Climate and Dengue Fever: 
Early warning based on temperature and rainfall

Yien Ling Hii

Umeå 2013
“Blessed is the man who finds wisdom, the man who gains understanding. She is a tree of life to those who embrace her; those who lay hold of her will be blessed.” Proverbs 3:13, 18
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Abstract

**Background:** Dengue is a viral infectious disease that is transmitted by mosquitoes. The disease causes a significant health burden in tropical countries, and has been a public health burden in Singapore for several decades. Severe complications such as hemorrhage can develop and lead to fatal outcomes. Before tetravalent vaccine and drugs are available, vector control is the key component to control dengue transmission. Vector control activities need to be guided by surveillance of outbreak and implement timely action to suppress dengue transmission and limit the risk of further spread. This study aims to explore the feasibility of developing a dengue early warning system using temperature and rainfall as main predictors. The objectives were to 1) analyze the relationship between dengue cases and weather predictors, 2) identify the optimal lead time required for a dengue early warning, 3) develop forecasting models, and 4) translate forecasts to dengue risk indices.

**Methods:** Poisson multivariate regression models were established to analyze relative risks of dengue corresponding to each unit change of weekly mean temperature and cumulative rainfall at lag of 1-20 weeks. Duration of vector control for localized outbreaks was analyzed to identify the time required by local authority to respond to an early warning. Then, dengue forecasting models were developed using Poisson multivariate regression. Autoregression, trend, and seasonality were considered in the models to account for risk factors other than temperature and rainfall. Model selection and validation were performed using various statistical methods. Forecast precision was analyzed using cross-validation, Receiver Operating Characteristics curve, and root mean square errors. Finally, forecasts were translated into stratified dengue risk indices in time series formats.

**Results:** Findings showed weekly mean temperature and cumulative rainfall preceded higher relative risk of dengue by 9-16 weeks and that a forecast with at least 3 months would provide sufficient time for mitigation in Singapore. Results showed possibility of predicting dengue cases 1-16 weeks using temperature and rainfall; whereas, consideration of autoregression and trend further enhance forecast precision. Sensitivity analysis showed the forecasting models could detect outbreak and non-outbreak at above 90% with less than 20% false positive. Forecasts were translated into stratified dengue risk indices using color codes and indices ranging from 1-10 in calendar or time sequence formats. Simplified risk indices interpreted forecast according to annual alert and outbreak thresholds; thus, provided uniform interpretation.

**Significance:** A prediction model was developed that forecasted a prognosis of dengue up to 16 weeks in advance with sufficient accuracy. Such a prognosis can be used as an early warning to enhance evidence-based
decision making and effective use of public health resources as well as improved effectiveness of dengue surveillance and control. Simple and clear dengue risk indices improve communications to stakeholders.

**Key words:** dengue fever, temperature, rainfall, forecasting model, early warning, epidemic, dengue risk index
Glossary of Terms

ACF Autocorrelation function
AIC Akaike Information Criterion
AR Autoregression
CCF Cross-correlation function
DALY Disability-adjusted life year
DENV Dengue virus
DF Dengue fever
DHF Dengue hemorrhagic fever
GCV Generalized cross-validation
GDP Gross domestic product
GIS Geographical Information System
HFMD Hand, foot, and mouth disease
IR Incidence rate
MoH Ministry of Health
NEA National Environment Agency, Singapore
NOAA National Oceanic and Atmospheric Administration, USA
PACF Partial autocorrelation function
RMSE Root mean square error
ROC Receiver operating characteristic curve
SOP Standard operating procedure
WHO World Health Organization
WMO World Meteorological Organization
Weather The state of the atmosphere at a particular place and time such as heat, sunshine, rain, wind, and etc.
Climate Statistics of weather that represent average weather conditions prevailing in an area in general or over a period of time
Climate change Long term trend of climate over a period of 10 years or more
Model A statistical expression for estimating risks or forecast of dengue cases
Enkel sammanfattning på svenska


Resultat: De statistiska analyserna visade på klara samband mellan nederbörd och temperatur och dengue med en fördröjning av 9-16 veckor. Studier av kontrollinsatser fann att en varning med 3 månaders tid för förberedelse var tillräckligt för att förhindra utbrott av dengue i Singapore. Prediktionerna visade träffsäkra prognoser av insjuknanden från 1 upp till 16 veckor framöver utifrån rådande förhållanden. Autoregressiva termer liksom modellering av tidstrender förbättrade prediktionsförmågan ytterligare. Sensitiviteten av modellprediktionerna på data som inte används vid modellbyggande visade över 90 % korrekt klassificerade epidemiiska veckor och specificiteten visade mindre än 20 % felaktigt klassificerade icke-
epidemiska veckor. Resultaten av modellprediktionerna översattes till ett riskindex med färgkodning som sträcker sig över 1-10 olika kategorier beskrivande risken för epidemiska utbrott över tid upp till 16 veckor framåt.

**Signifikans:** Prediktioner av dengue visade träffsäkra prognoser upp till 16 veckor framåt. Dessa bedöms kunna vägleda beslutsfattande och utnyttjande av samhällsresurser på ett effektivt sätt samt medföra effektivare övervakning och kontroll för att förhindra epidemisk smittspridning. Enkla kategoriska riskindex bedöms kunna för medföra effektivare kommunikation om risker till beslutsfattare.
Original Papers

This thesis is based on the following papers, which will be referred to by the corresponding Roman numerals:

I. Yien Ling Hii, Joacim Rocklöv, Nawi Ng, Choon Siang Tang, Fung Yin Pang, Rainer Sauerborn. Climate variability and increase in intensity and magnitude of dengue incidence in Singapore (Global Health Action 2009; doi: 10.3402/gha.v2i0.2036)


IV. Yien Ling Hii, Nawi Ng, Lee Ching Ng, Huaiping Zhu, Joacim Rocklöv. Dengue risk index as an early warning (submitted)

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Introduction

Dengue fever

Dengue fever (DF) is a mosquito-borne viral infectious disease that is also referred to as the “break bone disease”. DF is one of the fastest surging tropical and sub-tropical emerging infectious diseases and is caused by one of the four serotypes of dengue viruses (DENV1-4). The dengue viruses are transmitted via infective female mosquitoes, namely *Aedes aegypti* (principal vector) and *Aedes albopictus*, through bites or blood meals on human hosts. Symptoms of DF include sudden onset of fever, severe headache, muscle ache, joints pain, rashes, leucopenia, and thrombocytopenia [1]. The term “break bone disease” is associated with the symptoms of muscle and joint pain.

Currently, a vaccine against all serotypes of dengue virus is not available and there is no antiviral drug for treatment of DF. Dengue patients are treated symptomatically with appropriate patient management regimens. DF is usually self-limiting and the patient typically recovers within a week. A small percentage of dengue patients could develop fatal complications or severe dengue characterized by severe organs impairment, plasma leakage, and dengue hemorrhagic fever (DHF) which could lead to dengue shock syndrome [1]. DHF is characterized by general symptoms of DF plus symptoms that include skin hemorrhages, bleeding nose or gum, and possible internal bleeding. Case fatality rates from severe dengue could be lower than 1% with appropriate case management and medical care by healthcare professionals [1,2].

A person infected with dengue usually manifests symptoms after a 4 to 10 day of incubation period [1]. A large proportion of dengue infected persons may be asymptomatic or manifest only mild symptoms. The viraemic period ranges from 2 to 12 days with an average of 4-5 days. During this period, a dengue-infected person is capable of transmitting dengue viruses to *Aedes* mosquitoes [3]. Dengue viruses then undergo an extrinsic incubation period (approximately 8-12 days) in *Aedes* mosquitoes [1]. The chain of dengue infection continues when infected mosquitoes bite or feed on another susceptible person (Figure 1). Infection with one serotype of dengue virus confers lifelong immunity against that specific serotype [1,4]. Secondary infection might expose the individual to increasing risk of developing DHF [5].
Global burden of dengue

Dengue is a major public health burden to most countries in the tropical and subtropical regions of Asia, The Americas, Australia, and Africa [1]. DF outbreaks were recorded as early as in late 1940s in South East Asia [5]. During 1950-1970s, dengue was eliminated from most countries in the American region [5]. Nevertheless, dengue has re-emerged globally with intensified epidemic and geographical expansion since the 1980s, and has rapidly become a major epidemiological threat in Asia Pacific and South America. According to the World Health Organization (WHO), DF is currently endemic to more than 100 countries with an estimated 2.5 billion population at risk. The annual number of infections is estimated at around 50 million globally, with 500,000 severe cases accounting for the majority of the approximately 12,500 deaths [2]. Asia Pacific shoulders about two thirds of the global burden of dengue and is home to about 70% of the 2.5 billion world populations at risk [1,6]. In recent decades, the frequency of dengue epidemics in the region has increased, with dengue cases also being reported for the first time in countries such as Bhutan and Nepal [1]. In past decades, nearly all the countries in Southeast Asia reported dengue cases annually. The timing of the epidemics in these dengue endemic countries tends to vary with seasonal cycles. Dengue is mainly an urban disease; however, studies have suggested dengue has expanded territory from urban to rural [7].

The exact reasons for the re-emergence of dengue are not fully understood. However, unplanned urbanization and rapid increases in population density, escalated international travel and trade, lack of effective
vector control systems, poor public health infrastructure, climate change and extreme weather events, and poor socio-economic status have been identified as some of the key determinants [1,8]. Until vaccines against dengue viruses or drugs for dengue treatment are available, effective vector control and elimination of mosquito breeding sources remain the most effective methods of disrupting the transmission of the diseases. In order to reverse the proliferation of dengue, efficient and effective surveillance and control systems, with enhanced dengue control capacity and epidemic prediction capability, are required [9]. These programs could be hampered by financial and personnel limitations, as well as by a lack of support or low prioritization of national public health policies.

**Dengue in Singapore**

**Epidemiology**

Dengue is a major public health concern in Singapore. DF was first reported there since 1960s. A vector control Unit was established in the 60s and all physicians and laboratories were required to report dengue cases to the Ministry of Health by the 70s [10]. The disease was controlled or suppressed for almost 2 decades from the 70s to the 80s. However, dengue incidence surged in the 90s with the epidemics appearing at average time intervals of 6 years (Figure 2). As shown in Figure 2, the upward trend in dengue has continued in recent decade. This has been manifested by shortened time intervals between epidemics, increasing magnitude, and increased geographical expansion for transmission. Average dengue incidence rates (IR) per 100,000 populations were 11 for 1970-1979 and 1980-1989. The IR increased to 70 in 1990-1999 and 132 in 2000-2010. The average IR over 2000-2010 (excluding the exceptionally high rate for 2005) was 112. The nation has also reported a higher frequency of epidemics since year 2004. During the period from 2000-2012, the trend of dengue cases peaked in the year 2005 before declining following a revamp of the vector control program. Generally, the nation experiences a higher number of dengue cases in the second half of each year, with peak periods occurring between May and October.

There is considerable geographic variability in the number of cases across the island. Dengue had been contained in the central and eastern region until year 2004. Since then, *Aedes* mosquitoes and dengue viruses have spread to the western region [11-14]. During year 2008-2011, average weekly dengue incidence rates per 100,000 populations stratified by central, northeast, northwest, southeast, and southwest regions, were approximately
3.3, 2.8, 2.1, 3.9, and 1.9, respectively. Maximum dengue incidence rates in these zone occurred in the southeast region (13.9) in 2011, followed by northeast region (9.69) in 2008. Overall, the southeast and central regions reported about 55% of the total dengue cases over the year 2000 to 2011.

According to a report in 2011, residents living in public and private high rise buildings contributed to about 81% of reported cases [15]. The dengue premises index, or the percentage of premises detected with *Aedes aegypti* larvae or pupae, has shown the reverse pattern to the trend in dengue cases in the past decades [10]. The premises index was approximately 2% in the 70s and dipped further, to about 1%, since 2005 [10,15-17].

![Figure 2: Annual dengue incidence rate in Singapore. Triangle markers indicate epidemics (Data source: The National Environment Agency & MoH Singapore).](image)
Circulating dengue viruses

Dengue virus (DENV) is a widespread arborvirus that belongs to the genus of Flavivirus. All the four serotypes of the dengue virus have been co-circulating in Singapore for decades, with different serotypes claiming primary responsibility for outbreaks in different periods. Dengue virus surveillance in Singapore showed that DENV-2 had been the predominant circulating virus from 2001 to 2011, except in 2004-2006 [15]. DENV-1 was responsible for the epidemics in 2004 and 2005, whereas DENV-2 was the predominant circulating serotype during outbreaks in 2007 and 2011. DENV-3 and DENV-4 have been detected almost every year and they have not been the major circulating serotypes. Recent virus surveillance revealed high viral diversity, possibly due to high levels of travel and trade [18]. The introduction and evolution of dengue viruses could lead to an outbreak if the community is susceptible to the new strain of dengue virus.

Aedes mosquitoes

Characteristics & breeding habitats

Female Aedes aegypti and Aedes albopictus are two mosquitoes that transmit dengue viruses in Singapore [19]. Studies have shown that Aedes aegypti is the principal vector in most of the dengue endemic countries, and that the majority of the severe dengue cases were reported in areas where Aedes aegypti was found [5,20]. Aedes mosquitoes are commonly found in tropical and subtropical countries [1]. Aedes aegypti is endogenous to Africa, whereas Aedes albopictus was originally found in Asia [21]. It is believed that both species of mosquitoes have been distributed to most of the dengue endemic countries through international trade and travel.

Aedes aegypti lives in close proximity to human hosts, inside or around residential areas, whereas Aedes albopictus is found mainly in outdoor premises. Aedes mosquitoes breed both inside and outside residential areas, private or public premises, construction sites, institution compounds, parks, and etc. Aedes’ eggs can even be found on the sides of all types of containers including household utensils which are left undisturbed in days. Table 1 lists the top five breeding sites of Aedes mosquitoes in 2005 and 2011. As shown, there was a prominent change in breeding habitats for both Aedes aegypti and Aedes albopictus. In 2011, there was a reduction in breeding in ornamental containers and an increase in breeding in flower plot plate and other places.
Aedes mosquitoes feed in the morning and late afternoon [21]. *Aedes aegypti* prefers to bite humans, whereas *Aedes albopictus* will also bite domestic animals [21]. *Aedes aegypti* is easily disturbed by the movement of host during feeding; therefore, it is common for *Aedes* to bite several persons to complete a blood meal and therefore to infect several persons in the same household or in close proximity [5].

**Horizontal and vertical dispersion**

The horizontal and vertical dispersions of *Aedes* in a geographical area influences dengue transmission. In Singapore, *Aedes* mosquitoes could disperse farther than normally assumed flight range of less than 100m [22]. An entomologic study by Liew and Curtis (2004) showed that female *Aedes* mosquitoes, in search of breeding habitats, could disperse extensively within a radius of 320m as well as disperse from the 12th floor to the 21st floor (height = 60 meter) or down to ground level within 1 to 4 days after release [23]. This extensive dispersion in distance and height allows *Aedes* mosquitoes to lay eggs and transmit dengue rapidly, not only in the same apartment building, but also in the neighboring communities. Female *Aedes* mosquitoes can lay a small number of eggs in several breeding habitats till they complete an entire batch of eggs [24]. This breeding characteristic results in an increase in geographical dispersion of *Aedes* mosquitoes and dengue transmission. To fuel the process of dengue transmission across the island, greater distance of horizontal dispersion of *Aedes* mosquitoes could possibly be contributed to cars, trucks, and other modes of transportation, as it is common for local residents to travel from one end of the island to another for work.
Table 1: Common breeding places for Aedes mosquitoes in Singapore.

<table>
<thead>
<tr>
<th>Breeding sites</th>
<th>2005</th>
<th>2011</th>
<th>2005</th>
<th>2011</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Aedes aegypti</td>
<td>Aedes albopictus</td>
<td>Aedes aegypti</td>
<td>Aedes albopictus</td>
</tr>
<tr>
<td>Domestic containers</td>
<td>26%</td>
<td>10%</td>
<td>29%</td>
<td>10%</td>
</tr>
<tr>
<td>Ornamental containers</td>
<td>24%</td>
<td>10%</td>
<td>11%</td>
<td>3%</td>
</tr>
<tr>
<td>Flower pot plate/tray</td>
<td>4%</td>
<td>-</td>
<td>11%</td>
<td>9%</td>
</tr>
<tr>
<td>Discarded receptacles</td>
<td>7%</td>
<td>21%</td>
<td>2%</td>
<td>14%</td>
</tr>
<tr>
<td>Canvas/plastic sheet gully traps/roof gutter</td>
<td>3%</td>
<td>10%</td>
<td>-</td>
<td>6%</td>
</tr>
<tr>
<td>Puddle/ground depression</td>
<td>-</td>
<td>-</td>
<td>2%</td>
<td>-</td>
</tr>
<tr>
<td>Others</td>
<td>36%</td>
<td>49%</td>
<td>45%</td>
<td>58%</td>
</tr>
</tbody>
</table>


Figure 3: Influence of temperature and rainfall on Aedes’s development stages
Climate and dengue transmission

Clearly, many factors such as herd immunity, government vector control capacity, and changes in serotypes contribute to dengue epidemics. Nevertheless, climate may also influence the distribution of dengue incidence [25-32]. The impacts of temperature and rainfall on dengue transmission are partly translated through the effects of temperature and rain on the rates of biological development, feeding, reproduction, population density, and survival of *Aedes* mosquitoes. Furthermore, a study has shown that dengue viruses may reduce incubation time in mosquitoes from approximately two weeks to one week at temperatures of 32°C and above [33].

Temperature and mosquito’s life cycle

*Aedes* mosquitoes undergo two stages of life, namely the terrestrial and the aquatic stage. The terrestrial stage includes adult mosquitoes and eggs, whereas the aquatic stage includes immature stages of larvae and pupae. As shown in Figure 3, *Aedes* mosquitoes proceed through the life cycle from eggs to larvae to pupae to adult. This life cycle takes approximately 1-2 weeks or longer depending on temperature and availability of water and nutrients during aquatic or immature stages [34,35]. At higher temperatures, *Aedes* mosquitoes emerge from eggs to adults in a shorter period and also experience a shorter incubation period for dengue viruses [33,36-38]. However, the mortality rates of adult mosquitoes increases with increasing temperature above 30°C [37].

The average life span of an adult mosquito ranges from 2 to 4 weeks [34]. A recent study suggests that it is possible for *Aedes albopictus* to live for up to approximately 100 days, given optimal body size, nutrients, and environmental conditions [39]. Another study in French Guinea suggested that the life span of a female *Aedes* mosquito could range from a minimum of one day to a maximum of 76 days, with an average life span of 25 days [40]. In a temperature-controlled experiment, Yang *et al.* (2009) showed optimal ranges of mean temperature for survival of female adult mosquitoes, and for immature stages, to be 15°C-30°C and 15°C-35°C, respectively [37].

The female *Aedes* mosquitoes feed on human or animal blood to mature their eggs. Adult mosquitoes tend to be smaller in size as their life cycle development period shortens in relation to increasing temperature above 15°C [41,42]. A smaller size mosquito tends to have increased feeding frequency, which increases the rate of dengue transmission [36]. Increasing temperatures can also shorten gonotrophic development, or the cycle from blood-feeding to egg maturation and breeding [43]. In their lifetime, female
Aedes mosquitoes typically lay about 3 batches of eggs with approximately 100 eggs per batch [34]. During dry spells or in stressful environments, Aedes can lay eggs on dry surface and their eggs can withstand complete dryness for several months, depending on humidity [21,34,35,44]. Because of this ability, the eggs can be transported great distances by humans in a wide variety of containers or objects. These eggs can then hatch within short period after being exposed to rain and optimal temperatures [34].

The development period for larvae can range from day(s) to several weeks, depending on the environmental conditions [34,35]. Pupae survive without feeding and last about 2-3 days, after which an adult mosquito emerges. A study by Dickerson (2007) in Texas has shown that temperatures of 14°C and 36°C stress the immature stages of Aedes and lead to a high mortality rate [45]. The author also demonstrated variation of the relationships between temperature and development rates among the immature stages of Aedes aegypti and Aedes albopictus collected from different field locations and laboratories. [45].

Rainfall and mosquito density

The wet season provides ample breeding habitats for Aedes mosquitoes, although heavy rainfall can potentially flush away larvae or pupae or the immature stage of Aedes. Heavy rainfall can also increase the mortality rate of adult mosquitoes [40,46]. An experimental study on the flushing effects of simulated rain on container-inhabiting larvae and pupae of Aedes aegypti and Culex pipiens demonstrated the ability of Aedes immature stage to adapt to this phenomenon in containers (size=27cm x 20cm x 8cm) [47]. The study reported the majority of larvae (first and fourth instars) and pupae of Aedes aegypti remained in containers, levelled or tilted at a 70° angle, after exposure to flushing rain for up to 60 minutes [47]. Aedes’ larvae and pupae were found to survive the flushing effects of heavy rain better than Culex [47].

Rainfall converts numerous artificial and natural sources into breeding habitats for Aedes mosquitoes. Aedes mosquitoes adapt to harsh environmental conditions, which are sometimes produced by vector control programs, by laying their eggs in unusual outdoor habitats, or even on dry surfaces to wait up to several months for the appropriate amount of rain water to hatch [44]. Therefore, the population density of Aedes mosquitoes can increase rapidly after rainfall. In general, any object or container that holds or traps 10ml of water can be a potential breeding site; thus making vector control an extremely challenging task.
Dry spells can actually trigger human behaviors that increase water usage or storage which in turn creates breeding sources for *Aedes* mosquitoes if containers are improperly covered or attended. Water storage during the dry season is not common in Singapore. However, residents can increase water usage for plants or gardening, use of air-coolers to lower ambient temperature, and other activities that might trap a small amount of stagnant water that creates sources for mosquito breeding.

Figure 4 shows potential breeding habitats in residential areas during the wet season. Habitats such as unattended pails or flower pots, bamboo holes, tree cavities, plant axils, or even trapped water in an empty decorative shell, are breeding sources that could easily be missed by residents or vector control officers. *Aedes* mosquitoes can emerge from these habitats within a short period of time depending on the temperature and environmental conditions. Figure 5 shows temporary artificial breeding habitats found in an industrial area. These include canvas, corrugated aluminium sheets, sunshades, the rooftop of a cargo container, and other items that could be transformed into short-term breeding habitats during the wet season. The types and locations of these breeding habitats also determine ambient temperatures and food resources that in turn influence the rate of development for aquatic or immature stage of *Aedes*. Containers or breeding sites that are exposed to the sun provide an environment with higher temperatures for larvae and pupae.

In summary, mosquito population increase rapidly during warmer periods as a result of shorter life cycle development. Simultaneously, increase in temperatures shortens the duration of the extrinsic incubation period of dengue viruses, prolongs the infective days of a mosquito, and therefore increases the dengue transmission rate. Though heavy rainfall could shorten the life span of outdoor *Aedes* mosquitoes, and potentially destroy immature stage, it also creates numerous temporary breeding habitats for *Aedes* mosquitoes, which in turn impacts dengue transmission.
Figure 4: Some *Aedes* breeding habitats at residential areas during wet season

Figure 5: Possible *Aedes* breeding habitats at light industrial areas during wet season
Dengue control

Vector surveillance and control is a major component of dengue suppression. The National Environment Agency (NEA) has formulated an integrated, evidence-based, dengue surveillance and control strategy that is built on the vector surveillance and control, research and laboratory surveillance, risk assessment, community outreach and mobilization, and legislation [48].

Vector surveillance and control include regular surveillance and intensive source reduction operations to eliminate mosquito-breeding habitats. The vector surveillance includes analysis of *Aedes* density and breeding habitats based on geographical locations of thousands of ovitraps across the island. To combat the upward trend of dengue, the NEA has enhanced their vector control programs by intensifying vector surveillance and expanding surveillance to detect the serotype and genotype of circulating viruses in order to assess the risk of potential outbreak caused by a change in the predominantly circulating virus or the emergence of new strains [18,49].

Risk assessment, such as threat of outbreak, dengue hotspots, and high risk areas are performed routinely using the Geographical Information System (GIS). The risk is assessed based on data from multiple sources, including case reports from the MoH as well as vector and virus data derived from surveillance and laboratory studies. This risk information is disseminated to five regional offices for response or mitigation. Each regional office deploys several teams of vector control officers to conduct search and destroy exercises in residential areas to eliminate mosquito-breeding habitats. Each month, vector control officers inspect all public areas and thousands of residential and non-residential premises [48]. Outdoor chemical fogging is applied sparingly when necessary. The NEA’s pest control operators perform extensive inspections of ground areas in the residential compounds.

The NEA categorizes epidemiologically related cases occurring within a predefined distance as dengue clusters. When two or more dengue cases are reported in residences, working areas, or institutional premises within a 150 meter radius, and the onset for these reported dengue cases is within 14 days, a dengue cluster is declared and the NEA disseminates information to appropriate regional office(s). These offices then conduct mitigation and epidemiological studies within the cluster. The cluster will be tentatively closed if there are no reported cases two weeks after the last onset date and the cluster is monitored for additional weeks to ensure that a recurrent outbreak does not occur.

The intensive search and destroy of mosquito breeding habitats are strongly supported by intersectoral collaboration [48]. The Inter-Agency Dengue Task Force, public and private institutions, and the community itself have been orchestrated to combat the increasing dengue trend [50].
Community compliance in the area of breeding source removal and prevention would greatly enhance and sustain long-term dengue control in the nation. The strategies to increase public awareness and knowledge of dengue control are implemented through public health education and promotion programs. Communication media includes dengue alert posters, alert letters, talks and exhibitions, and weekly updates on dengue hot spots and dengue situations provided on the internet. The NEA also works with grassroots organizations and Community Development Councils in all districts. Regular updates of the dengue situation are provided to all Town Councils, Citizen Consultative Committee meetings, and schools [48]. Beginning in 2004, a community program was launched to encourage residents to perform regular search and destroy exercise on mosquito-breeding habitats based on simple steps. A study by Ong et al. (2010) on knowledge and practise of household mosquito-breeding prevention measures showed a gap between knowledge and practise among some residents [51]. This implies further effort may be required to strengthen the community commitment and participation.

Continual research on innovative ideas and tools for dengue surveillance and control helps to improve the effectiveness and efficiency of vector control in the nation. Legislation, such as the Control of Vector and Pesticides Acts and the Environmental Public Health Acts, are in place to enable vector control to be carried out and to simultaneously discourage persistent mosquito-breeding behavior.

**Early warning**

“An early warning is the provision of timely and effective information, through identified institutions, that allows individuals exposed to a hazard to take action to avoid or reduce their risk and prepare for effective response” (International Strategy for Disaster Reduction (ISDR/United Nations (UN), 2004) [52]

Early warning is essential in both the control and prevention of a disease outbreak in that it allows individuals and institutions in high risk areas to take timely action. A timely and effective response to an early warning could lower disease incidence rates and burden on healthcare and economic systems stemmed from epidemics. According to the United Nations, an early warning system comprises awareness and knowledge of the threat, surveillance and forecast, comprehensible communication, and timely response [52].
In Singapore, the frequency of dengue epidemics increased from every 5-7 years before 2000 to every 1-4 years from 2003-2011. Although the upward trend of dengue incidence has been curbed since 2005, the threat of cyclic dengue epidemic remains high. Lower herd immunity and continual introduction or evolution of new serotypes of the virus partially account for the increase in incidence in recent decades [10,18,49,53,54]. Also, high population density increases the rate of exposure of susceptible hosts. It has been hypothesized that the shift in surveillance emphasis to case detection in the 90s was a reason for the increasing trend of dengue since the late 90s [10]. Vector surveillance and control systems were further strengthened in late 2005 with strategies that combined multi-disciplinary efforts [48]. Nevertheless, the high resilience of *Aedes* mosquitoes and the evolution of viruses are continual challenges to the success of vector control.

Local authorities have been taking rising temperatures as indicators for increased risk for dengue cases. A warning message is communicated to regional offices and the public at large to increase vigilance during the periods. Nevertheless, warnings based on weekly or monthly high temperature trend may not provide sufficient information on risk levels, likelihood of occurrence, risk distribution during the subsequent period, and timing of the occurrence of a probable outbreak. Additionally, such risk indicators might not allow sufficient time for local authorities to respond in order to alleviate the problem.

Temperature and rainfall have been studied as possible early warning for climate-sensitive vector-borne diseases such as malaria, West Nile disease, and dengue [55-57]. In recent years, several studies on statistical modeling in dengue endemic countries have suggested feasibility of predicting dengue cases using various types of meteorological data [56,58-60]. A model-based dengue early warning using temperature and rainfall would provide evidence-based or scientific estimation of the risk of dengue in future weeks or months, estimate risk of dengue using long period of historical data, and allow simultaneous consideration of the influence of other non-climate factors.
Aim and objectives

The aim of this study is to explore the possibility of developing a dengue early warning system that uses temperature and rainfall to provide precise forecasts and also allows sufficient time for response and mitigation.

The idea of a dengue early warning system that was based on temperature and rainfall was predicated on the assumptions that 1) climate partly influences dengue incidence through its effects on mosquitoes and dengue viruses, 2) a model-based dengue forecast could provide comprehensive risk information for decision making, 3) a dengue early warning that provides timely and precise forecasts may enhance existing vector surveillance and control systems, 4) the use of available data such as temperature and rainfall allows the development of an economical early warning system and minimizes the utilization of scare resources, and 5) Simplicity and clarity are two important features of an early warning system that enhance communication and increases the likelihood of policy makers to integrate the system into their dengue control program.

The objectives of this study are to address the following issues which are also discussed sequentially in the four Papers as shown in Figure 6.

Objectives

1. To quantify the risk of dengue cases as a function of temperature and rainfall at various lag times.

2. To determine the optimal time required by authorities to control an outbreak.

3. To develop and validate dengue forecasting models based on temperature and rainfall that enhances dengue surveillance and control.

4. To establish a risk-stratified forecast strategy that relies on uniformly interpreted risk indices derived from forecast dengue cases.
Methodologies

Study design

This study uses statistical models to forecast dengue cases based on temperature and rainfall. As shown in Figure 6, the study evolved from first establishing a relationship between dengue cases and temperature and rainfall to translating forecasts to dengue risk indices. The process involved four objectives with each objective reported in papers I to IV.

Non-linear Poisson regression was the model selected to analyze and predict dengue cases. Poisson methodology is widely used for counting disease cases. Weekly mean temperature and cumulative rainfall were used as the key predictors. Autoregression of dengue cases, trend, seasonality, and midyear population were included in all the models.

A forecast is a statistical estimate of the likely occurrence of future dengue cases based on past events. The forecasting models were developed based on the assumptions that 1) the past dengue distribution pattern would repeat itself in the future, and 2) the actual number of dengue cases equaled the predicted number plus or minus forecast errors (i.e., the discrepancy between actual and predicted cases) [61]. Timing of forecast was considered for operational purposes. Translation of forecast values into risk indices standardized the warning messages according to alert and epidemic thresholds established for each respective year. The brief summary of each objective or paper was presented in Table 5.

Figure 6: Research process
Ethical issue

Ethical approval is not required for this study. This is an ecological or population-based study that uses published data from public domains that contain no information on human subjects. The data were obtained from public sources such as reports of the Ministry of Health in Singapore and the National Oceanic and Atmospheric Administration (NOAA).

Study area

Singapore is a tropical island nation located in the Southeast Asian region and near the equator (Figure 7). The nation is linked to the Southern tip of Peninsular Malaysia by two causeways. The land size of the Island was approximately 714 sq. km in 2011 with a population density about 7257 per sq. km [62]. As of 2011, there were about 1,146 million resident households with an average of 3.5 persons per household, and the majority of the population lives in public or private high rise buildings [62]. Figure 8 shows an example of public housing premises. The Island city is connected by well planned, convenient, and advanced transport infrastructure. It is common for residence to commute from one end of the Island to another for work or activities through the mass rapid transport system.

The nation is a high income country with estimated per capita Gross domestic product (GDP) of about S$ 64,451 and 96% literacy rate for residents age 15 and above as of 2011 [62]. The backbone of the economy includes both international trade and tourism. The nation receives a high volume of international arrivals year round; especially visitors from Asia.

The main features of the climate are the relatively stable temperature throughout the year and high humidity and abundant rainfall. The Island receives rainfall frequently with the wettest months being in the period from November to January. The Island experiences northeast monsoons from December to early March and the southwest monsoons from June to September [63]. The northeast monsoon brings moderate to heavy rainfall that can last three consecutive days.
Figure 7: Map of Singapore (Source: NEA 2010)

Figure 8: A type of public housing in Singapore
Data

The data used for this study include dengue case, temperature, and rainfall collected from year 2000 to 2012. The data were collected continuously over the time in which each of the papers was written. This permitted the development and training of a forecasting model using updated data.

Dengue cases and clusters

Dengue data is reported weekly by the Ministry of Health through the Weekly Infectious Diseases Bulletin [64]. Dengue case data comprises DF and DHF. During the study period, average DHF contributed to less than 1.5% of the total reported dengue cases. The Ministry of Health (MoH) monitors dengue transmission through case treatment and surveillance. All private and public clinics and hospitals are required to report any suspected, clinically diagnosed, or laboratory confirmed dengue cases to the MoH within one day.

Data on dengue clusters, including the duration of cluster management and vector control, are obtained from the annual reports of Communicable Diseases Surveillance by the Ministry of Health [65]. Dengue clusters are identified when two or more dengue cases occur within 150 meter and the onset for the dengue cases is within 14 days. If no new cases are reported within 14 days after the last onset, a dengue cluster will be tentatively closed with continual surveillance before permanent closure is issued.

Temperature and rainfall

Daily temperature and rainfall data were obtained from the National Climatic Data Center and the National Oceanic and Atmospheric Administration (NOAA), USA [66]. The climate data of Singapore was accessed from NOAA under the World Meteorological Organization (WMO) World Weather Watch Program. The WMO performs extensive automated quality control to minimize random errors contained in the original meteorological data. The mean daily temperature was computed based on the average of 24 hourly-recorded temperatures. Weekly mean temperature in degree Celsius (°C) was then computed based on the average of the seven days mean temperature. Weekly cumulative rainfall in mm was also calculated.
**Midyear population**

The annual midyear population of citizens, permanent residents, and non-permanent residents was obtained from the Statistics Singapore [62,67]. Non-permanent residents comprise of foreigners who are working, studying or living in Singapore. International tourists or visitors staying for short term visits are not included in the midyear population.

**Statistical methods**

**Summary**

Construction of a statistical model includes the process of model identification, estimation, selection, and validation. In the identification stage, the relationship between dengue cases and independent variables was examined based on bivariate analyses and literature review. A characteristic of infectious disease analyses is the autoregression or the serial relationship between past and current dengue cases. This implies that the current number of cases is partially influenced by the past number of cases. In this study, autoregressive terms were selected using Autocorrelation functions (ACF) and Partial Autocorrelation Functions (PACF), and prior knowledge on the chain of dengue transmission. Examination of ACF pattern showed spikes decayed slowly into the upper limit after 24 lags. This indicated strong serial relationship between current and past cases. The PACF analysis suggested a possible lag of up to 4 weeks with highest strength at lag of one week. A study by Focks and Barrera (2007) showed that serial correlation between current and past dengue cases in Bangkok, Thailand could lag by several months with reducing strength of relationship corresponding to increasing lag times [43].

The maximum lag terms between exposure to temperature and rainfall conditions and response, or occurrence of dengue cases, were selected based on literature reviews and statistical analyses using cross-correlation Function (CCF). Spline function was applied to allow non-linear relationship. Dengue outbreaks are a consequence of complex interactions among multiple factors. Therefore, a trend variable was included in the models to account for the long term changes of distribution pattern. The variable was created using the number of weeks during the study period. Midyear population was included to account for changes due to the influence of population variation during the study period. After offsetting the midyear population, the outcome of the studies can be better described as an incidence rate.
Next, Poisson regression models were developed to estimate parameters. Quasi Poisson was applied to allow for over-dispersion of the data. Generally, a bivariate model between dengue cases and each independent variable can be expressed as follows.

Let $D_x \sim \text{Poisson} (\mu_x)$,

where $D_x$ is the average weekly expected or predicted dengue cases as a function of independent variable $x$.

Thus,

$D_{\text{Temp}} = $ dengue cases as a function of mean temperature
$D_{\text{Rain}} = $ dengue cases as a function of cumulative rainfall
$D_{\text{AR}} = $ dengue cases as a function of autoregression
$D_{\text{Trend}} = $ dengue cases as a function of trend
$D_{\text{CSeason}} = $ dengue cases as a function of epidemic cycle and season

A Poisson multivariate regression model that considers effects from all the variables can be expressed as follows:

$$\log (\mu_t) = D_0 + D_{\text{Temp}} + D_{\text{Rain}} + D_{\text{AR}} + D_{\text{Trend}} + D_{\text{CSeason}} + \text{offset}(\text{pop}),$$

where $\log (\mu_t)$ is the average of weekly dengue cases predicted by model, $D_0$ is the constant or fixed number of cases, $t$ represents week, and offset(pop) represents log(pop) to offset midyear population.

Model selection was based on lowest Generalized Cross Validation (GCV) scores or Akaike Information Criterion (AIC), and Root Mean Square Error (RMSE). Validation of modeling assumptions for the fit of models was performed using residual diagnoses, graphical examinations, and partial autocorrelation function (PACF). These measures were also used to assess over-fitting. Validation of a forecasting model was performed using long term forecast and cross-validation methods. Forecast precision of models was compared using RMSE. Finally, the Receiver Operating Characteristics (ROC) curve was used to assess the sensitivity of the forecasting models to predict outbreak and non-outbreak. All parameters were summarized using 95% confidence intervals. All statistical analyses were conducted using R statistical software [68] and STATA 12 (StataCorp., Texas, USA).
Differences between models

The difference between the models used for analyzing effects of temperature and rainfall on dengue cases (objectives 1-2) and the forecasting models (objectives 3-4) was the parameterization of temperature, rainfall, and trend. A smoothing spline with selected degrees of freedom was applied in the model for objective 1-2. To enhance forecast precision in the forecasting model, a piecewise linear spline function was applied to the climate data, while trend line and sine function were used to mimic the long term distribution pattern.

The following statistical models were employed in each of the four objectives. Model (1) was adopted from Paper I and II [69,70], and models (2) and (3) were adopted from Paper III and IV [71].

Impacts of temperature and rainfall on dengue

To analyze the relationship between dengue and temperature and rainfall, a Poisson multivariate regression model was developed using data from 2000-2010.

Mean temperature and cumulative rainfall
Five lag terms of mean temperature and cumulative rainfall were computed to study the exposure-response effects at various lag periods. Each lag term equates average mean temperature or cumulative rainfall in four weeks. Therefore, lag term 1 to 5 represents periods up to 20 weeks. Spline function with three degrees of freedom was applied on temperature and rainfall.

Thus,

\[ D_{\text{temp}} = \alpha_0 + \sum_{i=1}^{5} S(\alpha_i, \text{Temp}_i, df), \]

and,

\[ D_{\text{rain}} = \beta_0 + \sum_{i=1}^{5} S(\beta_i, \text{Rain}_i, df), \]

where \( \alpha_0 \) and \( \beta_0 \) are the constants, \( \alpha_i \) and \( \beta_i \) = parameters of temperature and rainfall, respectively, \( \text{Temp}_i \) = mean temperature, \( \text{Rain}_i \) = cumulative rainfall, and \( i \) corresponds to lag term 1 = week 1-4, 2 = week 5-8, 3 = week 9-12, 4 = week 13-16, 5 = week 17-20, \( S \) is the spline function, and \( df = 3 \).
**Autoregression**

Dengue cases at lag times up to six weeks were analyzed in the model. Average of every two weeks of past dengue cases was computed. Thus, the model can be expressed as follows.

\[
D_{AR} = \phi_0 + \sum_{k=1}^{v} \phi_k AR_k,
\]

where \(\phi_0\) is the constant, \(\phi_k\) is the parameter for autoregression, and \(AR_k\) represents autoregressive terms, \(k = \) lag term, \(v = 3\) with 1 = lag week 1-2, 2= lag week 3-4, and 3 = lag week 5-6.

**Trend**

Spline function with eleven degrees of freedom was applied giving about 1 degree of freedom per year. The sensitivity of degrees of freedom was examined with a range from 7 to 20 degrees of freedom.

\[
D_{trend} = \theta_0 + S(\theta Trend, df)
\]

where, \(\theta_0\) is the constant, \(\theta\) is the parameter, \(S\) is the spline function, and \(Trend = \) week starting from 2000 week 1 to 2010 week 52.

**Multivariate model**

A Poisson multivariate regression model is developed by considering the independent variables described above [69,70].

Thus,

\[
D_s \sim Poisson(\mu_s),
\]

\[
\text{Log}(\mu_s) = D_0 + \sum_{i=1}^{5} S(\alpha_i, Temp_i, df) + \sum_{i=1}^{5} S(\beta_i, Rain_i, df) + \sum_{i=1}^{v} \phi_i AR_i + S(\theta Trend, df) + \text{offset(pop)}
\]

(1)

where, \(D_0 = \alpha_0 + \beta_0 + \phi_0 + \theta_0\) if functions of all the independent variables equate constant.

Model selection was based on lowest GCV or AIC. Model validation was based on residuals diagnoses using residual sequence plot, histogram, quantiles normality plot, and graphical examinations on time series of fitted against observed dengue cases.
**Optimal time for dengue forecast**

Timing is a key feature that determines effectiveness of a dengue early warning system. The optimal time window was identified by examination of the duration of past dengue cluster management for clusters ≥ 10 cases over the period 2000 to 2010. Dengue clusters with ten or more cases were analyzed as these clusters generally required longer periods for vector control and cluster management.

First, impacts of temperature and rainfall on the increase of dengue cases over five lag terms was analyzed using the Poisson model (1) to identify the possible period which can be used as forecast lead time. In the second analysis, the time window required for a successful mitigation was based on the duration of past dengue cluster management for 368 clusters with ten or more cases (Table 2). Yearly, the duration of dengue transmission in these clusters ranged from 2-81 days during 2000-2010 [65]. The duration of dengue cluster management was divided into epidemic years (2004-2005, and 2007) and non-epidemic years in order to examine the difference in time required to control localized outbreaks during these periods. The unit in month was used to measure duration, and clusters duration was stratified into ≤ x month(s).

The results were then contrasted with lag times that correspond to higher dengue risk periods. As shown in Table 3, a forecast-response deficit or surplus exists when an early warning provided insufficient or sufficient time, respectively for authorities to respond. The optimal time window was identified as providing sufficient time or more (forecast-response surplus) for response (Table 3).
Table 2: Estimated number of reported dengue clusters in past decade [17]

<table>
<thead>
<tr>
<th>Year</th>
<th>&lt;10 cases</th>
<th>≥10 cases</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000</td>
<td>8</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>2001</td>
<td>78</td>
<td>15*</td>
<td>93</td>
</tr>
<tr>
<td>2002</td>
<td>43</td>
<td>30*</td>
<td>73</td>
</tr>
<tr>
<td>2003</td>
<td>142</td>
<td>38</td>
<td>180</td>
</tr>
<tr>
<td>2004</td>
<td>525</td>
<td>34</td>
<td>559</td>
</tr>
<tr>
<td>2005</td>
<td>1097</td>
<td>93α</td>
<td>1190</td>
</tr>
<tr>
<td>2006</td>
<td>153</td>
<td>19</td>
<td>172</td>
</tr>
<tr>
<td>2007</td>
<td>891</td>
<td>58</td>
<td>949</td>
</tr>
<tr>
<td>2008</td>
<td>542</td>
<td>34</td>
<td>576</td>
</tr>
<tr>
<td>2009</td>
<td>375</td>
<td>17</td>
<td>392</td>
</tr>
<tr>
<td>2010</td>
<td>377</td>
<td>29</td>
<td>406</td>
</tr>
<tr>
<td>total</td>
<td>4231</td>
<td>368</td>
<td>4599</td>
</tr>
</tbody>
</table>

* Clusters not reported: 5 in 2001 & 1 in 2002
α Only clusters >=20 cases were reported in 2005

Table 3: Forecast-response gap between the forecast window for dengue outbreak and the estimated response duration by local authority

<table>
<thead>
<tr>
<th>Forecast-Response Gap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration for an outbreak control (month)</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
</tbody>
</table>
Forecast of dengue

A Poisson forecasting model was developed to forecast dengue cases from week t+1 to week t+16. Weekly average dengue cases were predicted using weekly mean temperature and cumulative rainfall. Additional model was developed using only temperature and rainfall to allow inter-model comparison. Both models were trained using data from 2000-2010. Forecast of dengue cases was performed for year 2011-2012.

First, the relationship between dengue and each independent variable was expressed as follows (Paper III & IV).

Mean temperature and cumulative rainfall
Weekly mean temperature and cumulative rainfall data were divided into four strata, as shown in Figure 9, using a piecewise linear spline function that placed knots at the 25th, 50th, and 75th percentiles. Stratification of these predictors by percentiles allowed detailed analyses and permitted the flexibility of grouping the predictors according to data distribution. Prior knowledge of chain of dengue infection, previous findings, and cross correlations between these predictors and dengue cases were considered to determine lag times and data cycle period for forecast. CCF between temperature and dengue showed stronger positive relationship from lag weeks 9-17 and an inverse relationship between rainfall and dengue was observed. The optimal lag time between climate data and dengue was explored by testing lag times up to 20 weeks with data cycle ranging from 12 to 24 weeks.

Figure 9: stratification of temperature and rainfall into four equally spaced strata using piecewise linear spline function.

\[
D_{\text{temp}} = \alpha_0 + \sum_{f=L}^{L+n-1} \alpha_{fp} Temp_{fp},
\]

where \(\alpha_0\) is the constant, \(\alpha_{fp}\) is the parameter of temperature, \(Temp_{fp}\) = mean temperature, \(p = \text{temp}_{41}\) to \(\text{temp}_{44}\), \(f\) = lag term from weeks \(L\) to \(L+n\), \(L\) = optimal lag time, \(n\) = data cycle period.
And,

\[ D_{\text{Rain}} = \beta_0 + \sum_{g=L}^{L+m} \beta_{gg} \text{Rain}_{gg}, \]

where \( \beta_0 \) is the constant, \( \beta_{gg} \) is the parameter of rain, \( \text{Rain}_{gg} = \) cum rainfall, \( q = \text{rain}_{41} \) to \( \text{rain}_{44}, \) \( g = \) lag term from weeks \( L \) to \( L+m, \) \( L = \) optimal lag time, \( m = \) data cycle period.

**Autoregression**

Past dengue cases from lag week 1 to 6 were considered to account for the influence up to 6 weeks. The influence of past cases was also examined by considering lag times up to 12 weeks. Biweekly average autoregression was computed up to 3 terms or 6 weeks. Therefore, both weekly and bi-weekly average autoregression were tested in the forecasting model. The bivariate model of \( D_{AR} \) is as described in model (1).

**Trend, cycle, and seasonality**

The trend and cycle parameters represented the long-term distribution pattern of cases, whereas seasonality revealed the annual distribution pattern. Graphical examination of trend, cycle, and seasonality showed that dengue cases increased from 2000 to a peak in 2005 before declining. Increases in dengue cases were typically observed in the second half of each year; while three major epidemics occurred during the study period. Therefore, a curvilinear is considered to represent long term distribution and sine function was included to account for epidemic cycle and seasonality.

\[ D_{\text{Trend}} = \theta_0^* - \theta_2 (t - t^*)^2, \]

where \( \theta_0^* = (\theta_1^2 + 4\theta_0\theta_2)/4\theta_2 \) is a constant, \( -\theta_2 \) is the parameter, and \( t^* = \theta_1/2\theta_2 \) represents peak or maximal point of trend, and

\[ D_{\text{Season}} = S_0 + S_1 \sin \left( \frac{2\pi}{3 \times 52} \right) \]

where \( S_0 \) is the constant, \( S_1 \) is the parameter, \( \sin \) is the sine function.

Finally, two Poisson forecasting models were developed based on the independent variables described above.

Thus,

\[ D_x \sim \text{Poisson}(\mu_x), \]
\begin{equation}
\text{Log}(\mu) = D_0 + \sum_{j=L}^{L+k} \alpha_j \text{Temp}_{\text{yj}} + \sum_{g=L}^{L+m} \beta_g \text{Rain}_{\text{y}g} + \sum_{i=1}^{r} \phi_i A R_i - \theta_i (v - t^*)^2 + S_i \sin \left( \frac{2\pi}{3 \times 52} \right) + \text{offset}(\text{pop}) \tag{2}
\end{equation}

\begin{equation}
\text{Log}(\mu) = D_0 + \sum_{j=L}^{L+k} \alpha_j \text{Temp}_{\text{yj}} + \sum_{g=L}^{L+m} \beta_g \text{Rain}_{\text{y}g} + \text{offset}(\text{pop}) \tag{3}
\end{equation}

Where, \(D_0 = \alpha_0 + \beta_0 + \phi_0 + \theta^* + S_0\) in model (2) and \(D_0 = \alpha_0 + \beta_0\) in model (3) if functions of all the independent variables = constant or baseline values.

Models selection was based on the lowest AIC, and RMSE. Residual diagnoses were performed to examine and validate the fit of the model. This involved using sequence plots and residual normality plots to examine constant variation and distribution of errors. Plots of fitted versus reported dengue cases were also examined to assess the fit of the model. To assess the forecasting ability and compatibility of both models, six cross-validations of 16-week forecasts from year 2011 to 2012 were performed. In each of the forecast windows, only cases up to the current week (t) were used to forecast cases for week t+1 to week t+16. This process was repeated for the forecast of each window. Therefore, only observed temperature and rainfall data and predicted autoregressive terms were used to forecast dengue cases in each window. RMSE for each model within individual time window was computed to contrast forecast precision between the models. Sensitivity of the models to diagnose outbreaks during the training and forecast periods were analyzed using ROC curve.

**Dengue risk index**

To enhance understanding and communication of warning messages, forecasts derived from model (2) and (3) were translated into simple, comprehensible, and uniform dengue risk indices. The forecasts were translated by creating a dengue risk calendar and time series formats according to the alert and epidemic thresholds for years 2011 and 2012. The dengue risk calendar was designed to provide information on risk levels for month and season for rapid communication. Time series stratified dengue risk indices provide a range of weekly dengue risk levels with upper and lower limits of prediction derived from the two models. Dengue risk indices from 1 to 10 were represented by ten color bars in the color legend. Each color bar represents an increment of 30 cases. The number of cases for each color bar can be adjusted according to needs. The dengue risk calendar and the time series dengue risk indices were established using STATA 12 (StataCorp., Texas, USA).
<table>
<thead>
<tr>
<th>Objective</th>
<th>Summary</th>
</tr>
</thead>
</table>
| I         | Climate variability and increase in intensity and magnitude of dengue incidence in Singapore  
Aim: To establish risks of dengue as a function of weekly mean temperature and cumulative rainfall.  
Methods: A Poisson multivariate regression model was developed to analyze risk relationship between dengue cases and temperature and rainfall based on five lag terms. Spline function was applied to allow non-linear relationship. |
| II        | Optimal lead time for dengue forecast  
Aim: To determine the optimal time for a dengue warning given the duration required by a local authority to curb an outbreak.  
Methods: Identification of time gap between dengue risk period and duration of vector control by 1) analyzing risk association between dengue cases and temperature and rainfall based on model developed in objective I, and 2) evaluating time required to control localized outbreaks in dengue clusters≥10 cases during epidemic and non-epidemic periods. |
| III       | Forecast of dengue incidence using temperature and rainfall  
Aim: To develop and validate a dengue forecasting model to enhance dengue or vector control.  
Methods: Two Poisson forecasting models were developed with the second model considered only temperature and rainfall. Climate data were divided into 4 subgroups using a piecewise linear spline function that placed knots at equally spaced percentiles. Six 16 weeks cross-validations were performed in years 2011-2012 and the forecast precision of both models was compared using RMSE. Sensitivity of the two models to diagnose outbreak and non-outbreak were analyzed using ROC curve. |
| IV        | Dengue risk index as an early warning  
Aims: To establish risk-stratified forecast strategy which relies on uniformly interpreted risk indices derived from forecasted dengue cases.  
Methods: Forecasts generated using model (2) and (3) were interpreted according to annual alert and epidemic thresholds and translated to dengue risk indices using calendar and time series formats. |
Results

Distribution of dengue cases

As shown in Figure 10A, weekly dengue cases peaked in 2005 and plunged to a low in 2006. The country experienced an unexpected outbreak in 2007 that was out of sequence with the typical epidemic cycle of 5-7 years. The nation reported weekly cases higher than the decadal median of 86 during epidemic years as well as 2008 and 2010. The highest median weekly cases occurred in 2005 (≈ 230 cases) followed by 2004 (≈177 cases). Figure 10B shows that a higher number of cases generally occurred from June to October. The long-term distribution pattern of dengue cases (Figure 10C) has exhibited an upward cyclical trend since year 2000. The drastic downward trend in 2006 was partially due to the effectiveness of strengthened vector control programs implemented at the end of 2005. The decadal average weekly dengue distribution (Figure 10D) showed that dengue cases were higher between weeks 20 and 45.

Figure 10: Distribution of reported dengue cases from 2000-2010. Panel A shows weekly reported dengue cases, B shows the range of decadal average monthly dengue cases in box plots, C presents the trend of the logarithm of dengue cases over the period, and D shows the decadal average of weekly dengue cases.
Distribution of temperature and rainfall

During 2000-2010, the weekly mean temperature ranged from 25.5°C to 30.4°C with a decadal average of 27.8°C. In the same period, the average weekly mean temperature was above 28°C from April to September with the two of highest values recorded in May (28.7°C) and June (28.5°C). The decadal average of weekly mean temperature follows a curvilinear distribution pattern as shown in Figure 11A. The temperature>28°C was recorded from week 15 to 41 with slightly lower temperature was observed in week 30. Yearly distribution of weekly mean temperature as shown in Figure 11C shows that median mean temperature was higher in year 2002, 2005, 2009, and 2010. Wide range of weekly mean temperature was observed in 2008 followed by warmer climate with an upward shift in minimum and median weekly mean temperature in 2009-2010. Figure 11B shows that higher rainfall was generally recorded in week 1-2 and from week 43-52. The decadal average and median weekly cumulative rainfall were 43mm and 30.5mm, respectively. The highest median cumulative rainfall was recorded as 39.50mm in 2003 followed by 37.59mm in 2008 and 36.5mm in both 2010 and 2007 (Figure 11D). The maximum amount of weekly cumulative rainfall (394.2mm) was recorded in year 2006.

A Figure 12 shows that minimum and maximum frequency of temperature>28°C occurred in 2008 and 2010, respectively. As shown, weekly mean temperature exceeded 28°C in more than 50% of the total number of weeks in four out of eleven years during the study period. Data examination showed that the overall distribution of dengue cases was similar to the distribution pattern of weekly temperature>28°C, although a weaker relationship was observed in 2007-2009. The frequency of rainfall below 10mm showed a similar distribution pattern as this range of temperature, whereas change in frequency of weekly cumulative rainfall between 10mm and 60mm (approximately 75th percentile) was inversely related to mean temperature. The frequency of weekly cumulative rainfall between 10mm and 60mm was inversely related to dengue cases before 2007; whereas it was positively linked with dengue cases in 2007, 2008, and 2010. Generally, in contrast to the weak inverse relationship of rain to dengue cases, temperature showed a strong positive link.
Figure 11: Panel A and B show distribution of decadal average weekly mean temperature and cumulative rainfall, and panel C and D show annual range of weekly mean temperature and cumulative rainfall, respectively.

Figure 12: Annual total number of weeks with weekly mean temperature and cumulative rainfall recorded at specified range.
**Impacts of temperature and rainfall on dengue**

Findings based on model (1) showed that the effects of temperature and rainfall preceded dengue cases by up to 5 months. Each unit increase in temperature and rainfall corresponded to different increases in dengue from week 1 to 20 depending on the lag times and range of temperature or rainfall.

Relative risk of increase in dengue cases elevated almost linearly with each unit increase in mean temperature at lag weeks 1-16, except lag weeks 5-8. Overall, higher relative risk of dengue occurred at lag weeks 9-12 and 13-16 subsequent to each unit increase in mean temperature (Figure 13). Relative risk of dengue was inversely related to increasing cumulative rainfall at the lag of 1-4 weeks. Increasing weekly cumulative rainfall from 0-60mm posed increasing relative risks of dengue at lag weeks 5-16, while, higher cumulative rainfall increased the risk of dengue at longer time delay of 13-20 weeks. The highest relative risk of dengue as a function of cumulative rainfall occurred at lag weeks 13-16, followed by lag weeks 9-12.

**Optimal time for dengue forecast**

The optimal time for forecast was identified by analyzing periods of high dengue incidence and recording both the average and maximum time required for mitigation. This study suggested that the optimal time for dengue forecast was at least three months.

Results showed that higher risk occurred at a lag of 3 and 4 months subsequent to mean temperature and cumulative rainfall conducive to increasing dengue transmission (Figure 13). Figure 14 suggests that the average time required to control localized outbreaks during epidemic and non-epidemic periods was similar. Approximately 28% and 16% of dengue clusters took ≤1 month to mitigate and 60% and 71% required ≤2 months during non-epidemic and epidemic years, respectively. A small percentage (13%) of clusters took two to three months to mitigate in both non-epidemic and epidemic years. Overall, localized outbreaks in dengue clusters were controlled within 2 months, with a maximum time of up to 3 months required.
Figure 13: Relative risks of dengue as a function of weekly mean temperature and cum rainfall at lag week 9-16.

Figure 14: Duration of dengue clusters≥ 10 cases with corresponding number of cases (2000–2010). Each bar in both panels represents the percentage of clusters≥10 that required corresponding duration (y-axis) for mitigation. Left pertains to non-epidemic years. Right panel pertains to epidemic years (2004, 2005, and 2007). Figure from Paper II [70].
**Forecast of dengue**

The lag between dengue and temperature and rainfall was identified as 16 weeks and forecast was based on climate data cycle of 20 and 24 weeks (Paper III). Examination of relationship between dengue cases and each subgroup of temperature and rainfall using cross correlation function showed variation of strengths and patterns. These relationship patterns also varied according to periods. These analyses also revealed that the relationship between dengue and cumulative rainfall could be masked by averaging decadal weekly impacts of rainfall on dengue. Stratification of temperature and rainfall into four levels permitted in-depth analysis of case distribution.

Results suggested that model (2) explained about 84% of the variance in dengue distribution. Figure 15 indicates that the forecasting model (2) fit the data reasonably well during the training period. Residual diagnosis showed approximately 75% of all forecast errors was contained within 50 cases above or below the line of 0 (Paper IV). The forecast error exceeded 100 cases for the outbreak of 2005, and for two separate weeks of high reported cases in 2003 and 2009. Model (3) explained about 70% of the variance. Figure 15 (lower panel) suggests model (3) predicted with larger errors compared to model (2). However, Figure 15 also suggested temperature and rainfall alone could also provide reasonably good prediction on rising dengue cases during the epidemic periods from 2000-2010.

During the cross-validation periods, the forecasting model (2) was able to predict all five of the weeks where cases exceeded the epidemic threshold in 2011 and predicted distribution of cases according to the trend of reported cases (Figure 16). The forecast from 2011 to 2012 using only temperature and rainfall and predicted cases as autoregressive terms to validate the forecasting model. Figure 16 (lower panel) shows model (3) predicted outbreak one week before reported cases and predicted 2 out of the 5 weeks above the epidemic threshold during the outbreak period in 2011.

RMSE for model (2) and model (3) during 2000-2010 was 30 and 53, respectively. The high RMSE of model (3) was partially due to large forecast errors in years 2002, and 2005-2006. During the cross-validations from 2011-2012, the estimated RMSE for period 1 to 6 were 26, 31, 15, 18, 24, and 55 for model (2) and 36, 46, 22, 16, 24, and 55 for model (3), respectively. Both models predicted cases with an average for period 1 to 6 of 28 and 33 for models (2) and (3), respectively. As shown in Figure 16, model (3) performed with higher errors in 2011 (periods 1-3) when outbreak occurred, but it predicted cases within a close range of errors as model (2) in 2012 (periods 4-6). Both models forecast with largest errors in period 6.

ROC curve showed that model (2) was able to detect outbreaks at above 90% accuracy, with approximately a 10%, and less than 3%, probability of
false alarm in 2004-2010 and 2011, respectively (Figure 17). Model (3) (Figure 17) predicted outbreaks with up to 90% accuracy, with approximately 21% and 10% false alarm rates for 2004-2010 and 2011, respectively. The limitations of using temperature and rainfall alone include less precision in the prediction of the exact number of cases, as shown in Figure 16, and in the forecast of the range of risk indices due to wide range of limits (Figure 19). Nevertheless, model (3) demonstrated sensitivity to predict outbreaks. In general, results suggested that both models were able to provide early warning of dengue up to 16 weeks.

Figure 15: Fitted cases versus observed cases from 2001-2010. Dotted line shows reported dengue cases and solid line shows cases fitted by respective model.
Figure 16: Cross-validation of models. Each graph shows cross-validation periods 1-6 from 2011w1 to 2012w44 and additional forecast for 2012 week 45-52. Gray line with triangle markers represents reported cases, and black line with round markers depicts predicted cases using respective model.

Figure 17: Sensitivity analysis of model (2) and (3) to diagnose outbreaks using ROC curve.
**Dengue risk index**

An outbreak is declared according to estimated thresholds that are derived from dengue cases in past years; therefore, these thresholds vary over time. Because of this, it may be difficult for stakeholders to keep track of previous epidemic thresholds. Translation of the forecast is essential to avoid misinterpretation or delayed response due to insufficient information.

Forecasts were translated into stratified risk indices using calendar or time series formats with color codes to indicate risk levels. Weekly forecasts of cases were recoded according to alert and epidemic thresholds established by local authorities to permit uniform interpretation. Color contours that showed weekly, monthly, and seasonal risk of dengue in calendar format were used to communicate warning messages to general stakeholders (Figure 18). Pictorial representation of dengue risk indices promotes rapid communication via simple graphical messages and requires no further effort to interpret. Dengue risk indices from 1-10 was used to represent the ascending threat of outbreak. Figure 19 demonstrates a range of weekly risk indices presented with upper and lower bounds. Each of the six windows showed 16 weeks forecasts derived from cross-validations from 2011-2012. Dengue risk indices were represented as 1-4 = “low”, 5-6 = “alert”, and 7-10 = “high” risk of epidemic. Simplified risk indices interpret forecasts according to annual alert and outbreak thresholds; thus, providing uniform interpretation to allow rapid and clear communications. Furthermore, time sequence risk indices provide upper and lower limits of forecasts that provide additional information for decision-makers.
Figure 18: Monthly or seasonal dengue risk indices for 2011 & 2012. Forecast of dengue cases were translated into monthly and seasonal risk indices. Dengue risk indices from 1-10 was used to represent the ascending threat of outbreak. Index 1-4 = low risk, 5-6 = alert, and 7-10 = high risk. Each color bar represents an increment of 30 cases. Left and right columns show dengue risk indices in year 2011 and 2012, respectively.
Figure 19: Weekly dengue risk index 2011-2012. Forecasts during cross-validation periods were translated into weekly dengue risk indices. Each graph (1-6) represents a 16-weeks forecast. Black square markers equate reported cases. Gray area with dark-dashed lines and brown area with light-dashed lines represents predicted cases with upper and lower limits derived from model (2) and (3), respectively. Each color bar represents an increment of 30 cases. Index 1-4 =low risk, 5-6=alert, and 7-10=high risk.
Discussion

Main Findings

This study 1) established that higher risk of dengue occurred at lag weeks 9-16 as a function of weekly mean temperature and cumulative rainfall; 2) suggested that dengue forecast should arrive at least 3 months in advance; 3) developed a dengue forecasting model to provide an early warning up to 16 weeks; and (4) translated these forecasts into a dengue risk index to enhance the simplicity and effectiveness of communicating early warnings to stakeholders including the public at large.

This study capitalizes on available secondary data and uses minimal capital investment to create a forecasting instrument. The use of this forecasting instrument helps to reduce the burden of dengue by enhancing the effectiveness of dengue surveillance and control. Forecast of dengue also allows local vector control to place emphasis on higher risk periods to minimize the cost of operations. The study also bridges the gap between research and operations by considering the lead time required for vector control and stressing simple, standardized, early warning messages. Dengue risk stratification allows policy makers to formulate vector control strategies including manpower deployment and intensive search and destroy exercises according to their standard operating procedures.

An effective mitigation in response to an early warning of dengue could reap multiple benefits ranging from a healthier community to a decreased economic burden and a decrease in disability-adjusted life years (DALYs). It has been estimated that dengue control has cost about 0.9 billion with $500 million attributable to the costs of vector control for the period from 2000 to 2009 [72]. Thus, the cost of vector control is a major economic burden. Furthermore, dengue has cost Singapore an annual average of 9 to 14 DALYs per 100,000 population depending on estimation methods [72]. A model-based forecasting system that combines ease of integration with minimal capital investment also increases the willingness of local authorities to integrate it into their dengue surveillance system.

Effects of climate on dengue

This study shows that temperature and rainfall precede the increase in dengue cases by 4 to 20 weeks. Each unit change in the two predictors influenced the risk ratios of dengue cases differently as the lag time varied from 4 to 20 weeks. The findings in this study are consistent with other
studies that also show positive influence of temperature and rainfall on reported dengue cases [30,56,58,59,73-76].

The weekly mean temperature range and high frequency of temperatures above 28°C provide a highly conducive environment for vector development and virus replication. Higher temperature could expedite the development of the aquatic stage, although the mortality rate of larvae and pupae also rises with increasing temperature [37,41,45,77]. It had been suggested that dengue transmission threshold measured by *Aedes aegypti* pupae per person was inversely related to increasing temperature [43]. Lambrechts *et al.* (2011) suggested that large daily temperature ranges decrease the probability of vector infection [78]. The average daily temperature range in Singapore was between 6°C and 8°C from 2000-2010, which suggests a favorable environment for vector infection.

The abundant rainfall in Singapore sustains the mosquito population by creating ample breeding habitats. It has been documented that rainfall and positive breeding habitats are linked non-linearly with dengue cases [79]. During the dry season, female mosquito could breeds in containers in household premises [80], whereas rainfall allows mosquitoes more selection of breeding sites and also permit eggs in dry areas to hatch. A recent study reported that more gravid female *Aedes* mosquitoes choose to lay eggs in sun exposed habitats [81].

The frequency and span of weeks with high temperatures and moderate rainfall play an important role for sustainable dengue transmission. However, this relationship could possibly be moderated through intensive vector control that suppresses an outbreak before it occurs. In turn, increasing resilience of *Aedes* mosquitoes, or their ability to adapt to changing environments, could also pose a challenge for vector control. Gravid mosquitoes could oviposit eggs at obscure or unusual habitats as a form of adaptation to a changing environment [81]. The fact that *Aedes* have shifted their breeding sites to less common habitats in 2011 versus 2005 may be an adaptation to the intensive breeding source reduction exercises implemented since 2006. It was found that a new generation of *Aedes* mosquitoes that survived in water containing insecticide were able to subsequently breed in this water [22]. This suggested that *Aedes* mosquitoes had acquired resistance against some of the traditional biological agents used against them. Furthermore, environmental changes, such as increasing concrete construction and reducing greenery or vegetation in a local area, could influence ambient temperature or urban heat effects.

Climate in the equatorial Pacific region can be influenced by sea surface temperature anomalies including La Niña (unusually cool temperatures) and El Niño (unusually warm temperatures) [82,83]. These anomalies occur at time interval of two to seven years and last for several months. During these periods, local weather patterns may vary according to geographical locations,
seasonality, and the intensity of La Niña and El Niño events [82,83]. La Niña affects climate in Southeast Asia by increasing rainfall [84]. During a strong El Niño event in 1997, drier and higher temperature was recorded in Singapore; the annual rainfall was significantly below average and temperature was approximately 1.4°C higher [84]. This coincided with higher dengue incidence in Singapore compared to previous years. Several studies from various countries have shown a positive influence of sea surface temperature anomalies on dengue transmission [26,32,85,86]. Conversely, other studies also suggested that these anomalies had little impacts on local dengue incidence or that the effects could be masked by localized weather patterns [58,87].

**Time window**

The time lags occurring between the exposure to temperature and rainfall and the occurrence of increasing dengue cases or outbreak offers a window for dengue forecast. This time gap encompasses the interval from vector and virus exposure to favorable weather conditions to the time dengue cases are actually reported. This study suggested a lag window of up to 5 months. A study in Bangkok, Thailand had documented a relationship between temperature and dengue cases with a lag from 1-5 months with the highest strength of relationship at 3-4 months [43]. In contrast, rainfall exhibited a high positive relationship with dengue cases at a lag of 0 to 2 months and an inverse relationship at a lag of 5-6 months [43]. A recent study in both urban and industrial settings in India showed significant increases in breeding sites and positive oviposition of *Aedes albopictus* 1-3 months after heavy rain [88].

The time required for cluster management could be affected by multiple factors ranging from environmental and building conditions to the commitment of the community to eliminate mosquito breeding habitats. It is important to note that it usually takes longer to curb an outbreak than to implement preventive measures ahead of time. As a result, the time required for mitigation in response to an early warning could be shorter than the time required for controlling a localized outbreak in a dengue cluster. Therefore, it is reasonable to assume that a forecast of dengue cases three months ahead of time will prove sufficient for mitigation.
Forecast of dengue

Assessment of risk of outbreak is mainly based on case, vector, and virus surveillance. During epidemics in recent years, outbreaks occurred in 3-7 weeks after reported cases exceeded the alert threshold [64]. A forecast of dengue in longer period in advance could therefore enhance the existing surveillance system. The predicted risk of dengue could be further augmented based on the current surveillance on mosquito density and predominant circulating serotypes of dengue virus.

Statistical modeling based on climate data has been continually studied over the years to analyze the impacts of climate on dengue and to study the feasibility of forecasting dengue incidence in weeks or months in advance using different statistical methods [26,56,58-60,89-92]. A recent systematic literature review that analyzed dengue predictive models and early warning systems based on sixty-three articles has reported statistical methods employed in these studies included Poisson, stepwise, logistic, and spatio-temporal regression as well as Autoregressive Integrated Moving Average (ARIMA) [93]. In view of the dynamic of disease transmission, the authors emphasized the benefits of combining epidemiological tools and the use of spatio and temporal data to increase forecast ability. A study by Fuller, Troyo, and Beier (2009) has developed a forecasting model that predicted dengue cases up to 40 weeks in Costa Rica using El Niño Southern Oscillation and vegetation indices [26]. The model was able to explain about 83% of the variance in weekly dengue cases. Another study by Descloux et al (2012) has developed dengue forecasting models using meteorological variables in New Caledonia [58]. The authors also reported that their models had been integrated into the local vector control policies.

In the past two decades, few studies had been carried out to analyze the effects of temperature and rainfall on dengue incidence in Singapore [73,94]. In addition to forecast precision, this study also emphasizes the operational function of the dengue forecasting model. Therefore, the time required for mitigation was considered in the model. In a scenario when longer lead time is required, a forecasting model could be developed using other climate variables, including ENSO or Niño index, which could possibly permit a long term forecast. To compare forecast precision with model (2) and (3), a stepwise regression model was also established using logarithm transformed weekly difference of cases (i.e. difference between cases in week (t) and (t-1)) (not shown). In the stepwise regression model, only autoregression and weekly climate data were used to forecast the changes of cases 16 weeks in advance. Compare to model (3) which considered only climate data, the stepwise model fitted dataset with lower errors during data training period, but it was not able to detect outbreak and predicted cases above the alert threshold in non-outbreak period during cross-validations in 2011.
**Limitations**

Statistical forecast modeling is challenged by several limitations. First, all disease models are imperfect codifications of the dynamics of disease transmission that occurred in the past. This makes forecasting models vulnerable to the effects of newly developing relationships and phenomena. Second, the precision of a forecasting model is largely influenced by the quality of the registered data it is based on. Under reported, un-reported, or miss-classified cases could diminish the accuracy of the model. Because of this, data quality concerns could restrict the development of a model-based dengue forecasting system in some developing countries. Also, the large numbers of undetected asymptomatic dengue-infected persons who are able to transmit dengue silently poses additional challenge. The 2004 seroepidemiologic study in Singapore has led to the suggestion that about 19-23 asymptomatic or subclinical infections exist for each clinical dengue case [95,96]. Third, forecasting is geographically bound due to differences in risk factors and the dynamics of disease transmission. Many of the risk factors, such as the predominant circulating dengue viruses, herd immunity, climate, and human behaviour, can be unique to different study areas. Therefore, dengue-forecasting model needs to study area-specific.

**Sustainability**

A major challenge for long-term disease forecasting is the evolution of complex risk factor patterns over time. As forecast projection is based on the assumption that the past distribution pattern is likely to repeat itself in the near future, the sustainability of forecast precision is inevitably threatened. A change in the seasonal and long-term distribution pattern of hand-foot-and-mouth disease (HFMD) in Singapore has been observed [97]. The disease has increased from single to double outbreaks in each year since 2004 and its trend has increased almost linearly since then. Similarly, a change in dengue vector control policy can have direct impacts on the distribution pattern of dengue cases. The revamped vector control programs that were started in response to the historical outbreak of 2005 partially explain the success in the control of Singapore’s dengue incidence in recent years when neighboring countries, such as Malaysia, Laos, Vietnam, and The Philippines, reported epidemics and upward trend of dengue incidence [98,99]. Conversely, the introduction of new strains of dengue viruses or changes in existing circulating strains have the potential to induce a national outbreak [18]. Thus, the impacts of control measures and changes in other risk factors can alter the long term distribution pattern of dengue.
Drastic and unfamiliar changes in the distribution pattern of dengue cases induced by risk factors such as new strains of virus are not likely to be detected in the initial period using a forecasting model based on temperature and rainfall. Integrating a qualitative forecasting method, such as the Delphi Method, which relies on a panel of experts from different disciplines including epidemiology, virology, entomology, and vector control could possibly help to predict the change of past distribution pattern and to sustain long term forecast precision [61]. Additionally, the information derives from routine serotypes surveillance could increase the possibility of detecting a drastic change of trend induces by a change in predominant circulating dengue virus. Nevertheless, cost and the limited availability of laboratory facilities are two factors that could be constraints for long-term virological surveillance in nations that have limited resources.

Future perspectives

Global warming and the increasing number of extreme weather events are some irreversible environmental consequences of climate change. According to the Intergovernmental Panel on Climate Change (IPCC) report in 2007, global mean surface temperature is possibly rising by likely range from 1.1ºC to 6.4ºC at the end of the 21st century, depending on the scenarios of each model [100]. A report from Australia documented that a small increase in annual mean temperature could be related to moderate variation in daily weather that in turn had impacts on the ecosystems and biodiversity of tropical regions [101]. Therefore, it is reasonable to speculate that the incidence of dengue is likely to increase in conjunction with anticipated increasing temperature trends and extreme weather events.

International trade and population movement have been identified as possible factors that have influenced the re-emergence of dengue [102]. Cross-border population movement can introduce diverse strains of dengue viruses that could cause outbreaks to susceptible communities. In recent decades, trade and travel among countries has increased through economic cooperation, improved socio-economic status, rapid increases in budget airlines and hotels, and other economic factors.

Singapore, an international trade and travel hub, is vulnerable to regional dengue transmission. One risk factor is the exponential growth of tourism in recent decades. Annual visitor arrivals to Singapore have increased linearly since 1970, with a rapid upsurge of visitors in recent years. In 2011 total annual visitors exceeded 13 million and this count excluded large numbers of Malaysian arriving by land [62]. Southeast Asian countries comprise about 41% of total annual visitors [103]. In the last decade, several dengue cases
were also traced to Singapore residents returning from travel. During the period from 2004 to 2010, the majority of imported cases came from Southeast Asian countries [17]. The influx of visitors from dengue endemic countries created the possibility of introducing new strains of the virus into Singapore [18, 104]. A switch in the predominant circulating dengue serotype could induce an outbreak. Thus, international travel and trade increases the risk of a dengue outbreak, since low herd immunity has been identified as one factor that sustains or increases dengue transmission in the nation [10]. Several studies have documented importation of dengue virus by residents returning from dengue endemic countries [104-106]. Studies in Taiwan reported detection of confirmed dengue cases through airport surveillance [104, 107]. WHO has initiated international collaboration among member nations in the Asia Pacific and South East Asian regions to combat dengue at the regional level [8]. The Dengue Strategic Plan for the Asia Pacific Region (2008-2015) was formulated with the goal of reversing the upward trend in the region [8].

Numerous efforts have also been applied to the development of innovative interventions for dengue control. In recent years, several dengue vaccines under different stages of development have been reported [108]. Vaccine development is challenged by the requirement of a tetravalent vaccine to simultaneously generate immune response against four serotypes of dengue virus. Moreover, a widespread vaccination program among dengue endemic countries cannot be implemented in a short period of time [108]. The cost-effectiveness of mass vaccination programs is an important consideration, since financial conditions of many dengue endemic nations are unfavorable.

Other innovative interventions include studies on genetically modified Aedes mosquitoes to control mosquito populations. Female mosquitoes that mate with genetically altered sterile male mosquitoes produce offspring that cannot complete the life-cycle to adulthood. Currently, an open field trial of releasing large numbers of genetically-modified sterile male Aedes aegypti is being carried out in Malaysia, Grand Cayman, and Brazil [109, 110]. The ability of Aedes mosquitoes to adapt to their environment necessitates a continual search for innovative control ideas.
Conclusion

Increasing regional population movement; community commitment to vector control, evolution of dengue viruses, mosquito adaptation, and environmental changes such as global warming will continue to challenge the effectiveness of dengue control. The value of a forecast system for dengue based on temperature and rainfall lies in enhancing the effectiveness of existing dengue surveillance and control systems, and with facilitating timely response and preparedness. This study demonstrated the feasibility of developing a model-based dengue early warning using temperature and rainfall. Although several limitations and challenges need to be addressed, these should not discourage further improvement and the use of a model-based approach.

The next phase of this study will involve calibrating the forecasting model while performing real time validation, and evaluating functionality and cost-effectiveness of the early warning system. To increase forecast precision and sustainability, it is essential to perform further study 1) to increase the ability of the forecasting model to predict changes in historical data and 2) to develop an automated early warning system which combines both quantitative and qualitative forecasting methods with the help of advanced technologies. An automated early warning system could include regular audits of forecast precision, periodical assessment of optimal trend and seasonality, and continual re-calibration of models based on current data.

Cost-effectiveness analyses of integrating a dengue forecasting model into the existing surveillance system would help policy makers to determine the value of adoption. An economic study could also help to identify acceptable thresholds for false alarms. It will be a challenge to quantify the benefits of a dengue early warning, as its value depends on timely response and mitigation. Nevertheless, cost-effectiveness studies of an early warning system could be performed based on reasonable or best-estimated assumptions combined with adequate sensitivity analysis. Furthermore, an understanding of community perception toward an early warning system, as well as social mobilization, will help local authorities to formulate strategies to communicate a warning message and foster stronger community commitment.

Dengue transmission is not confined within national borders. Therefore, regional dengue control is essential to sustain the efforts in Singapore. Future studies on developing a regional dengue early warning system may enhance efforts at control among endemic countries in the region.
Brief personal reflection

I experienced three dengue outbreaks in Singapore from 2004-2007. During the historical outbreak of 2005, the majority of public hospitals recorded average bed occupancy rate higher than normal. I wondered about the causes of the increasing dengue outbreaks during those years. Therefore, I chose to do thesis on dengue during my study in the Master of Public Health Program (2007-2009) in Umeå University. I decided to explore the issue from an environmental perspective since few studies documented the impacts between climate and dengue incidence before that. My supervisor, Nawi Ng, responded positively to the proposal. Then, Joacim Rocklöv was invited to support my study as a co-supervisor. With the help from Joacim, I embarked on my journey on statistical modeling and have enjoyed it ever since. Of course, there were many frustrating moments; especially when learning new statistical software.

After that, more questions began to emerge – can climate data be used to predict cases? What can I contribute as a public health researcher? During my PhD proposal seminar, Stig Wall asked me, “How early should an early warning be?” “Would you choose a “good” model that cannot predict or a “not-so-good” model that can predict?” Answering that question became objective 2 in this study. The second question became a realistic challenge during the period when I developed the forecasting models for objectives 3 & 4. My answer to the second question was a “not-so-good” model that can predict. In a study visit to the Laboratory of Mathematical Parallel Systems at York University, Toronto, I was glad to learn that a “perfect” model was not emphasized while developing a forecasting model. The trip expanded my knowledge on disease modeling. The forecasting model developed in this study might not be a fantastic model and it requires re-calibration or further improvement to sustain long term forecast precision. However, it was developed after numerous tests using different combination of variables, stratification using different breakpoints, differing ranges of data cycle, differing model training periods, and different statistical methods. Extensive data examination based on different time units had been performed. Effects of various strata of independent variables on dengue cases in different periods were analyzed. Overall, the forecasting model was a result derived from curiosity and by asking “what if” and repeated tests.

The idea of forecasting of dengue cases is a challenging thought, since the future implies uncertainty. Moreover, the link between dengue incidence and climate is not well received by some policy makers. Before I commenced my PhD study, a policy maker mentioned to me that research remained in academia and had little impact on practical operations. I took the remark as a motivation to carry out a study that is practical for operational purposes. A
field study on dengue control at the National Environment Agency of Singapore made me to realize that vector control operations could be more challenging than I imagined. The field experience also helped me understand more about operational needs such as that time requirements vary according to barriers in different localities. Communication with local authorities during these years allowed exchange of ideas that enhanced this study. An immediate challenge of this study is to carry out a joint study with the local authority to perform real time model validation and modification as well as to assess suitability of the model for integration into existing surveillance system. Also, it will be useful to integrate a qualitative forecasting method into the early warning system to enhance forecast precision.
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