Weather Factors Associated with Reduced Risk of Dengue Transmission in an Urbanized Tropical City

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Abstract

Introduction

The association of weather factors on dengue transmission in an urbanized tropical environment remains inconclusive. This study aims to assess the impact of weather factors on dengue incidence in Singapore between 2012 and 2019.

Methods

Data on weather variables (daily temperature, air quality, rainfall & wind speed) and weekly dengue incidence rates were collected from 1 January 2012 to 25 August 2019. Statistically significant correlated variables identified from cross-correlation analysis using Pearson's correlation were examined in univariate ARIMA model. Quasi-Poisson model with a distributed lag non-linear model (DLNM) was established to assess any non-linear association between climatic factors and dengue incidence.

Findings

Poor air quality (PSI: 150) and high wind speeds (12 km/h) were associated with reduced risk of dengue transmission in an urbanized tropical environment. Only a limited temperature range (27-32 °C and 23-25 °C) promotes dengue transmission whereas extreme heat inhibited dengue incidence (27°C, Ref. 25.14 °C; RR: 0.74, 95% CI: 0.58, 0.93). Rainfall exerts positive and negative influence alternately on weekly dengue cases across lags but the influence was not robust in sensitivity analysis. Based on split-sample model validation, mean temperature was the best predictor of dengue in prediction part (MAE: 43.15, RMSE: 51.39).

1. Introduction

Dengue is a mosquito-borne viral disease that is endemic in tropical and subtropical regions. Globalization and global warming, however, have facilitated its expansion to non-endemic countries over the years [1, 2]. An estimated 50 to 200 million dengue infections occur annually, with more than half the world at risk of infection [3]. The disease may escalate and cause dengue haemorrhagic fever (DHF) in a small minority, and the annual death toll from dengue lies between 20,000 and 25,000. Four antigenically distinct serotypes (DENV1/2/3/4) co-circulate globally, but DHF is more often associated with DENV2 and DENV3 infections [4-6].

The occurrence of dengue epidemics in endemic countries are multifactorial [7] and are reflective of the interplay between host, vector, virus & environment in disease transmission. Factors that drive epidemics include a change in predominant serotype [8, 9], or lowered herd immunity due to waning immunity and increased proportion of susceptible individuals accompanying population replacement [10, 11]. Climatic factors are also integral to dengue transmission, as reflected by the seasonal nature of the disease [12, 13]. -

Recent studies have attributed *Aedes Aegypti* adaptation to outdoor environments as a major factor driving dengue transmission worldwide [14]. In urban settings, outdoors breeding of *Aedes aegypti* in rainwater accumulating containers gives an indication of how climatic factors support environment factors that influence vector growth [15, 16]. There is much evidence that meteorological factors including temperature, rainfall, humidity, and air quality influence vector growth and distribution both directly and indirectly. Studies have found that a temperature rise of up to 34°C increases all stages of *Aedes Aegypti* developmental rates, resulting in population growth [17]. Increased dengue transmission under warmer temperatures can also arise from faster viral replication within the vector, shortened extrinsic incubation period, and increased feeding rate of *Aedes Aegypti* [17-19]. Humidity also increases viral propagation and hatch percentage of *Aedes Aegypti* eggs [20, 21]. Human practices coupled with climatic factors, such as water storage in dry climates, can also encourage mosquito productivity and dengue transmission [22].

In general, the significant effect of warmer temperatures on increased dengue rates is largely consistent across studies, while the role of humidity, air quality, rainfall and haze on dengue transmission is not clear and less often studied [8, 23, 24]. A comprehensive understanding of how meteorological factors influence vectors and humans is crucial for disease forecasting and control. Additionally, it has been recognised that predictive models for dengue transmission need to account for the interaction between climatic factors and be contextualized to specific population settings.

Singapore is a tropical country where dengue resurgence typically occurs in a 5-6 year cycle, but the last decade has seen dengue escalate to records numbers [9, 25]. Despite aggressive vector control programs and public awareness campaigns, dengue cases surpassed the tens of thousands between 2013 and 2019 [9, 26, 27]. Another strategy adopted by the Singapore government has been to publicise data on real-time distribution of cases and hotspots as part of timely alerts to the community [9, 25, 28]. Nonetheless, evidence has shown that vector control is the most effective means to reduce dengue transmission [11], and it is envisaged that predictive surveillance and targeted response would be an efficient long-term strategy.

Hence, this study aims to assess the association between multiple weather factors and dengue incidence in Singapore between 2012 and 2019, as well as examine the role of less well-characterised weather variables including air quality and wind speeds. This would help inform dengue predictive models in the regional guide targeted disease control efforts.

2. Materials And Methods

2.1 Data collection

Weekly notified dengue cases in Singapore from 1 January 2012 to 25 August 2019 were collected from the Weekly Infectious Diseases Bulletin published by the Ministry of Health [28]. Daily weather data collected included mean, maximum & minimum temperature (°C), total rainfall (mm), wind speed (km/h) and pollutant standard index (PSI), all of which were obtained from the National Environment Agency

[29]. The data was collected across 63 meteorological stations evenly distributed over Singapore. City-wide data points were aggregated by averaging across all stations while daily figures were averaged across each reporting week to obtain weekly-representative data. The total population data was based on the mid-year human population of the respective year from the Singapore Department of Statistics [30].

2.2 Statistical Analysis

Autoregressive integrated moving average (ARIMA) Model

Autoregressive integrated moving average (ARIMA) is a class of models that ‘explains’ a given time series based on historical values. For initial analysis, the univariate ARIMA model was built to capture the time structure of dengue cases. Weather variables with appropriate lags were added as exogenous variables to improve the model.

The equation used for ARMA(p, q) model is as follows:

$$y_t = c + a_1 y_{t-1} + \dots + a_p y_{t-p} + u_t + m_1 u_{t-1} + \dots + m_q u_{t-q} \text{ -- Equation 1}$$

Where y_t is the target time series value at time t ; c is constant; $u_t, u_{t-1}, \dots, u_{t-q}$ are white noise error terms; a_i ($i = 1, 2, \dots, p$) and m_i ($i = 1, 2, \dots, q$) are corresponding parameters.

Since the time series graph (Figure 1) indicated a long-term trend and non-stationary trait clearly, first-differencing of the data was conducted to build the ARIMA model. Log-transformation of weekly dengue cases numbers was conducted to stabilize the variance. Seasonal ARIMA model was also investigated but results were only included in the supplementary due to drawback of weekly data – seasonal period is not a common number usually representing one year (52 weeks).

The cross-correlation function (CCF) graphs showcase all weather factor correlations with weekly dengue incidence while accounting for lagged effects, at a significance level of 0.05. Due to autocorrelation of both time series, inference of coefficient’s correlation may not be robust and pre-whitening technique was applied to circumvent the issue [31]. Both Pearson and Spearman correlation were considered for linear and non-linear relationship respectively.

Distributed Lag Non-Linear Model

Recognising that relationships between weather and dengue are not simply linear in practice, non-linear associations were also explored using a Distributed Lag Non-linear Model (DLNM) [32]. DLNM is an advanced statistical method developed to simultaneously estimate the nonlinear and delayed effects of the exposure on response. The cross-basis function describing a two-dimensional relationship along the dimensions of factor and lag is the core of DLNM implementation.

The number of weekly dengue cases was assumed to follow an over-dispersed Poisson distribution [33]. Thus Quasi-Poisson regression coupled with DLNM cross basis was considered. Univariate exposure

analysis was conducted at first for simplicity. The model equation in this study is [20] as follows:

$$\log(E(y_t)) = \beta_0 + \beta_1 \log(y_{t-1}) + \beta_2 \log(y_{t-2}) + s_1(x_{t,j}, l_j, \delta_1, \delta_2, \Phi_j) + s_2(t, \delta, \Psi) + \log(N_t) - \text{Equation 2}$$

y_t is the number of dengue cases at week t , while β_1 and β_2 are the coefficients of the autoregression terms — Two autocorrelation terms were introduced into models as the ARIMA model and residual analysis indicated that dengue cases from the past two weeks would be significantly correlated with current number of cases. $s_1(x_{t,j}, l_j, \delta_1, \delta_2, \Phi_j)$ is the cross basis of distributed lag non-linear terms with $x_{t,j}$ representing a single weather factor at week t and l_j representing the maximum lag number. A natural cubic spline (ns) smoothing method with δ_1, δ_2 degree of freedom (df) was used to describe the non-linear effect in both weather factor and lag time respectively, with Φ_j denoting corresponding coefficients. $s_2(t, \delta, \Psi)$ is another term processed with the ns function to describe the long-term trend of dengue cases, with δ, Ψ representing df of ns function and corresponding coefficients. Here, the df is assigned to be 1 per year, therefore the δ equals to duration of study period in years (approximately 8 years). $\log(N_t)$ is the offset term that considers the effect of differences in Singapore's mid-year population.

Quasi Akaike's Information Criterion (QAIC) was applied to judge the goodness of fit.

$$QAIC = -2\mathcal{L}(\hat{\theta}) + 2\hat{\phi}k - \text{Equation 3}$$

As shown in the equation above, $\mathcal{L}(\hat{\theta})$ is the log-likelihood of estimated parameters, $\hat{\phi}$ is the estimated over-dispersion parameter and k is the number of parameters. Instead of using the same degree of freedom for all weather factors, we applied grid search method to derive the best degree of freedom for each factor, which satisfied both parsimony and fit accuracy based on QAIC. Thereafter, values between 2-6 was selected for δ_1 term in equation 2, while values between 3-5 was selected for δ_2 . The selected values for maximum lag numbers l_j in equation 2 was 0-16 weeks (i.e. roughly four months).

Relative risk (RR) with 95% confidence interval (CI) was selected to be the measure of effect. The exposure-response relationship estimated by DLNM was visualised with graphical representations, including 3D graphs, contour graphs, sliced graphs and overall effect graphs [32]. 3D and contour graphs display the variation of RR along 2-dimensions – exposure and lag. Sliced graphs comprise an extracted slice from 3D graphs to emphasize relationship at one specific exposure value or lag. Overall effect graphs were used to measure the overall performance of association by summing up RR of each lag. The median of each climatic variables was used as the reference, in line with the aim of examining non-linear trends with possible threshold effects..

Multivariate Analysis

Preliminary multivariate analysis was carried out by including cross basis of each weather factor into DLNM. The procedure of variable selection was based on QAIC and forward selection method was applied.

Sensitivity Analysis

In addition, sensitivity analysis was performed by changing degree freedom of natural cubic spline terms to check robustness of model. The degree freedom of time () was changed by setting 3, 5 and 7 df per year to interpret potential seasonality pattern. Moreover, df of weather () would be adjusted to validate if there is any discrepancy against the previous conclusions. In addition, both equal knots and logarithm knots methods were tried on lag-dimension. The former means internal knots are uniformly distributed within range while the latter applies it on logarithm of lag number which provides more flexibility at small lags. The benchmark of judgement was based on overall effect graphs.

Prediction performance of the models

In order to measure the predictive ability of the model, the data was split into two parts: The data from year 2012 till end of 2018 data was used as the training set, and the data from year 2019 was isolated as the validation set. Models were applied on training set to estimate the coefficients and make the prediction on validation set. The prediction power was measured by Root Mean Square Error (RMSE) and Mean Absolute Error (MAE) – The smaller these values, the better the prediction is.

All statistical analyses were performed on R software (version 3.6.1), and included the use of package 'dlnm', version 2.3.9 [34].

3. Results

3.1 Epidemiological characteristics of epidemics between 2012 and 2019 in Singapore

Between January 2012 and August 2019, there were a total of five major dengue epidemics with incidence above 100 per 100,000 in Singapore [35]. The time series data shows the trend of dengue cases over the study period, with epidemics in 2013, 2014, 2015, 2016 and 2019 characterised by peaks (Figure 1). The average weekly number of dengue infections was 217.02. There were generally small variations in weekly temperature and wind speed. Weekly rainfall and PSI varies in a wider range (Table 1)

The 2013 epidemic holds the current national record for the highest number of dengue cases recorded in a year, where the dengue incidence was 22,170 cases (404.9 cases per 100,000 population annually) and dengue 1 serotype was the predominant strain (Table S1). Thereafter high incidence levels continued to be seen in the 2014 epidemic, which became Singapore's second-largest outbreak within a year– the dengue incidence was 18,326 cases (325.6 cases per 100,000 population annually), with dengue 1 serotype as the predominant strain. The 2015 epidemic was comparatively mild with dengue incidence at

11,294 cases (196.1 cases per 100,000 population annually) and was predominated by strain 2. Subsequently, the 2016 epidemic saw a dengue incidence of 13,085 cases (229.1 cases per 100,000 population annually) and was predominated by dengue 2 serotype. After low dengue activity levels for a couple of years, the 2019 epidemic became the third-biggest dengue outbreak recorded nationally with a dengue incidence of 16,100 cases (282.3 cases per 100,000 population annually) and dengue 2 and 3 serotypes taking over as the co-predominant strains [30, 36, 37]

3.2 Linear relationship with weather factors in Cross-correlation & ARIMA modelling

Pearson's cross-correlation coefficients for each climatic factor after pre-whitening are shown in Table 2. In general, pollutant standards index (PSI) and wind speed have an inverse linear relationship associated with dengue incidence while mean, maximum and minimum temperature have a direct linear association with dengue incidence. No significant correlation was observed between rainfall and dengue incidence in Singapore. The maximum lag effect observed across all climatic correlations did not exceed 15 weeks. Both mean and minimum temperature exhibited a lag effect of 1-2 weeks. Additionally, an 11-week lag time for both mean and maximum temperature showed significant correlation with number of dengue cases. Other significant cross-correlations with dengue incidence observed include 5 and 7 weeks lag for PSI, and 5 weeks for wind speed variable. (Table 2)

Moreover, a significant autocorrelation coefficient was found at lag time of 1 week as indicated by the autocorrelation graph (Figure S1). ARIMA (1, 1, 0) was selected as the best model to describe the trend and autoregressive parameters of the dengue time series. Residual diagnostics were conducted to assess model appropriateness, including the use of Ljung-Box tests, which accepted the null hypothesis given a p-value of 0.3686. (Figure S2).

Using univariate ARIMA models with variables derived from significant cross-correlations, the following factors were found to be significantly associated with dengue incidence: PSI with a 5-week and 7-week lag time, mean temperature at 1-week & 11-week lag time, maximum temperature at an 11-week lag time and wind speed at a 5-week lag time (Table 2).

3.3 Non-linear relationship with weather factors in Cross-correlation & DLNM

Using Spearman cross-correlation analysis to explore possible non-linear trends (Figure S3), a positive correlation was found between temperature and dengue cases while PSI and wind speed showed negative correlation. Like the linear cross-correlation analysis, there was no apparent association between rainfall and dengue cases.

For the quasi-Poisson with DLNM association, estimated parameters with optimal fitting performance (the smallest QAIC) were chosen. The choice of df, parameters and corresponding QAIC of each weather factor were shown in Table 3. The models in univariate analysis included the effect of PSI on dengue cases lagged by a maximum of 16 weeks (lag 0-16), total rainfall (lag 0-15), mean temperature (lag 0-16), maximum temperature (lag 0-16) and wind speed (lag 0-5). The best-performing model was that of wind

speed with the lowest QAIC of 4842.808, suggesting that wind speed explained dengue incidence the best amongst all climatic factors. Autocorrelation of residuals was tested to ensure absence of autocorrelation and assumption of overdispersion was checked (Figure S4), justifying the use of a Quasi-Poisson regression. The DLNM model output had a fitted number of dengue cases that mirrored the observed trend of dengue cases closely as seen in Figure S5. The graphical output of dengue DLNM modelling for each climatic variable is described in the following subsections.

3.3.1 Effect of PSI

With a median of 48.22 PSI defined as reference, visualisation of DLNM model output with the 3D graph and contour graph (Figure 2(a)(b)) showed that the RR of dengue generally increased up to a PSI level of 100 approximately along with all lags, beyond which the RR falls sharply.

The sliced graph for PSI at lag 7 (Figure 2(c)) indicated that PSI between 15 and 107 increased the RR of dengue, and levels beyond around 107 reduced the RR of dengue. Taking median of PSI 48.22 as reference, the RR of dengue increased 6% (RR: 1.06, 95% CI: 1.03, 1.09) when PSI level is 107 and decreased 25% (RR: 0.75, 95% CI: 0.67, 0.85) when PSI level is 160. From fig. 2(d) different performances of lag-response association at different PSI level were observed. An immediate and inhibiting effect of high level PSI could be easily found.

A similar trend was observed in the overall effects graph (Figure 2(e)). The overall effect of PSI on RR of dengue increased around 63% (RR: 1.63, 95% CI: 1.20, 2.20) when PSI level was 100, and reduced by around 84% (RR: 0.16, 95% CI: 0.06, 0.41) when PSI level was 150. This further illustrates that moderate escalation of PSI would increase risk of dengue while extremely high PSI level would inhibit dengue. However, in the sensitivity analysis, CI around 100 expanded dramatically, corresponding to reduced statistical significance.

3.3.2 Effect of rainfall

Reference of rainfall level was 5.54 mm. In the 3D graph and Contour graph (Figure 3(a)(b)), it can be observed that associations between exposure and response across all the lags was identical – positive and negative effect appeared alternately along with lags. From sliced graph at lag 4 and lag 11, we can observe similar curve but slightly different confidence interval, which may indicate that rainfall at lag 11 had more significant effect on dengue infections (Figure 3(c)). A similar trend was observed in the overall effect graph (Figure 3(d)). The interval of rainfall between 0 and 7 (mm) promoted the dengue infections (Rainfall: 7 (mm), RR: 1.16, 95%: 1.01, 1.34). On the contrary, heavy rainfall had a 'protective' effect on dengue, with RR: 0.44 (0.28-0.70) at rainfall level 12 (mm) and RR: 0.19 (0.06, 0.58) at rainfall level 21(mm). The positive effect on RR observed between rainfall levels of 13-17 mm and 24-25 mm were, however, insignificant.

3.3.3 Effect of temperature

Median of mean, maximum and minimum temperature were 28.01 °C, 31.84 °C and 25.14 °C respectively. From the 3D and contour graphs of each temperature (Figure 4(a)(b)) three types of temperature showcased similar behaviour in exposure-lag-response relationship – each presented a different temperature-dengue correlation at each lag. Specific to one certain lag, lag 1 and lag 5 were selected as the benchmark to illustrate the variation of association at different lags. RR increased once the mean, maximum and minimum temperature escalated at lag 1 while RR decreased when temperature reached up to a high level at lag 5 (Figure 4(c)(d)(e)). On the other hand, lag-response association, holding the temperature constant, behaved similarly in 3 types of temperature (Figure 4(c)(d)(e)). A relatively cold temperature showed an inhibitive effect at lag 0 whereas a relatively hot temperature showed an inhibitive effect at lag 4 and a positive effect at lag 1. In terms of overall effect (Figure 4(f)), mean temperature was observed to have no significant association with the relative risk of dengue. Maximum and minimum temperature were found to have positive association within the relatively cold temperature interval (27-32 °C and 23-25 °C). The RR of maximum temperature model at 28 °C was 0.46 (Ref. 31.84 °C), with 95% CI (0.22, 0.94). while the RR of minimum temperature model at 24 °C was 0.76 (Ref. 25.14 °C), with 95% CI (0.65, 0.88). Moreover, a relatively hot temperature was always found to exert a negative influence on dengue infections, especially significant in minimum temperature situation (27°C, Ref. 25.14 °C; RR: 0.74, 95% CI: 0.58, 0.93).

3.3.4 Effect of wind speed

In terms of wind speed at a reference value of 7.52km/h, the 3D and contour graph showed different curves at marginal lags and middle lags (Figure 5(a)(b)). At lag 2 and lag 5 (Figure 5(c)), RR at lag 2 was consistently stagnant as wind speed increased.. However, wind speed-dengue association graph at lag 5 clearly illustrated a reduction in RR of dengue as wind speed increased.. Meanwhile, wind speed at 10 km/h, compared with 6 km/h, suggested stronger negative effect along the lags. From figure 5(d), an evident downward trend of RR related to overall effect along with wind speed was observed. Wind speed at 12 km/h was associated with a 38% (RR: 0.62, 95% CI: 0.50, 0.76, Ref : 7.52km/h) overall reduction in risk of dengue.

3.3.5 Multivariate analysis

Utilising the forward selection methodology, wind speed was first selected for the model based on its smallest QAIC of 4842.808. The model was introduced with a second variable PSI, which had a QAIC of 4523.012, as wind speed was kept constant. Subsequent selection of remaining variables failed to reduce QAIC further, which implied that only cross basis of wind speed and PSI would be considered for the final model. To check the robustness of our model, overall effect graphs of both of PSI and wind speed were redrawn and similar performances in univariate model were found (Figure S6).

3.3.6 Sensitivity analysis

In general, varying the df of time trend and seasonality did not change the direction of effect to a large degree (Figure S7). However, some statistical significance was lost when df per year increased, such as

PSI around 100, rainfall around 20 mm, minimum temperature under median value, wind speed beyond median value. This reduction in significance was likely due to the far fewer counts at these levels or collinearity introduced by more df of time trend and seasonality. Figure S8 displayed overall effect of weather factors when df of exposure ranging from 2-6 (Exclude the number used in previous sections). The general features of overall effect remain the same despite occurrence of some wider CI intervals. Figure S9 also illustrated the robustness while knots placement varied. Among all of above sensitivity analysis, an alert was proposed that at the marginal level of weather or interval where the level of weather rarely reached, the statistical significance of RR would expand dramatically when model parameters varied.

3.4 Evaluation of Model Prediction Performance

To exploit the predictive power of this model, data from 2012-2018 was used as the training set while data from 2019 was used for testing purposes. Among all models, mean temperature was the best variable to forecast the future number of dengue cases, with a mean absolute error 43.15 and root mean square error 51.39 (Table S2).

4. Discussion

This study explored the association between dengue incidence and several weather factors in Singapore between 2012 and 2019, furthering the analysis by Xu and co-authors, who explored weather factors' impact on dengue in Singapore between 2001 and 2009 [20]. Relationship between weather factors and dengue cases may vary across different periods, especially with increasing global warming and urbanisation. Therefore, an independent research on these relationships is critical to guide environmental-related policy. Apart from weather variables included in Xu et al., this study considered PSI as a new indicator that could influence dengue trend. During the process of model fitting, degree of freedom parameters and the largest number of weeks were estimated independently in each weather-related model instead of using the same setting of parameters in all models.

In this study, 3 types of temperature were found to decrease the risk of dengue transmission when they are extremely high. The reference (median) is reflective of the relatively uniform temperatures that Singapore experiences year-round, and suggests that any perturbation reduces dengue incidence - increasing temperatures in the future will hinder transmission. On the other hand, a systematic review of temperature's effect on dengue risk found that higher mean, maximum and minimum temperature were individually associated with increased dengue transmission[38], which is corresponding with our findings within relatively cold temperature interval, especially for maximum and minimum temperature. However, the same review also concluded that the odds of dengue increases steeply up to 29 °C, and that dengue risk begins to decrease if temperatures are higher than 29 °C. Hence, our study's results seem to support the idea of an optimum temperature range that promotes dengue transmission, rather than a general increase in dengue incidence accompanying increasing temperatures.

Another study looking at dengue patterns in Singapore from 1974 until 2011 found that higher minimum and mean temperature were related to higher dengue transmission, while maximum temperature was not statistically significant. [39] On the other hand, Xu et al. reported that dengue incidence in Singapore was amplified by mean temperatures above 27.8°C (reference value) in 2001-2009, while mean temperatures deviating from 27.8°C in 2004-2006 and 2007-2009 were associated with reduced dengue transmission [20]. Concurrently, molecular studies show that *Aedes Aegypti* survival and development thrives beyond the 30°C range [40, 41]. Others concluded that the ideal range of survival (88-93%) through all phases of development occurs between 20-30 °C [40], including Yang, et al. (2009) who reported 29.2 °C as the best temperature to produce the most offspring [24]. One possible explanation for these discrepancies could be the differing effects of temperature on various development stages of mosquitos and the dengue virus, accompanied by the dominant strategy of vector control employed at any specific period. The National Environment Agency in Singapore provides guidance to pest control operators on ideal times for outdoor fogging to kill adult mosquitos, while recognising that citizen efforts with indoor insecticides and elimination of stagnant water habitats (for mosquito larva) are more effective in non-cluster areas within Singapore. [42] Hence, it is important to note the context in which the role of temperature in dengue transmission is being investigated – this is because the predominance of indoor or outdoor breeding, fogging or source control methods employed in specific geographies and periods may differ.

When considering the exposure-response association at a specific lag this study found that 3 kinds of temperature showcased different patterns at lag 1 and lag 5. The overall increased effect on dengue was captured at lag 1 while high temperature restrain dengue cases at lag 5. The 5- week lag effect of temperature could be induced by ecological factors pertaining to the *Aedes* vector such as the length of gonotrophic cycle, larval development and growth rate of *Aedes* mosquitoes. On the other hand, the 1- week lag effect of temperature may be a result of behavioral tendencies of *Aedes* mosquitoes and human that have repercussion in the shorter term such as time to blood-feeding or health-seeking behavior after presentation of symptoms. These associations at specific lag should be emphasized to facilitate warning measures.

The decreased risk of dengue transmission with high wind speeds found in this study was consistent with the results of another study in subtropical city in Guangzhou, China, which reported that wind velocity was inversely associated with dengue incidence in the same month [43]. One potential mechanism that could account for the influence of wind speed is the suppression of mosquitoes' host-seeking flight activity [44], which translates to reduced oviposition and contact with hosts. As suggested by Hoffman et al. (2002), wind may deter plume following in mosquitoes due to their inability to progress upwind or dilute chemical attractants emitted by the host [45]. Alternatively, wind also directly affects the evaporation rate of both outdoor and indoor vector breeding sites [46], reducing availability of breeding sites and larval productivity.

From this analysis, we concluded that extremely high PSI values (>150) reduced the number dengue cases. This is supported by a study from Malaysia, wherein a moderate negative correlation was detected

between trapped larvae counts and Air Pollution Index (API) with a one-week lag [47]. Another found particulate matter 10 microns or less (PM10) to have a statistically significant negative correlation with dengue cases [48]. On the other hand, a lack of association between dengue activity and haze was concluded by another study from Singapore, investigating dengue activity between 2001-2008 [49]. It should be noted that the study only utilized the ARIMA model, which explored linear association, whereas this analysis was supplemented with the use of a non-linear quasi-poisson model. Smoke, a component of haze, is anecdotally claimed to repel insects from biting [50, 51]. The toxicity of haze was believed to reduce mosquito density, as deleterious effect from direct and indirect exposure to haze was found on the development and survival of butterflies [52]. Nonetheless, research pertaining to haze remains sparse. More evidence is required on the mechanisms by which air quality may affect mosquito development or biting habits.

The volume of rainfall has long been viewed as a plausible factor affecting dengue in domain of public health. Although we observed some significant intervals showing positive and negative effect alternately across the lags, the conclusion was challenged by variation of CI in sensitivity analysis -there have been conflicting evidence –another previous study looking at dengue incidence in Singapore from 2000 to 2007 [53] – demonstrating an absence of relationship between rainfall and dengue incidence [28, 29]. One possible explanation could be the role of indoor breeding in urban settings, which is sheltered from outdoor elements. The importance of stagnant water as breeding sites is emphasized by anti-dengue campaigns in Singapore compelling citizens to routinely empty water from flowerpots/trays, containers and closed perimeter drains. According to MOH's report on vector surveillance in 2018 [35], the top breeding habitats for *Aedes Aegypti* included domestic containers (32%), flowerpots/trays (11.1%), ornamental containers (9.3%) and closed perimeter drains (3.7%). On the other hand, a study looking at dengue incidence in Malaysia from 2008-2010 showed that increased bi-weekly accumulated rainfall had a positively strong effect on dengue cases [44]. Yet, experimental and observational studies have shown that excessive rainfall can 'flush out' breeding sites and destroy developing larvae, consistent with our conclusion in main analysis. At least two studies in Singapore have demonstrated that dengue incidence between 2000 & 2016 was significantly reduced following months where flushing events from wet weather were most frequent [54, 55]. These collectively indicate that more detailed analysis, including the use of spatial data to clarify areas prone to flooding and contribution of indoor breeding on mosquito breeding, may be required to understand the complex role of rainfall patterns on dengue transmission.

Limitations

Although some long-term significant lags indicated a weak seasonal pattern, the seasonal period is not exactly 52 weeks (one year) due to various situations every year. Thus for this weekly data, seasonal pattern remains to be studied further.

The generalisability of the predictive value may not be guaranteed since the model included autoregression parts as covariates. Only short-term predictions can be performed with these results, since long-term prediction would cause larger prediction errors and be inaccurate. With climatic variables

derived from our quasi-Poisson model, dengue predictions made a week in advance would have moderate performance, as assessed by split-sample model validation.

Additionally, this analysis did not include relative humidity and absolute humidity due to the absence of government API data before 2016, though they have proved to be crucial meteorological factors influencing dengue incidence in previous studies. In particular, Xu et al. (2014)'s Singapore study concluded that absolute humidity was the most useful weather factor in dengue forecasting.

Moreover, our model did not consider other major factors including circulating dengue serotypes and geospatial differences. In Singapore, the variations of urban housing across its geography, from landed estates to high-rise buildings have been found to influence differences in dengue distribution [14]. Additionally, weekly meteorological indicators in this analysis were calculated by averaging data across all 63 stations nationwide, and ignores potential geographical differences in weather (though this is minimised given the small size of Singapore). Nevertheless, the occurrence of dengue clusters is recognised as another important reason to adopt a geospatial perspective in dengue predictive modelling. Further studies should obtain these data with greater granularity, to describe patterns of dengue incidence more precisely. Lastly, the study assumes the effectiveness of vector control is only up to a constant limit, regardless of its intensity level, across this period.

Since the National Environmental Agency of Singapore has always responded rapidly to dengue outbreaks, strong interventions would undoubtedly suppress dengue epidemics in the short term. As such, intervention from government might be a major driver of the decline of dengue. Aggressive vector control prompted by the Zika outbreak in 2016, likely led to a drastic fall in dengue cases then[56]. Thus, this potential confounder should be further investigated in subsequent studies.

5. Conclusion

Only a limited temperature range promotes dengue transmission and extreme heat was associated with reduced dengue transmission in an urbanised tropical city. On the other hand, poor air quality and high wind speeds were associated with lower dengue transmission levels. Rainfall had positive and negative influence alternately on weekly dengue cases across all lags though sensitivity analysis suggested that this influence was not statistically significant. , Future studies incorporating these information along with geospatial data would allow further assessment of the relationships between these weather factors and dengue risk. This may guide public health and environmental policy in similar tropical urban environments for dengue control.

Declarations

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Author Contributions

GH, KJY and NL carried out the extraction of data. GH analysed the data and wrote the first manuscript draft. GH, GSXW and KJY edited subsequent versions of the draft. PJ conceived of the study.

Additional Information

Competing Interests

The authors declare no competing interests.

Data Availability

All data generated or analysed during this study are included in this published article (and its Supplementary Information files).

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Tables

Table 1. Descriptive summary of weekly dengue cases and weather conditions in Singapore during 2012-2019.

Variable	Mean	Std	Min	P25	Median	P75	Max	Hist
DengueFeverWeekly	217.02	179.72	24.00	73.75	170.50	303.75	891.00	▯▯▯▯▯
Rainfalltotal	6.37	4.67	0.00	2.72	5.54	8.93	25.36	▯▯▯▯▯
Meantemperature	27.97	0.86	25.04	27.38	28.01	28.51	30.02	▯▯▯▯▯
Maxtemperature	31.79	0.97	27.89	31.25	31.84	32.42	34.19	▯▯▯▯▯
Mintemperature	25.25	0.82	23.17	24.63	25.14	25.79	27.70	▯▯▯▯▯
PSI	46.78	17.15	16.45	35.29	48.22	54.74	165.85	▯▯▯▯▯
Windspeed	7.88	1.74	4.99	6.61	7.52	8.75	14.89	▯▯▯▯▯

Note: P25 and P75 refer to first and third quartile. Hist is the distribution of the variable representing by histogram

Table 2: Cross-correlation analysis and ARIMA modelling of meteorological factors to dengue incidence

Meteorological factor	Lag of week	Cross correlation coefficient	Autoregressive coefficient	(p-value)
PSI	5	-0.113	-0.2132	-0.002 (0.0373)*
	7	-0.115	-0.2047	-0.002 (0.0378)*
Mean temperature (°C)	1	0.116	-0.2123	0.0302 (0.0404)*
	2	0.101	-0.2171	0.0258 (0.0833)
	11	0.118	-0.1961	0.0318 (0.0295)*
Maximum temperature (°C)	11	0.155	-0.1983	0.0362 (0.0011)*
	13	0.110	-0.2043	0.0032 (0.7752)
	14	0.122	-0.2109	0.0157 (0.1572)
Minimum temperature (°C)	1	0.126	-0.2024	0.0196 (0.1717)
	2	0.113	-0.2061	0.0166 (0.2518)
	3	0.101	-0.2078	0.0201 (0.1644)
Wind speed (km/h)	5	-0.123	-0.2116	-0.0326 (0)***
Total rainfall (mm)	NS	NS	-	-

Note: α_1 is the coefficient of autoregressive term and α_2 is the coefficient of exogenous weather variables; Abbreviations: NS - Not significant

Table 3: Estimated parameters of distributed lag non-linear model

Meteorological Factor	QAIC	Maximum Lagged Number of Weeks		
PSI	4870.686	16	4	4
Total Rainfall	4969.801	15	6	3
Mean Temperature	5073.575	16	3	5
Max Temperature	5049.898	16	2	5
Min Temperature	5128.374	16	2	5
Wind Speed	4842.808	5	4	5

Figures

Figure 1. Weekly number of dengue fever cases with smoothed line

Figure 1

Weekly number of dengue fever cases with smoothed line

Figure 2(a). 3D graph of PSI-lag-dengue association

Figure 2(b). Contour graph of PSI-lag-dengue association

Figure 2(c). Sliced graph of PSI-dengue association at lag 7

Figure 2(d). Sliced graph of Lag-response association at PSI level of 20, 100, 150

Figure 2(e). Overall effect graph of PSI-dengue association

Figure 2

(a) 3D graph of PSI-lag-dengue association (b) Contour graph of PSI-lag-dengue association (c) Sliced graph of PSI-dengue association at lag 7 (d) Sliced graph of Lag-response association at PSI level of 20, 100, 150 (e) Overall effect graph of PSI-dengue association

Figure 3(a). 3D graph of rainfall-lag-dengue association

Figure 3(b). Contour graph of rainfall-lag-dengue association

Figure 3(c). Sliced graph of rainfall-dengue association at lag 4 & 11

Figure 3(d). Overall effect graph of rainfall-dengue association

Figure 3

(a) 3D graph of rainfall-lag-dengue association (b) Contour graph of rainfall-lag-dengue association (c) Sliced graph of rainfall-dengue association at lag 4 & 11(d) Overall effect graph of rainfall-dengue association

Figure 4(a). 3D graph of temperature-lag-dengue association

Figure 4(b). Contour graph of temperature-lag-dengue association

Figure 4(c). Sliced graph of mean temperature-lag-dengue association

Notes: Left top panel shows temperature-dengue association at lag 1 while left bottom one at lag 5; Right top panel shows lag-dengue association at mean temperature 26°C while right bottom one at mean temperature 29°C

Figure 4(d). Sliced graph of max temperature-lag-dengue association

Notes: Left top panel shows max temperature-dengue association at lag 1 while left bottom one at lag 5; Right top panel shows lag-dengue association at max temperature 29°C while right bottom one at max temperature 33°C

Figure 4(e). Sliced graph of min temperature-lag-dengue association

Notes: Left top panel shows min temperature-dengue association at lag 1 while left bottom one at lag 5; Right top panel shows lag-dengue association at min temperature 23°C while right bottom one at min temperature 27°C

Figure 4(f). Overall effect graph of mean temperature-dengue association

Figure 4

(a) 3D graph of temperature-lag-dengue association (b) Contour graph of temperature-lag-dengue association (c) Sliced graph of mean temperature/lag-dengue association (d) Sliced graph of max temperature/lag-dengue association (e) Sliced graph of min temperature/lag-dengue association (f) Overall effect graph of mean temperature-dengue association

Figure 5(a). 3D graph of wind speed-lag-dengue association

Figure 5(b). Contour graph of wind speed-lag-dengue association

Figure 5(c). Sliced graph of wind speed/lag-dengue association

Notes: Left top panel shows wind speed-dengue association at lag 2 while left bottom one at lag 5; Right top panel shows lag-dengue association at wind speed 6 km/h while right bottom one at wind speed 10 km/h

Figure 5(d). Overall effect graph of wind speed-dengue association

Figure 5

(a) 3D graph of wind speed-lag-dengue association (b) Contour graph of wind speed-lag-dengue association (c) Sliced graph of wind speed/lag-dengue association (d) Overall effect graph of wind speed-dengue association

Supplementary Files

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