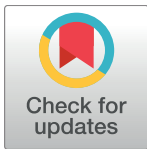


RESEARCH ARTICLE

The interplay of climate, intervention and imported cases as determinants of the 2014 dengue outbreak in Guangzhou

Qu Cheng¹, Qinlong Jing^{2,3}, Robert C. Spear⁴, John M. Marshall⁵, Zhicong Yang^{6,7*}, Peng Gong^{1,8*}

1 Ministry of Education Key Laboratory for Earth System Modeling, Department of Earth System Science, Tsinghua University, Beijing, People's Republic of China, **2** Department of Medical Statistics and Epidemiology, School of Public Health, Sun Yat-Sen University, Guangzhou, Guangdong, People's Republic of China, **3** Department of Infectious Diseases, Guangzhou Center for Disease Control and Prevention, Guangzhou, Guangdong, People's Republic of China, **4** Environmental Health Sciences, School of Public Health, University of California, Berkeley, Berkeley, California, United States of America, **5** Division of Biostatistics and Epidemiology, School of Public Health, University of California, Berkeley, Berkeley, California, United States of America, **6** Guangzhou Center for Disease Control and Prevention, Guangzhou, Guangdong, People's Republic of China, **7** Key Laboratory of Tropical Disease Control (Sun Yat-sen University), Ministry of Education, Guangzhou, Guangdong, People's Republic of China, **8** Joint Center for Global Change Studies, Beijing, People's Republic of China



OPEN ACCESS

Citation: Cheng Q, Jing Q, Spear RC, Marshall JM, Yang Z, Gong P (2017) The interplay of climate, intervention and imported cases as determinants of the 2014 dengue outbreak in Guangzhou. *PLoS Negl Trop Dis* 11(6): e0005701. <https://doi.org/10.1371/journal.pntd.0005701>

Editor: Laurent Coudeville, Sanofi Pasteur, FRANCE

Received: December 14, 2016

Accepted: June 10, 2017

Published: June 22, 2017

Copyright: © 2017 Cheng et al. This is an open access article distributed under the terms of the [Creative Commons Attribution License](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

Data Availability Statement: The number of daily reported new cases can be downloaded freely from the Health Department of Guangdong Province (<http://www.gdwst.gov.cn/a/yiqingxx/>). The monthly average mosquito surveillance data was provided in the supporting information file S1 Table of Ref. 7 (<http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0004417>). The number of foreign tourists staying overnight in Guangzhou and the number of tourists who travelled from Guangzhou with tour groups are provided in [S1 Table](#).

☯ These authors contributed equally to this work.

* penggong@tsinghua.edu.cn (PG); yangzc@gzcdc.org.cn (ZY)

Abstract

Dengue is a fast spreading mosquito-borne disease that affects more than half of the population worldwide. An unprecedented outbreak happened in Guangzhou, China in 2014, which contributed 52 percent of all dengue cases that occurred in mainland China between 1990 and 2015. Our previous analysis, based on a deterministic model, concluded that the early timing of the first imported case that triggered local transmission and the excessive rainfall thereafter were the most important determinants of the large final epidemic size in 2014. However, the deterministic model did not allow us to explore the driving force of the early local transmission. Here, we expand the model to include stochastic elements and calculate the successful invasion rate of cases that entered Guangzhou at different times under different climate and intervention scenarios. The conclusion is that the higher number of imported cases in May and June was responsible for the early outbreak instead of climate. Although the excessive rainfall in 2014 did increase the success rate, this effect was offset by the low initial water level caused by interventions in late 2013. The success rate is strongly dependent on mosquito abundance during the recovery period of the imported case, since the first step of a successful invasion is infecting at least one local mosquito. The average final epidemic size of successful invasion decreases exponentially with introduction time, which means if an imported case in early summer initiates the infection process, the final number infected can be extremely large. Therefore, dengue outbreaks occurring in Thailand, Singapore, Malaysia and Vietnam in early summer merit greater attention, since the travel volumes between Guangzhou and these countries are large. As

Funding: This research was partially supported by the Cyrus Tang Foundation (Grant No. 202006). QJ is funded by Guangdong Natural Science Foundation (No. S2013010013637, No. 2015A030313784) and the Medical Scientific Research Foundation of Guangdong Province (No. A2017481). ZY is supported by National Natural Science Foundation of China (NSFC) (No.81273139), the Project for Key Medicine Discipline Construction of Guangzhou Municipality (2017-2019-04), the Collaborative innovation project of Bureau of Science and technology of Guangzhou Municipality (No.201508020263). The funders had no role in 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.

the climate changes, destroying mosquito breeding sites in Guangzhou can mitigate the detrimental effects of the probable increase in rainfall in spring and summer.

Author summary

An unprecedented dengue outbreak occurred in Guangzhou, 2014, with 38,036 reported cases in contrast to 73,179 cases in all of mainland China from 1990 to 2015. In an earlier analysis using a deterministic model, we concluded the early timing of local transmission to be the most important determinant of this outbreak. Here we use a stochastic model to explore the reasons why the outbreak happened earlier in 2014. Our results identified the higher number of imported cases in May and June to be the most probable explanation. Based on the investigation of the determinants of success rate and final epidemic size, this work provides suggestions for reducing dengue outbreak potential and epidemic size in the future. More attention should be paid to imported case detection and vector control measures in early summer, because this is the time when successful invasion can result in high incidence of infection and the success rate of each imported case begins to rise. Destroying mosquito breeding sites can reduce the maximum water level of the system and attenuate the role played by climate. In addition, interventions within 10 days after the introduction of imported cases is still effective in preventing further transmission.

Introduction

As the most important mosquito-borne disease globally, the incidence of dengue has increased 30-fold in the past 50 years [1]. In 2013 alone, dengue was responsible for 576,900 years of premature life lost and 1.14 million disability-adjusted life-years globally [2]. However, dengue was not a serious concern in mainland China before 2014. There were only 73,179 cases from 1990 to 2015, among which 47,056 (64.3%) occurred in 2014, and 80.8 percent of these cases were contributed by Guangzhou [3]. Because of its warm and wet climate, as well as the close ties with dengue endemic Southeast Asian countries, Guangzhou has a high risk of local dengue transmission. The introduction of dengue virus (DENV) by imported cases is required annually for local epidemics in Guangzhou, since the dengue virus cannot disseminate to the salivary glands of *Aedes albopictus* when temperature is below 18°C [4] and adult mosquitoes rarely survive the winter.

Many studies have attempted to explain the unprecedented dengue outbreak in Guangzhou, 2014. Possible explanations include more imported cases, higher mosquito abundance due to a more favorable climate, higher larval development and adult survival rates caused by urbanization, and lack of diagnostic experience [5, 6]. The result of our earlier analysis using a deterministic mathematical model identified the early timing of local transmission and climate as the most important determinants of the large final epidemic size (FES) [7], but the model could not explain why local transmission occurred earlier that year. Because a stochastic model can produce different results every run under the same conditions, an imported case can lead to local transmission in some runs but not so in others. Therefore, a stochastic model can shed more light on the outbreak probability and can provide greater insight into the various explanations of earlier local transmission, such as a more favorable climate for mosquito growth and more imported cases. Clearly, understanding the reasons underlying the early and

large outbreak can help to prevent dengue outbreaks in the future, and reduce potential economic and health impacts.

Stochastic models have been widely used to study the invasion of a disease into non-endemic areas, such as dengue virus transmitted by *Ae. aegypti* mosquitoes [8], dengue virus in Madeira [9], and Chikungunya virus in the United States [10]. However, none of these models considered the importance of water availability in restricting the environmental carrying capacity and density-dependent rates.

In this paper, we simplify our deterministic model by leaving out vertical transmission from infected adults to eggs since it was found to be unimportant in the earlier analysis [7], and then extend it to incorporate stochastic effects. A hybrid deterministic/stochastic algorithm originally used in simulating chemical reactions [11–13] is used to simulate the dengue transmission dynamics. This algorithm can take advantage of the low computational burden of deterministic models while still incorporating stochastic effects. Six different scenarios are constructed to explore the determinants of early outbreak in 2014 and the effectiveness of interventions (insecticide spraying and pooled water removal) in reducing dengue transmission risk. We also address the determinants of the outbreak size and FES, as well as the implications for prediction and prevention.

Methods

Ethics statement

The Ethics Committee of the Guangzhou Center for Disease Control and Prevention reviewed and approved this study. All patient data was made anonymous prior to the analysis.

Study area

Guangzhou, with a population of 13.1 million at the end of 2014 [14], is the largest city in South China. The climate is characterized by warm and humid summers and mild and dry winters. The climate data downloaded from China Meteorological Data Sharing Service System (CMDSSS) indicates that the annual mean temperature from 1985 to 2014 was 22.4°C. January had the lowest average temperature of 13.7°C, while July and August had the highest at 28.9 and 28.7°C, respectively (Fig 1A). The average annual accumulated precipitation was 1,821 mm, of which 1,490 mm (81.9%) occurred between April and September (Fig 1B). The warm and wet summer is favorable for the growth of *Ae. albopictus*, the sole vector of dengue transmission in Guangzhou [15].

Because low temperature is unable to support virus replication in *Ae. albopictus* in the winter [4], the occurrence of dengue epidemics in Guangzhou depends highly on imported cases from surrounding endemic countries, such as Thailand, Singapore, Malaysia, Philippines, Vietnam, Cambodia, and Indonesia. Serving as a transportation hub for these countries increases the outbreak risk of Guangzhou further (Fig 1C).

Data

We collected daily reported dengue case numbers in 2013 and 2014 from the Guangzhou Center for Disease Control and Prevention (Guangzhou CDC). These data are also available from the Health and Family Planning Commission of Guangdong Province (<http://www.gdwst.gov.cn/>) in the transmission season. Both passive and active surveillance systems are used in China. Health-care providers are required to diagnose the disease according to the National Diagnostic Criteria for Dengue Fever (WS216-2008) and then report the new cases to the web-based National Notifiable Infectious Disease Reporting Information System within 24 hours.

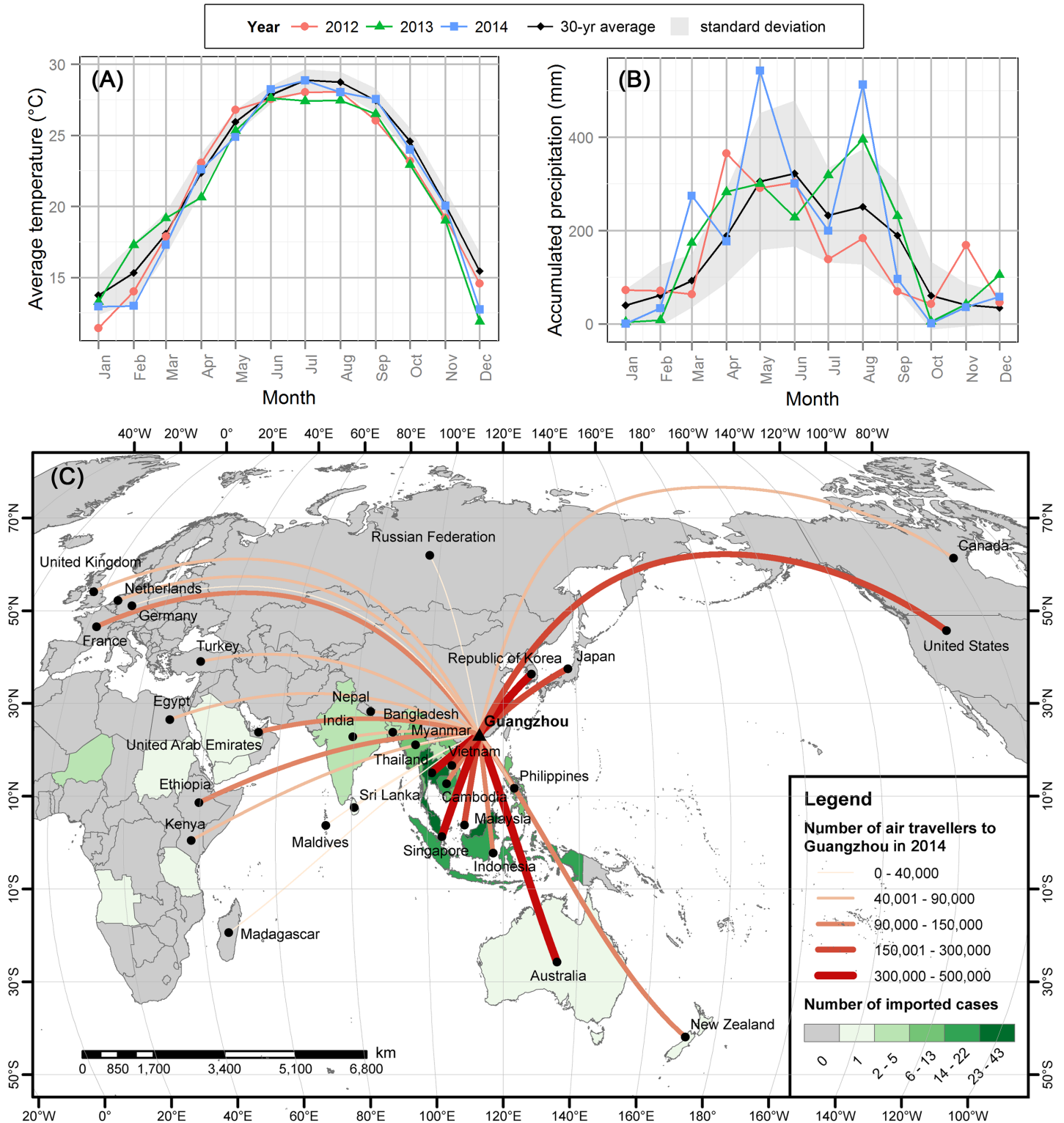


Fig 1. Climate in Guangzhou and the number of direct air travelers to Guangzhou in 2014. (A) Monthly mean temperature and (B) accumulated precipitation for 2012 to 2014, and 30-yr average (1985–2014). (C) Number of direct air travelers from different countries to Guangzhou in 2014 and the total number of imported cases from different countries from 2001 to 2015.

<https://doi.org/10.1371/journal.pntd.0005701.g001>

After the confirmation of a case, active detection is initiated and conducted by various means, such as interviewing residents in the same community, checking employee attendance records in the same work place, and checking the outpatient medical records in nearby health facilities [16]. Cases are categorized further into imported and indigenous cases based on the travel and mosquito biting history. Imported cases are those who have traveled to dengue endemic regions and been bitten by mosquitoes less than 15 days before the symptom onset [6]. This dataset was used to calibrate the deterministic model.

Entomological surveillance data, including the Breteau index (BI) and mosquito ovitrap index (MOI) for 2013 and 2014, were also obtained from Guangzhou CDC. BI is a representation of larva abundance, which is defined as the number of water containers infested with larva per 100 houses inspected, while MOI is a proxy for adult abundance defined as the percentage of positive ovitraps in a specific area. The daily temperature, precipitation and evaporation data for Guangzhou from 1985 to 2014 were downloaded from CMDSSS (<http://data.cma.cn/>). The 30-yr daily average climatic factors were calculated to represent a typical year and were used in *Scenario 2014 to Avg* described later. Climate datasets were used as inputs to the model.

Human population data were extracted from the Guangdong Statistical Yearbook [17–19] to estimate the birth and death rates, which were treated as known parameters in the deterministic model. In addition, the initial value for the susceptible human population in the model was set to the population at the end of 2011, because we assumed that all residents were susceptible to dengue virus infection since no big outbreaks had occurred in Guangzhou from 1978.

To investigate the tourist exchange between Guangzhou and dengue endemic countries, we also extracted the number of direct air travelers between Guangzhou and different countries from on-flight origin and destination (OFOD) data provided by International Civil Aviation Organization (ICAO) (<https://www4.icao.int/NewDataPlus/>). Since this dataset leaves out indirect air travelers or travelers by sea or by land, we also collected the number of foreign tourists staying overnight in Guangzhou and the number of tourists who traveled from Guangzhou with tour groups from the Tourism Administration of Guangzhou (<http://www.gzly.gov.cn/index.html>) as a complement (S1 Table).

Model description

To simulate the population dynamics and dengue virus infection status of both *Ae. albopictus* and humans, we constructed a compartment model shown in Fig 2 which is based on Ross-Macdonald model [20, 21]. Several modifications were made to the basic model to emphasize the influence of temperature and precipitation, such as modelling water level and aquatic stages explicitly, and using temperature- and density-dependent rates. The model has been described in detail elsewhere [7]. Because vertical transmission was found to be unimportant in the 2014 outbreak [7], here we removed the vertical infected egg, larva, pupa and emerging adult compartments to simplify the model structure and to reduce computational complexity. Immature life stages eggs (*E*), larvae (*L*), and pupae (*P*) were included to incorporate the effects of water availability and temperature on vector abundance. Emerging adults (*Aeu*) were also incorporated as a separate compartment because they do not bite. Then, according to infection status, the biting mosquito population was divided further into susceptible (*As*), exposed (*Ae*) and infectious (*Ai*) adults, and the human population was divided into susceptible (*Hs*), exposed (*He*), infectious (*Hi*) and recovered (*Hr*) individuals.

Transition rates in the model depend on temperature and water availability. Temperature can influence the development rate from eggs to larvae, larvae to pupae, and pupae to emerging adults (Events 2, 4 and 6 in Fig 2), the mortality rate of larvae, pupae and adults (Events 3,

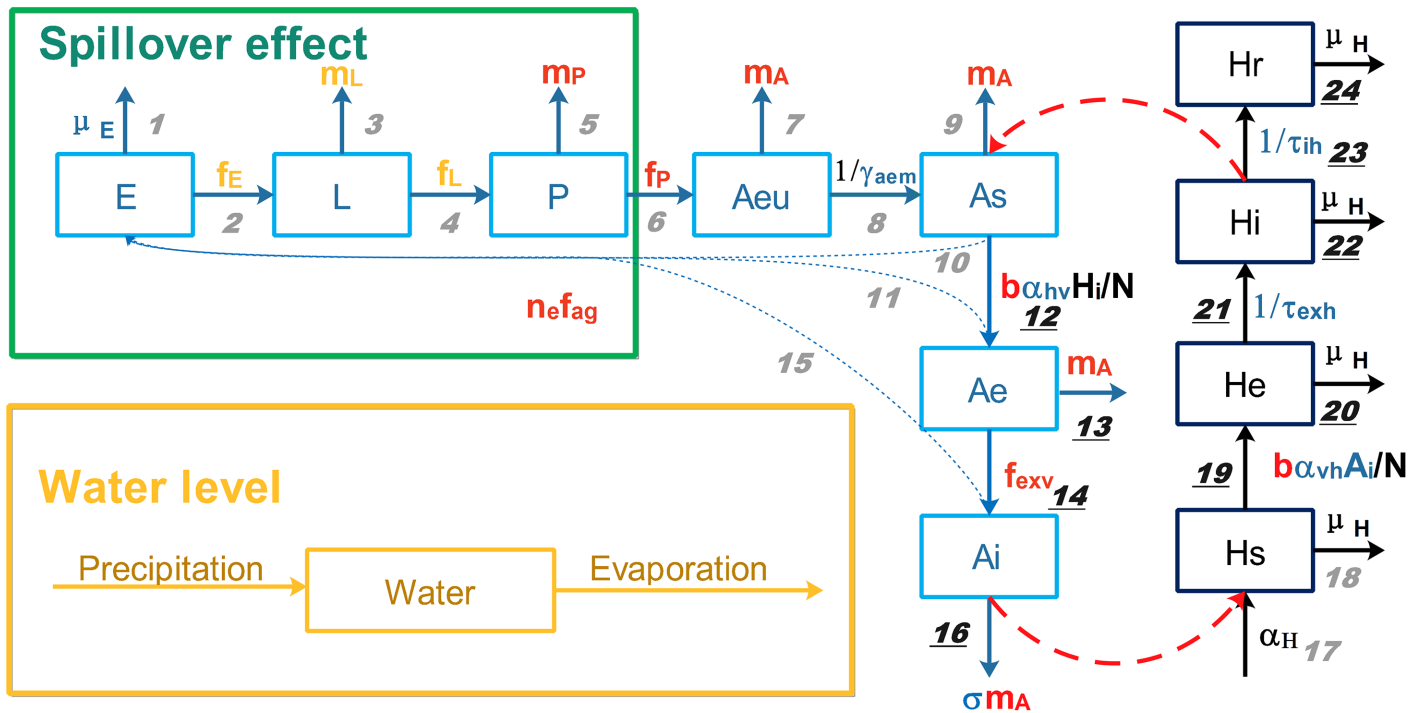


Fig 2. Model structure. Blue and black rectangles represent mosquito and human subpopulations, respectively. Greek letters stand for constant rates, among which the black letters can be estimated from statistical yearbooks, while the blue letters are unknown and need to be estimated in the deterministic model. English letters stand for transition functions, among which the red letters only depend on temperature, while the yellow letters depend on both temperature and water level. If a heavy rainfall occurs when the current water level is close to its maximum value, a fraction of the immature stage mosquitos will be washed out (spillover effect) [22]. Numbers are the IDs for different events. Only events with underlined IDs are modelled stochastically. More information can be found in [7] and S1 File.

<https://doi.org/10.1371/journal.pntd.0005701.g002>

5, 7, 9, 13 and 16), the biting rate of adults (Events 12 and 19), the extrinsic incubation period (EIP) of dengue virus (Event 14), and the average number of eggs and duration of each gonotrophic cycle (Events 10, 11 and 15) [23–25]. Therefore, temperature-dependent functions whose form is based on [23, 26] were used to describe these rates, and the coefficients in these functions were estimated from experiments conducted on *Ae. albopictus* strains from South China [25, 27]. Furthermore, the development rate from eggs to larvae, larvae to pupae, and the mortality rate of larvae also depend on the larval density (Events 2–4), which further depend on the current available water level determined by rainfall, evaporation, the minimum and maximum water level (ω_{\min} and ω_{\max}) of the system, and interventions (eg. emptying water containers) [28]. Minimum water level represents standing waters that are difficult to evaporate, such as the water in containers with lids or in shaded areas, while the maximum water level is the upper limit of the water in the system beyond which water will overflow. Since these two parameters cannot be obtained from the literature or surveys, they were estimated by the deterministic model. More information for the model structure can be found in the S1 File.

As in the previous paper [7], we still include the arrival of imported cases, intervention, the spillover effect and diapausing eggs in the current model. The model was run from 2012 to 2014, though we only fit the model to the observed daily reported cases of 2013 and 2014. Year 2012 was included to get a reliable mosquito population for 2013 and 2014, because the initial value for eggs can only affect the mosquito abundance of the first simulated year, but not in later years [29].

Parameterization, calibration and validation of the deterministic model

There are 19 parameters in our model and their values are highly uncertain. In addition, we are more confident about the pattern of the daily reported new cases and mosquito surveillance data than the exact value of these data on any given day. Therefore, instead of employing Markov Chain Monte Carlo (MCMC) fitting procedures common in epidemiologic mathematical modelling [9, 30], we used a parameter estimation strategy originally called regional sensitivity analysis (RSA) [31] to fit the model to the pattern of the surveillance data. The detailed process was described elsewhere [7], and only a brief description is provided here.

To calibrate the deterministic model, a broad range for each parameter was specified based on the literature or our best knowledge. Classification criteria were defined to describe whether the model output mimicked the observed timing and approximate number of reported cases at the onset, peak and end phase of the epidemics (see details for the criteria in [S1 File](#)). A Monte Carlo procedure was then followed in which random samples were drawn from the specified parameter space and used to run the model. The output of each realization was classified into one of two subgroups “pass” or “fail” according to whether the result met all of the classification criteria. After accumulating a sufficient number of parameter vectors in the “pass” group, the characteristics of the cumulative univariate distributions were used to trim the range for each parameter to get a smaller parameter subspace with a higher passing rate.

A total of 5 trimming cycles were conducted until the pass and fail univariate distributions offered no further guidance on identifying subspaces with higher pass rates. The results are presented in [S1 File](#). Unlike MCMC fitting, which gives only one parameter set with a confidence interval, RSA gives multiple parameter sets matching the passing criteria. Here we obtained 5,320 parameter sets out of 100,000 runs after the last trimming cycle (Cycle 5) in contrast with the 83 passing sets from 800,000 trials initially (Cycle 1). [Fig 3A](#) shows the trajectories and the envelope of the number of daily new cases produced by the 5,320 sets in Cycle 5. As expected, these passing parameter sets produce trajectories which mimic the pattern of the field data successfully, except that the peak number of cases in 2014 is a little lower and occurs earlier than observed. Although the observed initial exponential growth rate of 2014 is higher than that of 2013, the model produces very similar values, presumably because we assume that the intrinsic incubation period, recovery period, transmission probability from vector to human and from human to vector, and reporting rate remain the same from year to year. This lack of fit suggests difference in dengue virus virulence or reporting rate between these 2 years, which may need further investigation in the future.

The number of larvae and adult mosquitoes output by the model shows the same patterns as the mosquito surveillance data for both BI and MOI. Since these entomological datasets were not used in model calibration, they support the validity of our model and its parameterization.

Stochastic formulation

In transitioning from a purely deterministic model to one suitable for exploring stochastic effects, we must take account of the earlier finding that there are extended regions of the parameter space that led to good fits to the calibration data for the deterministic model. Since thousands of simulations were needed for each parameter set, it is impractical to use all the 5,320 passing sets of Cycle 5. As a result, 100 parameter sets were sampled randomly to represent the space of good fitting vectors ([S2 Table](#)). To reduce the computational costs further, a simulation procedure developed specifically for hybrid deterministic/stochastic models was utilized.

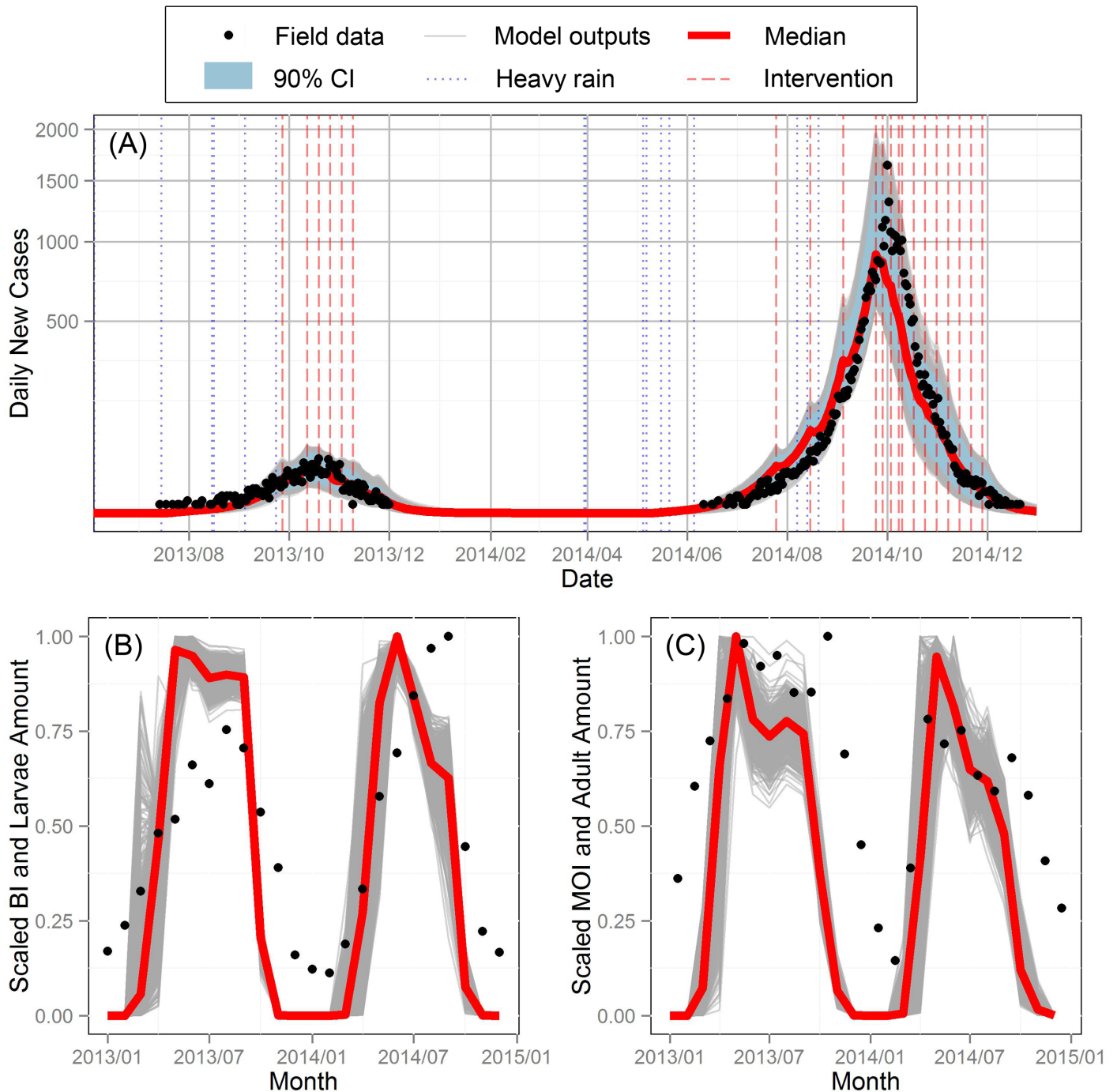


Fig 3. Model outputs and field data for (A) daily new cases, (B) larvae and (C) adults. Black dots indicate the number of reported daily new dengue cases in (A), the scaled monthly average BI and MOI in (B) and (C), respectively. Gray and red solid lines represent the model output of each parameter set and the median of these outputs, respectively. Dotted blue and dashed red vertical lines are the dates for heavy rain (part of the immature stages will be washed out if the water level is close to its maximum value) and interventions (insecticide spraying and pooled water removal).

<https://doi.org/10.1371/journal.pntd.0005701.g003>

The hybrid deterministic/stochastic algorithm can add stochasticity to the dengue transmission model and obtain estimates of the success invasion rate of one imported case and the distribution of FES. This method has been widely used in simulating chemical reactions. It can

improve the calculation efficiency significantly while still producing a similar pattern as that achieved by using the exact method [11–13, 32, 33]. The transitions between different compartments here, analogous to the chemical reactions in those studies, were partitioned into “fast” and “slow” subsets according to their transition rates. Fast events happen frequently and have lower level of stochasticity, thus they are simulated by the deterministic model using ordinary differential equations (ODEs) (Events 1–11, 15, 17 and 18 in Fig 2), while slow events happen infrequently so they must be modeled stochastically (Events 12–14, 16, and 19–24). Since there were only small numbers of exposed and infected mosquitoes (A_e and A_i), and of exposed, infected or recovered humans (H_e , H_i and H_r) at the beginning of the outbreak, the mortality rates of these compartments (Events 13, 16, 20, 22, and 24) and the transition rates from these compartments (Events 14, 21, and 23) were relatively low. Hence these events are considered as slow events. In addition, the transition rate of Event 12 ($b\alpha_{hv}H_iA_s/N$), which is the mosquito infection via human contagion, is also low, because b is the temperature-dependent biting rate which ranges from 0 to 1; α_{hv} is the transmission probability of dengue virus from infected human to susceptible adult mosquito which also ranges from 0 to 1; H_i is the number of infected humans which is a small number at the beginning of the outbreak; and A_s/N is the ratio of mosquitoes to humans, which is also small when compared with mosquito abundance or the human population. Therefore, Events 12 and 19 are slow events, for the same reason.

For the stochastic simulation of the slow events, instead of the widely utilized Gillespie’s stochastic simulation algorithm (SSA) in the chemical studies, here we used the adaptive *tau*-leap algorithm [34–36], which is more commonly used in epidemiological models to reduce the computational burden [10, 34, 35]. To test the validity of the *tau*-leap algorithm, Gillespie’s SSA was also tried for two randomly chosen parameter sets. The Kolmogorov–Smirnov two-sample test for both parameter sets indicated no significant difference between the FES distributions produced by different algorithms. Therefore, only the *tau*-leaping algorithm was applied in the following analysis. The time step *tau* was initially set to be 1/5 day, which is appropriate for a population of the order of millions [37]. If high numbers of events occurred in this time interval which led to negative population sizes, a new value of *tau* was adopted as *tau*/2 to shorten the time interval and avoid negative population sizes. The details of the implementation of the model are shown in S1 File.

Climate- and intervention-related scenarios

Dengue transmission risk is mainly determined by the mosquito-to-human ratio, temperature, and the immune status of human population [38]. Since the human population and its immune status do not vary much from year to year, the only differences between 2014 and other years were mosquito abundance and temperature. Mosquito abundance further depends on the availability of breeding sites, represented by water level in the model, and human interventions. The most common interventions in Guangzhou are insecticide spraying and emptying water containers, which can reduce the abundance of adults or aquatic stage of mosquitoes immediately. Emptying water containers can also affect the abundance through water availability and the density-dependent rate.

Six different scenarios were designed here to investigate the role of climate and human interventions in determining the potential and FES of the dengue outbreak in 2014 (Table 1). The first scenario used the observed climate data of 2014 and serves as the baseline for comparison (*Scenario 2014*). Then, to study the role of climate only, we replaced the climate files of 2014 in *Scenario 2014* with those of 2013 (*Scenario 2014 to 2013*) and the 30-yr average (*Scenario 2014 to Avg*). The 30-yr average was used here to represent the climate in a typical year.

Table 1. Climate file and intervention used in each scenario.

| Scenario ID and Name | Climate file | Intervention |
|---|-------------------------|------------------|
| (1) <i>Scenario 2014</i> | 2012 + 2013 + 2014 | NA + 2013 + 2014 |
| (2) <i>Scenario 2014 to 2013</i> | 2012 + 2013 + 2013 | NA + 2013 + 2014 |
| (3) <i>Scenario 2014 to Avg</i> | 2012 + 2013 + 30-yr Avg | NA + 2013 + 2014 |
| (4) <i>Scenario 2013</i> | 2012 + 2013 | NA + 2013 |
| (5) <i>Scenario 2013 w/o intervention</i> | 2012 + 2013 | NA + NA |
| (6) <i>Scenario 2014 w/o intervention</i> | 2012 + 2013 + 2014 | NA + 2013 + NA |

<https://doi.org/10.1371/journal.pntd.0005701.t001>

In addition to climate, year 2014 also differed from year 2013 in the initial water level, which was determined by the climate and interventions in the previous year. The initial water level in 2014 is lower than 2013, because more water was removed in 2013 than in 2012 by more frequent interventions. The number of reported dengue cases in Guangzhou increased from 139 in 2012, to 1,249 in 2013, and then to 37,341 in 2014, which led to increasing intervention frequency over these years. Therefore, we compared the results of *Scenario 2013* and *Scenario 2014* to determine the combined effect of climate and intervention. Moreover, aiming to understand the outbreak potential under only natural conditions, we also designed two additional scenarios without interventions (*Scenario 2014 w/o intervention* and *Scenario 2013 w/o intervention*). The previous deterministic model [7] suggested that the interventions can reduce the FES effectively, so here these two scenarios were included to estimate the quantitative effects of intervention in reducing dengue transmission risk.

Turning to the role of the timing of imported cases, the introduction date was varied between March 21st and November 26th (the mosquito growth season) at 10-day intervals (a total of 25 different introduction dates). As with the deterministic model, the stochastic model was also run from Jan 1st, 2012 to December 31st, 2014. Five hundred iterations were run for each combination of scenario and introduction date. The FES of the last simulated year was recorded for each iteration. Therefore, a total of 7.5 million simulations were conducted (100 sample sets, 25 introduction dates, 6 scenarios, and 500 repetitions).

The **successful invasion rate** of an imported case was defined as the proportion of repetitions with a FES greater than 0. The **average final outbreak size** only accounts for successful invasions, and can be calculated as the mean of FESs greater than 0 in 500 repetitions, while the **average final epidemic size** was the mean FES of all invasions.

R 3.2.3 [39] was used for simulation, data analysis and visualization. The package deSolve was used for solving the ODEs [40], Rcpp, foreach, and doSNOW for parallel computing to increase the computational speed [41, 42], and ggplot2 for data visualization [43].

Results

There are three possible explanations for the early timing of the local transmission in 2014, a higher success rate for a single imported case, more imported cases in early summer, or by chance alone. These possibilities are explored in this section, as well as the distribution and the mean of FES.

Success rate for a single imported case

In order to determine whether the early outbreak in 2014 was caused by a particularly favorable climate for mosquito growth, we held all the other conditions constant, such as initial water level and the timing of interventions, but only changed the temperature, precipitation and evaporation of 2014 to those of 2013 and then to the 30-yr average (*Scenario 2014 to 2013*

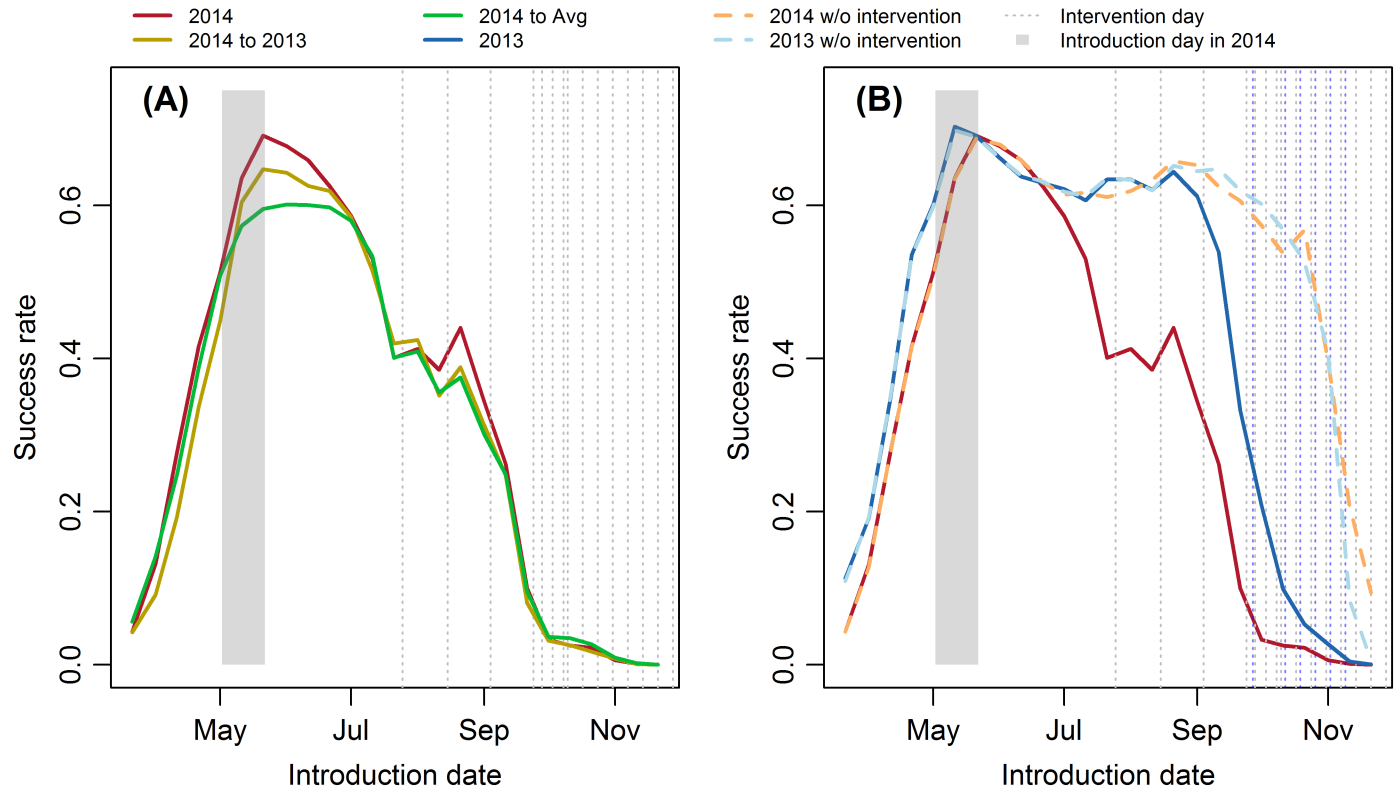


Fig 4. The mean success rates of 100 parameter sets for (A) Scenario 2014, 2014 to 2013 and 2014 to Avg, and (B) Scenario 2014, 2013, 2014 w/o intervention and 2013 w/o intervention. The shaded rectangle shows the range of the timing of the imported case which started local transmission in 2014 in Cycle 5 of the deterministic model. Blue and gray dashed lines in (B) represent the intervention date in 2013 and 2014, respectively.

<https://doi.org/10.1371/journal.pntd.0005701.g004>

and 2014 to Avg). Fig 4A shows that if an imported case is introduced to the system on the same day in early summer (the shaded rectangle), Scenario 2014 has the highest success rate. This implies that the climate in 2014 was more favorable for an early outbreak. For all the three scenarios, the success rate increases in late spring and early summer, remains at a high level from May to July, and then decreases until it reaches and stays at a low level in October. The biggest difference in the success rate between these scenarios occurs between May and July, the same period as the peak of success rate.

Fig 4B shows the comparison between two scenarios with observed climate and intervention (Scenario 2014 and 2013) and two scenarios with observed climate, but without intervention (Scenario 2014 w/o intervention and 2013 w/o intervention). The result for Scenario 2014 is depicted here again as a baseline for comparison. Although the success rate of Scenario 2014 is higher than that of Scenario 2014 to 2013 and 2014 to Avg when only the climate is considered (Fig 4A), it is lower than that of Scenario 2013 when the combined effect of lower initial water level and favorable climate is considered. Therefore, though the climate, especially adequate rainfall, in the early summer of 2014 is more favorable for mosquito growth and dengue transmission, the lower initial water level of 2014 caused by emptying water containers in late 2013 appears to have reduced the risk to a level even lower than that of 2013. In other words, the success rate of a single imported case in causing local transmission was not significantly higher in the time window of interest in 2014 and suggests other explanations, such as more imported cases in that time period or by chance alone.

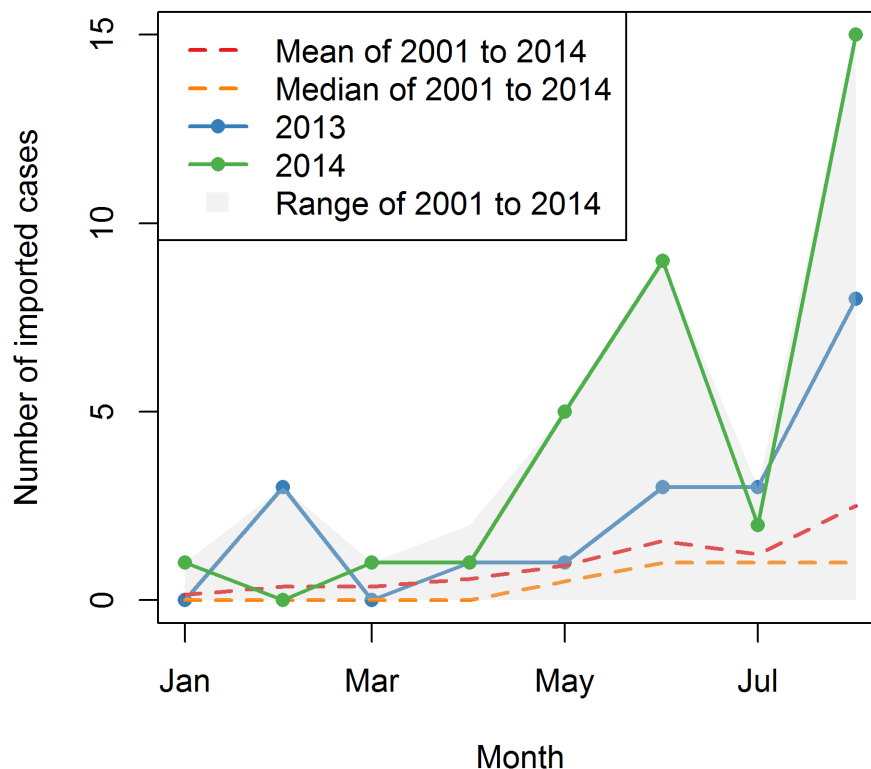


Fig 5. The monthly number of imported cases for 2013, 2014, and the mean, median, and range of 2001 to 2014.

<https://doi.org/10.1371/journal.pntd.0005701.g005>

The difference between *Scenario 2014* and *2014 w/o intervention*, as well as between *Scenario 2013* and *2013 w/o intervention* shows the effectiveness of intervention in reducing dengue transmission probability (Fig 4B). Similar to the three scenarios shown in Fig 4A, the success rates of *Scenario 2013*, *2014 w/o intervention*, and *Scenario 2013 w/o intervention* also increase in the early summer until May. However, the duration of the peak differs. The success rate of *Scenario 2014* stays at the peak until July, *Scenario 2013* until September, while the two scenarios without intervention continue until October. The intervention started on September 27th in 2013 and July 25th in 2014, so they have no influence on the success rate in the beginning of these years. The success rates are the same for *Scenario 2014* and *2014 w/o intervention*, as well as for *Scenario 2013* and *2013 w/o intervention* in the late spring and early summer. However, the success rate drops 20 days before the first intervention, which indicates that the intervention can reduce the transmission probability of a case imported up to 20 days ago. This could possibly due to the death of exposed or infected mosquitoes in the intervention or reduced virus transmission from imported or secondary cases to mosquitoes caused by mosquito population loss.

Number of imported cases in early summer and outbreak probability

Besides the success rate of one imported case on any given date, the **outbreak probability**, which is the probability that at least one indigenous case occurs in a particular year, also depends on the number of imported cases. It is clear that the outbreak probability will increase when there are more imported cases, although the increase may be quite small depending on the timing pattern. The outbreak probability can be calculated from the success rate of all imported cases in that year, once the timing of each imported case is known. Fig 5 illustrates

the number of identified imported cases into Guangzhou from other countries or Chinese cities in 2013, 2014, and the mean, median and range of 2001 to 2014. Since the detection and reporting rate of imported cases are likely to increase after August, 2014, when attention began to be paid to the serious dengue outbreak, only data from January to August are shown here. The number of imported cases known to have entered Guangzhou in May and June, 2014 is four times higher than the average or median of that in 2001 to 2014, which may be the main determinant of the early local dengue virus transmission in 2014.

Distribution of the final epidemic size

A different FES can be produced by stochastic effects in each simulation even with the same input. Fig 6 shows the histograms of the FES + 1 under different introduction dates when using the combination of sample set 1 and Scenario 2014 as an example. The FES for an imported case arriving May 11th, 2014, which is around the estimated timing of the first successful invasion in 2014, can range from 0 to 132,457 with a mean of 22,790 and a standard deviation of 25,219. These histograms also show that the FES of successful invasions decreases with the delay of the imported cases. In other words, though the success rate of an early imported case is low, the FES could be extremely high once it succeeds.

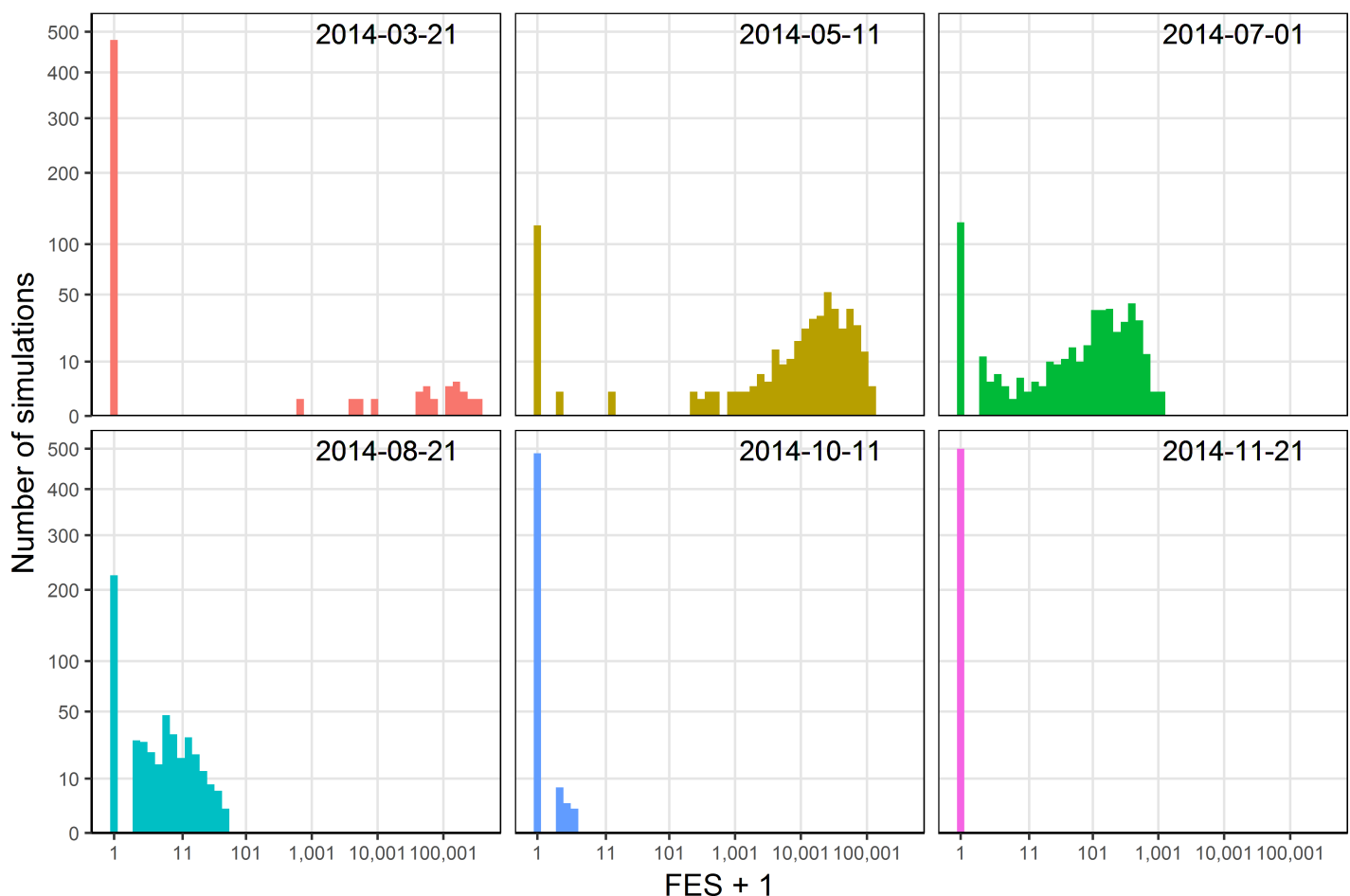


Fig 6. The distribution of FES+1 under Scenario 2014 by using sample set 1.

<https://doi.org/10.1371/journal.pntd.0005701.g006>

Average final outbreak size and average FES

Average final outbreak size is the mean FES of successful invasions, while average FES is the mean of all simulations. Since the average FES equals the product of the outbreak probability and the final outbreak size, and outbreak probability has been discussed above, here we first look into the average final outbreak size and then the FES. Because all scenarios show the same pattern, and while the results under the last three scenarios are several magnitudes higher than the first three scenarios, to make the figure readable, only the results of the first three scenarios were shown here.

Fig 7A shows that the average final outbreak size decreases exponentially with introduction date, and the decrease rate is affected by climate. Scenario 2014 has the highest average final outbreak size, and Scenario 2014 to Avg has the lowest. According to Fig 4A, the mosquito abundance and success rate is higher in Scenario 2014, so each case can infect others more easily under this scenario, which will then lead to a higher final outbreak size. Unlike the monotonically decreasing average final outbreak size, the average FES peaks in mid-April (Fig 7B), similar to the conclusion from the deterministic model [7]. In addition, the average FES given by the stochastic model is also comparable to that given by the deterministic model. Though the outbreak size is extremely high before April, the success rate is quite low, while after May, though the success rate reaches its peak, the outbreak size drops dramatically. Therefore, the average FES has the highest value in mid-April, and the peak time changes only slightly with climate. Similar to Fig 4A and Fig 7A, Scenario 2014 has the highest average FES.

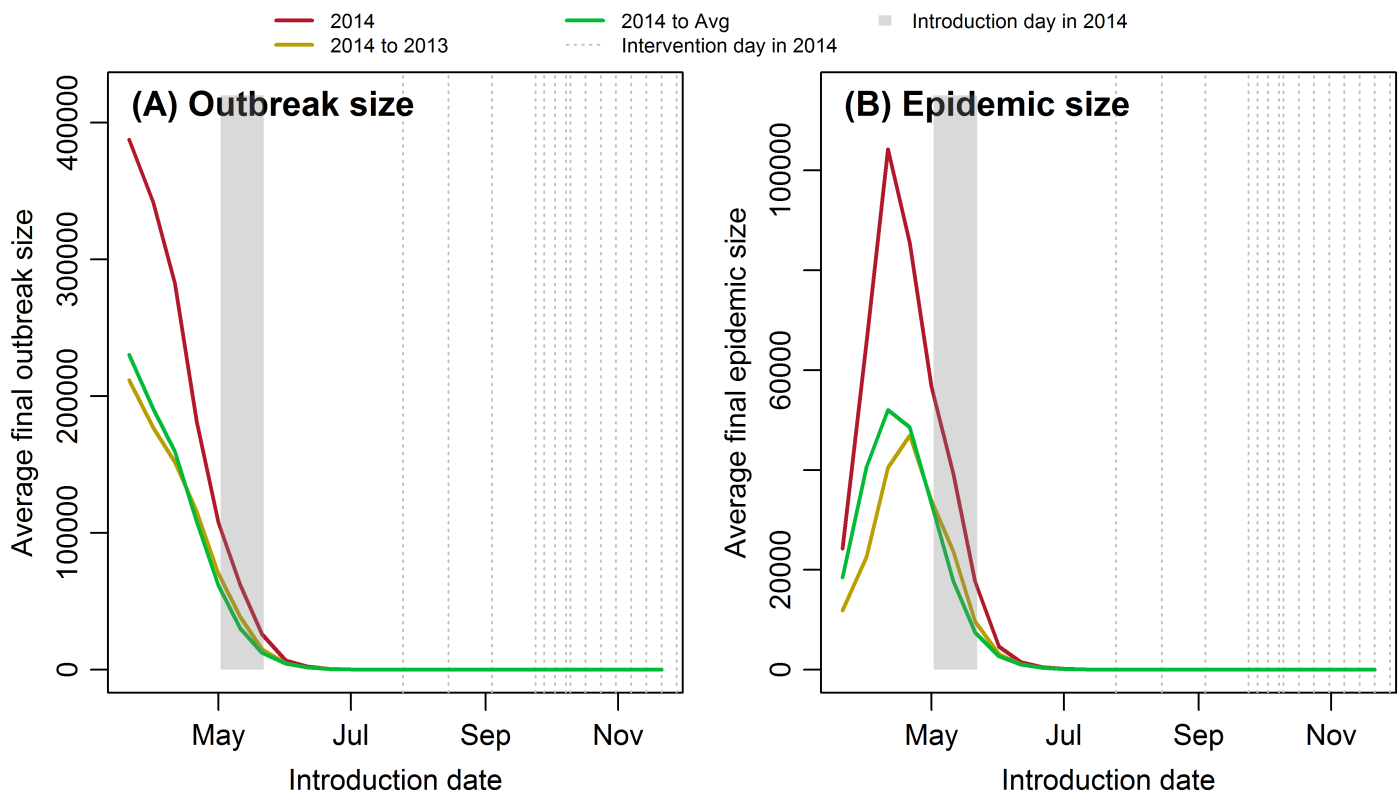


Fig 7. The (A) average final outbreak size and (B) average FES as a function of introduction date for 100 sample sets. The shaded rectangle shows the range of the timing of the imported case which started local transmission in 2014 in Cycle 5 of the deterministic model.

<https://doi.org/10.1371/journal.pntd.0005701.g007>

Discussion

One limitation of the previous deterministic model was that it failed to account for the effect of chance [7]. The transmission dynamics is highly affected by chance at the onset phase of an epidemic, when the populations of infected humans and vectors are low. Under the same situation, an imported case can sometimes result in local transmission, while not at others. However, every imported case can lead to local transmission in the deterministic model when the basic reproduction number R_0 is greater than one. Therefore, though the deterministic model concluded the early timing of local transmission to be the main determinant of the large FES in 2014, it was unable to answer the question that why it happened earlier in 2014. Here stochasticity was added to the previous model to investigate the successful invasion probability when the importation happens at different times and under different climate and intervention scenarios in 2014.

Determinants of the early outbreak in 2014

In [9], a stochastic model suggested that the slightly warmer summer was adequate to explain the large dengue outbreak in Madeira, 2012. However, in the Guangzhou outbreak, the favorable climate was only a necessary, but not sufficient condition, because human activities such as intervention and travel also matter. We find the higher number of imported cases in May and June to be the most important determinant of the early outbreak. Although the excessive rainfall in 2014 did increase the successful invasion rate, this effect was cancelled out by the low initial water level due to the interventions in late 2013. Because of a small outbreak in 2013, regular interventions were conducted from late September to early November, which markedly reduced the initial water storage in 2014. The entomological surveillance data shown in Fig 3C supports this interpretation. Specifically, the MOI, which represents the adult mosquito abundance, was lower in 2014 than in 2013, despite the more favorable climate. The increased number of imported cases in late April to early July was also identified as the driving force of the 2014 Guangzhou dengue outbreak by a deterministic model, which incorporated the number of imported case by a fitting function [44]. The result of a classification tree also suggested the number of imported cases, monthly average BI, and temperature as the most important determinants of the dengue outbreak occurrence in Guangzhou from 2002 to 2013 [45].

As noted in Fig 8A and 8B, dengue endemic countries Thailand, Singapore, Malaysia and Vietnam had the highest tourist exchange with Guangzhou. Therefore, more attention should be paid to identifying imported cases from these countries when they have significant dengue outbreaks, especially in late spring and early summer. Though the successful invasion rate is likely to be low in this period, the final outbreak size can be extremely large once it succeeds (Fig 7A). In all countries, the dengue incidences in 2014 were lower than 2013, except for Malaysia (Fig 8C). Although the incidences are somewhat comparable in time, it is questionable to compare the incidence of different countries, because the reporting rates may vary significantly between countries.

A phylogenetic analysis suggested that the dengue virus isolated in Guangzhou, 2014 was most similar to the isolates in Singapore, Malaysia, Indonesia and Thailand [46, 47]. The importation index, which incorporates both the incidence in country of origin and the travel volume between the target city and the country of origin [48, 49], also shows that Singapore, Thailand and Malaysia had the highest importation indices in 2013, and the order changed to Malaysia, Singapore and Thailand in 2014. However, because of the differences in reporting rates between countries, this result is inconclusive. When compared across time, the importation index of 2014 is lower than that of 2013, but more imported cases were observed in 2014,

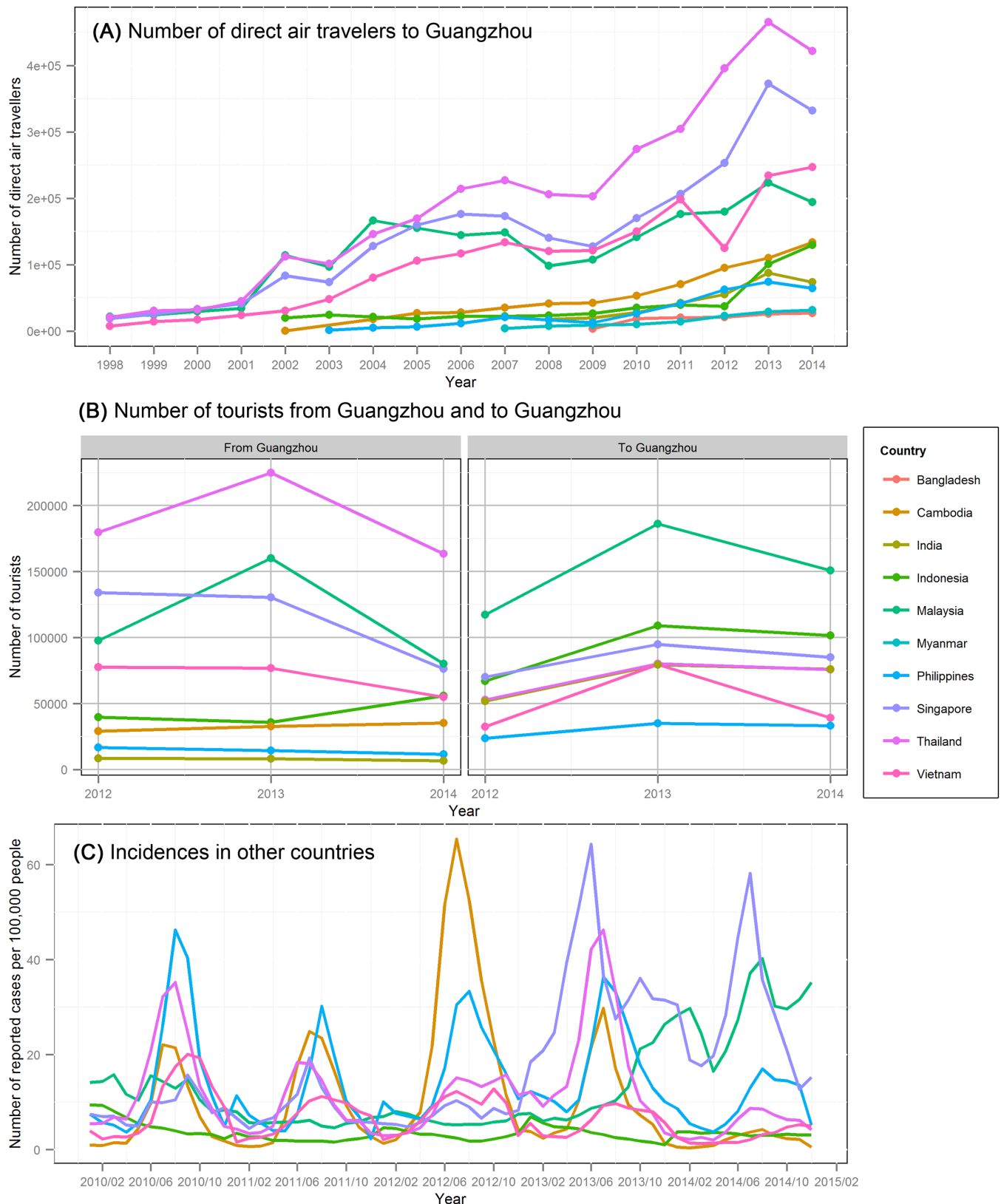


Fig 8. Number of travelers and incidence in surrounding dengue endemic areas. (A) the number of direct air travelers collected from ICAO DATA+; (B) number of tourists from Guangzhou by tour group, and number of foreigners staying overnight in Guangzhou from the Tourism

Administration of Guangzhou; (C) reported dengue incidences in the surrounding countries from WHO dengue situation updates and local health departments. Data for Bangladesh and Myanmar is not available for (B) and for Bangladesh, India, and Myanmar is not available for (C).

<https://doi.org/10.1371/journal.pntd.0005701.g008>

especially in May and June (Fig 5). Considering the epidemic had not started yet at that time, the excessive number of reported imported cases was unlikely to be caused by increasing reporting rate. One possible explanation is spatial heterogeneity. The importation index assumes that human and vector populations are well-mixed, which means that the contact rate between every person and every vector is the same. However, the actual contact rate can be affected by tour route, local transmission hotspots, as well as personal habits, such as whether take measures to avoid mosquito bites. The other explanation is the different reporting rate. For example, if the reporting rate is lower in Malaysia than in other countries, then its actual contribution to the total importation index should be higher, which may make the pattern of the total importation index more similar to that of Malaysia.

Determinants of success rate

The first step of a successful invasion is infecting adult mosquitoes (Event 12), which is described in the model by transition rate $b\alpha_{hv}HiAs/N$. Both the biting rate b and the transmission probability from human to vector α_{hv} ranges from 0 to 1, Hi equals to 1, and the total human population N changed little in the study time period. Hence, the size of the susceptible mosquito population, As , has the greatest influence on this transition rate. As can be seen from Figs 4, 9A and 9B, it is obvious that the success rate and As have almost the same pattern. Furthermore, we calculated the cross-correlation function (CCF) between the difference of success rate and the difference of As . First differences were taken here to remove trend of the time series. The result shows that success rate at day t is positively correlated with As at day $t + 10$ for all parameter sets under all scenarios. The average result for *Scenario 2014* is shown in Fig 9C. Since the average recovery period is assumed to be 6 days in the model [7], and we use a 10-day time window for the imported case, the 10-day time lag between As and success rate is reasonable.

When we explore the individual results for each of the 100 parameter sets, we found that the gap between the success rate under different climate scenarios is more marked when the maximum water level ω_{max} in that parameter set is larger (Fig 9D). This is because precipitation can affect the carrying capacity through water availability only before ω_{max} is reached, since water will overflow after reach this threshold. Therefore, if the ω_{max} is larger, it takes longer to reach this threshold, which will then lead to larger difference in the mosquito abundance and success rate. This phenomenon implies that reducing ω_{max} by destroying breeding sites can mitigate the effect of climate on dengue transmission dynamics.

Suggestions for dengue prediction with regression model in subtropical and tropical areas

Regression models are widely used to predict the occurrence of dengue outbreaks, monthly reported cases and the FES [5, 6, 45, 50]. Here we suggest the factors to include in these models according to the results of our stochastic model.

Once given the timing of each imported case, the outbreak probability can be calculated from the success rate curve (Fig 4), which depends mainly on mosquito abundance. Therefore, to predict the occurrence of dengue outbreaks in subtropical areas, variables, such as the number of imported cases and mosquito abundance, should be included. Mosquito abundance is related to temperature, water availability and interventions. Water availability can be estimated

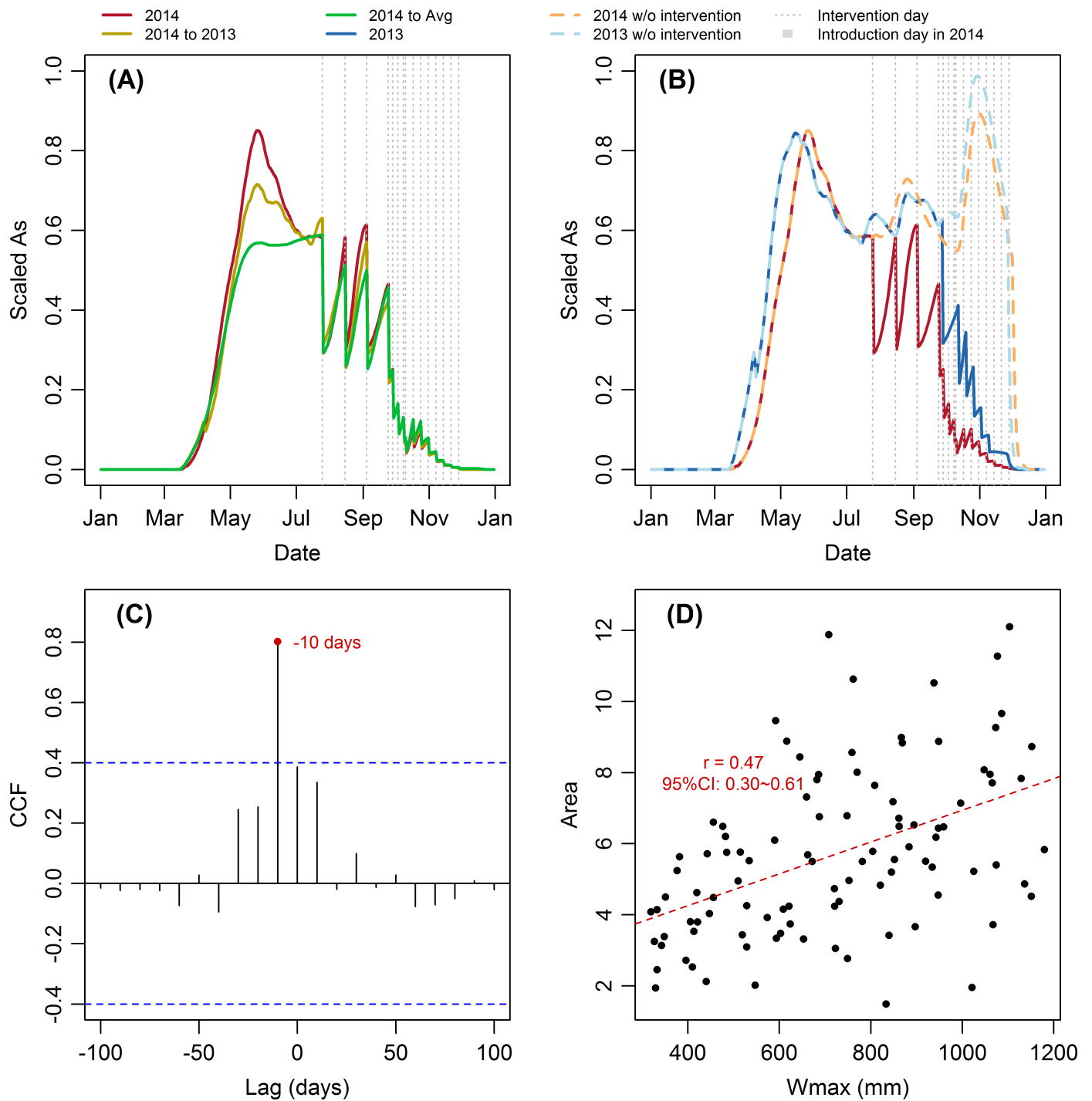


Fig 9. Relationship between A_s , ω_{max} and success rate. Average scaled A_s of 100 parameter sets under (A) *Scenario 2014*, *2014 to 2013*, and *2014 to Avg*, and (B) *Scenario 2014*, *2013*, *2014 w/o intervention*, and *2013 w/o intervention*. Since the absolute values of A_s may vary several magnitude between different parameter sets, the relative values of A_s were used by scaling the A_s to 0–1 to make them have the same weight on the mean value. (C) The average CCF between the difference of success rate and the difference of A_s under *Scenario 2014*. (D) Scatterplot of ω_{max} in each parameter set and the area between the success rate under *Scenario 2014* and *2014 to Avg* of the same parameter set.

<https://doi.org/10.1371/journal.pntd.0005701.g009>

from rainfall, evaporation, intervention, and the water limitation parameters ω_{max} and ω_{max} . Without all these data, water availability can be indirectly represented by precipitation, and

relative humidity. However, precipitation and relative humidity do not reflect the effects of intervention and the relationship between water level and precipitation or relative humidity is non-linear. The water level increases with precipitation in spring and early summer, but when it reaches its threshold ω_{\max} , the water level cannot increase further and remains at this value until evaporation outweighs precipitation or the occurrence of an intervention. In addition, the relationship between water level and mosquito abundance is complicated, which depends on previous water level, the environmental carrying capacity and the previous abundance of aquatic stages. As a result, mosquito indices might still be preferred among all these variables. By including the monthly maximum and minimum temperature, average BI, and number of imported cases, a classification tree can be used to predict the dengue outbreak occurrence in Guangzhou [45]. For tropical areas, since local epidemics continue throughout the entire year, there is no need to predict the outbreak occurrence.

The FES depends on both the final outbreak size and outbreak probability. The final outbreak size decreases exponentially as a function of the introduction date, while temperature, water storage, and human interventions can modify the decrease rate through changing the force of infection. Earlier introduction in subtropical areas means a longer period of transmission and more cases, because dengue transmission is terminated by the low temperature every winter. The force of infection can be affected by mosquito abundance, biting rate and virus virulence. Although both the length of transmission and the force of infection can affect the final outbreak size exponentially, the former fluctuates over a much wider range. Sometimes, though the climate is favorable for vector growth, no big outbreak occurs because of the low level or late importation. Thus the imported cases introduce high uncertainty to the prediction models, and a successful model should ideally include the number of imported cases and indigenous cases in the previous month to reduce this uncertainty. Time series regression models with the number of imported and indigenous cases in the previous month, lagged temperature, precipitation and relative humidity can give reasonable estimations of the number of new cases [6, 50]. Climate conditions in tropical areas can support overwinter local transmission, so the role of imported cases here is not as important as that in subtropical areas. Climate and interventions are the only crucial factors in tropical areas. Prediction models based on only climate can have good prediction power [51–53]. When considering the spatial aspects of the transmission, heterogeneity in the distribution of population, open water, vegetation, and host immunity can also influence the outbreak probability and FES for both subtropical and tropical countries [54, 55].

Implications for intervention

Currently, the most common interventions in China are chemical insecticide spraying and environmental management, such as water container emptying. Also, releasing mosquito larvae-eating fish *Gambusia affinis* and *wolbachia*-infected male mosquitoes are sometimes used in small scale tests.

Since the adult abundance and success invasion rate of imported cases increase sharply in April and May (Fig 4), the interventions should begin before or in this time period. However, the regular interventions in Guangzhou started on September 27th and July 25th in 2013 and 2014, respectively, both of which were at least one month later than the onset of local epidemics. In addition, interventions out of the transmission season, such as before the next transmission season can also be important, because it can reduce the water storage, increase the time needed to accumulate water in the next transmission season, and postpone the outbreak, which, in turn, can then decrease the final outbreak size significantly.

According to result of the PRECIS (Providing Regional Climate for Impact Study) regional climate modeling system, the spring and summer rainfall of South China will increase in the

future [56], which may increase the average FES by causing earlier outbreaks. However, destroying mosquito breeding sites can mitigate this detrimental impact of climate change, since it can reduce the maximum water level ω_{\max} and narrow the gaps in the success rate or final outbreak size between different climate scenarios (Fig 9D).

Increasing international travel, urbanization, global warming, and changes in precipitation patterns pose higher dengue outbreak risk for Guangzhou and other subtropical non-endemic areas. Moreover, secondary infection can worsen the situation by increasing the incidence of life-threatening dengue hemorrhagic fever and shock syndrome [57]. Under this situation, vector control and management of imported cases at entry points should be implemented strictly, especially around mid-April, to reduce possible health and economic loss caused by dengue or other mosquito-borne diseases, such as yellow fever and Zika. Since the travel volumes between Thailand, Malaysia, Singapore and Guangzhou are the highest, more attentions should be paid to the detection of imported cases when dengue outbreaks occur in these countries, especially at early summer. Besides international imported cases, cases from other Chinese cities should also be considered. Since Guangzhou is normally the first city to have dengue outbreak in mainland China, it is unusual for Guangzhou to have domestic imported cases in the early phase of an epidemic, although it happens on occasion. For example, the epidemic in Zhongshan started 2 weeks earlier than in Guangzhou [50]. On the other hand, the onset of an epidemic in Guangzhou signals that surrounding cities of the need to pay attention to case detection and vector control immediately. For example, from Figs 4B and 9C, it can be seen that, after detection, the model suggests that interventions should be conducted around the residences of the reported cases whose symptoms began less than 10 days ago, even if they have recovered.

Limitations

The model proposed here represents the transmission of only one serotype DENV-1, since 5,947 out of 6,024 cases (98.7%) tested in 2014 were infected by DENV-1, and only 74 and 3 were infected by DENV-2 and -3, respectively [48]. When adapted for use in other subtropical areas, the single serotype assumption may or may not be appropriate. Secondly, we assumed that dengue virus virulence and reporting rate were the same for 2013 and 2014, which led to similar initial exponential growth rates for these two years. However, from the daily reported new case data, the growth rate of 2014 was slightly higher than that of 2013 (Fig 3), the reasons for which deserve further investigation. Thirdly, the estimated success rates illustrated in Fig 4 are estimates of the upper bound on what might be expected in practice, because it estimates the success rates for imported cases who spend the whole viremic period in Guangzhou. However, an imported case can enter Guangzhou at the middle or even the last day of the viremic period and thereby have less time to infect *Ae. albopictus* and result in a lower successful invasion rate. In this model, we also assumed that humans and the mosquitoes are well-mixed, which means the contact rate is the same for every host and vector. However, studies of *Ae. albopictus* indicate that their flying range is as small as 300 meters, and that they normally they stay near their breeding sites for their whole life [58]. Therefore, a spatially-explicit model is needed to better simulate the spatial distribution of dengue cases and study the risk factors related to the observed distribution patterns in the future.

Supporting information

S1 File. Model details.

(DOCX)

S1 Table. Number of foreign tourists staying overnight in Guangzhou and number of tourists traveled from Guangzhou with tour groups.

(XLSX)

S2 Table. The 100 parameter sets used in the stochastic model.

(XLSX)

Acknowledgments

The authors would like to thank Dr. Yang Cao and Dr. Hernan G. Solari for discussion about the stochastic algorithm. We are also grateful to the Tourism Administration of Guangzhou for providing tourism statistics.

Author Contributions

Conceptualization: Qu Cheng, Qinlong Jing, Robert C. Spear, John M. Marshall, Zhicong Yang, Peng Gong.

Formal analysis: Qu Cheng, Qinlong Jing, Robert C. Spear, Peng Gong.

Funding acquisition: Qinlong Jing, Zhicong Yang, Peng Gong.

Investigation: Qu Cheng, Qinlong Jing, Zhicong Yang.

Methodology: Qu Cheng, Qinlong Jing, Robert C. Spear, John M. Marshall.

Resources: Qu Cheng, Qinlong Jing, Zhicong Yang.

Software: Qu Cheng, Robert C. Spear.

Supervision: Zhicong Yang, Peng Gong.

Visualization: Qu Cheng, Qinlong Jing, Robert C. Spear, John M. Marshall.

Writing – original draft: Qu Cheng, Qinlong Jing, Robert C. Spear.

Writing – review & editing: John M. Marshall, Zhicong Yang, Peng Gong.

References

1. World Health Organization. Global strategy for dengue prevention and control 2012–2020: World Health Organization; 2012. Available from: http://apps.who.int/iris/bitstream/10665/75303/1/9789241504034_eng.pdf.
2. Stanaway JD, Shepard DS, Undurraga EA, Halasa YA, Coffeng LE, Brady OJ, et al. The global burden of dengue: an analysis from the Global Burden of Disease Study 2013. *Lancet Infect Dis*. 2016; 16(6):712–23. [https://doi.org/10.1016/S1473-3099\(16\)00026-8](https://doi.org/10.1016/S1473-3099(16)00026-8) PMID: 26874619
3. Lai S, Huang Z, Zhou H, Anders KL, Perkins TA, Yin W, et al. The changing epidemiology of dengue in China, 1990–2014: a descriptive analysis of 25 years of nationwide surveillance data. *BMC Med*. 2015; 13(1):100.
4. Xiao F, Zhang Y, Deng Y, He S, Xie H, Zhou X, et al. The effect of temperature on the extrinsic incubation period and infection rate of dengue virus serotype 2 infection in *Aedes albopictus*. *Arch Virol*. 2014; 159(11):3053–7. <https://doi.org/10.1007/s00705-014-2051-1> PMID: 24990415
5. Shen JC, Luo L, Li LI, Jing QL, Chun Quan OU, Yang ZC, et al. The impacts of mosquito density and meteorological factors on dengue fever epidemics in Guangzhou, China, 2006–2014: a time-series analysis. *Biomed Environ Sci*. 2015; 28(5):321–9. <https://doi.org/10.3967/bes2015.046> PMID: 26055559
6. Sang S, Gu S, Bi P, Yang W, Yang Z, Xu L, et al. Predicting unprecedented dengue outbreak using imported cases and climatic factors in Guangzhou, 2014. *PLoS Negl Trop Dis*. 2015; 9(5):e0003808. <https://doi.org/10.1371/journal.pntd.0003808> PMID: 26020627

7. Cheng Q, Jing Q, Spear RC, Marshall JM, Yang Z, Gong P. Climate and the timing of imported cases as determinants of the dengue outbreak in Guangzhou, 2014: Evidence from a mathematical model. *PLoS Negl Trop Dis*. 2016; 10(2):e0004417. <https://doi.org/10.1371/journal.pntd.0004417> PMID: 26863623
8. Otero M, Solari H. Stochastic eco-epidemiological model of dengue disease transmission by *Aedes aegypti* mosquito. *Math Biosci*. 2010; 223(1):32–46. <https://doi.org/10.1016/j.mbs.2009.10.005> PMID: 19861133
9. Lourenço J, Recker M. The 2012 Madeira dengue outbreak: epidemiological determinants and future epidemic potential. *PLoS Negl Trop Dis*. 2014; 8(8):e3083. <https://doi.org/10.1371/journal.pntd.0003083> PMID: 25144749
10. Ruiz-Moreno D, Vargas IS, Olson KE, Harrington LC. Modeling dynamic introduction of chikungunya virus in the United States. *PLoS Negl Trop Dis*. 2012; 6(11):e1918. <https://doi.org/10.1371/journal.pntd.0001918> PMID: 23209859
11. Haseltine EL, Rawlings JB. Approximate simulation of coupled fast and slow reactions for stochastic chemical kinetics. *J Chem Phys*. 2002; 117(15):6959–69. <https://doi.org/https://doi.org/10.1063/1.1505860>
12. Alfonsi A, Cancès E, Turinici G, Ventura BD, Huisinga W. Adaptive simulation of hybrid stochastic and deterministic models for biochemical systems. *ESAIM Proc*. 2005; 14:1–13.
13. Liu Z, Pu Y, Li F, Shaffer CA, Hoops S, Tyson JJ, et al. Hybrid modeling and simulation of stochastic effects on progression through the eukaryotic cell cycle. *J Chem Phys*. 2012; 136(3):1120.
14. Statistics Bureau of Guangzhou Municipality. Population size and distribution of Guangzhou city in 2014 [cited 2016/05/11]. Available from: http://www.gzstats.gov.cn/tjgb/qtgb/201504/t20150430_37572.htm.
15. Jin LQ, D. LI. A recent survey of mosquito fauna in Guangdong Province, southern China, with a review of past records. *Med Vet Entomol*. 2008; 22(4):359–63. <https://doi.org/10.1111/j.1365-2915.2008.00758.x> PMID: 19120964
16. Xie C, Zhang Z, Tang W, Du C. Analysis of a dengue fever case causing no epidemic spread in sustained high-density mosquito environment. *Yi Xue Dong Wu Fang Zhi*. 2015; 31(3):311–4. (in Chinese)
17. Statistical Bureau of Guangdong. Guangdong statistical yearbook 2012. Beijing: China Statistical Publishing House; 2012. (in Chinese)
18. Statistical Bureau of Guangdong. Guangdong statistical yearbook 2013. Beijing: China Statistical Publishing House; 2013. (in Chinese)
19. Statistical Bureau of Guangdong. Guangdong statistical yearbook 2014. Beijing: China Statistical Publishing House; 2014. (in Chinese)
20. Ross R. Report on the prevention of malaria in Mauritius. London: Waterlow and sons; 1908.
21. Ross R. The prevention of malaria. New York: E. P. Dutton; 1910.
22. Seidahmed OME, Eltahir EAB. A Sequence of flushing and drying of breeding habitats of *Aedes aegypti* (L.) Prior to the low dengue season in Singapore. *PLoS Negl Trop Dis*. 2016; 10(7):e0004842. <https://doi.org/10.1371/journal.pntd.0004842> PMID: 27459322
23. Focks DA, Haile D, Daniels E, Mount GA. Dynamic life table model for *Aedes aegypti* (Diptera: Culicidae): analysis of the literature and model development. *J Med Entomol*. 1993; 30(6):1003–17. PMID: 8271242
24. Zhang H, Mi Z, Zhang Y. Observations of biological characteristics of *Aedes albopictus* in Yunnan. *Yi Xue Dong Wu Fang Zhi*. 1996; 12(3):2–4. (in Chinese)
25. Li J, Zhu G, Zhou H, Tang J, Cao J. Effect of different temperatures on development of *Aedes albopictus*. *Zhongguo xue xi chong bing fang zhi za zhi*. 2015; 27(1):59. (in Chinese) PMID: 26094417
26. Cailly P, Tran A, Balenghien T, L'Ambert G, Toty C, Ezanno P. A climate-driven abundance model to assess mosquito control strategies. *Ecol Model*. 2012; 227:7–17.
27. Zhong Z, He G. The life table of laboratory *Aedes albopictus* under various temperatures. *Zhongshan Yi Ke Da Xue Xue Bao*. 1988; 9(3):35–9. (in Chinese)
28. Karl S, Halder N, Kelso JK, Ritchie SA, Milne GJ. A spatial simulation model for dengue virus infection in urban areas. *BMC Infect Dis*. 2014; 14(1):447.
29. Otero M, Solari HG, Schweigmann N. A stochastic population dynamics model for *Aedes aegypti*: formulation and application to a city with temperate climate. *Bull Math Biol*. 2006; 68(8):1945–74. <https://doi.org/10.1007/s11538-006-9067-y> PMID: 16832731
30. Camacho A, Kucharski AJ, Funk S, Breman J, Piot P, Edmunds WJ. Potential for large outbreaks of Ebola virus disease. *Epidemics*. 2014; 9:70–8. <https://doi.org/10.1016/j.epidem.2014.09.003> PMID: 25480136

31. Beven K, Freer J. Equifinality, data assimilation, and uncertainty estimation in mechanistic modelling of complex environmental systems using the GLUE methodology. *J Hydrol.* 2001; 249(1–4):11–29.
32. Feller W. On the integro-differential equations of purely discontinuous Markoff processes. *T Am Math Soc.* 1940; 48(3):488–515.
33. Kendall DG. An artificial realization of a simple "birth-and-death" process. *Journal of the Royal Statistical Society Series B (Methodological).* 1950; 12(1):116–9.
34. Bartlett M. *Stochastic population models in ecology and epidemiology.* London: 1960.
35. Gillespie DT. Approximate accelerated stochastic simulation of chemically reacting systems. *J Chem Phys.* 2001; 115(4):1716–33.
36. Solari HG, Natiello MA. Stochastic population dynamics: the Poisson approximation. *Phys Rev E Stat Nonlin Soft Matter Phys.* 2003; 67(3):031918.
37. Keeling MJ, Rohani P. *Modeling infectious diseases in humans and animals.* Princeton: Princeton University Press; 2008.
38. Focks DA. *A review of entomological sampling methods and indicators for dengue vectors.* Geneva: WHO; 2003.
39. R Core Team. *R: A language and environment for statistical computing.* R Foundation for Statistical Computing, Vienna, Austria, 2012. ISBN 3-900051-07-0; 2014.
40. Soetaert K, Petzoldt T, Setzer RW. Solving differential equations in R: package deSolve. *J Stat Softw.* 2010; 33.
41. Eddelbuettel D. *Seamless R and C++ integration with Rcpp.* New York: Springer; 2013.
42. Analytics R, Weston S. doSNOW: Foreach parallel adaptor for the snow package 2013 [cited 2016 5–11]. Available from: <https://CRAN.R-project.org/package=doSNOW>.
43. Wickham H. *ggplot2: elegant graphics for data analysis.* Berlin: Springer Science & Business Media; 2009.
44. Li MT, Sun GQ, Yakob L, Zhu HP, Jin Z, Zhang WY. The Driving Force for 2014 Dengue Outbreak in Guangdong, China. *PLoS One.* 2016 Nov 18; 11(11):e0166211. <https://doi.org/10.1371/journal.pone.0166211> PMID: 27861514
45. Jing QL, Luo L, Li XN, Li YL, Cao Q, Xia Y, et al. Associations of Breteau index, imported cases, and meteorological factors with the risk of local epidemic of dengue fever. *Hua Nan Yu Fang Yi Xue.* 2015; 41(5):401–6. (in Chinese)
46. Sun J, Wu D, Zhou H, Zhang H, Guan D, He X, et al. The epidemiological characteristics and genetic diversity of dengue virus during the third largest historical outbreak of dengue in Guangdong, China, in 2014. *J Infect.* 2016; 72(1):80–90. <https://doi.org/10.1016/j.jinf.2015.10.007> PMID: 26546854
47. Huang L, Luo X, Shao J, Yan H, Qiu Y, Ke P, et al. Epidemiology and characteristics of the dengue outbreak in Guangdong, Southern China, in 2014. *Eur J Clin Microbiol Infect Dis.* 2016 Feb 1; 35(2):269–77. <https://doi.org/10.1007/s10096-015-2540-5> PMID: 26700953
48. Wilder-Smith A, Quam M, Sessions O, Rocklöv J, Liu-Helmersson J, Franco L, Khan K. The 2012 dengue outbreak in Madeira: exploring the origins. *Euro Surveill.* 2014; 19(8):pii = 20718.
49. Quam MB, Khan K, Sears J, Hu W, Rocklöv J, Wilder-Smith A. Estimating air travel-associated importations of dengue virus into Italy. *J Travel Med.* 2015 May 1; 22(3):186–93. <https://doi.org/10.1111/jtm.12192> PMID: 25756472
50. Zhang Y, Wang T, Liu K, Xia Y, Lu Y, Jing Q, et al. Developing a time series predictive model for dengue in Zhongshan, China based on weather and Guangzhou dengue surveillance data. *PLoS Negl Trop Dis.* 2016; 10(2):e0004473. <https://doi.org/10.1371/journal.pntd.0004473> PMID: 26894570
51. Gharbi M, Quenel P, Gustave J, Cassadou S, Ruche GL, Girdary L, et al. Time series analysis of dengue incidence in Guadeloupe, French West Indies: Forecasting models using climate variables as predictors. *BMC Infect Dis.* 2011; 11(1):1–13. <https://doi.org/10.1186/1471-2334-11-166> PMID: 21658238
52. Eastin MD, Delmelle E, Casas I, Wexler J, Self C. Intra- and interseasonal autoregressive prediction of dengue outbreaks using local weather and regional climate for a tropical environment in Colombia. *Am J Trop Med Hyg.* 2014; 91(3):598–610. <https://doi.org/10.4269/ajtmh.13-0303> PMID: 24957546
53. Phung D, Huang C, Rutherford S, Chu C, Wang X, Nguyen M, et al. Identification of the prediction model for dengue incidence in Can Tho city, a Mekong Delta area in Vietnam. *Acta Trop.* 2015; 141(2015):88–96.
54. Scott TW, Morrison AC. *Aedes aegypti* density and the risk of dengue-virus transmission. In: Takken W, Scott T, editors. *Ecological aspects for application of genetically modified mosquitoes.* Heidelberg: Springer Netherlands; 2003.

55. Qi X, Yong W, Yue L, Meng Y, Chen Q, Ma J, et al. The effects of socioeconomic and environmental factors on the incidence of dengue fever in the Pearl River Delta, China, 2013. *PLoS Negl Trop Dis*. 2015; 9(10):e000415.
56. Huang XY, Wen ZP, Du Y, Xu Y. Scenario analyses on the changes of future surface air temperature and precipitation in South China. *J Trop Meteorol*. 2008; 24(3):254–8.
57. Kliks SC, Nisalak A, Brandt WE, Wahl L, Burke DS. Antibody-dependent enhancement of dengue virus growth in human monocytes as a risk factor for dengue hemorrhagic fever. *Am J Trop Med Hyg*. 1989; 40(4):444–51. PMID: [2712199](https://pubmed.ncbi.nlm.nih.gov/2712199/)
58. Lu B. The dengue vector in China and its prevention. Guiyang: Guizhou People's Publishing; 1990. (in Chinese)