

# Dengue in Bangladesh: assessment of the influence of climate and under-reporting in national incidence

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A thesis submitted for the degree of Doctor of Philosophy  
of The Australian National University

10 May 2017

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## **Declaration**

I declare that the work presented in this thesis is an accurate account of research performed during the academic program towards the degree of Doctor of Philosophy of the Australian National University. This is a thesis by compilation and all the papers (three published and one ready to submit) included have been approved by the co-authors. Materials included in this thesis which are not my own work have been specifically indicated.

I certify that the work included in this thesis has not previously been submitted and accepted for any other degree.



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10 May 2017

## Acknowledgements

My immense gratitude goes to my supervisors-David Harley, Kathryn Glass, and Elvina Viennet for their patience, guidance, and encouragement. Each of them contributed to my understanding of the topic in diverse and incredibly significant ways. Their support has been invaluable on both academic and personal levels. My earnest thankfulness to all of them for always making available their support. The decision of doing thesis by compilation made the Ph.D. a very difficult task that would not be possible without all of their hard work. I am truly blessed to have them as my supervisors.

I thank Dr Ayesha Akhter from National Health Crisis Management Centre and Control room, Directorate General of Health Services, Dhaka for kindly providing dengue surveillance data. I am also thankful to my uncle Mosherraf Hossain who helped to source the data. A special thanks to Rehab Ahmad for his kind help on GIS. Besides, I would like to thank my fellow postgraduate students; Shehrin Shaila Mahmood, Erlidia Clark, Sarunya Sujaritpong, Savitri Gurung, Wimalin Rimpeekool, Wakako Takeda, Syarifah Liza Munira, Mafruha Alam, and Tam Tran for giving me the warmth of family and making my life abroad full of fun and colour.

In undertaking this research, I was supported financially by the Australian National University Research Scholarship (International). National Centre for Epidemiology and Population Health provided financial support to publish one of the papers as an open access article and to attend the International Congress for Tropical Medicine and Malaria 2016 in Brisbane, Australia.

I am eternally grateful to my parents and only sister for their infinite support, and for always encouraging me to follow my dreams, no matter how far they take me. My gratitude goes out to my husband, Muntasir, for his loving support and endless encouragement that kept me alive on the rocky road of the Ph.D. journey.

Last, but not least, I am sincerely grateful to my M.S. thesis supervisor Md Israt Rayhan who made me realise my capability of becoming a researcher.

## Abstract

Dengue occurs in many tropical countries, despite substantial effort to control the *Aedes* mosquitoes that transmit the virus. The majority of the burden occurs in the South-East Asian Region of the World Health Organization. Bangladesh is a lower-middle income country located in South Asia, with strong seasonal weather variation, heavy monsoon rainfall, and high population density. Dengue has been endemic in Bangladesh since an epidemic in 2000. The aim of my research was to investigate the influence of climate on dengue transmission in Bangladesh over the period January, 2000 - December, 2009. To achieve this aim, I conducted a series of studies integrating epidemiological and socio-environmental factors into a unified statistical modelling framework to better understand transmission dynamics.

In a narrative review (Chapter 3), I discuss the emergence and establishment of dengue along with the possibility of future epidemics of severe dengue. Introduction of a dengue virus strain from neighbouring Thailand likely caused the first epidemic in 2000. Cessation of dichlorodiphenyltrichloroethane (DDT) spraying, climatic, socio-demographic, and lifestyle factors also contributed to epidemic transmission and endemic establishment of the virus. However, there has been a decline in reported case numbers following the largest epidemic in 2002, albeit with relatively greater case numbers in alternate years. This occurred despite the absence of significant additional control measures and no changes in the surveillance system having been introduced during the study period. The observed decline from 2002 may be an artefact of the national hospital-based passive surveillance system even though a real decline in incidence could plausibly have occurred due to increased prevalence of immunity, greater public awareness, and reduced mosquito breeding sites.

From a temporal negative binomial generalised linear model (Chapter 4), developed using monthly dengue cases in Dhaka from January, 2000 - December, 2009, I identify that mean monthly temperature (coefficient estimate: 6.07; 95% confidence interval: 3.38, 8.67) and diurnal temperature range (coefficient estimate: 15.57; 95% confidence interval: 8.03, 22.85) influence dengue transmission, with significant interaction between the two (coefficient estimate: -0.56; 95% confidence interval: -0.81, -0.29), at a lag of one month in Dhaka, the capital city of Bangladesh where the highest number of cases were reported during the study period. In addition to mean monthly rainfall in the previous two months, dengue incidence is

associated with sea surface temperature anomalies in the current and previous months through concomitant anomalies in the annual rainfall cycle. Population density is also significantly associated with increased dengue incidence in Dhaka.

Chapter 5 reports an investigation into non-linear dengue–climate associations using the same dataset as used for the previous model in Chapter 4. A Bayesian semi-parametric thin-plate spline approach estimates that the optimal mean monthly temperature for dengue transmission in Dhaka is 29°C and that average monthly rainfall above 15mm decreases transmission. This study also reveals that between 2000 and 2009 only 2.8% (95% Bayesian credible interval 2.7-2.8) of cases estimated to have occurred in Dhaka were reported through passive case detection.

A Bayesian spatio-temporal model (Chapter 6), formulated using monthly dengue cases reported across the country from January, 2000 - December, 2009, identifies that the majority of dengue cases occur in southern Bangladesh with the highest in Dhaka (located almost in the middle of the country), accounting for 93.0% of estimated total cases across the country from 2000-2009. Around 61.0% of Bangladeshi districts are identified as affected with dengue virus during the high transmission season of August and September, contrasting with national surveillance data suggesting that only 42.0% of districts are affected.

My thesis provides a better understanding of the dengue-climate relationships that will enable more accurate predictions of the likely impacts of changing climate on dengue risk. Knowledge about the extent of under-reporting will facilitate precise estimation of dengue burden which is vital to assess the risk of severe epidemics. These will help public health professionals to design interventions to strengthen the country's capacity for prevention of severe dengue epidemics.

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# Chapter 1

## Introduction

## **1.1 Emergence of a national problem**

In 2000, Bangladesh experienced its first epidemic of dengue after more than three decades of sporadic transmission.<sup>1-6</sup> More than 5,000 cases were reported to the Directorate General of Health Services and 1.7% died due to severe dengue (comprising dengue haemorrhagic fever and dengue shock syndrome).<sup>1</sup> All four serotypes of the dengue virus (DENV) co-circulated during the epidemic. Three major cities and 17 towns reported dengue cases.<sup>6</sup> In 2002, following a smaller outbreak in 2001, the largest epidemic occurred with 6,132 cases and case fatality of 1.0%.<sup>1</sup> Cases continued annually with relatively higher numbers in alternate years.

More than 28,000 cases with hundreds of deaths have been reported over the period January, 2000 - December, 2014.<sup>1</sup> Since 2002, there has been a decline in reported case numbers. However, a global dengue burden study estimated more than 16 million dengue infections including four million symptomatic in Bangladesh in 2010.<sup>7</sup>

From 2000 to 2009, 29 of 64 Bangladeshi districts (the second largest administrative unit) reported dengue and the capital Dhaka consistently reported the largest number of cases.<sup>1</sup> Following mandating of serological confirmation for case reporting in 2010, very few cases have been reported outside Dhaka.<sup>1</sup> Whether variation across the country was due to variation in environmental risk determinants or lack of reporting has not been investigated.

## **1.2 Aim of this thesis**

The aim of this thesis was to investigate how climate influenced the transmission of dengue in Bangladesh over the period January, 2000 - December, 2009. I present statistical modelling using datasets including dengue surveillance data aggregated at the district level, meteorological data recorded from 32 monitoring stations across the country, and demographic data from population census reports to analyse the relationships between these factors. I performed sequential studies to address the research questions below.

### 1.3 Research questions

The following research questions motivated my thesis:

1. What are the factors that significantly influence dengue incidence in Bangladesh?
2. Can we develop a statistical model to estimate dengue-climate relationships in the presence of under-reporting and non-linear relationships between dengue and climate?
3. How much of the spatial variation in monthly dengue incidence can be explained by climatic and non-climatic factors?

I address each of these research questions through published studies included as thesis chapters, as outlined below.

***Research question 1: What are the factors that significantly influence dengue incidence in Bangladesh?***

I analyse dengue notification data from January, 2000 - December, 2009 sourced from the Directorate General of Health Services, Government of the People's Republic of Bangladesh. Dhaka district, the source of 91.0% of cases reported over 2000-2009, is the study area. Monthly population density during the study period is calculated from the 1991, 2001, and 2011 population census data of the Bangladesh Bureau of Statistics. Meteorological data including maximum and minimum temperature, daily fluctuation in temperature, rainfall, and relative humidity are obtained from the Bangladesh Meteorological Department, while data on large scale climatic events is sourced from United States National Oceanic and Atmospheric Administration Climate Prediction Center. This study provides an understanding of dengue epidemiology in Dhaka, involving both local and global climatic and demographic factors (Chapter 4).

***Research question 2: Can we develop a statistical model to estimate dengue-climate relationships in the presence of under-reporting and non-linear relationships between dengue and climate?***

Using a Bayesian method, I calculate model estimates for the percentage of dengue cases reported to the national surveillance system. I combine empirical data on dengue notifications with prior estimates of under-reporting of dengue incidence from neighbouring dengue endemic countries to calculate the percentage of estimated dengue cases reported between 2000 and 2009 in Dhaka. I then add semi-parametric thin-plate splines to the model to assess the non-linear relationships between dengue incidence and climate. This study will aid in understanding the effects of future changes in climate on dengue transmission (Chapter 5).

***Research question 3: How much of the spatial variation in monthly dengue incidence can be explained by climatic and non-climatic factors?***

I develop a spatio-temporal model to identify monthly changes in dengue incidence at the district level by taking into account the non-uniform effects of climatic and demographic factors by space and time (Chapter 6). In addition to modelling spatio-temporal dependence in dengue incidence, I also model under-reporting using climatic suitability for DENV transmission and prior information on the reporting percentage estimated in Chapter 5. The resulting maps show monthly variation in incidence and identify affected areas not reported to the surveillance system. These can guide intervention strategies to facilitate effective and timely allocation of limited resources.

## **1.4 Thesis structure**

This thesis is based on three published papers and one manuscript (to be submitted) addressing research questions concerning the epidemiology of dengue in Bangladesh, along with background, discussion, and conclusions chapters. All papers were prepared during my doctoral candidature and reproduced with the permission of the publishing company and co-authors. Authors' contributions are detailed in the Appendix.

**Chapter 2** provides a summary of the epidemiology of dengue globally and in Bangladesh and also provides background information on previous studies of dengue and climate.

In **Chapter 3**, I present a narrative review of the history of dengue in Bangladesh. I summarise dengue transmission considering virology, epidemiology, and clinical features from published literature from 1964 to 2015. The epidemic in 2000 after the first identification of dengue cases in 1964 and establishment of endemic dengue thereafter are described. Possibilities for future epidemics of severe dengue are considered.

**Chapter 4 and 5** present two papers describing the development of two temporal models for Dhaka using data from January, 2000 - December, 2009 to address the first two research questions. Counts of dengue cases are modelled with climatic and demographic variables using a negative binomial distribution within a generalised linear model framework.<sup>8</sup> This is appropriate because the dengue data set is over-dispersed (variance exceeds the mean). Based on exploratory analysis and existing literature, I consider climatic variables with and without interaction terms, and with lags of months for the delay in the effect of weather on dengue incidence.

The first model (**Chapter 4**) that elucidates factors determining dengue incidence in Dhaka is based on the traditional frequentist approach which assumes that the empirical data are a randomly generated subset from a larger population. Estimates of population parameters (e.g., mean and variance) that are assumed to be fixed and unknown are estimated using the maximum likelihood approach.

In the paper presented in **Chapter 5**, I estimate the percentage of dengue cases reported to the national surveillance system and investigate the relationships between dengue incidence and climate within a Bayesian modelling framework. The Bayesian approach is the standard method for incorporating prior (existing) information into statistical models to strengthen inference. Prior information is quantified in terms of probability distributions called the “prior distribution”. Following Bayes’ theorem, this distribution is then combined with the empirical data in a model framework to obtain the “posterior distribution” allowing inference about model parameters. In contrast to the frequentist approach, empirical data and model parameters are considered as random variables. In Chapter 5, I develop a Bayesian model that is built in stages to incorporate existing information about under-reporting in dengue surveillance data available from the neighbouring dengue endemic countries of Bangladesh. The Bayesian approach, however, is sensitive to the choice of prior distribution. I assume non-informative priors for parameters without any prior information. The model is fitted using Markov Chain

Monte Carlo (MCMC) sampling that allows simulation of draws from the posterior distribution, without having to calculate the posterior distribution. Using the Bayesian approach, uncertainties in model parameters are considered leading to precise estimates.

In **Chapter 6**, I present a paper regarding the spatio-temporal distribution of dengue in Bangladesh. Spatio-temporal modelling is a powerful tool for mapping disease incidence and investigating spatial heterogeneity over time. In the paper presented in Chapter 6, I develop a modelling framework for mapping monthly dengue incidence using a Bayesian generalised linear spatio-temporal model. The model is fitted to district-level dengue count data and spatio-temporally varying climatic and demographic variables expected to influence the transmission of dengue in Bangladesh from 2000-2009. Under-reporting is considered in two ways: (1) using climatic thresholds favourable for dengue transmission in Bangladesh; and (2) incorporating existing information about the reporting percentage of estimated dengue cases calculated in the model presented in Chapter 5. The model is estimated using MCMC simulation and attention is given to prior sensitivity.

A discussion and conclusions are presented in **Chapter 7**.

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# Chapter 2

## Background

## 2.1 Global dengue burden

Dengue, a mosquito-borne viral illness, is an important cause of morbidity and some mortality in many countries, mostly in Asia and Latin America, and is continuing to expand globally. From only nine countries before 1970 the disease is now endemic in over 100 countries.<sup>1</sup> Around 390 million infections (95% credible interval 284-528 million) occur each year with approximately 500,000 hospital admissions with potentially life-threatening forms of the disease, dengue haemorrhagic fever (DHF) and dengue shock syndrome.<sup>1</sup> Approximately 12,000 deaths, mostly among children, occur worldwide every year.<sup>1</sup> An estimated 50.0% of the global population are at risk of acquiring dengue<sup>1</sup> and over half reside in the World Health Organization's South-East Asia Region (SEAR)<sup>2</sup>.

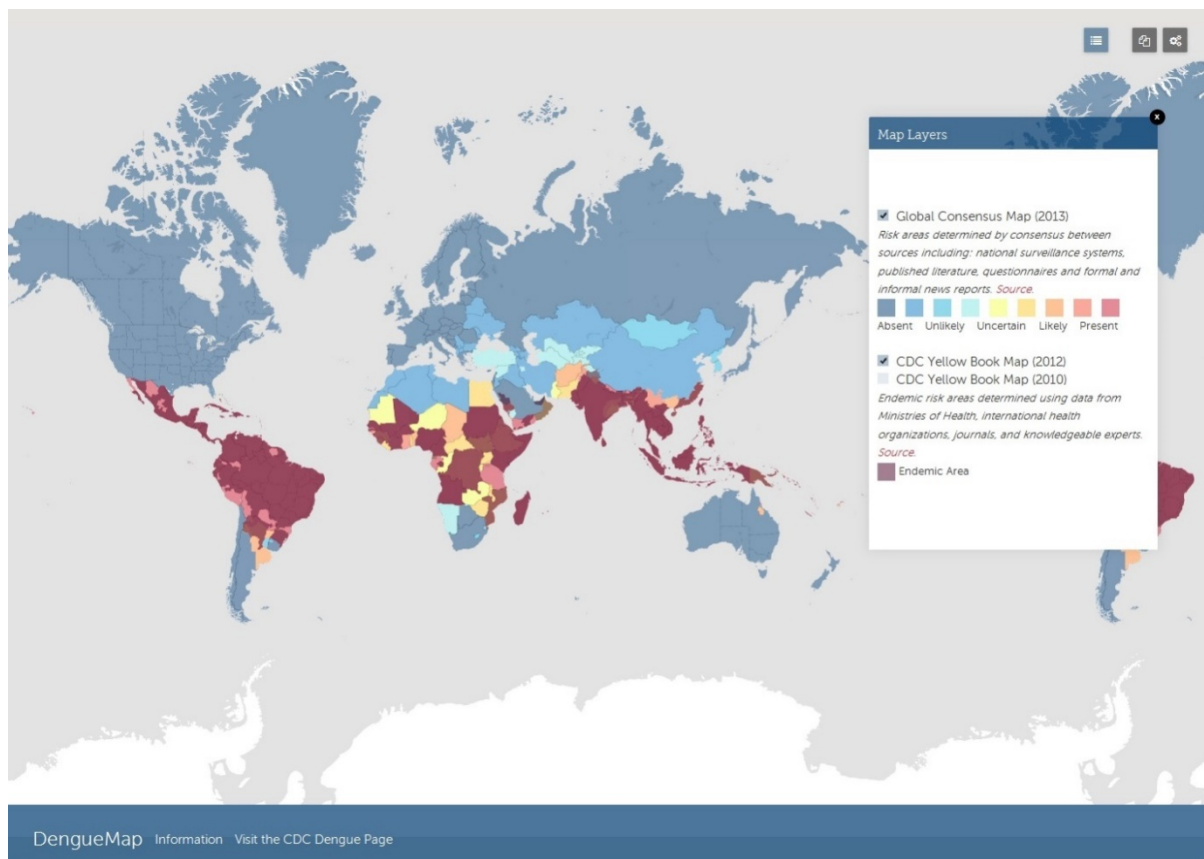


Figure 1: Dengue endemic areas reported by the Center for Disease Control and Prevention (CDC), determined based on the data from Ministries of Health, international health organisations, journals, and knowledgeable experts (2012). Source: <http://www.healthmap.org/dengue/en/> (accessed 31 August 2016)

All the 11 countries of the SEAR except the Democratic People's Republic of Korea are dengue endemic.<sup>2</sup> Forty eight percent of cases reported within the SEAR from 1985 to 2009 occurred in Thailand and 38.0% in Indonesia.<sup>2</sup> The first outbreak of DHF in Southeast Asia occurred in Thailand in 1958 and DHF then began to expand into other SEAR countries.<sup>3</sup> Following Thailand, Indonesia, and Myanmar, severe dengue has also emerged in Bangladesh, India, the Maldives, and Sri Lanka with more frequent cyclical epidemics of dengue.<sup>2</sup>

## **2.2 Transmission of dengue virus**

Dengue virus is transmitted when a person is bitten by an infected female *Aedes* mosquito, predominantly *Aedes aegypti* and *Aedes albopictus*. *Aedes aegypti* is the principal urban vector and is highly competent as an epidemic vector of DENV. *Aedes aegypti* females lay eggs in artificial receptacles and usually rest inside houses. *Aedes albopictus* females rest outdoors where they also lay eggs in artificial and natural containers (e.g., banana leaves, tree holes, and bamboo stumps).<sup>4</sup>

Clinical manifestations of dengue range from asymptomatic infection to life threatening shock and haemorrhage. Dengue fever manifests typically following a 4-7 day (maximum 10 days) intrinsic incubation period in a human host.<sup>5</sup> During the viraemic period of the following 4-5 days (maximum 12 days) the virus can be transmitted to mosquitoes through an infectious blood meal.<sup>5</sup> After 8-12 days of extrinsic incubation, mosquitoes become infectious and can transmit the virus to humans.<sup>5</sup> The mosquito remains infectious for life (usually a few days to four weeks).

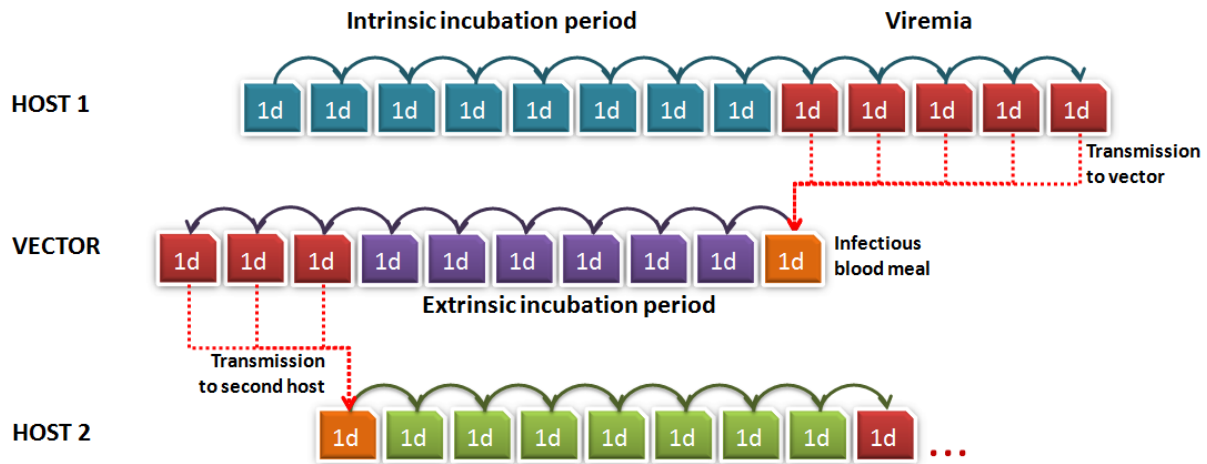


Figure 2: Schematic outline of DENV transmission from one host to another via the vector.<sup>6</sup>

## 2.3 Factors influencing transmission

### 2.3.1 Climatic determinants

Weather influences the ecology of dengue through biological mechanisms. Low temperature slows adult mosquito development<sup>7</sup> and prevents *Aedes* mosquitoes from transmitting DENV<sup>8</sup>. Consistent with these observations, in markedly seasonal regions, dengue transmission declines in cold weather.<sup>9</sup> Conversely, dengue transmission increases with rising temperature, which speeds mosquito development, increases biting frequency,<sup>10</sup> and shortens the extrinsic incubation period<sup>11</sup>. However, temperatures above 30°C and 35°C reduce the survival of adult and aquatic forms of mosquitoes, respectively.<sup>12</sup> Ambient temperature also affects the oviposition rate of female *Ae. aegypti* but the intensity is influenced by relative humidity with the highest rate reported at 25°C with relative humidity of 80.0%.<sup>13</sup> Diurnal temperature variation also influences survival and vectorial capacity of *Ae. aegypti* and therefore transmission of DENV.<sup>14-17</sup> In warmer environments, small fluctuations in temperature increase vectorial capacity<sup>15-17</sup> while in cooler environments, fluctuations in temperature reduce vectorial capacity<sup>14-17</sup>.

Transmission of DENV usually peaks during the wet season.<sup>18, 19</sup> However, the influence of rainfall on DENV transmission is non-linear. The availability of breeding sites is influenced by

rainfall interacting with water storage practices because *Ae. aegypti* breeds in artificial containers in and around houses.<sup>20</sup> Low rainfall may lead to storage of water and consequently dengue outbreaks as observed in Singapore, Bangkok (Thailand), and Jakarta (Indonesia).<sup>21-23</sup>

Transmission of DENV can also be driven by inter-annual weather variability caused by El Niño-Southern Oscillation (ENSO), a large-scale climatic phenomenon which is a combination of anomalous conditions in sea surface temperature associated with El Niño and atmospheric pressure associated with Southern Oscillation across the equatorial Pacific Ocean. The warm (cold) phase of the ENSO is known as El Niño (La Niña) when the 3-month moving average of sea surface temperature anomalies in the Niño 3.4 region, an index for ENSO in the Indian Ocean region, exceeds +0.5°C (-0.5°C) for five consecutive months.<sup>24</sup> The El Niño-Southern Oscillation influences local rainfall and temperature but the relationships are inconsistent across the years and countries.<sup>25, 26</sup> In Mexico, Puerto Rico, Thailand, French Guyana, Suriname, Indonesia, Columbia, and Brazil, El Niño was significantly associated with dengue incidence.<sup>18, 27-31</sup> However, the mechanisms involved are poorly understood.

The global increase in dengue incidence is concurrent with major anthropogenic climate change. But associations are complex, incompletely understood, and confounded by many other host, agent, and environmental factors, so it is naïve to assume causation.

### **2.3.2 Non-climatic determinants**

Socio-economic and behavioural factors influence DENV transmission. For example, with increasing temperature, people tend to stay inside in air-conditioned rooms where they are less exposed to mosquito bites, with consequent reduced incidence.<sup>32</sup> Conversely, in many low-income tropical areas housing is not air-conditioned and risk may be further increased by clothing appropriate to high ambient temperature.

High population density increases dengue incidence. Large households and short distances between houses increase the likelihood of multiple infections in a single household and the development of urban pockets of dengue infections.<sup>33</sup>

Unplanned urbanisation is associated with inefficient city management resulting in a lack of water supply, drainage, and waste disposal. Inadequate access to piped water encourages water storage that provides breeding sites.<sup>20, 32</sup> Absence of proper waste management provides artificial containers in which *Aedes* mosquitoes lay eggs.<sup>34</sup>

Historically, both *Ae. aegypti* and DENV were spread via sailing ships as the ships' water storage containers served as mosquito breeding sites and allowed the development of adult mosquitoes.<sup>35</sup> Increasing domestic and international travel facilitates the movement of viraemic individuals and vectors from endemic to susceptible regions.<sup>34, 35</sup>

## **2.4 Statistical modelling of the association between dengue and climate**

Statistical techniques for estimating the empirical relationships between dengue and climate range from time series models to various regression analyses.<sup>27, 29, 31, 36-38</sup> Climatic variables generally considered in these models include temperature, rainfall, humidity, wind speed, and ENSO index which are used to analyse the transmission dynamics of dengue across geographical regions. However, non-climatic determinants are often ignored, with consequent uncontrolled confounding of the observed associations.

Time series modelling approaches such as autoregressive integrated moving average (ARIMA) and seasonal autoregressive integrated moving average (SARIMA) models have been widely applied in assessing the impact of climatic variables on dengue incidence. In Kaohsiung city, Taiwan, warmer and less humid weather were found to be associated with dengue epidemics two months later during 1988-2003, using an ARIMA model.<sup>39</sup> A SARIMA model found that minimum temperature at five weeks lag time was the best climatic predictor of dengue outbreaks from 2000 to 2006 in French West Indies.<sup>40</sup> In Queensland, Australia, a lower Southern Oscillation Index was identified to be related to increased dengue cases over the period 1993-2005, using a SARIMA model.<sup>41</sup> An auto-regressive model, adjusted by population growth in two municipalities of the State of Veracruz, Mexico, during 1995-2003, estimated an increase of 46.0% and 42.0% in the weekly number of dengue cases with each degree centigrade increase in SST at a lag of 16 and 20 weeks, respectively.<sup>29</sup> Minimum

temperature during the same week, and precipitation with a lag of two weeks were also found positively associated with dengue cases in both municipalities.<sup>29</sup>

A wide range of regression models have been applied to determine the relationships between climate and dengue. A multiple linear regression model used to examine the associations between changes in the climate variability and dengue incidence in the warm and humid regions of Mexico for the years 1985-2007, identified higher incidence during El Niño events and in the warm and wet season.<sup>42</sup> However, during the cool and dry season, dengue incidence was positively associated with the strength of El Niño and the monthly minimum temperature.<sup>42</sup> A Poisson regression model determined that, in Singapore from 2000 to 2007, for every 2-10°C of variation of the weekly maximum temperature from April to August, dengue cases increased by 22.2-184.6% while for the same variation in minimum temperature, the average increase in dengue cases was 26.1-230.3%.<sup>43</sup> A multivariate non-linear model was adopted to develop an early warning system in Noumea, New Caledonia that predicted 79.0% of the epidemic years and 65.0% of the non-epidemic years over a period of forty years and identified maximal temperature and relative humidity as determinants of epidemic occurrence.<sup>44</sup>

However, omission of confounding factors in the model or failure to account for the seasonality present in both climate and dengue incidence may result in inconsistent associations between temperature, precipitation and dengue incidence. A hierarchical Poisson regression model, with a population offset and a natural cubic spline function of time to adjust for seasonal confounding, used in Puerto Rico (July 1986 - December 2006) was capable of interpreting the effects of inter-annual variation in climate (monthly average precipitation and temperature, lagged up to 2 months) on dengue incidence.<sup>37</sup> Alternative approaches to account for seasonal variation include using oscillatory sine and cosine functions<sup>45, 46</sup> or simply incorporating calendar month as a categorical variable in the model.<sup>31</sup>

Statistical techniques have also been used to investigate the variation in dengue transmission at spatial scales ranging from cities to countries and continents.<sup>47-52</sup> A spatial analysis at the municipality level in Taiwan explored increasing risk of dengue incidence associated with numbers of months in a year with average temperature over 18°C and degree of urbanisation.<sup>53</sup> In Queensland, Australia, a Bayesian spatial conditional autoregressive modelling approach identified 6.0% (95% credible interval: 2.0%, 11.0%) and 61.0% (95% credible interval: 2%, 241.0%) increase in locally acquired dengue during 2002-2005 with a 1-mm increase in

average monthly rainfall and a 1°C increase in average monthly maximum temperature, respectively.<sup>50</sup> However, overseas-acquired dengue cases were observed to increase by 1.0% (95% credible interval: 0%, 3.0%) and 1.0% (95% credible interval: 0%, 2.0%) in association with a 1-mm increase in average monthly rainfall and a 1-unit increase in average socioeconomic index, respectively.<sup>50</sup> A household study integrating entomological-serological data identified seroprevalence hotspots in three neighbourhoods with different socioeconomic profiles in Rio de Janeiro, Brazil using a spatial Generalised Additive Model.<sup>54</sup> Application of spatial scan statistics, measures of spatial autocorrelation and space-time analysis techniques reveal that dengue cases are clustered in space-time.<sup>47, 51, 55-57</sup>

Statistical models provide a sound approach to estimate risk and plan control in different environments. An understanding of the spatio-temporal distribution of risk is critical in implementing effective control measures since space and time are important dimensions to consider when investigating the dynamics and risk distribution of dengue.

## **2.5 Dengue in Bangladesh**

Bangladesh is densely populated with more than 142 million people living in an area of 147,570 square kilometres.<sup>58</sup> Poverty, socio-economic inequality, and unplanned urbanisation (29.0% of population urbanised<sup>59</sup>) render Bangladesh vulnerable to vector-borne diseases. Extreme weather events including droughts in the pre-monsoon season followed by floods during the monsoon season are commonplace and are projected to become more frequent and more severe with estimated increases in annual mean temperature of 1.4°C and annual mean rainfall of 5.6% by 2050.<sup>60</sup> Bangladesh comprises tropical and sub-tropical zones conducive to DENV transmission. Monsoon rainfall (80.0% of the annual 2000mm) is partly influenced by ENSO events with less than average rainfall in El Niño years while the opposite happens in La Niña years. However, the association of ENSO events and rainfall is inconsistent since moderate El Niño years have been associated with flooding and some La Niña events followed by El Niño were responsible for reduced monsoon rainfall.<sup>61, 62</sup>

In 2000, Bangladesh observed the first epidemic of dengue following sporadic transmission between 1964 and 1999. During the epidemic, 5551 cases were reported with 1.7% case

fatality<sup>63</sup> in three of the major cities (Dhaka, Chittagong, and Khulna) and 17 towns, including 79.0% classical dengue fever and 21.0% DHF cases.<sup>64</sup> In 2001, half the number of cases and deaths were reported, but this was followed in 2002 by the largest epidemic (6132 cases), with 1.0% case fatality.<sup>63</sup> Since the first reported epidemic in 2000 to December 2014 more than 28,000 cases and 242 deaths have been reported with 91.0% of reported cases from the capital Dhaka.<sup>63</sup> Although there has been an overall decline in the number of cases reported since 2002 (Figure 3), a global study on the burden of dengue estimated more than 16 million dengue infections in Bangladesh during 2010 of which around 4 million were symptomatic<sup>49</sup>. The national surveillance system is passive and hospital-based. Only severe cases seek treatment in hospital, females are less likely to seek and receive treatment<sup>65-67</sup>, and many areas have little hospital access<sup>68</sup>. It is probable that the incidence of dengue is under-estimated.

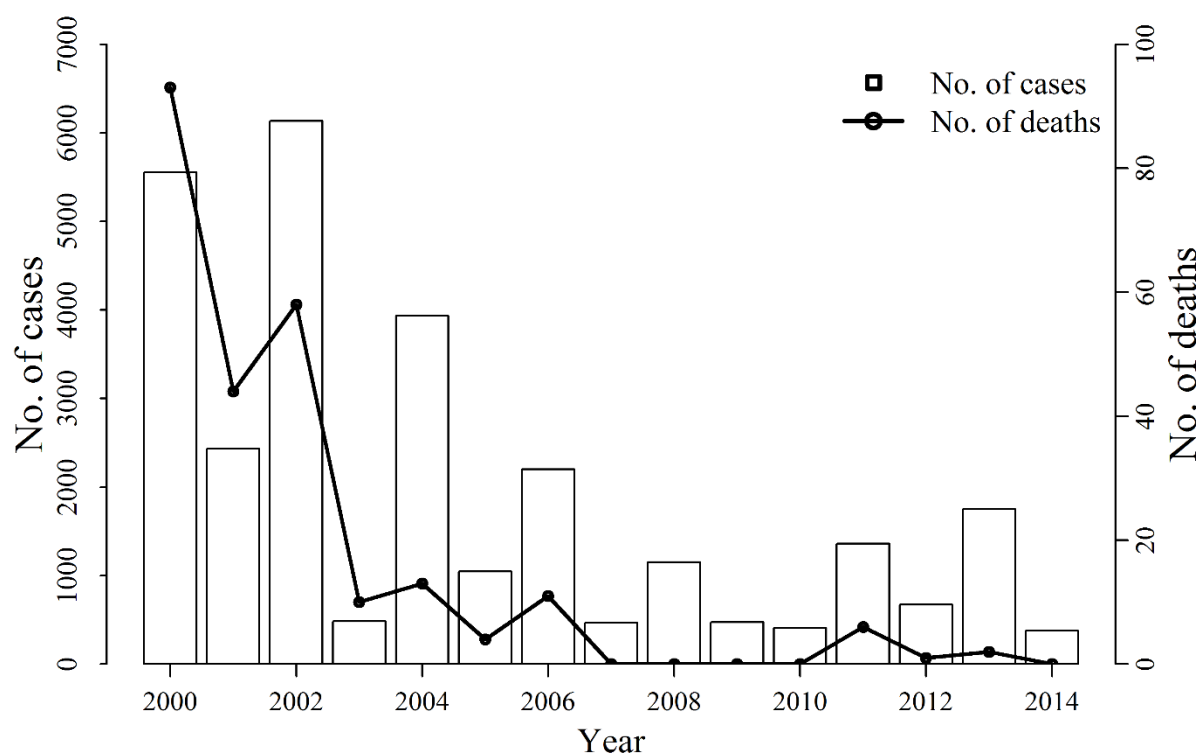


Figure 3: Number of reported dengue cases and deaths by year (2000–2014) in Bangladesh (Data source: Directorate General of Health Services, Dhaka<sup>63</sup>).

Seasonal fluctuations and year-to-year variation in the timing and magnitude of seasonal peaks have been observed with increased incidence usually from June with a peak in August (Figure 4) and gradual decline afterwards.<sup>69</sup> A similar pattern of seasonal fluctuations in dengue incidence was observed among febrile patients who sought care in tertiary hospitals from December 2008 to November 2009.<sup>70</sup> Changes in mosquito populations driven by weather

along with the inter-annual variation in DENV activity drive these changes. The pre-monsoon rain in May fills containers in which *Ae. aegypti* and *Ae. albopictus* lay eggs with consequent population increase; mosquito numbers remain high until the rainy season ends in September and decrease gradually afterwards.<sup>71</sup> Mean monthly temperature during the monsoon is nearly always in a range favourable for mosquito development and DENV transmission.

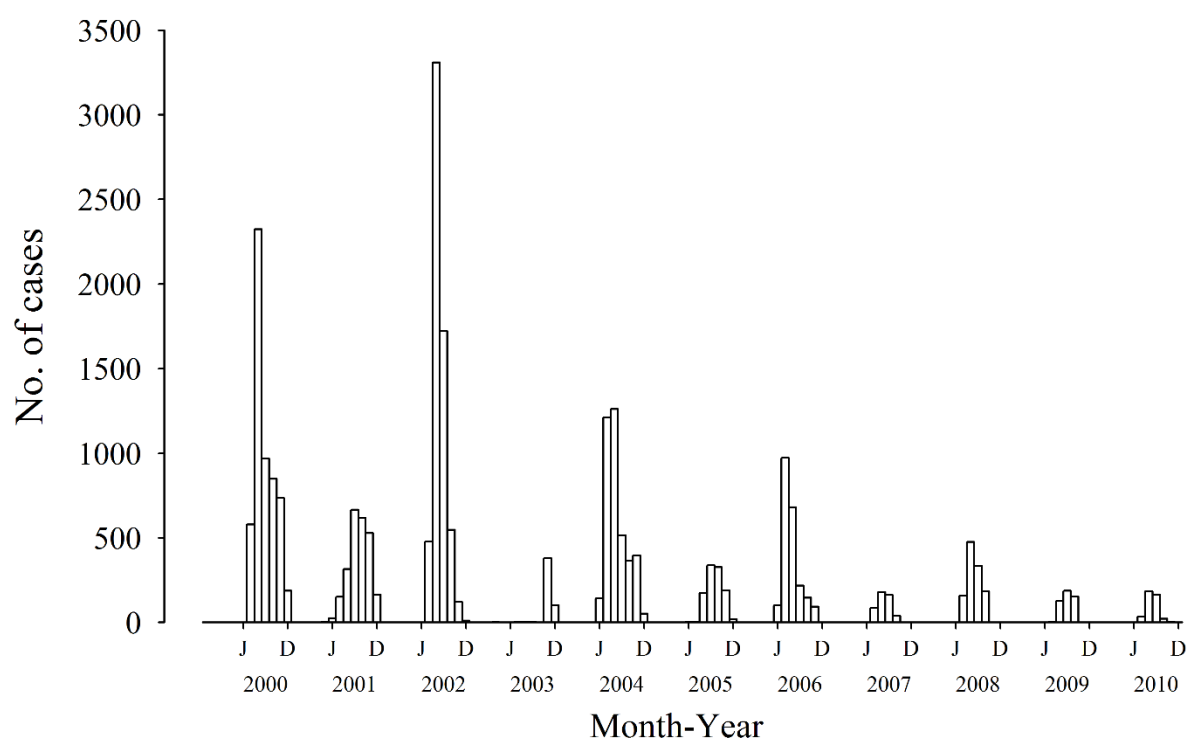


Figure 4: Reported cases of dengue by month from January 2000 to December 2010, showing seasonal incidence (Data source: Directorate General of Health Services, Dhaka<sup>63</sup>).

There has been little study of dengue and climate in Bangladesh. Existing studies include temporal analyses of dengue in Dhaka identifying temperature, rainfall, and relative humidity as the main determinants of increasing dengue incidence.<sup>72, 73</sup> A weak, non-linear relationship between dengue incidence and large-scale climatic events (El Niño Southern Oscillation and Indian Ocean Dipole) has recently been reported.<sup>74</sup> However, these studies have not analysed small-scale variation in temperature, which significantly influences vector and virus biology. Diurnal variation in temperature influences the impact of changes in mean temperature; if this is not accounted for, incidence may be overestimated at high temperatures. An understanding of the non-linear relationship between weather and dengue incidence is essential. Under-reporting makes analysis of the relation between climate and incidence challenging.

One study investigated spatial clustering of dengue cases from 2000-2009 and identified Dhaka as the most likely cluster of dengue.<sup>75</sup> A spatial cluster was defined as a circle with maximum radius of 40km containing a maximum of 50% of the at risk population for the defined study area.<sup>75</sup> A detailed understanding of the spatial distribution of dengue across the country is however invaluable for efficient distribution of limited resources to control the disease.

In this thesis, I explore how small-scale variation in daily temperature in combination with mean temperature influences dengue incidence when adjusted for other local and global climatic and demographic factors. I then investigate the non-linear dengue-climate relationships, while adjusting for under-reporting. I also analyse the seasonal spread of dengue at the district level and estimate incidence in districts without any reported dengue cases.

## 2.6 Modelling dengue count data

Dengue case data are often modelled using a Poisson distribution. However, a limitation of using the Poisson distribution is that the variance of the data is assumed to be equal to the mean,  $Var(y_i|x_i) = E(y_i|x_i) = \mu_i$ , while count data often display extra variation or *over-dispersion*.<sup>76, 77</sup> A common approach to model *over-dispersed* count data is to use a negative binomial model within a generalised linear model framework.<sup>78</sup>

Generalised linear models describe the dependence of the response variable  $Y$ , which is a count, on a vector of explanatory variables  $x_i$  ( $i = 1, 2, \dots, n$ ). A negative binomial model would stipulate that the distribution of  $Y|x_i$  is negative binomial with conditional mean and variance given by

$$\begin{aligned} E(y_i|x_i) &= \mu_i \\ Var(y_i|x_i) &= \mu_i + \phi\mu_i^2, \end{aligned}$$

where  $\phi \geq 0$  and is known as dispersion parameter.

The dependence of the conditional mean  $E(y_i|x_i) = \mu_i$  on the explanatory variables  $x_i$  is specified via

$$g(\mu_i) = x_i\beta,$$

where  $g(\cdot)$  is the log link function of  $x$  and a vector of regression coefficients,  $\beta$ .

### **2.6.1 The frequentist and Bayesian context for generalised linear models**

Generalised linear models can be applied in either classical frequentist or Bayesian contexts. Both of the approaches to statistical inference use the likelihood function which is the likelihood of observing the given data, conditional on the parameter (regression coefficients, mean, and variances) values.

In the frequentist approach, the response variable  $Y$  is assumed random while the parameters are fixed and unknown. Estimates of the parameters are typically computed by maximum likelihood estimation, where the estimates are calculated by maximising the likelihood function.

A Bayesian approach allows us to combine previous beliefs about underlying parameters, with the observed data to obtain probability distributions of the parameters. It assumes that both the response and the parameters are random. Because the parameters are assumed to be random, a distribution is assigned to each of the parameters which is called the *prior distribution*. Parameters that define the prior distribution are known as *hyperparameters*. Bayes theorem provides a method of combining the likelihood function with previous beliefs about the parameters' probability distribution (*prior distribution*) to obtain the posterior probability distribution. Markov Chain Monte Carlo (MCMC) methods are widely used to generate the *posterior distribution*.<sup>79</sup> A Bayesian model specification is appealing because the *posterior distribution* of the parameters allows for statistical estimation and inference permitting probabilistic decision making under uncertainty.

### **2.6.2 Technical issues in Bayesian model estimation: choice of priors**

The standard practice is to choose diffuse or non-informative priors for the parameters to be estimated implying imprecise prior beliefs about the parameters' probability distribution.<sup>80</sup> This allows the parameters to assume values over a large range, with approximately equal likelihood. The conventional choice is a uniform distribution over the range of interest. A uniform distribution implies that the *posterior distribution* has the same shape as the likelihood function leading to estimates and corresponding Bayesian intervals matched with the frequentist results. Other choices are a normal distribution, with mean zero and a large variance

for location parameters while for the precision parameters, a diffuse Gamma prior is often assumed. However, using a non-informative prior could be disadvantageous when there is a lack of data since the posterior distribution will be poorly identified and likely to include values that are implausibly high or low. An informative prior providing numerical information crucial to model estimation can be elicited from literature or from a previous model.

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# Chapter 3

## Paper 1: Emergence, establishment, and future risk of dengue in Bangladesh

Sharmin S, Viennet E, Glass K and Harley D. The emergence of dengue in Bangladesh: epidemiology, challenges, and future disease risk. *T Roy Soc Trop Med H.* 2015; trv067.

## **Summary of this chapter**

This chapter discusses the introduction and endemic establishment of dengue, and the likelihood of future epidemics of severe dengue in Bangladesh by synthesising grey literature, expert opinion, and published articles found using Google Scholar, PubMed, and the World Health Organization library database. The search terms were “dengue fever”, “dengue”, “transmission”, “incidence”, “prevalence”, “hospitalisation”, “hospitalization”, “mortality”, and “Bangladesh”. The disease has been endemic since the first epidemic in 2000 even though sporadic cases occurred from 1964. Many aspects of dengue epidemiology in Bangladesh previously not synthesised are considered in this narrative review paper. Differences in dengue epidemiology between Bangladesh and neighbouring high incidence countries are outlined. The paper discusses the potential causes of an apparent decline in notified case numbers, including control measures and population immunity, and whether bias in the national reporting system partially accounts for the decline. This synthesis of data enables assessment of the extent of under-reporting in surveillance data which is an essential component to quantify disease burden. The paper emphasises that socio-economic and environmental deterioration and an absence of active intervention produce the threat of severe dengue epidemics in Bangladesh.

# The emergence of dengue in Bangladesh: epidemiology, challenges, and future disease risk

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Received 3 June 2015; revised 22 July 2015; accepted 23 July 2015

Dengue occurred sporadically in Bangladesh from 1964 until a large epidemic in 2000 established the virus. We trace dengue from the time it was first identified in Bangladesh and identify factors favourable to future dengue haemorrhagic fever epidemics. The epidemic in 2000 was likely due to introduction of a dengue virus strain from a nearby endemic country, probably Thailand. Cessation of dichlorodiphenyltrichloroethane (DDT) spraying, climatic, socio-demographic, and lifestyle factors also contributed to epidemic transmission. The largest number of cases was notified in 2002 and since then reported outbreaks have generally declined, although with increased notifications in alternate years. The apparent decline might be partially due to public awareness with consequent reduction in mosquito breeding and increased prevalence of immunity. However, passive hospital-based surveillance has changed with mandatory serological confirmation now required for case reporting. Further, a large number of cases remain undetected because only patients with severe dengue require hospitalisation. Thus, the reduction in notification numbers may be an artefact of the surveillance system. Indeed, population-based serological survey indicates that dengue transmission continues to be common. In the future, the absence of active interventions, unplanned urbanisation, environmental deterioration, increasing population mobility, and economic factors will heighten dengue risk. Projected increases in temperature and rainfall may exacerbate this.

**Keywords:** Climatic factors, Dengue emergence, Passive surveillance, Socio-economic context, Urbanisation, Under-reporting

## Introduction

Dengue virus (DENV), spread by day-biting *Aedes* mosquitoes, primarily *Aedes aegypti* and *Aedes albopictus*, causes classical dengue fever (DF), dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS). While classical DF is typically a mild flu-like illness, DHF and DSS are potentially fatal, and together are termed 'severe dengue'. About 52.0% of the people at risk of acquiring dengue worldwide live in 10 countries of the WHO South-East Asia Region, which includes Bangladesh.<sup>1</sup> Here the disease has emerged as a significant threat to public health since an initial epidemic in 2000, when 5551 cases and 93 deaths were recorded.<sup>2</sup> Dengue infection in Bangladesh was first detected when an outbreak of a febrile illness called 'Dacca Fever' occurred in the capital (now Dhaka) during the late summer of 1964.<sup>3</sup> Dengue virus type 3 was isolated.<sup>3</sup> Between 1964 and 1999, sporadic cases and small outbreaks clinically suggestive of dengue occurred across the country but were not officially reported.<sup>4–6</sup> In the summer of 1999, an outbreak started in and around Dhaka followed by the first officially reported epidemic of DF in 2000.<sup>4,7</sup> Cases of severe dengue were also reported.<sup>4</sup> The epidemic was likely due to a dengue virus strain introduced from endemic countries to the east of Bangladesh.<sup>8</sup> Since 2000, dengue cases have been reported yearly

in all major cities of Bangladesh.<sup>2</sup> The largest reported epidemic was in 2002 with 6132 cases.<sup>2</sup> Since 2002, hospital-based surveillance notifications have declined, although true case numbers are under-ascertained.<sup>9,10</sup>

We discuss the history of dengue in Bangladesh and explore future disease risk. Causes for the emergence and establishment of the disease are considered, with a focus on population, human behaviour, socio-economic context, and climate. We also identify gaps in understanding of incidence and distribution and discuss critical challenges to control programs in the resource-limited setting of Bangladesh.

## Dengue epidemiology in Bangladesh

Bangladesh is located in South Asia bordered on the north, east, and west by India, southeast by Myanmar, and south by the Bay of Bengal (Figure 1). The Bengal delta, which is one of the world's largest river delta systems, occupies 80.0% of the country's area. Extreme flood events are commonplace and devastate the country on a regular basis.

All neighbouring countries reported DF, DHF, and DSS before the first epidemic in Bangladesh. In India, DF has occurred since

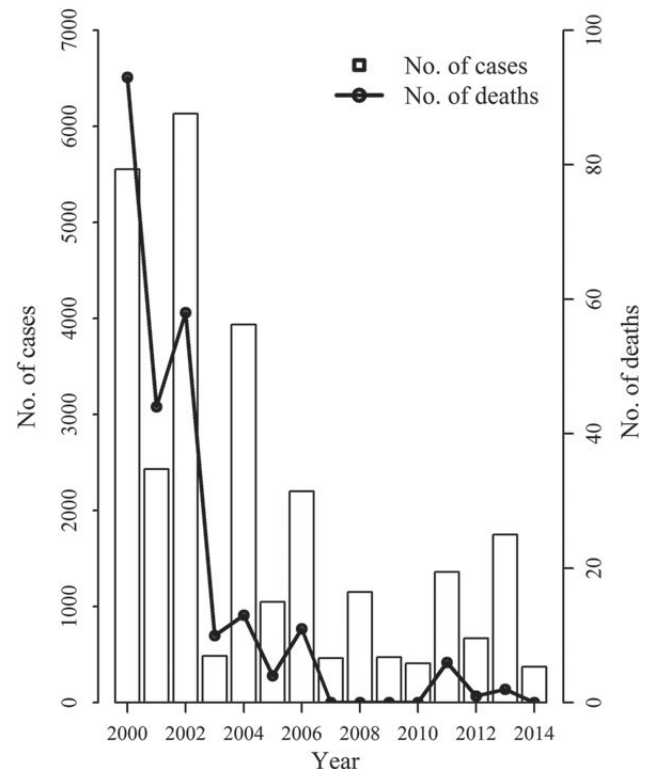


**Figure 1.** Location of Bangladesh. This Figure is available in black and white in print and in colour at Transactions online.

1945.<sup>11</sup> In 1963–1964, a large outbreak occurred in Kolkata (then Calcutta),<sup>12</sup> about 567 km west of Bangladesh, partially coinciding temporally with Dacca Fever in Bangladesh. Several outbreaks of classical dengue occurred in India between 1945 and 1988; in the latter year DHF and DSS were diagnosed for the first time using the WHO criteria in India.<sup>13</sup> A major outbreak of severe dengue occurred in Delhi in northern India during 1996.<sup>13,14</sup> Myanmar has had outbreaks every three to five years since the first in 1970.<sup>15</sup> Dengue endemic countries surround Bangladesh, placing it at continual risk of importation of new dengue strains.

## Incidence

In 2000, dengue incidence in Bangladesh suddenly increased following sporadic transmission between 1964 and 1999. During 2000 there were 5551 cases reported, with 1.7% case fatality,<sup>2</sup> in three of the major cities (Dhaka, Chittagong, and Khulna) and 17 towns, including 4385 (79.0%) DF and 1166 (21.0%) DHF cases.<sup>4</sup> In 2001, half the number of cases and deaths were reported, but this was followed in 2002 by a larger epidemic (6132 cases), with 1.0% case fatality.<sup>2</sup> More than 28 000 cases and 242 deaths have been reported to the Directorate General of Health Services from January 2000 to December 2014.<sup>2</sup> Since



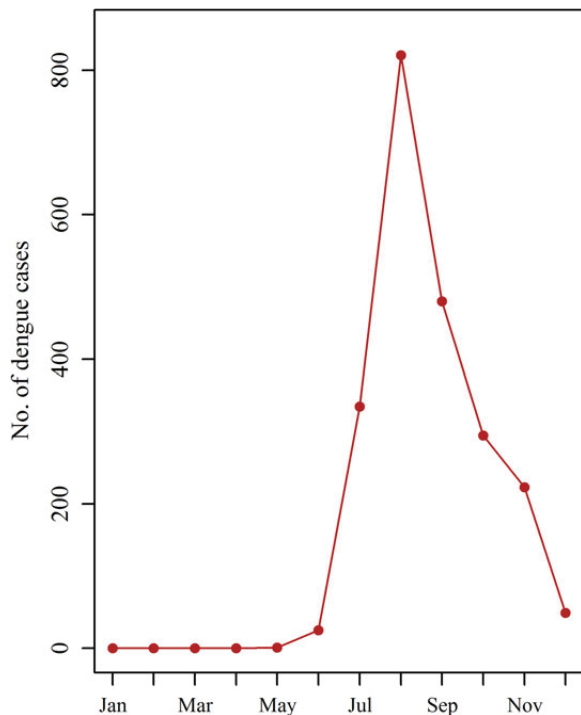
**Figure 2.** Number of reported dengue cases and deaths by year (2000–2014) in Bangladesh (Data source: Directorate General of Health Services, Dhaka<sup>2</sup>).

2002 a decline in the number of cases reported has been observed (Figure 2). However, a global study on the burden of dengue estimated more than 16 million dengue infections in Bangladesh during 2010 of which around 4 million were symptomatic.<sup>9</sup> As national surveillance is passive and hospital based, it is unsurprising that incident cases are under-ascertained.

## Seasonality

There are seasonal fluctuations in dengue incidence, with year-to-year variation in the timing and magnitude of seasonal peaks. Climate and resulting changes in mosquito populations along with the inter-annual variation in DENV activity drive these changes. The pre-monsoon rain in May fills containers in which *Ae. aegypti* and *Ae. albopictus* lay eggs with consequent population increase; mosquito numbers remain high until the rainy season ends in September and decrease gradually afterwards.<sup>16</sup> Mean monthly temperature during the monsoon is nearly always in a range favourable for mosquito development and DENV transmission.

National surveillance data usually shows increased incidence from June with a peak in August (Figure 3) and gradual decline afterwards. A similar pattern of seasonal fluctuations in dengue incidence was observed among febrile patients who sought care in tertiary hospitals from December 2008 to November 2009.<sup>17</sup>



**Figure 3.** Monthly dengue cases averaged over 2000–2010, showing seasonal incidence (Data source: Directorate General of Health Services, Dhaka<sup>2</sup>). This Figure is available in black and white in print and in colour at Transactions online.

### Spatial distribution

Twenty-nine of the 64 Bangladeshi districts reported dengue between 2000 and 2009 (Figure 4, left). The capital, Dhaka, consistently reports the highest number of cases, with few notifications from elsewhere since 2010.<sup>2</sup> A hospital-based cross-sectional study conducted from December 2008 to November 2009 reported almost equal proportions of patients testing seropositive for dengue among rural (outside sub-district municipalities) and urban (city corporation and district municipality) residents.<sup>17</sup> The reduced numbers of notifications outside Dhaka since 2010 is presumably because of the change in reporting criteria requiring confirmatory serological diagnosis (see Surveillance section). Under-reporting is also likely to vary due to the heterogeneous distribution of hospitals, treatment seeking, and reporting practices. Most hospitals across Dhaka Metropolitan Area reported dengue in 2011 (Figure 4, right). Nationwide population-based seroprevalence studies are essential to accurately estimate the geographical extent of dengue.

### Seroepidemiology

The high proportion of serologically determined secondary infections suggests active transmission of dengue occurred throughout Bangladesh before the first epidemic in 2000.<sup>5,18,19</sup> During the 2002 epidemic, hospital-based studies in Dhaka reported 31.2%<sup>20</sup> to 50.0%<sup>21</sup> seropositivity among clinically suspected dengue patients aged 1–15 years and 10–70 years, respectively. A population-based cross-sectional serosurvey in 2012 detected anti-dengue antibodies by IgM and IgG capture ELISA in 2.0%

and 80.0% of participants, respectively, living in 12 of 90 wards of Dhaka city.<sup>10</sup> This is indicative of significant transmission, not captured in national notification data.

### Virus isolation

Dengue virus type 3 was isolated from patients with Dacca Fever in 1964.<sup>3</sup> Since that time all four serotypes have been isolated.<sup>18,22,23</sup> In 2000, for the first time all four serotypes were found to be co-circulating, with DENV-3 predominating.<sup>7,22</sup> In this situation of hyperendemicity, Bangladeshis are at risk of severe disease resulting from sequential infection with multiple serotypes, as in Havana, Cuba, for example.<sup>24</sup> However, absence of virologic surveillance limits knowledge of circulating serotypes.

Phylogenetic analyses of envelope gene sequences demonstrated that Bangladeshi DENV-3 isolates collected during 2000–2002 belonged to the Asian group of genotype II, with Bangladeshi strains found to be very closely related to viruses from Thailand and Myanmar.<sup>8,21</sup> Most genotype II strains of DENV-3 isolated in South Asian countries come from Thailand<sup>25</sup> where this was the most common genotype between 1974 and 2002.<sup>26</sup> In Thailand several outbreaks were caused by DENV-3 over the period 1995 to 1999<sup>27</sup> and it is conceivable that genotype II was associated with those outbreaks. It is therefore plausible that importation of this virulent Thai strain of DENV-3 into Bangladesh led to the epidemic in 2000.

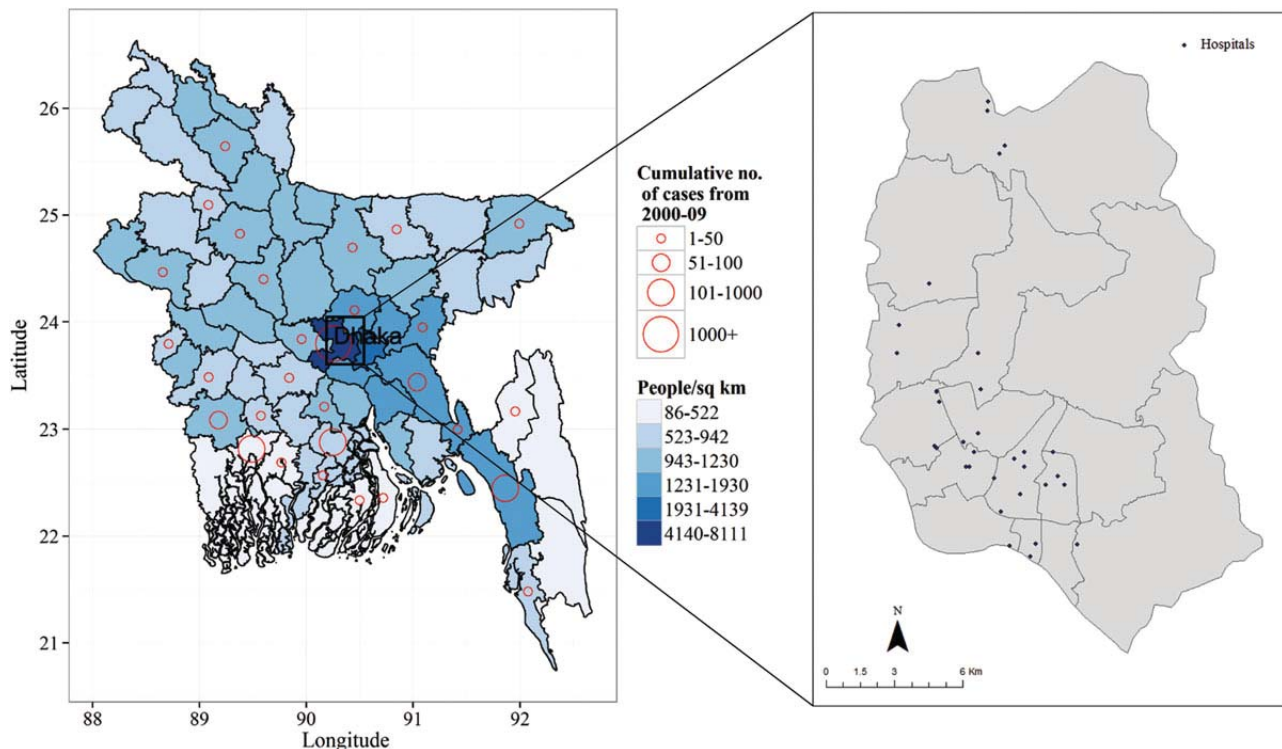
### Vector distribution

*Aedes aegypti* and *Ae. albopictus* have been collected in Bangladesh since 1952.<sup>28</sup> Although globally *Ae. albopictus* is less common in urban environments than *Ae. aegypti*, both were found in large numbers in urban areas of Bangladesh. A larval survey was carried out in Dhaka city between May 1977 and April 1978.<sup>29</sup> Among the 1898 water storage containers and natural sites sampled, 62.8% contained *Ae. albopictus* alone, 31.4% contained only *Ae. aegypti*, and 5.8% contained larvae of both species.<sup>29</sup> *Aedes aegypti* and *Ae. albopictus* larvae and adults have subsequently been collected from indoor and outdoor breeding sites throughout Bangladesh.<sup>30,31</sup> In response to the 2000 epidemic, mosquito larvae were collected during the epidemic period from 19 August to 11 October across all 90 administrative wards of Dhaka City Corporation and an adjacent locality of southwestern Dhaka. The mean Breteau Index (BI=number of infested containers per 100 houses inspected) was 22.6, with 11 wards over 50.0, indicating high risk of dengue transmission.<sup>32</sup> Over the same period, 9462 houses across Dhaka City Corporation were investigated and household premises with *Ae. albopictus* larvae were more likely, relative to those without *Ae. Albopictus*, to include a dengue patient (RR 1.5, 95% CI 1.1–1.8).<sup>33</sup> The presence of *Ae. aegypti* did not alter risk (RR 1.1, 95% CI 0.9–1.4).<sup>33</sup> However, the distribution of *Ae. aegypti* and *Ae. albopictus* is not known due to lack of regular entomological surveillance.

### Patient demographics

#### Age

During the 2000 epidemic, the mean age of hospitalised patients with serologically confirmed dengue in Dhaka was around 29



**Figure 4.** Population density in 2011<sup>52</sup> and distribution of dengue cases from 2000–2009 at district level<sup>2</sup> (Left). Location of hospitals reporting dengue cases in Dhaka Metropolitan Area in 2011<sup>2</sup> (Right). (Data source: Population and housing census 2011, Bangladesh Bureau of Statistics<sup>52</sup> and Directorate General of Health Services, Dhaka<sup>2</sup>). This Figure is available in black and white in print and in colour at Transactions online.

years.<sup>34</sup> In 2002, 62.0% of confirmed cases among patients aged 10–70 years admitted to a Dhaka hospital were 16–30 years old.<sup>21</sup> The adult predominance may be because dengue in childhood is either asymptomatic or causes few symptoms and consequently hospitalisation is not required.<sup>35</sup> In 2002, a hospital-based study in Dhaka reported the highest (43.3%) seroprevalence of dengue among the 11–15 year age group in a study of 1–15 year old children.<sup>20</sup> Risk of secondary infection and consequently severe dengue has also been higher among adults and older children<sup>36</sup> possibly due to exposure to DENV before 2000 although other factors including co-morbidities,<sup>37</sup> infecting serotype,<sup>38</sup> serotype sequence in consecutive infections,<sup>24</sup> time between infections<sup>39</sup> and varying virulence of different DENV strains<sup>40</sup> may also contribute. Workplace transmission may also increase the risk of infection for adults in Bangladesh.<sup>41</sup>

Dengue in Bangladesh is most commonly reported among adults and older children, consistent with other relatively low incidence countries in the region.<sup>12,42</sup> However, measles, which is one of the principal differential diagnoses for dengue, is among the most important causes of death among children under five years of age in Bangladesh.<sup>43</sup> While other febrile illnesses like Japanese encephalitis and leptospirosis also occur they are uncommon in this age group.<sup>44</sup> Therefore, dengue may frequently be misdiagnosed as measles, leading to under-reporting among younger children.

## Sex

The reported sex ratio among hospital and laboratory attendees is between 5.0:1.0 and 1.0:1.0 for males relative to females.<sup>5,36</sup>

However, both secondary dengue infection and DSS have been observed more frequently among females than males.<sup>5,36</sup> These estimates are likely biased due to a sex differential in care seeking. In both rural and urban areas female children are less likely than male children to be taken to facilities,<sup>45,46</sup> and men attend health facilities more commonly than women.<sup>45,47</sup> Therefore, the sex ratio for infection at the population level cannot be inferred due to sampling bias caused by the sex differential in hospital attendance. A recent population-based study reported no sex difference in dengue seroprevalence in Dhaka.<sup>10</sup>

## Clinical presentation of dengue

Clinical presentations during the 2000 and 2002 epidemics were most commonly consistent with WHO defined DF. However, severe dengue was also reported with signs of plasma leakage (oedema, ascites and pleural effusion) and haemorrhage (epistaxis, gingival bleeding, haemoptysis, haematuria and gastrointestinal bleeding).<sup>7,21,48</sup> A study in Dhaka reported thrombocytopaenia (platelet count less than 100 000/mm<sup>3</sup>) in 86.0% of confirmed dengue cases.<sup>21</sup>

Rare outcomes were also observed. A 59-year-old Bangladeshi immigrant living in the UK who visited Dhaka during the epidemic in 2002 developed DHF and subsequently fulminant hepatic failure, ultimately fatal.<sup>49</sup> A single case of vertical transmission of DENV was reported in Dhaka in 2003.<sup>50</sup> The mother became ill at 37 weeks gestation and underwent a caesarean section.<sup>50</sup> The baby developed mild illness, beginning on his third day of life. The mother

had IgG and IgM antibodies to dengue, but in the case of her baby, IgM was absent at day 6 but present at day 12 of illness.<sup>50</sup>

## Receptivity of Bangladesh to dengue

### Demographic profile and urbanisation

Bangladesh is one of the world's most densely populated countries. Over the years 1974 to 2001, population density increased from 484 to 843 people per square kilometre.<sup>51</sup> Current population density is 964 people per square kilometre<sup>52</sup> and there are more than three million births per year.<sup>53</sup> In 2012, 29.0% of Bangladesh's 154.7 million people lived in urban settings; by 2050, 52.2% of Bangladeshis are expected to do so.<sup>54</sup> More than half of the urban population live in the four largest cities: Dhaka, Chittagong, Khulna and Rajshahi, with Dhaka the most populous city in Bangladesh (Figure 4, left). Dhaka City Corporation (DCC), which administers the central part of this megacity, serves a population of 5.9 million in an area of 360.0 square kilometres.

Poor city management with an absence of proper waste disposal, sanitation, drainage systems, and water supply, together with the use of unprotected water reservoirs creates suitable habitats for *Ae. aegypti* and *Ae. albopictus*. Ample mosquito breeding sites, in combination with unrestricted mosquito-human contact due to the absence of window and door screens, enhance transmission. The urban poor, about 35.2% of the total population of the six major cities (Dhaka, Chittagong, Khulna, Rajshahi, Barisal and Sylhet) live in slum areas.<sup>55</sup> The slums are overcrowded settlements without access to piped water<sup>55</sup> and people store water in temporary containers like drums and earthen jars in which *Ae. aegypti* lays eggs.<sup>56</sup>

Given limited data comparing rich and poor populations,<sup>57</sup> we cannot assess whether incidence rates of dengue differ by socio-economic status. However, it is clear that the socio-demographic profile of Bangladesh facilitates dengue transmission.

### Population mobility

People migrate within Bangladesh because of environmental deterioration, economic necessity, conflicts and natural disasters. Movement across borders for business, tourism and for cultural and political reasons is also common. The movement of viraemic persons potentially expands the range for dengue, as does inadvertent transport of infected mosquitoes. The 2000 epidemic was caused by virus importation probably from Thailand, and further introductions are likely to occur in the future.

### Climate and environment

Bangladesh has a hot, humid, tropical monsoon climate. About four-fifths of the mean annual rainfall which ranges from 1527 mm in the west to 4197 mm in the east<sup>58</sup> falls in the monsoon season between June and September. Rainfall fills outdoor artificial containers, which then serve as breeding sites with a subsequent rise in dengue incidence.<sup>59</sup> Mosquito survival is also influenced by rainfall extremes with very low and very high rainfall generally reducing the survival of female *Ae. aegypti*.<sup>60</sup> Low rainfall, however, can also enhance mosquito breeding by encouraging the storage of water in artificial containers, while heavy rainfall can lead to increased human-mosquito contact in

the post-rainfall humid weather by discouraging people from covering themselves. Mean temperature averaged across the country is about 29.0°C during the monsoon with a mean diurnal temperature range of 6.1°C.<sup>61</sup> This is highly suitable for mosquito development and DENV transmission.<sup>62–64</sup> Weather extremes, including drought and flood, associated with the El Niño-Southern Oscillation are frequent. The western part of Bangladesh is relatively dry, and the southern part comparatively warm. Northwestern Bangladesh experiences prolonged droughts, with six severe droughts occurring between 1980 and 2000. In contrast, northeastern Bangladesh is prone to flash floods due to heavy monsoon rainfall. Severe floods inundate about 60.0% of the country every three to five years; three major floods occurred from 1987 to 2000, with the 1998 flood being the most prolonged and geographically extensive, leaving 21 million people homeless. This catastrophic flood associated with a strong La Niña event caused extensive damage to infrastructure, including the water supply, with consequent changes in water storage behaviour.<sup>65,66</sup> The following year also had high rainfall resulting from the moderate La Niña. In 2000, southwestern parts of the country experienced an unprecedented devastating flash flood that probably contributed to increased dengue transmission.

Increases in annual mean temperature of 1.4°C and annual mean precipitation 5.6% above baseline average are projected by 2050.<sup>67</sup> Ensuing increases in severe drought frequency in pre-monsoon due to increased winter (December–February) temperature and high monsoon rainfall may increase the abundance of *Ae. aegypti* and *Ae. albopictus*. In Dhaka, hospitalisation due to dengue fever increased during 2005–2009 with raised river levels following a prolonged low level.<sup>68</sup> Dengue transmission could increase in the future as a consequence of more frequent and prolonged drought in the pre-monsoon period followed by flooding during the monsoon.

It has been projected that an increase of 3.3°C in temperature would result in a 40-fold increase in dengue incidence in Dhaka in 2100 compared to 2010 if no adaptation measures are undertaken and socio-economic conditions remain unchanged.<sup>69</sup>

## Public health strategies and challenges

### Surveillance

Suspected dengue is clinically diagnosed according to national guidelines based on WHO criteria, with probable and confirmed cases requiring positive serological testing and virus isolation, respectively.<sup>70</sup> Reporting of all suspected, probable and confirmed cases to the Directorate General of Health Services has been legally mandated since 2000, but from 2010 only serologically confirmed cases have been reported.<sup>71</sup> The current passive surveillance system only reports patients admitted to hospital (A. Akhter, Directorate General of Health Services, Dhaka, personal communication, 29 January 2015) leading to under-ascertainment of symptomatic dengue cases. Treatment seeking behaviour, which is influenced by gender and socio-economic status, and varies spatially according to the quality and accessibility of health facilities is likely to bias estimation of incidence. Further, diagnosis is not uniform due to the lack of diagnostic facilities at district and sub-district levels.<sup>72</sup> Utilisation of informal health care is also common in rural Bangladesh.<sup>72</sup> Figure 5 shows the steps required for a case to be notified, highlighting the considerable under-reporting inherent in this system. Initially, surveillance was only performed

during the outbreak period starting soon after the advent of the monsoon and continuing until December, but subsequently surveillance has become continuous. The national surveillance system must be strengthened to generate credible incidence data. Information on vector distribution and populations, currently unavailable, is also required.

Public awareness

In response to the 2000 epidemic, the Government of Bangladesh commenced intensive public health campaigns involving media and volunteer organisations, focused on raising awareness of

the signs and symptoms of dengue and increasing community participation in mosquito control.<sup>56</sup> Red Crescent volunteers put up posters and distributed leaflets with preventive advice across Dhaka city, with around 200 000 leaflets printed for distribution across the country.<sup>73</sup> Dhaka City Corporation also launched campaigns to make people aware of the management of stagnant rainwater around houses and this has been continued as an annual activity during the monsoon.

Outbreak detection and response

There is no routine entomological surveillance, however, occasional larval surveys are carried out, particularly during the

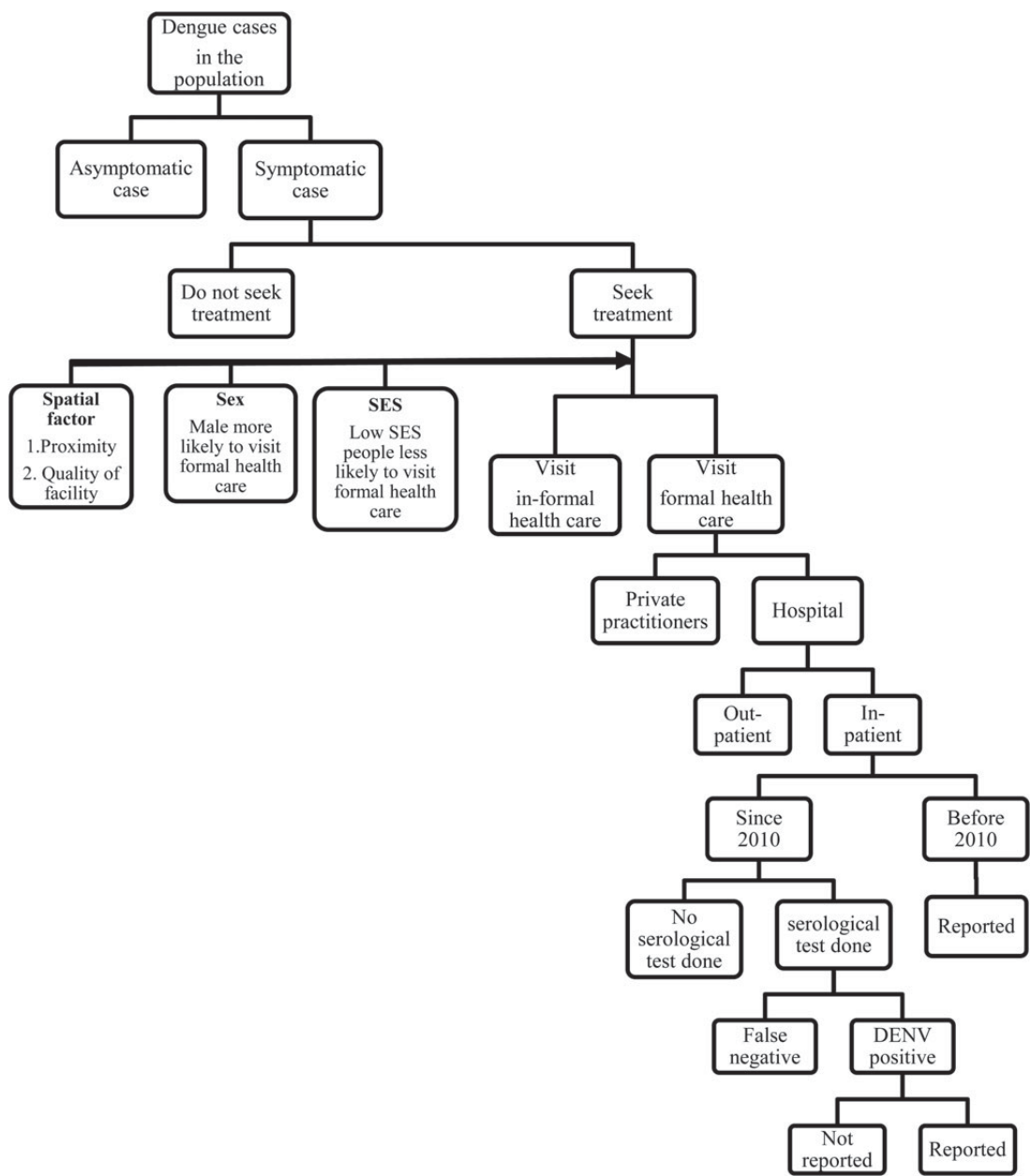


Figure 5. Hierarchy of under-reporting inherent in the hospital-based passive dengue surveillance system of Bangladesh.

monsoon. Hospital admissions are usually used as an indicator of an outbreak with mosquito control including larviciding and adulticiding in response.

Mass indoor residual spraying with DDT was interrupted because of the liberation war in 1971.<sup>74</sup> The incidence of vector-borne diseases increased soon after.<sup>74,75</sup> Limited use of DDT continued until 1994 when the insecticide was banned completely.<sup>74</sup> The withdrawal of DDT spraying likely permitted an increase in *Aedes* populations and consequently the outbreak of dengue in Dhaka in 1999 and the 2000 epidemic.

Currently, larvicides, adulticides, residual sprays, mosquito coils and aerosol sprays are the mainstay of mosquito control in Bangladesh. In the Dhaka City Corporation budget for the 2012–2013 fiscal year 0.6% of the total expenditure was allotted to mosquito control. However, lack of proper monitoring, shortage of field workers and absence of timely action against mosquitoes hampers mosquito control efforts, and control is irregular or non-existent in many districts.<sup>76,77</sup> High out-of-pocket health expenditure (96.6% of private expenditure on health in 2012) in Bangladesh causes financial hardship and limits use of preventive measures such as mosquito coils, aerosol sprays, bed nets, and mosquito repellents. Insufficient facilities (six hospital beds per 10 000 population) along with inadequate medical workforce (four doctors and two nursing and midwifery personnel per 10 000 population) hinder epidemic responsiveness.<sup>78</sup>

## Conclusions

Although introduction of a Thai strain was the probable cause of the 2000 epidemic, a combination of socio-demographic and climatic factors ignited and sustained endemic transmission afterwards. Despite no significant additional control measures having been introduced since the largest reported epidemic in 2002, the reported number of dengue cases has progressively declined, in contrast to Indonesia, Thailand, Sri Lanka and Timor-Leste. Although increased herd immunity and greater public knowledge with consequent reduction of peri-domestic *Ae. aegypti* and *Ae. albopictus* breeding may have caused some decline in incidence, the current passive hospital-based surveillance data is likely to grossly underestimate disease occurrence. Biases in case reporting are also likely, as treatment seeking behaviour in Bangladesh is significantly influenced by gender, socio-economic status, location and accessibility of health facilities. Population-based serosurvey and dengue burden studies also indicate substantial underestimation inherent in national surveillance estimates. Changes in reporting practices since 2010 requiring serological confirmation may have further influenced this trend. Although serological confirmation reduces the incorrect reporting of other diseases as dengue, it also reduces the likelihood of diagnosis due to limited access to laboratory facilities and the cost of testing.

In the absence of active intervention, epidemics of severe dengue may occur in the future. Changes in the human population, the virus, the vectors and the environment all contribute to uncertainty regarding future risks. While predicted changes in climate, including higher monsoon rainfall and more frequent severe drought increase the potential for epidemics, social factors are also crucial. Greater economic inequity, increased movement of people and poor planning leading to overcrowding of big cities

will all exacerbate disease risk. High fertility resulting in an increased immunologically naive proportion of the population will also increase incidence. Therefore, despite the apparent decline in reported case numbers, very probably an artefact of the surveillance system, complacency in Bangladesh towards dengue is misplaced. Passive public health surveillance and current control activities are insufficient to address future risk. Strengthening these surveillance and control programs as well as striving towards greater understanding of changes in risk with societal and environmental changes is crucial to a national dengue strategy for Bangladesh.

**Authors' contributions:** SS EV KG and DH conceived the study; SS carried out the literature review, analysis and interpretation of the data. SS drafted the manuscript; EV KG and DH critically revised the manuscript for intellectual content. All authors read and approved the final manuscript. DH is guarantor of the paper.

**Acknowledgements:** The authors would like to thank Ayesha Akhter, In-charge, National Health Crisis Management Centre and Control room, Directorate General of Health Services, Dhaka for generously providing information on the national dengue surveillance system.

**Funding:** The first author (SS) was supported by The Australian National University Higher Degree Research Merit Scholarship.

**Competing interests:** None declared.

**Ethical approval:** The study was approved by The Australian National University Human Research Ethics Committee.

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# Chapter 4

## Paper 2: Factors influencing dengue incidence in Bangladesh

Sharmin S, Glass K, Viennet E and Harley D. Interaction of mean temperature and daily fluctuation influences dengue incidence in Dhaka, Bangladesh. *PLoS Negl Trop Dis*. 2015; 9(7): e0003901.

## **Summary of this chapter**

Daily fluctuation in temperature, in addition to mean temperature, strongly influences vector and virus biology in laboratory experiments. The influence of short-term temperature fluctuations is a largely unexplored mechanism via which climate change effects on dengue incidence can be explained. In this chapter, I present an analysis of the influence of fluctuations in temperature on dengue incidence in Dhaka, Bangladesh, using epidemiological, meteorological, and demographic data over the period 2000-2009. Dhaka's climate is characterised by strong seasonality and heavy monsoon rainfall which is partly influenced by the ENSO phases. The model presented here is adjusted to examine whether ENSO influences dengue incidence through the concomitant anomalies in weather. This chapter contributes to answering the research question: "What are the factors that significantly influence dengue incidence in Bangladesh?" Before this paper there were no field studies of the influence of temperature fluctuations on dengue incidence in a tropical climate.

RESEARCH ARTICLE

# Interaction of Mean Temperature and Daily Fluctuation Influences Dengue Incidence in Dhaka, Bangladesh

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## OPEN ACCESS

**Citation:** Sharmin S, Glass K, Viennet E, Harley D (2015) Interaction of Mean Temperature and Daily Fluctuation Influences Dengue Incidence in Dhaka, Bangladesh. *PLoS Negl Trop Dis* 9(7): e0003901. doi:10.1371/journal.pntd.0003901

**Editor:** Matthew Kasper, Armed Forces Health Surveillance Center, UNITED STATES

**Received:** April 10, 2015

**Accepted:** June 11, 2015

**Published:** July 10, 2015

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**Data Availability Statement:** These data are the property of the Directorate General of Health Services, Dhaka, Bangladesh and consequently may not be uploaded to this site. However, data are available from the owner (email: [controlroomdghs@yahoo.com](mailto:controlroomdghs@yahoo.com)) to interested researchers.

**Funding:** The first author (SS) was supported by The Australian National University Higher Degree Research Merit Scholarship (<http://www.anu.edu.au/students/scholarships-support/anu-university-research-scholarships>). The funder had no role in

## Abstract

Local weather influences the transmission of the dengue virus. Most studies analyzing the relationship between dengue and climate are based on relatively coarse aggregate measures such as mean temperature. Here, we include both mean temperature and daily fluctuations in temperature in modelling dengue transmission in Dhaka, the capital of Bangladesh. We used a negative binomial generalized linear model, adjusted for rainfall, anomalies in sea surface temperature (an index for El Niño-Southern Oscillation), population density, the number of dengue cases in the previous month, and the long term temporal trend in dengue incidence. In addition to the significant associations of mean temperature and temperature fluctuation with dengue incidence, we found interaction of mean and temperature fluctuation significantly influences disease transmission at a lag of one month. High mean temperature with low fluctuation increases dengue incidence one month later. Besides temperature, dengue incidence was also influenced by sea surface temperature anomalies in the current and previous month, presumably as a consequence of concomitant anomalies in the annual rainfall cycle. Population density exerted a significant positive influence on dengue incidence indicating increasing risk of dengue in over-populated Dhaka. Understanding these complex relationships between climate, population, and dengue incidence will help inform outbreak prediction and control.

## Author Summary

The sensitivity of mosquito vector and dengue virus biology to diurnal temperature variability has been established, but this study is the first analyzing these relations with dengue occurrence. We show that Dhaka's tropical hot monsoon climate and small variation in daily temperature enhance dengue transmission one month later. Large-scale climatic events like El Niño-Southern Oscillation and increasing population density of Dhaka also increase incidence. Our results therefore enable us to accurately estimate dengue transmission dynamics in densely populated areas that are also vulnerable to global warming by considering diurnal variability. Our approach reduces the chance of overestimating the

study design, data collection and analysis, decision to publish, or preparation of the manuscript.

**Competing Interests:** The authors have declared that no competing interests exist.

effect of increasing temperature on dengue transmission intensity with the ultimate goal of outbreak prediction and control.

## Introduction

Dengue virus (DENV) [1] transmission occurs in more than 100 countries; however, the burden of dengue is not evenly distributed. Approximately half of the global population at risk of acquiring dengue infection resides in the South-East Asia Region of the World Health Organization [2], a region characterized by strong seasonal weather variation and heavy monsoon rainfall. This reflects the influence of local weather, particularly temperature and rainfall, on the transmission of DENV by *Aedes* mosquitoes. Higher temperature, for example, shortens mosquito development time [3], increases the frequency of blood feeding presumably by decreasing body size [4, 5], and reduces the extrinsic incubation period of DENV within mosquitoes [6]. However, transmission of DENV is influenced not only by average temperature, but also by diurnal temperature range (DTR, the difference between daily maximum and minimum temperature). Temperature-dependent empirical and mathematical experiments show that temperature fluctuation influences vectorial capacity of *Aedes aegypti*, the principal mosquito vector of DENV, via biting rate, DENV transmission probability, extrinsic incubation period, and vector mortality rate [7–10]. At high mean temperatures, vectorial capacity increases with narrow daily temperature variation [7–9]. At low mean temperatures, the relationship between DTR and vectorial capacity is reversed [7–10]. Temperatures above 30°C reduce survival of adult *Ae. aegypti* [11] as does either very low or very high rainfall [12]. The positive relationship between rainfall and dengue incidence has been observed in several locations [13–15]. Seemingly paradoxical is the observation that the incidence of dengue increases in the dry season in some locations [16]. Large scale climatic events, such as the Southern Oscillation, resulting from the interplay of large scale ocean and atmospheric circulation processes in the equatorial Pacific Ocean have been identified as a remote driver of inter-annual weather variability across the globe. The warm and cold phases of the Southern Oscillation, El Niño and La Niña, respectively, are known to influence local temperature and rainfall and hence year-to-year variations in dengue incidence [13, 17, 18]. Socio-demographic and economic factors also influence dengue incidence. While the population at risk of dengue is likely to rise with increasing population, economic development would be expected to reduce risk [19].

Bangladesh, a member country of the World Health Organization South-East Asia Region experienced its first epidemic of dengue fever in 2000 after more than three decades of sporadic dengue [20]. Dengue is highly seasonal in Bangladesh with increased incidence during the monsoon. From 2000 to 2009, cases have been reported from 29 of the 64 Bangladeshi districts, with around 91.0% from the capital, Dhaka [21]. Since 2010 very few cases have been notified from districts other than Dhaka [21] presumably because of a change in reporting criteria requiring confirmatory laboratory diagnosis.

Studies of dengue in Bangladesh before ours have not considered daily temperature variation [22, 23]. We present an analysis of the influence of daily temperature variation on the transmission of dengue adjusted for rainfall and population density, using a monthly dengue case time-series over 10 years from Dhaka. We also considered anomalies in sea surface temperature (SSTA), an index for El Niño-Southern Oscillation (ENSO) that is associated with extreme weather in Bangladesh and has not been included in other studies. Analyses such as ours are critical for understanding the associations between weather, population, and dengue incidence and will allow the development of a reliable dengue early warning system.

## Materials and Methods

### Ethics Statement

The study was approved by The Australian National University Human Research Ethics Committee. The national surveillance data of dengue fever cases was anonymized.

### Study Area

Dhaka district, comprising Dhaka Metropolitan area (DMA) and adjacent sub-districts, is a 1,464 km<sup>2</sup> area near the center of Bangladesh. Of the 64 districts this is the most densely populated, currently with 8,229 people per square kilometer. Over the years 2001 to 2011, there was a 41.0% increase in the population density of Dhaka [24]. More than 37.0% of the population of DMA live in slums with a population density of 220,246 people per square kilometer [25]. Slums have no access to piped water and temporary containers like drums and earthen jars are commonly used to store water in which *Ae. aegypti* lays eggs [26]. Inadequate supplies of piped water and an absence of proper waste management in most locations of Dhaka result in abundant indoor and outdoor mosquito breeding sites. Both *Ae. aegypti* and *Aedes albopictus*, the latter a secondary vector of dengue, were observed in Dhaka during the 2000 epidemic [27]. Unscreened doors and windows permit mosquito entry to dwellings.

Dhaka has a hot and humid tropical climate, with an average temperature of approximately 25°C, which nearly always permits mosquito development and DENV transmission. Rainfall is highly seasonal, with the wettest period (June to September) occurring during the warmest months. About 80.0% of the annual rainfall of 2,000 mm falls during the monsoon. Rainfall in Bangladesh is partly influenced by the Southern Oscillation with El Niño years usually associated with less than average monsoon rainfall while the opposite has been observed in La Niña years. However, the influence of the Southern Oscillation on monsoon rainfall is not linear and is inconsistent, as observed in the moderate El Niño years causing flooding while some La Niña events during the monsoon preceded by El Niño are associated with reduced monsoon rainfall in Bangladesh [28, 29].

### Data Set

Monthly dengue cases for Dhaka district, from January 2000 to December 2009, were obtained from the Directorate General of Health Services. This time period was chosen to avoid the influence of the change in reporting practice started in 2010.

The daily maximum, minimum, and mean temperatures (°C), relative humidity (%), and rainfall (mm) data for Dhaka were collected from the Bangladesh Meteorological Department. A single missing value for maximum temperature was replaced by linear interpolation. Diurnal temperature range was derived as the difference between maximum and minimum daily temperature. Monthly means of these climatic variables were calculated from the daily records. A monthly time series of SSTA over the Niño 3.4 region was obtained from the United States National Oceanic and Atmospheric Administration Climate Prediction Center (<http://www.cpc.ncep.noaa.gov/data/indices/ersst3b.nino.mth.81-10.ascii>). The Niño 3.4 index was used because of its correlation with Indian Ocean region monsoon rainfall. An increase (decrease) of >0.5°C (<-0.5°C) in three-month moving average of SSTA is referred to as an El Niño (a La Niña) event.

Population estimates were extracted from the 1991, 2001, and 2011 census data (there was no census taken between these years) of the Bangladesh Bureau of Statistics. Linear interpolation was used to calculate the monthly population for each of the years between 2000 and 2009.

The population density (people/km<sup>2</sup>) for Dhaka was estimated by dividing the district population size by the area (km<sup>2</sup>).

## Analyses

To examine temporal patterns over the study period, monthly dengue cases and climatic averages were plotted over the 10-year period. To display seasonal patterns, monthly averages of mean temperature, DTR, and rainfall, and monthly numbers of total dengue cases over the 10 years were aggregated and plotted by month.

Overall correlation between dengue cases and climatic variables (mean monthly temperature, mean monthly DTR, mean monthly relative humidity, mean monthly rainfall, and monthly SSTA) were examined using Spearman's rank correlation test. To avoid multicollinearity arising from correlated variables, the final set of candidate variables was restricted to those with pair-wise correlations of  $\leq 0.8$ .

Cross-correlation functions of dengue cases with each of the climatic variables were then estimated to investigate their lagged effects on dengue incidence ( $p \leq 0.05$ ). Time lags were included to account for the influence of climatic variables on the development, maturation, and survival of the vector (*Aedes* mosquitoes) as well as the extrinsic incubation period of DENV in the vector and the intrinsic incubation period in the human host. Lags of up to three months were considered for all weather variables, with SSTA also considered at a lag of four months.

The counts of dengue cases were then fitted by a generalized linear model (GLM) with negative binomial distribution to allow for overdispersion in dengue counts. The population of Dhaka was added as an offset to the model on a logarithmic scale to adjust for population size. Population density was also included in the model to account for the potential influences of associated socio-demographic changes on dengue transmission in Dhaka.

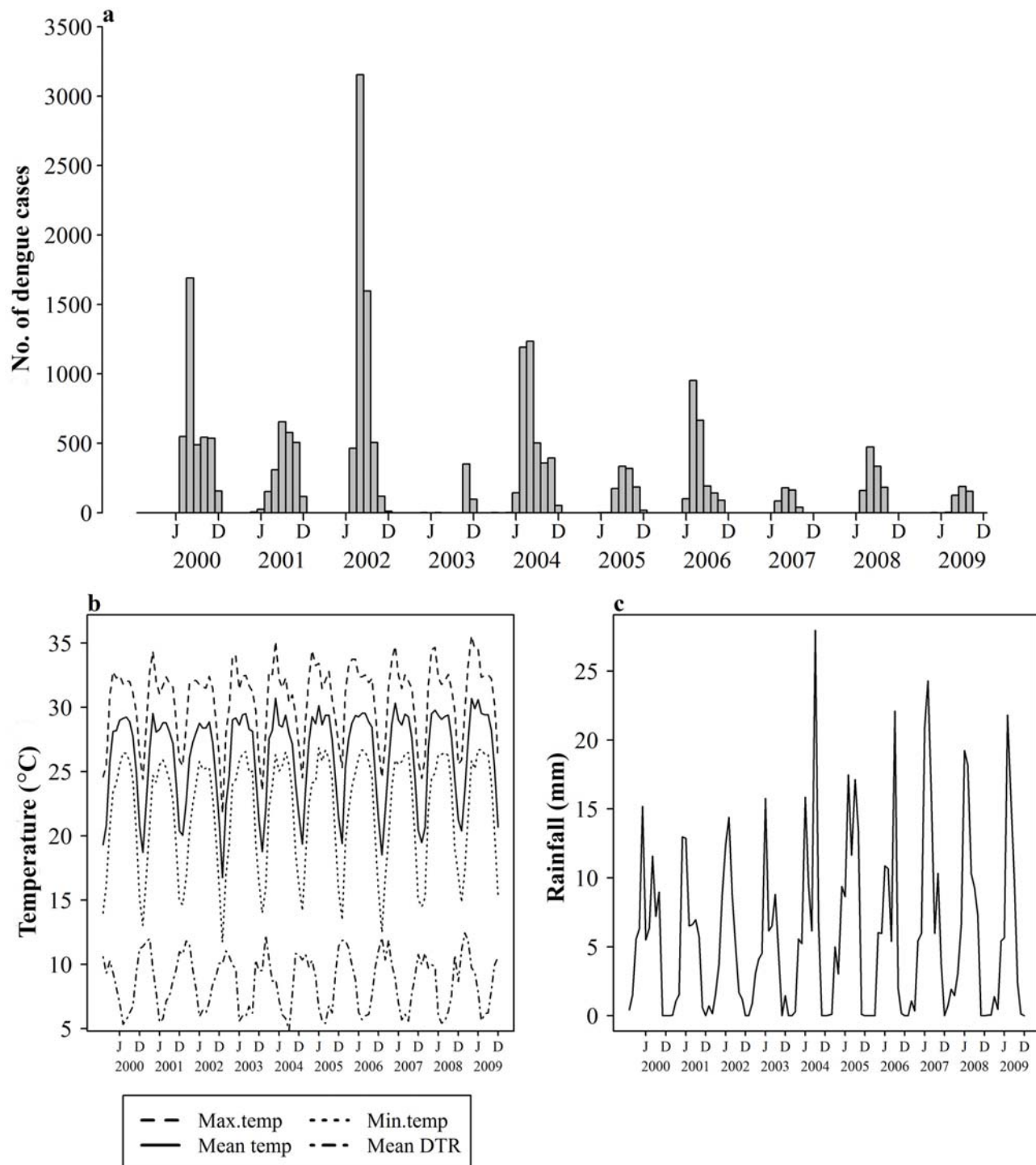
An indicator variable for outbreak months was added to prevent occasional extreme values from distorting the analyses. A month with the number of dengue cases exceeding the 10-year mean plus two standard deviations was defined as an outbreak month. To account for the long term trend in dengue incidence over time, an indicator variable for year was incorporated in the model. An autoregressive term at order 1 was also included to allow for autocorrelation in monthly numbers of dengue cases. To determine whether seasonal variation had any influence on dengue incidence, a categorical variable for winter (December–February), pre-monsoon (March–May), monsoon (June–September), and post-monsoon (October–November) was also considered.

The analyses were performed using STATA 13.1 (StataCorp., Texas, USA) and figures were drawn using RStudio (R development Core Team, 2015).

## Results

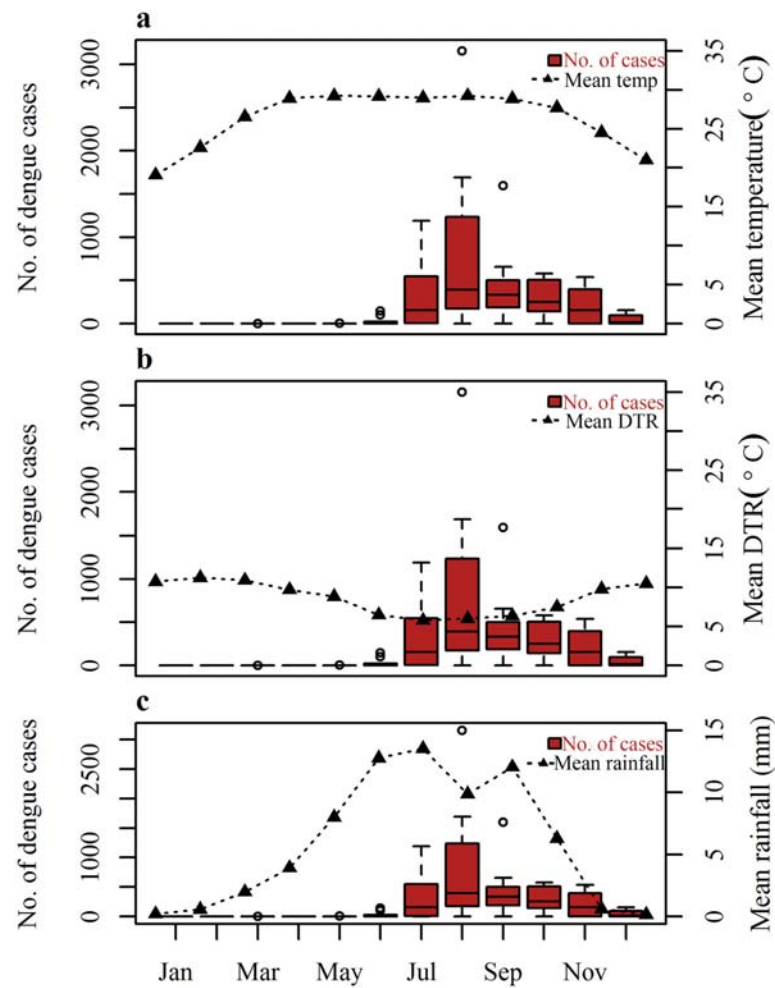
Inter-annual and seasonal variations for dengue and weather over the period 2000–2009 are presented (Figs 1 and 2). The number of dengue cases during winter is low and starts to increase from June (Fig 2) with the advent of the monsoon with considerable annual variation (Fig 1). The peak comes one month after the initial rainfall peak in July and starts declining afterwards. Temperature reaches its peak in April and plateaus until October when it drops (Fig 2).

Because of the high correlation with mean temperature and DTR, relative humidity was excluded at the initial stage of model formulation. Consideration of both temperature and rainfall was, however, expected to minimize the potential confounding effect of relative humidity on dengue incidence. The categorical variable for season was also subsequently removed



**Fig 1. Time series of dengue cases and meteorological variables from Dhaka (2000–2009).** a) Monthly dengue cases b) Average maximum, mean, and minimum monthly temperatures (°C) and mean monthly DTR (°C) (top to bottom) c) Mean monthly rainfall (mm).

doi:10.1371/journal.pntd.0003901.g001



**Fig 2. Boxplots of the monthly distribution of total dengue cases during 2000–2009 and a) Mean monthly temperature (°C) b) Mean monthly DTR (°C) c) Mean monthly rainfall (mm) for Dhaka, averaged for each month over 2000–2009.** The boxplots display the median value as a line inside the box, the 25th and 75th percentile by the box, the range of values by the whiskers outside the box, and potential outliers by unfilled circles.

doi:10.1371/journal.pntd.0003901.g002

because it did not improve model fit. Therefore, the model finally fitted is as follows:

$$y_t \sim \text{NegBin}(\mu_t, \theta)$$

$$\log(\mu_t) = \alpha + \sum_{j=0}^3 \beta_{1j} T_{jt} + \sum_{j=0}^3 \beta_{2j} DTR_{jt} + \sum_{j=0}^3 \beta_{3j} (T_{jt} \times DTR_{jt}) + \sum_{j=0}^3 \beta_{4j} R_{jt} + \sum_{j=0}^4 \beta_{5j} SSTA_{jt} + \beta_6 \text{Popden}_t + \text{outbreak} + \text{year} + y_{t-1} + \log(\text{Population}) + \varepsilon_t \quad (1)$$

where  $y_t$  is the dengue count in Dhaka in month  $t$  ( $t = 1, \dots, 120$ );  $\mu_t$  is the corresponding mean dengue count;  $T$ ,  $DTR$ ,  $R$ , and  $SSTA$  are the mean monthly temperature (°C), mean monthly

diurnal temperature range ( $^{\circ}\text{C}$ ), mean monthly rainfall (mm), and monthly sea surface temperature anomaly respectively; ( $T \times \text{DTR}$ ) represents the interaction between mean monthly temperature and mean monthly DTR;  $j = 0, \dots, 4$  represent the time lag periods in months; *outbreak* is the categorical variable for outbreak months; *year* represents time trend;  $y_{t-1}$  is the dengue count of previous month; and  $\epsilon_t$  is the error term.

[Table 1](#) shows estimates of the significant covariates from model (1). Mean temperature, DTR, and the interaction between these two variables are all significant predictors of dengue incidence at a lag of one month. However, the opposing directions of main and interaction effects indicate a negative synergy between mean temperature and DTR. Therefore, dengue incidence increases with higher temperature and lower DTR or lower temperature and higher DTR in the previous month but decreases when both are either high or low.

Rainfall at lag one and two months was found to be positively associated with dengue incidence, suggesting that increased incidence of dengue in a given month is associated with higher rainfall during the previous two months.

The negative effect of SSTA on dengue incidence at lag zero month indicates that the incidence goes up with increasing negative values of the SSTA in the current month, while the inverse relationship was observed at lag of one month.

Increasing population density, as anticipated, increases dengue incidence.

To investigate how SSTA influences climatic anomalies in Dhaka, standardized anomalies of temperature, relative humidity ([S1 Fig](#)), and rainfall were calculated and plotted with SSTA over the study period ([Fig 3](#)). Simple linear regression of temperature, relative humidity ([S1 Fig](#)), and rainfall anomaly on SSTA at lag of zero and one month revealed a weak negative correlation between rainfall and SSTA ([Fig 4](#)) even though the relationship is not temporally consistent ([Fig 3](#)) presumably due to a non-linear relationship between them.

Model diagnostics were performed as follows. Firstly, a model was run without the interaction terms and compared with model (1). The likelihood ratio test confirmed that the addition of interaction terms resulted in a significantly improved fit compared to the model without interactions ( $p < 0.000$ ). The Pearson dispersion statistic (0.98) also provided evidence for the goodness-of-fit of the model (1). Secondly, residual analyses were performed to ensure that the model provided an adequate fit to the data. Serial autocorrelation of the residuals was checked by examining a time plot and a partial autocorrelation plot of the residuals ([S2](#) and [S3 Figs](#)). In addition, observed vs fitted plot of dengue cases was examined ([S4 Fig](#)).

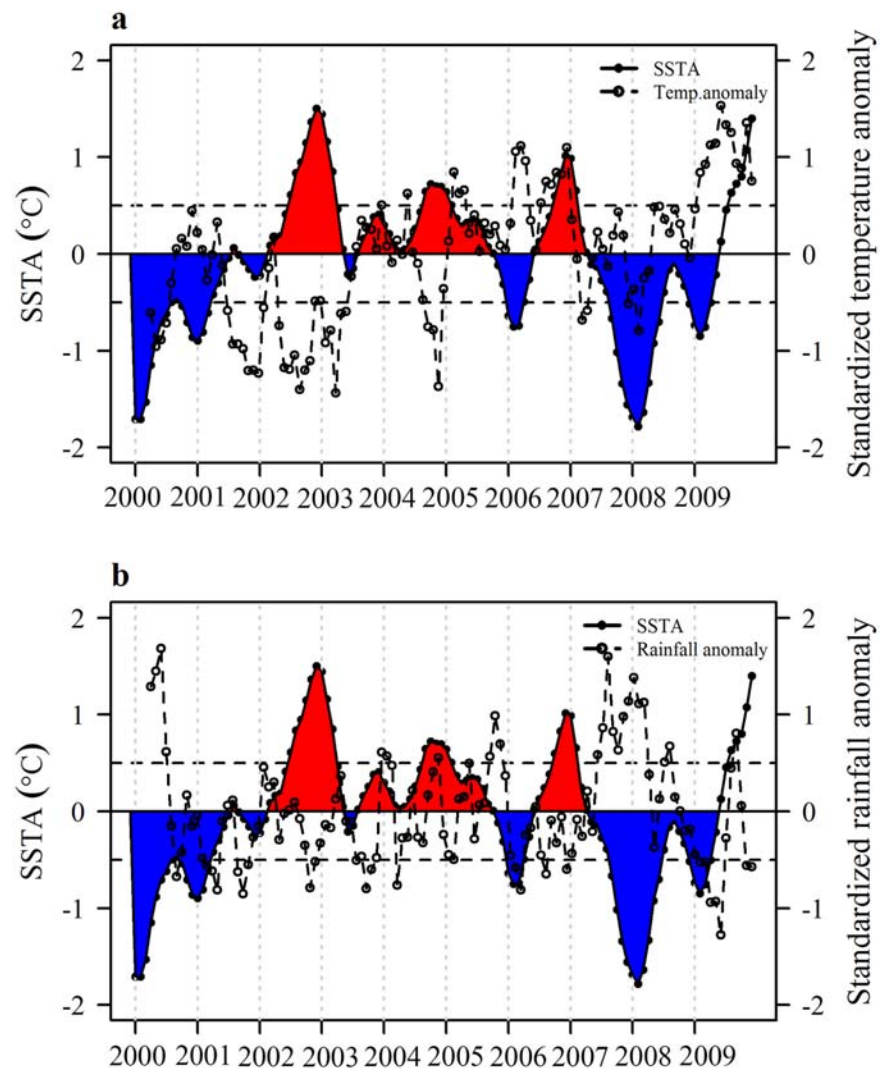
**Table 1. Parameter estimates for significant covariates.**

| Variable                | Coefficient estimate | 95% Confidence Interval |
|-------------------------|----------------------|-------------------------|
| Temperature lag 1       | 6.07**               | 3.38, 8.67              |
| DTR lag 1               | 15.57**              | 8.03, 22.85             |
| (Temperature*DTR) lag 1 | -0.56**              | -0.81, -0.29            |
| Rainfall lag 1          | 0.14**               | 0.04, 0.23              |
| Rainfall lag 2          | 0.17**               | 0.07, 0.28              |
| SSTA lag 0              | -3.37**              | -5.22, -1.51            |
| SSTA lag 1              | 2.63*                | 0.16, 5.09              |
| Popden                  | 0.05*                | 0.01, 0.09              |

\* Significant at  $p < 0.05$ ,

\*\* Significant at  $p < 0.01$ .

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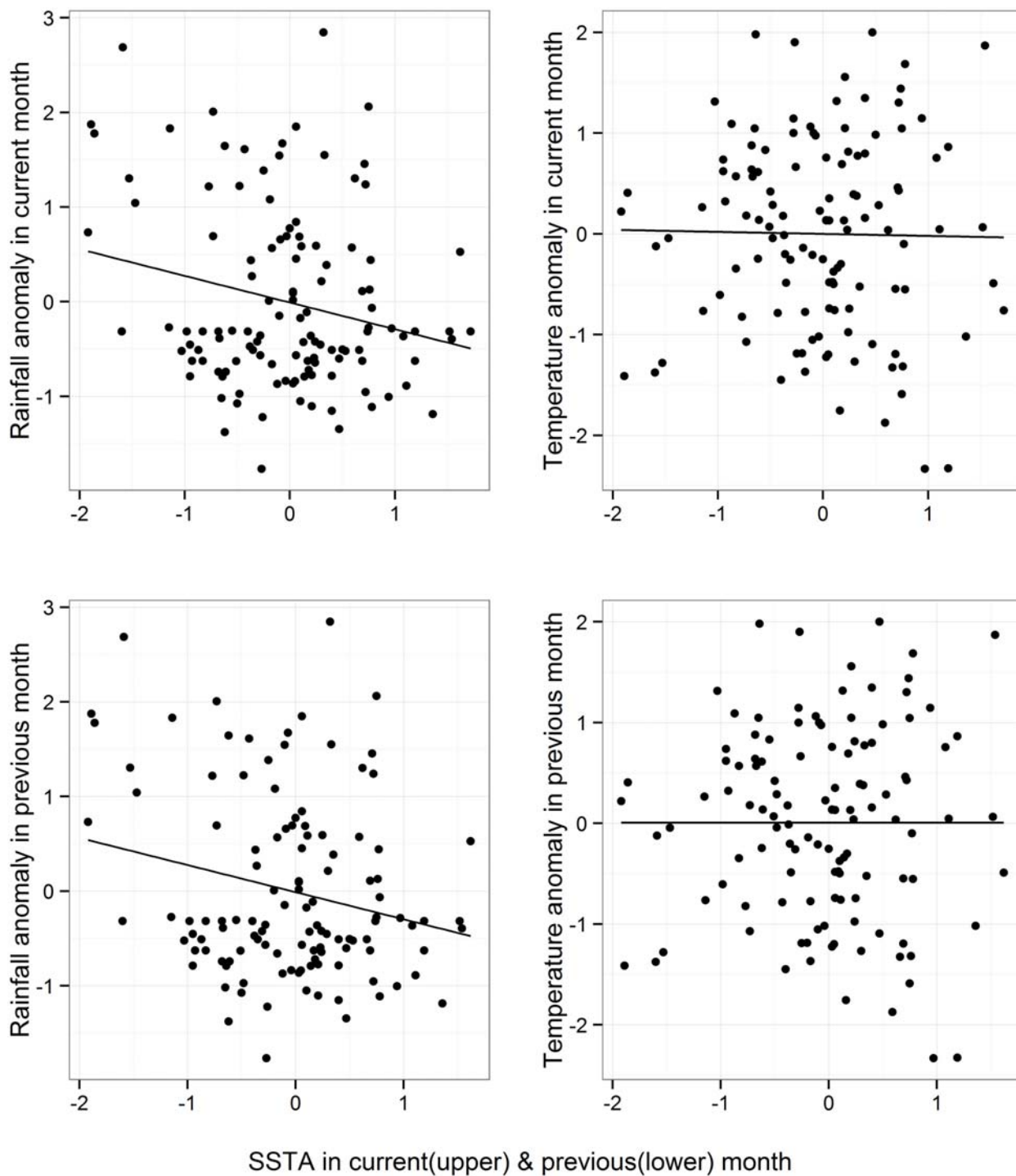


**Fig 3. Three-month moving average plot of SSTA (°C) with standardized anomalies of a) mean monthly temperature and b) mean monthly rainfall.** Red (Blue) filled segments of the SSTA plot that are above (below) 0.5°C (-0.5°C) represent an El Niño (a La Niña) event.

doi:10.1371/journal.pntd.0003901.g003

## Discussion

It is well established that temperature influences vector and virus biology and therefore dengue transmission. Monthly changes in average temperature have been reported to be positively associated with dengue transmission in Puerto Rico [30]. In addition to average temperature, temperature fluctuations also have an impact. Large fluctuation around warmer temperature reduces transmission whereas around cooler temperature this speeds up the process and vice versa [7, 8, 10]. However, studies of climate and dengue usually ignore diurnal temperature variation. We found that dengue incidence in Dhaka was significantly influenced by mean temperature, DTR, and their synergistic effect, after adjusting for rainfall, anomalies in sea surface temperature, population density, autoregression and the long term temporal trend in dengue



**Fig 4. Scatterplot of standardized anomalies of mean monthly rainfall and mean monthly temperature versus SSTA (°C) in current and previous months.** The solid line shows the “best-fit” linear regression line.

doi:10.1371/journal.pntd.0003901.g004

incidence. Although mean temperature and DTR were positively associated with dengue incidence, the opposing direction of their interaction term suggested a negative synergy between these two variables. This indicates that although increased mean temperature and reduced DTR or reduced mean temperature and increased DTR increase dengue incidence one month later, an increase or decrease in both lessen dengue incidence. This is consistent with studies showing a positive association between DTR and dengue at low temperatures and a negative association at high temperatures [7, 8, 10]. Use of mean temperature alone in predicting dengue outbreaks will therefore fail to capture the full complexity of the relationship between temperature and dengue transmission.

We demonstrated that increased incidence of dengue in Dhaka was associated with an increase in rainfall in the previous two months. However, an earlier study in Dhaka identified a significant positive association only at lag of two months [22]. The effect of rainfall on *Ae. aegypti* breeding is lessened by the species' egg laying in artificial containers filled with water by humans. But *Ae. albopictus* has also been found in Dhaka [31]. Its dependence on rain-fed outdoor artificial containers as larval habitats might explain the positive association between rainfall and dengue incidence. Such a relationship has also been reported in other countries [13, 32]. In Puerto Rico, rainfall has been proposed to have caused increases in dengue incidence by increasing *Ae. aegypti* density, egg laying in water storage containers and discarded tires [33].

In Thailand, monthly dengue incidence and epidemics of dengue have been associated with ENSO, which is believed to cause changes in temperature and relative humidity [34]. At time lags of one to 11 months, both epidemics and monthly cases are correlated with El Niño, which is associated with higher temperature and in some places with lower relative humidity [34]. A multivariate ENSO index, lagged at one to six months, alone explains a maximum 22% of the variations in monthly dengue cases [34]. An increase in the number of dengue cases following El Niño was also observed in Mexico, French Guiana, Indonesia, Colombia, and Surinam [13, 18]. The role of ENSO in the inter-annual variability of monsoon rainfall in Bangladesh has been examined demonstrating that El Niño is generally associated with lower rainfall, whereas La Niña and sometimes moderate El Niño generate higher rainfall [35]. However, the relationship is not consistent over time and ENSO is only partially responsible for the rainfall anomalies in Bangladesh. Our study found a negative effect of SSTA on current dengue incidence together with a positive effect at a lag of one month. Possible explanations for the negative association with current SSTA could be that the dry weather resulting from a strong El Niño or the heavy rainfall associated with a moderate El Niño both reduce adult mosquito survival [11, 12] and thereby reduce DENV transmission. Heavy rainfall, on the other hand, could increase transmission because people do not cover themselves in the post-rainfall humid weather resulting in increased human-mosquito contact. The positive effect of SSTA on dengue incidence at a lag of one month is biologically plausible because moderate rainfall is needed for mosquito development, and is also consistent with our findings of a positive influence of rainfall on dengue transmission at a lag of one month. However, heavy rainfall washes away mosquito larvae reducing vector numbers thereby transmission in the following month. Consideration of the non-linear influence of ENSO on rainfall may provide a richer insight into the relationship between dengue and SSTA.

Socio-demographic and economic factors, as well as climate, powerfully influence dengue incidence. A study projects the population at risk of dengue in 2050 under global climate change considering gross domestic product per capita (GDPpc) as an indicator of socio-economic development [19]. The study reports 5.0% and 4.0% increases in the population at risk of dengue in 2050 compared to the baseline risk population in 2000 considering only the projected increase in population and the projected changes in both climate and GDPpc,

respectively. Positive but non-significant effects of population growth on dengue cases have also been reported in Mexico [13]. In our study in Dhaka population density was used as a proxy for socio-demographic factors and was found to be positively associated with dengue incidence.

The strength of the present study is that we considered both small and large-scale climatic influences on dengue incidence along with the interaction between mean temperature and DTR and included population density in the model as a proxy for socio-demographic changes over time. However, while we demonstrated significant associations between temperature and rainfall with dengue transmission we did not model non-linear relationships, and we excluded relative humidity from our model due to its strong correlation with mean temperature and DTR. We used months as our temporal unit of study because daily data on dengue incidence were not available. As a consequence, short-scale influences of climatic parameters on dengue incidence may not be fully captured by our model, and lag effects cannot be determined at a fine time-scale. Another limitation of the model used here is that it did not allow for under-reporting from passive surveillance data or possible changes in the rate of under-reporting. However, inclusion of a temporal trend variable in the model may indirectly capture variation in the rate of under-reporting.

In conclusion, our findings indicate that the association between weather and dengue transmission is complex, which is further confounded by socio-demographic factors like population density. Models designed for forecasting should account for this complexity in order to minimize the risk of overestimation in relation to increasing mean temperature, thereby optimizing resource allocation in tropical overpopulated countries with limited resources.

## Supporting Information

**S1 Fig. a) Three-month moving average plot of SSTA (°C) with standardized anomalies of mean monthly relative humidity. Red (Blue) filled segments of the SSTA plot that are above (below) 0.5°C (-0.5°C) represent an El Niño (a La Niña) event b) Scatterplot of standardized anomalies of mean monthly relative humidity versus SSTA (°C) in current month.** The solid line shows the “best-fit” linear regression line.  
(TIF)

**S2 Fig. Partial autocorrelation plot of Pearson residuals.**  
(TIF)

**S3 Fig. Time series plot of Pearson residuals.**  
(TIFF)

**S4 Fig. Observed vs fitted plot of dengue cases.**  
(TIFF)

## Acknowledgments

We thank Ayesha Akhter, In-charge, National Health Crisis Management Centre and Control room, Directorate General of Health Services, Dhaka for generously providing dengue surveillance data.

## Author Contributions

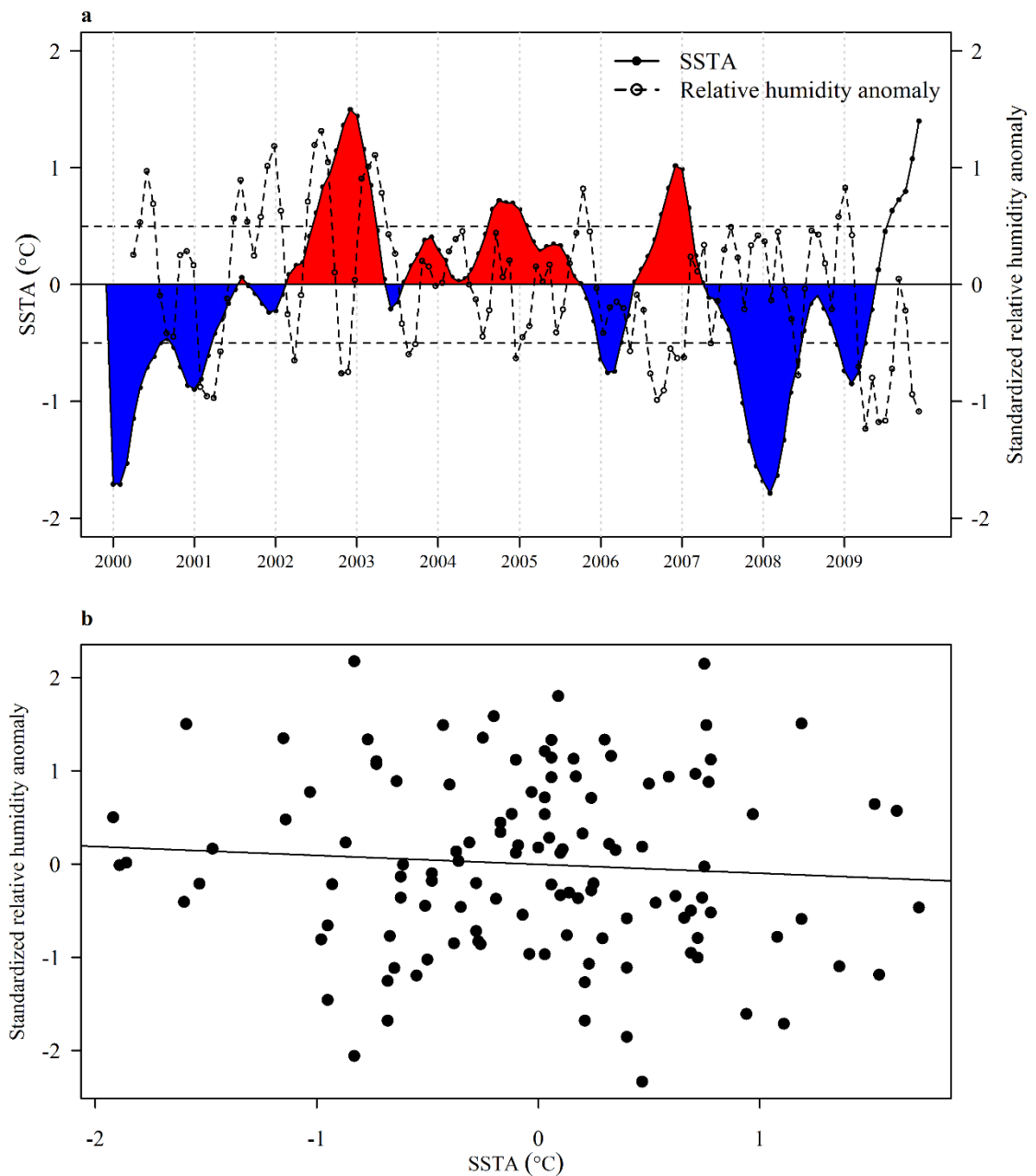
Conceived and designed the experiments: SS KG EV DH. Analyzed the data: SS. Wrote the paper: SS KG EV DH.

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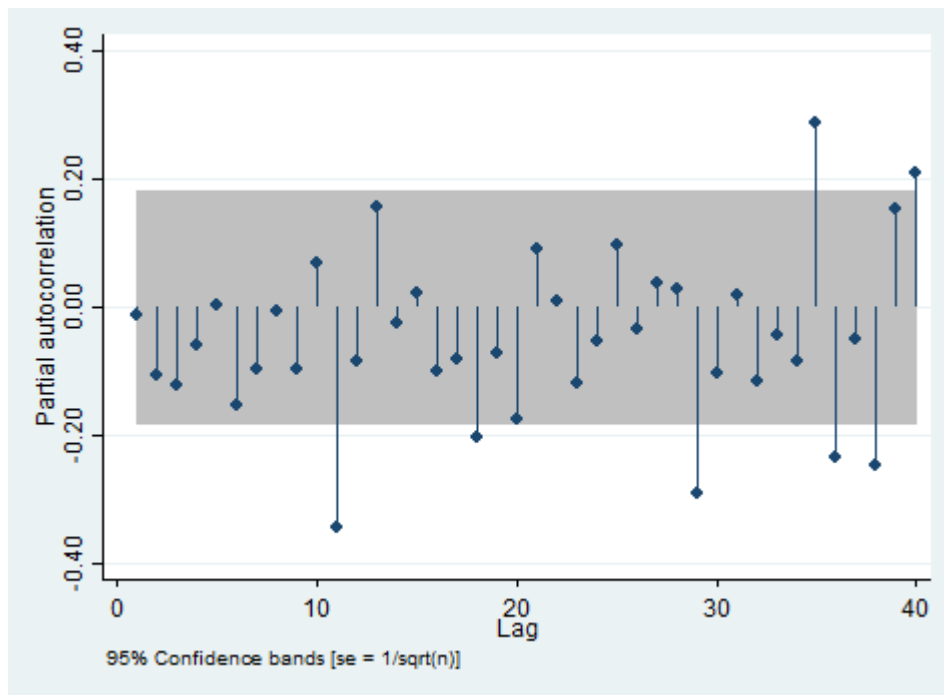
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## Supporting Information



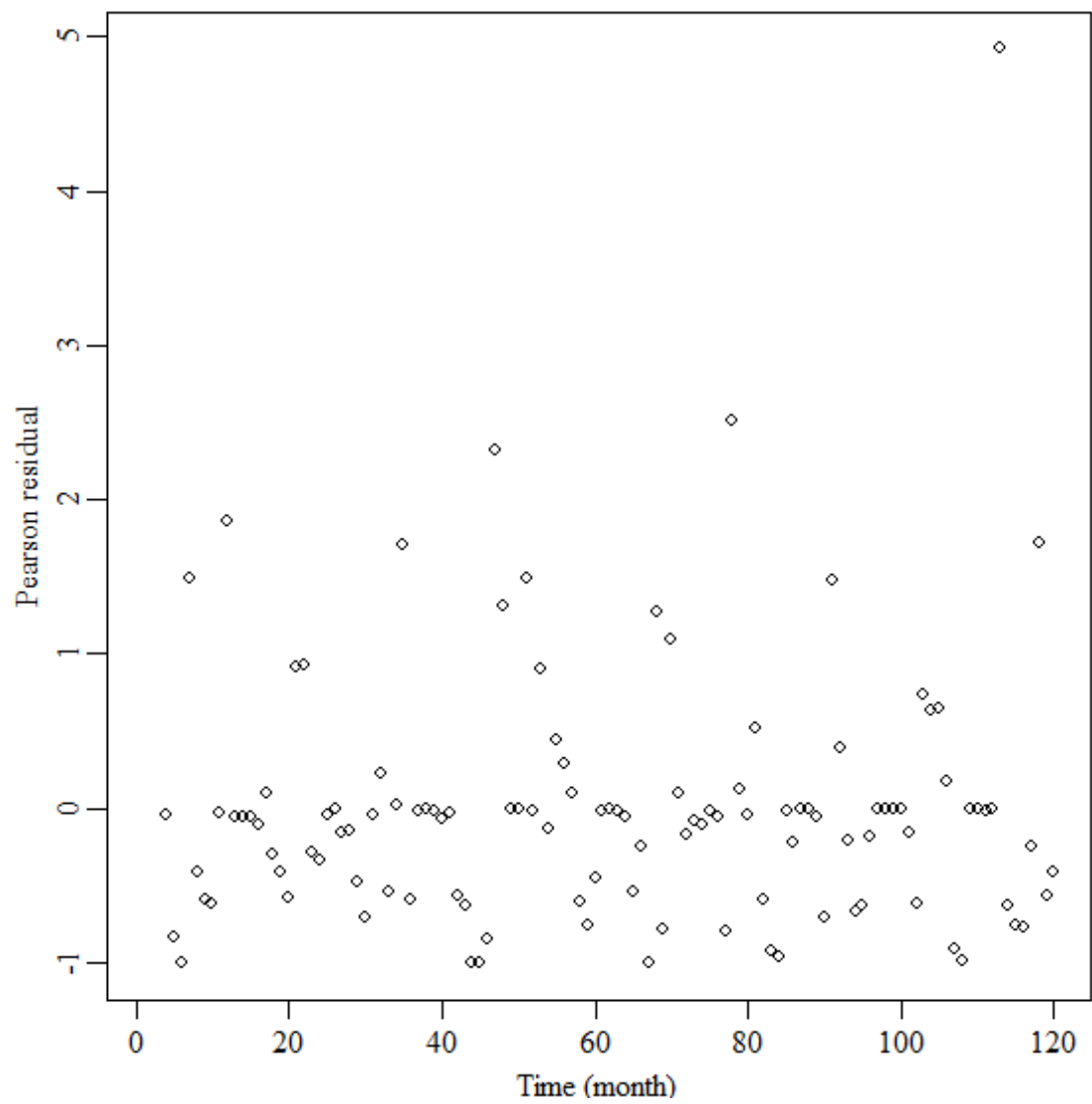
**S1 Fig. a) Three-month moving average plot of SSTA (°C) with standardized anomalies of mean monthly relative humidity. Red (Blue) filled segments of the SSTA plot that are above (below) 0.5°C (-0.5°C) represent an El Niño (a La Niña) event b) Scatterplot of standardized anomalies of mean monthly relative humidity versus SSTA (°C) in current month. The solid line shows the “best-fit” linear regression line.**

doi:10.1371/journal.pntd.0003901.s001



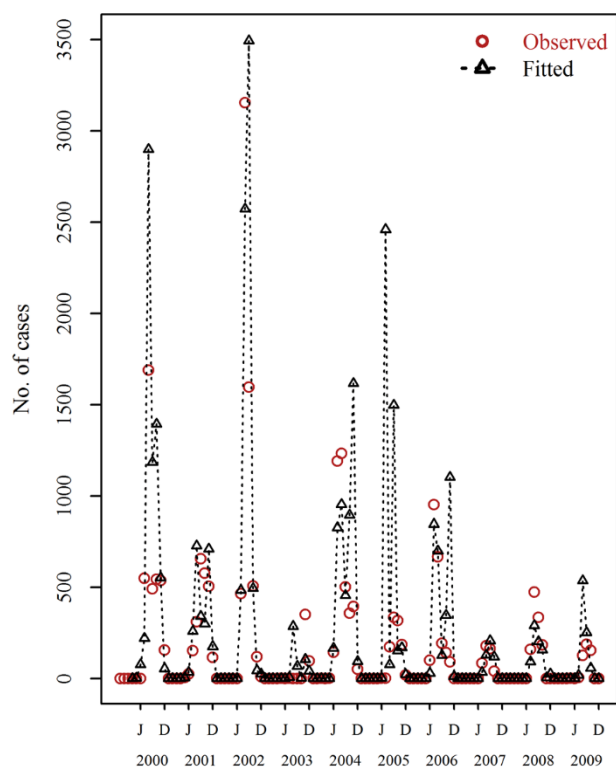
**S2 Fig. Partial autocorrelation plot of Pearson residuals.**

doi:10.1371/journal.pntd.0003901.s002



**S3 Fig. Time series plot of Pearson residuals.**

doi:10.1371/journal.pntd.0003901.s003



**S4 Fig. Observed vs fitted plot of dengue cases.**

doi:10.1371/journal.pntd.0003901.s004

# Chapter 5

## Paper 3: Estimation of under-reported dengue incidence in Dhaka, Bangladesh: a focus on non-linear dengue-climate relationships

Sharmin S, Glass K, Viennet E and Harley D. A Bayesian approach for estimating under-reported dengue incidence with a focus on non-linear associations between climate and dengue in Dhaka, Bangladesh. *Stat Methods Med Res.* 2016; 0962280216649216.

## Summary of this chapter

Passive hospital-based surveillance data detects only a small fraction of community cases leading to difficulty in analysing dengue-climate relationships, which is further complicated by non-linear associations. If we are to assess the impact of changing climate on dengue transmission, an understanding of these non-linear relationships is essential. In this chapter, I describe a Bayesian model developed in stages to estimate the proportion of cases reported in Dhaka from 2000-2009 combining empirical data with existing information about dengue under-reporting from India, Thailand, and Cambodia. To estimate non-linear dengue-climate relationships, I employ a semi-parametric approach to allow the shape of the relationships to be determined by the data rather than the model within the Bayesian modelling framework. The proposed model addresses the research question, “Can we develop a statistical model to estimate dengue-climate relationships in the presence of under-reporting and non-linear relationships between dengue and climate?”

# A Bayesian approach for estimating under-reported dengue incidence with a focus on non-linear associations between climate and dengue in Dhaka, Bangladesh

Sifat Sharmin, Kathryn Glass, Elvina Viennet and David Harley

Statistical Methods in Medical Research  
0(0) 1–10

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DOI: 10.1177/0962280216649216

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## Abstract

Determining the relation between climate and dengue incidence is challenging due to under-reporting of disease and consequent biased incidence estimates. Non-linear associations between climate and incidence compound this. Here, we introduce a modelling framework to estimate dengue incidence from passive surveillance data while incorporating non-linear climate effects. We estimated the true number of cases per month using a Bayesian generalised linear model, developed in stages to adjust for under-reporting. A semi-parametric thin-plate spline approach was used to quantify non-linear climate effects. The approach was applied to data collected from the national dengue surveillance system of Bangladesh. The model estimated that only 2.8% (95% credible interval 2.7–2.8) of all cases in the capital Dhaka were reported through passive case reporting. The optimal mean monthly temperature for dengue transmission is 29°C and average monthly rainfall above 15 mm decreases transmission. Our approach provides an estimate of true incidence and an understanding of the effects of temperature and rainfall on dengue transmission in Dhaka, Bangladesh.

## Keywords

Bayesian generalised linear model, spline, dengue, climate, passive surveillance, under-reporting

## 1 Introduction

Dengue, a mosquito-borne virus, produces symptoms ranging from mild febrile illness to its sometimes fatal haemorrhagic form. Global incidence has increased 30-fold over the last 50 years.<sup>1</sup> The World Health Organization's South-East Asia and Western Pacific Regions bear around 75% of the global dengue burden.<sup>2</sup>

Surveillance systems, particularly in low- and middle-income countries, where most cases occur, underestimate dengue incidence. Hospital-based passive reporting is biased towards severe cases. In one study, conducted in Thailand and Cambodia, the average proportion of total (inpatient and outpatient) laboratory-confirmed dengue cases reported during 2003 to 2007 was 11.5% and 11.0%, respectively, calculated comparing prospective cohort studies with national passive surveillance data.<sup>3</sup> Using these estimates, it was determined that in India in 2012, 6.8% to 7.5% of dengue cases were reported.<sup>4</sup> However, uncertainty around these estimates was not calculated. Improved estimates of the global distribution of dengue burden have been made using Bayesian hierarchical modelling that define the relationship between the probability of dengue occurrence and incidence of both clinically apparent and sub-clinical infection available from 54 cohort studies.<sup>5</sup> However, the estimated number of total infections might be biased for countries without detailed longitudinal information, due to spatial variation in disease incidence, treatment-seeking behaviour and reporting capacity. It was estimated that in 2010, 4,097,833 symptomatic infections occurred in Bangladesh<sup>5</sup> but only 409 were reported to authorities.<sup>6</sup> Bayesian methodology has also been used to estimate the under-reporting rate of notifiable diseases when prior information for each

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sequential step required for a case to be notified to a surveillance system is available.<sup>7,8</sup> In developing countries like Bangladesh where detailed health system data are not available, incorporating a single prior may be adequate operationally for adjusting incidence estimates for under-reporting.

Transmission of dengue virus (DENV) depends on the abundance of *Aedes aegypti* and *Aedes albopictus*, the principal vectors. Biological characteristics of these mosquitoes – including the rate of immature development, larval and adult survival, biting rates, the extrinsic incubation period of DENV in mosquitoes and vector competence – are all influenced by temperature<sup>9–12</sup> with a consequent positive association between temperature and incidence.<sup>13–15</sup> However, the relationship is non-linear; temperature above 30°C reduces adult survival<sup>16</sup> which in turn reduces transmission. Additionally, the diurnal temperature range (DTR) which is a measure of daily fluctuation in temperature also influences the biology and vectorial capacity of *Ae. aegypti*. A large fluctuation around high mean temperatures has been found to slow down immature development leading to reduced larval survival and reproduction by adult females,<sup>17</sup> and also a reduced probability of virus transmission.<sup>18</sup> Rainfall also influences mosquito abundance by creating pools of standing water suitable for mosquito breeding and ensuring a suitable relative humidity to prolong mosquito survival.<sup>19</sup> In Mexico and Singapore, dengue incidence was positively associated with rainfall at a lag of 2–3 weeks and 8–20 weeks, respectively.<sup>20,21</sup> Heavy rain, however, flushes away mosquito larvae,<sup>22</sup> potentially leading to non-linear associations of rainfall and dengue transmission. In many regions, inter-annual variability in temperature and rainfall is linked to the El Niño Southern Oscillation (ENSO) cycle and outbreaks of dengue have been reported in El Niño years.<sup>21,23,24</sup>

From a clinical and public health perspective, it is important to accurately estimate dengue incidence and to identify the factors that promote transmission. Existing models that include effects of climate have typically used monotonically increasing relationships between temperature, rainfall and dengue transmission,<sup>15,20,21</sup> except in a recent study<sup>25</sup> reporting a non-linear association between ENSO and dengue incidence in Bangladesh.

Ideally, epidemiological studies estimating incidence must adjust for under-reporting and incorporate non-linear exposure–disease relationships. Therefore, we propose a Bayesian framework using minimal information to calculate a reliable estimate of dengue incidence in Dhaka, Bangladesh, using data from the national dengue surveillance system and allowing for non-linear relationships between dengue and climatic variables. These will help public health professionals to understand the disease dynamics and design interventions in order to strengthen the country's capacity for prevention of severe dengue outbreaks in the absence of a vaccine. Knowing the true incidence is vitally important to policy makers to assess the economic and human cost of the disease and therefore to determine priorities.

## 2 Methodology

The study was approved by The Australian National University Human Research Ethics Committee.

### 2.1 Study site

Bangladesh, a lower middle income country of South Asia, experienced its first epidemic of dengue fever in 2000 after more than three decades of sporadic dengue.<sup>26</sup> From 2000 to 2009, around 91% of the cases reported from 29 of the 64 districts were from the capital, Dhaka.<sup>6</sup> The high dengue incidence rate in Dhaka is presumably due to human (e.g. population density) and climatic factors. In 2011, there were 8229 people per square kilometre; a 41% increase from 2001.<sup>27</sup> A population density of 220,246 people per square kilometre has been estimated in slum areas.<sup>28</sup> Inadequate piped water supply across the city encourages water storage in temporary containers. Both *Ae. aegypti* and *Ae. albopictus* were observed in outdoor breeding sites across Dhaka<sup>29</sup> which may partly be a consequence of an absence of proper waste management.

The monsoon (June to September) is the wettest period of the year, with about 80% of the annual rainfall of 2000 mm and an average daily temperature of 25°C. El Niño and La Niña events in some years influence the annual rainfall cycle with less than average monsoon rainfall in El Niño years while the opposite happens in La Niña years.<sup>30,31</sup>

### 2.2 Data set

We obtained monthly dengue cases from January 2000 to December 2009 for the Dhaka district of Bangladesh from the Directorate General of Health Services. Daily maximum, minimum and mean temperatures (°C) and

daily rainfall (mm) for Dhaka were obtained from the Bangladesh Meteorological Department. The daily DTR was calculated as the difference between the maximum and minimum daily temperatures. Monthly averages of these climatic variables were calculated from daily records. A monthly time series of the sea surface temperature anomaly (SSTA) over the Niño 3.4 region which is an index of ENSO was obtained from the United States National Oceanic and Atmospheric Administration Climate Prediction Center (<http://www.cpc.ncep.noaa.gov/data/indices/ersst3b.nino.mth.81-10.ascii>).

Population estimates were extracted from census data collected in 1991, 2001 and 2011 by the Bangladesh Bureau of Statistics. Monthly population numbers for each of the years between 2000 and 2009 were calculated by linear interpolation. The district population size was divided by the area (in km<sup>2</sup>) to obtain the population density (people/km<sup>2</sup>) for Dhaka district.

## 2.3 Model formulation

Our model builds on a negative binomial generalised linear model (GLM) developed in STATA 13.1 (Stata Corp., Texas, USA) to assess the relationship between monthly dengue incidence and average monthly values of climatic and demographic variables.<sup>32</sup> While this foundational analysis identified key exposure variables for our model, in this paper, we have adopted a Bayesian approach to take account of uncertainty associated with parameter estimation and to incorporate existing knowledge via prior distributions for parameters. This Bayesian model was developed in stages as described below.

**2.3.1 Base model.** Let  $y_i$  be the observed count of dengue cases in Dhaka in month  $i$  ( $i = 1, 2, \dots, 120$ ). At the first stage of model development, observed counts were modelled using a GLM with a negative binomial distribution, a logarithmic link function and with the population of Dhaka as an offset to adjust the count of cases for population size. All the covariates significant at the 5% level in prior analysis were included in this model, namely: the mean monthly temperature at a lag of one month, mean monthly DTR at a lag of one month, interaction between mean monthly temperature and mean monthly DTR at a lag of one month, mean monthly rainfall at a lag of one and two months, monthly SSTA at a lag of zero and one month and monthly population density. A first-order autoregressive month effect,  $AR(1)_{(i)}$ , with month 1 (April) set to 0 was used which allowed for correlation between consecutive months (i.e. cases at month  $i$  are influenced by cases at month  $i - 1$ ) following Lowe et al.<sup>33</sup> A year-specific random effect,  $year_{(i)}$ , was also introduced to take into account any unobserved confounding factors and consequent long-term trends over the years. The model was further adjusted for seasonal variation (Monsoon: June–September; Dry: October–May) that was evident in the observed dengue incidence.

$$y_i \sim \text{NegBin}(\mu_i, r); i = 1, 2, \dots, 120$$

$$\log(\mu_i) = \log(\text{Population}_i) + \alpha + \sum_{j=1}^8 \beta_j x_{ji} + \text{season} * \text{ind.season}_i + AR(1)_{(i)} + year_{(i)} \quad (1)$$

Because of the absence of any prior knowledge, independent diffuse Gaussian priors (with mean 0, precision  $1 \times 10^{-6}$ ) were assigned to the intercept  $\alpha$  and fixed effects  $\beta_j$  ( $j = 1, \dots, 7$ ) and season. A uniform prior (0, 100) was assumed for  $\beta_8$  because the coefficient of population density can take only positive values. Weakly informative gamma hyperpriors (shape parameter 0.5, inverse scale parameter 0.5) were assigned to the precision parameters of  $AR(1)_{(i)}$  and  $year_{(i)}$  in a second stage of the hierarchy. The scale parameter  $r$  was also set to a gamma prior (0.5, 0.5).

We fitted the model using Markov chain Monte Carlo (MCMC) sampling in WinBUGS 14 (MRC Biostatistics Unit, Cambridge, UK). We standardised all covariates to have zero mean and unit variance to aid MCMC convergence. We ran a single chain of 10,000 iterations keeping every 50th with the first 1000 used as a burn-in. All trace and history plots of model parameters indicated convergence.

**2.3.2 Adjusting the base model for under-reporting.** At the second stage of model development, we introduced under-reporting by assuming that the observed counts,  $y_i$ , are Poisson distributed and are a function of the proportion of cases reported and the true number of cases,  $z_i$ . The true numbers of cases were modelled by a negative binomial GLM as equation (1)

$$y_i \sim \text{Poisson}(\lambda_i); i = 1, 2, \dots, 120$$

$$\begin{aligned}
\lambda_i &= \text{prop. reported} * z_i \\
z_i &\sim \text{NegBin}(\mu_i, r); i = 1, 2, \dots, 120 \\
\log(\mu_i) &= \log(\text{Population}_i) + \alpha + \sum_{j=1}^8 \beta_j x_{ji} + \text{season} * \text{ind. season}_i + \text{AR}(1)_{(i)} + \text{year}_{(i)}
\end{aligned} \tag{2}$$

The new parameter *prop. reported* was assigned a Beta distribution, commonly used to model uncertainty about a proportion. Based on Wichmann et al.<sup>3</sup> and Amarasinghe et al.,<sup>4</sup> the prior for this parameter was chosen to have a median of 0.08, with 95% confidence interval from 0.01 to 0.16. That is, we believe that about 8% cases are reported, and that the true reporting percentage lies between 1% and 16%. The same non-informative priors for other parameters were used as for the base model.

A single chain of 60,000 iterations saving every 50th was run to limit autocorrelation with a burn-in of 55,000 iterations and convergence was assessed using the trace and history plots of model parameters as before. History plots of the key parameters are provided in the Supplementary Material (Figure 1S).

**2.3.3 Modelling non-linear exposure-disease relationships.** Following Crainiceanu et al.,<sup>34</sup> a semi-parametric modelling approach using low-rank thin-plate splines was employed to model the non-linear relationships between dengue incidence and selected climatic variables. Low-rank thin-plate splines, compared to truncated polynomials, greatly improve the mixing of MCMC chains by reducing the posterior correlation of the parameters. Equation (2) was therefore modified as below

$$\log(\mu_i) = \log(\text{Population}_i) + \alpha + \sum_{j=1}^3 \beta_j x_{ji} + \sum_{l=1}^5 f_l(x_{li}) + \text{season} * \text{ind. season}_i + \text{AR}(1)_{(i)} + \text{year}_{(i)}$$

where  $f$  is a smooth function of the climatic variables  $x_{li}$  ( $l = 1, \dots, 5$ ) that may have a non-linear influence on dengue incidence. These climatic variables include mean monthly temperature at a lag of one month, mean monthly rainfall at a lag of one and two months and monthly SSTA at a lag of zero and one month.

The smooth function  $f$  was defined as

$$f_l(x_{li}, \theta) = \gamma_l x_{li} + \sum_{k=1}^K u_{lk} |x_{li} - k_{lk}|^3$$

where  $\theta = (\gamma_1, \dots, \gamma_5, u_{11}, \dots, u_{5K})^T$  is the vector of regression coefficients,  $k_{lk} = (k_{1k}, \dots, k_{5k})$  is a vector of  $K$  knots such as  $k_{l1} < k_{l2} < \dots < k_{lK}$  and  $|x_{li} - k_{lk}|^3$  is a third-order polynomial spline basis. We used 5 knots that were spaced evenly on the percentiles of the respective climatic variables. Higher numbers of knots, however, showed no significant change in the model fit. To avoid overfitting, a smoothing parameter and a penalty matrix were considered as recommended by Crainiceanu et al.<sup>34</sup> The precisions of the spline basis coefficients, obtained after adjustment through the penalty matrix, were assigned weakly informative gamma hyperpriors with shape parameter 0.5 and inverse scale parameter 0.5.

This time we discarded the first 55,000 iterations as a burn-in and ran the single chain for a further 11,000 iterations to confirm convergence which was assessed by inspection of trace and history plots of model parameters.

### 3 Results

Table 1 presents the posterior estimates (median and the 95% credible interval) of the parameters from the base model and model adjusted for under-reporting. The estimates from both models are quite similar except for that associated with DTR. Population density is found to be a highly significant factor (95% credible interval: 0.005, 0.875) with higher number of cases with increasing population per square kilometre. Mean temperature at a lag of one month is significantly and positively associated with dengue incidence in both models. The effect of rainfall on dengue transmission at both lags is positive and marginally significant at a lag of two months. SSTA in the current month exerts a negative but insignificant influence on dengue while at a lag of one month the association becomes positive, although still insignificant. The precision parameters for the month and year effect are both significant and therefore confirm their significance in model fit. The posterior predictive medians and corresponding 95% credible intervals of the over-dispersion parameter indicate the need for a negative binomial distribution.

**Table 1.** Posterior estimates for the standardised covariates, hyperparameters and proportion of dengue cases reported from the base model and model adjusted for under-reporting.

|                                                             | Median (95% credible interval) |                                    |
|-------------------------------------------------------------|--------------------------------|------------------------------------|
|                                                             | Base model                     | Model adjusted for under-reporting |
| Mean temperature lagged one month                           | 3.591 (1.108, 6.577)           | 1.488 (0.155, 3.028)               |
| DTR lagged one month                                        | 0.012 (−1.660, 1.779)          | −0.349 (−1.388, 0.740)             |
| Interaction between mean temperature & DTR lagged one month | −0.165 (−2.107, 1.673)         | −0.003 (−0.982, 0.968)             |
| Rainfall lagged one month                                   | 0.519 (−0.275, 1.314)          | 0.282 (−0.295, 0.862)              |
| Rainfall lagged two months                                  | 0.539 (−0.157, 1.299)          | 0.392 (−0.113, 0.968)              |
| SSTA at current month                                       | −1.415 (−3.354, 0.484)         | −0.779 (−2.155, 0.537)             |
| SSTA lagged one month                                       | 1.723 (−0.305, 3.843)          | 0.966 (−0.384, 2.426)              |
| Population density                                          | 0.183 (0.007, 1.189)           | 0.139 (0.005, 0.875)               |
| Season                                                      |                                |                                    |
| Dry (Ref)                                                   | —                              | —                                  |
| Monsoon                                                     | 1.154 (−2.308, 4.669)          | 1.042 (−1.144, 3.211)              |
| Over-dispersion parameter ( $1/r$ )                         | 2.534 (1.737, 3.743)           | 1.649 (1.240, 2.231)               |
| Precision of month effect                                   | 0.249 (0.065, 0.864)           | 0.679 (0.183, 2.173)               |
| Precision of year effect                                    | 0.250 (0.062, 0.984)           | 0.486 (0.115, 1.774)               |
| Proportion of cases reported                                | —                              | 0.028 (0.027, 0.028)               |

SSTA: sea surface temperature anomaly; DTR: diurnal temperature range

We extended the base model to estimate the true number of monthly dengue cases and the proportion of cases that are reported. The median estimate of this proportion is 0.028, indicating that of every 100 cases only 3 are reported.

For model comparison, we plotted the observed dengue counts with the fitted values and found that the model adjusted for under-reporting (Figure 1(b)) provides a better fit than the base model (Figure 1(a)).

To assess the adequacy of this model adjusted for under-reporting, we conducted posterior predictive assessment to compare the observed data with data replicated from the posterior predictive distribution. The Bayesian  $p$  value (0.545) confirms that the model provides a reasonable fit to the observed data.

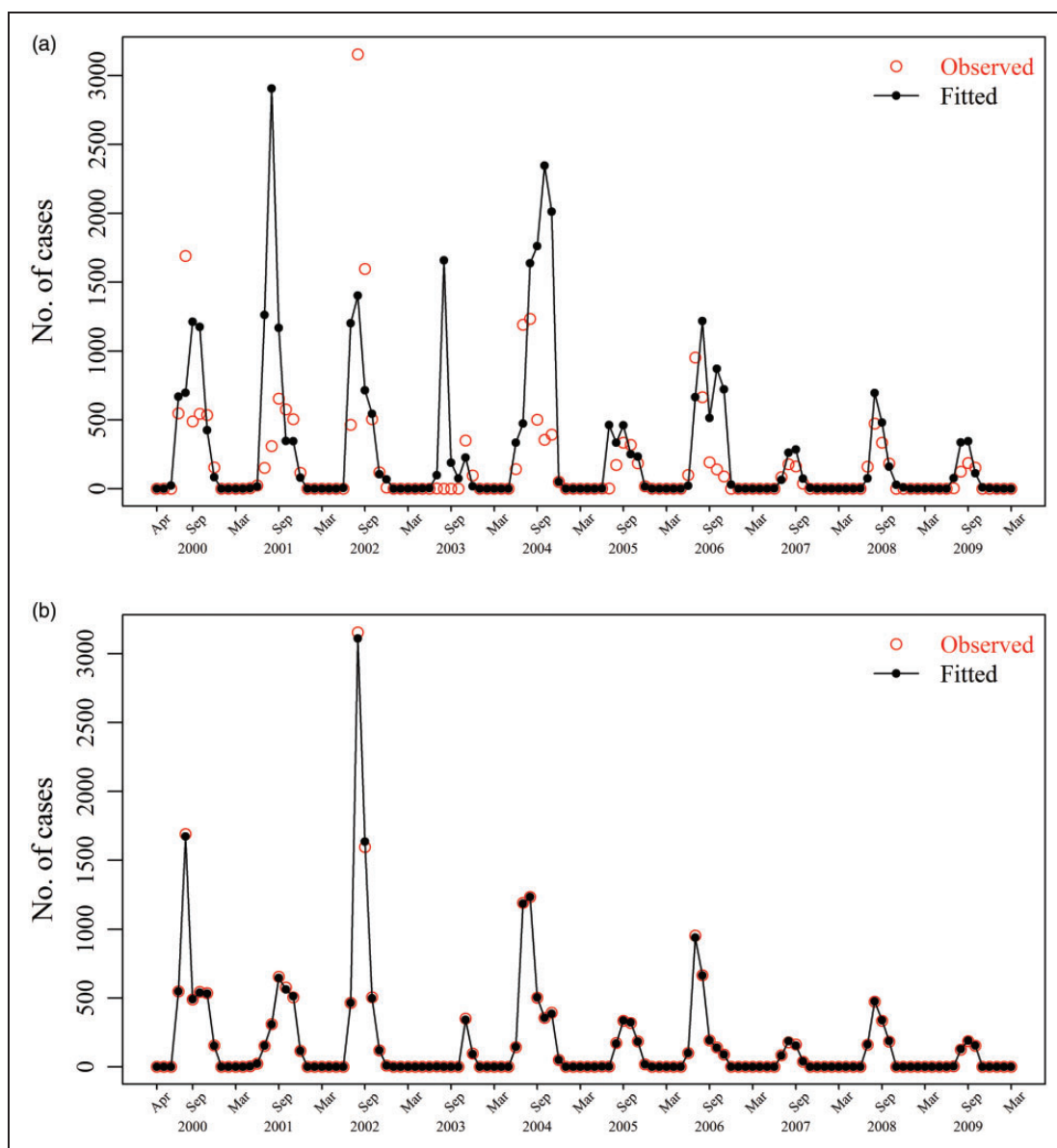
Figure 2 illustrates the median number of total cases per month from 2000 to 2009 in Dhaka with a 95% credible interval about this median value estimated from the model adjusted for under-reporting. The model clearly captures the temporal trend of higher cases in alternate years that has been observed in surveillance data with the exception of 2001. Reported case numbers in 2001 were lower than the previous year when the first epidemic of dengue fever in Bangladesh took place.

Modelling key weather variables using splines allows us to investigate their non-linear associations with dengue incidence. An average monthly temperature of 29°C at a lag of one month is optimal for dengue transmission in Dhaka, with declining transmission above this temperature (Figure 3(a)). High mean monthly rainfall, at lags of one and two months, is associated with increased incidence; however, incidence decreases when mean monthly rainfall exceeds 15 mm (Figure 3(b)). There is a bimodal association between SSTA and dengue incidence (Figure 3(c)).

To assess the impact of prior choice on our results, we performed a sensitivity analysis. The posterior estimates of the parameters corresponding to different choices of prior distribution and prior parameters are listed in Table 2. The results presented in Table 1 for over-dispersion parameter were very robust to the choice of the prior parameters. This again confirms the appropriateness of a negative binomial model. Very similar results were obtained with gamma prior (0.5, 0.0005) for the precision parameters. The parameters  $\beta_j$  ( $j = 1, \dots, 8$ ) were also tested with a uniform prior (−100, 100) and only  $\beta_8$  which is the coefficient of population density was sensitive to the altered prior parameters.

## 4 Discussion

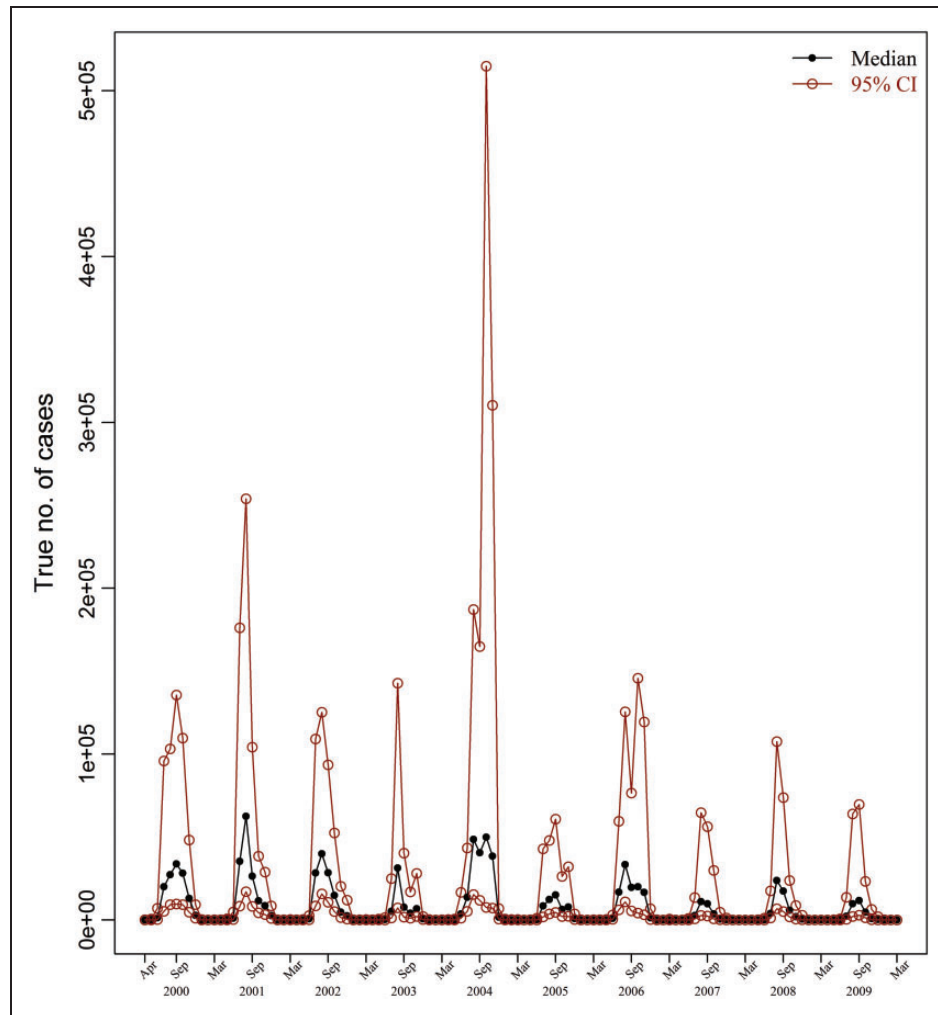
This study presents a Bayesian approach to estimate dengue incidence in the community using passive surveillance data. This approach takes account of uncertainty associated with all model parameters, adjusts for under-



**Figure 1.** Monthly number of observed dengue cases from 2000 to 2009 and fitted values from (a) the base model and (b) the model adjusted for under-reporting.

reporting of cases and leads to more robust estimates when information is limited. Using data from Bangladesh's national dengue surveillance system, which is passive and hospital based, we found that cases reported to the surveillance system represent only 2.8% (95% credible interval 2.7–2.8) of all cases in the capital city. Our result is of the same order of magnitude as estimates from neighbouring India where in 2012, 6.8% to 7.5% of all dengue cases were reported, based on expansion factors from Cambodia and Thailand, respectively.<sup>4</sup> Our model also captures the inter-annual differences in dengue incidence with higher cases in alternate years as observed in surveillance data. We used hospital in-patient data and therefore our incidence estimate does not account for differential reporting dependent on disease severity. Also, our estimate may not be valid for districts other than the capital.

This is the first time the non-linear influence of climate on dengue has been investigated using semi-parametric splines within a Bayesian framework. Most epidemiological studies are based on an underlying assumption that high temperature or rainfall will increase dengue transmission by influencing the abundance and vectorial capacity of mosquitoes. Here, we allowed selected climatic variables to have a non-linear influence on dengue transmission



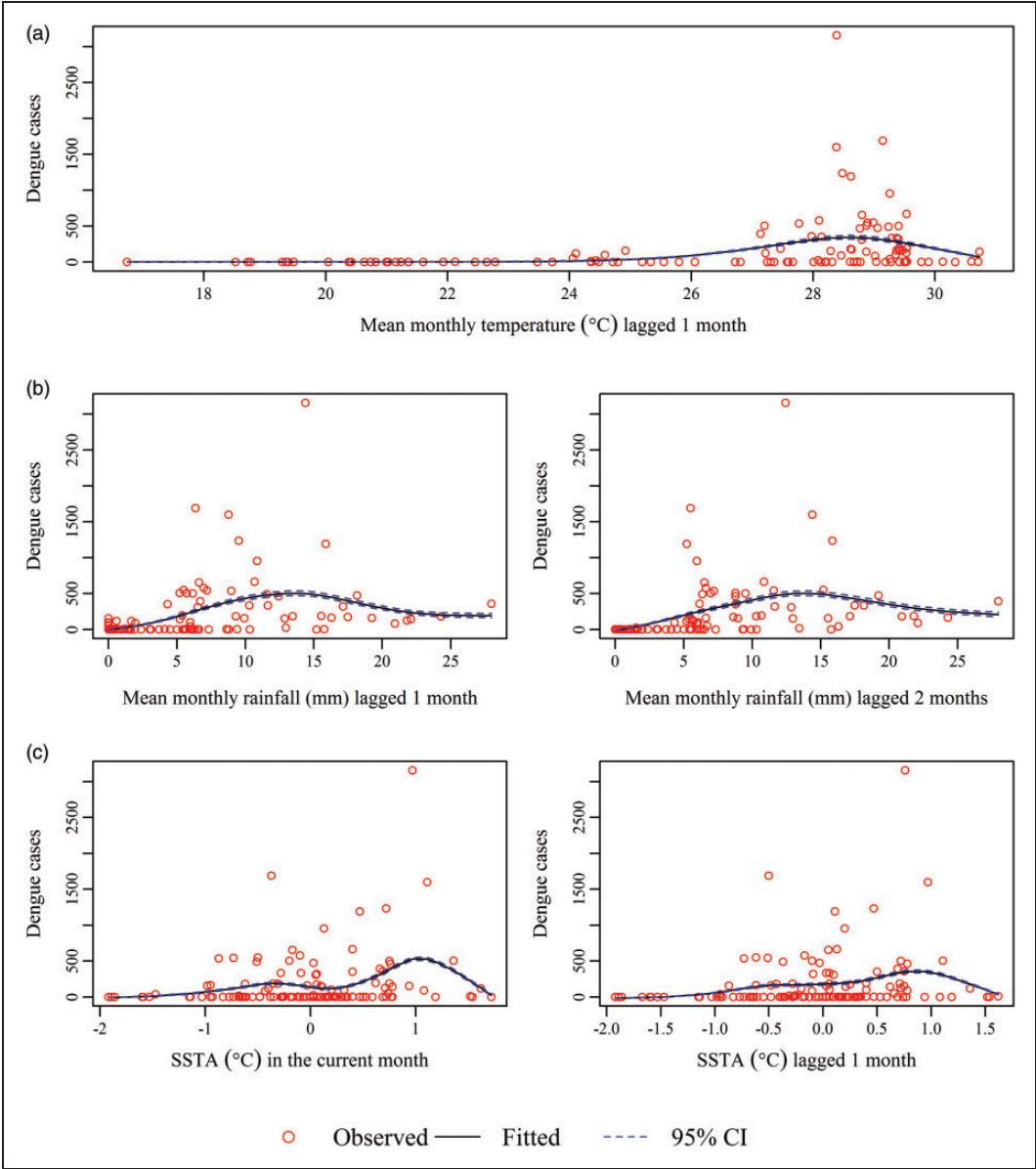
**Figure 2.** Median number of true dengue cases in Dhaka per month from 2000 to 2009 with 95% credible intervals, calculated from the reported cases in a model that adjusts for under-reporting.

and adopted a semi-parametric approach using Bayesian thin-plate splines to model non-linearity in the climate–dengue associations.

We found that mean monthly temperature is significantly and positively associated with dengue incidence one month later in Dhaka, with values above  $26^{\circ}\text{C}$  and below  $29^{\circ}\text{C}$  associated with high risk. The non-linear associations between temperature and dengue detected by our model likely reflect mosquito biology; as temperatures increase from  $20^{\circ}\text{C}$  to  $35^{\circ}\text{C}$ , the mosquito rate of development increases while survival decreases.<sup>9,11,16</sup>

We observed a marginally significant positive influence of rainfall on dengue transmission at a lag of two months with decreasing incidence when mean monthly rainfall increases beyond 15 mm. This is biologically plausible since mosquito larvae are flushed away with heavy rainfall, and consequently there are fewer adult mosquitoes to transmit disease. Similarly, when rainfall decreases to extremely low levels, DENV transmission reduces, probably due to the drying up of breeding habitats.

A bimodal relationship was noticed between SSTA and dengue incidence, with higher incidence when SSTA is above  $0.5^{\circ}\text{C}$  and a second peak at around  $-0.5^{\circ}\text{C}$ . This may reflect the influence of both El Niño (three-month moving average of SSTA greater than  $0.5^{\circ}\text{C}$ ) and La Niña events (three-month moving average of SSTA less than  $-0.5^{\circ}\text{C}$ ) on monsoon rainfall in Bangladesh; there is lower and higher than average rainfall during El Niño and La Niña years, respectively.<sup>30,31</sup> A recent study identified similar non-linear influences of ENSO on the incidence of dengue at a lag of four months in Bangladesh.<sup>25</sup> However, contrary to our results, increasing risk of dengue was reported with higher Niño 3.4. This inconsistency can be explained considering the difference in time lags between two models; strong El Niño that often causes drought may encourage water storage with consequent increased



**Figure 3.** Scatter plot of observed dengue cases versus climatic variables with posterior median (middle solid black line) number of fitted cases ( $\lambda$ ) and corresponding 95% credible intervals (dashed blue lines).

**Table 2.** Posterior estimates of the parameters and hyperparameters from the model adjusted for under-reporting with changed prior specifications.

| Prior                                                      | Posterior median | 95% credible interval |
|------------------------------------------------------------|------------------|-----------------------|
| $\beta_1 \sim \text{dunif}(-100,100)$                      | 1.487            | 0.129, 2.956          |
| $\beta_2 \sim \text{dunif}(-100,100)$                      | -0.341           | -1.358, 0.723         |
| $\beta_3 \sim \text{dunif}(-100,100)$                      | -0.0002          | -1.023, 1.009         |
| $\beta_4 \sim \text{dunif}(-100,100)$                      | 0.267            | -0.298, 0.842         |
| $\beta_5 \sim \text{dunif}(-100,100)$                      | 0.397            | -0.103, 0.958         |
| $\beta_6 \sim \text{dunif}(-100,100)$                      | -0.786           | -2.108, 0.497         |
| $\beta_7 \sim \text{dunif}(-100,100)$                      | 0.970            | -0.371, 2.383         |
| $\beta_8 \sim \text{dunif}(-100,100)$                      | -1.120           | -1.810, -0.461        |
| season $\sim \text{dunif}(-100,100)$                       | 1.016            | -1.167, 3.417         |
| $r \sim \text{dgamma}(0.5,0.0005)$                         | 0.604            | 0.449, 0.805          |
| Precision of month effect $\sim \text{dgamma}(0.5,0.0005)$ | 0.795            | 0.202, 2.959          |
| Precision of year effect $\sim \text{dgamma}(0.5,0.0005)$  | 0.599            | 0.137, 4.320          |

incidence after four months whereas drought can reduce incidence in the current month or one month later by decreasing the adult mosquito population due to reduction of the number of oviposition sites.

Our analysis uses a Bayesian modelling approach incorporating non-linear relationships between dengue and climate. We believe this approach provides a more accurate estimate of disease incidence than is otherwise possible. A better understanding of the climate–dengue relationships which quantifies the influence of temperature and rainfall on dengue transmission will contribute to more accurate predictions about the likely impacts of changing climate on dengue risk.

## Acknowledgements

We thank Ayesha Akhter, in-charge, National Health Crisis Management Centre and Control Room, Directorate General of Health Services, Dhaka, for generously providing dengue surveillance data.

## Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: The first author was supported by The Australian National University Higher Degree Research Merit Scholarship (<http://www.anu.edu.au/students/scholarships-support/anu-university-research-scholarships>).

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## Supplementary material

### R program:

```
stT_L1=as.vector(scale(T_L1))
stR_L1=as.vector(scale(R_L1))
stR_L2=as.vector(scale(R_L2))
stSSTA=as.vector(scale(SSTA))
stSSTA_L1=as.vector(scale(SSTA_L1))

#Define knots used for the thin-plate spline at equal spaced quantiles of the covariates
knots1=quantile(unique(stT_L1),seq(0,1,length=7)[-c(1,7)])
knots2=quantile(unique(stR_L1),seq(0,1,length=7)[-c(1,7)])
knots3=quantile(unique(stR_L2),seq(0,1,length=7)[-c(1,7)])
knots4=quantile(unique(stSSTA),seq(0,1,length=7)[-c(1,7)])
knots5=quantile(unique(stSSTA_L1),seq(0,1,length=7)[-c(1,7)])

#Obtain the design matrix for random coefficients (b1, b2,..., b5) using thin-plate splines
S1_K=(abs(outer(stT_L1,knots1,"-")))^3
OMEGA1_all=(abs(outer(knots1,knots1,"-")))^3
svd.OMEGA1_all=svd(OMEGA1_all)
sqrt.OMEGA1_all=t(svd.OMEGA1_all$v %*%
                  (t(svd.OMEGA1_all$u)*sqrt(svd.OMEGA1_all$d)))
S1=t(solve(sqrt.OMEGA1_all,t(S1_K)))
dput(S1)

S2_K=(abs(outer(stR_L1,knots2,"-")))^3
OMEGA2_all=(abs(outer(knots2,knots2,"-")))^3
svd.OMEGA2_all=svd(OMEGA2_all)
sqrt.OMEGA2_all=t(svd.OMEGA2_all$v %*%
                  (t(svd.OMEGA2_all$u)*sqrt(svd.OMEGA2_all$d)))
S2=t(solve(sqrt.OMEGA2_all,t(S2_K)))
dput(S2)
```

```

S3_K=(abs(outer(stR_L2,knots3,"-")))^3
OMEGA3_all=(abs(outer(knots3,knots3,"-")))^3
svd.OMEGA3_all=svd(OMEGA3_all)
sqrt.OMEGA3_all=t(svd.OMEGA3_all$v %*%
                  (t(svd.OMEGA3_all$u)*sqrt(svd.OMEGA3_all$d)))
S3=t(solve(sqrt.OMEGA3_all,t(S3_K)))
dput(S3)

```

```

S4_K=(abs(outer(stSSTA,knots4,"-")))^3
OMEGA4_all=(abs(outer(knots4,knots4,"-")))^3
svd.OMEGA4_all=svd(OMEGA4_all)
sqrt.OMEGA4_all=t(svd.OMEGA4_all$v %*%
                  (t(svd.OMEGA4_all$u)*sqrt(svd.OMEGA4_all$d)))
S4=t(solve(sqrt.OMEGA4_all,t(S4_K)))
dput(S4)

```

```

S5_K=(abs(outer(stSSTA_L1,knots5,"-")))^3
OMEGA5_all=(abs(outer(knots5,knots5,"-")))^3
svd.OMEGA5_all=svd(OMEGA5_all)
sqrt.OMEGA5_all=t(svd.OMEGA5_all$v %*%
                  (t(svd.OMEGA5_all$u)*sqrt(svd.OMEGA5_all$d)))
S5=t(solve(sqrt.OMEGA5_all,t(S5_K)))
dput(S5)

```

## Bugs program:

```
model{
  for(i in 1:n){
    # Standardizing the variables
    Tc_L1[i]<-(T_L1[i]-mean(T_L1[1:n ]))/sd(T_L1[1:n ])
    DTRc_L1[i]<-(DTR_L1[i]-mean(DTR_L1[1:n ]))/sd(DTR_L1[1:n ])
    Rc_L1[i]<-(R_L1[i]-mean(R_L1[1:n ]))/sd(R_L1[1:n ])
    Rc_L2[i]<-(R_L2[i]-mean(R_L2[1:n ]))/sd(R_L2[1:n ])
    SSTAc[i]<-(SSTA[i]-mean(SSTA[1:n ]))/sd(SSTA[1:n ])
    SSTAc_L1[i]<-(SSTA_L1[i]-mean(SSTA_L1[1:n ]))/sd(SSTA_L1[1:n ])
    Pop_denc[i]<-(Pop_den[i]-mean(Pop_den[1:n ]))/sd(Pop_den[1:n ])

    TDTR[i]<-Tc_L1[i]*DTRc_L1[i]
    D.season[i]<-equals(ind.season[i],2) #ref=1; Dry

    y[i]~dpois(lambda[i])
    lambda[i]<-p.y*z[i]

    z[i]~dnegbin(p[i],r)
    p[i]<-r/(r+mu[i])

    log(mu[i])<-log(offset[i])+alpha
    +gamma[1]*Pop_denc[i]+gamma[2]*DTRc_L1[i]+gamma[3]*TDTR[i]
    +season*D.season[ i ]
    +omega.month[month[i]]+omega.year[year[i]]
    +spline1[i]+spline2[i]+spline3[i]+spline4[i]+spline5[i]

    spline1[i]<-inprod(b1[ ],S1[i, ])+beta[1]*Tc_L1[i]
    spline2[i]<-inprod(b2[ ],S2[i, ])+beta[2]*Rc_L1[i]
    spline3[i]<-inprod(b3[ ],S3[i, ])+beta[3]*Rc_L2[i]
    spline4[i]<-inprod(b4[ ],S4[i, ])+beta[4]*SSTAc[i]
    spline5[i]<-inprod(b5[ ],S5[i, ])+beta[5]*SSTAc_L1[i]
  }
}
```

```

#Prior distributions for climate and non-climate covariates
  for(l in 1:5){
    beta[l]~dnorm(0,0.000001)
  }
  gamma[1]~dunif(0,100)
  gamma[2]~dnorm(0,0.000001)
  gamma[3]~dnorm(0,0.000001)
  season~dnorm(0,0.000001)

#Improper uniform prior distribution for the intercept
  alpha~dnorm(0,0.000001)

#Prior distribution for scale parameter
  r~dgamma(0.5,0.5)

# Overdispersion parameter
  od<-1/r

# Prior distributions for autocorrelated month effect
  omega.month[1]<-0
  for (t in 2:12){
    omega.month[t]~dnorm(omega.month[t-1],tau.omega.month)
  }
  tau.omega.month~dgamma(0.5, 0.5)

# Prior distribution for yearly effect
  for (t in 1:10){
    omega.year[t]~dnorm(0,tau.omega.year)
  }
  tau.omega.year~dgamma(0.5, 0.5)

# Prior distributions for spline basis coefficients
  for(k in 1:5){
    b1[k]~dnorm(0,taub)
  }

```

```

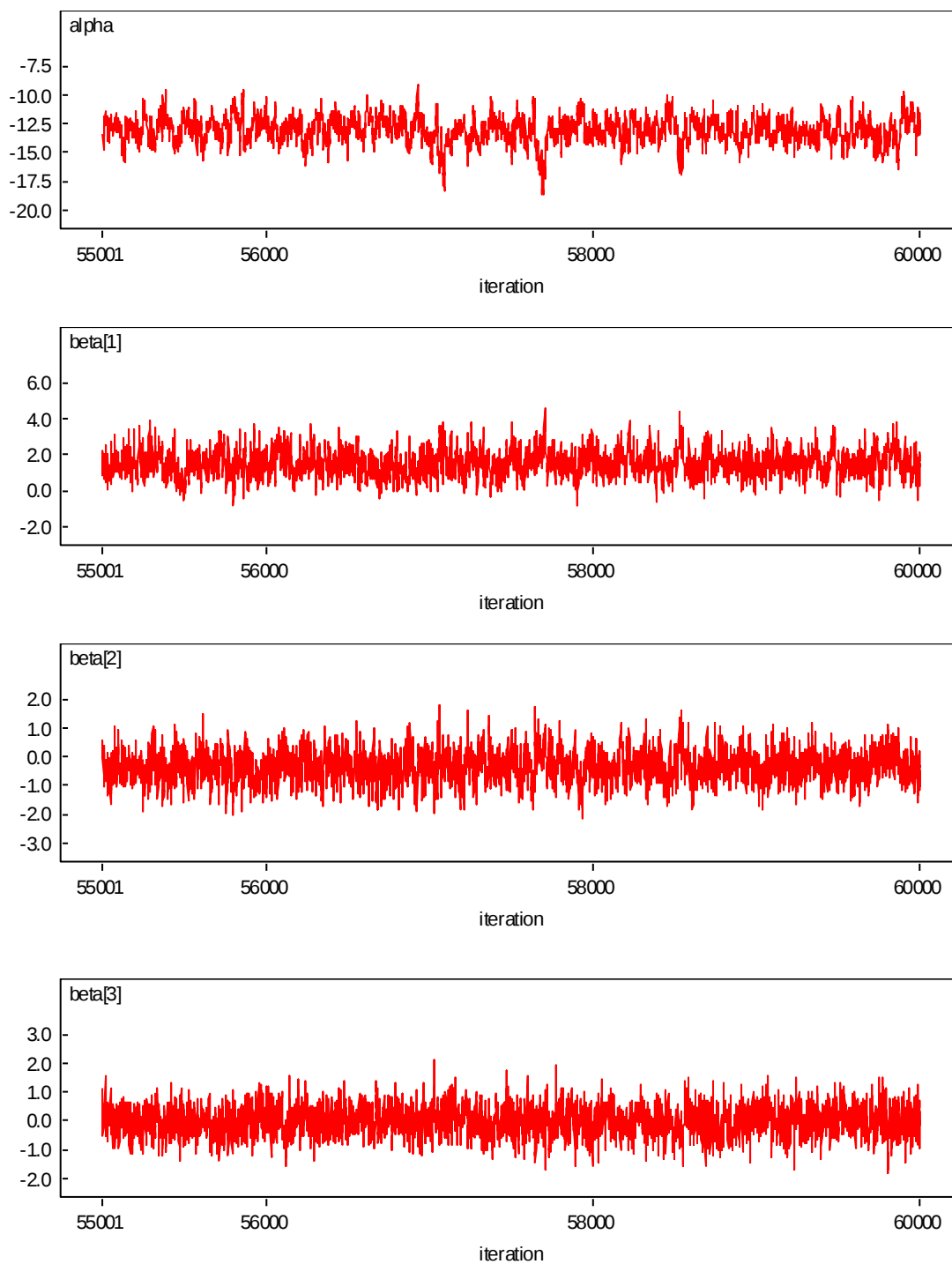
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    }
    for(k in 1:5){
      b4[k]~dnorm(0,taub)
    }
    for(k in 1:5){
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    }
    taub~dgamma(0.5,0.5)

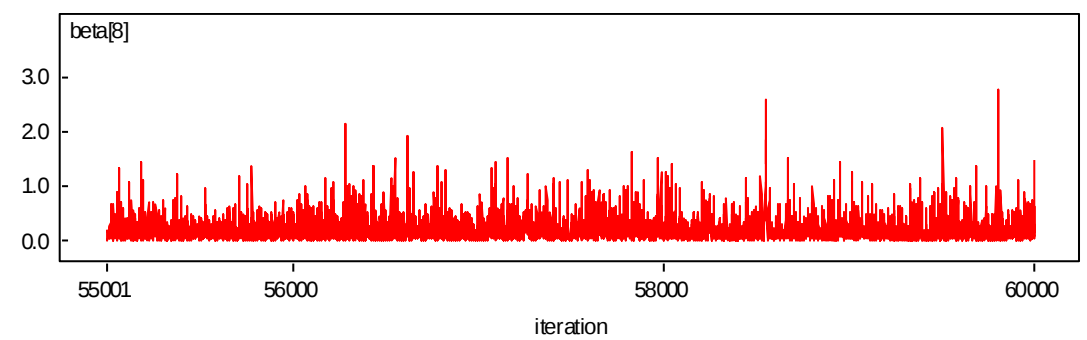
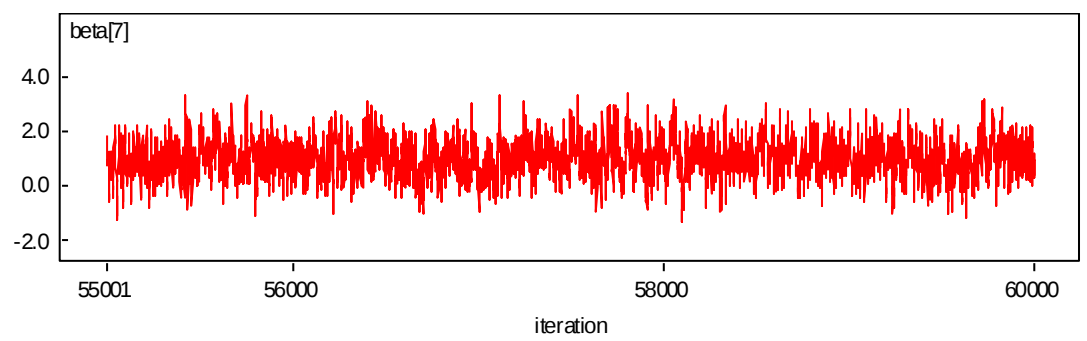
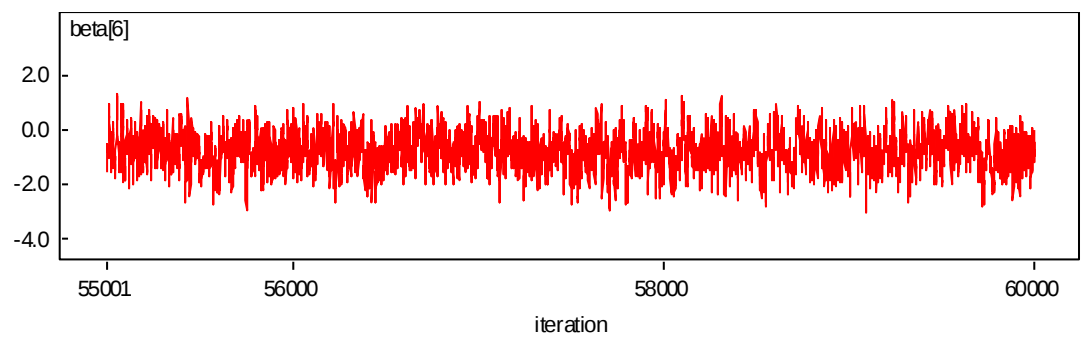
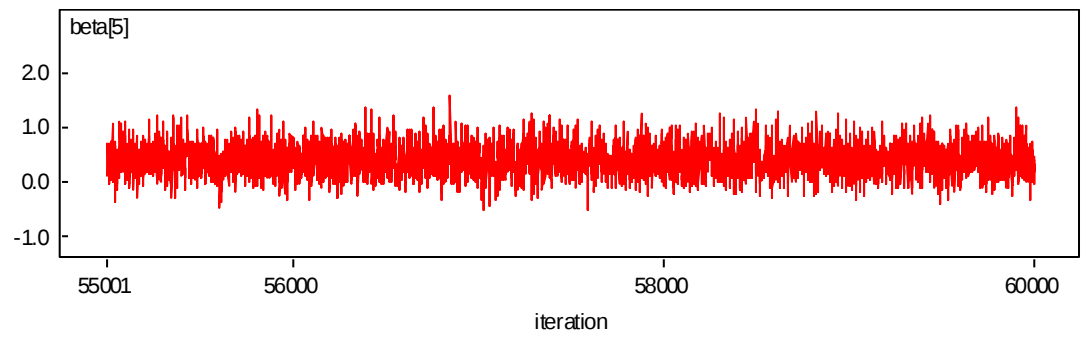
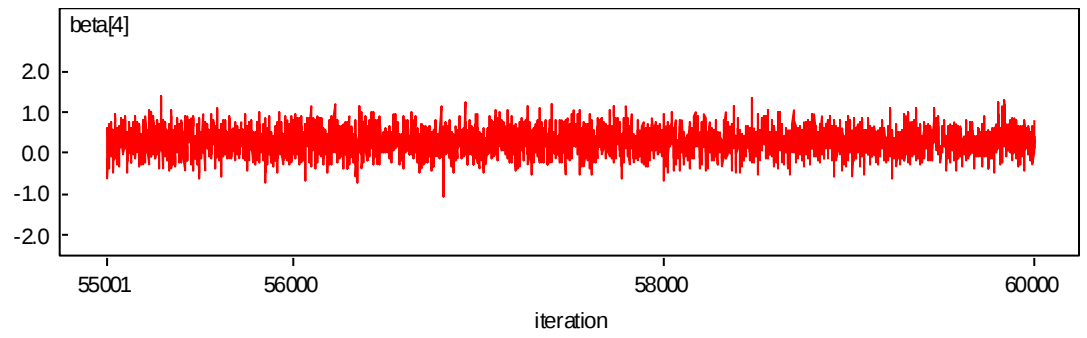
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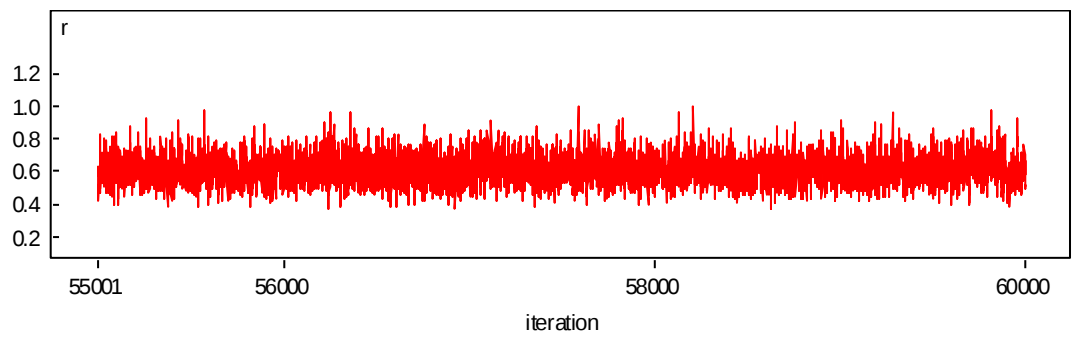
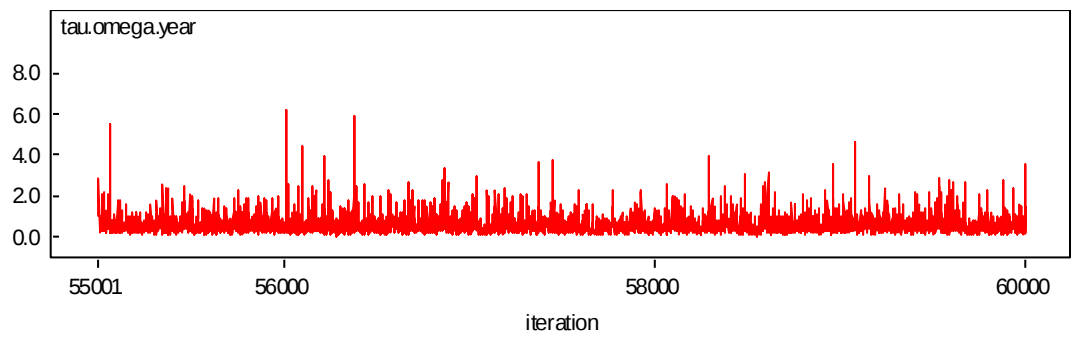
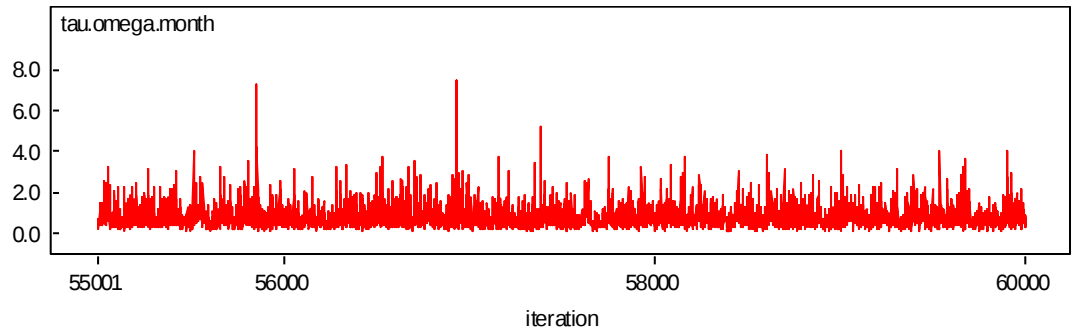
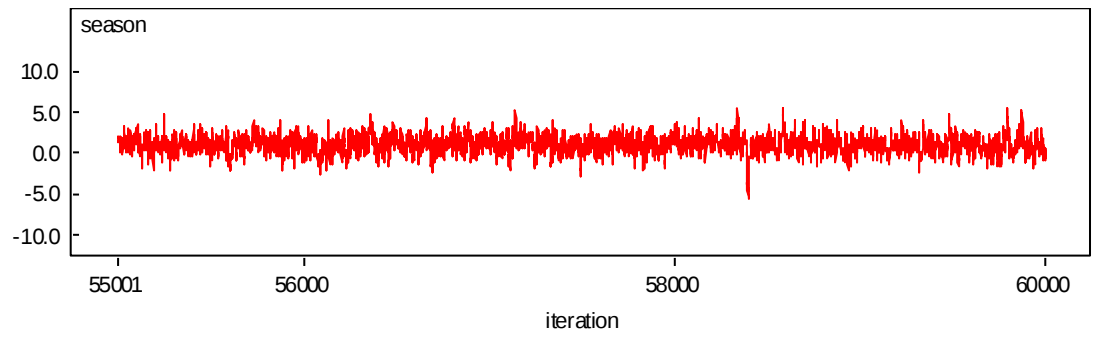
}

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Figure 1S. History plots of the key parameters from the model adjusted for under-reporting.







# Chapter 6

Geostatistical mapping of the seasonal  
spread of under-reported dengue cases  
in Bangladesh

Sifat Sharmin, Kathryn Glass, Elvina Viennet, David Harley

## Abstract

Geographical mapping of dengue in resource-limited settings is crucial for targeting control interventions but is challenging due to the large number of unreported cases and lack of infrastructure for data collection. We investigated the spatial variation in monthly dengue cases in Bangladesh in relation to climatic and demographic variables. A Bayesian spatio-temporal model was applied to the district level monthly number of reported dengue cases aggregated over the period 2000 to 2009. Under-reporting in national hospital-based passive dengue surveillance data was captured using climatic thresholds suitable for dengue transmission in Bangladesh and by incorporating a prior estimate of the percentage of cases reported in neighbouring dengue endemic countries. The model estimated that 80% of the annual dengue cases occurred between August and September. Around 67% of the districts across the country were identified as affected with dengue virus during this high transmission season, contrasting with routine surveillance data suggesting only 42%. Of the 67% districts estimated as affected, 79% had cases in both months while 56% of the 42% districts reported cases, as observed from the surveillance data, had continuous transmission suggesting the failure of the surveillance in identifying lower incidence as the time progress. Most cases were identified in southern Bangladesh with around 92% of the estimated total in the capital Dhaka (located almost in the middle of the country). The findings provide useful information to help direct surveillance in areas where dengue is transmitted but not detected by routine surveillance.

**Key words** Bayesian analysis, dengue, spatio-temporal mapping, under-reporting, passive surveillance

## Introduction

Dengue is a neglected tropical disease caused by the dengue virus (DENV) and is transmitted by female *Aedes* mosquitoes, predominantly *Aedes aegypti* and *Aedes albopictus*. The severe forms of the disease are potentially fatal. The World Health Organization (WHO) estimates that about 52% of the people at risk of dengue worldwide live in 10 countries of the WHO South-East Asia Region.<sup>1</sup> Bangladesh, located in South Asia and surrounded by India and Myanmar (Figure 1), within which dengue is endemic, experienced the first epidemic of dengue in 2000.<sup>2</sup> Since then cases have been reported every year, most commonly among adults and older children, throughout the country.<sup>3</sup> Of the 64 Bangladeshi districts (Bangladesh's second largest administrative unit), 29 reported dengue cases between 2000 and 2009, with Dhaka consistently reporting the largest number of cases.<sup>4</sup> Heterogeneity in the distribution of hospitals across the country and differentials in treatment seeking behaviour based on location are likely to bias reporting.<sup>3</sup> However, despite no effective control program being introduced and no changes in surveillance until 2010 when serological confirmation was mandated for case reporting, nationally reported cases have declined since 2002.<sup>3</sup> This might be partially attributable to increased prevalence of immunity and reduction in mosquito breeding sites resulting from public awareness.<sup>3</sup> However, there is considerable under-reporting inherent in the surveillance system.<sup>3</sup> A study investigating the global distribution of dengue burden estimated an average of 4,097,833 symptomatic infections (95% Bayesian credible interval: 2,952,879-5,608,456) occurred in Bangladesh in 2010<sup>5</sup> but only 409 were reported to authorities.<sup>4</sup>

Climatic factors (mainly temperature and rainfall) play an important role in dengue transmission, influencing the survival and development rate of vector and virus. The aquatic larval and pupal stages of the *Aedes* mosquitoes require fresh water and rainfall interacting with water storage practices influences the availability of breeding sites.<sup>6</sup> Temperature influences mosquito development, the mosquito biting rate, the extrinsic incubation period of DENV, and vector-virus-host interaction.<sup>7-9</sup> The well-established causal relationships between temperature, rainfall, and dengue transmission are, however, non-linear as excessive rainfall and extreme heat adversely affect mosquito survival.<sup>10, 11</sup> In Dhaka, mean monthly temperatures above 29°C in the previous month and mean monthly rainfall of more than 15mm in the previous two months were found to be associated with reduced transmission of dengue.<sup>12</sup>

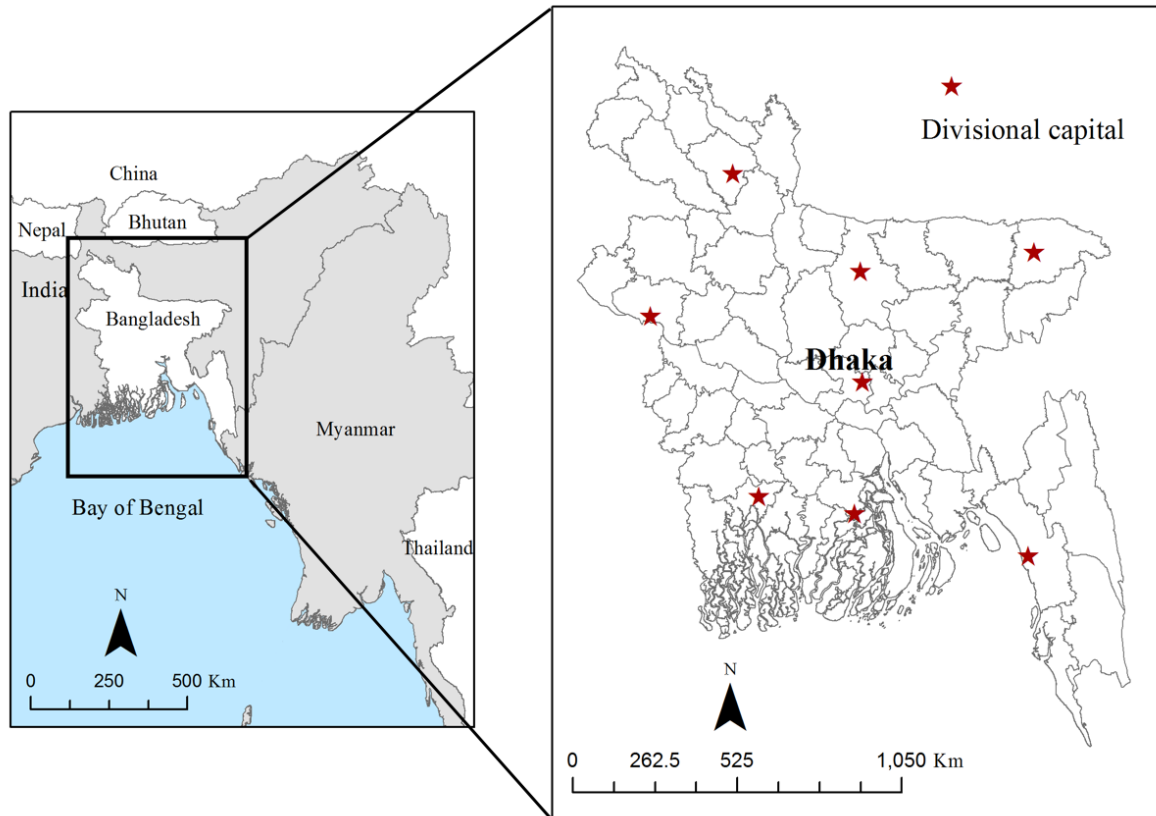


Figure 1: Location of Bangladesh (left) and district level map of Bangladesh with the eight divisional (largest administrative unit) capitals marked with a red star (right).

Climatic similarity and the movement of viraemic individuals in geographically neighbouring areas introduce spatial correlation in dengue incidence<sup>13, 14</sup> and might lead to spurious model-based incidence estimates if ignored. Bayesian geostatistical modelling approaches are powerful for disease mapping, by explicitly accounting for spatial correlation in disease data while incorporating uncertainty in data and model parameters.<sup>15, 16</sup> Within a Bayesian paradigm, inference about model parameters is based on the posterior distribution derived from the combination of data and pre-existing knowledge of parameter values, and therefore does not require a large sample size assumption as does the frequentist approach. Therefore, more robust estimates can be obtained when the disease is rare<sup>17</sup> or data on case numbers are limited.

Effective dengue control requires reliable maps of its spatial distribution, so that intervention strategies can be implemented cost-effectively. The only existing spatial mapping study of dengue in Bangladesh identified Dhaka as the most likely cluster for dengue transmission during 2000-2009 with a small number of secondary clusters in the southern part of the country in 2000.<sup>18</sup> However, under-reporting in surveillance data was not considered in the analysis.

Also, potential causes of geographical variation in dengue transmission (such as climate and socio-demographic factors) were not considered.

The aim of this study was therefore to produce maps of the monthly spatial variation in dengue incidence at the district level in Bangladesh in relation to climatic and demographic factors. The resulting maps can aid the efficient distribution of vector control interventions to areas of highest need. The method is useful for identifying locations where DENV transmission occurs but prevalence data are lacking.

## **Materials and methods**

### ***Study area***

Bangladesh has a hot, humid, tropical climate with monsoon occurring during June to September. Monsoon rainfall, about four-fifths of the mean annual rainfall, ranges from 1,527mm in the west to 4,197mm in the east, and the mean monthly monsoon temperature of 29°C averaged across the country is generally suitable for dengue transmission.

High population density and unplanned urbanization leading to over-crowding in divisional cities with inadequate water supply, and inefficient drainage and waste disposal increase risk for dengue since the vector mosquitoes breed in water storage containers in and around houses.<sup>6, 19, 20</sup>

### ***Data***

Dengue notification data, consisting of suspected, probable, and confirmed cases reported to the Directorate General of Health Services between January 2000 and December 2009 were used in the analysis. Under-ascertainment of symptomatic dengue cases is highly likely since the passive surveillance system only reports cases admitted to hospital.<sup>3</sup> Daily rainfall (mm), and minimum and maximum temperatures (°C) measured from 35 stations were sourced from the Bangladesh Meteorological Department with around 2%, 3%, and 3% missing data, respectively. Weather values for days with missing data were filled by averaging data from

adjacent days. Monthly averages of these weather variables were then calculated from daily records. Missing values for months were supplemented with the average of non-missing values from three neighbouring stations. Bayesian kriging<sup>21</sup> was used thereafter to predict weather values in districts without a meteorological station. Mean monthly rainfall, mean monthly temperature, and monthly total dengue cases over the 10 years were then aggregated by month and used in the model development discussed below.

The population density for each district used in the analysis was the mid-year estimate derived by linear interpolation between two population census years (2001 and 2011).

### ***Model formulation***

More than half of Bangladeshi districts did not report any dengue cases during the study period 2000 to 2009. It was unclear whether these missing values corresponded to true zeros or a lack of reporting, so we specified reported case numbers as lower bound for the true counts in our model only when the corresponding district had a suitable climate for dengue transmission (mean monthly temperature 26-29°C in the previous month and mean monthly rainfall 10-15mm in either of the previous two months).<sup>12</sup>

To model the monthly spread of dengue, district-wise dengue notification data were aggregated by month over the period 2000 to 2009 and modelled via a generalized linear mixed model with a logarithmic link function and the population of the districts as an offset. Let  $y_{it}$  be the number of reported dengue cases for the  $i^{th}$  ( $i = 1, 2, \dots, 64$ ) district in the  $t^{th}$  ( $t = 1, 2, \dots, 12$ ) month. To incorporate current knowledge about the reporting percentage of dengue cases<sup>22, 23</sup>, we assumed that the reported dengue cases,  $y_{it}$ , are Poisson distributed and are a function of the proportion of cases reported and the estimated total number of cases,  $z_{it}$ . Given that the reporting percentage can vary over time and district, we allowed considerable variation in the reporting percentage by assuming that 95% of true reporting percentages lie between 1% and 16% with a median of 8%. However, due to the lack of data about spatial-temporal variation in reporting, the reporting percentage was assumed to be the same for each of the districts and months. Preliminary non-spatial analysis indicated that the following factors should be included in the analysis: mean monthly temperature at lag one month, mean monthly

rainfall at lag one and two months, and population density.<sup>24</sup> Because of the potential confounding effect, the variable “border” indicating whether a district bordered India or Myanmar was included in the model. This variable was used as a proxy for movement across borders with neighbouring dengue endemic countries. District-wise variation in population age structure was not considered since cases have been reported in both children and adults, making it unlikely that the spatial incidence is influenced by the age pattern of the districts. The model is then specified by:

$$y_{it} \sim \text{Poisson}(\lambda_{it}) I(\text{censored}[i, t],); i = 1, 2, \dots, 64; t = 1, 2, \dots, 12$$

$$\lambda_{it} = \text{prop.reported}_{it} * z_{it}$$

$$z_{it} \sim \text{NegBin}(\mu_{it}, r)$$

$$\log(\mu_{it}) = \log(\text{Population}_i) + \alpha + \beta_1 * \text{Temp}_{i,t-1} + \beta_2 * \text{Rain}_{i,t-1} + \beta_3 * \text{Rain}_{i,t-2} + \beta_4 * \text{border}_i + \beta_5 * \text{Popden}_i + \phi_i + \text{AR}(1)_t + \text{Month}_t,$$

where  $\lambda_{it}$  and  $\mu_{it}$  denote the average number of reported and estimated total cases, respectively, for the  $i^{\text{th}}$  district in the  $t^{\text{th}}$  month.  $\text{Month}_t$  is a random month effect and  $\text{AR}(1)_t$  is a first order autoregressive month effect that captures the correlation in dengue cases between consecutive months. Dengue incidence is expected to be correlated in space due to similar climatic exposures and therefore it is expected that nearby locations will have similar dengue risk. To take into account spatial correlation, random area effects,  $\phi_i$ , were introduced at the district level assuming a conditional autoregressive (CAR) structure. The spatial correlation is defined among neighbouring districts having a common border.

A posterior predictive assessment, which compares the lack of fit of the model to the data with the lack of fit of the model to a replicated data set, was performed by calculating a Bayesian p-value to check the adequacy of the model. The Bayesian p-value quantifies the proportion of times that the discrepancy measure (sum of squared residuals) for the replicated data is greater than the discrepancy measure computed for the actual data set. A Bayesian p-value nearer to 0.5 than 0 or 1 suggests a reasonable fit of the model to the observed data.<sup>25</sup>

Following a Bayesian model specification, prior distributions were assigned to the model parameters. Independent diffuse Gaussian priors (with mean 0, precision  $1 \times 10^{-3}$ ) were chosen for the intercept  $\alpha$  and regression coefficients  $\beta_j$  ( $j = 1, \dots, 4$ ) due to the absence of

any prior knowledge. A uniform prior (0, 1) was assumed for  $\beta_5$ , the coefficient of population density, which is known to exert a positive influence on dengue incidence. To model the parameter *prop.reported*, a beta prior was assigned which was chosen to have a median of 0.08 with 95% confidence interval (0.01, 0.16) to reflect the variation in reporting percentage mentioned earlier. Weakly informative gamma hyperpriors (shape parameter 0.5, inverse scale parameter 0.5) were assigned to the precision parameters of  $\phi_i$ ,  $AR(1)_t$ , and  $Month_t$  in the second stage of the hierarchy. The scale parameter  $r$  was also set to a gamma prior (0.5, 0.5).

To assess model sensitivity to the prior specification, alternative prior distributions were considered for regression coefficients,  $\beta_j$  ( $j = 1, \dots, 5$ )  $\sim d_{unif}(-1, 1)$ . Gamma distributions with shape parameter 0.5 and inverse scale parameter 0.0005 were considered for the precision parameters. The variation in estimated values of regression coefficients and precision parameters across the different prior distributions reflect whether the results are dependent on the choice of prior.

The model parameters were estimated using Markov chain Monte Carlo (MCMC) simulation in WinBUGS 14 (MRC Biostatistics Unit, Cambridge, UK). All continuous variables were mean centred to aid MCMC convergence. A single chain of 20,000 iterations was run keeping every 30<sup>th</sup> with the first 5,000 used as a burn-in. All trace and history plots of model parameters indicated convergence.

## Results

Table 1 displays parameter estimates from the spatio-temporal model. Only population density was significantly (positively) associated with dengue. Districts adjoining the borders with India and Myanmar were not found to have significantly higher incidence compared with non-adjacent districts. The model had large residual spatial variation (48.00; 95% credible interval: 25.26, 96.82) indicating a tendency for clustering of dengue cases that is not explained by the climatic and demographic variables included in the model. However, the Bayesian p-value (0.49) confirms that the model provides a reasonable fit to the observed data.

**Table 1.** Posterior median values and 95% credible intervals for estimates of the spatio-temporal model.

| Variable                                 | Posterior median | 95% credible interval |
|------------------------------------------|------------------|-----------------------|
| Mean temperature (°C) at lag one month   | -0.48            | -64.24, 61.00         |
| Mean rainfall (mm) at lag one month      | 0.01             | -62.38, 63.46         |
| Mean rainfall (mm) at lag two months     | 0.24             | -60.85, 61.97         |
| Border                                   |                  |                       |
| No (Ref)                                 | —                | —                     |
| Yes                                      | -0.97            | -3.35, 1.40           |
| Population density                       | 0.51             | 0.02, 0.97            |
| Spatial variance                         | 48.00            | 25.26, 96.82          |
| Precision of autoregressive month effect | 0.31             | 0.09, 1.00            |

No significant changes in estimates were observed in the model with altered prior specifications except for population density (Table 2). The Uniform priors for regression coefficients resulted in narrower 95% credible intervals and the gamma prior for the precision parameters resulted in very similar estimates. Therefore, our results were robust across a reasonable range of prior specifications.

**Table 2.** Posterior median values and 95% credible intervals for estimates of the spatio-temporal model with altered prior specifications.

| Prior                                                                         | Posterior median | 95% credible interval |
|-------------------------------------------------------------------------------|------------------|-----------------------|
| Mean temperature (°C) at lag one month;<br>$\beta_1 \sim \text{dunif}(-1, 1)$ | -0.01            | -0.95, 0.95           |
| Mean rainfall (mm) at lag one month;<br>$\beta_2 \sim \text{dunif}(-1, 1)$    | -0.0001          | -0.95, 0.96           |
| Mean rainfall (mm) at lag two months;<br>$\beta_3 \sim \text{dunif}(-1, 1)$   | -0.002           | -0.95, 0.95           |
| Border; $\beta_4 \sim \text{dunif}(-1, 1)$                                    |                  |                       |
| No (Ref)                                                                      | —                | —                     |
| Yes                                                                           | -0.30            | -0.97, 0.84           |
| Population density;<br>$\beta_5 \sim \text{dunif}(-1, 1)$                     | 0.01             | -0.95, 0.95           |
| Precision of spatial correlation<br>$\sim \text{dgamma}(0.5, 0.0005)$         | 0.02             | 0.01, 0.04            |
| Precision of autoregressive month<br>effect $\sim \text{dgamma}(0.5, 0.0005)$ | 0.35             | 0.10, 1.25            |
| Precision of month<br>effect $\sim \text{dgamma}(0.5, 0.0005)$                | 280.40           | 1.10, 4659.00         |

Figure 2 shows the spatial variation in monthly aggregated dengue cases reported over 2000-2009, compared with the corresponding fitted values obtained from the spatio-temporal model. The model clearly captures the trend of increasing case numbers from June with the highest in August and gradual fall afterwards (Figure 2).

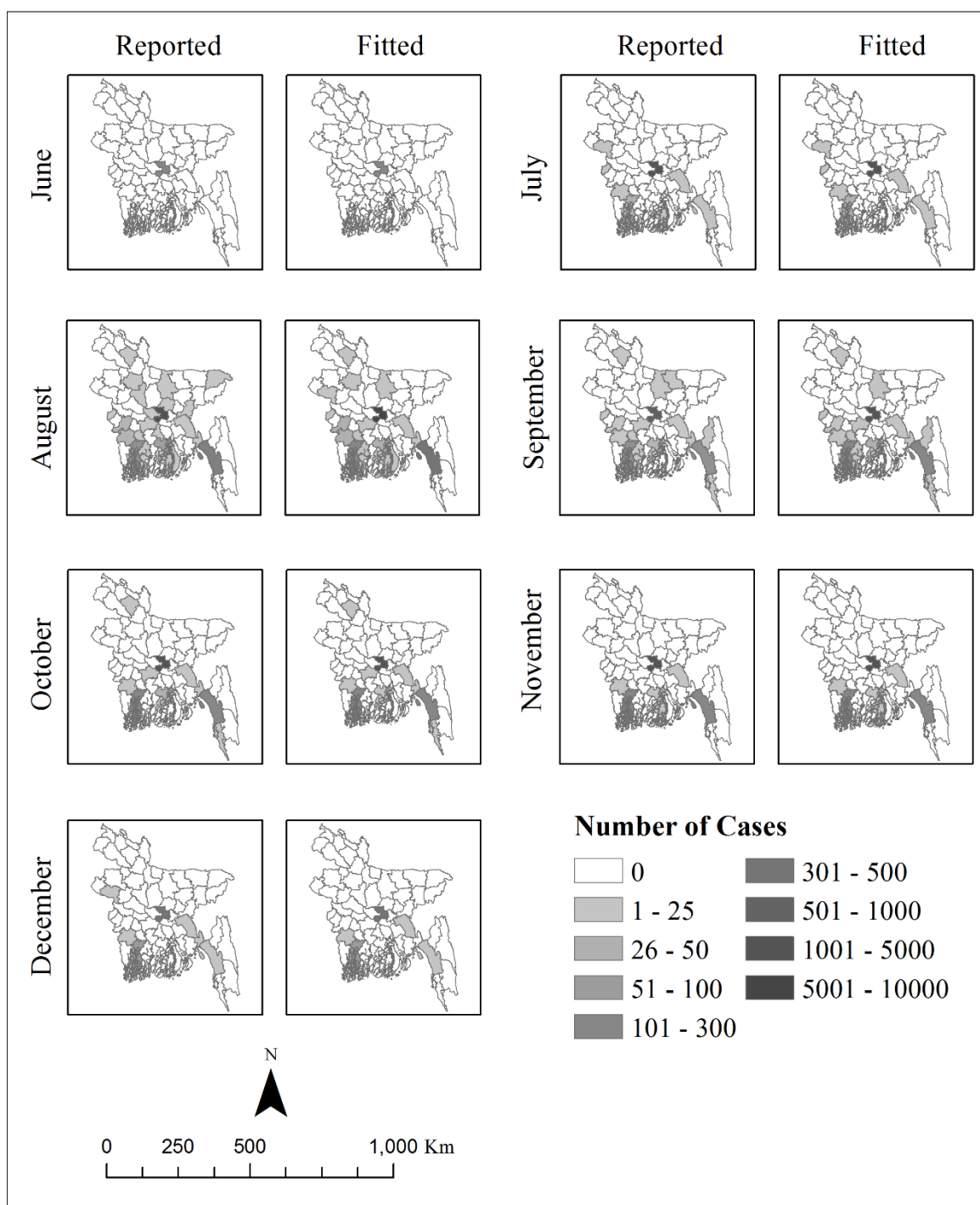


Figure 2: Spatial pattern in monthly aggregated dengue cases reported between 2000 and 2009 and median number of fitted dengue cases, estimated by the spatio-temporal model. Only 0.05% of cases were reported outside the period June-December, and are not shown here.

The maps in Figure 3 depict spatial variation in reported and total case numbers estimated by the spatio-temporal model within and between months. The maps show higher transmission in

the south than the north. Dhaka, located almost at the centre of the country, has the majority of cases, around 92% of all cases estimated across the country.

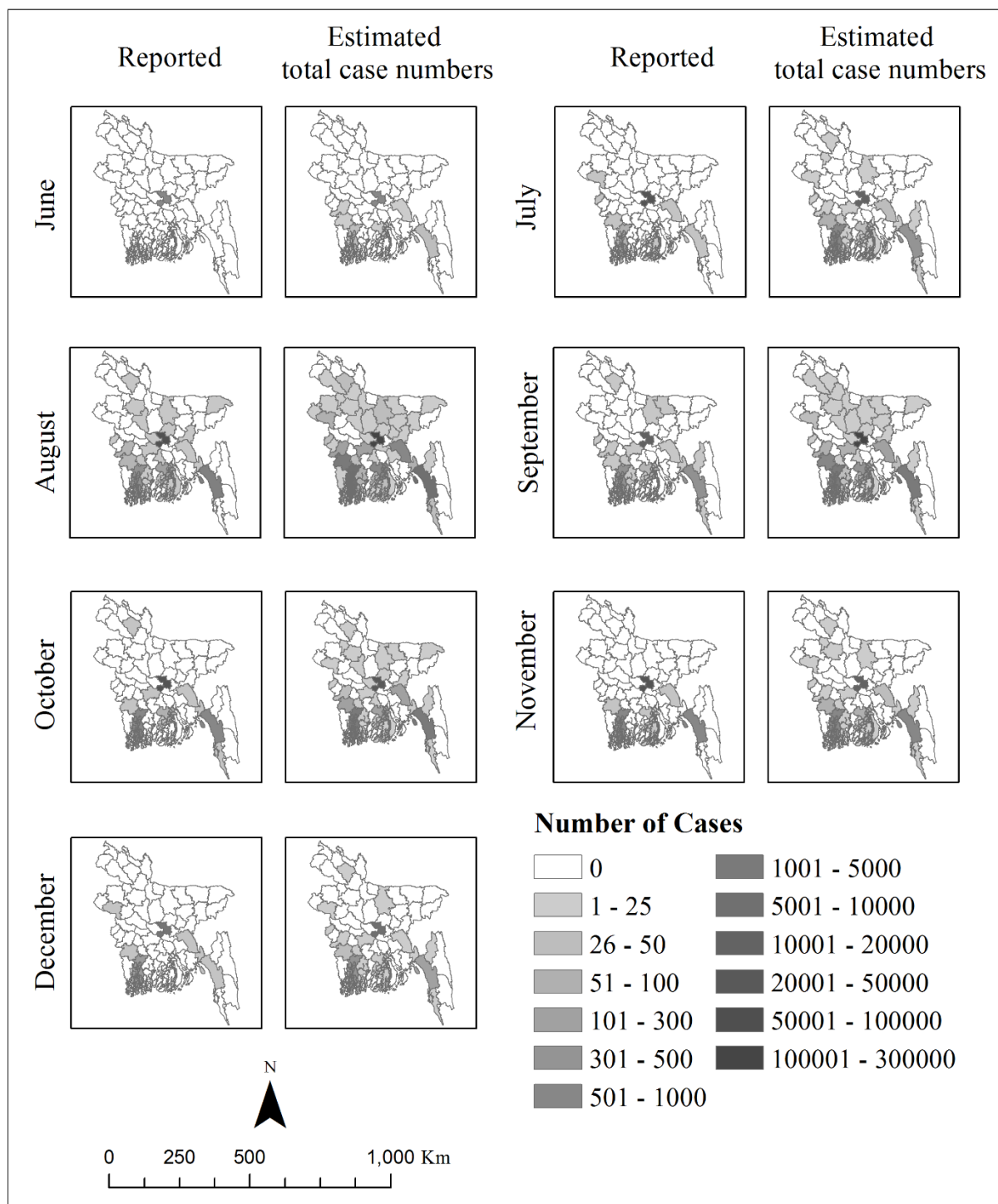


Figure 3: Comparison between spatio-temporal patterns of reported and total case numbers, estimated from the spatio-temporal model.

Dengue transmission fluctuated over the months with the highest transmission (80% of estimated annual cases) occurring in August and September. During this period, 67.19% of districts were estimated to have cases, of which 79.07% had cases in both months and 20.93% had cases only in August. However, national surveillance data reports cases from only 42.18% of districts of which 55.56% had reported cases in both months, 33.33% only in August, and 11.11% only in September.

The model identified several districts (mostly in the northern part of the country, see Figure 3) with modelled transmission but without any reported cases (Figure 4). The Venn diagram in Figure 4 demonstrates the intersections between reported and estimated number of districts affected with dengue. The small circles (*Estimated*) refer to the estimated number of districts affected (e.g., 7 districts in June) in each of the months from June-December while the large one (*Reported*) refers to the number of districts that reported dengue (e.g., 1 district in June) in the corresponding month. The intersection (dark shaded area) between *Estimated* and *Reported* is the number of districts estimated as well as reported with dengue cases in that month (e.g., 1 district in June). In August, when the highest number of cases was reported, 24 districts reported cases but the model identified a further 19 (Figure 4).

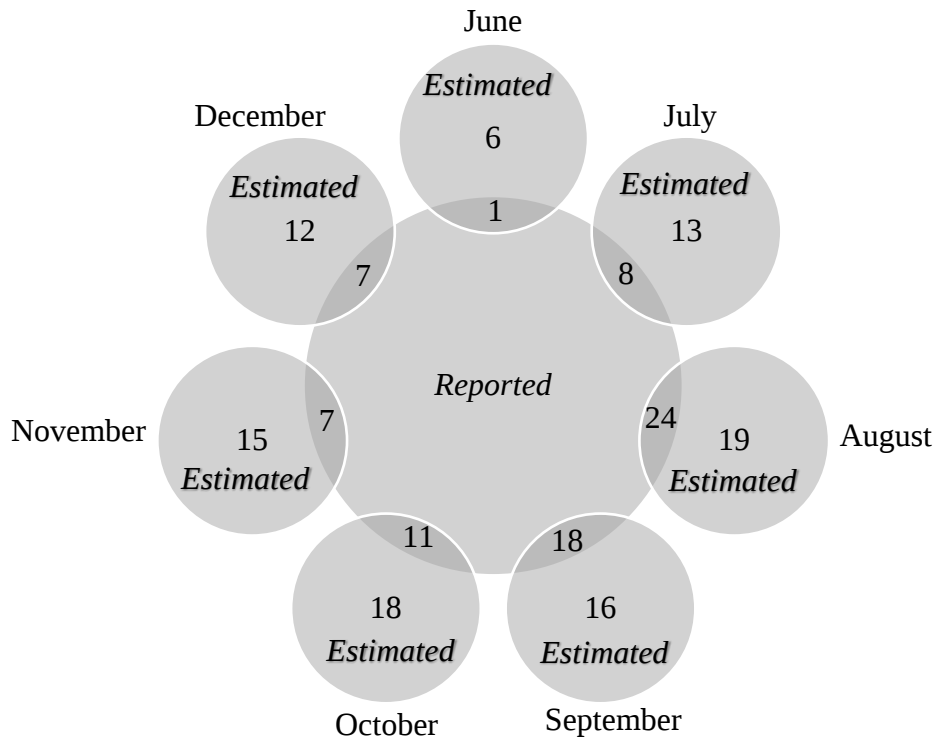


Figure 4: Venn diagram to show the number of districts that reported dengue cases during 2000-2009 and the number of districts with transmission estimated from the spatio-temporal model.

Figure 5 shows the spatial variation in the percentage of estimated cases reported by month (July-September). In general, districts with lower case numbers had a higher percentage of estimated cases reported compared to the districts with higher case numbers during the high transmission months of August and September.

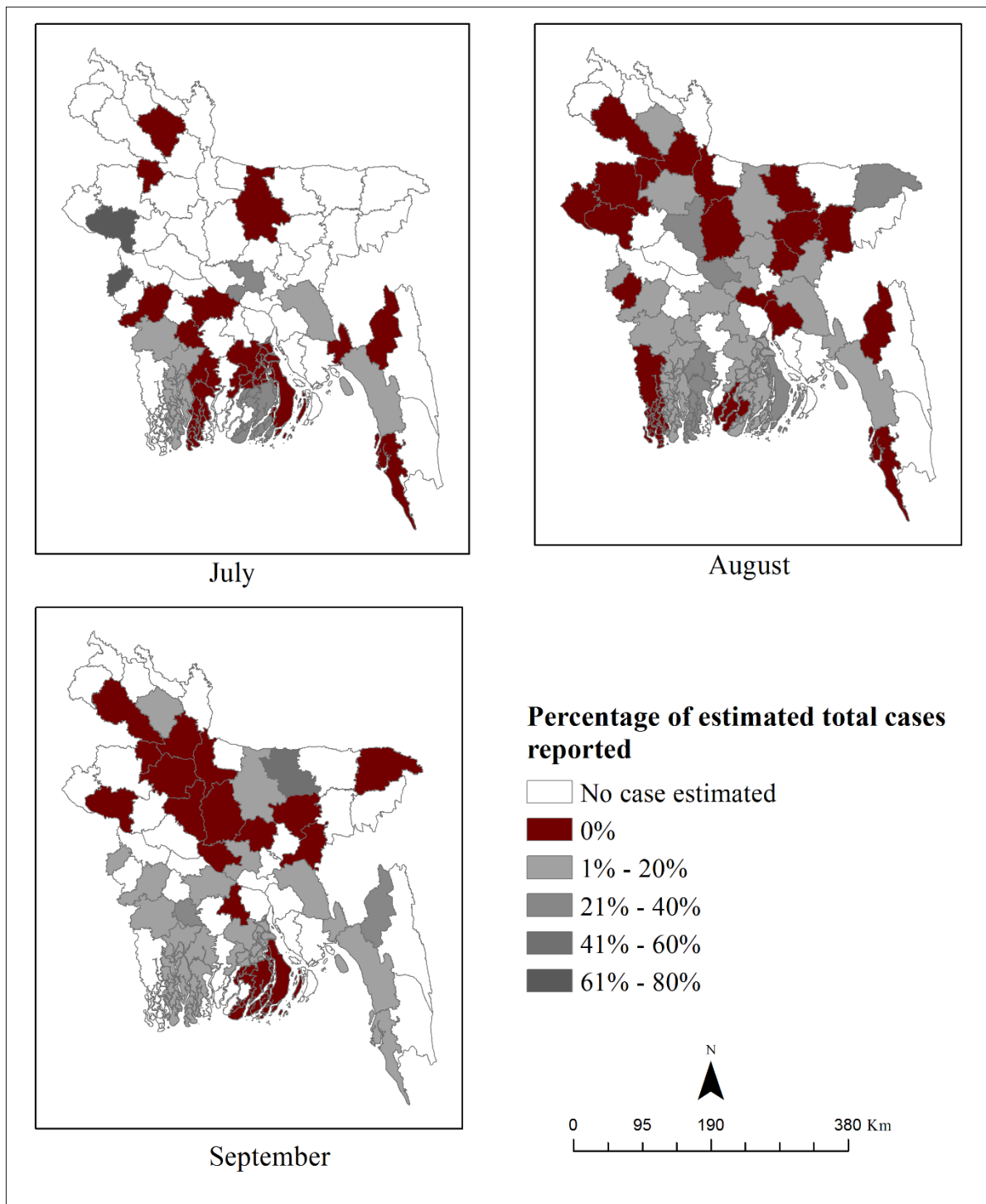


Figure 5: Monthly spatial variation in the percentage of estimated total cases that were reported to surveillance system, calculated as  $(\text{reported case numbers} / \text{median estimate of total case numbers estimated by the model}) \times 100$ .

## Discussion

Ours is the first model-based estimates of the monthly geographical distribution of dengue cases in Bangladesh. The model identifies highest transmission during August and September with 80% of estimated total cases across the year. Transmission is spatially heterogeneous, with higher number of cases estimated in the south, and the highest in Dhaka. An earlier study investigated space-time clusters of dengue transmission in Bangladesh from 2000 to 2009 and reported Dhaka as the most likely cluster throughout the study period, with a small number of secondary clusters in the south of the country in 2000.<sup>18</sup> June-November was reported as the high transmission season when all the clusters were identified.<sup>18</sup>

Our model also identifies districts with transmission that went unreported; during the high transmission months of August and September, cases were reported from 42% of districts whereas the model estimated that 67% of districts were affected. We estimate that the reporting percentage varies over months. During the high transmission months, reporting is generally higher in districts with low transmission compared to the districts with high transmission. However, with the end of the high transmission season, lower case numbers are often unreported.

Population density, as expected, was found to be significantly associated with dengue. High transmission of dengue in densely populated areas has been reported in multiple studies.<sup>26, 27</sup> We found no significant relationships between dengue and climatic variables, despite significant spatial variation in temperature and rainfall across Bangladesh. During the study period only 29 of the 64 Bangladeshi districts reported dengue.<sup>4</sup> Because of data scarcity, the standard practice of excluding areas with no cases reported was infeasible. Absence of dengue cases from over half of the total districts during the high transmission season renders the identification of the dengue-climate relationships difficult.

The strength of our model is its ability to generate estimates of dengue in areas with suspected under-detection by assuming that the reported number of dengue cases is the lower bound for the true case numbers, provided the climate in the previous two months was suitable for transmission. The assumption that transmission is governed by climatic suitability is reasonable, especially in the absence of control intervention. Use of pre-existing knowledge

about the reporting percentage further strengthens our model.<sup>22, 23</sup> However, given the absence of information on the spatial and temporal variation in reporting percentage in Bangladesh, in the Bayesian model, we assumed the same prior distribution for the parameter *prop.reported* for all districts and months. Our model was incapable of capturing the inter-annual variation in dengue and climate variables due to the aggregation of monthly counts over the study period which was done to model the monthly spread of dengue across the country.

In conclusion, our study provides model-based estimates of spatial variation in monthly dengue cases across Bangladesh without compromising data for model fit. We believe that our findings provide a valuable assessment of the national dengue situation accounting for under-reporting. This study will contribute useful information for prioritizing and targeting interventions at suitable times for dengue control and elimination across Bangladesh.

## Acknowledgements

We thank Dr. Ayesha Akhter, In-charge, National Health Crisis Management Centre and Control room, Directorate General of Health Services, Dhaka for generously providing dengue surveillance data.

SS was supported by The Australian National University Higher Degree Research Merit Scholarship (<http://www.anu.edu.au/students/scholarships-support/anu-university-research-scholarships>).

Conflict of interest: The authors report no conflicts of interest.

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# Chapter 7

## Discussion and Conclusions

## 7.1 Discussion of main findings

The work presented in this thesis extends our knowledge of dengue epidemiology in Bangladesh. This enables us to gain a better understanding of the effects of weather and demographic factors on dengue, filling knowledge gaps from prior studies.

Although dengue has been endemic in Bangladesh since the first epidemic in 2000, little had been published on its transmission dynamics and epidemiology. The narrative review in Chapter 3 discusses the emergence and establishment of endemic dengue, the apparent fall in reported dengue case numbers following the largest epidemic in 2002, and the key risk factors for dengue, including demographic, epidemiologic, and climatic factors. An extensive literature search was performed to understand the relative influence of climatic and non-climatic factors on incidence of dengue. It appears that while projected changes in climate increase the potential for epidemics, demographic, environmental, and social factors are also crucial. High fertility, greater economic inequity, increased movement of people, and fast urbanisation will all exacerbate dengue risk<sup>1, 2</sup> and therefore, must be considered in predicting the impact of future changes in climate on dengue transmission. This review offers a comprehensive understanding of the history and epidemiology of dengue in Bangladesh, laying down the foundations for the modelling which follows.

The three models developed in Chapter 4, 5, and 6 combine meteorological data, demographic data, and dengue surveillance data to create models accounting for the spatial and temporal variation in these variables.

I first used a negative binomial generalised linear model to account for the over-dispersion present in the dengue count data. The model was implemented using a frequentist approach with the aim of identifying climatic and non-climatic factors that significantly influence dengue transmission in Dhaka. The dengue notification data used in the model had very few cases outside the transmission season (June-December), presumably an artefact of the passive hospital-based surveillance system. However, the improved surveillance with year round reporting, wider coverage of hospitals, and mandatory serological confirmation for case reporting that commenced in 2010 also reports very few cases during this period (January-May). Therefore, this under-estimation is unlikely to influence the findings regarding the risk

factors of dengue. A wide range of diagnostic tests were performed to confirm the goodness-of-fit of the model. The model reveals that dengue incidence is not only influenced by ambient temperature but also by fluctuation in daily temperature. High mean monthly temperature with low fluctuation increases dengue incidence one month later in Dhaka, a finding that is consistent with laboratory experiments, confirming the sensitivity of *Ae. aegypti* and DENV to the diurnal temperature range.<sup>3-5</sup> The highly significant synergistic effect demonstrated by the interaction between mean monthly temperature and diurnal temperature range indicates that the use of either mean temperature or diurnal temperature range alone is insufficient to explain the influence of temperature on dengue. The significant positive influence of temperature on dengue incidence in Dhaka reported in this thesis is consistent with the findings of other studies.<sup>6, 7</sup>

The abundant monsoon rainfall in Bangladesh creates breeding sites with consequent increase in the mosquito population. The model identifies a significant increase in dengue incidence following higher rainfall in the previous two months in Dhaka. The positive association between rainfall and dengue incidence has been described previously in Dhaka, Bangladesh, and in other countries.<sup>2, 7-10</sup>

Findings from Chapter 4 include the identification of the influence of ENSO on dengue incidence in Dhaka. The strength of ENSO events defined in terms of SSTA are usually classified into four categories: very strong ( $SSTA \geq 2.0$ ), strong ( $1.5 \leq SSTA \leq 1.9$ ), moderate ( $1.0 \leq SSTA \leq 1.4$ ), and weak ( $0.5 \leq SSTA \leq 0.9$ ). The sea surface temperature anomaly in a given month is found to exert a negative effect on dengue incidence of the same month in Dhaka while the effect is opposite at a lag of one month. A biologically plausible explanation for this finding relates to the influence of ENSO on monsoon rainfall in Bangladesh; strong El Niño events are usually associated with dry weather whereas moderate events sometimes cause flooding, both of which can lead to fewer adult mosquitoes and consequently lower transmission in that month. On the other hand, heavy monsoon rainfall associated with La Niña events can cause an increase in transmission as the post-rainfall humid weather increases mosquito-human contact. The positive influence of SSTA on incidence could be explained through the increase in mosquito populations resulting from water storage during drought. Similar non-linear influences of ENSO on dengue incidence in Bangladesh have recently been reported at a lag of four months.<sup>11</sup> The increasing incidence of dengue during El Niño has been observed in Mexico,<sup>12, 13</sup> Thailand,<sup>14</sup> and several countries of the South Pacific.<sup>15</sup>

In Chapter 5, I extend the model to examine the non-linear effects of weather on dengue using a semi-parametric thin-plate spline approach. This model was fitted within a Bayesian framework in order to quantify under-reporting in national dengue surveillance data using information on proportion of dengue cases reported to surveillance in neighbouring countries<sup>16</sup>,<sup>17</sup>. While the frequentist model developed in Chapter 4 performed well in identifying the key exposure variables for dengue transmission, here I adopted a Bayesian approach to take account of uncertainty in data and parameter estimates and to incorporate existing knowledge about under-reporting via a prior distribution. Inference about model parameters in a Bayesian framework is based on the posterior distribution derived from the combination of data and pre-existing knowledge of parameter values and therefore does not require a large sample size assumption unlike the frequentist approach. Therefore, more robust estimates can be obtained when the disease is rare or data on case numbers are limited.

The Bayesian temporal model identifies that mean monthly temperature above 29°C decreases transmission one month later. A similar fall in transmission is noticed with mean monthly rainfall over 15mm during the previous two months. There are biologically plausible reasons for these associations, such as (1) decreased survival of adult and aquatic forms of mosquitoes at temperatures above 30°C and 36°C, respectively<sup>18</sup> and (2) reduction in adult mosquito population due to the heavy rainfall that washes away breeding sites<sup>2</sup>. These findings linking dengue and weather corroborate a previous study reporting non-linear relationships between minimum and maximum temperature and rainfall with dengue in Mexico.<sup>19</sup> The optimal average monthly maximum temperature for dengue transmission was 32°C and monthly total rainfall above 550mm was associated with lowered transmission at lags of one and two months. The presence of non-linearity in dengue-climate relationships highlights the importance of correct specification of the relationship to avoid over-estimation of the effect of increasing temperature. The model presented here allows the projection of potential impacts of changing climate on dengue incidence with greater statistical confidence.

The model estimated that only 2.8% (95% credible interval: 2.7-2.8) of total cases estimated in Dhaka were reported through the surveillance system. The parameter, *prop. reported*, used to supply existing information about the extent of under-reporting into the model was considered fixed in time and therefore, was unable to consider variability in under-reporting over time or season.

Both models are adjusted for inter-annual variability that is common in dengue incidence.<sup>14</sup> Further, correlation in monthly dengue incidence is also captured.

Chapter 6 describes the first study to use dengue-climate relationships to model spatio-temporal variation in dengue incidence in Bangladesh at the district level. A Bayesian spatio-temporal model is developed to estimate the spatial heterogeneity in monthly dengue incidence using the climatic and demographic risk factors that influence dengue transmission. An obstacle in modelling monthly spatial transmission at the district level is the absence of reported cases from over half of the total districts during the high transmission season. However, it was not clear whether these missing values correspond to true zeros or a lack of reporting. Therefore, censoring was introduced by assuming reported case numbers are a lower bound for the true counts, provided the climate in previous two months were suitable for transmission.

The highest transmission is estimated for Dhaka with the majority of the burden concentrated in southern Bangladesh. The lack of association between dengue and climatic variables may have been caused by the absence of dengue cases in surveillance data from over half of the districts during the study period and the aggregation of data to produce January-December monthly averages from the 10-year study period. Aggregating month-year data to monthly averages over the study period could have averaged out the inter-annual variation in climate, lowering the likelihood of significant associations.

Although the spatio-temporal model identified districts with transmission that were not identified through surveillance, a large proportion of the spatial correlation was unexplained by the parameters of the model. Another limitation is the use of same prior for each of the districts and months ignoring the variation in under-reporting in space and time. Also, the seasonal movement of human hosts around the country was not considered in the modelling approach. The proximity matrix used to account for spatial correlation assumes dependence among the neighbouring districts. However, divisional capital cities, for example, are more closely connected by road transport links, in terms of dengue transmission, to certain areas through the trade of good and services, rather than neighbouring districts.

All three models developed in this thesis provide robust evidence of a significant increase in dengue incidence with an increase in population density. In densely populated areas, interaction

between humans and mosquitoes and human mobility have been associated with spatial dispersion of dengue infection.<sup>20, 21</sup>

A key aspect of this thesis is that I investigate and reveal the extent of under-reporting in dengue surveillance data; this is essential to estimate the changing burden of dengue along with the transition from mild dengue to fatal haemorrhagic forms. Only 2.8% (95% Bayesian credible interval 2.7-2.8) of cases estimated in Dhaka during 2000-2009 were reported to the surveillance system and the reporting percentage was found to vary over months and districts. During the high transmission season of August and September, 42.0% of districts reported dengue cases whereas 67.0% of the districts are identified as affected. The findings emphasise the importance of accounting for under-reporting when analysing surveillance data.

## **7.2 Data limitations**

Data quality is one of the greatest limitations in analysing dengue epidemiology in Bangladesh. Before 2010, when serological confirmation was made mandatory for reporting dengue cases, surveillance data comprised cases diagnosed solely on clinical grounds and some with laboratory confirmation. There could have been systematic bias in the reported case numbers due to misdiagnosis of dengue-like diseases as dengue. Under-reporting and misclassification of dengue cases due to the lack of specificity of the symptoms, limited access to health facilities, and inefficient surveillance is common in many countries in Asia<sup>16, 17</sup> and Bangladesh is no exception. To address this, I adjusted the analysis for under-reporting based on available data from neighbouring dengue endemic countries although it is difficult to assess under-reporting accurately.

Lack of serological and demographic information (e.g., age, sex) associated with each case was an additional limitation of the surveillance data.

Before 2006, dengue surveillance data was only available at monthly level making it impossible to analyse the temporal variability in dengue dynamics at a finer resolution.

### **7.3 Significance and implications**

The findings reported in this thesis are useful for public health decision making. This thesis offers a knowledge base towards the development of a model-based dengue early warning system. The findings suggest that in order to optimise dengue control efforts in response to the changing climate, risk maps must be adjusted for daily temperature fluctuations and the non-linear dengue-climate relationships to avoid overestimation of risk in warmer areas. The assessment of the degree of under-reporting with precision provides a unique opportunity to unravel the huge burden of dengue and subsequent high risk of severe dengue epidemics in Bangladesh.

Although this thesis is focused on Bangladesh, the modelling frameworks developed here could be extended to other resource-poor countries.

### **7.4 Future directions**

More research is needed to explain the relationships between dengue and ENSO events identified in this thesis. Understanding the relationships between ENSO, local weather, and dengue within Bangladesh would be an important advance towards better dengue prevention programs since the effects of ENSO vary greatly between regions.

To capture the environmental changes in the coming years, proxy variables like coverage of protective measures, percentage of urban population, and access to piped water will need to be considered to improve the performance of predictive models.

Linking epidemiological data with entomological indices would be an important advance towards the development of an early warning system since mosquito populations can be controlled at larval and pupal stages.

## 7.5 Conclusions

This thesis presents empirical approaches to understanding dengue dynamics in Bangladesh using epidemiologic, geographic, and demographic data. The analysis presented is a marked improvement on previous approaches to modelling of dengue transmission in Bangladesh. It highlights that assessment of the climatic influence on dengue transmission requires consideration of not only coarse aggregated climatic measures like mean temperature and rainfall, but also small and large scale variability in weather. Further, the importance of consideration of non-linear relationships between temperature, rainfall, and dengue while investigating the potential influence of changing climate on dengue incidence is stressed. Non-climatic variables such as population distribution and structure and the built environment must also be accounted for. The method I present in this thesis to adjust for under-reporting inherent in routine surveillance data permits an estimate of the full dengue burden. This would, in turn, enhance early warning enabling health authorities to take actions to prevent severe epidemics.

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## Appendix: Authors' contributions to papers

Sharmin S, Viennet E, Glass K and Harley D. The emergence of dengue in Bangladesh: epidemiology, challenges, and future disease risk. *T Roy Soc Trop Med H.* 2015; 109: 619-27.

Authors' contributions: All authors made substantial contributions to the conception of the study. SS carried out the literature review, analysis and interpretation of the data, and drafting and revision of the manuscript. SS was the principle author and submitted the final version of the manuscript; she also responded to comments from reviewers. EV, KG, and DH were involved in interpretation of the data, and drafting the manuscript and critically revising it for intellectual content. All authors read and approved the final manuscript. DH is guarantor of the paper.

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Sharmin S, Glass K, Viennet E and Harley D. Interaction of mean temperature and daily fluctuation influences dengue incidence in Dhaka, Bangladesh. *PLoS Negl Trop Dis*. 2015; 9(7): e0003901.

Authors' contributions: All authors made substantial contributions to the conception of the study. SS sourced the data, designed the statistical analysis plan, performed the analysis, and interpreted the results. SS wrote the first draft and revised the manuscript. SS was the principle author and submitted the final version of the manuscript; she also responded to comments from reviewers. KG, EV, and DH were involved in designing the analysis plan, and drafting and revising the manuscript critically for intellectual content. All authors read and approved the final version of the manuscript. DH is guarantor of the paper.

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Sharmin S, Glass K, Viennet E and Harley D. A Bayesian approach for estimating under-reported dengue incidence with a focus on non-linear associations between climate and dengue in Dhaka, Bangladesh. *Stat Methods Med Res.* 2016; 0962280216649216.

Authors' contributions: All authors made substantial contributions to the conception of the study. SS sourced the data, designed the statistical analysis plan, performed the analysis, and interpreted the results. SS wrote the first draft and revised the manuscript. SS was the principle author and submitted the final version of the manuscript; she also responded to comments from reviewers. SS is guarantor of the paper. KG made substantial contributions to the analysis and was involved in drafting and revising the manuscript critically for intellectual content. DH was involved in designing the analysis plan and drafted and revised the manuscript critically for intellectual content. EV contributed to drafting and critical revision of the manuscript for intellectual content. All authors read and approved the final version of the manuscript.

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| Sifat Sharmin (SS)   | 29.08.2016 |
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Sharmin S, Glass K, Viennet E and Harley D. Geostatistical mapping of the seasonal spread of under-reported dengue cases in Bangladesh. Ready to submit.

Authors' contributions: All authors made substantial contributions to the conception of the study. SS sourced the data, designed the statistical analysis plan, performed the analysis, and interpreted the results. SS wrote the first draft and revised the manuscript. SS was the principle author and submitted the final version of the manuscript. SS is guarantor of the paper. KG made substantial contributions to the analysis and was involved in drafting and revising the manuscript critically for intellectual content. DH and EV were involved in designing the analysis plan and drafted and revised the manuscript critically for intellectual content. All authors read and approved the final version of the manuscript.

| Name & Signature                                                                                        | Date       |
|---------------------------------------------------------------------------------------------------------|------------|
| Sifat Sharmin (SS)   | 10.05.2017 |
| Kathryn Glass (KG)   | 10.05.2017 |
| Elvina Viennet (EV)  | 10.05.2017 |
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