Weather-Driven Variation in Dengue Activity in Australia Examined Using a Process-Based Modeling Approach

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Abstract. The impact of weather variation on dengue transmission in Cairns, Australia, was determined by applying a process-based dengue simulation model (DENSIM) that incorporated local meteorologic, entomologic, and demographic data. Analysis showed that inter-annual weather variation is one of the significant determinants of dengue outbreak receptivity. Cross-correlation analyses showed that DENSIM simulated epidemics of similar relative magnitude and timing to those historically recorded in reported dengue cases in Cairns during 1991–2009, ($r = 0.372$, $P < 0.01$). The DENSIM model can now be used to study the potential impacts of future climate change on dengue transmission. Understanding the impact of climate variation on the geographic range, seasonality, and magnitude of dengue transmission will enhance development of adaptation strategies to minimize future disease burden in Australia.

INTRODUCTION

Dengue is a cosmopolitan mosquito-borne virus, affecting 50–100 million persons annually, and approximately 40% of the world's population live in dengue-endemic regions.¹ Clinical manifestations range from a nonspecific viral syndrome to severe and life-threatening dengue hemorrhagic fever and dengue shock syndrome.¹ The four dengue viruses are transmitted to humans by the bite of infected female *Aedes* (*Stegomyia*) mosquitoes, of which *Aedes aegypti* is the predominant vector.² Climate influences dengue transmission through impacts on the vector (e.g., growth and development, availability of habitat, survivorship)³ and impacts on the virus (e.g., length of extrinsic incubation period, [EIP]).^{4,5} Correlations have been found between weather and climate variability and dengue incidence, including distinct seasonal variability,⁶ El Niño Southern Oscillation index variability,^{7–11} and monthly^{12–14} and weekly¹⁵ weather variability. The potential impact of climate change on dengue has been extensively explored and estimated via scenario-based modeling, with prediction of expansion in the geographic distribution of dengue under climate change scenarios.^{5,16–18}

Dengue is not endemic to Australia; in far northern Queensland, the only area where dengue occurs, transmission is greatly reduced or absent during the dry season.¹⁹ Viremic travelers from dengue-endemic regions, especially Southeast Asia, are the source of frequent introductions.^{19–21} Because *Ae. aegypti* is established across northeastern Queensland, Australia, well inside theoretical and modeled temperature limits for dengue transmission, there is potential for dengue outbreaks in this region.²² However, dengue outbreaks are largely restricted to major population centers such as Cairns and Townsville, where they have occurred almost annually in the past 15 years.¹⁹ Dengue outbreaks did not occur in Australia during 1955–1981,²³ but were previously widespread in eastern Australia, from northern New South Wales to northern Queensland.²⁴ Since 1990, regular outbreaks have occurred, including outbreaks with up to 1,000 reported cases.^{19,25,26}

There is concern that the geographic range and magnitude of outbreaks may increase in Australia as the climate changes.²⁷

The World Health Organization recommends estimating the future burden of disease attributable to climate change by quantifying current climate-disease relationships and making statistical projections under future climate scenarios.²⁸ All local studies of dengue and climate in the Asia-Pacific region have used an empirical approach²⁹ relying on statistical models, in which the input variables and their coefficients are assumed to remain unchanged.¹⁷ The mechanistic processes of disease transmission are not explicitly represented, but rather are implicit in statistical models, meaning that the impact of variation in these processes on disease transmission cannot be assessed.³⁰

Process-based models, in contrast to statistical models, explicitly describe each aspect of pathogen transmission and its underlying biological processes, which can be individually influenced by climate change. To examine the effects of weather and other determinants on dengue transmission, a process-based dengue simulation model (DENSIM) (Supplementary Table 1), has been developed that uses daily temperature, precipitation, and humidity to first produce simulations of the vector population (in the entomologic model Container Inhabiting Mosquito Simulation [CIMSIM]).^{3,31} The DENSIM then combines this information with meteorologic, virologic, demographic, and epidemiologic data to model virus transmission.⁴ A modified version of DENSIM has been used to investigate global dengue-climate associations.⁵

Global empirical models of dengue distribution under climate change scenarios have limited validity for Australia because their predictions do not accord with the current or historical distribution of dengue.²⁴ Data in these models may be too coarse to predict the occurrence of dengue in small regions of the continent. There is ongoing debate about the relative contributions of climate compared with social conditions, economic and resource factors, and topographic conditions, to future vector-borne disease risks.^{22,27,32} Some studies seeking to model dengue at local and regional scales, and using monthly weather variables, have returned weak correlations, and authors have identified the need to incorporate epidemiologic, demographic, and socioeconomic data to improve the predictive capacity of these models.^{33,34}

To improve understanding of dengue-climate relationships at a regional scale, there is a need for dengue models based on

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local biological, meteorologic, and epidemiologic characteristics. In 2008–2009, the largest dengue outbreak in Australia since vector control programs were initiated in the 1950s occurred in Cairns, far northern Queensland, with more than 1,000 reported cases.³⁵ This outbreak overwhelmed the capacity of the local Dengue Action Response Team to contain transmission, necessitating provision of additional Queensland State Government resources to achieve control.²⁶ Anomalous weather conditions, the arrival of a dengue-infected traveler to Cairns who did not immediately seek medical attention, and a dengue virus with a reduced EIP may have contributed to the magnitude and force of transmission of this epidemic.²⁶

Process-based modeling enables an investigation of the biology and ecology of dengue-climate relations and how different dengue determinants might respond synergistically to predicted scenarios of global climate change. To explore the utility of mathematical modeling in projections for dengue under climate change, we determined the effect of inter-annual weather variation on the frequency and magnitude of dengue outbreaks in Cairns, Queensland, in conjunction with simulations of the human and vector populations experiencing regular importations of dengue virus by using DENSIM.

MATERIALS AND METHODS

Study site. Cairns is the economic and tourism capital of far northern Queensland and had a population of approximately 140,000 in 2007 (www.abs.gov.au). Cairns is located in the Wet Tropics region (16.87°S, 145.75°E), and has a tropical monsoonal climate and average annual precipitation of 2,064.5 mm, 82% of which falls during December–April. Daily mean maximum and minimum temperatures show little annual variation (25.6°C–31.5°C and 16.9°C–23.6°C, respectively) and humidity is consistently high (9:00 AM mean relative humidity = 66–79% and 3:00 PM mean relative humidity = 55–69%) (climate statistics for 1961–1990, Australian Bureau of Meteorology, 2010).

Dengue surveillance. Dengue is a reportable disease in Australia and may be suspected if, in the presence of an appropriate travel history or during an outbreak, the clinical presentation includes fever, headache, arthralgia, myalgia, rash, lethargy, and/or nausea. During an outbreak, suspected cases may also be identified by epidemiologic linkage. For all suspected cases, dengue infection and serotype must be confirmed by laboratory analysis. Data on reported dengue cases for the Cairns Local Government Area during January 1990–December 2009 were obtained from the Notifiable Conditions System, Communicable Disease Unit of Queensland Health.

Imported dengue cases. Records of overseas-acquired dengue cases in Cairns have been maintained since 1998 (Hanna J, Queensland Health, unpublished data). The data include country of origin, date of arrival in Cairns, date of onset of symptoms, date of first medical consultation, and date of reporting. Imported viremic dengue cases are detected by reporting of clinical dengue to the Tropical Public Health Unit Network, Queensland Health, in Cairns. To establish a baseline of overseas arrivals to Cairns, Australian customs records of the annual number of arrivals at Cairns International Airport during 2000–2009 were obtained (Fitzsimmons G, Commonwealth Department of Health and Ageing, unpublished data).

Process-based model (DENSIM) calibration. DENSIM (version 3.27, contained within Dengue Models version 3.0; University of California, Davis, CA) was used to investigate climatic determinants of dengue in Cairns; combining comprehensive biological modeling of climate-dengue virus interactions with key demographic features of the local human population. The version used here is a modified version of the original (Scott T, Garcia A, University of California, Davis, CA, unpublished data).

Meteorologic data. Daily maximum and minimum temperature, precipitation, and relative humidity at 9:00 AM and 3:00 PM during January 1990–December 2009 were obtained from the Australian Bureau of Meteorology (Cairns Aero weather station, 6 km north of central Cairns). Yearly weather files were created for 1990 through 2009 in DENSIM, incorporating daily precipitation, maximum and minimum temperature, daily average relative humidity, and saturation deficit.

Entomologic data. CIMSIM has been calibrated and field validated for use in Cairns.³⁶ In brief, water flux and pupal productivity of six key containers (pot plant bases, tarpaulins, tires, buckets, rainwater tanks, and subterranean pits) that produced approximately 80% of the *Ae. aegypti* pupae in Cairns were monitored; CIMSIM was then iteratively adjusted to match the observed container productivities. The calibrated model was then validated in a blind field test.³⁴ Model runs were performed by using empirically validated field data for low and high container density.³⁶ Dengue epidemic projection data are presented for container densities fitting with observed vector density and dengue incidence.

Demographic data. The age-stratified population for Cairns Statistical Subdivision A (Cairns City) was obtained from the 1996 Australian census data. Population density was calculated from the total population and area defined as Cairns Statistical Subdivision A. Age-stratified fertility and death rates were obtained for 1998. Demographic data were downloaded from the Australian Bureau of Statistics website. The population size at the beginning of simulations (1991) was 92,630 (www.abs.gov.au).

Serologic data. Given the lack of reliable historical seroprevalence data, it was assumed that the Cairns population was immunologically naive to dengue in 1990. Outbreaks in the region before this date occurred in 1953–1955 and 1981–1983; the outbreak in 1981–1983 caused an estimated 855–1,710 infections in Cairns²³ and a seroprevalence of up to 1.8–3.5% immediately afterwards. For the purposes of our simulation, we assume that the IgG seroprevalence in 1990 was 0%.

Virologic data. Infection parameters for dengue virus 2 (DENV2) were set at default values in DENSIM.⁴ Dengue virus 2 was used because it accounted for most outbreaks in Cairns during 1990–2009.²⁵

Dengue simulations. The DENSIM simulation was run during January 1990–December 2009, which included an equilibration year (1990) as required for CIMSIM. A single simulation was run with fixed food delivery rates to mosquito larvae as described.³⁶ In DENSIM, a single human infected with DENV2 was introduced on the first day of each month, commencing in January 1991. Although the imported dengue data shows that on average there is one imported dengue case every two months in Cairns, there is no regularity in timing of introduction and introductions have been recorded in each month since 1998. This importation rate is most likely an underestimate because not all dengue imports will be

reported. Therefore, DENV2 was introduced monthly to assess the risk of a dengue outbreak from a single introduction in each month of the study period.

To examine the effect of variables other than weather conditions on DENSIM outputs, single simulations were also conducted to investigate the effect of multiple interrupted feeding attempts by biting mosquitoes (three attempts compared with the default two attempts for the first simulation) and frequency (weekly, monthly, bimonthly) of dengue introduction in DENSIM.

Analysis of dengue simulations. Cross-correlation (STATA Version 11.0; StataCorp LP, College Station, TX) was used to examine the relationship between monthly reported dengue cases and modeled dengue infection prevalence; a five-month lag and lead time associations were calculated. Cross-correlations were performed for the period 1992–2009. Significance was determined at the $P < 0.01$ level.

RESULTS

Reported and imported dengue cases in Cairns. There were 2,690 reported dengue cases in Cairns during 1990–2009, including 75 imported cases recorded since 1998. Although not strongly seasonal, imported cases were most frequent during January–June (Figure 1). During the study period, DENV2 outbreaks constituted 8 of 13 outbreaks during 1990–2009, although DENV3 outbreaks accounted for two of the four largest outbreaks.²⁵ The annual rate of imported dengue cases in Cairns has increased since records commenced in 1998, despite decreasing numbers of international arrivals at Cairns Airport since 2000 (approximately 350,000 in 2000, peaking at nearly 450,000 in 2005, then decreasing to approximately 225,000 in 2009). An imported dengue case occurred every two months on average, but no seasonal trend was apparent (Figure 1).

DENSIM simulations. Local transmission occurred only during the wet season and outbreaks decreased, and further transmission only occurred after re-introduction of dengue virus (Figure 2). The DENSIM simulations produced large

activity peaks that coincided with large dengue outbreaks (> 50 incident cases per week). Notably, the large outbreaks of 1997–1998, 2004–2005, and 2008–2009 were all predicted to be high risk years by DENSIM. DENSIM did not predict a high risk year for the large outbreak that occurred in 2003–2004, but overpredicted risk for 2007–2008, when there was no large outbreak.

There was a noticeable lag between observed and modeled dengue infections of approximately 2–3 months (Figure 2). Cross-correlation between monthly reportings and modeled incidence showed significant correlations for 1992–2009 (Table 1), and the strongest values ($r = 0.372$) were observed at a lag time of three months, which is consistent with the lag between observed and modeled incidence (Figure 2).

Increasing the number of interrupted blood feeding attempts by *Ae. aegypti* from two to three per gonotrophic cycle increased the size of modeled outbreaks (Figure 3). There were also more years in which outbreaks occurred compared with the default settings (two feeds per cycle). Despite this increase in transmission, endemicity of dengue in Cairns was not predicted.

Increasing the frequency of viremic introductions also increased the size of outbreaks (Figure 4). Bimonthly and weekly introductions created larger outbreaks compared with originally modeled monthly frequency. Despite this increase, endemicity of dengue was not predicted.

DISCUSSION

This study assesses the impact of inter-annual weather variation on dengue transmission in Cairns, in the presence of regular importations of dengue virus and simulations of the human and vector populations. By simulating outbreaks of infections that vary in magnitude in a similar way to observed outbreaks, we have demonstrated that DENSIM may be used to model the magnitude of future dengue outbreaks in Australia under climate change scenarios.

DENSIM reproduces the seasonal epidemic transmission of dengue in Cairns. Most dengue transmission occurs in the warmer, wetter months of October through March, which is

FIGURE 1. Total monthly imported dengue cases to Cairns, Australia, 1998–2009, determined by laboratory confirmation.

FIGURE 2. Notified dengue cases in Cairns, Australia, 1992–2009, grouped by month of onset of symptoms and modeled dengue infections from a dengue simulation model (DENSIM).

explained by the reduction in the EIP of the dengue virus at higher temperatures and the increased abundance of *Ae. aegypti* during the wet season.^{4,19} In DENSIM, the availability of susceptible hosts does not influence the magnitude of outbreaks beyond four years post-introduction in the time-series presented here, confirming that weather variation is the main driver of inter-annual variation in modeled dengue outbreaks. Thus, it is a reasonable inference that the significant correlations between notified and modeled dengue (Table 1) reflects the extent to which weather and climate determines dengue outbreaks in Cairns.

The Dengue Action Response Team program in North Queensland, the control activities of which cannot be incorporated in DENSIM, undoubtedly also has a major impact on transmission.³⁷ Thus, our observation of a strong concordance between observed and modeled dengue epidemics implies powerful meteorologic influence on dengue transmission. In

Singapore, despite extensive dengue control programs, large dengue outbreaks frequently occur and are influenced by weather conditions, as in North Queensland.¹⁵ This observation has important implications in Australia because it suggests that high standards of living and extensive public health programs may not be fully protective against the effects of climate change on dengue to the extent that has been supposed.^{38,39}

It is notable that one of the largest dengue outbreaks predicted by DENSIM occurred in the 2008–2009 wet season, the period during which the largest epidemic observed in Cairns since the introduction of extensive vector control programs in the 1950s (Figure 2). This finding is consistent with a meteorologic influence on the magnitude of the epidemic. Reduced EIP in the circulating dengue virus may also have influenced the magnitude of this outbreak.²⁶

Despite the overall strength of correlation between DENSIM simulations and reported dengue cases, there is limited concordance for some years (Figure 2). Furthermore, there appears to be an approximate 2–3-month lag in DENSIM predicting outbreaks (Figure 2 and Table 1). This finding is probably caused by factors unaccounted for in DENSIM, such as the fact that although we modeled single monthly introductions, introductions were less regular (Figure 1). With monthly dengue introductions, DENSIM also predicts regular outbreaks in the 1990s but dengue importations in this decade were rare and sporadic. Differences between predicted and observed dengue outbreaks are likely to be influenced by these discrepancies in the timing and frequency of introduction of dengue viruses. DENSIM can be used to investigate seasonal and inter-annual receptivity of Cairns to virus introductions and estimate the potential extent of an outbreak in the absence of vector control and public health responses. However, prompt reporting of imported dengue cases to health authorities can avert dengue outbreaks because intensive control strategies

TABLE 1

Cross-correlation analysis for observed monthly dengue infection notifications in Cairns, Australia, and modeled infections in a dengue simulation model

Lead (–)/lag (+) time (months)	1992–2009
–5	–0.049
–4	–0.048
–3	–0.039
–2	–0.032
–1	0.018
0	0.046*
1	0.179*
2	0.348*
3	0.372*
4	0.216*
5	0.062

*Statistically significant correlation ($P < 0.01$).

FIGURE 3. Modeled dengue infections from a dengue simulation model (DENSIM) for Cairns, Australia, 1992–2009, for two and three interrupted blood meals per gonotrophic cycle of the vector *Aedes aegypti*.

are initiated. Delayed notification was a factor in the 2003–2004 and 2008–2009 epidemics.^{19,20}

DENSIM predicted that the 2003–2004 wet season was relatively high risk for dengue outbreaks (Figure 2), which is consistent with the large outbreak that occurred. However, DENSIM failed to predict the substantial outbreak in 2002–

2003. This finding implies that Cairns is vulnerable to dengue outbreaks even when wet season weather conditions are not optimal for dengue transmission and also that non-climatic factors have a substantial influence on whether local dengue transmission occurs. These non-climatic factors may include spatial heterogeneity in dengue transmission in Cairns,⁴⁰

FIGURE 4. Modeled dengue infections from a dengue simulation model (DENSIM) for Cairns, Australia, 1992–2009, for three frequencies of virus introduction by viremic travelers.

which is unaccounted for in DENSIM. Such unmodeled heterogeneity may include the density of susceptible hosts, mosquito breeding sites, and biting rates related to housing design and quality. Furthermore, we have not taken into account differences between particular dengue virus strains, some of which have shorter EIPs in mosquitoes (as demonstrated for the large epidemic in 2008–2009).²⁶

Process-based dengue modeling for Cairns is important for two reasons. First, the inter-annual variation in dengue activity shown by simulations here highlights the importance of investigating weather variability rather than long-term climate averages. Second, estimating future dengue risks under climate change scenarios will require a biological understanding of dengue-climate interactions that cannot be revealed by empirical modeling. Empirical models implicitly include confounding variables such as vector control that mask the effects of climate. Projecting future dengue transmission with empirical models assumes that observed relationships between determinants will be preserved over time. However, this assumption is unjustified when considering the novel human-climate-environment interactions that may arise under global climate change.

The process-based modeling approach used in this study showed several unique characteristics of dengue epidemiology in Cairns that would not have been apparent from an empirical approach. DENSIM modeling demonstrates that there is an inter-annual weather-driven variability in the receptivity of Cairns to dengue outbreaks, and importantly, estimates the potential extent of outbreaks in the absence of vector control measures. The unexpected intensity of the 2008–2009 epidemic overwhelmed the local vector control capability and had widespread effects on the health system, including a substantial reduction in availability of donated blood in the state of Queensland.^{26,41} DENSIM modeling suggests that comparatively large outbreaks could have occurred in several non-outbreak years in the study period. By comparison, empirical modeling is limited to using data on observed outbreaks; the occurrence of which may be also caused by delayed notification of imported cases and subsequent vector control responses rather than the effects of weather.

Process-based modeling enables investigation of the risk of endemic dengue in Cairns. The increasing frequency and magnitude of dengue outbreaks in Cairns has led to speculation that dengue may become endemic.¹⁹ However, endemic dengue does not establish even with a maximum of approximately 2,700 cases (Figure 2). Furthermore, simulations in which we increased the biting frequency per gonotrophic cycle and increased the importation rate also did not predict endemic transmission (Figures 3 and 4), although larger outbreaks were predicted. This finding implies not only that the risk of endemic dengue in Cairns may only arise if much larger outbreaks occur than recently observed, but that there are other characteristics of Cairns (e.g., climate, population density) that may prevent dengue endemicity.

This study is the first to integrate meteorologic, demographic, virologic, and human ecologic data to investigate the relationship between weather and dengue transmission in Australia and addresses the need to develop local dengue-climate models that include local vector and virus data in the context of rapid globalization and climate change.^{24,42} However, there are several limitations to this study. There have not been enough large dengue outbreaks in Cairns to thor-

oughly assess the concordance between observed dengue outbreaks and DENSIM simulations. DENSIM is not routinely used in non-endemic settings and estimates only the potential extent of an outbreak if targeted public health measures are not initiated. DENSIM is also limited by entomologic inputs from CIMSIM.

Migration to and from Cairns may increase the availability of susceptible hosts but this is not modeled in DENSIM.^{43,44} It is also problematic that DENSIM reports the prevalence of dengue infection whereas observed dengue is based only on reported cases. Reported cases underestimate infection prevalence; the ratio of clinical to subclinical infections in Cairns is estimated to be 1:1.09, and an estimated 70% of dengue infections in the Cairns population are asymptomatic.⁴¹ Measurement bias may also affect dengue notification rates; i.e., diagnosis of dengue may have increased over time as dengue becomes more prevalent and diagnostic tests improve. However, estimates of the prevalence of infection suffice in this study, and are less prone to that particular bias, given that its primary aim is to assess relative inter-annual differences in weather-driven dengue risk. Thus, only relative differences in the magnitude of modeled and observed outbreaks are considered.

Furthermore, DENSIM currently assumes a homogeneous human and mosquito population, which may cause underestimations and over-estimations of dengue activity. Further development of the DENSIM model to include spatial heterogeneities in the disease transmission environment would help to add further realism to such work.

Through emphasis on biological processes, process-based models can project climate effects on dengue transmission. DENSIM successfully simulates the seasonal and inter-annual receptivity of Cairns to dengue virus introductions.

Weather is a significant determinant of receptivity to dengue, but is clearly not the only important factor. A better understanding of population susceptibility to infection before and after outbreaks would help to clarify just how important weather and immunity are in determining outbreak probability. Discordance between modeled and actual dengue transmission depends on factors that are not modeled, such as public health efforts that prevent escalation of outbreaks. DENSIM could be calibrated for other centers in far northern Queensland where dengue transmission currently occurs and also used to estimate the receptivity of other areas in tropical Australia to dengue introductions, particularly where *Ae. aegypti* is capable of establishing.^{22,32}

This study provides the basis for investigating the impact of climate change on local dengue transmission in Cairns through incorporation of statistically downscaled daily weather projections.⁴⁵ Provided that climate change scenarios can be downscaled for incorporation in DENSIM, this model may be useful for providing future projections about the distribution of dengue virus and vectors in Australia in the future.

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