	113.21
Federal State of Labuan	36	36.25

(Source of data: National CPRC, 2020)

Dengue affected all age group in Malaysia but is most predominantly seen among the reproductive age group, which is between 15 to 49 years (Mudin, 2015). More infections occurred in men (57%) compared to women (43%) (Suli, 2015). The dengue vulnerable group being men and people above 15 years old are shown to be similar across other Asian countries including Singapore, the Philippines and Sri

Lanka (Anker and Arima, 2011). The role of ethnicity as a risk factor for dengue infection is scarce in local literature. Globally, dengue data segregated by ethnicity reflects local demography. For instance, in Brazil, non-whites are considered dengue vulnerable group (Chiaravalloti-Neto *et al.*, 2019) whereas in Australia, the indigenous group of people are considered vulnerable for dengue (Akter *et al.*, 2017). Further explanations on host factors are elaborated under section 2.7, non-environmental factors influencing dengue incidence.

Since the 1970s, dengue has been listed as a mandatory notifiable disease in Malaysia. Following this ruling, dengue epidemics in Malaysia have been identified and observed to occur every five to eight years (Gill, 2017). At present, measures taken by the country to control dengue cases and prevention from the occurrence of epidemics is through integrated vector control approaches. This includes multipronged strategies aimed to prevent transmission of the virus by disrupting various stages of the mosquito life cycle such as reduction of mosquito breeding sites and killing of adult and immature mosquitoes (Packierisamy *et al.*, 2015; Singh and Taylor-Robinson, 2017). Approximately 92.2% of the total national cost for vector control in 2010 are incurred at the district level which is mainly used for fogging activities and premise inspection for mosquito breeding sites (Packierisamy *et al.*, 2015). The substantial US$73.5 million spent by the Malaysian government in 2010 for vector control activities is comparable to the amount spent by the Singapore government (US$50 million in 2010) and Thailand government (US$62 million in 2005) as they also face the significant burden of dengue (Packierisamy *et al.*, 2015).

Despite the substantial amount of cost incurred, a full evaluation of the effectiveness of these vector control activities is yet to be done at the national level.

Interestingly, there is limited evidence of the effectiveness of fogging or space-spraying programs which constitutes a major part of most dengue response activities worldwide towards dengue incidences (Bowman *et al.*, 2016). The closest relatable study on the effectiveness of space-spraying activities was conducted by Stoddard *et al.* (2014) in Peru. Their study shows evidence that three cycles of non-residual, intra-domicile, ultra-low volume (ULV) city-wide space spraying with an adulticide in Iquitos city has the potential to reduce the number of dengue incidences when implemented early at the start of the transmission season. Another study by Farajollahi *et al.* (2012) in New Jersey, USA, shows similar effectiveness of space-spraying activities. However, they used the *Aedes albopictus* population as a proxy for dengue cases in their study. A more recent cluster-randomized control trial to evaluate the effectiveness of space-spraying activities has been proposed in Thailand and are currently collecting baseline data in enrolled village clusters (Overgaard *et al.*, 2018).

The second most common vector control strategy in Malaysia is the inspection of premises for breeding sites (Packierisamy *et al.*, 2015). However, most studies in the literature combine premise inspection with other community-driven activities including larviciding and health promotional campaigns to be evaluated in tandem (Bowman *et al.*, 2016). Therefore, it is difficult to evaluate their specific contribution to reducing the number of dengue incidences. Despite the lack of individual pieces of evidence, the World Health Organization has recommended a combined approach through community participation for a sustainable dengue control initiative. The lack of active community involvement has been associated with failure of vector control activities (Achee *et al.*, 2015). Embracing this strategy, the Ministry of Health Malaysia has adopted the WHO's Communication for Behavioural Impact (COMBI) approach as part of the national dengue prevention strategy. The Hulu Langat COMBI is one of the success stories of this community approach in reducing the number of premises with mosquito larvae breeding detected during an inspection (Rozhan *et al.*, 2006).

2.3. Malaysian Dengue Surveillance System

There are two components for the dengue surveillance system in Malaysia. This includes laboratory surveillance for circulating dengue viruses and mandatory disease notification surveillance for dengue case or dengue outbreak detection. Both components are passive surveillance. They are used to track, monitor and manage ongoing dengue situation in Malaysia.

The Dengue Virus Surveillance System in Malaysia is the laboratory component of the Malaysian dengue surveillance system. It was established in 2009. Currently, serology samples are collected from all 14 states on a weekly basis and sent to the Institute of Medical Research for analysis. All four dengue serotypes are co-circulating in Malaysia with the predominant serotype reported by Suli (2015) being DENV1 and DENV2 (Figure 2.2). The serotype shift from DENV4 to DENV 2 in 2013 and from DENV2 to DENV1 in 2014 had contributed to the increase in dengue incidence rates, four to six months after the serotype shift occurred (Mudin, 2015).

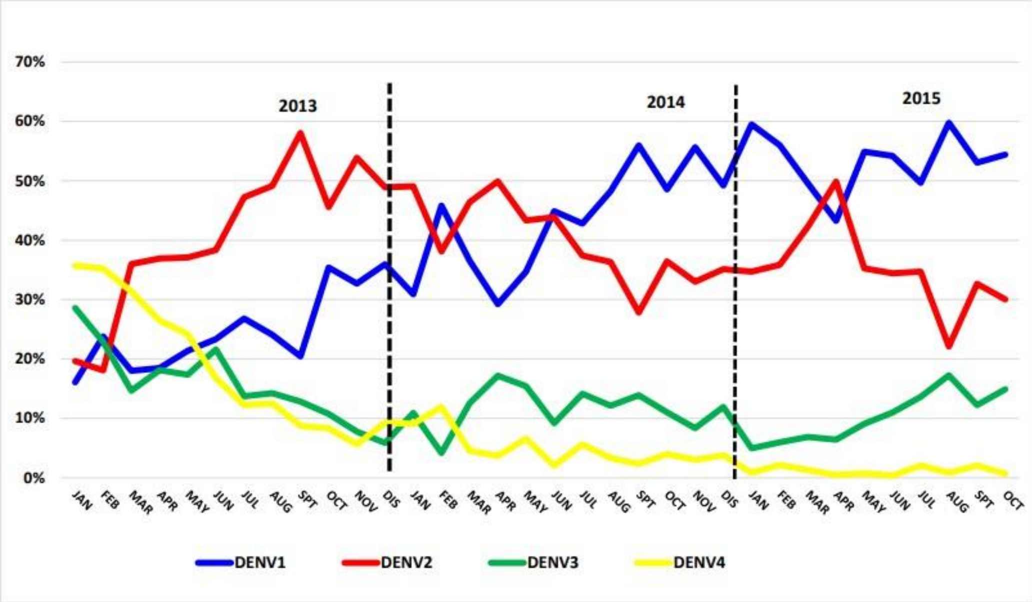

Figure 2.2: Circulating dengue serotypes in Malaysia from 2013 to 2015 (source of data: Suli, 2015)

The mandatory notification component of the surveillance system includes both the eNotifikasi system for notified dengue cases and eDengue system for registered dengue cases. Detailed information pertaining to each dengue case including age, gender, ethnicity, occupation, address, date of symptom onset and the final outcome, either dead or alive, are collected at point-of-care. The input of data into the systems are done by registered healthcare workers. These data are then analysed at the local, state and national level to detect trends and outbreaks by the Vector-Bourne Disease Sector and the Crisis and Preparedness Response Centre (CPRC). The CPRC will also proceed by sending analysed data to the World Health Organization (WHO) for a regional and global view on dengue.

Container-based indices such as the Breteau Index has been used as part of the dengue surveillance system (Achee *et al.*, 2015). Despite its role in the surveillance system, the Breteau Index which calculates the number of containers inhabited by immature mosquito per 100 houses inspected, does not show a significant statistical relationship with dengue fever incidences (Morin *et al.*, 2013). Thus, the use of this index in preventive activities may vary. In terms of control activities, the use of water container covers together with community-based environmental management has been shown to reduce the odds of dengue incidence to 0.22 (95% CI 0.15, 0.32; $p<0.0001$) (Bowman *et al.*, 2016).

2.4. *Aedes* Mosquito

There is no definitive treatment for dengue to date. Patients infected with dengue are managed symptomatically, supportively, and through monitoring of their laboratory tests, including the full blood count and haematocrit level (Ministry of Health Malaysia and Academy of Medicine Malaysia, 2015). Therefore, the mainstay of prevention is through vector control activities.

Dengue is transmitted by the day-biting, adult female *Aedes* mosquito. The primary vector is *Aedes aegypti* and followed by *Aedes albopictus* (Guo et al., 2017). Humans contributed to the life cycle of the mosquito through providing breeding places for the mosquitoes in the form of water-holding containers in and around the home and providing blood meals for the female mosquitoes for egg development (Ebi and Nealon, 2016). Eggs are laid on the side of water-holding containers. Although the eggs require water to hatch, they can withstand drying and survive without water for up to eight months at the side of the container they were laid before hatching into larvae as soon as they are submerged in water (Centers for Disease Control and Prevention, 2020; Ebi and Nealon, 2016). The larvae take as little as seven days to transform into pupae and finally into an adult mosquito (Centers for Disease Control and Prevention, 2020). The adult female *Aedes* mosquito can survive up to 40 days in favourable condition (Goindin *et al.*, 2015).

The adult *Aedes* mosquitos prefer to stay near humans and human dwelling areas. Their flight range and main activity area are reported to be between 100m to 1km from their birthplace (Chen *et al.*, 2019). This finding correlates with a study by Mala and Jat (2019b) where dengue incidences have a strong, inversed association with waterbodies that provides suitable breeding places for the mosquitoes.

The most common water-holding containers where mosquitoes lay their eggs are bottles, cans, tires, house gutters, animal watering dishes, birdbaths, flowerpots and natural holes in vegetation (Fairos *et al.*, 2010). These containers can be found in abundance around the home (Bowman *et al.*, 2016). In fact, these containers were speculated to be the cause for the rapid geographical expansion of dengue disease as these egg-laden containers were transported through the global shipping industry (Ebi and Nealon, 2016). Changes in climate such as droughts may also promote the storage of waters in containers in urban slum areas (Caminade *et al.*, 2019).

2.5. Impact of Climate on Dengue Infection

Several factors that directly or indirectly influences the human, vector, virus and environment may determine the magnitude and distribution of dengue infections. These factors can be broadly classified into climatic factors; temperature, rainfall, humidity, atmospheric pressure and non-climatic factors; housing quality in the urban area, provision of safe water, access to waste management and global trade and travel (Ebi and Nealon, 2016).

Many studies globally (Ebi and Nealon, 2016; Gama, 2013; Morin *et al.*, 2013; Sirisena *et al.*, 2017; Xu *et al.*, 2017; Zahirul Islam *et al.*, 2018), and locally (Cheong *et al.*, 2013; Mustafa *et al.*, 2015; Rahman, 2012) have shown how climatic factors impact dengue incidences through directly and indirectly affecting vector density and distribution, the dengue virus development and human behaviour. Climate variables are incorporated into mathematical models to help with the prediction of cases and understanding how climate change is likely to shift the dengue transmission dynamics spatiotemporally (Caldwell, 2018).

2.5.1 Temperature

Temperature plays an important role throughout a mosquitos' life cycle. This includes a mosquito's survival, development, reproductive behaviour and feeding behaviour (Ebi and Nealon, 2016). Goindin *et al.* (2015) and Mahmood *et al.* (2019) both reported a non-linear relationship between temperature and feeding behaviour of female *Aedes* mosquito. Goindin *et al.* (2015) found that a low (24˚C) or high (30˚C) temperature are both less favourable as compared to a medium (27˚C) temperature for blood meal appetite, ability to mature and able to deposit eggs. On the contrary, Mahmood *et al.* (2019) reported a decrease in feeding activity when the temperature is below 15˚C and above 35˚C. The differences may be due to the set temperature used in the study by Goindin *et al.* (2015) as compared to modelling with collected temperature variable by Mahmood *et al.* (2019).

The viral replication in an infected female mosquito is also temperature dependent (Ebi and Nealon, 2016). The extrinsic incubation period (EIP) is the infective cycle of the dengue virus where the virus replicates and migrates inside the body of the female *Aedes* mosquito (Goindin *et al.*, 2015). It started when the virus is ingested during a blood meal and ends when the virus reaches the salivary gland (Goindin *et al.*, 2015). This period takes an average of eight (8) to 12 days when the ambient temperature is between 25˚C to 28˚C (World Health Organization, 2020). Comparatively, Ebi and Nealon (2016) reported a broader EIP range between five (5) to 33 days with when the ambient temperature is 25˚C. A higher ambient temperature of 30˚C was reported by Chan and Johansson (2012) to reduce the EIP range between two to 15 days. After the EIP, the adult female mosquito will become infectious and is capable of transmitting the virus for the rest of its life (World Health Organization, 2020).

The temperature has also been reported to impact human behaviour. Warmer months during the summer has shown an increase in vector-borne disease incidences due to increased contact with the vector in their habitat (Smith, 2019). Indirectly, an increasing global temperature which causes a rise in sea level has forced people to flee their homes at low-lying islands and coastal regions. This mass population movement has contributed to the spread of dengue as these displaced people could provide as a human reservoir for dengue and other vector-borne diseases (Rahman, 2012).

2.5.2 Rainfall

There are mixed results in the literature with regards to the correlation of rainfall with dengue. Aziz *et al.* (2012) noted that there is no significant correlation between monthly rainfall with the number of dengue cases. This relation is contradictory with the findings from Rohani *et al.* (2011) and Dom *et al.* (2012), which shows a strong positive correlation between rainfall and dengue. The difference in result may be because both latter studies use vector density as an inference for dengue cases as compared to the earlier research.

Some studies reported a positive association between rainfall and dengue incidences as higher rainfall provides ideal breeding places for mosquitoes and stimulates the egg hatching thus leading to increased vector density (Chen *et al.*, 2019; Guo *et al.*, 2017; Phanitchat *et al.*, 2019). However, a study by Jayaraj *et al.* (2019) in Tawau, Malaysia reported a negative correlation between rainfall and dengue incidence which was speculated to be secondary to the improved pipe water supply and waste management which reduces the risk of potential breeding sites. Other studies by Swain *et al.* (2019) and Jemal and Al-Thukair (2018) reported an initial decrease in dengue incidences with increasing mean monthly rainfall due to washout of breeding places and peak incidences of dengue up to six months lag after heavy rainfall.

2.5.3 Wind speed

Association between wind speed and dengue incidences vary based on local variation and usually shows a non-linear relation. A study by Mala and Jat (2019b) in Delhi indicate a positive association between increasing mean wind speed up to 3 km/h with a rise in dengue incidence. A similar finding but with a higher range of wind speed (between 5.5 km/h to 9.3 km/h) is noted by Cheong *et al.* (2013) in a study in Putrajaya. This increase was attributed to an increase in the mosquito flight range, which allows for a wider range of feeding.

Stronger wind speed, however, was noted to decrease the mosquito population density and reduces host-seeking activity (Ehelepola *et al.*, 2015). A decrease in host-seeking flying activity reduces contact with humans for feeding which subsequently affects oviposition (Cheong *et al.*, 2013). Two (2) studies in Putrajaya by Fairos *et al.* (2010) and Cheong *et al.* (2013) showed how strong wind speed is negatively correlated with dengue incidences at 21 days lag up to three (3) months lag. Although Mala and Jat (2019a) reported a similar inverse relationship between stronger wind speed and dengue incidence, they also noted a wider spatial dispersion of dengue incidences due to strong wind speed.

2.5.4 Other climatic variables

Humidity and precipitation are both considered as predictors for dengue epidemics especially in a temperate climate (Campos *et al.*, 2019; Ebi and Nealon, 2016; Gama, 2013; Smith, 2019; Stolerman *et al.*, 2019). Humidity is the amount of water vapour suspended in the air (Rutledge *et al.*, 2011) whereas, precipitation is any liquid (for example rain) or frozen water (for example snow) that forms in the atmosphere and falls to the earth due to gravity (National Geographic Society, 2019). In Malaysia with an average annual relative humidity between 69% to 82%, humidity shows inconsistent association with dengue incidences which suggest a local variation of its impact. Two studies reported no association (Cheong *et al.*, 2013; Dom *et al.*, 2012), one study reported positive association (Rohani *et al.*, 2011), and another one study reported inverse association at 14 days lag (Fairos *et al.*, 2010). All studies on the effect of climate on dengue in Malaysia uses rainfall rather than precipitation as an independent variable.

A study by Chen *et al.* (2019) reported the significant inverse effect of weekly average atmospheric pressure on the dengue incidence with the strongest effect seen at a lag of 11 weeks (correlation coefficient -0.92). The mosquitoes' flying activity is affected by the atmospheric pressure as they prefer flying at a lower altitude when the atmospheric pressure is low. Therefore, it increases the risk of dengue transmission through the increased possibility of human exposure to mosquitoes. The effect of atmospheric pressure on dengue incidence in Malaysia, however, has yet to be studied.

It was previously reported that days with low sunshine (overcast days) changes the feeding habit of adult female mosquitoes from feeding at dawn and dusk to feeding throughout the day indoors (Gubler, 1998). A recent study by Ehelepola *et al.* (2015) shows a positive correlation between average sunshine hours with dengue incidence. Longer average sunshine hours during the day results in a higher number of dengue cases as increased human activity increases human exposure to the vector. A further study by Mala and Jat (2019b) reported similar findings but only up to eight hours of sunshine hours. Beyond eight hours, a decline in dengue cases was noted. The length of sunshine hours is correlated with mean and maximum temperature (correlation coefficient 0.725 and 0.325 respectively with no lag) as longer sunshine hours means more solar radiation on Earth (Ehelepola *et al.*, 2015). The increase in temperature creates a more favourable environment for the mosquitoes which may explain the rise in dengue incidence.

The *El Niño*-Southern Oscillation cycle is the fluctuations in temperature that occurs in the east-central Equatorial Pacific between the ocean and the atmosphere (National Oceanic and Atmospheric Administration, 2020). A synchronous increase of dengue incidence was seen in countries in the Southeast Asia Region in 1997 – 1998, which coincided with *El Niño* episode (van Panhuis *et al.*, 2015). This seasonal variability was mainly attributed to the effect of *El Niño* towards regional climate especially with regards to temperature and precipitation (Nguyen *et al.*, 2020).

2.6. Other Environmental Factors Influencing Dengue Incidence

Other environmental factors such as urbanisation, poor waste management, vector ecology and agricultural land use also play a critical role in affecting the life cycle and breeding site for *Aedes* mosquito (Campos *et al.*, 2019; Chen *et al.*, 2019; Mustafa *et al.*, 2015). However, the association between these factors are inconsistent with local variability. For example, a study by Phanitchat *et al.* (2019) shows higher clusters of dengue cases in the rural area of Khon Kaen, Thailand, compared to urban locations as compared to higher dengue cases in urban areas of Odisha, India (Swain *et al.*, 2019). It was speculated that the presence of swamp areas in Khon Kaen might reduce the local environmental temperature providing optimum ambience for dengue population density. Additionally, improved road systems and establishment of agricultural settlements in rural areas may increase the abundance of the vector in the rural area which has gradually changed the previously urban nature of dengue (Guo *et al.*, 2017). Population immunity (Abubakar and Shafee, 2002), circulating dengue genotype (Mohd-Zaki *et al.*, 2014), and population movements (Cheng *et al.*, 2017) are other speculated predictors of dengue incidences and outbreaks worldwide.

2.7. Non-environmental Factors Influencing Dengue Incidence

The epidemiological triad is one of the theoretical models for infectious disease causation. It consists of the infectious agent (pathogen), a susceptible host and an environment of which the agent and host can interact together (Centers for Disease Control and Prevention, 2012). For dengue, the vector also plays a pivotal role in disease transmission as shown in Figure 2.3. When

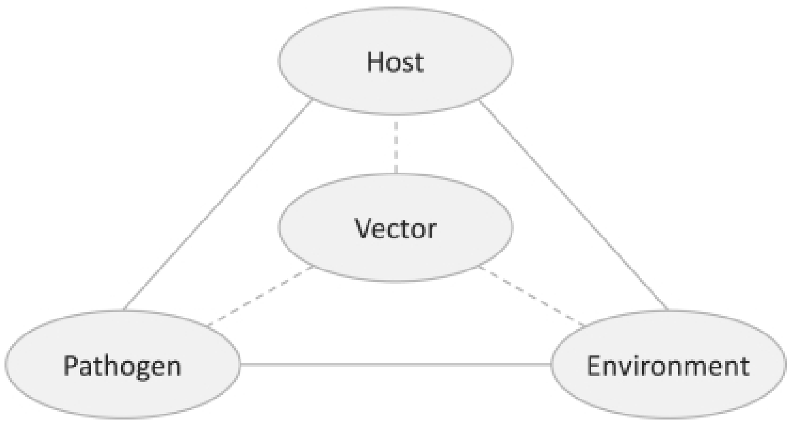

Figure 2.3: The epidemiological triad (source of image: Santana *et al.*, 2011)